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Epoxyethers. XIV.[1,2] The Reaction with Grignard Reagents without Rearrangement

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Epoxyethers which contain two alkyl groups on the epoxide carbon atom were shown to react with Grignard reagents without rearrangement. From epoxyether I the methoxy alcohols III, IV, and V were prepared in about 75% yield using phenyl-, α-naphthyl-, and *p*-tolylmagnesium bromide, respectively. The structures of III and V were proven by independent synthesis. Epoxyether II gave the methoxyalcohol VI, the structure of which was shown by degradation. The methoxyalcohols were characterized by pinacol rearrangements.

One of the reactions studied early in the investigation of the chemistry of epoxyethers was the reaction with Grignard reagents.[3] The two examples of epoxyethers used at that time were prepared from *alpha*-bromopropiophenone and desyl chloride. Each of these epoxyethers reacted with phenylmagnesium bromide to give two isomeric products. One product resulted from the attack of the Grignard reagent upon the ketal carbon of the epoxide and the other product resulted from rearrangement of the epoxyether to an *alpha*-methoxyketone followed by reaction with the Grignard reagent. The rearrangement could be eliminated by the use of diphenylmagnesium instead of the Grignard reagent. Subsequent investigation of the rearrangement of epoxyethers[4] showed that rearrangements involving migration of an alkyl group were significantly more difficult than those involving migration of an aryl group or a hydrogen. Those results led to the prediction[4] that dialkyl epoxyethers such as I or II might react with the Grignard reagent without the complication of rearrangement and provide a useful route to the methoxyalcohols of the type shown by formula III–VI. The present investigation has confirmed that prediction.

The epoxyether I reacted smoothly with three different aromatic Grignard reagents to give about 75% yield of products. The product from phenylmagnesium bromide was a low-melting solid III, the structure of which was proven by independent synthesis. The methoxyketone VII had previously been prepared in this laboratory[5] and when allowed to react with methylmagnesium bromide gave III in 51% yield.

The product from the reaction of I with *p*-tolylmagnesium bromide was also synthesized independently by the same approach. The methoxyketone VIII was prepared in 57% yield from the parent ketone by bromination followed by solvolysis of the bromoketone with methyl alcohol. The methoxyketone VIII, when treated with methylmagnesium bromide, gave 54% of IV identical in all respects with the product from the epoxyether.

A second example of a dialkyl epoxyether (II) also reacted readily with phenylmagnesium bromide to give 80% of a crystalline methoxyalcohol (VI). Evidence for the structure VI was the isolation of 54% of cyclohexanone from a cleavage reaction with strong base. Since the epoxyether II is known to rearrange to an *alpha*-methoxy cycloheptanone in the presence of magnesium bromide,[4] rearrange-

(1) The previous paper in this epoxyether series involved the determination of stereochemistry, *J. Org. Chem.*, **23**, 336 (1958).

(2) This work was supported in part by the Office of Ordnance Research, U. S. Army.

(3) C. L. Stevens, M. L. Weiner, and C. T. Lenk, *J. Am. Chem. Soc.*, **76**, 2698 (1954).

(4) C. L. Stevens and S. J. Dykstra, *J. Am. Chem. Soc.*, **76**, 4402 (1954).

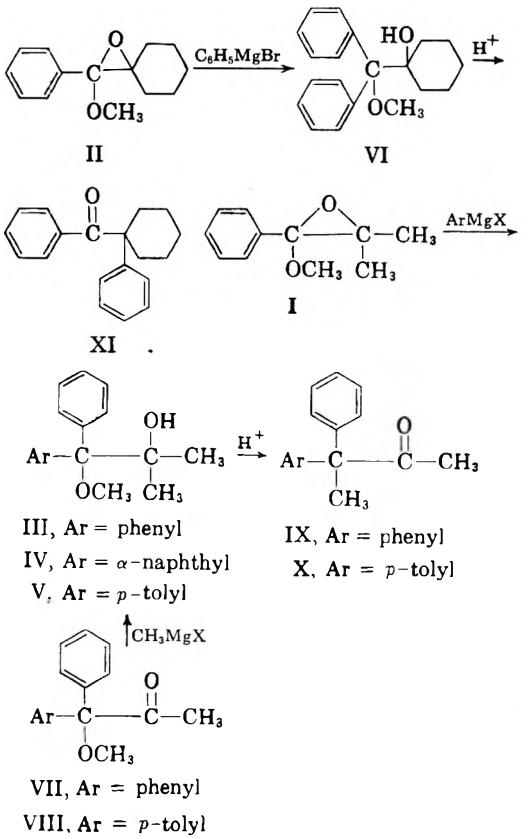
(5) C. L. Stevens and C. T. Lenk, *J. Org. Chem.*, **19**, 538 (1954).

ment prior to addition of the Grignard reagent would be expected to result in a cycloheptanol derivative. The isolation of cyclohexanone from the basic degradation eliminates the cycloheptanol structure for VI.

In each of the Grignard reactions reported here the nucleophilic reagent has cleanly attacked the ketal carbon, which is in accord with the direction of opening of the oxide ring in the other acid catalyzed reactions of epoxyethers. A comparison of the synthetic approach to the methoxyalcohols *via* the epoxyethers with the approach followed in the independent synthesis indicates the former is the method of choice.

The methoxyalcohols III, IV, and VI were further characterized by an acid catalyzed pinacol-type rearrangement. The methoxyalcohol III was converted by concentrated sulfuric acid into the methyl ketone IX in 60% yield. With IV the same transformation was best done with concentrated hydrochloric acid in dioxane solution. The product of methyl migration X was formed in 58% yield. The methyl ketone IX is a known compound and the infrared and ultraviolet spectra of IX and X support the assigned structure. The carbonyl absorption bands in the infrared occur at 5.83 and 5.84 microns, respectively, indicating unconjugated carbonyl groups and the ultraviolet curves have no maxima near 240 mμ.

A similar rearrangement of the cyclohexyl methoxyalcohol VI would be expected to yield a cycloheptanone derivative. Instead, the methyl ether group was cleaved, the aromatic group migrated, and the product was the known phenyl ketone XI. The carbonyl absorption band in the infrared occurred at 5.95 microns and the ultraviolet spectrum had λ_{max} 240; ϵ 8,650.



EXPERIMENTAL

Reaction of epoxyethers I and II with the Grignard reagents. The following directions apply for each reaction. An ether solution of the Grignard reagent was prepared from 5.84 g. (0.24 g.-atom) of magnesium and 37.7 g. (0.24 mole) of bromobenzene and cooled to 0°. At this temperature 10 g. (0.06 mole) of epoxyether[6] (1,2-epoxy-2-methyl-1-methoxy-1-phenylpropane, I) was added slowly. After addition was complete, the reaction was brought to the reflux temperature for five minutes and then poured onto a mixture of 50 g. of ice and 200 ml. of water containing 25 g. of dissolved ammonium chloride. The organic layer was separated, dried, and the ether evaporated. The residue was distilled to give 11.2 g. (72%) of 1,1-diphenyl-1-methoxy-2-methyl-2-propanol (III), b.p. 134–135° (4 mm.); n_D^{29} 1.5631; m.p. 51–52°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87. Found: C, 79.79; H, 8.23.

From 5 g. (0.03 mole) of epoxyether I and 0.056 mole of α-naphthylmagnesium bromide was obtained 6.8 g. (79%) of 1-(α-naphthyl)-1-phenyl-1-methoxyl-2-methyl-1-propanol (IV), b.p. 173–174° (0.4 mm.). The product was a glass at room temperature.

Anal. Calcd. for $C_{21}H_{22}O_2$: C, 82.32; H, 7.23. Found: C, 82.14; H, 7.23.

With *p*-tolylmagnesium bromide and the epoxyether I (5 g., 0.03 mole) the product was 73% of 1-phenyl-1-(*p* tolyl)-1-methoxy-2-methyl-2-propanol (V), b.p. 125–130° (0.2 mm.); n_D^{22} 1.5623.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.15. Found C, 79.85; H, 8.11.

The reaction of 0.15 mole of phenylmagnesium bromide with 0.01 mole of epoxyether II (2-methoxy-2-phenyl-1-oxaspiro[2.5]octane)[7] gave 80% yield of 1-(α-methoxybenzhydryl)cyclohexanol (VI), m.p. 137–139°.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.00; H, 8.10. Found: C, 81.18; H, 8.17.

Methoxyalcohols III and V by independent synthesis. 1,1-Diphenyl-1-methoxy-2-propanone[5] (1 g., 4.1 mmoles) was allowed to react with excess methymagnesium iodide in ether solution at the reflux temperature for five minutes. From the reaction was obtained 0.41 g. (51%) of III, m.p. 51–53°. A mixture melting point with III from the epoxyether was not depressed.

The synthesis of V started with phenylacetone. The Organic Syntheses[8] procedure for diphenylacetone was used except that toluene was substituted for benzene. From 37 g. (0.277 mole) of phenylacetone was obtained 32 g. (52%) of 1-phenyl-1-(*p*-tolyl)-2-propanone, b.p. 130–132° (0.8 mm.); n_D^{24} 1.5730.

From 1 g. of the ketone was obtained 0.55 g. of an oxime derivative, m.p. 134–136°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.27; H, 7.16. Found: C, 80.47; H, 7.35.

The ketone was brominated and the resulting bromoketone solvolyzed in methyl alcohol according to the procedure published for the preparation of III.[5] From 7 g. of ketone was obtained 4.55 g. (57%) of 1-phenyl-1-(*p*-tolyl)-

(6) C. L. Stevens and T. H. Coffield, *J. Am. Chem. Soc.*, 80, 1919 (1958).

(7) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 618 (1952).

(8) E. M. Schultz and S. Mickey, *Org. Syntheses*, **29**, 38 (1949).

1-methoxy-2-propanone, b.p. 120–121° (0.15 mm.); n_D^{23} 1.5652.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.16. Found: C, 80.54; H, 7.23.

Excess methylmagnesium bromide reacted with 2.26 g. of the α-methoxyketone to give 1.3 g. (54%) of V, identical with the product from the epoxyether reaction as shown by the physical properties, b.p. 110–112° (0.08 mm.), n_D^{22} 1.5623 and the infrared spectra.

Cleavage of 1-(α-methoxybenzhydryl)-cyclohexanol (VI) *with base.* A solution of 3.2 g. of methoxyalcohol VI in 10 ml. of 40% sodium hydroxide and 10 ml. of 95% glycerin was heated to the reflux temperature and 10 ml. of distillate removed and discarded. The remainder was heated at the reflux temperature for 1 hr., after which a distinct odor of cyclohexanone was present. Ten ml. of water was added and a 10-ml. portion of distillate collected. After this procedure was repeated once, the 20 ml. of distillate were combined, saturated with sodium chloride, and extracted with ether. The ether was evaporated and the cyclohexanone content of the residue determined by the method of Iddles and Jackson.[9] The yield of 2,4-dinitrophenylhydrazone of cyclohexanone was 54% and the identity was established by comparison with an authentic sample.

Pinacol rearrangement of the methoxyalcohols III, IV, *and* VI. One-half gram of III was dissolved in 5 ml. of concentrated sulfuric acid, allowed to stand at room temperature for 2 hr., and then poured onto cracked ice. The resulting mixture was extracted with ether and the ether solution washed and dried. After the solvent was removed the residue crystallized. Recrystallization from petroleum ether gave 0.26 g. (60%) of the known 1,1-diphenyl-1-methyl-2-propanone,[10] m.p. 40–42°. The semicarbazone[11] melted at 175–177°.

For the pinacol rearrangement of IV, a solution of 0.4 g. of the methoxyalcohol in 5 ml. of dioxane and 5 ml. of concentrated hydrochloric acid was allowed to remain at room temperature overnight. The product was isolated as from the sulfuric acid procedure and recrystallized from petroleum, m.p. 98–100°. The yield was 0.21 g. (58%).

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.55; H, 6.61. Found: C, 87.59; H, 6.87.

The methoxyalcohol VI gave 36% of 1-phenyleyclohexyl phenyl ketone,[12] m.p. 73–75° using the sulfuric acid procedure. Because the yield was low, an infrared spectrum was taken of an aliquot of the total crude product to determine whether a ketone was present with an unconjugated carbonyl group. Only the absorption band corresponding to the conjugated carbonyl (6.0 microns) appeared in the spectrum.

The hydrochloric acid–dioxane procedure gave 66% of the same ketone, m.p. 65–70°, but in this case an aliquot of the total crude ketone gave an infrared spectrum which contained a very small unconjugated carbonyl band at 5.85 microns.

The fused zinc chloride–acetic anhydride procedure of Lyle and Lyle[12] gave 100% of crude product, m.p. 58–66° with no evidence for the isomeric ketone.

Acknowledgment. The authors wish to thank Dr. J. M. Vanderbelt, R. B. Scott, and their associates at Parke-Davis and Co. for the ultraviolet and infrared spectral determinations and for their helpful discussions. We are also grateful to Mr. C. E. Childs and associates at Parke-Davis for microanalyses.

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(9) H. A. Iddles and C. E. Jackson, *Ind. Eng. Chem., Anal. Ed.*, **6**, 454 (1934).

(10) K. Sisido and H. Nozaki, *J. Am. Chem. Soc.*, **70**, 777 (1948).

(11) W. Parry, *J. Chem. Soc.*, **99**, 1169 (1911).

(12) R. E. Lyle and G. G. Lyle, *J. Am. Chem. Soc.*, **74**, 4059 (1952).

[CONTRIBUTION FROM THE RESEARCH STATION, THE BRITISH PETROLEUM COMPANY LIMITED]

Preparation and Physical Properties of Sulfur Compounds Related to Petroleum. VIII. *trans*-2-Thiabicyclo[3.3.0]octane

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trans-2-Thiabicyclo[3.3.0]octane has been synthesized; its physical properties are recorded, and it has been characterized by the preparation of derivatives.

In previous papers in this series, the preparation and properties of eight of the nine possible thiabicyclo-octanes containing fused five- and six-membered rings, have been described.[1–3] The preparation and properties of the remaining isomer, *trans*-2-thiabicyclo[3.3.0]octane (V), referred to in a note[4] on the *cis-trans* isomerization of cyclic sulfones, are detailed below.

In view of the attention recently paid to systems which contain two *trans*-1,2-fused five-membered rings, *trans*-2-thiabicyclo[3.3.0]octane is of special interest; little has been reported of these systems and only a few are known.[5] Until recently, stereochemical considerations indicated that in such a system the *trans*-configuration would involve considerable strain within the molecule. The work of

(1) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **20**, 1178 (1955).

(2) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **22**, 1590 (1957).

(3) S. F. Birch and R. A. Dean, *Ann.*, **585**, 234 (1954).

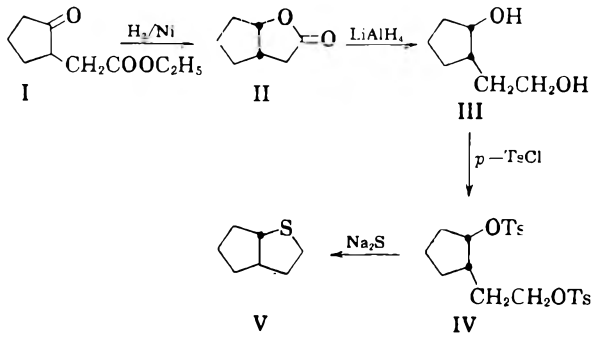
(4) S. F. Birch, R. A. Dean, and E. V. Whitehead, *Chem. & Ind. (London)*, 409 (1956).

(5) H. Booth, F. E. King, J. Parrick, and R. L. St. D. Whitehead, *Chem. & Ind. (London)*, 466 (1956).

Linstead and his co-workers,[6-8] and that of Owen and his associates[9,10] as well as our own work[1] has shown that, using comparatively mild conditions, the *trans*-isomer of a system containing two 1,2-fused five-membered rings is much more readily formed than might be expected. There is, however, little doubt that the *trans*-isomer involves a more strained configuration with the result that the *cis*-isomer is favored at equilibrium.[4] *cis*- and *trans*-2-Thiabicyclo[3.3.0]octanes like the 3-thia analogs[1,9] do not obey the Auwers-Skita rule, which again indicates that the *trans*-isomer has a greater degree of strain than the *cis*-isomer.

The assignment of a *trans*-configuration to this thiabicyclo[3.3.0]octane has been based primarily on the fact that its sulfone can readily be isomerized, under mild conditions, to the sulfone of the *cis*-isomer (the configuration of which has already been established[1]). This assignment of *trans*-configuration confirms that the lactone (II) from which it is derived has a *cis*-configuration[11,12] since it has been shown that a Walden inversion occurs in analogous cyclization reactions used in the preparation of 6-thiabicyclo[3.2.1]octane and 2-thiabicyclo[2.2.2]-octane.[2] The previous assignment of configuration of this lactone was based on its ease of formation, a method which now appears to be less reliable than was originally thought.

The route used in the synthesis of *trans*-2-thiabicyclo[3.3.0]octane was as illustrated in the accompanying formulas.



The *cis*-lactone (II), accompanied by a small quantity of the corresponding *trans*-hydroxy ester, was obtained in good yield when ethyl cyclopentanone-2-acetate (I) was reduced with hydrogen over Raney nickel. Separation of the lactone from the *trans*-hydroxy acid was effected, after hydrolysis, by removal of the acid as its ammonium salt, a method described by Hückel and Gelmroth.[11] These authors found that catalytic hydrogenation of cyclopentanone-2-acetic acid over a platinum catalyst gave a mixture of the *cis*-lactone (II) and *trans*-cyclopentanol-2-acetic acid, but using their conditions, hydrogenation was found to be very slow, the yield of the required lactone low, and isolation of cyclopentaneacetic acid from the product indicated that some hydrogenolysis had occurred.

Reduction of the lactone (II) with lithium aluminum hydride gave the *cis*-glycol (III) in good yield. On tosylation, this yielded a thermally unstable ditosylate[13] with the cyclic ether, 2-oxabicyclo[3.3.0]octane, as a by-product.[14] (The stereochemical configuration of the latter is unknown but from its behavior on freezing it appears to be substantially a single stereoisomer.) Attempts to crystallize the ditosylate invariably resulted in partial conversion into an unsaturated monotosylate, apparently by elimination of a tosylate group. The crude ditosylate was accordingly used for the next stage without purification. Cyclization of the *cis*-ditosylate (IV) with sodium sulfide at 50° gave the *trans*-sulfide (V) in poor yield as expected, the by-products being polymeric sulfides boiling from 130–240°/0.8 mm. Analysis of the lower boiling portion of the latter indicated that it was probably the unsaturated sulfide $C_{14}H_{22}S$; the higher boiling material appeared to contain three atoms of sulfur per molecule.

The derivatives of *trans*-2-thiabicyclo[3.3.0]-octane were prepared as described previously;[15] their physical properties and those of the sulfide are given in Table I. The infrared absorption spectrum[16] was obtained for this sulfide in the range 2–15μ using a Grubb-Parsons double beam spectrometer. Both *cis*- and *trans*-2-thiabicyclo[3.3.0]-octane appear to undergo an autoxidation reaction similar to that described by Bateman *et al.*[17] for thiacyclohexane. Pure samples of each sulfide stored in stoppered glass containers for several months in diffuse light were re-examined spectroscopically and found to exhibit strong absorptions 5.74μ and 9.56μ at characteristic of carbonyl and sulfoxide groups, respectively. Distillation of the *trans*-sulfide after storage yielded almost pure sulfide and left a residue which contained, by titration[18] 25% of sulfoxide. Reduction of the residue with

(6) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).
(7) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 946 (1934).
(8) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 436 (1935).
(9) L. N. Owen and A. G. Peto, *Chem. & Ind. (London)*, 65 (1955).
(10) L. N. Owen and A. G. Peto, *J. Chem. Soc.*, 2383 (1955).
(11) W. Hückel and W. Gelmroth, *Ann.*, **514**, 233 (1934).
(12) W. E. Grigsby, J. Hind, J. Chanley, and F. H. Westheimer, *J. Am. Chem. Soc.*, **64**, 2606 (1942).
(13) Di-*p*-toluenesulfonate.
(14) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2108 (1950).
(15) E. V. Whitehead, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3632 (1951).
(16) To be submitted to A.P.I. Research Project 44 for inclusion in their Catalog of Spectral Data.
(17) L. Bateman, J. I. Cunneen, and J. Ford, *J. Chem. Soc.*, 1539 (1957).
(18) D. Barnard and K. R. Hargrave, *Anal. Chim. Acta*, **5**, 536 (1951).

TABLE I

PHYSICAL PROPERTIES OF *trans*-2-THIABICYCLO[3.3.0]OCTANE AND ITS DERIVATIVES

Sulfide

Temp., °C.	Refractive Index[a] Wave Length Ångstrom Units 6678	6563	5893	5461	5016	4861	4358	B.P., °C. at 20 mm.	M.P., °C.
20	1.52475	1.52521	1.52845	1.53124	1.53497	1.53654	1.54302		
25	1.52249	1.52295	1.52619	1.52898	1.53272	1.53429	1.54077	86.5	−8
30	1.52018	1.52065	1.52388	1.52666	1.53039	1.53196	1.53843		

Derivatives

Formula of Derivative	M.P., °C. (Corrected)	Analyses Calcd. C	H	S	Found C	H	S
$C_7H_{12}Cl_2HgS$	129.5–132.0	21.0	3.0	8.0	21.0	3.1	8.1
$C_7H_{12}O_2S$	62.2–62.7	52.5	7.6	20.0	52.5	7.7	20.1
$C_8H_{15}IS$	An oil						

[a] These values have been smoothed by the method of Forziati.[19]

lithium aluminum hydride gave an evil-smelling product containing both mercapto- and hydroxy-groups. This was possibly cyclopentanol-2-β-ethanethiol derived from dicyclopentanone-2-β-ethyl disulfide, a probable end product of the autoxidation of the *trans*-sulfide. Unfortunately the quantity available was insufficient for further examination.

The physical properties of the sulfide being available, the appropriate fraction of the sulfur-containing oil, obtained in the process of refining kerosine, was examined but this sulfide was not found.

EXPERIMENTAL

All melting points are corrected. The purity was estimated by the freezing point method of Mair, Glasgow and Rossini.[20] The cryoscopic constant was estimated from the freezing time. Microanalyses are by Dr. Ing. A. Schoeller of Kronach/Oberfranken, Bambergerstrasse 20, Germany.

Cyclopentanone-2-acetic acid, m.p. 52.3–53.3°, was obtained in 79% yield from 2-carbethoxycyclopentanone using the method[21] of Linstead and Meade.[6] Continuous esterification[22] of this acid gave the ethyl ester (I) in almost theoretical yield, b.p. 131°/18 mm., n_D^{20} 1.4528, and the methyl ester, b.p. 128–131°/25 mm., n_D^{20} 1.4579.

cis-Cyclopentanol-2-acetic acid lactone (II). (*a*) Cyclopentanone-2-acetic acid (40 g.) was hydrogenated over a platinum black catalyst in ether until hydrogen ceased to be absorbed (32 hr.). After removal of catalyst and extraction with sodium bicarbonate solution (500 ml., 6%) the *cis*-lactone (II) (6.4 g.) was obtained. Acidification and extraction of the aqueous portion yielded an oil (33 g.) which on distillation gave a fraction b.p. 130–140°/23 mm.; n_D^{20} 1.4582; (7.2 g.), which was dissolved in ether, saturated with dry ammonia, and filtered. Acidification of the ammonium salt gave an oil (3.7 g.); b.p. 134–140°/25 mm.; n_D^{20} 1.4542; m.p. 14–15°. Eykman[23] gives b.p. 139–140°/26 mm.; m.p. 13–14°; n_α^{18} 1.45234 for cyclopentaneacetic acid.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4. Found: C, 65.6; H, 9.6.

(*b*) Methyl cyclopentanone-2-acetate (69 g.) in methanol was hydrogenated over a Raney nickel catalyst at 140° and a pressure of 2000 p.s.i.g. The product (54 g.) distilled at 133–140°/25 mm.; n_D^{20} 1.4710 and was separated into *cis*-lactone (33 g.) and *trans*-acid (5.6 g.).

(*c*) The ethyl ester (I) (735 g.) hydrogenated without solvent gave a mixture of the *cis*-lactone and *trans*-ester, b.p. 124–140°/17 mm., which could not be separated by fractionation. This material was hydrolyzed with 10% aqueous potash, the ethanol removed by distillation, and the aqueous layer acidified and extracted with ether to give an oil (541 g.). This was dissolved in dry ether and separated into *cis*-lactone and the ammonium salt of the *trans*-acid by the technique described in (*a*). A portion of the *cis*-lactone (yield 83% on I) was crystallized twice from ether and redistilled, b.p. 124–126°/16 mm.; m.p. −14.28°; cryoscopic constant 3.0 mole % per deg.; purity 98 mole %; n_D^{20} 1.4755; d^{20} 1.1200.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0. Found: C, 66.7; H, 8.2.

The ammonium salt on acidification gave *trans*-cyclopentanol-2-acetic acid in 16% yield on I. Crystallized from benzene it melted at 52.3–54.3°. Hückel and Gelmroth[11] gave m.p. 52.5–53.5° for this acid. The ethyl ester boiled at 107–108°/2.5 mm.; n_D^{20} 1.4595.

cis-β-(2-Hydroxycyclopentyl)ethanol (III). The *cis*-lactone (II), (430 g.), was reduced with lithium aluminum hydride (100 g.); the product worked up in the usual way gave 89% of the expected *cis*-diol (III) which boiled at 107–116°/0.4 mm.; n_D^{20} 1.4870; 396 g. It solidified on standing and crystallized from ether, had a constant melting point of 35.8–36.8° (Hückel and Gelmroth,[11] m.p. 36°).

Ditosylate of cis-β-(2-hydroxycyclopentyl)ethanol (IV), was prepared by the usual method[1] which involved the slow addition (5 hr.) at 0° of the *cis*-diol (III), (350 g.) in redistilled pyridine (853 g.) to a solution of *p*-toluenesulfonyl chloride in the same solvent (853 g.). The product (808 g., 69%) melted at 113–114° dec. (plunging sample just below melting point otherwise decomposition occurs). A portion recrystallized below room temperature from ethanol melted at 113.5–114° (dec., plunge).

(19) A. F. Forziati, *J. Research Natl. Bur. Standards*, 44, 373 (1950).

(20) B. J. Mair, A. R. Glasgow, and F. D. Rossini, *J. Research Natl. Bur. Standards*, 26, 591 (1941).

(21) To obtain the yield of carbethoxycyclopentanone reported by Linstead it is essential to add the total quantity of ester in one portion to the prescribed quantity of molecular sodium. Similarly the carbethoxycyclopentanone used in the preparation of cyclopentanone-2-acetic acid should be redistilled immediately prior to use [F. Ramirez and J. W. Sargent, *J. Am. Chem. Soc.*, 77, 6297 (1955)].

(22) H. T. Clarke and A. W. Davis, *Org. Syntheses*, Coll. Vol. I, 261 (1944).

(23) J. F. Eykman, *Chem. Weekblad*, 6, 699 (1909).

Anal. Calcd. for $C_{21}H_{26}S_2O_6$: C, 57.5; H, 6.0; S, 14.6. Found: C, 57.5; H, 6.0; S, 14.8.

Evaporation of the mother liquors from crystallization of the ditosylate from hot ethanol gave an oil, acid to litmus, which after washing well with alkali reacted with 50% of the quantity of bromine required to brominate the unsaturated monotosylate of III.

The aqueous mother liquors from the preparation of the ditosylate (IV) yielded an oil (54 g., 18% on the glycol) which boiled at 143–144°/760 mm.; n_D^{20} 1.4570. This was 2-oxabicyclo[3.3.0]octane for which Hückel and Gelmroth[11] give m.p. 144–145°/760 mm.

Anal. Calcd. for $C_7H_{12}O$: C, 75.0; H, 10.8. Found: C, 73.0; H, 10.3.

A freezing point determination indicated the presence of two crystalline modifications, m.p. −107° and −100° and although it appeared probable from the cooling curve that the sample was essentially one isomer no purity could be estimated.

trans-2-Thiabicyclo[3.3.0]octane (V). A solution of sodium sulfide nonahydrate (373 g.) in water (0.2 l.) and ethanol (5.6 l.) was stirred at 50° and the crude ditosylate (IV) (688 g.) was added portionwise to it concurrently with a solution of sodium sulfide nonahydrate (373 g. in water 0.2 l.) (4.6 hr.). Stirring at 50° was continued for a further 12 hr. after which the mixture was steam distilled. The steam-distillate was diluted with water (20 l.), treated with caustic soda (160 g.) and extracted with *n*-pentane; after removal of the solvent, distillation gave an oil (17 g., 8.5%) boiling below 44°/0.5 mm. which was mainly the required sulfide. The residue and that from steam distillation, on distillation gave the following fractions (1) b.p. 130–140°/0.8 mm.; 86 g.; (2) 140–230°/0.8 mm.; 16 g.; (3) 230–240°/0.8 mm.; 37 g., and a residue 12 g.

Anal. Calcd. for $C_{14}H_{22}S$: C, 75.6; H, 10.0; S, 14.4. Found: C, 73.5; H, 9.9; S, 15.1 for Fraction 1.

Anal. Calcd. for $C_{28}H_{46}S_3$: C, 70.2; H, 9.7; S, 20.1. Found: C, 70.9; H, 9.5; S, 19.5 for Fraction 3.

The crude *trans*-2-thiabicyclo[3.3.0]octane (V) was purified by crystallization of its mercuric chloride complex from ethanol, and the sulfide regenerated by adding the complex suspended in Carbitol,[24] to a refluxing solution of aqueous sodium sulfide nonahydrate solution (50% w./w. in water) and collecting the sulfide in an oil water separator. After thorough water washing and drying the sulfide distilled at 86.5°/20 mm.; m.p. −8°; n_D^{20} 1.52845.

Anal. Calcd. for $C_7H_{12}S$: C, 65.6; H, 9.4; S, 25.0. Found: C, 65.6; H, 9.4; S, 25.0.

The sulfide proved to be susceptible to oxidation by air. Distillation of a sample which had been stored for several months in a glass-stoppered container in diffuse light gave, in addition to a distillate of the almost pure *trans*-sulfide, a residue (0.31 g.) which by titration contained 25% of sulfoxide, estimated as $C_7H_{12}OS$. This residue in ether was reduced with lithium aluminum hydride (0.15 g.), the product was separated into a neutral portion (0.23 g.) (mainly *trans*-sulfide) and an evil-smelling acidic portion which gave a positive doctor test reaction and infrared examination confirmed the presence of a hydroxyl grouping. There was insufficient of this material left for characterization.

Acknowledgement. The authors wish to thank the Chairman and Directors of The British Petroleum Company Limited for permission to publish these results and Mr. J. C. Stalley for the determination of the physical constants.

SUNBURY-ON-THAMES, ENGLAND

(24) Carbide and Carbon Chemical Corp. trade name; Carbitol is the monoethyl ether of diethylene glycol.

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

Dehydrogenation of 1-Isopropylindan and 1-Isopropylhydrindan

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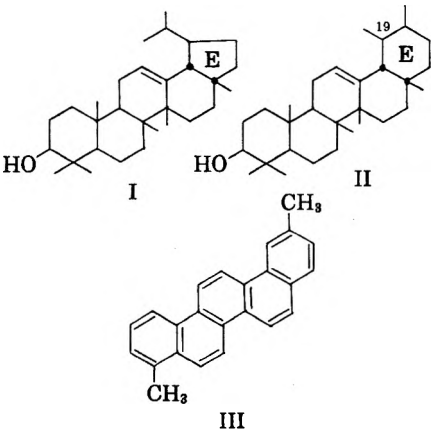
Received December 6, 1957

The dehydrogenation of the hydrocarbons in the title has afforded 2,2-dimethyltetralin, β-methylnaphthalene, and a $C_{20}H_{16}$ hydrocarbon of unknown constitution. The significance of these results with regard to the structure of α-amyrin is discussed.

Spring and his co-workers[3] have recently proposed for the triterpene, α-amyrin, a new structure (I) that differs from the generally accepted one (II)[4] by having an isopropyl group attached to the five-membered ring E. Among the reasons for preferring structure I, Spring has suggested[5] that it



more satisfactorily explains the formation of 2,9-dimethylpicene (III) on selenium dehydrogenation

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(2) Alfred P. Sloan Predoctoral Fellow in Chemistry, 1956–1957.

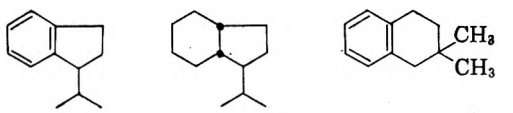
(3) J. M. Beaton, F. S. Spring, R. Stevenson, and W. S. Strachan, *J. Chem. Soc.*, 2610 (1955).

(4) A. Meisels, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **32**, 1075 (1949); A. Meisels, R. Rüegg, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **38**, 1298 (1955); A. Melera, D. Arigoni, A. Eschenmoser, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **39**, 441 (1956).

(5) F. S. Spring, private communication.

of α-amyrin since expansions of five-membered rings under these circumstances are well known.[6] Conversely, the loss during dehydrogenation of the *non-quaternary* C_{19} methyl in structure II has but few analogies in the literature and some of these are not well authenticated.[7]

We decided to test the validity of Spring's suggestion by investigating the dehydrogenation of 1-isopropylindan (IV) and its perhydro derivative (V). The latter compound approximates very closely the geometry and environment of rings D and E of α-amyrin and was therefore of particular interest in connection with this structural problem. However, since V was first converted to IV during dehydrogenation (as expected), most of our experiments



IV V VI

were performed on the more readily available indan (IV).

Both hydrocarbons (IV and V) were relatively stable to selenium at temperatures below 350° but were dehydrogenated when heated to 380–390° with an equal weight of the catalyst. The rather complex mixture that resulted was best purified by chromatography on alumina followed by fractional distillation of the more volatile components. In this way it was possible to isolate as the main product (*ca.* 40% yield) from IV a hydrocarbon which was originally thought to be unreacted isopropylindan. Various physical properties were significantly different, however, and further investigation showed that the hydrocarbon was in reality the *expanded* product, 2,2-dimethyltetralin (VI) (see Figs. 1 and 2). Although no isopropylindan (IV) was recovered fron the reaction mixture *per se*, its presence in small amounts (<7%) was inferred by the isolation of 1-indanone from the distillation residues. Since a fine stream of air had been bubbled through the flask during this distillation, the indan (IV) had apparently been completely oxidized to indanone and isopropyl alcohol, although the latter was not isolated.

In a somewhat smaller yield (4%) we were able to isolate and characterize β-methylnaphthalene, the product of subsequent dehydrogenation of VI. The low yields were not unexpected in view of the reported stability of VI to dehydrogenation.[8] The formation of both VI and β-methylnaphthalene from IV (and V) is significant in that it establishes a precedent for the dehydrogenation of I to III although the high temperatures involved obviously reduce the reliability of the results for structural purposes.

In addition to the compounds mentioned above, there was isolated a very small amount of a crystalline hydrocarbon, m.p. 146–148°, whose ultraviolet absorption spectrum and analysis indicated that it was tetracyclic in nature. The low yield of this product has made complete structural studies impractical to date although we have tentatively assigned to the hydrocarbon a dimethylchrysene structure. The compound is obviously a result of rather deep-seated rearrangements and recombinations of the starting material and its formation emphasizes the caution that must be observed in the interpretation of dehydrogenation data in structural studies.

EXPERIMENTAL[9]

1-Isopropylideneindan. To the Grignard reagent prepared from 25.8 g. (0.21 mole) of isopropyl bromide and 7.2 g. (0.22 mole) of magnesium in 50 ml. of anhydrous ether was added, over a period of one hour at 5°, a solution of 27.7 g. (0.21 mole) of 1-indanone in 50 ml. of benzene. The reaction mixture was heated under reflux for two hours and worked up in the usual fashion to afford 25.0 g. (73%) of 1-isopropylideneindan as a pale yellow oil, b.p. 99–100° (2 mm.), n_D^{20} 1.5533. Lit.[10] b.p. 133–135° (17 mm.).

1-Isopropylindan (IV). A solution of 25.0 g. (0.16 mole) of 1-isopropylindeneindan in 250 ml. of 95% ethanol was hydrogenated at 3-atm. pressure in the presence of 0.72 g. of platinum oxide catalyst to afford 22.4 g. (89%) of 1-isopropylindan as a colorless mobile oil, b.p. 92–94° (9 mm.), n_D^{20} 1.5205, d_4^{20} 1.9480. Lit.[11] b.p. 98–110° (17 mm.).

Anal. Calcd. for $C_{12}H_{16}$: C, 89.93; H, 10.07. Found: C, 90.18; H, 10.16.

1-Isopropylhydrindan (V). A solution of 25.0 g. (0.16 mole) of 1-isopropylideneindan in 200 ml. of glacial acetic acid containing 1.6 g. of platinum oxide catalyst was hydrogenated at 4 atm. of pressure. The usual work-up gave 20.3 g. (78%) of *cis* 1-isopropylhydrindan (V) as a colorless mobile oil, b.p. 84–85° (5 mm.), n_D^{20} 1.4740, d_4^{20} 1.8746; M_RD (calcd.) 53.72, M_FD (obs.) 53.44.

Anal. Calcd. for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.38; H, 13.36.

Dehydrogenations. a. 1-Isopropylindan (IV). A mixture of 14.1 g. (0.088 mole) of the indan (IV) and 14.0 g. of finely powdered selenium was heated in a sealed tube for 42 hr. at 385–400°. The contents were taken up in 30 ml. of hexane and chromatographed on 200 g. of acid-washed alumina (*p*H 3.3). After 400 ml. of hexane had been collected there was obtained on evaporation 7.2 g. of a colorless mobile liquid, n_D^{25} 1.5198. This material was fractionally distilled to afford 0.35 g. of a forerun, b.p. 95–100° (12.5 mm.), 4.60 g. of the main fraction, b.p. 101.5–103° (12.5 mm.), n_D^{27} 1.5183 and 0.93 g. of residue, n_D^{27} 1.5384. The main fraction was shown by independent synthesis to be *2,2-dimethyl-*

(6) L. Ruzicka and E. Peyer, *Helv. Chim. Acta*, 18, 676 (1935); N. D. Zelinsky, *Ber.*, 58, 2755 (1925); N. D. Zelinsky, I. Titz, and L. Fatejeu, *Ber.*, 59, 2580 (1926); C. D. Nenitzescu and E. Cioranescu, *Ber.*, 69, 1040 (1936).

(7) The few examples are discussed by W. Cocker, B. E. Cross, and J. McCormick, *J. Chem. Soc.*, 72 (1952).

(8) G. R. Clemo and H. G. Dickenson, *J. Chem. Soc.*, 255 (1937).

(9) Melting points and boiling points are both uncorrected. Ultraviolet absorption spectra were measured on a Beckman model DK automatic recording spectrophotometer. Analyses are by Schwarzkopf Labs., Woodside 77, N. Y.

(10) C. Courtot, *Ann. chim.*, 61 (1916).

(11) Ref. 10, p. 84.

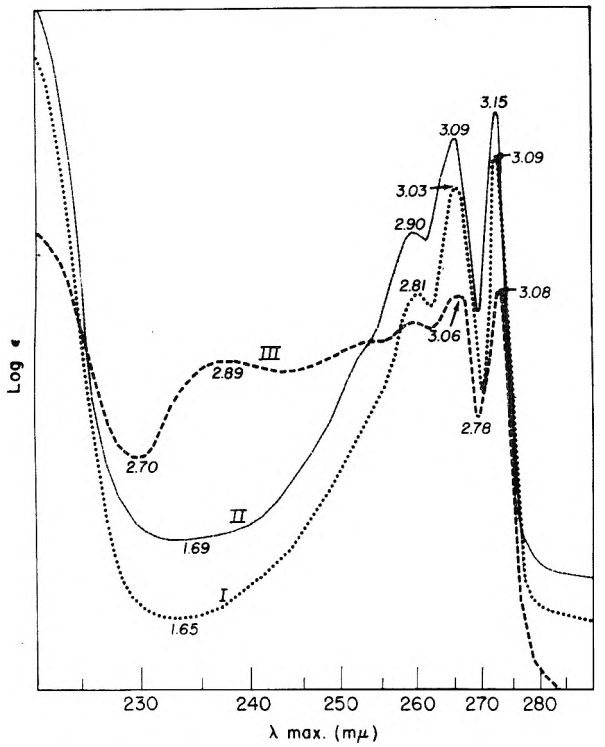


Fig. 1. Curve I: 2,2-Dimethyltetralin (VI) from the dehydrogenation of 1-isopropylindan (IV). Curve II: Synthetic 2,2-dimethyltetralin (VI).[12] Curve III: 1-Isopropylindan (IV). (The numbers refer to the log ϵ values as the log ϵ scale is arbitrary)

tetralin (VI).[12] The residue from the distillation possessed very strong infrared absorption in the aromatic carbonyl region and was identified as *1-indanone* by formation of its characteristic red 2,4-dinitrophenylhydrazone, m.p. 263–264°.

(12) Prepared according to the method of Clemo and Dickenson, ref. 8, who record b.p. 104° (12 mm.). S. C. Sengupta, *J. Prakt. Chem.*, **151**, 82 (1938), reports b.p. 123° (34 mm.) and n_D^{24} 1.5185. Our synthetic material had b.p. 101.5–102.5° (12 mm.) and n_D^{25} 1.5190.

Anal. Calcd. for $C_{12}H_{16}$: C, 89.93; H, 10.07. Found: C, 89.98; H, 10.10.

Although these values are very similar to those for isopropylindan(IV), the ultraviolet (Fig. 1) and the infrared (Fig. 2) absorption spectra of the two compounds are significantly different (note especially the presence of peaks at 10.30 and 13.85 μ in IV (curve III, Fig. 2) that are missing in curves I and II).

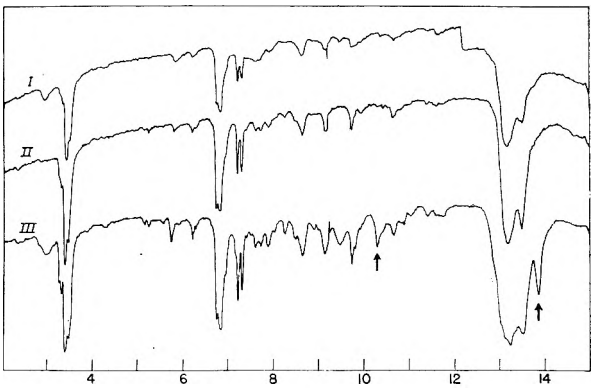


Fig. 2. Curve I: 2,2-Dimethyltetralin (VI) from the dehydrogenation of 1-isopropylindan (IV). Curve II: Synthetic 2,2-dimethyltetralin (VI).[12] Curve III: 1-Isopropylindan (IV)

The addition of 30% benzene to the hexane eluent afforded 0.51 g. of a colorless, viscous liquid, n_D^{20} 1.6062. The ultraviolet absorption spectrum of this material was superimposable on that of *β-methylnaphthalene*, and positive identification was made through the *picrate*, m.p. 114–115°, undepressed on admixture with an authentic sample, m.p. 115–116°.

Pure benzene eluted 0.32 g. of a yellow semisolid that was rechromatographed on 10 g. of acid-washed alumina to afford 0.25 g. of a pale yellow oil. On trituration with hexane, this oil deposited 0.13 g. of a hydrocarbon as pale yellow needles, m.p. 135–137°. Two recrystallizations from alcohol afforded 30 mg. of the unknown as colorless needles, m.p. 146–148°.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.67; H, 6.26.

The ultraviolet absorption spectrum in 95% alcohol was reminiscent of chrysene: λ_{max} (log ϵ): 267 mμ (4.9), 294 (3.8), 307 (2.9), and 321 (2.7) but lacked the fine structure between 280 and 320 mμ usually associated with this ring system.

The addition of ether to the eluting solvent afforded 1.3 g. of a yellow viscous oil, the properties of which have not been investigated.

b. 1-Isopropylhydrindan (V). When the perhydrogenated indan (V) was dehydrogenated as described above, the results were essentially the same as those reported for the indan (IV). In the temperature range 330–360°, however, V was dehydrogenated in good yield to isopropylindan (IV) but subsequent reactions did not occur until the temperature was raised to 390–400°.

ITHACA, N. Y.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

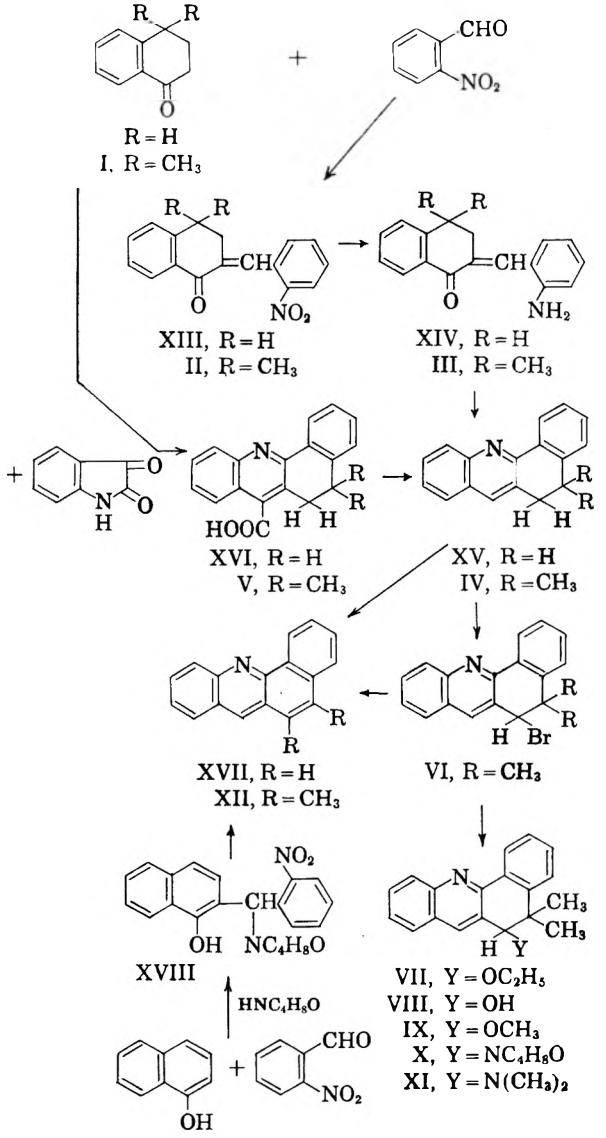
Benzacridines. I. Synthesis and Reactions of 5,6-Dihydrobenz[c]acridines

VERNON L. BELL AND NORMAN H. CROMWELL[1]

Received November 21, 1957

A convenient synthesis has been developed to prepare a number of substituted dihydrobenz[c]acridines and benz[c]-acridines. 5,6-Dimethylbenz[c]acridine was obtained through a Wagner-Meerwein rearrangement brought about by an "α-elimination" of hydrogen bromide from 6-bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine. The ultraviolet absorption spectra of these new compounds are reported and compared.

During the course of a general program involving the synthesis of potential carcinogenic and antitumor agents, a new method of synthesis of benz[c]acridines has been developed, which has led to the hitherto unknown 5,6-dimethylbenz[c]acridine (XII). This compound is of particular interest in view of the fact that methyl groups are substituted on both carbon atoms of the so-called "K-region," which has been postulated to be a factor in the carcinogenic activity of the benz[c]acridines and condensed polynuclear hydrocarbons.[2]



The starting ketone I, 4,4-dimethyl-1-tetralone, was prepared using a revision of the procedure employed by Campbell and Cromwell.[3] It was found that condensation of the substituted tetralone I with *o*-nitrobenzaldehyde could be accomplished in a 94% yield in glacial acetic acid with sulfuric acid as the catalyst. Previous condensations of this type have been carried out under basic conditions,[4-6] or in 80% sulfuric acid.[7] The most satisfactory means found to reduce the nitroketone II to 4,4-dimethyl-2-(*o*-aminobenzal)-1-tetralone (III) was with iron and acetic acid. Catalytic reduction with Raney nickel gave in only one instance a trace of the cyclized compound IV. The aminoketone III was cyclized to 5,5-dimethyl-5,6-dihydrobenz[c]-acridine (IV) with extreme ease, as has been reported for the corresponding 2-(*o*-aminobenzal)-indanones leading to indenoquinolines.[8] This ready cyclization is reflected by the nearly identical ultraviolet spectra found for III and IV. It was shown that ultraviolet light brings about this ring closure of 2-(*o*-aminobenzal)-1-tetralones to 5,6-dihydrobenz[c]acridines.

Compound IV was also prepared *via* the Pfitzinger-Borsche reaction,[9] by condensing the ketone-I with isatin to give 7-carboxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (V), which on thermal decarboxylation resulted in the dihydrobenzacridine IV. Of the two routes to compound IV, the series involving condensation with *o*-nitrobenzalde-

(1) To whom correspondence concerning this article should be addressed.

(2) For an excellent discussion of the theoretical significance of the "K-region" and its relationship to carcinogenicity in benzacridines, see C. A. Coulson, *Advances in Cancer Research*, Academic Press, Inc., New York, N. Y., 1953, Vol. I, pp. 1–56.

(3) R. D. Campbell and N. H. Cromwell, *J. Am. Chem. Soc.*, **77**, 5169 (1955).

(4) W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, 637 (1940).

(5) J. van Alphen and G. Drost, *Rec. trav. chim.*, **69**, 1080 (1950).

(6) A. Hassner, N. H. Cromwell, and S. J. Davis, *J. Am. Chem. Soc.*, **79**, 230 (1957).

(7) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 893 (1958).

(8) S. Ruhemann and S. I. Levy, *J. Chem. Soc.*, **103**, 551 (1913).

(9) J. von Braun and P. Wolff, *Ber.*, **55**, 3675 (1922).

hyde and ring closure of III gave higher yields and cleaner products than the method involving the Pfitzinger-Borsche reaction.

When compound IV was treated with *N*-bromosuccinimide, the 6-bromo derivative (VI) was obtained in 82% yield. This proved to be an especially versatile reagent, in view of the high order of reactivity of the bromine group. Compound VI was converted to the 6-ethoxy- and 6-methoxy-derivatives (VII and IX) by treatment with ethanol and methanol, respectively, and to the 6-hydroxy-derivative VIII by treatment with sodium hydroxide.[10] In a like manner, the bromo compound was readily converted to the 6-morpholino- and 6-dimethylamino-derivatives, X and XI.

Perhaps the most interesting reaction carried out with the bromo compound was its conversion to 5,6-dimethylbenz[*c*]acridine (XII). When the bromo compound was heated to 160°, the light yellow molten mass turned to a bright red solid. This solid proved to be the hydrobromide salt of the benz[*c*]acridine XII resulting from a combination of an "α-elimination" of hydrogen bromide and a Wagner-type rearrangement of a 5-methyl group to the 6-position. Studies are currently being made to determine the mechanism of this rearrangement, as well as to find other means of bringing it about.

The two routes described above for IV were also used to synthesize the unsubstituted parent 5,6-dihydrobenz[*c*]acridine (XV) for purposes of comparison. α-Tetralone was condensed with *o*-nitrobenzaldehyde to yield 2-(*o*-nitrobenzal)-1-tetralone (XIII), which was then reduced to 2-(*o*-aminobenzal)-1-tetralone (XIV). Compound XIV was readily cyclized with hydrochloric acid or ultraviolet light (see Table I) to 5,6-dihydrobenz[*c*]-acridine (XV), which was also prepared by the method of von Braun and Wolff.[9] Aromatization of XV by heating with lead oxide produced benz[*c*]-acridine (XVII).[9]

Benz[*c*]acridine was also obtained by another route, though in a very small yield. A Mannich condensation of α-naphthol, morpholine, and *o*-nitrobenzaldehyde resulted in 2-(*N*-α-morpholino-*o*-nitrobenzyl)-1-naphthol (XVIII). Reduction of XVIII with iron and acetic acid gave benz[*c*]-acridine (XVII). The mechanism by which this transformation proceeds is not known at present.

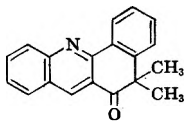
Discussion of ultraviolet spectra. The ultraviolet spectra of the dihydrobenz[*c*]acridines and benz-[*c*]acridines are given in Table I. The spectra of the unsubstituted and substituted dihydrobenzacridines are seen to be quite identical, differing only slightly in both wave length and ϵ_{max}. The only notable exception is 6-bromo-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (VI), which has only a single high intensity absorption band in 220–330 mμ range of the spectrum and a different longer wave length fine structure than is found for the other dihydrobenzacridines.

TABLE I

SUMMARY OF ULTRAVIOLET SPECTRA OF BENZACRIDINE DERIVATIVES

Compound	No.	Ultraviolet Max.[a] λ mμ	ε × 10^{-3}
2-(*o*-Aminobenzal)-1-tetralone	XIV[b,c]	213	34.0
		(220)	29.0
		(258)	28.6
		265	35.4
		300	7.76
		315	8.48
		330	11.6
		345	13.1
4,4-Dimethyl-2-(*o*-amino-benzal)-1-tetralone	III[d,e]	212	36.1
		(214)	35.2
		(223)	27.3
		(258)	28.2
		265	34.9
		315	8.04
		329	10.2
		344	11.5
Benz[*c*]acridine	XVII[f]	(214)	24.8
		224	37.9
		(267)	47.6
		274	66.5
		285	56.4
		347	6.32
		363	8.12
		382	8.18
5,6-Dimethylbenz[*c*]acri-dine	XII[g]	221	34.8
		(270)	46.5
		278	53.9
		292	47.6
		323	5.00
		338	5.97
		351	6.10
		369	7.05
		387	7.10
5,6-Dihydrobenz[*c*]acridine	XV[b]	214	35.7
		(220)	30.3
		(258)	31.1
		265	38.5
		287	8.34
		300	8.00
		315	8.70
		330	12.2
		344	14.0
7-Carboxy-	XVI[b]	214	31.1
		(266)	21.2
		(260)	26.2
		226	33.1
		316	7.24
		331	9.80
		345	11.2
5,5-Dimethyl-	IV[b]	213	35.5
		(220)	29.3
		(259)	29.4
		265	36.9

(10) The structure of the hydroxy compound VIII is shown by the fact that it is readily oxidized to the corresponding ketone, m.p. 89–90° in 80% yield with CrO_3



in 80% acetic acid. This ketone shows an infrared carbonyl band at 1685 cm.$^{-1}$ and its analysis agrees with the following structure. The chemistry of this compound will be discussed in a forthcoming publication.

TABLE I (*Continued*)

Compound	No.	Ultraviolet Max.[a] λ mμ	ε × 10^{-3}
		300	8.30
		315	9.00
		330	12.4
		345	14.2
		257[d]	30.0
		265	37.8
		299	9.02
		314	8.72
		329	11.9
		344	14.0
7-Carboxy-5,5-dimethyl-	V[b]	214	34.4
		(226)	23.7
		(260)	29.9
		267	36.0
		317	8.10
		331	10.1
		345	12.3
5,5-Dimethyl-6-ethoxy-	VII[h]	214	36.4
		(220)	32.2
		(260)	28.8
		267	34.0
		299	8.96
		314	8.56
		329	11.2
		343	12.7
5,5-Dimethyl-6-methoxy-	IX[b]	213	41.9
		(215)	40.5
		(224)	30.5
		(260)	30.0
		267	35.4
		298	9.20
		313	8.84
		328	11.4
		343	12.8
5,5-Dimethyl-6-hydroxy-	VIII[d]	212	38.7
		215	38.9
		(226)	30.6
		(259)	32.3
		266	36.0
		313	9.20
		328	11.0
		343	12.6
5,5-Dimethyl-6-(*N*-morpholino)-	X[d]	(223)	25.6
		(260)	31.4
		266	34.3
		316	9.30
		330	10.3
		346	11.5
5,5-Dimethyl-6-dimethylamino-	XI[d]	212	43.7
		215	44.0
		(225)	30.0
		(260)	33.1
		267	38.6
		315	9.08
		330	11.1
		345	11.6
6-Bromo-5,5-dimethyl-	VI[d]	266	38.5
		334	7.40
		(340)	7.00
		349	7.29

[a] Ultraviolet determinations were made at about 25° using a Cary recording spectrophotometer, model 11 MS. [b] 5.0×10^{-5} molar concentration in 95% ethanol. [c] This compound was converted to compound XV during the determination. [d] 5.0×10^{-5} molar concentration in isooctane. [e] This compound was converted to compound IV during the determination. [f] 2.5×10^{-5} molar concentration in 95% ethanol. [g] 2.5×10^{-5} molar concentration in isooctane. [h] 4.25×10^{-5} molar concentration in 95% ethanol.

The differences between the spectra of the completely aromatic benz[*c*]acridines and the dihydrobenzacridines are quite apparent, however. The maxima for the benz[*c*]acridines (XII and XVII) have generally higher extinction coefficients, and there are two peaks of high intensity absorption and a shoulder in the 250–300 mμ region, while the dihydrobenzacridines have only one high intensity band with a shoulder in the same region. The fine structure for the dihydrobenzacridines is found in the region of 280–350 mμ, while the corresponding absorption bands for the benz[*c*]acridines are found in the 320–390 mμ region.

EXPERIMENTAL

4,4-Dimethyl-1-tetralone (I). Compound I was synthesized by the procedure of Campbell and Cromwell[3] with two simplifying modifications.

4-Methyl-4-phenylpentanothiomorpholide,[3] 246 g. (0.89 mole), was refluxed with 1.5 l. of concentrated hydrochloric acid for 48 hr. The mixture was cooled and extracted with one liter of benzene. The benzene layer was extracted twice with the theoretical amount of 25% sodium hydroxide solution. The alkaline solution was acidified with sulfuric acid and the aqueous mixture was then extracted with benzene. The benzene extract was washed with water and dried over magnesium sulfate, and the benzene was removed under reduced pressure. The crude 4-methyl-4-phenylpentanoic acid was distilled at 140–141° (0.8 mm.), giving 163.7 g. (96% yield) of pure acid.

The acid was then directly converted to ketone I. Polyphosphoric acid, 500 g., was placed in an 800 ml. beaker and heated to 90° on a steam bath. 4-Methyl-4-phenylpentanoic acid, 172 g. (0.9 mole), was heated separately to 65°. The polyphosphoric acid was removed from the steam bath, the warm 4-methyl-4-phenylpentanoic acid added in one lot, and the mixture stirred for 3 min. The mixture was then placed on the steam bath, an additional 300 g. of polyphosphoric acid was added, and the mixture stirred for 25 min., while maintaining the temperature at 90°. After cooling it was poured into ice water with stirring. When the brown, viscous oily precipitate had changed completely to a light yellow color, it was extracted with three portions of ether. The ether extract was washed successively with 300 ml. of water, two 200 ml. portions of 5% sodium hydroxide solution, 300 ml. of water, 200 ml. of 3% aqueous acetic acid, and 100 ml. of water. The ether layer was dried over magnesium sulfate and the ether evaporated. Distillation at 125–131°[3] (2 mm.) gave 136.9 g. (88% yield) of ketone I.

4,4-Dimethyl-2-(o-nitrobenzal)-1-tetralone (II).[11] To a solution of 25 g. (0.167 mole) of *o*-nitrobenzaldehyde and 29 g. (0.167 mole) of I in 170 ml. of glacial acetic acid was added 35 ml. of 95% sulfuric acid. The mixture was allowed to stand at room temperature for three days, after which time the crystals were collected by filtration. Recrystallization from glacial acetic acid resulted in 48 g. (94% yield) of 4,4-dimethyl-2-(*o*-nitrobenzal)-1-tetralone, m.p. 188–189°.

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.34; H, 5.48; N, 4.53.

4,4-Dimethyl-2-(o-aminobenzal)-1-tetralone (III). Compound II, 48 g. (0.156 mole), was dissolved with heating in 800 ml. of glacial acetic acid and 80 ml. of water. While heating the mixture on a steam bath, a total of 20 g. of reduced iron powder was added in small portions, with occasional shaking. The solution was heated for 15 min. after the

(11) This compound was first prepared in this laboratory by Mr. Ronald Bambury, M.S. Thesis, University of Nebraska, 1958.

evolution of hydrogen had ceased and was then poured into 1.5 l. of ice water with rapid stirring. To the aqueous mixture was added 1.8 l. of 33% potassium hydroxide, and the mixture allowed to stand overnight. The solid material was collected by filtration, washed with water, and dried. The solid was extracted thoroughly with absolute ethanol. The alcoholic extract was evaporated to 500 ml. volume, water was added, and the solution cooled. Bright yellow crystals of 4,4-dimethyl-2-(*o*-aminobenzal)-1-tetralone precipitated from solution, wt., 36 g.; m.p., 135–137° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 81.98; H, 6.78; N, 5.12.

Treatment of III with picric acid produced the picrate of 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine, m.p. 202–203° (see below).

5,5-Dimethyl-5,6-dihydrobenz[c]acridine (IV). Ketone III was dissolved in 95% ethanol, 50 ml. of concentrated hydrochloric acid was added, and the solution evaporated to dryness on a steam bath. The residue was redissolved in 95% ethanol and treated with charcoal. After filtration, the bright yellow solution was neutralized with 5% sodium bicarbonate solution. Water was added and the mixture was cooled. The precipitated solid was collected by filtration and recrystallized, with charcoal treatment, from aqueous acetone. White needles of IV, m.p. 112–113°, were obtained. The over-all yield from the nitroketone II was 33.6 g. (83%).

Anal. Calcd. for $C_{19}H_{17}N$: C, 88.00; H, 6.60; N, 5.40. Found: C, 87.92; H, 6.69; N, 5.30.

The picrate of IV was prepared by adding a solution of IV in 95% ethanol to a saturated solution of picric acid in ethanol, and cooling. The picrate melted at 202–203°.

Anal. Calcd. for $C_{25}H_{20}N_4O_7$: C, 61.47; H, 4.13. Found: C, 61.64; H, 4.22.

Compound IV was also obtained by ring closure of the aminobenzal ketone III by irradiation with ultraviolet light. A solution of 0.2 g. of compound III in one liter of 95% ethanol was irradiated for 30 hr. with a Hanovia Utility Model Quartz Lamp, 115 volts, 60 cycles, 4.6 amps. The solution gradually turned colorless and fluorescence became evident. The solution was concentrated to a volume of 25 ml. under vacuum and charcoaled. Upon the addition of water and cooling, colorless crystals of IV precipitated from solution.

7-Carboxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (V). Compound V was prepared by the Pfitzinger-Borsche reaction, using the procedure of von Braun.[9] A solution of 6 g. (0.034 mole) of ketone I, 5.05 g. (0.034 mole) of isatin, 6.5 g. of potassium hydroxide, 10 ml. of methanol, and 6.5 ml. of water was refluxed for 8 hr. The basic solution was diluted with water and extracted with ether. The alkaline solution was acidified to methyl orange with hydrochloric acid. Recrystallization from dioxane (charcoal) gave 6.5 g. (63% yield) of V, m.p. 256.5–257°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 5.12. Found: C, 78.76; H, 5.51; N, 5.12.

Thermal decarboxylation of acid V. Compound V, 7.6 g. (0.025 mole), was melted in a small Erlenmeyer flask, and the molten material was maintained at 260° until the evolution of carbon dioxide had ceased (about 2 hr.). After cooling, the residue was triturated with 10% potassium hydroxide and the alkaline mixture was extracted with ether. The ether layer was washed with water and the ether was evaporated. Recrystallization of the solid from ethanol gave 6.1 g. (94% yield) of IV, m.p. 112–113°, identical with that prepared by ring closure of the aminoketone III.

6-Bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine (VI). To a solution of 19.7 g. (0.076 mole) of IV in 250 ml. of carbon tetrachloride was added 13.5 g. (0.076 mole) of *N*-bromosuccinimide and 0.25 g. of benzoyl peroxide. The mixture was refluxed for 3 hr., after which time the heavy NBS had changed completely to the light succinimide. The mixture was cooled and filtered, and extracted first with 200 ml. of 5% sodium bicarbonate solution and then washed with two 150-ml. portions of water. After drying the carbon tetrachloride layer over magnesium sulfate, the solvent was removed under reduced pressure. The solid residue was dissolved in acetone *at room temperature*, treated with charcoal, and reprecipitated by the addition of water. The fine white needles were dried immediately in a vacuum desiccator, resulting in 21 g. (82% yield) of VI, m.p. 145–147°.

Anal. Calcd. for $C_{19}H_{16}NBr$: C, 67.49; H, 4.74; Br, 23.63. Found: C, 67.40; H, 4.87; Br, 23.76.

5,5-Dimethyl-6-ethoxy-5,6-dihydrobenz[c]acridine (VII). A solution of 0.85 g. of the bromo compound VI in 20 ml. of absolute ethanol was heated on a steam bath for 1 hour. After charcoal treatment, the solution was neutralized with 5% sodium bicarbonate solution, water was added, and the solution was cooled. The crude product was collected by filtration and recrystallized from ethanol to give 0.70 g. (92% yield) of VII in the form of white needles, m.p. 96–97°.

Anal. Calcd. for $C_{21}H_{21}NO$: C, 82.94; H, 7.08; N, 4.61. Found: C, 83.14; H, 6.98; N, 4.61.

The picrate was prepared in the usual manner and melted at 197–198° (with decomposition).

Anal. Calcd. for $C_{27}H_{24}N_4O_8$: C, 60.90; H, 4.54. Found: C, 60.71; H, 4.76.

5,5-Dimethyl-6-hydroxy-5,6-dihydrobenz[c]acridine (VIII). To a solution of 2 g. of the bromo compound VI in 25 ml. of dioxane was added 10 ml. of 10% sodium hydroxide solution. The solution was heated for 1 hr. on a steam bath. The solvent was evaporated and the residue dissolved in aqueous ethanol. The ethanolic solution was neutralized with dilute hydrochloric acid, treated with charcoal, and cooled. Large, white needles formed which melted at 155–157°. Another recrystallization from ethanol gave 1.25 g. (77% yield) of the hydroxy compound, m.p. 159–160°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.98; H, 6.22; N, 5.09. Found: C, 83.21; H, 6.57; N, 5.02.

A picrate of VIII softened at about 215°, but did not melt up to 250°.

5,5-Dimethyl-6-methoxy-5,6-dihydrobenz[c]acridine (IX). A solution of 1 g. of the bromo compound VI in 20 ml. of methanol was refluxed for 3 hr. Neutralization of the solution with 5% sodium bicarbonate solution, followed by recrystallization from aqueous methanol, gave 0.8 g. (94% yield) of colorless crystals of IX, m.p. 152.5–154°.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.25; H, 6.76; N, 4.89.

5,5-Dimethyl-6-(N-morpholino)-5,6-dihydrobenz[c]acridine (X). A solution of 3 g. (0.0089 mole) of the bromo compound VI and 15 ml. of morpholine was refluxed for 24 hr. The solution was then cooled, poured into water with stirring, and the solid collected by filtration. The crude product was dissolved in ethanol, treated with charcoal, and reprecipitated by adding water and cooling. Recrystallization from ethanol gave 2.6 g. (85% yield) of 5,5-dimethyl-6-(N-morpholino)-5,6-dihydrobenz[*c*]acridine, m.p. 159–161°.

Anal. Calcd. for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.28; H, 6.85; N, 8.07.

5,5-Dimethyl-6-dimethylamino-5,6-dihydrobenz[c]acridine (XI). Five grams of the bromo compound VI and 15 ml. of anhydrous dimethylamine were heated at 100° in a sealed tube for 8 hr. The tube was then cooled, opened, and the contents poured into ice water. The aqueous mixture was extracted with 75 ml. of benzene. The benzene layer was washed repeatedly with water until the water extract was neutral. The benzene solution was dried and evaporated and the residual material recrystallized from ethanol to give colorless crystals of the dimethylamino compound XI, m.p. 93–95°, yield 3.0 g. (67%).

Anal. Calcd. for $C_{21}H_{22}N_2$: C, 83.40; H, 7.34; N, 9.26. Found: C, 83.55; H, 7.13; N, 9.13.

5,6-Dimethylbenz[c]acridine (XII). Two grams of the bromo compound VI was heated in a small Erlenmeyer flask in an oil bath. The bromo compound melted to a light yellow liquid, and changed to a bright red solid at about

160°. Heating was continued for 10 min. at 170°. The red-brown residue was dissolved in warm, aqueous dioxane and the solution neutralized with 5% sodium bicarbonate solution. Upon cooling, a solid precipitated and was collected by filtration. The solid was dissolved in acetone, treated with charcoal, and reprecipitated by the addition of water. Another recrystallization from acetone gave 1.1 g. (72% yield) of XII in the form of fine, light yellow needles, m.p. 162–163°.

Anal. Calcd. for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.94; H, 5.86; N, 5.26.

The picrate was prepared in the usual manner and melted with decomposition at 253–254°.

Anal. Calcd. for $C_{25}H_{18}N_4O_7$: C, 61.73; H, 3.73. Found: C, 61.51; H, 3.79.

2-(o-Nitrobenzal)-1-tetralone (XIII).[7] *o*-Nitrobenzaldehyde, 15 g. (0.1 mole), was dissolved in 150 ml. of glacial acetic acid and 30 g. of 95% sulfuric acid was added with cooling. α-Tetralone, 14.6 g. (0.1 mole), was added to this solution with stirring. The reaction mixture was allowed to stand at room temperature for 72 hr., after which time the crude product was collected by filtration. Recrystallization from glacial acetic acid (charcoal) gave 20.9 g. (75% yield) of 2-(*o*-nitrobenzal)-1-tetralone, m.p. 121–122°.[7]

2-(o-Aminobenzal)-1-tetralone (XIV). The nitroketone XIII, 5.8 g. (0.02 mole), was dissolved in a solution of 40 ml. of glacial acetic acid and 20 ml. of water. The solution was heated on a steam bath to 70°, and 2.5 g. of iron powder added in small portions. Heating was continued for 45 min. with occasional shaking. The solution was then poured over 200 g. of ice and water. One hundred fifty ml. of 33% potassium hydroxide solution was added, and the mixture allowed to stand overnight.

The solid material was filtered off and extracted with 200 ml. of absolute ethanol. The addition of water precipitated bright, yellow-orange crystals of 2-(*o*-aminobenzal)-1-tetralone, m.p. 123–124°; yield 3.3 g. (64%).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.85; H, 5.98; N, 5.97.

Treatment of XIV with picric acid produced the picrate of 5,6-dihydrobenz[*c*]acridine, m.p. 206°.[9]

5,6-Dihydrobenz[c]acridine (XV). Ring closure of XIV was effected by evaporating a hydrogen chloride containing 95% alcoholic solution of 3.3 g. of the aminoketone to dryness on a steam bath. The hydrochloride product was redissolved in aqueous ethanol, treated with charcoal, and neutralized with 5% sodium bicarbonate solution. Water was added, the solution cooled, and the precipitate collected by filtration. Recrystallization from ethanol gave 2.6 g. (85% yield) of 5,6-dihydrobenz[*c*]acridine, m.p. 65° (lit. 60°).[9] The over-all yield from the nitroketone XIII was 54%.

Compound XV was also prepared using the procedure of von Braun and Wolff.[9] Decarboxylation of "Tetrophan" (XVI) (see below) gave an 88% yield of XV. The crude product melted at 59–60°, but treatment of an alcoholic solution of the hydrochloride salt with charcoal, neutralization with Na_2CO_3 and recrystallization from alcohol gave colorless crystals, m.p. 65°, identical with the product obtained by ring closure of the amino ketone XIV.

7-Carboxy-5,6-dihydrobenz[c]acridine, "Tetrophan" (XVI). The Pfitzinger-Borsche reaction was used to prepare "Tetrophan," employing the procedure of von Braun.[9] Dioxane was found to be a more satisfactory solvent for recrystallization of the crude acid. A yield of 83% of XVI was obtained, m.p. 250° (lit. 252°).[9]

2-(α-N-Morpholino-o-nitrobenzyl)-1-naphthol (XVIII).[12] A solution of 19.3 g. (0.134 mole) of α-naphthol, 20 g. (0.134 mole) of *o*-nitrobenzaldehyde, and 12.7 g. (0.148 mole) of morpholine in 17 ml. of ethanol was allowed to stand for 24 hr. under nitrogen. After adding a small amount of ethanol, the mixture was cooled and the crude product crystallized from solution. Recrystallization from ethanol gave 25 g. (52% yield) of compound XVIII in the form of bright yellow crystals, m.p. 128–129.5°.

Anal. Calcd. for $C_{21}H_{21}N_2O_4$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.10; H, 5.60; N, 7.50.

Benz[c]acridine (XVI). *A.* The procedure of von Braun[9] was used to dehydrogenate XV to benz[*c*]acridine. A 60% yield of light yellow needles of the fully aromatic compound was obtained, melting at 107–108° (lit. 108°).

The picrate salt was prepared in the usual manner, m.p. 249° (lit. 226–229°).[9]

Anal. Calcd. for $C_{23}H_{14}N_4O_7$: C, 60.27; H, 3.08; N, 12.22. Found: C, 60.16; H, 3.16; N, 12.84.

B. Compound XVIII, 5.5 g. (0.015 mole), was added to a solution of 35 ml. of glacial acetic acid and 15 ml. of water. The mixture was warmed to 70° on a steam bath, and 1.9 g. of reduced iron powder added in small portions. After the addition of iron was complete, the reaction mixture was heated an additional 30 min. on the steam bath. The mixture was poured over 200 g. of ice and water, 100 ml. of 33% potassium hydroxide solution was added and allowed to stand overnight. The solid precipitate was collected by filtration and extracted with 200 ml. of hot, absolute ethanol. The alcohol solution was evaporated to dryness on the steam bath, and the residue extracted with 1:1 hydrochloric acid. The acidic solution was charcoaled and then neutralized with dilute sodium carbonate solution. Recrystallization of the resulting solid from ethanol gave a 10% yield of benz[*c*]acridine in the form of light yellow needles which melted at 107.5–108°. A mixed melting point determination with authentic benz[*c*]acridine showed the two compounds to be identical.

The picrate was prepared in the usual manner, m.p. 249°. A mixed melting point determination with authentic benz[*c*]acridine picrate, from *A* above, showed the two picrates to be identical.

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LINCOLN, NEBR.

(12) This compound was first prepared in this laboratory by Dr. A. Hassner, Ph.D. Thesis, University of Nebraska, 1956.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Polycyclic Compounds Containing Nitrogen. II. Hydroindoles

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Octahydro-5,6-dimethylindole was prepared by reduction of 4-(2-ethoxyethyl)-1,2-dimethyl-5-nitrocyclohexene to 2-(2-ethoxyethyl)-4,5-dimethylcyclohexylamine followed by cyclization. A product which probably contains 2,3,3a,4,7,7a- or 2,3,3a,6,7,7a-hexahydroindole was prepared by a similar method from 4-(2-ethoxyethyl)-2-methoxy-5-nitrocyclohexene. Attempts to prepare the usual derivatives from the products of this latter cyclization were unsuccessful.

A general method for the preparation of substituted cyclohexylamines, by the Diels-Alder reaction of nitroalkenes with dienes, and reduction of the nitrocyclohexenes, has been reported.[3] A study of the conversion of certain of the resulting cyclohexylamines to heterocyclic substances is described in this paper. Similar cyclizations have yielded *cis* and *trans* octahydroindole and 8-azabicyclo[5·3·0]decane.[4,5] The availability of cyclohexylamines such as 2-(2-ethoxyethyl)-4,5-dimethylcyclohexylamine, I, makes possible the preparation of a variety of hydroindoles; substituted 2-(3-ethoxypropyl)cyclohexylamines could also be prepared by the same method and converted into hydroquinolines.[6]

Treatment of 2-(2-ethoxyethyl)-4,5-dimethylcyclohexylamine with hydrobromic acid, followed by cyclization of 2-(2-bromoethyl)-5,6-dimethylcyclohexylamine hydrobromide with dilute sodium hydroxide, gave octahydro-5,6-dimethylindole. The nitrocyclohexene, prepared from a *trans*-1-nitro-1-alkene,[7] would give a hydroindole with a *trans* ring fusion. In a compound derived from 2,3-dimethyl-1,3-butadiene, two additional carbon atoms become asymmetric during catalytic hydrogenation to the cyclohexylamine by the use of a palladium or platinum catalyst in acetic acid. The expected *cis* arrangement of the methyl groups would limit the possible configurations to two racemates. Confirmation of the stereochemical nature of our product has not yet been obtained.

Use of 2-methoxybutadiene in the Diels-Alder process under discussion leads to some interesting compounds. Chart I shows the reactions carried out.

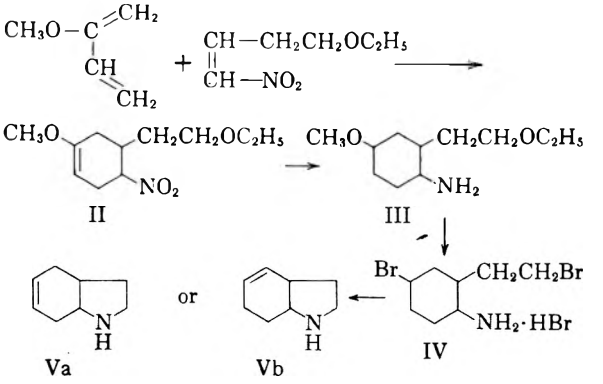

CHART I

The adduct of 2-methoxybutadiene and 4-ethoxy-1-nitrobutene is an enol ether. It was readily converted to 3-(2-ethoxyethyl)-4-nitrocyclohexanone. The carbonyl frequency of the latter was at 1722 cm.$^{-1}$, while the infrared spectrum of the adduct, II, had strong maxima at 1658 cm.$^{-1}$(C=C), and 1178, 1166 cm.$^{-1}$ (C=C-OR).[8]

The directive influence of the alkoxyl group of the diene[9,10] would cause formation of the adduct shown, II, rather than 4-(2-ethoxyethyl)-1-methoxy-5-nitrocyclohexene. Catalytic hydrogenation of II by the use of palladium in 95% ethanol gave 2-(2-ethoxyethyl)-4-methoxycyclohexylamine, III. Cyclization to a hexahydroindole was carried out by the same reactions used for the ring closure which produced octahydro-5,6-dimethylindole described above.

The product, V, was an intractable oil; derivatives could not be crystallized. Maxima in the infrared spectrum of the amine indicated the presence of a *cis* double bond (677, 1655, and 3030 cm.$^{-1}$); the maximum at 3390 cm.$^{-1}$ was assigned to the NH group.[8]

The intermediate 4-bromo-2-(2-bromoethyl)cyclohexylamine hydrobromide, IV, was not identified or purified. Cyclization of the 2-bromoethyl side chain by 0.2*N* sodium hydroxide would be accompanied by reactions at the 4-bromo group

(1) From the thesis submitted by A. B. Ross in partial fulfillment of the requirements for the Ph.D. degree, University of Maryland, 1957.

(2) Monsanto Chemical Co. Fellow, 1956–57.

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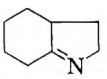
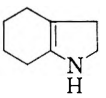
such as elimination to give the cyclohexene, displacement to give the cyclohexanol, or reaction with an amino group. Elimination was favored[11,12] and the product was formulated as 2,3,3a,4,7,7a-hexahydroindole, Va, or 2,3,3a,6,7,7a-hexahydroindole, Vb; it has proved impossible, thus far, to prepare any of the usual derivatives of this cyclization product with the exception of the chloroplatinate. Benzoyl chloride and *p*-nitrobenzoyl chloride both yielded resinous products which did not crystallize. Both resinous derivatives decolorized bromine in carbon tetrachloride but the addition products, like the starting materials, showed no tendency to crystallize. The picrate also formed a dark red oil which failed to crystallize. A chloroplatinate prepared in ethanol melted with decomposition at 180–181° but could not be successfully recrystallized.

The hexahydroindoles which have been reported have the pyrroline structure, VI[4,12] or VII.[13] Other polycyclic nitrogen compounds, containing



VI



VII

one double bond, could be prepared from adducts of 2-alkoxybutadienes by the method described here.

EXPERIMENTAL

Melting points are corrected and were determined with the Hershberg apparatus. Boiling points are uncorrected. We are indebted to Miss M. Kathryn Gerdeman, Dr. Mary Aldridge, and Miss Jane Swan for the microanalyses. The infrared spectra were determined on a Perkin-Elmer infrared spectrophotometer, Model 12-C, and a Beckmann IR-4 double beam infrared spectrophotometer.

2-(2-Bromoethyl)-4,5-dimethylcyclohexylamine hydrobromide. Into a 100-ml. flask fitted with a capillary inlet for nitrogen was put 4.83 g. of 2-(2-ethoxyethyl)-4,5-dimethylcyclohexylamine, I;[3] 40 ml. of 68% hydrobromic acid was added. There was a vigorous reaction and the flask became warm. Nitrogen was bubbled through the solution while it was heated in an oil bath at 150° for 3 hr. and then cooled. The reaction mixture was almost solid; filtration gave 6.62 g. (87%) of grey-pink needles. The hydrobromide could not be recrystallized; the crude product melted at 196–197.5°.

The picrate, yellow needles from 50% methanol, melted at 139.5–140°.

Anal. Calcd. for $C_{16}H_{23}BrN_4O_7$: C, 41.48; H, 5.01; N, 12.09. Found: C, 41.85, 41.97; H, 4.85, 4.82; N, 12.73.

Octahydro-5,6-dimethylindole, IV. Two liters of 0.1*N* sodium hydroxide was heated to about 50°. A solution of 4.82 g. of 2-(2-bromoethyl)-4,5-dimethylcyclohexylamine hydrobromide in 2 l. of water was added dropwise with stirring over a period of 6.5 hr., while the temperature was maintained at 50°. The solution was then extracted with 500 ml. of ether in a continuous extractor for 2 days. About 50 ml. of benzene was added to the ether and the solvents were removed at reduced pressure. The residue was an amber oil, 1.50 g. (64%), n_D^{25} 1.4804.

The *picrate,* yellow needles from 50% ethanol, melted at 178–179°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.65. Found: C, 50.20, 50.48; H, 5.62, 5.41; N, 14.90, 14.95.

The *3,5-dinitrobenzoyl derivative* (prepared by the Schotten-Baumann procedure) crystallized as colorless microneedles from absolute ethanol, m.p. 175.6–176.6°.

Anal. Calcd. for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09. Found: C, 58.85, 58.75; H, 5.66, 5.84. Mol. wt., Calcd.: 347; Found: 346 (Rast).

4-(2-Ethoxyethyl)-2-methoxy-5-nitrocyclohexene. The procedure which was used has been described for the preparation of Diels-Alder adducts of nitroalkenes.[3] A solution of 7.0 g. (0.048 mole) of 4-ethoxy-1-nitro-1-butene, 19.8 g. (0.24 mole) of 2-methoxybutadiene, a few mg. of hydroquinone, and 20 ml. of acetonitrile was heated, in a glass liner in a steel bomb, at 100° for 6 hr. Distillation gave 5.7 g. (52%) of adduct, b.p. 124–126° (0.5–1.0 mm.), n_D^{25} 1.4788. The dark brown residue weighed 4.4 g. The results were similar when the acetonitrile was omitted; a 56% yield of adduct, b.p. 126–128° (0.8 mm.), n_D^{25} 1.4758, was obtained.

Redistillation gave a pale yellow-green oil, b.p. 137–138° (2 mm.), 82% recovery, n_D^{20} 1.4782, d_4^{20} 1.102, MR_D^{20} Calcd.:[14] 59.76. Found: 58.88. The infrared spectrum of a 2.5% solution of the product in carbon tetrachloride showed the following strong maxima (cm.$^{-1}$): 2844 (C—H); 1658 (C=C); 1377 (NO_2); 1178, 1166 (—C=C—OR); 1117 (C—O—C).

3-(2-Ethoxyethyl)-4-nitrocyclohexanone. To a solution of 8.9 g. of II in 20 ml. of 95% ethanol was added 3 ml. of concentrated hydrochloric acid and 4 ml. of water with thorough mixing. After storage in a refrigerator for 3 hr., the mixture was diluted to 100 ml., neutralized with sodium carbonate solution, and extracted with ether. The dried ether extract was evaporated and the product, 8.2 g. (97.5%), was a red-brown oil, n_D^{25} 1.4728.

The ketone was distilled (b.p. about 116° at 0.8 mm.), with about 80% recovery. A second distillation gave a golden yellow oil, n_D^{20} 1.4742, d_4^{20} 1.128, MR_D^{20} Calcd.:[14] 53.75. Found: 53.65.

The infrared spectrum of a 2.5% solution of the product in carbon tetrachloride showed the following strong maxima (cm.$^{-1}$): 2844 (C—H); 1722 (C=O); 1373, 1350 (NO_2); 1117 (C—O—C).

The *thiosemicarbazone* was prepared[15]; it crystallized as cream colored needles from 50% ethanol, m.p. 113.5–114°.

Anal. Calcd. for $C_{11}H_{20}N_4O_3S$: C, 45.82; H, 6.99; N, 19.43. Found: C, 45.85, 45.84; H, 6.64, 6.75; N, 19.23, 19.38.

2-(2-Ethoxyethyl)-4-methoxycyclohexylamine. A solution of 5.35 g. of II in 50 ml. of 95% ethanol was shaken with 2.0 g. of 10% palladium-on-charcoal with hydrogen at atmospheric pressure (25°). Four molar equivalents of hydrogen were absorbed in 2 hr.; the solution was filtered and the solvent removed by distillation at reduced pressure under nitrogen. The product was 4.20 g. of colorless oil, n_D^{25} 1.4630.

The benzoyl derivative, fine colorless needles from 50% ethanol, melted at 163–163.5°.

Anal. Calcd. for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; —OR (as OC_2H_5 + OCH_3), 24.92. Found: C, 71.13, 71.06; H, 8.89, 9.33; —OR (as OC_2H_5 + OCH_3), 24.99, 25.20.

4-Bromo-2-(2-bromoethyl)cyclohexylamine hydrobromide. Treatment of 3.65 g. of 2-(2-ethoxyethyl)-4-methoxycyclohexylamine, III, with 50 ml. of 48% hydrobromic acid (b.p. 125–126°), caused warming to about 40°. The mixture was heated in an oil bath at 150° for 1.5 hr. in a nitrogen

(11) H. C. Brown, R. S. Fletcher, and R. F. Johannesen, *J. Am. Chem. Soc.*, **73,** 212 (1951).

(12) J. v. Braun and K. Schwarz, *Ann.*, **481,** 56 (1930). W. E. Bachmann and E. J. Fornefeld, *J. Am. Chem. Soc.*, **73,** 51 (1951)

(13) M. Hadano and T. Matsuno, *J. Pharm. Soc. Japan,* **48,** 904 (1924); *Chem. Abstr.*, **23,** 1635 (1929).

(14) A. I. Vogel, W. T. Cresswell, G. F. Jeffrey, and J. Leicester, *Chem. & Ind. (London),* 358 (1950).

(15) P. P. T. Sah and T. C. Daniels, *Rec. trav. chim.*, **69,** 1545 (1950).

atmosphere and at 100° for 1.5 hr. Crystallization did not occur after cooling; evaporation at reduced pressure under nitrogen left a sticky amber residue which was not purified.

Attempted cyclization of IV. A solution of IV in 2 l. of water was added, over a period of 9 hr., to 2.5 l. of 0.2*N* sodium hydroxide at about 50°, with stirring. Continuous extraction of the mixture for 2 days with ether, and evaporation of the ether gave 1.52 g. (68%) of light amber oil, n_D^{25} 1.5059, with a strong amine-like odor.

The product did not react with sodium iodide in acetone or with 2,4-dinitrophenylhydrazine reagent.

The infrared spectrum of a 20% solution of the product in carbon tetrachloride showed the following maxima (cm.$^{-1}$): 3390 (m) NH; 3030 (shoulder) CH=CH; 2960 (s) CH_2 and CH; 1759 (m) CO; 1655 (m) C=C; 1460 (m) CH_2; 1268 (m), 1163 (m), 1098 (m), 1038 (m), 677 (s), cis C=C.

Treatment of the product with benzoyl chloride or *p*-nitrobenzoyl chloride, by the Schotten-Baumann method, gave brown gums which could not be crystallized. Both derivatives decolorized bromine in carbon tetrachloride; the dibromides were also noncrystalline. The picrate was a dark red oil which would not crystallize.

The chloroplatinate, prepared by addition of an excess of chloroplatinic acid in 95% ethanol to the amine, melted at 180–181° with decomposition (preliminary darkening at 170°). Recrystallization could not be effected.

Anal. Calcd. for $(C_8H_{13}N)_2H_2PtCl_6$: C, 29.28; H, 4.30; N, 4.27; Pt, 29.74. Found: C, 30.55; H, 4.59; N, 4.20; Pt, 28.45.

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

Some Factors Influencing the 1,4-Addition of Grignard Reagents to Arylidenemalonic Esters

MELVIN S. NEWMAN AND HAROLD R. FLANAGAN[1]

Received December 26, 1957

The 1,4-addition of Grignard reagents to α, β-unsaturated esters has long been known.[2] In this laboratory this type of reaction has often been used to build up compounds needed for the synthesis of polycyclic aromatic hydrocarbons.[3] In each case the product was a compound of the symmetrical benzhydryl type, I.

$$ArMgBr + ArCH{=}C(COOC_2H_5)_2 \longrightarrow (Ar)_2CHCH(COOC_2H_5)_2, \text{ I.}$$

yield.[4] Thus, the yield is significantly better when the Grignard reagent with the larger steric requirement is added to the unsaturated ester with the lesser steric requirement, than in the reverse case. The greater tendency of 1-naphthylmagnesium bromide to add to α, β-unsaturated malonic ester is also apparent in the 45–53% yields obtained in the addition to II[5], whereas the addition of phenylmagnesium bromide to II afforded at most a 22% yield.

$$C_6H_5MgBr + \underset{\text{II}}{1\text{-}C_{10}H_7CH{=}C(COOC_2H_5)_2} \xrightarrow{22\%} 1\text{-}C_{10}H_7(C_6H_5)CHCH(COOC_2H_5)_2 \quad \text{III}$$

$$1\text{-}C_{10}H_7MgBr + C_6H_5CH{=}C(COOC_2H_5)_2 \xrightarrow{84\%} 1\text{-}C_{10}H_7(C_6H_5)CHCH(COOC_2H_5)_2 \quad \text{III}$$

We became interested in the question of whether the yield of type I compound would vary significantly depending on the order of introduction of two different aryl groups. We have found that when phenylmagnesium bromide is added to diethyl 1-naphthylidenemalonate, II, the yield of diethyl phenyl-1-naphthylmalonate, III, is 22%, whereas the addition of 1-naphthylmagnesium bromide to diethyl benzylidenemalonate affords III in 84%

In an attempt to account for the erratic yields previously obtained[3c] in the addition of 1-naphthylmagnesium bromide to II, we have found that the addition of excess magnesium bromide solution to the Grignard reagent prior to reaction with II had little effect on the yield. However, when di-1-naphthylmagnesium was used, no addition reaction occurred and II was recovered in 97% yield.

When 1-naphthylmagnesium bromide was added to ethyl 1-naphthylidenecyanoacetate, IV, a 94% yield of ethyl di-1-naphthylmethylcyanoacetate,

(1) The work reported herein was part of a thesis presented by H. R. Flanagan to the Ohio State University, 1956, for the M.S. degree.

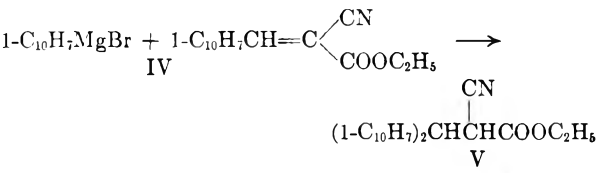
(2) The first example was provided by E. P. Kohler, *Am. Chem. J.*, **34**, 132 (1905) who added phenylmagnesium iodide to diethyl benzylidenemalonate.

(3) (a) M. S. Newman and M. Wolf, *J. Am. Chem. Soc.*, **74**, 3225 (1952). (b) M. S. Newman and R. M. Wise, *J. Am. Chem. Soc.*, **78**, 450 (1956). (c) M. S. Newman and D. Lednicer, **78**, 4765 (1956).

(4) Inverse addition, *i.e.* addition of ester to Grignard reagent, was used in all cases since previous work had indicated no difference when direct addition was made. However, the results reported herein were not checked by direct addition experiments.

(5) The yields of diethyl di-1-naphthylmethylmalonate were more consistently in the 45–53% range in the present work than in that reported previously.[3c]

V, was obtained. Since the latter could be hydrolyzed to the corresponding malonic acid in 93% yield a distinct improvement in the synthesis of hexahelicene[3c] has been attained.



EXPERIMENTAL

Diethyl 1-naphthylidenemalonate, II. In a flask fitted with a small packed column and a phase-separating head were placed 157 g. of 1-naphthaldehyde, 160 g. of diethyl malonate, 3 g. of benzoic acid, and 500 ml. of benzene. At reflux 5 ml. of piperidine was added. After 11 hr., during which four 2-g. additions of piperidine were made, slightly more than the theoretical amount of water had been collected. On distillation[3c] there was obtained 252 g. (85%) of II, b.p. 187–197° at 1.5–2.0 mm.

Diethyl phenyl-1-naphthylmethylmalonate, III. To a solution of 1-naphthylmagnesium bromide freshly prepared from 21 g. (0.1 mole) of 1-bromonaphthalene was added slowly with cooling 21 g. (0.085 mole) of diethyl benzylidenemalonate[6] in 50 ml. of ether and the mixture was then stirred at room temperature for 6 hr. After treatment with saturated ammonium chloride solution and removal of ether from the washed and dried ether layer, there was obtained a crude solid mass which was heated with Skellysolve B (petroleum ether, b.p. 60–70°) and cooled. Filtration yielded 26.7 g. (84%) of III, m.p. 96–99°, good enough for further work. A sample recrystallized from absolute alcohol several times melted at 99.5–101.5°.[7]

When a solution of 21.5 g. of II in 50 ml. of ether was added to a solution of phenylmagnesium bromide freshly prepared from 17 g. of bromobenzene an insoluble complex separated. After stirring at room temperature for 6 hr., the reaction mixture was treated as above to yield 6.0 g. (22%) of III, m.p. 98–100°. In addition some biphenyl and a large quantity of tar were obtained.

Diethyl di-1-naphthylmethylmalonate. To a stirred mixture of 0.1 mole of freshly prepared magnesium bromide and 15 g. (0.05 mole) of II in ether was added 140 ml. of 0.5*N* (0.07 mole) 1-naphthylmagnesium bromide. After refluxing for 2 hr. the reaction mixture was treated with ammonium chloride solution and worked up as usual to yield 8.0 g. (38%) of III.[5]

To 3.0 g. (0.01 mole) of II in 20 ml. of dry ether was added under nitrogen 200 ml. of 0.1*N* di-1-naphthylmagnesium solution and 250 ml. of dry benzene. The mixture was heated and the ether distilled. After 40 hr. of refluxing, the mixture was decomposed by treating with ammonium chloride solution and worked up to yield 2.9 g. (97%) of II.

Ethyl 1-naphthylidenecyanoacetate, IV. A mixture of 100 g. of 1-naphthaldehyde, 74 g. of ethyl cyanoacetate, 6 g. of piperidine, 5 g. of benzoic acid, and 700 ml. of benzene was refluxed into a phase-separating head. After 1 hr. the theoretical amount of water had been collected. After the usual workup there was obtained 149 g. (92.8%) of crude IV, b.p. 180–195° at 1 mm. Recrystallization from alcohol afforded 142.6 g. (88.8%) of IV, m.p. 80.0–81.4°. The analytical sample melted at 81.0–81.4°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.6. Found:[8] N, 5.3.

Ethyl di-1-naphthylmethylcyanoacetate, V. To the Grignard reagent prepared from 20.7 g. of 1-bromonaphthalene in ether-benzene and cooled to 0–5° was added 12.5 g. of IV in ether-benzene. After coming to room temperature the mixture was heated at reflux for 12 hr. and then poured into dilute hydrochloric acid. After the usual treatment 17.7 g. (94%) of V was isolated as a colorless solid, m.p. 189.8–191.0°, by crystallization from ethanol.

Anal. Calcd. for $C_{26}H_{21}NO_2$: C, 82.3; H, 5.6; N, 3.7. Found:[8] C, 82.3; H, 5.6; N, 3.7.

Di-1-naphthylmethylmalonic acid. A mixture of 3.9 g. of V and 200 ml. of 50% aqueous alcoholic potassium hydroxide was refluxed for 31 hr., cooled, and poured into water. This aqueous solution was then poured into excess hydrochloric acid. The solid was collected and recrystallized from alcohol to yield 3.5 g. (92%) of the desired malonic acid,[3c] m.p. 196° dec. Decarboxylation afforded the known 2,2-di-1-naphthylpropionic acid,[3c] m.p. 248°.

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(6) C. F. H. Allen and F. W. Spangler, *Org. Syntheses*, 25, 42 (1945).

(7) G. A. Holmberg, *Acta Acad. Aboensis Math. et Phys.*, 16, 138 (1948) gives the m.p. as 98–99°.

(8) Analyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

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

Syntheses of 1′-Methyl- and 4′-Methyl-1,2-benzanthracenes[1]

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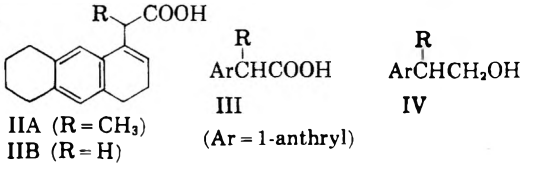
Received January 31, 1958

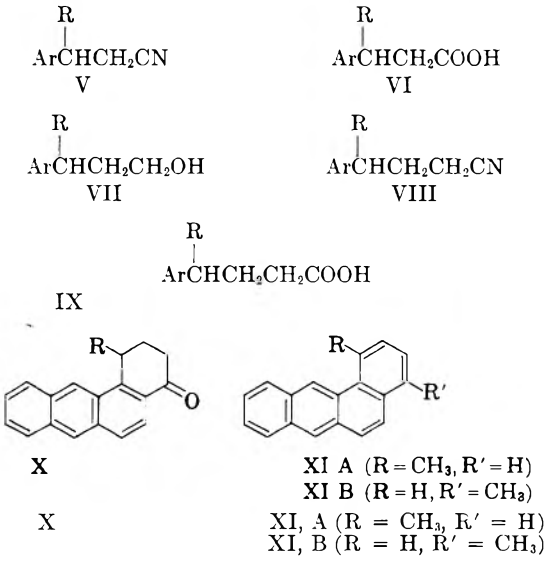
The syntheses of 1′-methyl- and 4′-methyl-1,2-benzanthracene are described.

In a previous paper, the reasons for synthesizing relatively large amounts of all of the monomethyl-1,2-benzanthracenes were outlined and the syntheses of all but 1′-methyl- and 4′-methyl-1,2-benzanthracene were described.[2] In this paper are described syntheses for the latter two compounds as outlined in the chart. More than 10 g. of each was made and is available for research workers.



(1) The work herein reported was supported by a grant, C-2484, from the U. S. Public Health Service to whom grateful acknowledgment is made.

(2) M. S. Newman and R. Gaertner, *J. Am. Chem. Soc.*, 72, 264 (1950).



EXPERIMENTAL[3]

2-(3,4,5,6,7,8-Hexahydro-1-anthryl)propionic acid, IIA, and *3,4,5,6,7,8-Hexahydro-1-anthrylacetic acid*, IIB. 1-Keto-1,2,3,4,5,6,7,8-octahydroanthracene,[4] I, was condensed with methyl α-bromopropionate as described[5] to yield crude hydroxyester which was dehydrated by heating with a trace of iodine. The distilled unsaturated ester thus prepared was saponified and the resulting acid, IIA, was obtained in about 70% yield in sufficient purity to proceed. A pure sample of IIA formed crystals, m.p. 139–140°, on recrystallization from isopropyl ether.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.7; H, 7.9. Found:[6] C, 79.4; H, 8.0.

In a similar way, methyl 3,4,5,6,7,8-hexahydro-1-anthrylacetate, b.p. 172–181° at 1.5 mm., was obtained in 85% yield from I by the Reformatsky reaction[5] followed by dehydration. The methyl ester thus obtained was submitted to dehydrogenation as described below.

2-(1-Anthryl)propionic acid, IIIA, and *1-anthrylacetic acid*, IIIB. The crude acid, IIA, described above, was converted almost quantitatively into methyl ester, b.p. 168–178° at 0.05 mm. by esterification with methanolic hydrogen chloride. After heating 27.0 g. of this ester with 0.27 g. of 20% palladium-on-charcoal[7] in 13 g. of pure diphenyl ether at 260 to 305° for two hours (theoretical hydrogen evolved) the reaction mixture was saponified with alcoholic potassium hydroxide. The acidic portion of the product, on crystallization from benzene, afforded IIIA as pale yellow prisms, m.p. 169–171°, in 60% yield based on starting acid IIA. Several recrystallizations from benzene afforded pure IIIA, m.p. 171.0–172.5°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.6; H, 5.6. Found: C, 81.7; H, 5.5.

In a similar way IIIB, m.p. 168–170°, was obtained in 70% yield from IIB. Pure IIIB, m.p. 170.0–171.2°, was obtained by crystallization from benzene.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.3; H, 5.1. Found: C, 81.4; H, 5.4.

3-(1-Anthryl)butyronitrile, VA, and *3-(1-anthryl)propionitrile*, VB. Either the ethyl ester, b.p. 192–195° at 2 mm., of III or the methyl ester was reduced by lithium aluminum hydride in ether at room temperature in almost quantitative yield to 2-(1-anthryl)propanol, IVA, m.p. 89–92°. The analytical sample, m.p. 93–94°, was prepared by crystallization from isopropyl ether.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.4; H, 6.8. Found: C, 86.4; H, 6.8.

The alcohol, IVA (23.6 g.), was treated in dry pyridine at 5–15° with a small excess of methanesulfonyl chloride to yield the methanesulfonate, a viscous oil, which was dissolved in a small amount of dry dimethylformamide and treated with a threefold excess of sodium cyanide, partly dissolved and suspended in 150 ml. of dimethylformamide. After heating at 40–60° for 3 hr. the organic product was isolated by extraction with ether-benzene and purified by passing a benzene solution through a short column of alumina. After concentration of the eluate and dilution with Skellysolve F (petroleum ether, b.p. 35–40°) the nitrile, VA, was obtained in 85% yield as crystals, m.p. 99–103°. Recrystallization from benzene–Skellysolve F and from isopropyl ether yield a pure sample, m.p. 105–106°, with little loss.

Anal. Calcd. for $C_{18}H_{15}N$: C, 88.1; H, 6.2; N, 5.7. Found: C, 88.3; H, 6.2; N, 5.7.

In a similar way, the methyl ester of IIIB was reduced to crude alcohol, IVB, m.p. 80–83°, methanesulfonylated, and converted to nitrile, VB, m.p. 125–128°, in 80% yield based on IIIB. A pure sample of VB melted at 128.3–129.1°.

Anal. Calcd. for $C_{17}H_{13}N$: C, 88.3; H, 5.7; N, 6.1. Found: C, 88.4; H, 5.7; N, 6.2.

3-(1-Anthryl)butyric acid, VIA, and *3-(1-anthryl)propionic acid*, VIB. A solution of 23.1 g. of VA and 8.4 g. of potassium hydroxide in 150 ml. of ethylene glycol was heated from 160° to 200° during 5 hours (under nitrogen) to yield 18.5 g. (70%) of VIA, m.p. 152–156°. A sample recrystallized 3 times from benzene melted at 156–158°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1. Found: C, 81.6; H, 6.2.

In a similar way, except that the hydrolysis was effected at 150–165°, VB was converted into VIB in about 70% yield. Undoubtedly, better conditions for hydrolysis could be worked out. The pure sample of VIB, obtained by crystallization from acetone and acetone-ether, melted at 197.5–198.5°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.6; H, 5.6: Found: C, 81.6; H, 5.8.

4-(1-Anthryl)pentanonitrile, VIIIA, and *4-(1-anthryl)-butyronitrile*, VIIIB. The crude alcohol, VIIA, obtained by the lithium aluminum hydride reduction of VIA did not crystallize and was converted *via* the methanesulfonate to the nitrile, VIIIA, as described above for VA, in 60% over-all yield from VIA. As the nitrile VIIIA did not crystallize, the 2,4,7-trinitrofluorenone derivative,[8] m.p. 159–160°, after preparation in and crystallization from acetic acid, was made.

Anal. Calcd. for $C_{32}H_{22}O_7N_4$: C, 66.9; H, 3.9; N, 9.8. Found: C, 66.9; H, 3.9; N, 9.8.

On reduction of the methyl ester of VIB with lithium aluminum hydride, the alcohol, VIIB, was obtained crystalline in almost quantitative yield. The pure sample, m.p. 109.7–110.7°, was obtained by recrystallization from isopropyl ether.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.4; H, 6.8. Found: C, 86.2; H, 7.0.

The nitrile, VIIIB, was obtained in 80% over-all yield from VIIB. A pure sample, m.p. 68.4–69.5°, was obtained by recrystallization from isopropyl ether.

Anal. Calcd. for $C_{18}H_{15}N$: C, 88.1; H, 6.2; N, 5.7. Found: C, 88.2; H, 6.1; N, 5.7.

4-(1-Anthryl)pentanoic acid, IXA, and *4-(1-anthryl)-butyric acid*, IXB. The crude nitrile, VIIIA, was saponified

(3) All melting points of pure compounds corrected.

(4) D. L. Turner, *J. Am. Chem. Soc.*, **76**, 5175 (1954).

(5) See expt. 26, M. S. Newman and F. J. Evans, Jr., *J. Am. Chem. Soc.*, **77**, 946 (1955).

(6) All analyses by the Galbraith Laboratory, Knoxville, Tenn.

(7) R. P. Linstead, *J. Chem. Soc.*, 1127 (1940).

(8) M. Orchin and O. Woolfolk, *J. Am. Chem. Soc.*, **68**, 1727 (1946).

to the acid, IXA, in 80% yield by heating at 180–200° for two hours with potassium hydroxide in diethylene glycol. Crystallization from isopropyl ether afforded IXA, m.p. 97–100°.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5. Found: C, 82.1; H, 6.7.

Similarly the nitrile, VIIIB, was converted into IXB in 85% yield, the hydrolysis being effected by heating in diethylene glycol at 120–145° for two hours. Recrystallization of the crude acid from isopropyl ether afforded pure IXB, m.p. 151.4–152.2°.

Anal. Calcd. for $C_{18}H_{16}O_2$. C, 81.8; H, 6.1. Found. C, 81.8; H, 6.3.

4'-Keto-1'-methyl-1',2',3',4'-tetrahydro-1,2-benzanthracene, XA, and *4'-keto-1',2',3',4'-tetrahydro-1,2-benzanthracene*, XB. A mixture of 13.9 g. of crude acid, IXA, and 75 g. of polyphosphoric acid was heated at 80–110° for 45 min. The crude ketone, XA, m.p. 102–104°, was obtained in 80% yield. A pure sample, m.p. 105.0–106.5°, was obtained by chromatography over alumina and recrystallization from benzene and from isopropyl ether. A similar yield of crude ketone, XA, was obtained by cyclization of IXA with hydrogen fluoride.

Anal. Calcd. for $C_{19}H_{16}O$: C, 87.7; H, 6.2. Found: C, 87.9; H, 6.3.

In a similar way, IXB was cyclized to the ketone, XB, in 85% yield, with hydrogen fluoride. Pure XB, m.p. 189.0–198.6°, was obtained by crystallization from benzene-isopropyl ether.

Anal. Calcd. for $C_{18}H_{14}O$: C, 87.8; H, 5.7. Found: C, 88.0; H, 6.0.

1'-Methyl-1,2-benzanthracene, XIA, and *4'-methyl-1,2-benzanthracene*, XIB. After reduction of 2.6 g. of XA with lithium aluminum hydride in ether the crude alcohol was dehydrated by boiling with xylene to which a trace of iodine had been added. The crude dehydration product was treated with a slight excess of sulfur and heated at 220–240° for 10 min. A small amount of zinc dust was added and the heating continued for 10 min. at 200–220°. The product was taken up in benzene, filtered, chromatographed over alumina, treated with charcoal (Darco G-60) in acetone, and crystallized from acetone and from benzene to yield XIA, m.p. 137–138°, in 60% yield based on XA. Further purification along the same lines afforded XIA,[9] m.p. 139.2–139.9°.

A solution of 4.9 g. of XB in 200 ml. of tetrahydrofuran was added at 5–10° to the methyllithium prepared from 5.5 g. of lithium and 57 g. of methyl iodide[10] and the mixture was stirred for 30 min. After the usual workup the carbinol, m.p. 126–130°, was obtained in 85% yield. Without further purification the carbinol was dehydrated by boiling with xylene to which a trace of iodine had been added and the dehydration product was heated at 220–240° with a slight excess of sulfur for 10 min. Treatment with zinc dust and further treatment as above described for XIA afforded XIB, m.p. 190–192°, in 75% yield based on crude carbinol. Pure XIB,[11] 197.4–198.0°, was obtained after further crystallizations from acetone and benzene, and by chromatography over alumina.

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(9) For other syntheses of 1'-methyl-1,2-benzanthracene, see L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938), J. W. Cook and A. M. Robinson, *J. Chem. Soc.*, 505 (1938), and W. E. Bachmann and R. O. Edgerton, *J. Am. Chem. Soc.*, **62**, 2550 (1940).

(10) K. Ziegler, *Ann.*, **479**, 135 (1930).

(11) For other syntheses of 4'-methyl-1,2-benzanthracene, see J. W. Cook, A. M. Robinson, and F. Goulden, *J. Chem. Soc.*, 505 (1938), C. Descamps and R. H. Martin, *Bull. soc. chim. Belges*, **61**, 223 (1952), B. M. Mikhailov and T. K. Kozminskaya, *Zhur. Obschei Khim.*, **23**, 1220 (1953); *Chem. Abstr.*, **47**, 12334 (1953); S. C. S. Gupta and D. N. Chatterjee, *J. Ind. Chem. Soc.*, **31**, 11 (1954).

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON]

Derivatives of Fluorene. V. 9-Hydroxyfluorenes; Reduction of Fluorenones in the Presence of Aralkylideneamino Groups[1]

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Thirty-nine substituted 9-hydroxyfluorenes have been prepared and characterized. Sodium borohydride reduction of fluorenones is a convenient method for preparing many 9-fluorenols in good yields. Under certain conditions the —N=CH— group in some 2-aralkylideneaminofluorenones can be preserved while the carbonyl group is reduced. The reducibility of the —N=CH— group in 2-aralkylideneaminofluoren-9-ols can be made to vary by changing the type of para substituent in the aralkylidene group or by introducing a bromine in the 3-position of the fluorene moiety.

We have prepared[3] a number of substituted 9-hydroxyfluorenes by sodium borohydride reduction of the corresponding fluorenones,[4] and find that simplicity and high yields make this an excellent procedure (see Table I).

Upon being treated with sodium borohydride in our usual procedure, fluorenones with a ring —N=CHAr group gave mixtures including, in most instances, the corresponding benzylaminofluorenol compound. Billman and Diesing[5] recently reported

(1) This investigation was supported in part by a grant (C-1744) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

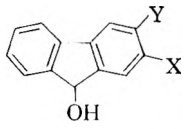
(2) To whom correspondence regarding this paper should be addressed.

(3) T. L. Fletcher and H. L. Pan, *J. Am. Chem. Soc.*, **78**, 4812 (1956).

(4) M. S. Newman and W. B. Lutz, *J. Am. Chem. Soc.*, **78**, 2469 (1956). These authors reported the reduction of fluorenone with sodium borohydride in acetonitrile and methanol, obtaining 84% of the 9-ol after 6-hr. reflux of the complex in 20% aqueous potassium fluoride and dioxane.

(5) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957).

TABLE I. SUBSTITUTED 9-HYDROXYFLUORENES



X	Y	Ketone,[a,b] M.P., °C.	Yield, %	M.P.,[b] °C.	Empirical Formula	Analyses,[c] % Calcd. C	H	N	Br	Found C	H	N	Br
H	H	84.5–85	99	156–156.5 (Lit. m.p. 154–155[od])									
NH_2	H	160–161	94	201–201.5 (Lit. m.p. 200[oe])									
CH_3NH-	H	159.5–160.5[g]	85	132–133	$C_{14}H_{13}NO$	79.59	6.20	6.63		79.59	6.29	6.54	
$(CH_3)_2N$	H	166–166.5[g]	100	159–159.5	$C_{15}H_{15}NO$	79.97	6.71	6.22		79.84	6.75	6.02	
C_2H_5NH	H	153–154.5[g]	94	146.5–147	$C_{15}H_{15}NO$	79.97	6.71	6.22		79.78	6.72	6.40	
$(C_2H_5)_2N$	H	101.5–102.5	90	135.5–136.5	$C_{17}H_{19}NO$	80.57	7.56	5.53		80.38	7.94	5.70	
n-C_3H_7NH	H	134–135	96	141–142	$C_{16}H_{17}NO$	80.30	7.16	5.85		80.30	7.32	6.00	
$(n$-$C_4H_9)_2N$	H	(Oil)	25[h]	111–112	$C_{21}H_{27}NO$	81.51	8.80	4.53		81.37	8.77	4.42	
n-C_4H_9NH	H	127.5–128.5	100	144–144.5	$C_{17}H_{19}NO$	80.57	7.56	5.53		80.85	7.57	5.58	
C_5H_9NH[i]	H	164–165	90	162–163	$C_{18}H_{19}NO$	81.47	7.22	5.28		81.55	7.20	5.43	
$C_6H_5CH_2NH$	H	149.5–150.5	100	159.5–160.5	$C_{20}H_{17}NO$	83.59	5.96	4.88		83.61	6.20	4.71	
$(C_6H_5CH_2)_2N$	H	139–140	97	150–151	$C_{27}H_{23}NO$	85.91	6.14	3.71		85.79	5.96	3.60	
$(p$-$BrC_6H_4CH_2)_2N$[j]	H	186–187	100	152–153	$C_{27}H_{21}Br_2NO$	60.58	3.96	2.62	29.86	60.64	3.98	2.64	29.71
p-$NO_2C_6H_4CH_2NH$	H	206–207	94	169.5–170.5	$C_{20}H_{18}N_2O_3$	72.28	4.85	8.43		72.21	4.78	8.52	
$(p$-$NO_2C_6H_4CH_2)_2N$[k]	H	212–213	92	177.5–178.5	$C_{27}H_{21}N_3O_5$	69.37	4.53	8.99		69.63	4.31	9.21	
p-Tosyl-NH	H	193.5–194.5[g]	78	218.5–219.5	$C_{20}H_{17}NO_3S$	68.35	4.88	3.99		68.05	4.50	3.99	
CH_3CONH	H	235–235.5	100	248.5–249.5[l]									
CH_3CONCH_3	H	157.5–159[g]	55	130.5–131.5	$C_{16}H_{15}NO_2$	75.87	5.97	5.53		76.11	6.00	5.38	
$CH_3CONC_2H_5$	H	138.5–139.5	100	141.5–142.5	$C_{17}H_{17}NO_2$	76.38	6.41	5.24		76.31	6.48	5.47	
CF_3CONH	H	249.5–250.5[m]	67	211.5–212.5	$C_{15}H_{10}F_3NO_2$	61.44	3.44	4.78		61.36	3.55	4.80	
$C_2H_5OOCCH_2NH$	H	146.5–147.5	100	130.5–131.5	$C_{17}H_{17}NO_3$	72.06	6.05	4.94		72.21	6.13	5.08	
HOOCCH=CHCONH[n]	H	225–230 (dec.)	100	>280	$C_{17}H_{13}NO_4$	69.14	4.44	4.74		69.35	4.54	4.75	
$C_6H_5CH{=}N$	H	134–135	50–55	181–182[p]									
p-$NO_2C_6H_4CH{=}N$[o]	H	231.5–232.5	45	200–201[p]									
p-$(CH_3)_2NC_6H_4CH{=}N$[q]	H	177.5–178.5	10	212–213[p]									
OH[r]	H	211.5–212	90	197–198 (Lit. m.p. 188–189[s])	$C_{13}H_{10}O_2$	78.77	5.09			78.60	5.01		
H[t]	Br	165.5–166	87	169.5–170.5									
NH_2	Br	215.5–216[t]	100	204.5–205.5 (dec.)	$C_{13}H_{10}BrNO$	56.54	3.65	5.07	28.94	56.73	3.70	5.18	28.86
C_2H_5NH	Br	164.5–165.5[t]	90	137.5–138.5	$C_{15}H_{14}BrNO$	59.22	4.64	4.61		59.16	4.52	4.75	
n-C_3H_7NH	Br	108–108.5	100	143.5–144	$C_{16}H_{16}BrNO$	60.39	5.07	4.40	25.11	60.23	5.16	4.36	25.20
n-C_4H_9NH	Br	97–97.5	100	143–144	$C_{17}H_{18}BrNO$	61.45	5.46	4.22	24.05	61.52	5.50	4.09	24.02

TABLE I (*Continued*)

$C_6H_5CH_2NH$	Br	139–140	91	169.5–170.5	$C_{20}H_{16}BrNO$	65.58	4.40	3.83	21.82	65.54	4.57	3.67	21.68
p-$BrC_6H_4CH_2NH$	Br	159–160	100	174.5–175.5	$C_{20}H_{15}Br_2NO$	53.96	3.40	3.15	35.90	53.82	3.50	3.31	35.89
p-$NO_2C_6H_4CH_2NH$	Br	185–186	100	178.5–179	$C_{20}H_{15}BrN_2O_3$	58.41	3.68	6.81	19.43	58.15	3.40	6.93	19.52
$HOCH_2CH_2NH$[a]	Br	146–148	100	164–164.5 (dec.)	$C_{18}H_{14}BrNO_2$	56.27	4.41	4.38	24.96	56.20	4.80	4.32	25.46
$C_6H_5OOCCH_2NH$	Br	186–187	72	170.5–171.5 (slight dec.)	$C_{17}H_{16}BrNO_3$	56.37	4.45	3.87	22.06	56.38	4.73	3.77	22.20
CH_3CONH[i]	Br	271–271.5	100	256.5–257.5 (slight dec.)	$C_{15}H_{12}BrNO_2$	56.62	3.80	4.40	25.12	56.37	3.81	4.40	25.20

[a] Many of the substituted fluorenones were prepared by alkylating the aminofluorenone with alkyl bromide in triethyl phosphate or in dimethyl sulfoxide (Reference 3) or by alkyl phosphates in the presence of lithium bromide [T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *J. Org. Chem.*, **20**, 1021 (1955)]. The azomethines were prepared by condensation of the aminofluorenones with the corresponding aldehydes. Reports including preparation of these ketones are in progress. [b] Melting points are corrected. [c] W. Mansner, Zurich; Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.; Mr. M. E. Taylor, this laboratory, and Weiler and Strauss, Oxford. [d] See Reference 4. [e] O. Diels, *Ber.*, **34**, 1758 (1901). [f] In diglyme. [g] See second reference in (a). [h] The 2-di-*n*-butylaminofluorenone was reduced as an oil. [i] Cyclopentylamino-. [j] In chloroform-methanol (2.5:1 by volume). [k] In methanol-diglyme (1:3 by volume). [l] Identical with the melting point (and mixture melting point) of the compound prepared by acetylation of 2-aminofluoren-9-ol (see Experimental). [m] The melting point of this ketone was erroneously reported as 245.5–246° (see second reference in *a*). [n] In dilute aqueous NaOH. [o] In chloroform-methanol (4:1 by volume) at 60°. [p] The mixture melting point with an authentic sample prepared by direct condensation of 2-aminofluoren-9-ol with the aldehydes (see Experimental) showed no depression. [q] With equimolar quantities of the ketone and sodium borohydride 88–94% of 2-*p*-dimethylaminobenzylaminofluoren-9-ol was obtained, m.p. 193.5–194.5°. *Anal.* Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.30; H, 6.91; N, 8.40. [r] In water. This ketone was prepared by Mr. Murray E. Taylor of this laboratory. [s] See Reference 6. [t] See Reference 3. [u] This ketone was prepared by Mr. William H. Wetzel of this laboratory by hydroxyethylation of 2-amino-3-bromofluorenone with ethyl oxide. *Anal.* Calcd. for $C_{15}H_{14}BrNO_2$:N, 4.40; Br, 25.12. Found: N, 4.45; Br, 25.45.

selective reduction of the —N=CH— group in *N*-benzylideneaniline type Schiff bases with sodium borohydride in the presence of other reducible groups. We were interested, however, in determining the possibility of preservation of the —N=CHAr group with concomitant reduction of the carbonyl group.

In our study with a limited number of 2-*N*-aralkylideneaminofluorenones (Table II), we found that the reducibility of the —N=CH— group varies considerably. These differences were more evident in the reduction of 2-*N*-aralkylideneaminofluoren-9-ols. Equivalent amounts of 2-*N*-*p*-dimethylaminobenzylideneaminofluoren-9-ol and sodium-borohydride gave a high yield (80%) of the benzylaminofluoren-9-ol, whereas 2-*N*-*p*-nitrobenzylideneaminofluoren-9-ol, under the same conditions, gave a low yield (18%) of the reduced product. The reducibility of the —N=CH— group in 2-*N*-benzylideneamino-3-bromofluoren-9-ol is also low, as shown in Table II.

The reduction of the aralkylideneamino ketones presented a somewhat more complicated picture. Insolubility of the ketone was an obscuring factor in the room temperature reactions. However, Table II shows the same general picture with regard to preservation of the —N=CH— group. With 2-*N*-benzylideneaminofluorenone and the *p*-nitro derivative, the corresponding 9-fluorenol can be obtained conveniently in about 50% yield.

Reduction of 2-nitrofluorenone with sodium borohydride in the room temperature procedure gave a high-melting (>300°) yellow material instead of 2-nitrofluoren-9-ol.[6] We made the latter compound from 2-nitro-9-bromofluorene and anhydrous sodium acetate followed by acid hydrolysis. Reduction of 2-nitro-9-acetoxyfluorene with zinc and calcium chloride gave 2-amino-9-acetoxyfluorene. Acetylation of 2-aminofluoren-9-ol yielded 2-acetamidofluoren-9-ol or 2-acetamido-9-acetoxyfluorene depending on the conditions.

EXPERIMENTAL

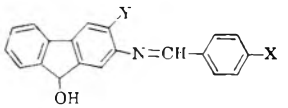
General procedure. To the ketone in methanol (magnetic stirrer), one-half mole equivalent of sodium borohydride was added in small portions over a period of 5 min. The resulting solution or suspension was continuously stirred for 5–25 min. (the temperature rose to 30° or slightly higher) and diluted with water. The precipitate was filtered, washed, dried, and recrystallized from a suitable solvent. (For alternative conditions see Tables I and II.)

2-Acetamidofluoren-9-ol. To a stirred hot solution of 2-aminofluoren-9-ol (9.9 g., 0.05 mole), in glacial acetic acid (100 ml.), a mixture of acetic anhydride (5.5 g., 0.054 mole) and acetic acid (30 ml.) was added in small portions (5 min.). Stirring was continued for another 10 min. then the reaction mixture was poured into cold water. The precipitate was filtered, washed with water and air dried,

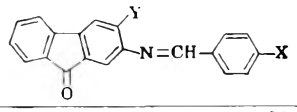
(6) C. L. Arcus and M. M. Coombs, *J. Chem. Soc.*, 3977 (1954). The melting point of this compound was erroneously reported as 227° by E. A. C. Calderón, *Anales asoc. quím. arg.*, **36**, 19 (1948).

TABLE II

SUBSTITUTED 2-*N*-BENZYLAMINOFLUOREN-9-OLS (A) FROM 2-*N*-BENZYLIDENEAMINOFLUOREN-9-OLS (B) AND SUBSTITUTED (A) AND/OR (B) FROM THE CORRESPONDING 2-*N*-BENZYLIDENEAMINOFLUORENONES (C) BY SODIUM BOROHYDRIDE REDUCTION



X	Y	Molar Ratio, $NaBH_4$/B	Yield, %[a] A	% Unreacted, B
H	H	0.25	26–32	62–70
		1.00	90	—
$(CH_3)_2N$	H	0.25	80	18
		1.00	88	6
NO_2	H	0.25	18	79–82
		1.00	94	—
H	Br	0.25	—	88
		1.00	—	50



X	Y	Molar Ratio, $NaBH_4$/C	Yield, %[a] A	Yield, %[a] B	% Unreacted, C
H	H	0.25	8 (8[b])	52 (55[b])	4 (21[b])
		1.00	67	—	—
$(CH_3)_2N$	H	0.25	—	10	60
		1.00	88–94	—	—
NO_2	H	0.25	6 (3[c])	0 (45[c])	94 (50[c])
		1.00	13	—	78
H	Br	0.25	—	—	64
		1.00	—	—	29

[a] Only the yields of identified products are given. The first reaction in each pair was with equivalent quantities of ketone and sodium borohydride in methanol at a temperature of 30–35° (added heat was from magnetic stirrer) for 10 min. The second reaction was with equimolar reactants in methanol at 30–35° for 20 min. In all reactions, $NaBH_4$ was added in small portions over a period of 5 min. — Represents mixtures, difficult to purify. [b] Yield from the reaction in which $NBaH_4$ was added in one portion and the reaction mixture stirred as in (a) for 10 min. [c] Yield from the reaction in chloroform-methanol (4:1 by volume) at 50–60° for 5 min. The hydride was added in one portion.

yielding 11.7 g. (98%), m.p. 248.5–249°. Recrystallization from ethyl acetate-acetone gave short white needles, m.p. 249.5–250°.[7]

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48. Found: C, 75.46; H, 5.28.

2-Acetamido-9-acetoxyfluorene. A mixture of acetic anhydride (11.2 g., 0.11 mole), and pyridine (20 ml.) was added dropwise (10 min.) with constant agitation to a cooled (ice water) solution of 2-aminofluoren-9-ol (9.9 g., 0.05 mole) in pyridine (80 ml.). The reaction mixture was heated on a steam bath for 3 hr. then poured into cold water. The precipitate was filtered, washed with water, and dried, yielding 13.7 g. (97%), m.p. 223.5–228°. Recrystallization from acetic acid–ethanol gave white needles, 12.1 g. (86%), m.p. 227.5–228.5°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37. Found: C, 72.53; H, 5.61.

2-Nitro-9-acetoxyfluorene. A mixture of 2-nitro-9-bromofluorene (29 g., 0.1 mole) and anhydrous sodium acetate (27 g., 0.33 mole) in hot glacial acetic acid (300 ml.) was refluxed for 24 hr. The reaction solution was cooled to room temperature and the product was filtered, washed with water, and dried (18.5 g.). The acetic acid filtrate upon concentration gave a second crop of the product (8.0 g.). Recrystallization from acetone gave 24.8 g. (92%) of yellow needles, m.p. 155.5–156°.[8]

(7) J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *Cancer Research*, **15**, 188 (1955). These authors reported the melting point of this compound as 240–241°. This perhaps contained some 2,9-diacetyl derivative.

(8) J. Schmidt and K. Bauer, *Ber.*, **38**, 3737 (1905).

Anal. Calcd. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.73; H, 4.17; N, 5.20.

2-Nitrofluoren-9-ol. A solution of 2-nitro-9-acetoxyfluorene (5.4 g., 0.02 mole) in absolute ethanol (150 ml.) was refluxed 5 hr. with concentrated hydrochloric acid (15 ml.). After standing overnight at room temperature the mixture was heated and filtered. The filtrate was neutralized with dilute ammonia (1:1), a large quantity of water was added and the product filtered, washed, and dried. The yield was 4.3 g. (96%). Recrystallization from ethanol gave small yellow needles (4.2 g.), m.p. 126–126.5° (reported: 128–129°[6]).

Anal. Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.17. Found: C, 68.42; H, 4.20; N, 6.00.

2-Amino-9-acetoxyfluorene. 2-Nitro-9-acetoxyfluorene (2.7 g., 0.01 mole) and zinc dust (4 g., 0.06 mole) were ground, stirred in 78% ethanol (200 ml.) and heated to boiling. A solution of anhydrous calcium chloride (3.3 g., 0.03 mole) in water (5 ml.) was then added. The mixture was refluxed with slow stirring for 4 hr. and filtered hot. The product isolated from the filtrate weighed 1.2 g. (50%), m.p. 124–125°. Recrystallization from ethanol-water gave shiny straw colored leaflets, m.p. 125–126°.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.41; H, 5.76; N, 6.16.

2-N-Benzylideneaminofluoren-9-ol. A mixture of 2-aminofluoren-9-ol (3.9 g., 0.02 mole), benzaldehyde (5.3 g., 0.05 mole), and methanol (60 ml.) was boiled for 30 min. then cooled to room temperature. The product was filtered, washed with ethanol, and dried, yielding 5.2 g. (91%), m.p. 181–182°.

Anal. Calcd. for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.26; H, 5.27; N, 5.01.

2-N-p-Dimethylaminobenzylideneaminofluoren-9-ol. To a boiling solution of 2-aminofluoren-9-ol (1 g., 0.005 mole) in 50% acetic acid (15 ml.), *p*-dimethylaminobenzaldehyde (0.76 g.) in 50% acetic acid (5 ml.) was added during a period of 5 min. The reaction solution was heated at 105–110° for 10 min. and diluted with an equal volume of water. The acid solution was rendered alkaline with concentrated ammonium hydroxide, and the product filtered and recrystallized from ethanol containing a small amount of acetic acid, yielding 1.2 g. (73%), m.p. 211–212°. Recrystallization from acetone gave m.p. 212–213°.

Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14. Found: C, 80.67; H, 6.05.

2-N-p-Nitrobenzylideneaminofluoren-9-ol. To a boiling solution of 2-aminofluoren-9-ol (7.9 g., 0.04 mole) in absolute ethanol (250 ml.) containing a few drops of glacial acetic acid, *p*-nitrobenzaldehyde (6 g., 0.04 mole) in hot absolute ethanol (30 ml.) was added dropwise within 5 min. The reaction solution was then concentrated until crystallization of the product took place. After cooling to room temperature the shiny yellow plates were filtered, yielding 11.6 g. (88%), m.p. 200–201°.

Anal. Calcd. for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48. Found: C, 72.64; H, 4.44; N, 8.44.

2-N-Benzylideneamino-3-bromofluoren-9-ol. A mixture of 2-amino-3-bromofluoren-9-ol[3] (2.2 g., 0.008 mole), benzaldehyde (5.3 g., 0.05 mole), and glacial acetic acid (2 drops) was heated under reflux at 155–160° (bath) for 1 hr. and excess benzaldehyde removed under reduced pressure. The yellow solid residue was recrystallized from methanol giving 2.2 g. (76%) of light yellow needles, m.p. 175–178°. Two recrystallizations from methanol gave an analytical sample, m.p. 178.5–179.5°.

Anal. Calcd. for $C_{20}H_{12}BrNO$: C, 66.32; H, 3.34; N, 3.87. Found: C, 66.34; H, 3.89; N, 3.87.

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[CONTRIBUTION NO. 412 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENT STATION, E. I. DU PONT DE NEMOURS AND CO.]

Alkylidene Derivatives of 3-Pentenenitrile

P. ARTHUR, JR., JOAN K. MIEGEL, WALTER E. MCCHEL, BURT C. PRATT, AND JAMES H. WERNTZ

Received March 8, 1957

The synthesis of nine new alkylidene derivatives of 3-pentenenitrile (1-substituted-2-cyano-4-methyl-1,3-butadienes) by the condensation of 3-pentenenitrile with aldehydes and ketones is described. The compounds derived from aldehydes form low molecular weight polymers on heating.

The Knoevenagel modification of the Perkin reaction has been used previously to prepare unsaturated acids or nitriles by condensation of aldehydes or ketones with such active methylene compounds as phenylacetic acid, malonic acid, cyanoacetic acid, and benzyl cyanide in the presence of alkaline reagents.[1] Cope[2] prepared a series of alkylidene cyanoacetic esters, $R_1R_2C{=}C(CN)\text{-}COOCH_3$, by condensing ketones with methyl cyanoacetate and interpreted the experimental evidence in favor of an aldol-type mechanism for the Knoevenagel reaction.

Compounds in which a methylene group is activated by a double bond and a nitrile group have now been found to undergo this reaction. Alkylidene derivatives of 3-pentenenitrile have been synthesized by condensation of aldehydes and ketones with 3-pentenenitrile, prepared by reaction of butadiene with hydrogen cyanide, in the presence of sodium alkoxides. The mechanism is similar to that proposed by Cope:[2] (*1*) formation of a carbanion of the 3-pentenenitrile, probably through dissociation of a hydrogen ion,

$$CH_3CH{=}CHCH_2CN \rightleftharpoons H^+ + [CH_3CH{=}CHCH(CN)]^-;$$

(*2*) addition of the carbanion to the carbonyl compound,

$$R_1R_2C{=}O + [CH_3CH{=}CHCH(CN)]^- + H^+ \rightleftharpoons CH_3CH{=}CHCH(CN)CR_1R_2;$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OH$$

and (*3*) elimination of water from the aldol-like intermediate,

$$CH_3CH{=}CHCH(CN)CR_1R_2 \rightleftharpoons$$
$$\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\quad OH$$
$$CH_3CH{=}CHC(CN){=}CR_1R_2 + H_2O.$$
$$\qquad\qquad\qquad\qquad\qquad\quad A$$

The physical properties of the 2-alkylidene derivatives of 3-pentenenitrile are summarized in the table.

Structural assignment was based on elemental analysis, infrared and ultraviolet absorption, the high exaltation in molecular refraction, and the formation of a crystalline dibromide to which the structure, $CH_3CHBrCHBrC(CN){=}CR_1R_2$,[3,4] was assigned.

(1) J. R. Johnson, *Org. Reactions*, **1**, 210 (1947).

(2) A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937).

(3) Mahan, U. S. Patent **2,384,630** (1945), describes an analytical method based on the fact that 3-pentenenitrile adds bromine whereas 2-pentenenitrile does not add bromine.

(4) Linstead, *J. Chem. Soc.*, 358 (1927), reports that bromine adds to $\beta\gamma$-unsaturated acids about 100 times faster than to $\alpha\beta$-unsaturated acids.

TABLE I

2-ALKYLIDENE DERIVATIVES OF 3-PENTENENITRILE $CH_3CH{=}CHC(CN){=}CR_1R_2$

Cpd.	Substitution R_1	Substitution R_2	Yield, %	B.P., °C./Mm.	n_D^{25}	d_{25}^{25}	MD Calcd.	MD Obsd.	Formula	Analyses Calcd. N	Analyses Found N
I	H	C_6H_5	70	135–137/4	1.6110	1.1040	52.83	53.50	$C_{12}H_{11}N$	8.28	8.30
II	H	C_4H_3O	52	117–118/6	1.6270				$C_{10}H_9NO$	8.81	8.87
III	H	$CH(CH_3)_2$	63	97–102/32	1.4627	0.8490	40.16	43.80	$C_9H_{13}N$	10.36	10.35
IV	H	CH_3	9	68–72/37	1.4360						
V	H	$CH{=}CHCH_3$	10	96–98/29	1.4309				$C_9H_{11}N$	10.52	10.65
VI	H	p-$CH_3OC_6H_4$	5	153–155/2					$C_{13}H_{13}NO$	7.04	7.11
VII	[a]	[a]	3	137–138/17	1.5170	0.9510	49.61	51.20	$C_{11}H_{15}N$[b]	8.68	8.51
VIII	CH_3	CH_3	66	81–81.5/13	1.4961	0.8766	37.96	40.40	$C_8H_{11}N$[c]	11.56	11.48
IX	CH_3	C_2H_5	55	102/20	1.4891	0.8760	42.58	44.40	$C_9H_{13}N$	10.36	10.17

[a] R_1R_2 = cyclohexylidene. [b] Calcd.: C, 81.93; H, 9.37. Found: C, 81.6; H, 9.87. [c] Calcd.: C, 79.29; H, 9.15. Found: C, 79.43; H, 9.3.

The hindered nitrile structure A was assigned to the compounds instead of the structure B, $R_1R_2C{=}C(CH_3){-}CH{=}CHCN$, on the basis of ultraviolet absorption spectra and the lack of reactivity of the nitriles. The hindered nitriles showed great resistance to reaction with thioglycolic acid, to hydrolysis to acids, to formation of tertiary butyl amides by reaction with *tert*-butyl alcohol in sulfuric acid as in the case of acrylonitrile, and where R_1 and R_2 are alkyl groups to formation of Diels-Alder adducts with maleic anhydride.

Maximum ultraviolet absorption in ethyl alcohol was observed at 2440 A. (ϵ = 15,250) for 2-isopropylidene-3-pentenenitrile. The low intensity favors the hindered conjugated nitrile structure, A, since an unhindered, conjugated, terminal nitrile, 2,4-pentadienenitrile, has $\lambda_{max}^{methanol}$ 2410 A. (ϵ = 18,550). Values for the backbone hydrocarbon structure for each case are 2,4-hexadiene,[5] λ_{max}^{hexane} 2270 A. (ϵ = 22,500), and 1,3-butadiene,[6] λ_{max}^{hexane} 2170 A. (ϵ = 20,900).

A molecular model of the hindered nitrile structure, A, in which R_1 and R_2 are methyl groups has a *trans* form but cannot add maleic anhydride. Experimentally no crystalline Diels-Alder adduct was obtained by reaction of 2-isopropylidene-3-pentenenitrile with maleic anhydride. This observation is in agreement with that of Craig[7] which indicated that a similar *trans* form of piperylene did not add maleic anhydride.

Most of the 2-alkylidene-3-pentenenitrile derivatives polymerized when heated at about 200° even in the presence of antioxidants. The polymers had little unsaturation as judged by iodine-number determinations. The 2-benzylidene (I) and 2-furfurylidene (II) derivatives formed solid polymers. The 2-isobutylidene (III), 2-ethylidene (IV), and 2-cyclohexylidene (VII) derivatives formed viscous oils, while the 2-isopropylidene (VIII) and 2-(2-butylidene) (IX) derivatives did not polymerize. The highest molecular weight obtained for a polymer of the 2-benzylidene derivative was 440 by the boiling point method.

(5) Booker, Evans and Gillam, *J. Chem. Soc.*, 1453 (1940).

(6) Smakula, *Angew. chem.*, **47**, 657 (1934).

(7) Craig, *J. Am. Chem. Soc.*, **65**, 1006 (1943).

EXPERIMENTAL

3-Pentenenitrile. The method described by Coffman, Salisbury, and Scott[8] was employed. In a 1.3-l. Monel metal bomb chilled with solid carbon dioxide was placed a mixture of 146 g. (5.4 moles) of hydrogen cyanide, 298 g. (5.5 moles) of butadiene, and 1.07 g. (0.54 mole) of cuprous chloride. The bomb was rocked and heated for 2 hr. during which time the temperature increased to 102° and the gauge pressure rose to 285 pounds per square inch. The reaction became exothermic and in 3 min. the temperature surged to 128° and the gauge pressure reached 460 pounds per square inch. The temperature continued to rise during the next 4 min. to 182°, but the pressure dropped to 180 pounds per square inch. The crude product (345 g.) was isolated by steam distillation of the reaction mixture. The upper organic layer was separated, dried over anhydrous sodium sulfate, and distilled through a 110-cm. long, helix-packed column. The fraction boiling at 142–144.5° was collected; n_D^{25} 1.4199; 266 g. (yield 60%).

Anal. Calcd. for C_5H_7N: N, 17.29. Found: N, 17.03.

The infrared spectrum showed a distinct band at 4.45μ characteristic of the nitrile group and a pronounced band at 10.33μ characteristic of a *trans* internal double bond. The 3-pentenenitrile was treated with *tert*-butyl alcohol in sulfuric acid to form the *N-tert*-butyl amide, m.p. 48.5–50°.

Anal. Calcd. for $CH_3CH{=}CHCH_2CONHC(CH_3)_3$: N, 9.02. Found: N, 8.71.

2-Benzylidene-3-pentenenitrile[9] (I). A solution of 3 g. (0.13 mole) of sodium dissolved in 47 g. of absolute ethyl alcohol was added dropwise to a solution of 53 g. (0.5 mole) of freshly distilled benzaldehyde and 32.4 g. (0.4 mole) of 3-pentenenitrile in 316 g. of absolute ethyl alcohol. During the addition of the sodium ethoxide solution over a period of about 45 min., the reaction mixture was stirred and blanketed with nitrogen and the temperature rose from 21° to 36°. The reaction mixture was next heated on a steam bath under a reflux condenser for 3 hr. The crude reaction product was then poured into ice water and extracted with ethyl ether. This ether solution was dried over anhydrous sodium sulfate, filtered, and evaporated on the steam bath. Distillation of the residual oil under reduced pressure yielded 47 g. of 2-benzylidene-3-pentenenitrile (1-phenyl-4-methyl-2-cyano-1,3-butadiene), a light yellow oil, b.p.

(8) Coffman, Salisbury, and Scott, U. S. Patent 2,509,859 (1950).

(9) Pratt, U. S. Patent 2,773,857 (1956).

160°/16 mm.; n_D^{25} 1.6112. On redistillation, through a 30-cm. Fenske ring-packed column at a reflux ratio of 1:10, the product obtained possessed the following constants: b.p. 135–137°/4 mm.; n_D^{25} 1.6110; d_{25}^{25} 1.1040.

2-Isopropylidene-3-pentenenitrile[9] (VIII). Acetone was condensed with 3-pentenenitrile in the same manner as described above for benzaldehyde. The product was distilled through a 76-cm. Nester spinning band column at a reflux ratio of 1:10. The liquid product melted at −8°. The compound added oxygen readily, and it was stored under nitrogen prior to analysis. Low results, particularly for carbon, were obtained until it was discovered that the analytical sample had to be burned very slowly.

The compound showed infrared absorption at 3.4μ for saturated CH, 3.5μ for unsaturated CH, 4.5μ for conjugated nitrile, 6.17μ for conjugated unsaturation, 7.25μ for CH_3, and 10.45μ for a *trans* internal double bond.

2-Isopropylidene-3-pentenenitrile proved difficult to hydrolyze. In contrast with 3-pentenenitrile, no acid or lactone formed when it was boiled with concentrated hydrochloric acid. The nitrile was hydrolyzed by boiling two days with 17% aqueous sodium hydroxide. On acidification and distillation, about 10% of 3-pentenoic acid and about 10% of crude liquid 2-isopropylidene-3-pentenoic acid were recovered. Following a procedure employed by Whyte and Cope[10] to hydrolyze hindered nitriles, 48 g. of 2-isopropylidene-3-pentenenitrile was stirred 15 hr. at reflux temperature with a mixture of 45 g. of potassium hydroxide, 20 g. of water, and 100 ml. of diethylene glycol. After acidification and fractional distillation, 1.7 g. of a straw-colored liquid acid was recovered, n_D^{25} 1.4489, b.p. 82–90°/5 mm.

Anal. Calcd. for $CH_3CH{=}CHC(COOH){=}C(CH_3)_2$: neut. equiv., 140. Found: neut. equiv., 137.3.

Some acetone was liberated, but most of the product was a solid polymer.

2-Isopropylidene-3-pentenenitrile was treated with two mole equivalents of bromine in chloroform at 3°, conditions employed by Craig[11] to prepare the tetrabromide of piperylene. From 4.4 g. of 2-isopropylidene-3-pentenenitrile there was obtained 6.1 g. of needles which were recrystallized from boiling heptane, m.p. 114–116°. No tetrabromide was formed.

Anal. Calcd. for $C_7H_{11}Br_2(CN)$: C, 34.20; H, 3.94; N, 4.99; Br, 56.95. Found: C, 34.26; H, 4.22; N, 5.06; Br, 56.95.

2-Isopropylidene-3-pentenenitrile, unlike 3-pentenenitrile, did not yield a solid *N-tert*-butylamide when reacted with *tert*-butyl alcohol and sulfuric acid in glacial acetic acid by the procedure used by Plaut and Ritter[12] to prepare amides from acrylonitrile.

There was no evidence of reaction when 2-isopropylidene-3-pentenenitrile was mixed with thioglycolic acid and hydrogen chloride in ethyl ether. Under these conditions, Shriner and Fuson[13] indicate that unhindered nitriles form solid α-iminoalkyl mercaptoacetic acid hydrochlorides.

The other compounds listed in the table, II from furfuraldehyde, III from isobutyraldehyde, IV from acetaldehyde, V from crotonaldehyde, VI from *p*-methoxybenzaldehyde, VII from cyclohexanone, and IX from methyl ethyl ketone, were prepared by the same procedure using 32 mole per cent sodium ethoxide, based on 3-pentenenitrile, as the condensing agent. Erroneous carbon and hydrogen results were obtained unless the samples were burned slowly and carefully. These compounds also added oxygen readily, and it was necessary to store samples in an inert atmosphere prior to analysis.

Polymerization. A soft, tacky polymer was obtained by heating 2-benzylidene-3-pentenenitrile with 0.1% of its weight of hydroquinone under nitrogen in a sealed glass tube for 48 hr. at 175°. The resulting benzene-soluble polymer possessed an iodine number 14.7. X-ray diffraction measurements indicated it to be noncrystalline.

Treatment of 2-benzylidene-3-pentenenitrile under 7500 atmospheres pressure at 200° for 5 hr. produced a tough, transparent, red-brown polymer which was harder and less tacky than the polymer prepared by heating for 48 hr. at 175° under atmospheric pressure. It was soluble in benzene and chloroform, but insoluble in ethyl alcohol or acetic acid. The iodine number was 6.4. The molecular weight determined by elevation of the boiling point of a benzene solution was 440.

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(10) Whyte and Cope, *J. Am. Chem. Soc.*, 65, 1999 (1943).

(11) Craig, *J. Am. Chem. Soc.*, 65, 1011 (1943).

(12) Plaut and Ritter, *J. Am. Chem. Soc.*, 73, 4077 (1951).

(13) Shriner and Fuson, *Identification of Organic Compounds*, John Wiley & Sons, Inc., 1948, p. 205.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Some Reactions of Methanesulfinyl Chloride[1]

IRWIN B. DOUGLASS AND BASIL SAID FARAH[2]

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Methanesulfinyl chloride has been found to react with excess of alkanethiols to form mixtures of simple disulfides, with boiling alcohols to form alkyl chlorides, with benzene in the presence of anhydrous aluminum chloride to form methyl benzyl sulfone, and with aromatic amines to form methanesulfinamides.

The ease with which the alkanesulfinyl chlorides can be prepared by the controlled hydrolysis or alcoholysis of alkylsulfur trichlorides according to the equations:

$$RSCl_3 + H_2O \longrightarrow RSOCl + 2HCl$$

$$RSCl_3 + CH_3OH \longrightarrow RSOCl + HCl + CH_3Cl$$

has made these compounds readily available[3] and has led us to study certain reactions of methanesulfinyl chloride.

J. von Braun and Weisbach[4] have reported that some of the lower alkanesulfinyl chlorides are con-

(1) This work has been supported in part by the Office of Naval Research.

(2) Taken from the Master's thesis of Basil Said Farah.

(3) I. B. Douglass and Donald Poole, *J. Org. Chem.*, 22, 536 (1957).

(4) J. von Braun and K. Weisbach, *Ber.*, 63B, 2836 (1930).

verted to the corresponding thiolsulfonate esters, RSO_2SR, by sodium mercaptides, dithiocarbamate salts, and mercaptans. In the present study no thiolsulfonate esters were found among the reaction products when excess ethanethiol was treated with methanesulfinyl chloride. There was found instead, a mixture of the symmetrical methyl and ethyl disulfides in quantities indicated by the equation:

$$2CH_3SOCl + 6C_2H_5SH \longrightarrow CH_3SSCH_3 + 3C_2H_5SSC_2H_5 + 2HCl + 2H_2O$$

No fraction corresponding to the mixed disulfide was found. Further work will be necessary to indicate the successive stages of the reduction and to harmonize these results with those reported by von Braun and Weisbach.

Our experience has also confirmed the observation of Small, Bailey, and Cavallito[5] that alkanethiolsulfinate esters, RSOSR', cannot be prepared by the action of mercaptans on alkanesulfinyl chlorides. Backer and Kloosterziel[6] have prepared aromatic thiolsulfinate esters by the action of thiophenols on aromatic sulfinyl chlorides but they indicate that the thiosulfinate esters readily disproportionate according to the equation:

$$2ArS(=O)SAr' \longrightarrow ArSO_2SAr + Ar'SSAr'$$

Alcohols and alkanesulfinyl chlorides when brought together at low temperatures have been reported by Braun and Weisbach, and later by Meuwsen and Gebhardt[7] to yield sulfinate esters. The present study indicates that when an alcohol and methanesulfinyl chloride are refluxed together the alcohol is converted in high yield to the alkyl chloride. In the case of benzyl alcohol, in addition to an 83% yield of α-chlorotoluene, an 8.3% yield of methyl benzyl sulfone was also recovered.

Attempts to prepare a sulfoxide by the reaction of methanesulfinyl chloride with benzene in the presence of anhydrous aluminum chloride were fruitless until the aluminum chloride was added in small portions to a mixture of benzene and the sulfinyl chloride. This procedure gave a 26% yield of methyl phenyl sulfoxide.

Methanesulfinyl chloride reacted readily with ether solutions of aniline and *p*-toluidine at the temperature of solid carbon dioxide. The resulting substituted methanesulfinamides could be isolated by the low-temperature evaporation of their ether solutions. They readily decomposed at higher temperatures, however, forming the corresponding sulfonamides and oily products. The decomposition was possibly a disproportionation according to the following equation although the expected sulfenamides were not identified among the oily by-products.

$$2RSONHR' \longrightarrow RSO_2NHR' + RSNHR'$$

EXPERIMENTAL

Methanesulfinyl chloride was prepared by a method already described.[3]

Reaction of methanesulfinyl chloride with thiols. Sixteen grams (0.1 mole) of 2-naphthalenethiol was dissolved in 200 ml. of 3*N* sodium hydroxide solution and cooled at 0°. An equivalent amount of methanesulfinyl chloride was added dropwise with constant stirring. The solid which separated immediately, after recrystallizing from acetone, melted 143–144° and was shown to be 2-naphthyl disulfide by a mixed melting point with an authentic sample. The yield corresponded to 90.4% based on the 2-naphthalenethiol used.

In a similar manner, benzenethiol gave phenyl disulfide in 86% yield and α-toluenethiol gave benzyl disulfide in 38% yield.

In order to avoid the presence of moisture and to study the reaction more precisely, one mole of ethanethiol was placed in a three-neck flask surrounded by a Dry Ice bath and fitted with sealed stirrer and dropping funnel. The outlet of the reaction flask was connected in series with two traps cooled in Dry Ice and a third containing water for absorbing hydrogen chloride. The whole system was protected by a calcium chloride tube. One-half mole (49.5 g.) of pure methanesulfinyl chloride was added dropwise with constant stirring. When addition was complete the reaction flask was packed in Dry Ice and allowed to stand overnight.

When next examined, the reaction mixture had separated into two layers. An aliquot from the lower layer was titrated with standard alkali and another portion was allowed to stand with benzoyl chloride until the latter had been hydrolyzed to benzoic acid, thus proving the presence of water. The hydrogen chloride from the bottom layer, together with that absorbed in the water trap, corresponded to .383 mole or 76.5% of the chlorine in the sulfinyl chloride used.

The organic layer from the reaction flask was washed with water and sodium bicarbonate solution and then dried. Careful fractionation yielded 14.2 g. (0.13 mole) of methyl disulfide and 54 g. (0.442 mole) of ethyl disulfide.

Considering the 1:3 molar ratio of disulfides recovered from the experiment as indicative of the reacting proportions, 0.22 mole of methanesulfinyl chloride was caused to react with 0.66 mole of 1-butanethiol in a similar manner. The products isolated were 8.3 g. methyl disulfide (0.088 mole, 79%) and 46.3 g. of *n*-butyl disulfide (0.26 mole, 77%).

Reaction of methanesulfinyl chloride with alcohols. Seventeen grams of pure dried benzyl alcohol (0.16 mole) was refluxed with 9.85 g. methanesulfinyl chloride (0.10 mole) for 2.5 hr. On cooling, 1.40 g. of white crystals separated and were identified as methyl benzyl sulfone by mixed melting point with an authentic sample. The liquid portion of the reaction mixture was diluted with ether and extracted with sodium bicarbonate solution. From the ether layer 10.5 g. α-chlorotoluene was isolated and identified by its boiling point, refractive index, and molecular weight. The yield of methyl benzyl sulfone was 8.3% and that of α-chlorotoluene 83%, both based on the methanesulfinyl chloride used.

Twenty grams (0.22 mole) of methanesulfinyl chloride was treated dropwise with 9.2 g. (0.20 mole) of absolute ethanol in a reaction flask, attached to suitable traps for the absorption of hydrogen chloride and condensation of chloroethane, and refluxed for 6 hr. From the cold trap there was obtained 6.3 g. of colorless liquid which was identified as chloroethane (49% yield) by its boiling point, molecular weight and by the formation of ethyl mercuric chloride melting at 192–193°.

(5) La V. D. Small, J. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, 69, 1710 (1947).

(6) H. J. Backer and H. Kloosterziel, *Rec. trav. chim.*, 73, 129 (1954).

(7) A. Meuwsen and H. Gebhardt, *Ber.*, 69B, 937 (1936).

The residue in the reaction flask was diluted with ether and extracted with sodium bicarbonate solution. On boiling the bicarbonate extract with α-chlorotoluene there was obtained 25.5 g. of methyl benzyl sulfone (68% yield), indicating that the aqueous extract had contained sodium methanesulfinate.

The acid found in the hydrogen chloride trap corresponded to only 7% of the original chlorine.

Reaction of methanesulfinyl chloride with benzene. One-half mole of methanesulfinyl chloride (49.25 g.) and 300 ml. dry benzene were placed in a three-neck flask fitted with sealed stirrer and reflux condenser. To the third neck was attached, by means of a large-diameter rubber tubing, a 125-ml. Erlenmeyer flask containing 135 g. (1.00 mole) of powdered anhydrous aluminum chloride. While maintaining the liquid reactants at 0° the aluminum chloride was added in small portions over a period of 30 min. and the reactants were then refluxed on the steam bath overnight. After working up the reaction mixture in the usual manner there was obtained 21 g. of colorless methyl phenyl sulfoxide boiling at 115° (2 mm.), having n_D^{25} 1.5880 and showing strong infrared absorption in the vicinity of 1040 cm.$^{-1}$ This liquid solidified when placed in the refrigerator overnight but melted on warming to room temperature. Oxidation of the product gave a solid melting 86–88° and unchanged when mixed with an authentic sample of methyl phenyl sulfone. Methyl phenyl sulfoxide is reported to have n_D^{20} 1.5885, to melt at 30.0–30.5°, to boil at 104° (0.7 mm.)[8] or 140–142° (13 mm.)[9] when absolutely dry and to show infrared absorption, when a liquid, at 1044 cm.$^{-1}$.[10] The yield corresponded to 26%, based on the sulfinyl chloride used.

The method described, of adding anhydrous aluminum chloride to the mixture of sulfinyl chloride and benzene, proved superior to the usual method of adding the chloride to a mixture of benzene and aluminum chloride. Numerous attempts to follow the latter procedure, using a variety of reactants, yielded only tars.

Reaction of methanesulfinyl chloride with aromatic amines. Nine and three-tenths grams of redistilled aniline (0.10 mole), dissolved in 100 ml. of anhydrous ether, was added dropwise with constant stirring to a solution of 4.95 g. methanesulfinyl chloride (0.05 mole) in 100 ml. ether cooled to −40 or −50°. After the reaction mixture had stood overnight, aniline hydrochloride was filtered out in quantitative yield. The ethereal solution was washed repeatedly with water and sodium bicarbonate solution, dried over calcium chloride, and evaporated either under vacuum or by blowing through it a stream of cold air. Decomposition always occurred when the ether solutions were evaporated by heating.

As the solvent was removed, crude methanesulfinanilide crystallized. Repeated recrystallization from anhydrous ether, washing with petroleum ether and with carbon tetrachloride gave a 71% yield of pure methanesulfinanilide melting at 86.88°.

Anal. Calcd. for C_7H_9ONS: N, 9.02. Found: N, 8.87.

Methanesulfin-p-toluidide, obtained in the same manner, melted at 96–98°, with decomposition occurring 103–106°.

Anal. Calcd. for $C_8H_{11}ONS$: N, 8.28. Found: N, 8.05.

ORONO, ME.

(8) C. C. Price and J. J. Hydock, *J. Am. Chem. Soc.*, **74**, 1943 (1952).

(9) L. Horner and C. Belzel, *Ann.*, **579**, 175–192 (1953).

(10) D. Barnard, J. M. Fabian, and H. P. Koch, *J. Chem. Soc.*, 2442 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DE PAUL UNIVERSITY]

Acetylenic Reactions of 2-(Phenylethynyl)tetrahydropyran[1]

ROBERT ZELINSKI[2] AND JAMES LOUVAR

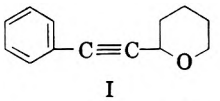
Received December 16, 1957

2-(Phenylethynyl)tetrahydropyran (I) was hydrogenated to 2-(2-phenylethyl)- and 2-(2-cyclohexylethyl)-tetrahydropyran. Addition of bromine and iodine to I yielded crystalline dihalides, hydration gave α-(2-tetrahydropyranyl)acetophenone, and addition of methanol formed α-(2-tetrahydropyranyl) acetophenone dimethylacetal.

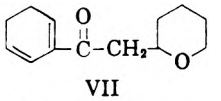
In parallel with the glucosylation of acetylene and phenylacetylene by coupling of alkynylmetal compounds with tetraacetyl-α-D-glucopyrannosyl bromide,[3] racemic 2-(phenylethynyl)tetrahydropyran (I) was prepared as a model compound and examined in some reactions intended for its carbohydrate counterpart.

Like the glycosyl halides, 2-halotetrahydropyrans show the characteristic reactivity of alpha halogen ethers toward organometallic compounds. For example, a series of 2-alkynyl-3-chlorotetrahydropyrans[4] has been prepared from 1-alkynylmagnesium halides and 2,3-dichlorotetrahydropyran. It is not unlikely that organolithium would yield similar products.[5]

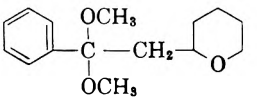
The racemic 2-(phenylethynyl)tetrahydropyran (I) was obtained in 66% yield from 2-chlorotetrahydropyran and phenylethynylmagnesium bromide. It very easily formed peroxides upon exposure to air.



I



VII



VIII

(1) The financial assistance of the Research Corp. is gratefully acknowledged.

(2) Present address: 1653 S. Elm Avenue, Bartlesville, Okla.

(3) R. Zelinski and R. Meyer, *J. Org. Chem.*, **23**, 810 (1958).

(4) O. Riobe, *Compt. rend.*, **231**, 1312 (1950); **236**, 2073 (1953).

(5) L. Summers and M. L. Larson, *J. Am. Chem. Soc.*, **74**, 4498 (1952).

Low pressure hydrogenation of the phenylethynyl compound I over platinum oxide removed both the aromatic and the alkyne unsaturation, forming 2-(2-cyclohexylethyl)tetrahydropyran (II). However, by using palladium on charcoal it was possible to reduce I to 2-(2-phenylethyl)tetrahydropyran (III). Both II and III were also prepared by alkylation of 2-chlorotetrahydropyran with the appropriate Grignard reagent.

A considerable number of attempts were made to reduce the acetylenic bond to the olefin. A combination of zinc, copper, and acetic acid[6] was without effect, lithium aluminum hydride[7] caused only a minor amount of reduction, and sodium and ammonia[8] gave an unidentified product which did not appear to be the desired *trans*-2-(2-phenylethenyl)tetrahydropyran.

Experiments to accomplish this by partial hydrogenation were unsatisfactory because the reaction could not be sufficiently controlled and because it proved impossible to separate the resultant mixtures by fractional distillation at the necessary reduced pressure. Thus both Raney nickel[8] and palladium on calcium carbonate[9] gave inseparable mixtures even when with the latter catalyst the amount of hydrogen absorbed was limited to the stoichiometric quantity for olefin formation.

2-(Phenylethynyl)tetrahydropyran (I) showed the expected reactivity of the acetylenic bond. It readily formed a 1 : 1 crystalline adduct (IV) with 2,4-dinitrobenzenesulfenyl chloride. Like diphenylacetylene,[10,11] I added molar equivalents of bromine and of iodine to form a crystalline dibromide (V) and diiodide (VI). However, attempts to obtain the dichloride were unsuccessful.

Hydration of I to α-(2-tetrahydropyranyl)-acetophenone (VII) was catalyzed by mercuric oxide in aqueous alcohol.[12] It was identical to the ketone prepared from 2-tetrahydropyranylacetyl chloride[13] and diphenylcadmium. The 2,4-dinitrophenylhydrazones were also identical. That VII was not the alternate hydration product, 2-(phenylacetyl)tetrahydropyran,[14] was clearly evident from comparison of physical properties and melting points of the dinitrophenylhydrazones.

Lithium aluminum hydride easily reduced the racemic ketone VII to a mixture of the four stereoisomeric alcohols. However, attempts to prepare crystalline urethans or dinitrobenzoates gave only oily products.

α-(2-Tetrahydropyranyl)acetophenone dimethylacetal (VIII) was obtained by methanolysis of I catalyzed by mercuric oxide and boron trifluoride etherate.[15] The structure was substantiated by hydrolysis to the ketone VII, which was characterized through its 2,4-dinitrophenylhydrazone. Attempts to add only an equimolar amount of methanol to I and so to obtain the enol ether of VII were unsuccessful.

In an analogous way,[15] reaction of 2-(phenylethynyl)tetrahydropyran (I) with acetic acid was attempted. The addition product was formed, but fractionation was erratic and accompanied by decomposition since the odor of acetic anhydride was present in all fractions. The presence of the *gem* diacetate or the enol acetate of VII or of VII itself was demonstrated by the rapid formation of the 2,4-dinitrophenylhydrazone of VII upon addition of 2,4-dinitrophenylhydrazine to one of these fractions.

EXPERIMENTAL[16,17]

2-(Phenylethynyl)tetrahydropyran. 2-Chlorotetrahydropyran was freshly prepared by addition of the calculated amount of anhydrous hydrogen chloride to anhydrous dihydropyran cooled in an ice bath. The solution was then diluted with dry ether and used directly. Phenylethynylmagnesium bromide was prepared by refluxing for 1 hr. a solution of 20.0 g. (0.20 mole) of phenylacetylene in 50 ml. of ethyl ether with the ethylmagnesium bromide obtained from 32.7 g. (0.30 mole) of ethyl bromide and 7.3 g. (0.30 g.-atom) of magnesium in 150 ml. of ether. The crude 2-chlorotetrahydropyran (0.30 mole) was added in one portion to form a pasty mass in a few minutes. This was hydrolyzed after 10–15 min. by a cold solution of ammonium chloride. The ether extract was distilled through an 18-in. Vigreux column to give 24.6 g. (65%) of colorless 2-(phenylethynyl)-tetrahydropyran (I), b.p. 149° (8 mm.), n_D^{25} 1.5600, d_{25} 1.020.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.59. Found: C, 83.51; H, 7.64.

The 2,4-dinitrobenzenesulfenyl chloride adduct (IV) of 2-(phenylethynyl)tetrahydropyran (I) was obtained by warming 0.19 g. of I and an equimolar amount of 2,4-dinitrobenzenesulfenyl chloride in 2.0 ml. of glacial acetic acid. The crude solid which formed on standing at room temperature was crystallized from benzene to give 83% of the adduct (IV), m.p. 203–204°.

Anal. Calcd. for $C_{18}H_{17}N_2O_5SCl$: Cl, 8.67; N, 6.85. Found: Cl, 8.52; N, 6.74.

A sample of I which was stored in a corked container at room temperature for a week was found[18] to contain 84 m. equiv. of peroxide per 1000 g. of sample. If a molecular weight of 218 is assumed for the hydroperoxide, its concentration was 2%.

(6) B. S. Rabinovitch and F. S. Looney, *J. Am. Chem. Soc.*, **75**, 2652 (1953).

(7) J. D. Chanley and H. Sobotka, *J. Am. Chem. Soc.*, **71**, 4140 (1949).

(8) B. B. Elsner and P. F. Paul, *J. Chem. Soc.*, 3156 (1953).

(9) E. B. Hershberg, E. P. Olveto, C. Gerold, and L. Johnson, *J. Am. Chem. Soc.*, **73**, 5073 (1951).

(10) S. Lempricht, *Ber.*, **4**, 379 (1871).

(11) A. Fischer, *Ann.*, **211**, 233 (1882).

(12) R. J. Thomas, K. N. Campbell, and G. F. Hennion, *J. Am. Chem. Soc.*, **60**, 718 (1938).

(13) R. Zelinski, N. G. Peterson, and H. R. Wallner, *J. Am. Chem. Soc.*, **74**, 1504 (1952).

(14) R. Zelinski and K. Yorka, *J. Org. Chem.*, **23**, 640 (1958).

(15) G. F. Hennion and J. A. Nieuwland, *J. Am. Chem. Soc.*, **56**, 1802 (1934).

(16) Elemental analyses by Micro Tech Laboratories, Skokie, Ill.

(17) Unless otherwise specified, fractional distillations were conducted in a Piros-Glover spinning band column.

(18) I. M. Kolthoff and A. I. Medalia, *Anal. Chem.*, **23**, 595 (1951).

2-(2-Cyclohexylethyl)tetrahydropyran (II). A mixture of 7.5 g. (0.04 mole) of 2-(phenylethynyl)tetrahydropyran (I), 0.1 g. of platinum oxide, and 20 ml. of absolute methanol was hydrogenated at 60 p.s.i.g. and room temperature for 8 hr. Fractional distillation[17] gave 5.5 g. (66%) of 2-(2-cyclohexylethyl)tetrahydropyran (II), b.p. 155–160° (12–15 mm.), n_D^{25} 1.4712, d_{25} 0.921.

Anal. Calcd. for $C_{13}H_{24}O$: C, 79.52; H, 12.32. Found: C, 79.45; H, 12.42.

Compound II was also prepared by dropwise addition of 37 g. (0.30 mole) of crude 2-chlorotetrahydropyran in 50 ml. of dry ether to the Grignard reagent prepared from 38.6 g. (0.20 mole) of 2-cyclohexylethyl bromide, 7.3 g. (0.30 g.-atom) of magnesium, and 100 ml. of dry ether. Fifteen minutes after addition of the halopyran, the reaction mixture was hydrolyzed with cold water and a little hydrochloric acid. The ether layer was separated, neutralized, dried over sodium sulfate, and distilled through the Vigreux column to give 24 g. (59%) of 2-(2-cyclohexylethyl)tetrahydropyran, n_D^{25} 1.4707.

2-(2-Phenylethyl)tetrahydropyran (III). A mixture of 5.6 g. (0.03 mole) of 2-(phenylethynyl)tetrahydropyran (I), 1.0 g. of palladium on charcoal[19] and 50 ml. of alcohol was hydrogenated for 2.5 hr. at room temperature and 60 p.s.i.g. Fractional distillation gave 4.0 g. (70%) of 2-(2-phenylethyl)tetrahydropyran (III), b.p. 125° (5 mm.), n_D^{25} 1.5122, d_{25} 0.976.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.73; H, 9.50.

By the procedure described for the preparation of II, the Grignard reagent from 0.3 mole of 2-phenylethyl bromide reacted with 0.30 mole of 2-chlorotetrahydropyran to give after fractional distillation 30 g. (52%) of colorless III, b.p. 142° (10 mm.), n_D^{25} 1.5121, d_{25} 0.979.

Other attempts to reduce 2-(phenylethynyl)tetrahydropyran. The first three methods were attempts to cause reduction to a *cis* olefin. Following the general procedure described in the literature for reduction of diphenylacetylene to *cis*-stilbene,[6] an attempt to reduce 2-(phenylethynyl)tetrahydropyran (I) with acetic acid and a zinc-copper couple caused essentially no reduction.

Catalytic hydrogenation of I occurred with Raney nickel[8] or palladium on calcium carbonate,[9,19] but a pure product could not be separated.

Two methods were tested to reduce the ethyne (I) to a *trans*-olefin. Lithium aluminum hydride[7] had no effect. On the other hand, sodium and liquid ammonia[8] caused reduction, but the product did not have an elemental analysis corresponding to *trans* 2-(2-phenylethynyl)tetrahydropyran.

Addition of halogen to 2-(phenylethynyl)tetrahydropyran. A solution of 10.8 g. (0.0600 mole) of bromine in 25 ml. of carbon tetrachloride was slowly added to an ice cold solution of 11.2 g. (0.0600 mole) of 2-(phenylethynyl)tetrahydropyran (I) in 25 ml. of the same solvent. The whole was stirred in the cold for 15 min. and then the solvent was evaporated on a steam bath. The semisolid residue was crystallized from petroleum ether to yield 4.8 g. (33%) of 2-(phenylethynyl)tetrahydropyran dibromide (V), m.p. 118–119°.

Anal. Calcd. for $C_{13}H_{14}OBr_2$: C, 45.30; H, 4.16; Br, 46.32. Found: C, 45.24; H, 3.80; Br, 46.55.

When 1.86 g. (0.0100 mole) of I and 2.54 g. (0.0100 mole) of iodine were allowed to stand in 25 ml. of carbon tetrachloride for two days, evaporation of the solvent and recrystallization from petroleum ether gave 3.8 g. (86%) of the diiodide (VI), m.p. 137–138°.

Anal. Calcd. for $C_{13}H_{14}OI_2$: C, 35.48; H, 3.21; I, 57.68. Found: C, 35.77; H, 3.37; I, 57.80.

Bubbling chlorine through a solution of I in carbon tetrachloride at 0° left an oily product which could not be crystallized. The increase in weight suggested that substitution might have occurred as well as addition.

(19) Baker and Co., Newark, N. J.

α-(2-Tetrahydropyranyl)acetophenone (VII). A mixture of 9.3 g. (0.050 mole) of 2-(phenylethynyl)tetrahydropyran (I), 0.5 g. of sulfuric acid, 0.5 g. of mercuric oxide, and 100 ml. of 70% alcohol was heated in a magnesium citrate bottle on a steam bath for 6 hr. After having been cooled to room temperature, the contents were poured into a saturated sodium bicarbonate solution. This mixture was then extracted with petroleum ether and the extract was filtered and fractionally distilled to give 8.6 g. (84%) of α-(2-tetrahydropyranyl)acetophenone (VII), b.p. 123–124° (0.8 mm.), n_D^{25} 1.5373, d_{25} 1.062.

Anal. Calcd. for $C_{13}H_{16}O$: C, 76.44; H, 7.90. Found: C, 76.40; H, 7.99.

The *2,4-dinitrophenylhydrazone* of VII, m.p. 188–189°, was obtained[20] in 81% yield after one recrystallization from alcohol and ethyl acetate.

Anal. Calcd. for $C_{19}H_{20}O_5N_4$: C, 59.36; H, 5.24; N, 14.58. Found: C, 59.33; H, 5.55; N, 14.33.

The *semicarbazone* of VII, m.p. 133–135°, was obtained[20] in 31% yield after recrystallization from aqueous alcohol.

Anal. Calcd. for $C_{14}H_{19}O_3N_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.63; H, 7.24; N, 15.82.

Compound VII was also made another way. The undistilled 2-tetrahydropyranylacetyl chloride[13] from 0.20 mole of the corresponding acid was dissolved in 100 ml. of dry benzene and added as rapidly as possible to the diphenylcadmium prepared from 0.30 g.-atom of magnesium, 0.30 mole of bromobenzene, and 0.16 mole of cadmium chloride. After 15 min. of reflux, the mixture was poured into cold aqueous ammonium chloride and extracted with ether which was then dried and distilled to give a 9% yield of α-(2-tetrahydropyranyl)acetophenone (VII), b.p. 161–163° (10 mm.), n_D^{25} 1.5362. A mixture of its 2,4-dinitrophenylhydrazone, m.p. 187.5–188.5°, with the 2,4-dinitrophenylhydrazone of VII prepared by hydration of I showed no melting point depression.

Reduction of α-(2-tetrahydropyranyl)acetophenone (VII). A solution of 6.1 g. (0.030 mole) of VII with 25 ml. of a saturated ether solution of lithium aluminum hydride was shaken at room temperature for 2 hr. and then was cautiously poured into cold 5% sulfuric acid. The petroleum ether extract of this was dried and fractionally distilled to give 5.5 g. (89%) of a colorless mixture of stereoisomers of 1-phenyl-2-(2-tetrahydropyranyl)ethanol, b.p. 125–128° (1 mm.), n_D^{25} 1.5285.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.35; H, 8.66.

Attempts to prepare the 3,5-dinitrobenzoate and the phenylurethan gave oils.

α-(2-Tetrahydropyranyl)acetophenone dimethylacetal (VIII). A solution of 5.6 g. (0.03 mole) of 2-(phenylethynyl)tetrahydropyran (I) in 9.6 g. of anhydrous methanol was slowly added with stirring and occasional cooling to a warm mixture of 0.5 g. of red mercuric oxide, 0.2 ml. of boron trifluoride etherate, and 0.5 ml. of methanol. The mixture was cooled, the flask was stoppered tightly, and the whole was heated on a steam bath for 1 hr. with occasional shaking. It was then cooled, 0.5 g. of potassium carbonate was added, and the mixture was filtered. The filtrate was fractionally distilled to give 4.0 g. (53%) of α-(2-tetrahydropyranyl)-acetophenone dimethylacetal (VIII), b.p. 109–114° (2–3 mm.), n_D^{25} 1.5075, d_{25} 1.068.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.96; H, 8.81.

To prepare a solid derivative, VIII was treated[20] with 2,4-dinitrophenylhydrazine. The immediate yellow precipitate was recrystallized from alcohol and ethyl acetate to give the 2,4-dinitrophenylhydrazone of VII, m.p. 189–190°,

(20) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, third edition, John Wiley and Sons, Inc., New York, 1948, p. 171–172.

which showed no melting point depression with an authentic sample.

Acetolysis of 2-(phenylethynyl)tetrahydropyran (I). A tightly stoppered flask containing 5.6 g. (0.30 mole) of I, 0.5 g. of mercuric oxide, 0.2 ml. of boron trifluoride etherate, and 18 g. of glacial acetic acid was heated on a steam bath for 1 hr. The mixture was poured into cold water which was then extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, dried, and fractionally distilled at 107–148° (1 mm.). Separation was unsatisfactory, but refractive indices varied from 1.5285 to 1.5380 at 20°. Decomposition seemed to occur and the odor of acetic acid or anhydride was noticeable in many fractions.

The 2,4-dinitrophenylhydrazone of VII was obtained from one of the fractions.

CHICAGO 14, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUL UNIVERSITY]

Glucosylation of Acetylenes[1]

ROBERT ZELINSKI[2] AND ROBERT E. MEYER

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The first example of a glucosylated acetylene has been prepared by reaction of tetraacetyl-α-D-glucopyranosyl bromide with phenylethynylmagnesium bromide. The hydrate (II) of this compound, 1-phenyl-2-(tetraacetyl-β-D-glucopyranosyl)-ethyne (I), was catalytically reduced to 1-phenyl-2-(tetraacetyl-β-D-glucopyranosyl)ethane (IV) which was also prepared by the analogous glucosylation of 2-phenylethylmagnesium bromide. Glucosylation of sodium acetylide gave a small yield of a crystalline carbohydrate derivative of undetermined structure.

The glucosylation of hydrocarbons with a carbohydrate moiety in which the pyranose ring is preserved has been accomplished by using glycosyl halides in two familiar organic reactions. Thus the Friedel-Crafts reaction has led to the glycosylation of aromatic hydrocarbons. The second and more general way is the coupling of organometallic compounds with α-halo ethers, as extended to include glycosyl halides, a procedure of obviously greater scope. Both approaches were originated by Hurd and Bonner[3] and extended by them in work which has been largely reviewed by Bonner.[4] Since then the glycosylation of organometallics has been applied to a variety of carbohydrates[5] and Grignard reagents[5–9] as well as to organocadmium[10] and organoalkali[11] compounds. It was our purpose to extend the scope of this synthesis still further by employing organometal derivatives of 1-alkynes.

The only report in the literature concerning attempted glycosylation of acetylenes is that of unsuccessful efforts[5] to couple tetraacetyl-α-D-glucopyranosyl bromide with ethynebis(magnesium bromide) and with sodium or lithium acetylide. Since the application of common reactions of acetylenes to glycosylated acetylenes would obviously provide a starting point for the preparation of many novel carbohydrates and derivatives, the problem of glycosylating acetylenes was attempted again. However, in view of the reported lack of success with metal derivatives of acetylene itself,[5] phenylacetylene was selected first.

The procedures developed by Hurd and Bonner were applied to the coupling of one mole of tetraacetyl-α-D-glucopyranosyl bromide with twelve of phenylethynylmagnesium bromide. From the ether phase of the usual hydrolysis mixture methylbisphenylethynylcarbinol was recovered in good yield. Acetylation of the dehydrated aqueous phase and crystallization of the crude material from anhydrous alcohol or hydrocarbon solvent gave a levorotatory, crystalline compound, m.p. 134–135°, which we describe as anhydrous 1-phenyl-2-(tetraacetyl-β-D-glucopyranosyl)ethyne (I). Evaporation of the mother liquor left a dextrorotatory sirup which could not be crystallized.

Recrystallization of I or the crude product from wet isopropyl or 95% ethyl alcohol gave a different crystalline species (II), m.p. 125–126°. The specific rotations of I and II were identical, the two compounds were interconvertible by crystallization from suitable solvents such as benzene and even ethanol, and II was readily dried to yield I. All the analytical evidence supports designation of

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(1) This work was made possible by grant from the Research Corp.

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(3) C. D. Hurd and W. A. Bonner, *J. Am. Chem. Soc.*, **67**, 1664, 1972 (1945).

(4) W. A. Bonner, *Friedel-Crafts and Grignard Processes, Advances in Carbohydrate Chemistry*, Academic Press, Inc., New York City, 1951, Vol. 6, pages 251–289.

(5) C. D. Hurd and R. P. Holysz, *J. Am. Chem. Soc.*, **72**, 1732 (1950).

(6) Yu. A. Zhdanov, L. I. Shcherbakova, and T. N. Egorova, *Doklady Akad. Nauk S.S.S.R.*, **83**, 403 (1952); *Chem. Abstr.*, **47**, 2710 (1953).

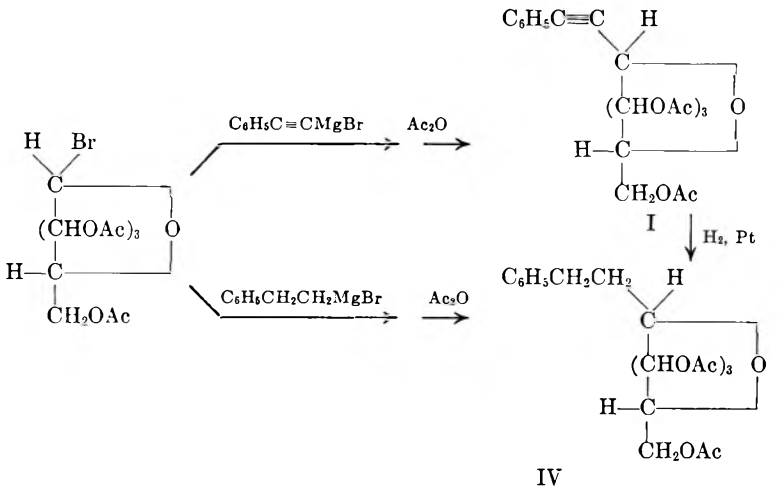
(7) Yu. A. Zhdanov and L. I. Shcherbakova, *Doklady Akad. Nauk S. S. S. R.*, **90**, 185 (1953); *Chem. Abstr.*, **48**, 5114 (1954).

(8) Yu. A. Zhdanov, L. I. Shcherbakova, and R. V. Golovnya, *Doklady Akad. Nauk S.S.S.R.*, **107**, 259 (1956); *Chem. Abstr.*, **50**, 15476 (1956).

(9) Yu. A. Zhdanov and G. F. Drofeenko, *Doklady Akad. Nauk S.S.S.R.*, **112**, 433 (1957).

(10) C. D. Hurd and R. P. Holysz, *J. Am. Chem. Soc.*, **72**, 2005 (1950).

(11) C. D. Hurd and R. P. Holysz, *J. Am. Chem. Soc.*, **72**, 1735 (1950).



II as $(C_{22}H_{24}O_9)_4 \cdot H_2O$, a stable hydrate of 1-phenyl-2-(tetraacetyl-β-D-glucopyranosyl) ethyne (I).

Deacetylation of I or of II was readily accomplished to yield 1-phenyl-2-(β-D-glucopyranosyl) ethyne. When this was recrystallized from 95% ethanol, it was collected as a hydrate or alcoholate, m.p. 122–122.5°, but vacuum drying left an anhydrous form (III), m.p. 142–143°. Both forms had very similar levorotation.

Deacetylation of the levorotatory sirup left by evaporation of the mother liquor from cystallization of I or II gave a non-crystallizable, dextrorotatory glass which undoubtedly contained the α-form of III.

Hydrogenation of 1-phenyl-2-(tetraacetyl-β-D-glucopyranosyl)ethyne hydrate (II) over platinum oxide formed 1-phenyl-2-(tetraacetyl-β-D-glucopyranosyl)ethane (IV) in almost quantitative yield. This was identical to the product obtained by reaction of the glucosyl bromide with 2-phenylethylmagnesium bromide and subsequent acetylation. By the usual deacetylation procedure it gave glassy 1-phenyl-2-(β-D-glucopyranosyl)ethane (V).

The glucosylated phenylethynes and phenylethanes described above have been designated alpha or beta according to their signs of rotation, alpha being the more dextrorotatory form in the D series.[12] On the basis of Bonner and Hurd's[13] degradation studies there is no reason to expect racemization or inversion of an asymmetric alcoholic carbon or change in ring size during glucosylation of Grignard reagents. Periodate oxidations[5,13,14] of glycosylated benzenes prepared in this manner also support retention of the pyranose ring. It may also be noted that the products obtained from either the alpha or beta glucosyl chloride are substantially identical.[5] Only in glucosylation of phenyllithium has evidence of inversion at an alcoholic carbon been found.[11]

With this demonstration that the acetylenic linkage itself was no barrier to glycosylation, experiments to glucosylate acetylene were conducted. Hurd and Holysz had obtained only tars from boiling acetobromoglucose with a suspension of sodium or lithium acetylide in toluene. By carrying out the coupling under milder conditions we have with difficulty obtained very low yields of a crystalline, strongly levorotatory acetate VI and a much less levorotatory sirup. The composition of the crystalline compound VI closely agreed with that calculated for tetraacetyl-β-D-glucopyranosylethyne (VII). However, catalytic reduction of VI over platinum oxide gave a dextrorotatory sirup which was not tetraacetyl-β-D-glucopyranosylethane (VIII). The latter was separately prepared from the glucosyl bromide and ethylmagnesium bromide and was obtained as a crystalline, levorotatory compound accompanied by a dextrorotatory sirup containing the anomer. It is clear, therefore, that the levorotatory solid VI was not tetraacetyl-β-D-glucopyranosylethyne (VII).

The structure of VI is unknown but it is probably a carbohydrate moiety containing an ethynyl group. It is possible that it differs from the expected ethyne VII only by inversion of one or more alcoholic carbons as has been suggested for an acetate resulting from glucosylation of phenyllithium.[11] However, other courses of reaction can be postulated such as the formation of 1,2-alkylidenetriacetylglucose from reaction of certain organocadmiums.[10] In any event, the physical constants of VI did not agree with those of any compound which could be formed by base-catalyzed elimination from the glucosyl bromide.

Attempts to couple tetraacetyl-α-D-glucopyranosyl bromide with ethynebis(magnesium bromide) in ethyl ether were no more successful than earlier work.[5] The usual reaction procedure gave only intractable tars.

(12) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909).
(13) W. A. Bonner and C. D. Hurd, *J. Am. Chem. Soc.*, **73**, 4290 (1951).
(14) W. A. Bonner and J. M. Craig, *J. Am. Chem. Soc.*, **72**, 348 (1950).

EXPERIMENTAL[15]

1-Phenyl-2-(tetraacetyl-β-D-glucopyranosyl)ethyne (I). A solution of 1.0 mole of phenylethynylmagnesium bromide was prepared by 30-min. addition of 105 g. (1.08 mole) of phenylacetylene in 150 ml. of anhydrous ether to isopropylmagnesium bromide. The latter was made from 33 g. (1.08 mole) of isopropyl bromide and 25.5 g. (1.05 g.-atom) of magnesium turnings in 350 ml. of anhydrous ether. After the phenylethynylmagnesium bromide solution was boiled for 30 min., heating was discontinued and 37 g. (0.09 mole) of tetraacetyl-α-D-glucopyranosyl bromide[16] in 400 ml. of anhydrous ether was added in one hour. The resultant mixture was heated under reflux with stirring for 6 hr. The ether layer was decanted and the gummy residue was decomposed by the cautious addition of water and a little acetic acid. The ether and aqueous phases were shaken together, filtered, and separated. The ether layer was washed with water, the water layer was washed with ether, and then the ether solutions were combined and the water solutions were combined.

Decolorization of the ether solution with Norit was followed by solvent removal under vacuum at 100°. The 98 g. of residue (89 g. theoretical) was recrystallized from benzene and petroleum ether to give 55 g. (63%) of methylbisphenylethynylcarbinol, m.p. 110–110.5°, identical with the literature value.[17]

The water layer was neutralized to litmus with 10% aqueous sodium hydroxide and evaporated under vacuum at 100°. The residue was stirred and heated at 100° with 200 ml. of acetic anhydride and 10 ml. of pyridine for 3 hr. Acetylation may be very rapid. The mixture was then poured into 200 ml. of ice and water and stirred for two hours before being extracted with ether. This was decolorized with Norit, filtered through infusorial earth and stripped of solvent under vacuum at 100° to leave 19 g. (49%) of a sirupy mixture. Crystallization from 110 ml. of isopropyl alcohol gave 12.7 g. (33%) of 1-phenyl-2-(tetraacetyl-β-D-glycopyranosyl)-ethyne hydrate (II), m.p. 125–126°, $[\alpha]_D^{25}$ −27.4 ($CHCl_3$, *c* 2).

Anal. Calcd. for $(C_{22}H_{24}O_9)_4 \cdot H_2O$: C, 60.47; H, 5.65; loss on drying at 125°, 1.03. Found: C, 60.39, 60.55; H, 5.48, 5.64; loss on drying, 1.00, 1.00.

Benzoic acid was recovered from the alkaline permanganate oxidation of II. When II was melted, cooled, and reheated, the new melting point of 134–135° was observed.

The mother liquor left from crystallization of II was vacuum dried to leave 6.0 g. of amber sirup, $[\alpha]_D^{24}$ +86.7, $[\alpha]_{5461}^{24}$ +101.3 ($CHCl_3$, *c* 2), presumably rich in the alpha anomer of I.

When either the hydrate II or the sirupy mixture was crystallized from anhydrous ethanol or benzene and petroleum ether, the product was anhydrous 1-phenyl-2-(tetraacetyl-β-D-glucopyranosyl)ethyne (I), m.p. 134–135°, $[\alpha]_D^{25}$ −28.7, $[\alpha]_{5461}^{25}$ −33.4 ($CHCl_3$, *c* 2).

Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 61.01, 61.09; H, 5.64, 5.71.

Crystallization from a solution of I in 95% isopropyl or ethyl alcohol gave the hydrate, II.

1-Phenyl-2-(β-D-glucopyranosyl)ethyne (III). A 4.0-g. sample of the hydrate II was boiled for 10 min. in 40 ml. of anhydrous methanol containing a small piece of potassium. After standing 40 hr., the solution was deionized by passage down a column of 50 g. of Amberlite IR-100 resin followed by 300 ml. of methanol. The combined methanol solution was stripped of solvent to give 2.4 g. (98%) of a hard glass. Five recrystallizations from 95% ethyl alcohol and ethyl ether gave a crystalline substance, m.p. 122–122.5°, $[\alpha]_D^{25}$ −6.3 (H_2O, *c* 4). After vacuum drying for 3 hr. at 100°, there was obtained anhydrous 1-phenyl-2-(β-D-glucopyranosyl)ethyne (III), m.p. 142–143°, $[\alpha]_D^{25}$ −5.6, $[\alpha]_{5461}^{25}$ −6.9 (H_2O, *c* 2).

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 63.62; H, 6.10. Found: C, 63.42; H, 6.34.

Similar deacetylation of the sirup rich in the α-anomer of I gave a noncrystallizable glass, $[\alpha]_D^{26}$ +34.7, $[\alpha]_{5461}^{26}$ +41.1 (H_2O, *c* 2).

1-Phenyl-2-(tetraacetyl-β-D-glucopyranosyl)ethane (IV). Catalytic reduction of 4.3 g. (0.01 mole) of the glucopyranosylethyne hydrate (II) with 0.1 g. of platinum oxide in 150 ml. of 95% ethanol at 40 p.s.i. and 25° resulted in the theoretical pressure drop. Separation of the catalyst and evaporation of two thirds of the alcohol caused crystallization of 4.2 g. (98%) of 1-phenyl-2-(tetraacetyl-β-D-glucopyranosyl)ethane (IV), m.p. 110.5–111°, $[\alpha]_D^{24}$ −26.4 ($CHCl_3$, c 2). A mixture with IV prepared by glucosylation *via* 2-phenylethylmagnesium bromide had a melting point of 111–112°.

Compound IV was also prepared by addition of 16.4 g. (0.04 mole) tetraacetyl-α-D-glucopyranosyl)bromide in 150 ml. of dry ether to the Grignard prepared from 89 g. (0.48 mole) of β-phenylethyl bromide and 11.3 g. (0.47 g. atom) of magnesium in 200 ml. of ether. Hydrolysis, evaporation of the aqueous phase, and heating the dry residue with 300 ml. (2.9 moles) of acetic anhydride and 20 g. of sodium acetate for 8 hr. at 100° gave by the usual procedure 11.6 g. (62%) of a sirupy mixture of anomers. Six recrystallizations from isopropyl alcohol gave 4.1 g. (35%) of IV, m.p. 111–112°, $[\alpha]_D^{27}$ −26.3 ($CHCl_3$, *c* 2).

Anal. Calcd. for $C_{22}H_{28}O_9$: C, 60.53; H, 6.46. Found: C, 60.57; H, 6.29.

Oxidation with permanganate formed benzoic acid.

Concentration in vacuum of the mother liquors left from crystallization of IV gave 7.5 g. of amber sirup, $[\alpha]_D^{25}$ +28.8 ($CHCl_3$, *c* 2) which could not be crystallized.

1-Phenyl-2-(β-D-glucopyranosyl)ethane (V). In exactly the same manner as described for deacetylation of the ethyne II to III, so the deacetylation of IV gave 1.3 g. (53%) of glassy 1-phenyl-2-(β-D-glucopyranosyl)ethane (V), $[\alpha]_D^{23}$ −33.5, $[\alpha]_{5461}^{23}$ −39.6 (H_2O, *c* 2). It could not be crystallized.

Deacetylation of the residue left by evaporation of the mother liquor from crystallization of IV also gave a noncrystallizable, hard glass, $[\alpha]_D^{25}$ +36.2 (H_2O, *c* 2).

Tetraacetyl-α-D-glucopyranosyl bromide and sodium acetylide. Fifteen hundred milliliters of liquid ammonia was saturated with acetylene, 23.5 g. (1.02 g.-atom) of sodium was added slowly with stirring. Then acetylene was passed through the solution as 34.8 g. (0.09 mole) of tetraacetyl-α-D-glucopyranosyl bromide in 500 ml. of dry ether was added with stirring in 1 hr. The mixture was stirred for 8 hr. and allowed to stand for 48 hr. as the ammonia boiled away. Then 500 ml. of benzene was added and followed by stirring with cautious addition of 200 ml. of acetic acid. The whole was taken to dryness by vacuum distillation from a water bath.[18] The residue was boiled and stirred with 200 ml. of acetic anhydride and 30 g. of sodium acetate for 5 hr. before being hydrolyzed in 400 ml. of ice water. This mixture was extracted with ether which was then washed with sodium bicarbonate solution, dried, and stripped of solvent in vacuum at 100°. There was left 12.6 g. (41.6%) of sirup which after three recrystallizations from isopropyl alcohol gave 1.3 g. (4.2%) of a crystalline product (VI), m.p. 183–185.5°, $[\alpha]_D^{25}$ −68.8 ($CHCl_3$, *c* 2).

Anal. Calcd. for $C_{16}H_{20}O_8$: C, 53.94; H, 5.66. Found: C, 54.06; H, 5.77.

(15) Microanalyses by Micro Tech Laboratories, Skokie, Ill.

(16) E. J. Bates, *Polarimetry, Saccharimetry and the Sugars*, United States Printing Office, Washington, D. C., 1942, p. 500.

(17) I. Iositsch, *J. Russ. Phys. Chem.*, **35**, 1273 (1903).

(18) In spite of repeated efforts, none of the expected but unknown by-product, methyl-bisethynylcarbinol, could be isolated. Nor has it been possible to synthesize it by other means.

For the first mother liquor there was obtained 2.7 g. (8.9%) of an amber, non-crystallizable sirup, $[\alpha]_D^{25}$ −1.0 ($CHCl_3$, *c* 2).

Various modifications of the glucosylation procedure were examined in the hopes of improving the yield, but all failed to give VI. These included increasing the mole ratio of sodium acetylide to acetobromoglucose to 18:1 and adding the latter as a solid to the liquid ammonia. Attempts were also made to obtain VI by boiling acetobromoglucose with sodium acetylide in ethyl ether or in benzene.

Catalytic reduction over platinum oxide at 25° and 40 p.s.i. of 0.30 g. of compound VI in 200 ml. of ethanol, followed by filtration and evaporation, gave a sirup $[\alpha]_D^{26}$ +38.2, $[\alpha]_{5461}^{26}$ +47.0 ($CHCl_3$, *c* 1.3.).

Tetraacetyl-β-D-glucopyranosylethane (VIII). By the general procedure described earlier 49 g. (0.12 mole) of tetraacetyl-α-D-glucosyl bromide in 600 ml. of ethyl ether was caused to react with the Grignard reagent prepared from 131 g. (1.2 moles) of ethyl bromide and 30 g. (1.2 g.-atom) of magnesium in 200 ml. of ether. After hydrolysis, distillation of the dried ether phase gave 34 g. (72%) of 3-methyl-3-pentanol, b.p. 121–122°, n_D^{22} 1.4170 (lit. b.p. 123°, n_D^{20} 1.4196).[19] The dry residue from stripping the aqueous phase was acetylated to give 10.5 g. (24%) of sirup which slowly crystallized. Recrystallization from isopropyl ether gave 3.1 g. (7.2%) of tetraacetyl-β-D-glucopyranosylethane (VIII), m.p. 91.5–92.5°, $[\alpha]_D^{25}$ −9.0, $[\alpha]_{5461}^{26}$ −10.5 ($CHCl_3$, *c* 2).

Anal. Calcd. for $C_{16}H_{24}O_9$: C, 53.32; H, 6.71. Found: C, 53.31; H, 6.75.

The mother liquors left from crystallization of VIII were stripped of solvent at 100° in a vacuum to leave 6.1 g. of amber, non-crystallizable sirup, $[\alpha]_D^{26}$ +12.2, $[\alpha]_{5461}^{26}$ +13.7 ($CHCl_3$, *c* 2).

CHICAGO 14, ILL.

(19) R. Henry, *Rec. Trav. Chim.*, 26, 94 (1907).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF AEROJET-GENERAL CORPORATION]

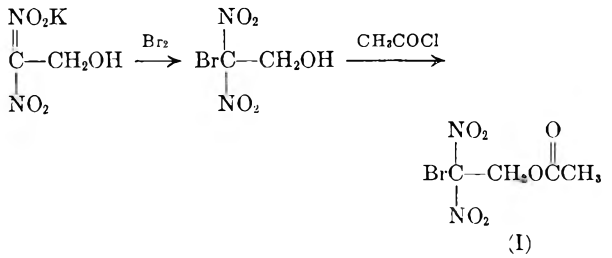
The Dinitroethylation Reaction[1]

MILTON B. FRANKEL

Received October 28, 1957

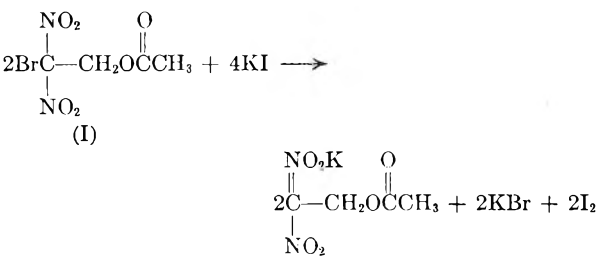
A new reaction has been discovered in the preparation of potassium 2,2,4,4-tetranitrobutyl acetate from 2-bromo-2,2-dinitroethylacetate (I) and potassium iodide. A mechanism is proposed in which 1,1-dinitroethylene is postulated as the reactive intermediate. The generality of this dinitroethylation reaction is indicated by the preparation of potassium 1,1,3,3-tetranitrobutane (VIII) and sodium 1,1-dinitro-2-phthalimidoethane (V) from I and the corresponding salts of 1,1-dinitroethane and phthalimide, respectively. Derivatives of VIII and V are reported.

In continuing the work on aliphatic *gem*-dinitro compounds in this laboratory,[2] attempts were made to prepare potassium 2,2-dinitroethyl acetate. One of the most promising methods for preparing this salt was from the corresponding bromo compound. 2-Bromo-2,2-dinitroethyl acetate (I) was made in an unequivocal manner from potassium 2,2-dinitroethanol.



(I)

It was expected that treatment of 2-bromo-2,2-dinitroethyl acetate with potassium iodide would produce potassium 2,2-dinitroethyl acetate. An analogous reaction was reported by Meisenheimer,[3] who converted 2-bromo-2,2-dinitro-1-ethoxyethane to the corresponding potassium salt by the use of potassium iodide. Klager[4] generalized this procedure and showed that compounds with terminal bromodinitromethyl groups react quantitatively with potassium iodide; the amount of iodine formed corresponds to the theoretical amount of bromine present in the molecule. However, treatment of I with potassium iodide did not give the expected potassium 2,2-dinitroethyl acetate, but a new salt was produced in 64% yield whose analysis was in agreement with potassium 2,2,4,4-tetranitrobutyl acetate (II). Acidification of this salt with dilute sulfuric acid gave a compound whose analysis and neutral equivalent were in agreement with 2,2,4,4-tetranitrobutyl acetate (III). The formation of potassium 2,2,4,4-tetranitrobutyl acetate can be explained as shown in the following equations:



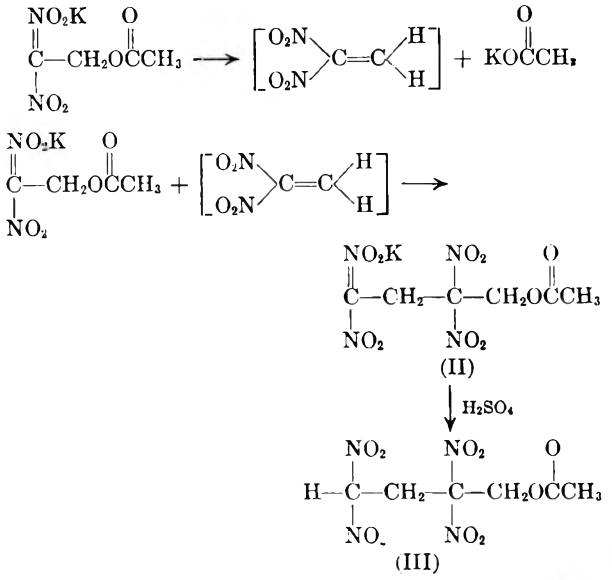
(I)

(1) Presented before the Division of Organic Chemistry at the 133rd meeting of the American Chemical Society, April 13–18, 1958, San Francisco, Calif.

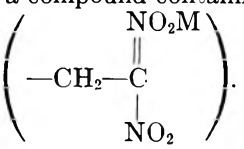
(2) L. Herzog, M. H. Gold, and R. D. Geckler, *J. Am. Chem. Soc.*, **73**, 749 (1951).

(3) J. Meisenheimer, *Ber.*, **36**, 437 (1903).

(4) K. Klager, *Anal. Chem.*, **23**, 534 (1951).

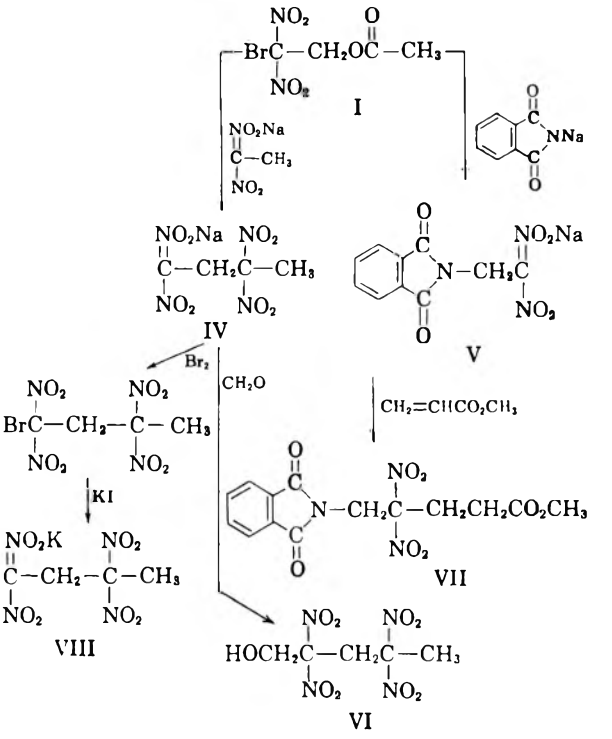


All attempts to isolate potassium 2,2-dinitroethyl acetate were unsuccessful. This indicates that potassium 2,2-dinitroethyl acetate is not stable under such conditions and probably decomposes into 1,1-dinitroethylene and potassium acetate. Since 1,1-dinitroethylene also was not isolated, presumably because of its high reactivity, it must have been present as a transitory intermediate, capable of undergoing a Michael condensation with potassium 2,2-dinitroethyl acetate to form potassium 2,2,4,4-tetranitrobutyl acetate.[5]

If these assumptions are valid, then the metallic salts of a variety of organic and inorganic compounds which are weak acids are capable of reacting with 2-bromo-2,2-dinitroethyl acetate. One mole of the salt would liberate 1,1-dinitroethylene which would immediately condense with a second mole of the salt, forming a compound containing a dinitroethyl grouping  . Several examples of this general reaction were realized. When potassium iodide was replaced with the salt of an organic nitro compound or a phthalimide salt, the corresponding salts containing the dinitroethyl grouping were formed. Thus, treatment of I with sodium 1,1-dinitroethane and sodium phthalimide yielded the corresponding salts of 1,1,3,3-tetranitrobutane (IV) and 1,1-dinitro-2-phthalimidoethane (V).

This evidence indicates that the process of dinitroethylation is a general type of reaction, with 2-bromo-2,2-dinitroethyl acetate functioning as a source of 1,1-dinitroethylene which can participate in a Michael type of reaction with other compounds.

(5) L. Zeldin and H. Shechter, *J. Am. Chem. Soc.*, **79**, 4708 (1957), recently reported that the reaction of 1,1,1-trinitroethane with certain bases caused elimination of nitrous acid to give 1,1-dinitroethylene, a reactive intermediate, which underwent addition of the base to yield β-substituted derivatives of 1,1-dinitroethane.



In the reactions of 2-bromo-2,2-dinitroethyl acetate (I), both the sodium and potassium salts of the organic compounds were used. The sodium salts gave higher yields because of their greater solubility; however, the potassium salts of the products were more readily isolated and purified. Thus, treatment of I with sodium 1,1-dinitroethane gave sodium 1,1,3,3-tetranitrobutane (IV) which was difficult to purify, so it was brominated and then treated with potassium iodide to give potassium 1,1,3,3-tetranitrobutane (VIII), which was easily crystallized.

The salts formed in the Michael condensation can react further as illustrated in the preparation of 2,2,4,4-tetranitro-1-pentanol (VI) from IV and formaldehyde and also methyl 4,4-dinitro-5-phthalimidopentanoate (VII) from V and methyl acrylate.

EXPERIMENTAL[6,7]

2-Bromo-2,2-dinitroethyl acetate (I). A slurry of 215 g. of damp potassium 2,2-dinitroethanol[2] (equivalent to 1 mole of dry salt) and 500 ml. of water was cooled to 0° and 176 g. (1.1 mole) of bromine was added during a 40 min. period. The reaction mixture was extracted 4 times with 100 ml. portions of ether. The ether extracts were combined, washed twice with water, and dried over sodium sulfate overnight at 0°. The ether solution was concentrated and distilled from a Claisen flask at 88–93° (2 mm.). The distillate, 2-bromo-2,2-dinitroethanol, was a white mushy solid which liquefied on contact with moist air. It was treated directly with a solution of 86 g. (1.1 mol.) of acetyl chloride in 500 ml. of dry chloroform. The solution was refluxed for 3.5 hr., the solvent was evaporated under reduced pressure leaving a light yellow liquid which was distilled from a Claisen

(6) All melting points are uncorrected.

(7) Microanalyses by Elek Micro Analytical Laboratories, Los Angeles, Calif.

flask. The overall yield of 2-bromo-2,2-dinitroethyl acetate was 193.4 g. (75%), b.p. 70–71°/0.35 mm., n_D^{25} 1.4728.

Anal. Calcd. for $C_4H_5N_2O_6Br$: Br, 31.10; N, 10.90. Found: Br, 30.96; N, 10.59.

Potassium 2,2,4,4-tetranitrobutyl acetate (II). A solution of 25.7 g. (0.10 mole) of 2-bromo-2,2-dinitroethyl acetate in 100 ml. of methanol was cooled to 0° and a solution of 83 g. (0.50 mole) of potassium iodide in 150 ml. of 50% methanol was added dropwise. The purple reaction mixture was filtered and the yellow solid was washed thoroughly with ether to remove the iodine liberated in the reaction. The yield of potassium 2,2,4,4-tetranitrobutyl acetate was 24.0 g. (equivalent to 21.5 g. or 64.5% of dry salt). The salt was recrystallized 3 times from water, m.p. 174° explodes.

Anal. Calcd. for $C_6H_7N_4O_{10}K$: C, 21.56; H, 2.11; N, 16.76. Found: C, 21.89; H, 2.27; N, 16.67.

2,2,4,4,-Tetranitrobutyl acetate (III). A slurry of 12 g. (0.035 mole) of potassium 2,2,4,4-tetranitrobutyl acetate and 150 ml. of water was cooled to 0° and a solution of 5 ml. of concentrated sulfuric acid in 30 ml. of water was added. At the end of the addition the reaction mixture turned from orange to yellow. Stirring was continued for another hour and the reaction mixture was filtered. The cream colored solid was collected, washed well with water, and air dried. The yield of 2,2,4,4-tetranitrobutyl acetate was 7.0 g. (67.5%), m.p. 57–58°. The product was recrystallized twice from ethyl chloride at −70° to give a white crystalline solid, m.p. 58–59°.

Anal. Calcd. for $C_6H_8N_4O_{10}$: C, 24.33; H, 2.72; N, 18.92; neut. equiv., 296. Found: C, 24.62; H, 2.89; N, 18.50; neut. equiv., 297, 298.

Potassium 1,1,3,3-tetranitrobutane (VIII). 1,1-Dinitroethane,[8] 12.0 g. (0.10 mole), was cooled in an ice bath and a solution of 4.2 g. (0.10 mole) of 95% sodium hydroxide in 30 ml. of water was added. Then a solution of 12.85 g. (0.05 mole) of 2-bromo-2,2-dinitroethyl acetate in 25 ml. of methanol was added dropwise while the sodium 1,1-dinitroethane solution was maintained at 10°. Stirring was continued while the solution warmed to room temperature. The reaction mixture was extracted with ether to remove any starting material. The aqueous layer was cooled to 5° and treated with 8.0 g. (0.05 mole) of bromine. The solution was extracted with ether, dried, and concentrated to give 4.4 g. of 1-bromo-1,1,3,3-tetranitrobutane. One and seven-tenths g. of this orange liquid was dissolved in 3 ml. of methanol and cooled to 0°, then a solution of 1.78 g. of potassium iodide in 6 ml. of 50% methanol was added. The purple reaction mixture was filtered and the yellow salt was washed with ether, wt. 1.0 g. The salt was recrystallized 3 times from ethanol, m.p. 137–138° dec.

Anal. Calcd. for $C_4H_5N_4O_8K$: C, 17.39; H, 1.83; N, 20.29. Found: C, 17.71; H, 1.83; N, 20.69.

2,2,4,4-Tetranitro-1-pentanol (VI). 1,1-Dinitroethane, sodium hydroxide, and 2-bromo-2,2-dinitroethyl acetate were treated in the same amounts and in the same manner as above. The reaction mixture was extracted with ether to remove any unreacted starting material. At room temperature, 4.1 g. of 37% formalin was added to the aqueous layer, the solution was stirred for 1 hr., and 3 g. of glacial acetic acid was added dropwise. The orange solution was extracted 3 times with ether, the ether extracts were combined, washed with water, dried, and concentrated leaving 2.5 g. of a yellow liquid. The liquid was heated in a bulb tube at 70–110° (1 micron), 0.5 g. of the liquid distilled leaving a viscous yellow liquid which solidified. This residue was recrystallized from carbon tetrachloride to give 0.3 g. of a white crystalline solid, m.p. 66–67°.

Anal. Calcd. for $C_5H_8N_4O_9$: C, 22.40; H, 3.01; N, 20.90. Found: C, 22.44; H, 2.87; N, 21.31.

Sodium 1,1-dinitro-2-phthalimidoethane (V). To a solution of 110.0 g. (0.65 mole) of sodium phthalimide in 500 ml. of 60% methanol, at room temperature, was added a solution of 83.7 g. (0.325 mole) of 2-bromo-2,2-dinitroethyl acetate in 150 ml. of methanol. A yellow solid separated in about 5 min.; stirring was continued for an additional 30 min. The yellow solid was collected, washed with ether, and air dried. The yield of sodium 1,1-dinitro-2-phthalimidoethane was 60.0 g. (64.3%), m.p. 238° explodes.

Methyl 4,4-dinitro-5-phthalimidopentanoate (VII). A mixture of 3.0 g. (0.01 mole) of sodium 1,1-dinitro-2-phthalimidoethane, 30 ml. of water, and 2.6 g. (0.03 mole) of methyl acrylate was heated at 50° for 3.5 hr.; the solid dissolved and an oil separated. On cooling, the oil solidified, and the tan solid was collected and dried. The yield of methyl 4,4-dinitro-5-phthalimidopentanoate was 1.7 g. (48.4%), m.p. 107–113°. The product was recrystallized 3 times from absolute ethanol to give a white crystalline solid, m.p. 113–115°.

Anal. Calcd. for $C_{14}H_{13}N_3O_8$: C, 47.87; H, 3.73; N, 11.96. Found: C, 47.95; H, 3.74; N, 12.12.

Acknowledgment. We are indebted to the Office of Naval Research for the financial support of this work.

(8) E. ter Meer, *Ann.*, **181**, 1 (1876).

AZUSA, CALIF.

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

Derivatives of Nitromethylamine. II. Nitromethyl Imides[1]

L. W. KISSINGER AND H. E. UNGNADE

Received December 26, 1957

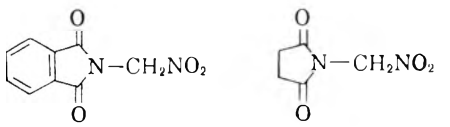
N-Nitromethylphthalimide and *N*-nitromethylsuccinimide have been prepared from the corresponding *N*-bromomethyl imides and silver nitrite in acetonitrile. The new imides are crystalline solids which are stable at temperatures up to their melting points. They react with bases by displacement of the nitro group and decompose on heating with acids to mixtures from which nitromethylamine could not be isolated.

In the course of further investigations of nitromethylamine derivatives in this laboratory,[2] it has been found that *N*-nitromethyl imides can be prepared in fairly good yield by the reaction of *N*-bromomethyl imides with silver nitrite in aceto-

(1) (a) This work was performed under the auspices of the U. S. Atomic Energy Commission. (b) Presented before the Organic Section of the American Chemical Society at the 133rd Meeting, San Francisco, Cal., April 1958.

(2) Paper I: H. E. Ungnade and L. W. Kissinger, *J. Org. Chem.*, **22**, 1662 (1957).

nitrile. In this fashion *N*-nitromethylphthalimide (I) and *N*-nitromethylsuccinimide (II) have been prepared from the corresponding *N*-bromomethyl compounds. Both are accompanied by the *N*-hydroxymethyl imides which are assumed to derive



I II

from the unstable nitrite esters, formed simultaneously with the nitro compounds by the action of silver nitrite on the *N*-bromomethyl imides. Under the usual conditions of the Victor Meyer reaction *N*-bromomethylphthalimide gives only a 2% yield of compound I. The reaction is heterogeneous in ether and furnishes as main products nitrogen oxides and bisphthalimidomethyl ether, arising from *N*-hydroxymethylphthalimide and unchanged bromo compound.

The spectral characteristics of the imides I and II agree well with the assigned structures. Two bands in the C=O stretching region, a strong band near 5.75μ and a band of medium intensity near 5.60μ correspond to similar bands in related imides[3] (Table I). Additional bands near 6.30μ and 7.30μ are assigned to *asym.* and *sym.* stretching vibrations of the nitro group and fall within the ranges characteristic of mononitro compounds.[4] In the ultraviolet, the nitromethyl imide I shows an increased absorption compared to phthalimide in the region of 260–280 mμ, where nitroparaffins absorb. In the case of *N*-nitromethylsuccinimide (II) a discrete band without fine structure is observed in ethanol (λ_{max} 276 mμ, log ϵ 1.57), which is shifted toward the blue in alcoholic hydrochloric acid (λ_{max} 272 mμ, log ϵ 1.57), does not occur in succinimide, and is characteristic of nitroparaffins.[5]

TABLE I

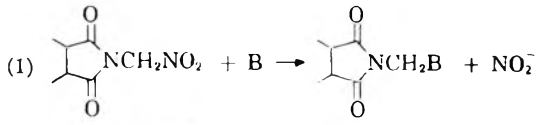
INFRARED ABSORPTION BANDS FOR SUBSTITUTED IMIDES[a]

Compound	λ, μ	λ, μ
Phthalimide	5.56	5.70
N-Hydroxymethylphthalimide	5.58	5.75
N-Bromomethylphthalimide	5.59	5.74
N-Methoxymethylphthalimide	5.57	5.76
N-Ethoxymethylphthalimide	5.56	5.74
N-Nitromethylphthalimide	5.60	5.73
N-Piperidinomethylphthalimide	5.62	5.81
N-Acetylphthalimide	5.50	5.62
Succinimide	5.63	5.78
N-Hydroxymethylsuccinimide	5.57	5.80
N-Bromomethylsuccinimide	5.52	5.78
N-Methoxymethylsuccinimide	5.62	5.83
N-Ethoxymethylsuccinimide	5.62	5.83
N-Nitromethylsuccinimide	5.57	5.75
N-Piperidinomethylsuccinimide	5.62	5.84

[a] Determined in chloroform solution

Several attempts were made to hydrolyze these *N*-nitromethyl imides to nitromethylamine ($NO_2CH_2NH_2$). Under conditions sufficiently mild to avoid the conversion of mononitro aliphatics to the corresponding hydroxamic or carboxylic acids,[6] for example room temperature and aqueous or ethanolic 1 : 1 concentrated hydrochloric acid, no reaction is observed with I or II. On boiling, the same reagents rapidly decompose the imides to phthalic (and succinic) acid, ammonium chloride, oxides of nitrogen, and some formaldehyde. The alternate hydrolysis procedure for phthalimide with hydrazine[7] yields, from I, formaldehyde and, after the hydrochloric acid treatment,[7] phthalic acid.

Other bases react with the *N*-nitromethyl imides with elimination of nitrite ion, even under mild conditions. Thus I gives a quantitative yield of nitrite ion at 0° with sodium methoxide in methanol. Hydroxide ion and piperidine also displace nitrite ion from I and II and, in each case, the substituted methylimide is formed. This is pictured (Equation 1) as a nucleophilic displacement of a nitro group on carbon, which is rarely observed with mononitro compounds.



(B = $\bar{O}H$, $\bar{O}CH_3$, or $C_5H_{11}N$)

Anhydrous ammonia reacts only slowly with I in ether to form a complex which still contains the nitro group. On prolonged standing the complex decomposes with the formation of nitrite ion and other unidentified products. Attempts to brominate the complex have led only to degradation of the compound to phthalimide.

The *N*-nitromethyl imides are stable at their respective melting points, in boiling inert solvents and in boiling alcohols (in contrast with the corresponding bromomethyl imides which are solvolyzed by the alcohols).

EXPERIMENTAL[8]

N-Bromomethylphthalimide. *N*-Hydroxymethylphthalimide, prepared by heating of phthalimide and formalin,[9] was converted to the bromo compound, m.p. 146–148°, by

(3) W. G. Roderick and W. A. Brown, *J. Am. Chem. Soc.*, 79, 5196 (1957).

(4) N. Kornblum, H. E. Ungnade, and R. A. Smiley, *J. Org. Chem.*, 21, 377 (1956) and references cited therein.

(5) H. E. Ungnade and R. A. Smiley, *J. Org. Chem.*, 21, 993 (1956) and references cited therein.

(6) H. B. Hass and E. F. Riley, *Chem. Revs.*, 32, 395 (1943).

(7) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).

(8) All temperatures uncorrected. Analyses by M. J. Naranjo and C. A. Esquibel.

(9) M. B. Winstead and H. W. Heine, *J. Am. Chem. Soc.*, 77, 1913 (1955).

refluxing with phosphorus tribromide and benzene;[10] yield 82%.

N-Nitromethylphthalimide (I). A. *Victor Meyer procedure.*[11] A suspension of 24 g. (0.1 mole) of N-bromomethylphthalimide in 50 ml. of anhydrous ether was added slowly to a stirred mixture of 23.1 g. (0.15 mole) of silver nitrite and 50 ml. of ether at 0°. The bromo compound was completely transferred to the reaction flask by rinsing with 50 ml. of ether and the entire mixture was stirred at 0° for 17 hr., then at room temperature for 72 hr. The ether solution was filtered under nitrogen pressure and the remaining salts were washed with ether. Distillation of the combined ether solutions gave 6.5 g. of yellow oil which solidified on cooling. The oil was digested with ether. The ether-insoluble solid melted at 140–142° after crystallization from benzene–petroleum ether (yield 1.4 g., 8%), and was identified as hydroxymethylphthalimide by its infrared spectrum and mixed melting point with an authentic specimen. The ether digest was freed from solvent, taken up in benzene, and adsorbed on F-20 (Alcoa) alumina. The column was eluted successively with benzene and ether. The first 150 ml. of benzene eluate contained 0.8 g. (4%) of colorless solid, m.p. 75–80° (from benzene–petroleum ether), which was identified as *N*-ethoxymethylphthalimide by its infrared spectrum and mixed melting point (79–85°) with the authentic ether (m.p. 84–85°).[12,13] The remaining 300 ml. of benzene eluate furnished *N*-nitromethylphthalimide, obtained as a yellow oil (0.45 g., 2%), which was crystallized from benzene-hexane to a constant m.p. of 110.5–111°. Its major absorption bands were: λ (C=O) 5.60, 5.73 μ; λ (NO_2) 6.32, 7.33 μ; λ_{max} (EtOH) 236 mμ (log ε 3.92); λ_{max} 294 mμ (log ε 3.27); shoulder 300 mμ (log ε 3.26).

Anal. Calcd. for $C_9H_6N_2O_4$: C, 52.44; H, 2.93; N, 13.59. Found: C, 52.70, 52.77; H, 2.86, 3.13; N, 13.51.

The main ether eluate yielded phthalimide (1.3 g., 9%) and the last portion 0.9 g. (5%) of bisphthalimidomethyl ether, m.p. 205–207° (lit. m.p. 207°).[12]

Anal. Calcd. for $C_{18}H_{12}N_2O_5$: C, 64.29; H, 3.59; N, 8.33. Found: C, 64.21; H, 3.49; N, 8.21.

Continued extraction of the silver salts with several portions of ether and with benzene gave a total of 8.7 g. (52%, of bisphthalimidomethyl ether, m.p. 205–207°, leaving 26.0 g. of silver salts (0.1 mole of silver bromide + 0.05 mole of nitrite = 26.5 g.).

B. *Reaction in acetonitrile.* *N*-Bromomethylphthalimide (24 g., 0.1 mole) in 130 ml. of acetonitrile was added slowly, with stirring, to a suspension of silver nitrite (16.9 g., 0.11 mole) in 50 ml. of acetonitrile. The mixture was stirred at 0° for 20 hr. and at room temperature for 20 hr. The precipitated silver bromide was filtered with suction, washed with acetonitrile, and dried, yield 19.0 g. (theory 18.8 g.). The filtrate was diluted with 3 volumes of water and the separated oil was taken up in ether. The ether solution was washed with water and distilled to remove the solvent. The residue was dried by adding 100 ml. of benzene and collecting the water in a Dean-Stark trap. The benzene-insoluble solid, m.p. 149–150°, weighed 1.6 g. (9%) and was identified as hydroxymethylphthalimide. The benzene solution was chromatographed on F-20 (Alcoa) alumina and the reaction products were eluted successively with benzene and ether. The fractions with similar infrared spectra were combined and recrystallized from benzene or benzene-hexane. In this fashion there was obtained 5.5 g. (27%) of *N*-nitromethylphthalimide, 6.8 g. (38%) of *N*-hydroxymethylphthalimide, and 1.3 g. (9%) of phthalimide.

N-Nitromethylphthalimide is a colorless solid which burns with luminous flame. It is stable in boiling methanol, from which it crystallizes in needles, and it is thermally stable at its melting point.

Hydrolysis of N-nitromethylphthalimide (I) *with hydrochloric acid.* *N*-Nitromethylphthalimide (1.6 g., 0.0078 mole) was unaffected by cold 1:1 hydrochloric acid (50 ml.). On refluxing of the mixture for one hr., the solid went partially into solution while oxides of nitrogen were evolved. The aqueous solution was allowed to cool. After shaking with benzene, phthalic acid [1.1 g., 85%, m.p. 226–227° (dec.)] crystallized, which was identified by its infrared spectrum. Evaporation of the benzene extract furnished unchanged starting material (0.2 g., 12%). The aqueous filtrate was distilled under reduced pressure into a Dry Ice trap. The distillate gave a positve test for formaldehyde with sodium 1,8-dihydroxynaphthalene-3,6-sulfonate. The solid residue (0.4 g.) contained ammonium chloride, identified as an ammonium salt, by adding 1 ml. of 50% potassium hydroxide, drying the gas over ascarite, and determination of its infrared spectrum.

Hydrolysis of N-nitromethylphthalimide (I) *with hydrazine.* *N*-Nitromethylphthalimide (1.5 g., 0.0072 mole), suspended in 10 ml. of 95% ethanol, was treated with hydrazine (64%, 0.1 ml., 0.02 mole). The imide went into solution with yellow color when the mixture was heated on the steam bath for 1 hr. A trace of starting material was filtered off, the filtrate was poured into excess water and extracted with benzene. On treatment with dimedone, the aqueous solution yielded formaldimethone (0.3 g., 14%), m.p. 191–193°. The benzene extract contained a yellow oil which gave phthalic acid (0.9 g., 75%) on hydrolysis with concentrated hydrochloric acid.

Reaction of N-nitromethylphthalimide (I) *with sodium methoxide.* A solution of *N*-nitromethylphthalimide (1.6 g., 0.0078 mole) in 100 ml. of methanol was added with ice cooling to a solution of sodium, (0.23 g., 0.01 g.-atom) in 50 ml. of methanol. Immediately after the addition, a 1-ml. sample was withdrawn, quenched with 5 ml. of glacial acetic acid, and treated with 5 ml. of a solution of sulfanilic acid (1.0 g.) in 1:10 aqueous hydrochloric acid (100 ml.). After 10 min., 5 ml. of a solution of α-naphthol (1.0 g.) and sodium acetate (1.0 g.) in 50% aqueous acetic acid (100 ml.) was added, the mixture was allowed to stand for 30 min., diluted, and its absorbance determined spectrophotometrically. Other samples, withdrawn after 0.5, 1.5, and 3.0 hr. at room temperature, all had the same absorbance at 475 mμ, corresponding to complete conversion of the nitro group to nitrite ion by comparison with a series of standard solutions.

When *N*-nitromethylphthalimide (0.8 g., 0.0039 mole) was allowed to stand with sodium methoxide (0.005 mole) in methanol (75 ml.) at 25° for 30 min., *N*-methoxymethylphthalimide was isolated in 82% yield. The solution was evaporated under reduced pressure, the residue extracted with hot benzene and crystallized from benzene-hexane. Melting point and mixed melting point with *N*-methoxymethylphthalimide 122–123°.

Reaction with ammonia. When ammonia gas was passed into a solution of 1.0 g. (0.0048 mole) of *N*-nitromethylphthalimide in 100 ml. of ethyl ether, an oil separated, which on standing solidified to a waxy solid, m.p. 100–150° (dec.). This material still contained a nitro group [λ(NO_2) 6.33 μ], had imide C=O bands, and was therefore regarded as an ammonia complex. It was dissolved in 50 ml. of ethanol and brominated with 0.9 g. of bromine. The mixture was diluted with 125 ml. of water and allowed to stand for 12 hr. The aqueous solution gave a positive test for formaldehyde and nitrite ion. Extraction with 5 × 50 ml. of benzene gave 0.6 g. (84%) of phthalimide.

Reaction with piperidine. Piperidine (0.17 g., 0.002 mole) was added to a solution of *N*-nitromethylphthalimide (0.206 g., 0.001 mole) in 10 ml. of 95% ethanol and the mixture was refluxed for 1 hr. The yellow solution was evaporated to dryness leaving 0.35 g. of brown solid residue which was taken

(10) O. Mancera and O. Lemberger, *J. Org. Chem.*, **15**, 1253 (1950).

(11) N. Kornblum, B. Taub, and H. E. Ungnade, *J. Am. Chem. Soc.*, **76**, 3209 (1954).

(12) F. Sachs, *Ber.*, **31**, 1230 (1898).

(13) The formation of *N*-ethoxymethylphthalimide is accounted for by the reaction of the *N*-bromomethyl imide with the ethanol contained in the solvent ether.

up in methylene chloride, washed with water, dried, and freed from solvent. The aqueous washings gave a strong nitrite test. The organic residue was sublimed at 120° (7 mm.) and the sublimate digested with hexane-benzene. The insoluble portion (0.006 g.) was identified as phthalimide by mixed melting point and infrared spectrum. The digest deposited colorless needles (0.01 g.) which after vacuum sublimation gave *N*-piperidinomethylphthalimide, identical with authentic material (m.p. 117–118°)[12] in infrared spectrum and R_f value. A persistent oily impurity, believed to be bis-methylenepiperidine, lowered the m.p. to 108°.

N-Bromomethylsuccinimide. *N*-Bromomethylsuccinimide can be prepared in 92% yield by action of phosphorus tribromide on *N*-hydroxymethylsuccinimide,[14] which in turn is available from succinimide in 52% yield. A much higher over-all yield (91%) was obtained by running these reactions without isolating the hydroxymethyl compound, as follows:

Succinimide (25 g., 0.25 mole) was refluxed with 25 ml. of 37% formalin for 4 hr. on a steam bath. Benzene (150 ml.) was then added and the water removed by distillation of the azeotrope. To the dry benzene solution was added 30.6 g. (0.11 mole) of phosphorus tribromide and the mixture was refluxed for 1.5 hr. The benzene solution was decanted and the residue was boiled with 25 ml. of benzene. The combined benzene solutions were distilled to remove the solvent. The residual oil (48 g.) was distilled under reduced pressure. The distillate, b.p. 128–130° (1 mm.), yield 44 g. (91%), solidified on cooling, m.p. 60–63° (lit. m.p. 63–64°).[14]

N-Nitromethylsuccinimide (II). A suspension of 33.8 g. (0.22 mole) of silver nitrite in 100 ml. of acetonitrile was added to a stirred solution of 38.4 g. (0.2 mole) of *N*-bromomethylsuccinimide and 2 g. of urea in 100 ml. of acetonitrile at 0°. The silver nitrite was completely transferred by use of another 100 ml. of acetonitrile, and the mixture was stirred at 0° for 22 hr. and at room temperature for 5 hr. The precipitated silver bromide was filtered, washed with acetonitrile, and dried, yield 36.9 g. (98%). The filtrate was distilled from a steam bath to remove acetonitrile, the last traces under reduced pressure. The oily residue was taken up in hot benzene (75 ml.) and the benzene solution was adsorbed on acid-washed alumina (Merck). The benzene eluates from the alumina column gave 17.3 g. (55%) of pale yellow oil which solidified on cooling, was crystallized from benzene-hexane, and melted at 86–87°. It had the following absorption bands: λ (NO_2) 6.34, 7.36 μ; λ_{max} (EtOH) 276 mμ; log ϵ 1.57.

Anal. Calcd. for $C_5H_6N_2O_4$: C, 37.99; H, 3.82; N, 17.72. Found: C, 38.57; H, 3.77; N, 17.48, 17.71.

When the alumina column was eluted successively with ether and acetone, viscous oils were obtained in yields of 7.2 g. (28%) with the infrared spectrum of *N*-hydroxymethylsuccinimide. The combined oils were crystallized from benzene and melted at 60–65°, lit. m.p. 63–64°.[14]

Reaction of N-nitromethylsuccinimide with sodium methoxide. *N*-Nitromethylsuccinimide (0.40 g., 0.0025 mole) was dissolved in a solution of sodium (0.0644 g., 0.0028 g.-atom) in methanol (7 ml.). The pale yellow mixture was allowed to stand at room temperature for 3 hr. Then it was evaporated under reduced pressure. The residual colorless oil which was extracted with methylene chloride weighed 0.25 g. (70%). It boiled at 70° (0.1 mm.) and was identical with authentic material prepared by reaction of *N*-bromomethylsuccinimide with sodium methoxide, b.p. 70° (0.1 mm.), n_D^{25} 1.4813.

Anal. Calcd. for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.78. Found: C, 50.73; H, 6.19; N, 9.52, 10.14.

Reaction of nitromethylsuccinimide with piperidine. A solution of piperidine (1.53 g., 0.0188 mole) in 95% ethanol (5 ml.) was added to a suspension of nitromethylsuccinimide (1.42 g., 0.00898 mole) in 25 ml. of ethanol. After 10 min. of mechanical shaking at room temperature, the imide had dissolved. The pale yellow solution was allowed to stand at 25° for 1 hr. and evaporated under reduced pressure. The crude yellow oil (3.39 g.) was dissolved in benzene and adsorbed on acid-washed alumina. The benzene and ether eluates contained only traces of product but the subsequent acetone eluate furnished 1.2 g. of yellow oil which gave a colorless solid, m.p. 95–97°, after two sublimations at 0.01 mm. Tenaciously adhering impurities were removed by crystallization from benzene–petroleum ether. The resulting colorless needles (m.p. 104–105°) did not depress the melting point of authentic *N*-piperidinomethylsuccinimide (m.p. 104–105°), prepared from *N*-bromomethylsuccinimide and piperidine, lit. value, m.p. 106–107°.[14]

Hydrogenation of N-nitromethylsuccinimide. *N*-Nitromethylsuccinimide (1.58 g., 0.01 mole), dissolved in 100 ml. of 95% ethanol, was shaken with platinum catalyst (0.2 g.) and hydrogen under 10-mm. pressure. The required amount of hydrogen (0.03 mole) was taken up in 13 hr. The colorless solution was filtered and evaporated, leaving 1.5 g. of oil which was identified as a mixture of starting material and phthalimide.

Absorption spectra. Ultraviolet absorption spectra were determined with a Beckman Model DR spectrophotometer, 1-cm. silica cells, and 1×10^{-3} to 1×10^{-5} molar solutions.

A solution of *N*-nitromethylsuccinimide (II) in 1:1 ethanol-concentrated hydrochloric acid was examined at 272 mμ as a function of time. The broad maximum decreased 0.7% in intensity after 6 hr. and 12% after 26 hr. at 25 ± 1°. At reflux temperature (75°/580 mm.) the decrease was 79% in 2 hr.

Infrared absorption spectra were obtained in solution in matched cells or in capillary films with a Perkin Elmer model 21 instrument.

Los Alamos, N. M.

(14) E. Cherbuliez and G. Sulzer, *Helv. Chim. Acta*, **8**, 568 (1925).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

Reaction of Cyanogen with Organic Compounds. XI. Amino Alcohols[1]

HENRY M. WOODBURN AND EDMOND L. GRAMINSKI[2]

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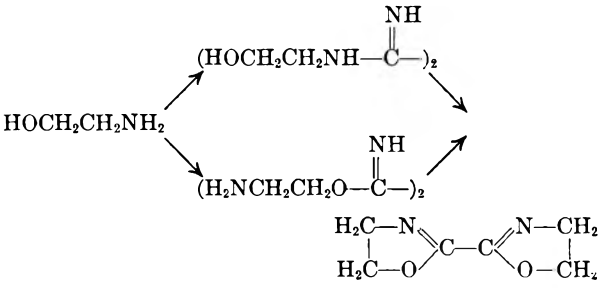
Amino alcohols react with cyanogen to produce oxamidines or oxaldiimidates depending upon the reaction medium. *N*-alkyl- and *N*-dialkylamino alcohols produce only diimidates. Aminoethers produce oxamidines. No evidence for the intermediate formation of cyanoformimidates or cyanoformamidines could be found.

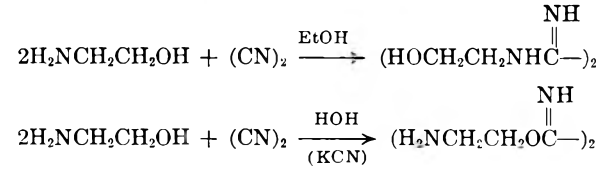
In previous papers of this series[3-5] we have discussed the reaction of cyanogen with bifunctional compounds containing NH_2 and SH groups. The commercial availability of several substituted and unsubstituted amino alcohols made these compounds attractive for an extension of this work. Furthermore, while information on the behavior of alcohols is scanty,[6,7] the indications are that conditions under which the aliphatic OH group will react with cyanogen are quite different from those required for the NH_2 group. Thus, there should be an opportunity to favor the reaction of one group over the other by controlling the conditions of the reaction. On the other hand if both groups work together, cyclic or bicyclic compounds of the oxazoline type could be formed:



In this investigation we have studied the behavior under different reaction conditions of several unsubstituted amino alcohols and of a number of compounds resulting from alkyl substitution in the NH_2 or the OH group. Results justify the following conclusions: (1) With unsubstituted amino alcohols, reaction with cyanogen can be directed by proper selection of the reaction medium, either to the NH_2 group or to the OH group. The products are oxamidines or oxaldiimidates respectively. (2) *N*-Alkylethanolamines yield oxaldiimidates regardless of the reaction medium. (3) *N*-Dialkylethanolamines and 2-alkoxyalkylamines react as would be expected of compounds in which one of the functional groups is blocked by complete substitution.

Several unsuccessful experiments with ethanolamine proved that, with the unsubstituted compounds, both the amino alcohol and the cyanogen must be completely free of carbon dioxide before a cyanogen reaction would take place. Furthermore only polar solvents would serve as reaction media; complete failure resulted from the use of a solvent like ethyl acetate. Presumably, this could be due to the necessity of dissociating the intramolecular hydrogen bond of the amino alcohol[8] before the functional groups could be attacked.

When ethanolamine in ethanol was treated with cyanogen the principal product was *sym*-bis(2-hydroxyethyl)oxamidine, but when the solvent was water, or water containing a small amount of potassium cyanide, *sym*-bis(2-aminoethyl)oxaldiimidate resulted.



The latter reaction emphasized a need, which we are presently attempting to meet, of a thorough study of the cyanogen reactions of simple alcohols, since the literature would indicate that a more potent catalyst should be required to bring both halves of cyanogen into reaction with an alcohol.[7] The effect of the potassium cyanide solution on other alkanolamines must also be investigated.

Proof of structure was especially important in this work since the oxamidine and the oxaldiimidate have the same ultimate analysis. To distinguish between the two, we have made use of the following information: (*a*) While not all oxamidines are stable as free bases, they almost always form stable, non-hygroscopic hydrochlorides.[9] (*b*) Hy-

(1) From the thesis presented by Edmond L. Graminski in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1956.

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(3) H. M. Woodburn and R. C. O'Gee, *J. Org. Chem.*, **17**, 1235 (1952).

(4) H. M. Woodburn and B. G. Pautler, *J. Org. Chem.*, **19**, 863 (1954).

(5) H. M. Woodburn and J. R. Fisher, *J. Org. Chem.*, **22**, 895 (1957).

(6) A. Pinner and Fr. Klein, *Ber.*, **10**, 1889 (1887).

(7) J. U. Nef, *Ann.*, **287**, 274 (1895).

(8) E. D. Bergman, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, **75**, 68 (1953).

(9) H. M. Woodburn, B. A. Morehead, and M. C. Chen, *J. Org. Chem.*, **15**, 535 (1950).

drogen sulfide reacts with oxamidines to give derivatives of dithiooxamide.[10] This is impossible with oxaldiimidates. (*c*) Oxamides can be produced by

$$(HOCH_2CH_2NHC(=NH)-)_2 + 2H_2S \longrightarrow (HOCH_2CH_2NHC(=S)-)_2 + 2NH_3$$

partial hydrolysis of oxamidines but not from oxaldiimidates.[9]

Unlike the diamines which form bicyclic compounds spontaneously when the chain length is favorable,[5] no such substances were obtained from this series and concerted efforts to produce cyclic compounds ended in failure. This was regrettable, not only because the compounds would be interesting but because they would have furnished an incontrovertible proof of structure.

The product from *N,N*-diethylethanolamine, which could only be an oxaldiimidate, confirmed the unstable nature of these compounds and their tendency to form unstable salts. On this basis the reaction products of *N*-alkylethanolamines were also deduced to be oxaldiimidates. Confirmation was obtained later in a study of the hydrogen sulfide reaction of oxamidines.[10] In the one case studied, the cyanogen reaction product was the same whether the reaction medium was ethyl ether, water, or water containing a small amount of potassium cyanide.

From 2-alkoxyethylamines we isolated stable oxamidines which in every case easily formed stable, non-hygroscopic hydrochlorides.

EXPERIMENTAL

Reagents. Cyanogen was prepared from aqueous sodium cyanide and dry copper sulfate by the method of Janz.[11] To reduce the amount of carbon dioxide in the product, the sodium cyanide (Du Pont Cyanegg) solution was treated with 10–20 ml. of a saturated solution of barium chloride and filtered before use. Hydrogen cyanide was removed by two silver nitrate scrubbing towers, water by anhydrous calcium sulfate followed by phosphorus pentoxide. Finally the cyanogen was frozen out in a trap maintained at −80° by Dry Ice and acetone. These precautions produced cyanogen in which residual carbon dioxide was too low to interfere with the reaction of unsubstituted alkanolamides.

N-Alkylethanolamines, except for *N-n*-propylethanolamine, were obtained through the courtesy of Union Carbide Corp. *N-n*-propylethanolame was prepared by the method of Biel[12] from *n*-propylamine, ethylene oxide, and hydrochloric acid. Ethanolamine, purchased from Distillation Products Industries, was fractionated immediately before use to ensure freedom from carbonate.

1-Aminopropanol-2 was purchased from Distillation Products Industries and fractionated before use. *3-Aminopropanol-1* was obtained through the courtesy of American Cyanamid Co. and fractionated before use. *2-Methoxyethylamine* and *3-methoxypropylamine* were purchased from Distillation Products Industries. They were purified by extraction from their water solutions with ether, drying, and fractionation.

2-Ethoxyethylamine and *2-propoxyethylamine* were prepared from 2-bromoethylamine hydrobromide as follows: A solution of 205 g. (1 mole) of 2-bromoethylamine hydrobromide in 500 ml. of absolute ethanol was added dropwise to a solution of 2 moles of the sodium alkoxide in 500 ml. of the anhydrous alkanol. The temperature rose to the reflux point and was maintained there for 4 hr. Sodium bromide was filtered off, the alkanol removed by distillation and the remaining liquid fractionated at atmospheric pressure. *2-Ethoxyethylamine:* b.p. 108°/758 mm., $n_D^{25°}$ 1.4070; yield 15%.[13] *2-Propoxyethylamine:* b.p. 125–126°/750 mm., $n_D^{25°}$ 1.4160; yield 14%.[14]

Method. In general cyanogenation was accomplished as follows: To provide a reasonable contact time between cyanogen and reagent, gas washing bottles with ground glass joints were used as reaction vessels. A solution of the alkanolamine in the appropriate solvent was cooled to 0° and cyanogen gas was distilled into it. In most cases removal of the Dry Ice–acetone mixture from around the cyanogen trap was sufficient to cause moderately rapid distillation. If extra heat was needed the warmth of the hand was used. The weight of cyanogen absorbed was obtained by weighing the reaction vessel before and after the cyanogenation.

Reaction of cyanogen with alkanolamines: sym-Bis(2-hydroxyethyl)oxamidine from ethanolamine. A solution of 55 g. (0.9 mole) of ethanolamine in 110 ml. of 95% ethanol was treated with 21 g. (0.43 mole) of cyanogen. At the end of the cyanogenation the mixture was orange in color. The reaction mixture was allowed to stand in an ice chest for 24 hr. during which time crystals formed.

The solid was suction-filtered and washed with ethanol. The yield of the crude product was 22 g. (29% based on cyanogen). Recrystallization from ethanol, using Norit gave white crystals; m.p. 126–127° (dec.).

Anal. Calcd. for $C_6H_{14}N_4O_2$: C, 41.3; H, 8.1; N, 32.1. Found: C, 41.2; H, 8.4; N, 31.9.

The *hydrochloride* was prepared by dissolving 0.5 g. of the free base in 25 ml. of 95% ethanol and saturating the solution with dry hydrogen chloride. A precipitate formed which was filtered off and recrystallized from 95% ethanol; m.p. 123–124° (dec.).

Anal. Calcd. for $C_6H_{16}N_4O_2Cl_2$: Cl, 28.7; N, 22.6. Found: Cl, 28.8; N, 22.5.

The *picrate* was prepared by dissolving 0.5 g. of the free base in 25 ml. of 95% ethanol and treating this solution with 25 ml. of a saturated alcoholic picric acid solution. The mixture was heated to boiling and upon cooling a yellow solid precipitated. This solid was filtered and recrystallized from ethanol; m.p. 178–180° (dec.).

Anal. Calcd. for $C_{18}H_{20}N_{10}O_{16}$: N, 22.2. Found: N, 21.8.

Details of the conversion of the oxamidine to *sym*-bis(2-hydroxyethyl)dithiooxamide by reaction with hydrogen sulfide have been reported in a previous paper.[10]

Attempts at cyclization: (*a*) A suspension of 3.4 g. (0.02 mole) of the oxamidine in 100 ml. of anhydrous carbon tetrachloride was refluxed for four hours in an apparatus fitted with a water-separating trap. At the end of this time the oxamidine had turned black but there was no evidence of dehydration as would have been indicated by the formation of two layers in the distillation trap. (*b*) To a suspension of 5 g. (0.03 mole) of the oxamidine in 100 ml. of dry benzene was added 4 g. (0.03 mole) of phosphorus pentoxide. The resulting suspension was refluxed for four hours. There was some evidence of dehydration since a portion of the pentoxide became glassy, however no product could be isolated from the reaction mixture. (*c*) To 100 ml. of dry dimethylformamide was added 3.48 g. (0.02 mole) of the oxamidine along with 2 g. of phosphorus pentoxide. The mixture was heated

(10) H. M. Woodburn, W. Platek, and E. L. Graminski, *J. Org. Chem.*, 23, 319 (1958).

(11) G. J. Janz, *Inorganic Syntheses*, V, 43 (1957).

(12) J. H. Biel, *J. Am. Chem. Soc.*, 71, 1306 (1949).

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gently at first and then to a higher temperature. As the temperature increased the mixture darkened and gave off the odor of ammonia. Diluting a portion of the mixture with ether produced only tar. It appeared that the oxamidine had completely decomposed.

sym-Bis(2-aminoethyl)oxaldiimidate from ethanolamine. (*a*) A solution of 24.4 g. (0.04 mole) of ethanolamine in 75 ml. of water containing 5 g. (0.07 mole) of potassium cyanide was treated with 19.4 g. (0.37 mole) of cyanogen. At the completion of the reaction, the mixture was extracted 5 times with 50-ml. portions of diethyl ether. Evaporation of the ether left 3 ml. of an oil which undoubtedly contained some water. A *picrate* was formed by adding 10 ml. of a saturated ethanol solution of picric acid to the oil. Yellow crystals began to form immediately. The mixture was allowed to stand for one hour and the crystals were filtered off. The solid was recrystallized from ethanol with Norit; m.p. 185–187°.

Anal. Calcd. for $C_{18}H_{20}N_{10}O_{16}$: C, 34.1; H, 3.1; N, 22.1. Found: C, 34.1; H, 3.1; N, 22.1.

(*b*) The procedure of (*a*) was repeated except that potassium cyanide was omitted. There was no difference in yield and the picrates were identical as evidenced by a mixed melting point, 185–187°.

sym-Bis(2-hydroxyethyl-2-methylethyl)oxamidine from 1-aminopropanol-2. A solution of 20 g. (0.293 mole) of 1-aminopropanol-2 in 45 ml. of ethanol was treated with 7.6 g. (0.147 mole) of cyanogen. Since there was no apparent change, the reaction mixture was protected from the atmosphere and placed in an ice chest. After 20 hr., the mixture was placed on a watch glass and the solvent was removed by evaporation hastened by blowing a stream of air over the top of the dish. The film that formed on the top of the reaction mixture had to be broken constantly to enable evaporation to continue. When the residue became viscous, it was suction filtered. The yield of crude material was 6 g. or 20% based on the amount of cyanogen used. The solid was recrystallized from absolute alcohol; m.p. 143–144° (dec.).

Anal. Calcd. for $C_8H_{18}N_4O_2$: C, 47.5; H, 8.9; N, 27.7. Found: C, 47.1; H, 9.0; N, 27.6.

All attempts to form a picrate or a hydrochloride resulted in the formation of ammonium picrate or ammonium chloride.

The reaction of 3-aminopropanol-1 with cyanogen. (*a*) Seventy-five grams (1 mole) of 3-aminopropanol-1 in 225 ml. of ethyl acetate was treated with 18 g. (0.346 mole) of cyanogen. During cyanogenation, two layers formed. The reaction mixture was placed in an ice chest for 24 hr.

At the end of this time the two layers were separated. The upper layer consisted of solvent and some 3-aminopropanol-1. To remove amino alcohol, the bottom layer was extracted 3 times with 50-ml. portions of ethyl acetate. The remaining liquid was then distilled through a 12-inch jacketed and heated column packed with glass helices. At 81.5°/9 mm. an oil began to come off which had a refractive index, n_D^{25}, 1.4720. After 12 g. of the oil had been collected the temperature began to rise steadily and a viscous liquid came off with no fractionation taking place. By treatment with methyl iodide, the liquid first obtained was proved to contain an appreciable amount of 3-aminopropanol-1.

(*b*) One-half mole (37.5 g.) of 3-aminopropanol-1 in 100 ml. of water was treated with 11.9 g. of cyanogen and the reaction mixture kept for 24 hr. in an ice chest. The water was then evaporated under 2-mm. pressure and a solid presently began to come out of solution. This was filtered and crystallized from acetone with Norit to decolorize it. The pure solid weighed 4 g.; m.p. 155–157°. A mixture with a pure sample of bis(3-hydroxypropyl)oxamide[15] showed no depression of melting point.

Anal. Calcd. for $C_8H_{16}N_2O_4$: C, 47.5; H, 7.8; N, 13.7. Found: C, 47.2; H, 8.0; N, 13.8.

(c) One mole of 3-aminopropanol-1 (75 g.) in 160 ml. of absolute ethanol was treated with 24.3 g. (0.467 mole) of cyanogen. The reaction mixture was allowed to stand in an ice bath for 24 hr. At the end of this time it was dark brown in color.

Preparation of the *picrate* was attempted by treating 10 ml. of the reaction mixture with 25 ml. of a saturated ethanol solution of picric acid and heating to boiling. The solution was allowed to come to room temperature and finally cooled in an ice bath. No crystals formed even after 2 days.

The *hydrochloride* was formed by saturating the remainder of the reaction mixture with dry hydrogen chloride at 0°. A solid precipitated which contained some organic material and some ammonium chloride. The solid was filtered, washed twice with ethanol, and dried in a vacuum desiccator. It was recrystallized from ethanol, however each crystallization produced a greater amount of ammonium chloride. After one recrystallization the substance melted at 145–148° (dec.).

Three grams of the impure hydrochloride was treated with an excess of *n*-butylamine. The reaction mixture was refluxed for two hours. At the end of this time, 50 ml. of water was added and a fibrous solid came out. The solid was recrystallized from petroleum ether with Norit; m.p. 85–86°. Admixture of tetra-*n*-butyloxamidine[16] gave no melting point depression. This was taken as evidence that *sym-bis(3-hydroxypropyl)oxamidine* had been formed in the reaction of 3-aminopropanol-1 with cyanogen, although we could not isolate it in the pure state.

Attempted reaction of 2-amino-2-methyl-propanol-1 with cyanogen. All attempts to find conditions favorable for a reaction between this amino alcohol and cyanogen ended in failure. Cyanogenations were performed in ethanol and diethyl ether solutions. Two moles of the amino alcohol was used for one mole of cyanogen in each run and the volume of the solvent was varied from 75 to 200 ml. Evaporation of the solvent gave only a dark, oily residue. Attempts to form a hydrochloric acid salt of the product gave quantitative yields of the hydrochloric acid salt of the starting material.

Reaction of cyanogen with N-alkylsubstituted ethanolamines: sym-Bis(2-methylaminoethyl)oxaldiimidate from *N*-methylethanolamine. A solution of 2 ml. of *N*-methylethanolamine in 6 ml. of diethyl ether was placed in a test tube and cooled to 0°. Cyanogen (0.65 g.) was distilled from a trap into the solution at a slow rate since it had been found that if the rate of cyanogenation was too rapid, the mixture would heat up considerably, darken, and yield very little product. During the passage of cyanogen, the solution turned milky and finally separated into 2 layers. Cyanogenation was continued until the solution was just saturated. By this time the mixture was dark brown. Too much or too little cyanogen rendered the reaction unsuccessful.

The lower layer solidified upon standing or scratching the walls of the test tube. The solid could not be isolated by suction filtration since when exposed to the atmosphere it darkened and formed an oil within a few minutes.

To form the more stable *hydrochloride*, 4 ml. of 95% ethanol was added to the reaction mixture and the resulting solution was slowly saturated with hydrogen chloride gas, making sure that the temperature stayed below 10° at all times. If ethanol was not added before saturating with hydrogen chloride, an oil formed, and if this was not separated quickly from the upper layer it finally resulted in the formation of ammonium chloride. With ethanol present, long needles formed, or an oil which could be induced to crystallize by placing it in a vacuum desiccator and evacuating to about 20 mm. of mercury.

(15) Prepared from oxalyl chloride and 3-aminopropanol-1.

(16) H. M. Woodburn, B. A. Morehead, and M. C. Chen, *J. Org. Chem.*, **15**, 541 (1950).

Recrystallization was carried out successfully only in absolute solvents since the crystals were quite hygroscopic. They were recrystallized from an absolute ethanol–diethyl ether pair with Norit for decolorizing. The yield of crude material was 1.5 g. (45% based on cyanogen); the melting point of the pure crystals was 165–166°.

Anal. Calcd. for $C_8H_{20}N_4Cl_2O_2$: C, 34.9; H, 7.3; N, 20.4; Cl, 25.8. Found: C, 34.6; H, 7.0; N, 20.4; Cl, 25.5.

sym-Bis(2-ethylaminoethyl)oxaldiimidate from *N*-ethylethanolamine. (*a*) With the same volume of *N*-ethylethanolamine and the same procedure described above, a 56% yield (based on cyanogen) of *sym-bis(2-ethylaminoethyl)oxaldiimidate dihydrochloride* was produced. The pure solid melted at 169–170°.

Anal. Calcd. for $C_{10}H_{24}N_4Cl_2O_2$: C, 39.6; H, 7.9; N, 18.4; Cl, 23.4. Found: C, 39.3; H, 7.7; N, 18.3; Cl, 23.8.

(*b*) A solution of 27.3 g. (0.307 mole) of *N*-ethylethanolamine in 75 ml. of water containing 5 g. (0.07 mole) of potassium cyanide was treated with 16 g. (0.307 mole) of cyanogen at a moderate rate. The reaction mixture was then extracted 6 times with 50-ml. portions of diethyl ether. The ether was evaporated and about 3 ml. of oil remained. This was dissolved in 3 ml. of ether and 3 ml. of ethanol, cooled to 0°, and saturated very slowly with dry hydrogen chloride gas. An oil came out which crystallized in a vacuum desiccator. After recrystallization from absolute ethanol–diethyl ether, the solid gave no depression of melting point when mixed with the solid obtained in (*a*). The yield was 1.5 g. or 2.2% based on cyanogen.

(c) The reaction was repeated exactly as in (*b*) with the exception that potassium cyanide was not used. The hydrochloride was identical to that formed in (*a*) and (*b*).

Attempted reaction of cyanogen with N-propylethanolamine. The same quantities of the amino alcohol and diethyl ether were used as above. The results of cyanogenation were similar, however the oil which formed on saturating the reaction mixture with dry hydrogen chloride was very difficult to purify. It was extremely hygroscopic and loathe to crystallize. After 4 recrystallizations from absolute ethanol–diethyl ether the solid still melted over the range 180–225°. When the temperature of the melting point block was elevated to 300° it was evident that ammonium chloride was present since the walls of the capillary tube were coated with sublimed solid. No further attempts at purification were made.

Attempted reaction of cyanogen with N-n-butylethanolamine. (*a*) The same volume of amino alcohol and ether were used as above. No layers formed during or after the reaction. When the formation of a hydrochloride was attempted, only ammonium chloride was produced.

(*b*) A solution of 4 ml. of the amino alcohol in 4 ml. of absolute ethanol was saturated with cyanogen at 0°. This mixture was treated with dry hydrogen chloride until saturated. Only ammonium chloride was produced.

(c) The same procedure was followed as in (*b*) except that the cyanogenation mixture was treated with 10 ml. of a saturated ethanolic solution of picric acid. The mixture was brought to a boil and allowed to cool. No crystals formed even after two days.

(*d*) A solution of 2 ml. of the amino alcohol in 6 ml. of diethyl ether was saturated with cyanogen at 0°. The reaction mixture was then treated with a saturated solution of dry hydrogen chloride in ether. A solid formed which became gummy and formed ammonium chloride after filtration.

Attempted isolation of cyanoformimidates. *N*-methyl-, *N*-ethyl-, and *N*-butylethanolamines were cyanogenated at 0° in various solvents such as ethanol, ethyl acetate, and diethyl ether in a ratio of 2 moles of the amino alcohol to 1 mole of cyanogen, with the solvent volume varying from 100 to 250 ml. After cyanogenation the solvent was distilled off at atmospheric pressure and the residue fractionated at pressures from 1–5 mm. of mercury using a 12-inch jacketed and heated column packed with glass helices. After the first fraction, which was solvent, no clean cut fractions were obtained. A steady flow of viscous liquid came off as the temperature rose. Analysis of various portions of the distillate and of picrates formed from them did not give results which coincided with calculated percentages for cyanoformimidates.

Reaction of cyanogen with N-dialkylsubstituted ethanolamine: sym-Bis(2-diethylaminoethyl)oxaldiimidate from *N*-diethylethanolamine. A solution of 41.6 g. (0.356 mole) of *N*-diethylethanolamine in 75 ml. of water containing 5 g. (0.07 mole) of potassium cyanide was treated with 18.5 g. (0.356 mole) of cyanogen. At the end of the reaction the mixture was extracted 6 times with 50-ml. portions of diethyl ether. The ether was evaporated and 50 ml. of an impure oil was obtained which decomposed rapidly even under reduced pressure. A picrate of the oil was formed by adding 250 ml. of a saturated ethanol solution of picric acid. The solid which came down was filtered off immediately. If the reaction mixture was allowed to stand or if it was heated to boiling, the solid that first come down redissolved and another crystalline material formed which was ammonium picrate. No solvent was found which was suitable for recrystallizing the picrate. Therefore the solid was placed in a large volume of ethanol, brought to a boil, and filtered while hot. This procedure removed the soluble impurities. When heated in a capillary tube, the solid contracted in volume at about 130°, finally melting at 195–198° with decomposition.

Anal. Calcd. for $C_{25}H_{36}N_{10}O_6$: C, 41.9; H, 4.8; N, 18.8. Found: C, 41.8; H, 4.6; N, 18.7.

Reaction of cyanogen with 2-alkoxyethylamines: sym-Bis(2-methoxyethyl)oxamidine from 2-methoxyethylamine. Fifty-eight grams of a 65–70% water solution of 2-methoxyethylamine (approximately 0.5 mole) was further diluted with 40 ml. of ethanol and treated with 12.8 g. (0.246 mole) of cyanogen. The reaction mixture was allowed to stand for 24 hr. in an ice chest. At the end of this time it was placed in a large watch glass and the solvent removed at room temperature by blowing air over the top of the dish.

When approximately one-half of the solvent had been removed crystals began to form. These were filtered when only a small amount of the solvent remained. They were recrystallized from diethyl ether with Norit; m.p. 73–75°. The yield of crude material was 23 g. (46% based on cyanogen). The compound appeared to decompose upon standing, since after two weeks the crystals had darkened in color.

Anal. Calcd. for $C_8H_{18}N_4O_2$: C, 47.5; H, 8.9; N, 27.7. Found: C, 47.4; H, 8.8; N, 27.4.

The *hydrochloride* was prepared by dissolving 1 g. of the free base in 5 ml. of ethanol and saturating the resulting solution with dry hydrogen chloride. The reaction mixture was cooled to 0° in an ice bath and the resulting crystals were filtered off. The hydrochloride was recrystallized from ethanol–diethyl ether. The melting point of the purified solid was 194–195° (dec.).

Anal. Calcd. for $C_8H_{20}N_4Cl_2O_2$: C, 34.9; H, 7.2; N, 20.3; Cl, 25.9. Found: C, 34.8; H, 7.1; N, 20.3; Cl, 26.2.

sym-Bis(2-ethoxyethyl)oxamidine from 2-ethoxyethylamine. Using the same conditions as above, 13.4 g. (0.149 mole) of 2-ethoxyethylamine in 32 ml. of ethanol was treated with 3.9 g. (0.075 mole) of cyanogen. The yield of crude crystals was 9 g. (52% based on cyanogen). The melting point of the solid, purified by recrystallization from ether, was 87–89°.

Anal. Calcd. for $C_{10}H_{22}N_4O_2$: C, 52.1; H, 9.5; N, 24.3. Found: C, 52.0; H, 9.4; N, 24.3.

The *hydrochloride*, prepared as above, was recrystallized from ethanol; m.p. 197–198° (dec.).

Anal. Calcd. for $C_{10}H_{24}N_4Cl_2O_2$: C, 39.6; H, 7.9; N, 18.4; Cl, 23.4. Found: C, 39.5; H, 7.7; N, 18.3; Cl, 23.7.

sym-Bis(2-propoxyethyl)oxamidine from 2-propoxyethylamine. A solution of 11.7 g. (0.136 mole) of 2-propoxyethylamine in 26 ml. of ethanol was treated with 3.5 g. (0.068 mole) of cyanogen. The yield of crude product was 6 g. (35% based on cyanogen). The solid was difficult to re-

crystallize, therefore it was converted to the hydrochloride before analysis. The hydrochloride required 5 recrystallizations from absolute ethanol before a reasonable degree of purity was achieved. The melting point was 219–220° (dec.).

Anal. Calcd. for $C_{12}H_{28}N_4Cl_2O_2$: C, 43.5; H, 8.4; N, 16.9; Cl, 21.4. Found: C, 43.3; H, 8.2; N, 16.8; Cl, 21.7.

sym-Bis(3-methoxypropyl)oxamidine from 3-methoxypropylamine. A solution of 75 g. (0.833 mole) of 3-methoxypropylamine in 175 ml. of ethanol was treated with 19 g. (0.365 mole) of cyanogen. The yield of crude crystals was 54.5 g. (64.4% based on cyanogen). After recrystallization from ethanol with Norit the solid melted at 89–91°.

Anal. Calcd. for $C_{10}H_{22}N_4O_2$: C, 52.1; H, 9.5; N, 24.3. Found: C, 52.0; H, 9.1; N, 24.6.

The *hydrochloride* prepared as above, was recrystallized from ethanol and melted at 227–228° (dec.).

Anal. Calcd. for $C_{10}H_{24}N_4Cl_2O_2$: C, 39.9; H, 7.9; N, 18.4; Cl, 23.4. Found: C, 39.7; H, 7.7; N, 18.8; Cl, 23.7.

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[CONTRIBUTION NO. 487 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Syntheses in the Pyrrole Series

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A number of pyrryl ketones and their derivatives were prepared for screening for pharmacological and chemotherapeutic activity. For comparison purposes, some other related heterocyclic compounds were also prepared. A few of the pyrryl ketones, especially 3-propionylpyrrole, were active as muscle relaxants in the anti-strychnine test in mice and cats.

Extracts of Valerian root[1] (Valeriana officinalis) have been claimed to reduce blood pressure and have some cardiac and sedative action. The finding of 2-acetylpyrrole in such extracts,[2] and also the reported hypnotic activity of 2-isobutyl pyrryl ketone[3] suggested further examination of pyrrole ketones and related compounds in order to determine the range of their biological actions.

A number of new pyrrole ketones (Table I) were prepared and tested as muscle relaxants in the anti-strychnine[4] test in mice and cats. The following previously reported pyrrole ketones were also prepared using the Grignard reaction for comparison purposes: 2- and 3-propionylpyrroles, 1-methyl-2-propionylpyrrole, 2-pyrryl isobutyl ketone, 1-(2-pyrryl)-1,3-butadione, 2-furyl 2-pyrryl ketone, 2-phenylacetylpyrrole, 2,5-dimethyl-3-propionylpyrrole, and 2,5-dimethyl-3-acetylpyrrole. Although many of the pyrrole ketones exhibited some activity as muscle relaxants, 3-propionylpyrrole[5] only (m.p. 117°), was found to be of the order of Myanesin in this test, while interestingly, 2-propionylpyrrole (m.p. 54°) was inactive.

The reduction of 3-propionylpyrrole to 3-propylpyrrole, the partial reduction to α-ethyl-3-pyrrolemethanol, and methylation to yield 1-methyl-3-propionylpyrrole eliminated anti-strychnine activity.

The heterocyclic analogs of 3-propionylpyrrole, 3-propionylfuran, 3-propionylthiophene, and also 2-propionylpyrazine, were inactive in the anti-strychnine test. During the work on the *C*-propionylpyrroles, some errors in the literature were cleared up. 2-Propionylpyrrole readily formed the phenylhydrazone (m.p. 112–114°) but failed to yield a semicarbazone; while 3-propionylpyrrole gave a semicarbazone (m.p. 181°) but failed to yield a phenylhydrazone. Previous reports[6] on the ketone derivatives of *C*-propionylpyrroles undoubtedly described mixtures of the 2 and 3 isomers.

2-Propionylpyrrole yielded a hydrazone and oxime but 3-propionylpyrrole failed to give either.

The *C*-propionylpyrroles failed to react with acetylene in liquid ammonia using sodium, potassium, or lithium to yield the acetylenic alcohols. We were unable to prepare hydantoins or substituted glycidamides using a modified Darzens' reaction[7] with chloroacetamide. The failure of the modified Darzens' reaction is probably due to the acidic pyrrole hydrogen on the nitrogen.[8]

The mixed acycloins, α-hydroxybenzyl-2-pyrryl ketone, the 4-chlorbenzyl and the 2,4-dichlorbenzyl acycloins were prepared. The presence of a high band in the ultraviolet spectrum near 290 mμ (ε 16000) of the mixed acycloins suggested the possibility of an enediol structure. However, comparison with α-pyridoin[9] which is known to be a

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TABLE I

PYRRYL KETONES

Ketone	Formula	Cryst. from	M.P., °C.	Yield, %	Color	Analysis Calcd. N	Analysis Found N
4-Pyridyl 2-pyrryl	$C_{10}H_8N_2O$	Ethanol	127–128	6	Brown to purple	16.3	16.5[a]
4-Pyridyl 2-pyrryl hydrochloride	$C_{10}H_8N_2O\cdot HCl$	Ethanol	170–171	—	Greenish yellow	13.4	12.8
3-Pyridyl 2-pyrryl hydrochloride	$C_{10}H_8N_2O\cdot HCl$	Ethanol	187–188	[b]	Greyish green	13.4	13.3
2-Pyridyl 2-pyrryl hydrochloride	$C_{10}H_8N_2O\cdot HCl$	Ethanol + ether	>250	[c]	Violet	13.4	13.8[d]
2-Pyridyl 2,5-dimethyl-3-pyrryl	$C_{12}H_{12}N_2O$	Ethyl acetate–ether	118–120	20[e]	Yellow	14.0	13.3
2-Pyridyl 2,5-dimethyl-3-pyrryl hydrochloride	$C_{12}H_{12}N_2O\cdot HCl$	Ethyl acetate–pet. ether	208–210	—	Orange	11.8	11.1
3-Pyridyl 2,5-dimethyl-3-pyrryl	$C_{12}H_{12}N_2O$	Ethanol	166–168	12	Yellow	14.0	13.7
3-Pyridyl 2,5-dimethyl-3-pyrryl hydrochloride	$C_{12}H_{12}N_2O\cdot HCl$	Ethanol	203–204	—	Yellow	11.8	11.9
4-Pyridyl 2,5-dimethyl-3-pyrryl	$C_{12}H_{12}N_2O$	Ethanol	190–191	8	Light brown	14.0	13.7
4-Pyridyl 2,5-dimethyl-3-pyrryl hydrochloride	$C_{12}H_{12}N_2O$	Ethyl acetate–pet. ether	261–263	—	Orange	11.8	11.1
Diphenylmethyl 2-pyrryl	$C_{18}H_{15}NO$	Ether–pet. ether	104–106[f]	21	Colorless	5.4	5.9
Benzyl 2,5-dimethyl-3-pyrryl	$C_{14}H_{15}NO$	Ether–pet. ether	170–171	2	Light pink	6.6	6.4
Phenyl 2,5-dimethyl-3-pyrryl	$C_{12}H_{13}NO$	Ether–pet. ether	129–130	4	Yellow	7.0	6.9
2-Furyl 2,5-dimethyl-3-pyrryl	$C_{11}H_{11}NO_2$	Ether–pet. ether	96–97[g]	36	Light brown	7.4	7.2
Isobutyl 2,5-dimethyl-3-pyrryl	$C_{11}H_{17}NO$	Ether–pet. ether	90–91[h]	47	Light pink	7.8	7.4
Diphenylmethyl 2,5-dimethyl-3-pyrryl	$C_{25}H_{19}NO$	Ether	163–164	2	Light cream	4.9	4.9
2-Thienyl 2,5-dimethyl-3-pyrryl	$C_{11}H_{11}NOS$	Water or ether–pet. ether	110–112	19	Tan	[i]	
5-Methyl-3-isoxazolyl 2-pyrryl	$C_9H_8N_2O_2$	Ether	103–104	5	Yellowish red	15.9	15.6
4-Chlorophenyl 2-pyrryl	$C_{11}H_8ClNO$	Ether	110–111	15	Light pink	6.8	6.6[j]

[a] Calcd.: C, 69.8; H, 4.7. Found: C, 70.0; H, 4.8. On distillation at 2 mm. violet vapors were obtained. [b] The yield of the free base before conversion to the hydrochloride was 15%. The free base was reported by B. Oddo, *Gazz. chim. ital.*, **42**, I, 348 (1912). [c] Free base reported by Oddo[b] with a 75° m.p. We obtained a 7% yield with ethyl picolinate in the Grignard reaction, m.p. 72–74°. [d] Calcd. for $C_{10}H_8N_2O.HCl$: C, 57.9; H, 4.3. Found: C, 57.9; H, 4.4. [e] Ethyl picolinate was used in the Grignard reaction. The yield reported was the crude yield before recrystallization. [f] B.p. 230° at 5 mm. [g] B.p. 205° at 5 mm. [h] B.p. 163–165° at 3 mm. [i] Calcd.: C, 64.4; H, 5.4. Found: C, 64.4; H, 5.5. [j] Calcd.: Cl, 17.3. Found: Cl, 17.3.

stable enediol, eliminated this type of structure. Similarities in the infrared spectra of the mixed acycloins and a number of 2-substituted pyrrole ketones indicate that the carbonyl group in the acycloins is adjacent to the pyrrole moiety.

It was found in the preparation of benzopyroins that the ratio of 2-pyrrolecarboxaldehyde to the aromatic aldehydes affected yields significantly and that the length of time of heating was also critical.

Attempted "benzoin"-type condensations with 2-pyrrolecarboxaldehyde, under the best conditions for benzopyroin, failed to yield the desired product using the following aldehydes: 3,4-dichlorobenzaldehyde, 2,6-dichlorobenzaldehyde, *m*-nitrobenzaldehyde, 2-thiophenealdehyde, and furfural. The desired product was not obtained on self-condensation of 2-pyrrolecarboxaldehyde.

The reductive condensation using Raney nickel and hydrogen of 2-pyrrolecarboxaldehyde with diethyl malonate gave diethyl-α-(2-pyrrylmethyl)-malonate, while it has been shown that the use of platinum oxide as a catalyst yields the corresponding pyrrolidyl[10] compound. Diethyl-α-(2-pyrrylmethyl)malonate was converted to the diamide, the dihydrazide, and also reduced to the propanediol but failed to yield a 5-substituted barbituric acid on condensation with urea using sodium ethoxide as a condensing agent.

(10) G. R. Clemo, N. Fletcher, G. R. Fulton, and R. Raper, *J. Chem. Soc.*, 1140 (1950).

Nitration of 2-propionylpyrrole gave the 5-nitro compound from which the semicarbazone was prepared. The assignment of the nitro group to the 5-position is made by analogy with 5-nitro-2-acetylpyrrole[11] prepared in the same manner. In contrast, a semicarbazone could not be prepared from 2-propionylpyrrole itself.

Biologic findings. 3-Propionylpyrrole was of the order of activity of Myanesin as a muscle relaxant in the anti-strychnine test[4] in mice and cats. Isobutyl-2,5-dimethyl-3-pyrryl ketone, 3-pyridyl 2-pyrryl ketone hydrochloride, and 2-pyrryl 5-methyl-3-isoxazolyl ketone exhibited some activity in this test also. α-(2-Pyrrylmethyl)malonamide and 3-propionylpyrrole semicarbazone were active as stimulants in the spinal reflex[12] in cats. All the other compounds were without pharmacological or chemotherapeutic interest.

It was also observed that a number of the pyrrole compounds gave dark colored urines to the mice, rats and dogs.

EXPERIMENTAL[13]

Methyl 5-dimethylaminomethyl-2-pyrryl ketone hydrochloride. 2-Acetyl pyrrole (10 g.) was heated with 9 g. of dimethylamine hydrochloride and 10 g. of paraformaldehyde in 75 ml. of isoamyl alcohol for 7 hr. The solution was concentrated to a small volume and poured into cold water saturated with potassium carbonate. The product was separated by extraction with ether. The ether solution was dried with anhydrous sodium sulfate and decolorized with activated carbon. Addition of 6*N* HCl in ethanol gave an oily precipitate which crystallized at 4°. This was recrystallized from ethanol-ether; yield, 11 g., m.p. 170–171°.

Anal. Calcd. for $C_9H_{14}N_2O.HCl$: N, 14.0. Found: N, 14.2.

The assignment of structure was based on reaction in the Ehrlich test using *p*-dimethylaminobenzaldehyde in hydrochloric acid. In this test, pyrrole gives a deep red color, and 2-acetyl pyrrole a pink to light red. The compound described above gave a yellow color indicative of both α-positions being blocked.

α,α-Diethyl-2-pyrrolemethanol. This compound was prepared using the Grignard reaction with 2-propionylpyrrole and ethyl iodide. The hydrolyzed reaction product was extracted by ether and vacuum distilled at 200° at 3 mm. 2-Propionylpyrrole (12 g.) gave 8 g. of the tertiary alcohol which distilled as a colorless liquid but darkened rapidly on standing.

Anal. Calcd. for $C_9H_{15}NO$: N, 9.2. Found: N, 9.8.

Diethyl α-(2-pyrrylmethyl)malonate. 2-Pyrrolecarboxaldehyde (22.5 g.), 42 g. of diethyl malonate and 5 ml. of piperidine was allowed to stand for 2 days and then the condensation product was diluted with ethanol and reduced with Raney nickel and hydrogen at 500 p.s.i. for 1 hour at 60°. When a theoretical hydrogen uptake was obtained, the catalyst was removed by filtration and the solvent removed. The remaining oil was fractionated under vacuum to give 26 g. (46%) of diethyl pyrrylmethyl malonate, b.p., 137° at 2 mm., n_D^{22} 1.4871.

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.2; H, 7.1. Found: C, 60.2; H, 7.0.

α-(2-Pyrrylmethyl)malonamide. Diethyl-(α-pyrrylmethyl)-malonate (10 g.) was dissolved in 100 ml. of 25% NH_3 in methanol and heated at 100° for 6 hr. under 500 p.s.i. N_2 pressure. The reaction product was concentrated to a solid and crystallized from methanol yielding a light tan compound, m.p. 188–189°.

Anal. Calcd. for $C_8H_{11}N_3O_2$: N, 23.2. Found: N, 23.6.

(2-Pyrrylmethyl)malonic acid dihydrazide. Diethyl (2-pyrrylmethyl)malonate (24 g.) was treated with 6.5 g. of 85% hydrazine hydrate in 2-propanol at reflux temperature for 6 hr. Concentration under vacuum gave a solid which was crystallized from boiling water to yield a light brown product; yield, 4 g., m.p. 178–180°.

Anal. Calcd. for $C_8H_{13}N_5O_2$: C, 45.5; H, 6.2; N, 33.2. Found: C, 46.0; H, 6.2; N, 33.3.

2-(2-Pyrrylmethyl)-1,3-propanediol. Diethyl α-(2-pyrrylmethyl)malonate (20 g.) was dropped into a solution of 10.0 g. of $LiAlH_4$ in 300 ml. of dry ether, stirred for 3 hr. and stood at 25° overnight. The excess $LiAlH_4$ was decomposed with ethyl acetate and the complex was decomposed by the addition of 18 ml. of water. This was worked up in the usual manner and the oil was distilled at 160–170° at 2–4 mm.; yield, 3 g., $n_D^{24.5}$ 1.5283.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 62.0; H, 8.4. Found: C, 62.3; H, 8.3.

The diol turned dark at 25° but remained a light yellow in color at 4°.

2-Propionylpyrrole oxime. 2-Propionylpyrrole (100 g.) was treated at 25° in aqueous ethanol with 70 g. of hydroxylamine hydrochloride and 85 g. of sodium acetate. The product crystallized from the solution and was recrystallized from ethanol; yield, 54 g., m.p. 125–126°.

Anal. Calcd. for $C_7H_{10}N_2O$: N, 20.3. Found: N, 20.2.

α-Hydroxybenzyl 2-pyrryl ketone (benzopyroin). Benzaldehyde (5 g.), 5 g. of 2-pyrrolecarboxaldehyde, 10 g. of KCN and 10 g. of water were added to 120 ml. of ethanol. The solution was heated at reflux temperature for 3 hr., diluted to 500 ml. with water, and chilled. The crude product crystallized and was obtained as a colorless compound by crystallization from ethanol or ethanol-water after decolorization with carbon; yield, 3 g., m.p. 157–158°.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.5; H, 5.5; N, 6.8.

4-Chloro-α-hydroxybenzyl 2-pyrryl ketone. p-Chlorobenzaldehyde (37 g.) and 20 g. of 2-pyrrolecarboxylaldehyde in a typical benzoin condensation as described above gave 20 g. of a light yellow compound crystallizable from aqueous ethanol; m.p. 131–132°.

Anal. Calcd. for $C_{12}H_{10}ClNO_2$: Cl, 15.1. Found: Cl, 15.3.

2,4-Dichloro-α-hydroxybenzyl 2-pyrryl ketone. 2,4-Dichlorobenzaldehyde (10 g.) and 10 g. of 2-pyrrolecarboxaldehyde in the benzoin type condensation gave 8 g. of a pale cream colored compound, m.p. 138–139°.

Anal. Calcd. for $C_{12}H_9Cl_2NO_2$: N, 5.2; Cl, 26.3. Found: N, 4.6; Cl, 26.2.

Phenyl-2-pyrrylglyoxal. Pyridine (80 ml.), $CuSO_4 \cdot 5H_2O$ (82 g.), and 32 ml. of water were warmed and stirred until solution was obtained. To this solution was added 34 g. of α-hydroxybenzyl 2-pyrryl ketone and the solution heated at 80° for 3.5 hr. The solution was poured into water and chilled at 4° for 14 hr. The separated product was stirred with 10% hydrochloric acid for 0.5 hr., filtered, washed with water, and dried. The dried product was crystallized from ethyl acetate–*n*-hexane solution as yellow crystals; yield, 32 g., m.p. 101–102°.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.3; H, 4.5. Found: C, 71.9; H, 4.3.

This compound did not condense with *o*-phenylenediamine and $NaHSO_3$ to give a substituted quinoxaline. The starting compound was recovered unchanged.

α-Methoxybenzyl N-methyl 2-pyrryl ketone. α-Hydroxybenzyl 2-pyrryl ketone (10 g.) was heated with 2.3 g. of sodium in 500 ml. of dry toluene. The sodium salt which formed as a suspension on vigorous stirring was treated with

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(12) W. Koll and M. Ergang, *Arch. exptl. Pathol. Pharmakol.*, **199**, 577 (1942); F. M. Berger, *Brit. J. Pharmacol.*, **2**, 241 (1947); *Pharmacol. Revs.*, **1**, 243 (1949).

(13) All melting points are corrected.

an excess of methyl iodide (50 ml.) and gently refluxed for 2 hr. The sodium iodide formed was filtered off and the toluene removed. The residual solid distilled at 150–160° at 2–3 mm.; yield, 4 g. The distillate solidified at 4° and on addition of ether crystallized. The colorless product was recrystallized from ether; m.p. 82–83°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.4; H, 6.6; *O*-methoxy, 13.5. Found: C, 73.2; H, 6.5; *O*-methoxy, 13.6.

Infrared analysis showed absence of —NH band indicating methylation on the pyrrole nitrogen.

5-(2-Pyrrylmethylidene)barbituric acid.[14] A solution of 4.7 g. of 2-pyrrolecarboxaldehyde in 25 ml. of 80° water was added to a solution of 12.8 g. of barbituric acid in 70 ml. of boiling water. On mixing, a solid product began to separate. The suspension was heated for one hour at 80° and then filtered and washed with hot water. The yellow product was practically insoluble in boiling water, hot ethanol, or hot ethyl acetate. It was recrystallized from acetic acid; yield, 9.2 g., m.p. >280°.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.6; H, 3.4. Found: C, 52.6; H, 3.5.

3-Propylpyrrole. 3-Propionylpyrrole (7 g.) in 100 ml. of ether was added to 2.2 g. of $LiAlH_4$ in 100 ml. of ether. After reaction, destruction of excess $LiAlH_4$ with ethyl acetate, and decomposition of the complex with water, the solvent was removed from the separated ether layer and the residue distilled at 47–50° at 2 mm., to yield 5 g. of a dark yellow oil; n_D^{25} 1.4900.

Anal. Calcd. for $C_7H_{11}N$: C, 77.1; H, 10.1. Found: C, 76.8; H, 10.0.

2-(2-Pyrrylmethyl)furan. 2-Furyl 2-pyrryl ketone (16 g.) was reduced in dry ether using $LiAlH_4$ (3.8 g.) to give 6 g. of a dark yellow oil; b.p. 80–96° at 3 mm., n_D^{21} 1.5460.

Anal. Calcd. for C_9H_9NO: C, 73.6; H, 6.2. Found: C, 74.2; H, 6.8.

2,5-Dimethyl-3-(2,2-diphenylethyl)pyrrole. 2,5-Dimethyl-3-(diphenylacetyl)pyrrole (12 g.) was reduced in dry ether with $LiAlH_4$ (1.6 g.). The recovered product was distilled at 180–185° at 5 mm. The distillate crystallized and the light brown compound was recrystallized from ether–*n*-hexane; yield, 6 g., m.p. 95–96°.

Anal. Calcd. for $C_{20}H_{21}N$: C, 87.3; H, 7.6. Found: C, 87.2; H, 7.5.

α-Ethyl-3-pyrrolemethanol. $LiAlH_4$ (5.8 g.) in 100 ml. of ether was added dropwise to 24.5 g. of 3-propionylpyrrole in 150 ml. of dry ether. The solution was refluxed for 0.5 hr. The cooled material was decomposed with ice and the product worked up in the usual fashion. The residual oil was distilled in vacuum at 117–125° at 2–3 mm., giving a light yellow oil; yield, 5 g., n_D^{23} 1.5205.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.1; H, 8.8; N, 11.2. Found: C, 66.3; H, 8.4; N, 11.6.

The isomeric 2 compound has been prepared by the same reversed addition procedure.[15]

3-Propionylpyrrole semicarbazone. 3-Propionylpyrrole (8 g.), 30 g. of semicarbazide hydrochloride, and 60 g. of sodium acetate in 200 ml. of water was heated for 0.5 hr. On concentrating to 100 ml. and addition of concentrated ammonia, a colorless crystalline material separated which was recrystallized from water containing ammonia; yield, 3 g., m.p. 180–181°.

Anal. Calcd. for $C_8H_{12}N_4O$: N, 31.1. Found: N, 30.7.

Ethyl 2-pyrryl ketone hydrazone. 2-Propionylpyrrole (30.5 g.) was treated in 2-propanol with 85% hydrazine hydrate (50 g.) at 80° for 6 hr. The solution was concentrated to a small volume and on cooling, the hydrazone crystallized. The colorless product was recrystallized from ether; yield, 22 g., m.p. 103–104°.

Anal. Calcd. for $C_7H_{11}N_3$: N, 30.7. Found: N, 31.3.

1-Methyl-3-propionylpyrrole. Metallic potassium (6.5 g.) was suspended in ligroin, b.p. 90–120°, and 3-propionylpyrrole (20 g.) was added in small portions during vigorous agitation. After the addition of the ketone, the suspension was refluxed for 0.5 hr. and the ligroin was decanted from the potassium salt of the ketone. Dry ethyl ether containing 50 g. of methyl iodide was added and the reaction was stirred for 15 hr. at reflux. The potassium iodide formed was filtered off and the ether solution concentrated to an oil which was distilled at 8–10 mm. at 135–142° to give a yellow liquid; yield, 10 g., n_D^{26} 1.5338.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.0; H, 8.0. Found: C, 70.1; H, 8.1.

The known 1-methyl-2-propionylpyrrole[16] was also prepared by the above procedure using 2-propionylpyrrole and also by the action of propionyl chloride on 1-methylpyrrole in the Grignard reaction. 1-Methyl-2-propionylpyrrole had the physical constants, n_D^{27} 1.5282, b.p. 95° at 14 mm.

3-Propionylfuran.[17] To a Grignard solution prepared from 8.4 g. of magnesium and 38.5 g. of ethyl bromide in 500 ml. of ether was added 33 g. of pulverized $CdCl_2$ and the suspension stirred for 0.5 hr. Thirty g. of 3-furoyl chloride (b.p. 87° at 85 mm.) in ether was then added and the suspension refluxed for one hour. The cooled suspension was decomposed with ice and dilute sulfuric acid solution. The ether layer was washed with water, dilute sodium hydroxide solution, and finally with ice water. The dried ether solution was concentrated and the product distilled as a colorless oil at 70° and 4 mm. pressure; yield, 16.5 g., n_D^{25} 1.4770.

Anal. Calcd. for $C_7H_8O_2$: C, 67.8; H, 6.5. Found: C, 67.6; H, 6.5.

3-Propionylthiophene. A modified Grignard reaction,[17] as described above for 3-propionylfuran, gave 43 g. of crude ketone from 50 g. of 3-thiophenecarboxylic acid chloride (b.p. 120° at 60 mm.). The fraction (25 g.) boiling at 78–84° at 4 mm. was treated with 69 g. of Girard's reagent "T" in the usual procedure. The recovered ketone was vacuum-distilled at 125° at 42 mm.; yield, 10 g., n_D^{25} 1.5460.

Anal. Calcd. for C_7H_8OS: C, 60.0; H, 5.7. Found: C, 60.1; H, 6.0.

2-Propionylpyrazine. Pyrazinoic acid (42 g.) was converted to the acid chloride using thionyl chloride (500 g.) to give a violet colored liquid.[18] The acid chloride was used in the $CdCl_2$ modified Grignard reaction described for 3-propionyl furan above. Distillation of the ketone at 77–82° at 4 mm. gave a colorless liquid having a tar-oil odor which crystallized to a white solid at 4° but melted to a pale yellow liquid at 25°; yield, 2 g.

Anal. Calcd. for $C_7H_8N_2O$: C, 61.8; H, 5.9. Found: C, 61.9; H, 6.1.

2-Diethylaminoethyl α-(2-pyrryl) benzyl ether DL*-tartrate.* 2-Benzoyl pyrrole (66 g.) was reduced to the alcohol in 1 liter of ether solution by the reverse addition of $LiAlH_4$ (24 g.). The crude product (66 g.) was dissolved in xylene and reacted with 10 g. of sodium. After formation of the sodium salt, 80 g. of freshly prepared diethylaminoethyl chloride was added. The reaction mixture was stirred and heated at 100° for 6 hr. On completion of the reaction, the cooled suspension was extracted with dilute hydrochloric acid solution. The aqueous solution was made basic with dilute sodium hydroxide solution and extracted with ether. The ether extract was dried with anhydrous sodium sulfate, decolorized, and concentrated to an oil under high vacuum to remove traces of diethylaminoethyl chloride. The oil was dissolved in acetone and treated with an acetone

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saturated solution of DL-tartaric acid. The separated dark purple crystalline solid was recrystallized from hot acetone; yield, 24 g., m.p. 100–102°.

Anal. Calcd. for $C_{17}H_{24}N_2O.1.75C_4H_6O_6$: C, 53.9; H, 6.5; N, 5.3. Found: C, 53.9; H, 6.6; N, 5.3.

1-(3-Dimethylaminopropyl)-2-propionylpyrrole acid tartrate. Metallic potassium (3.5 g.) was suspended in toluene (200 ml.) at 65° and 10 g. of 2-propionylpyrrole in 100 ml. of toluene was added. After the reaction was completed, 12 g. of dimethylaminopropyl chloride in 50 ml. of toluene was added and the mixture heated at reflux for 6 hr. with efficient stirring. The cooled suspension was treated with ice water and the water layer saturated with sodium chloride. The separated toluene layer contained most of the product and the water layer was extracted with ether three times to remove residual product. The combined solvent layers were concentrated to an oil under high vacuum and the residual oil dissolved in acetone.

The acetone solution was decolorized and treated with a saturated solution of DL-tartaric acid in acetone. The separated light pink salt was purified by extraction with hot acetone; yield, 16 g. of light pink crystals, m.p. 116–117°.

Anal. Calcd. for $C_{12}H_{20}N_2O.C_4H_6O_6$: N, 7.8. Found: N, 7.8.

1-(3-Dimethylaminopropyl)-3-propionylpyrrole. This compound was prepared in the same manner as the 2-propionyl isomer above. Ten grams of 3-propionylpyrrole gave 10 g. of free base as a dark red oil; n_D^{27} 1.5144.

Anal. Calcd. for $C_{12}H_{20}N_2O$: N, 13.4. Found: N, 13.0.

3-Dimethylaminopropyl α-(2-pyrryl)benzyl ether ascorbate hydrate. The free base was prepared in the same manner as the 2-diethylaminoethyl-α-(2-pyrryl)benzyl ether described above. The free base was dissolved in ether and an ethanolic solution of ascorbic acid added. The ascorbate separated as a brown powder. The powder was dissolved in 95% ethanol and precipitated by ether as a very hygroscopic brown powder; yield, 8 g.

Anal. Calcd. for $C_{16}H_{22}N_2O.C_6H_8O_6.1^1/_2H_2O$: C, 57.2; H, 7.2; N, 6.1. Found: C, 57.3; H, 7.3; N, 5.5.

2,2'-[1,2-Bis(3-dimethylaminopropoxy)vinylene]bis(6-methylpyridine). 1,2-Di(6-methyl-2-pyridyl)-1,2-ethenediol[19] (24 g.) on treatment with sodium (5 g.) in toluene and then dimethylaminopropyl chloride (31 g.) as previously described, gave 11.8 g. of a red oil, b.p. 200–210° at 2 mm.

Anal. Calcd. for $C_{24}H_{36}N_4O_2$: C, 70.0; H, 8.8; N, 13.6. Found: C, 70.0; H, 9.0; N, 13.7.

The usual ketone–hydroxy benzoin type of structure has been assigned[19] to the self-condensation product of 6-methyl picolinaldehyde. However, the formation of the bis-3-dimethylaminopropoxy derivative justified the new enediol structure and name given above.

α-(3-Dimethylaminopropoxy)benzyl 2-pyrryl ketone. α-Hydroxybenzyl 2-pyrryl ketone (9 g.) on treatment with sodium (2.3 g.) in toluene, and then dimethylaminopropyl chloride (32 g.) as previously described gave 9.4 g. of an orange colored oil; b.p. 180–200° at 2–4 mm.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.3; H, 7.7; N, 9.8. Found: C, 71.5; H, 8.0; N, 9.8.

5-Nitro-2-propionylpyrrole. 2-Propionylpyrrole (25 g.) in 150 ml. of acetic anhydride cooled to −10° was dropped into 22 g. of fuming nitric acid (d = 1.5) in 50 ml. of acetic anhydride cooled to −10°. The solution was cooled to −20° and stirred for 3 hr. and then poured into ice and water. On standing overnight, the product crystallized. The yellow compound was recrystallized from hot water; yield, 14 g., m.p. 100–101°.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.0; H, 4.8; N, 16.7. Found: C, 50.0; H, 5.0; N, 17.1.

This compound failed to give a hydrazone, oxime, or guanylhydrazone under the usual conditions.

5-Nitro-2-propionylpyrrole semicarbazone. 5-Nitro-2-propionylpyrrole (10 g.) was dissolved in aqueous ethanol to which 10 g. of semicarbazide hydrochloride and 10 g. of sodium acetate were added. Overnight, a few yellow crystals separated. However, the solution was heated at 80° for two hours and then on standing for 3 days the product separated as crystalline yellow-orange needles. The separated crystals were recrystallized from boiling water; yield, 10 g., m.p. 203–204°.

Anal. Calcd. for $C_8H_{11}N_3O$: C, 42.7; H, 4.9. Found: C, 42.5; H, 4.8.

2,5-Dimethyl-3-pyrrolecarboxaldehyde. Dimethylformamide (500 g.) was cooled to 10° and 338 g. of phosphorus oxychloride dropped in. Aftter stirring for 15 min., 192 g. of 2,5-dimethylpyrrole, dissolved in 200 ml. of ethylenedichloride, was dropped in while the reaction solution was maintained at 0–5°. The solution was stirred for one hour at 10° and then heated to 40° for one hour. The completed reaction solution was mixed with 5 kg. of cracked ice and after stirring for 15 min., 600 g. of solid sodium hydroxide was stirred into the water solution, while ice was added to keep the temperature down. After 20 min., ice and concentrated hydrochloric acid was added to *p*H 7. The mixture was permitted to stand overnight and then extracted several times with ether. Concentration of the combined ether extracts gave a dark colored solid that could be crystallized from ethanol, m.p. 143°. The solid residue was distilled with sublimation at 2–4 mm. The distilled material was recrystallized to give buff-colored crystals, m.p. 144–145°; yield, 31 g.

Anal. Calcd. for C_7H_9NO: N, 11.4. Found: N, 11.1.

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[CONTRIBUTION FROM THE ORGANIC BASIC RESEARCH DEPARTMENT, THE DOW CHEMICAL COMPANY, FREEPORT, TEX.]

Reaction of Epoxides with Ferric Chloride[1]

ALEXEJ B. BOŘKOVEC

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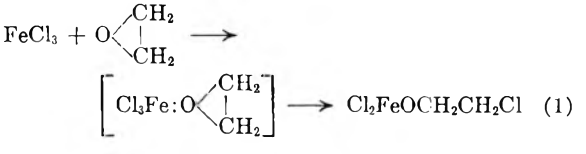
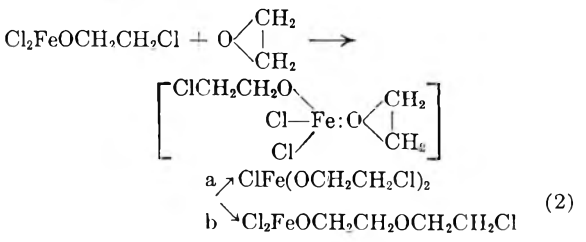
The reactions of ferric chloride with ethylene oxide and propylene oxide are described. The structure of the reaction products indicates that "internal polymerization" takes place before all of the three chlorine atoms are displaced by the epoxide. The effect of solvents upon the reaction and the formation of by-products is discussed.

The epoxy group is, in general, quite reactive towards reagents of the Lewis-acid type, especially certain halides of metallic and semi-metallic elements, in which, under suitable conditions, all of the halogen can be ultimately replaced by an alkoxy group derived from the corresponding epoxide.

In this work the reaction between ethylene and propylene oxides and anhydrous ferric chloride was investigated. The two epoxides react quite violently with chlorides of Al,[2] Ti,[3] Sb,[4] Bi,[4] Si[5] and B[6] and if the molar ratio of the reactants is sufficient, completely substituted metal chloroalkoxy compounds result. Ferric chloride,[2] on the other hand, when allowed to react with three or more moles of ethylene oxide, yields an oily product which contains approximately one-third of the total chlorine in ionic (*i.e.*, hydrolyzable) form, presumably as unreacted Fe-Cl groups. The reaction may be imagined to proceed in several steps *via* iron compound–epoxide intermediates.[7] The first step is analogous



$$FeCl_3 + O\langle CH_2 \atop CH_2 \rangle \longrightarrow \left[Cl_3Fe{:}O\langle CH_2 \atop CH_2 \rangle\right] \longrightarrow Cl_2FeOCH_2CH_2Cl \quad (1)$$

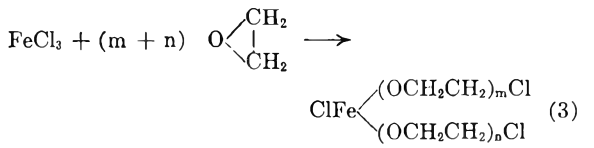


$$Cl_2FeOCH_2CH_2Cl + O\langle CH_2 \atop CH_2 \rangle \longrightarrow \left[ClCH_2CH_2O\text{—}Fe(Cl){:}O\langle CH_2 \atop CH_2 \rangle\right]$$

$$\text{a} \nearrow ClFe(OCH_2CH_2Cl)_2$$

$$\text{b} \searrow Cl_2FeOCH_2CH_2OCH_2CH_2Cl \quad (2)$$

to the reaction of other metal halides[3,4] with an epoxide but in the second step ferric chloride is distinct from all the elements hitherto investigated in that it forms (2b) a compound containing a dimerized OCH_2CH_2 unit. There seems to be a competition between the functional groups (—OCH_2CH_2Cl and —Cl) for the epoxide depending upon the number of undisplaced Cl atoms. As shown in equation (3), which summarizes the reaction in general terms, even if (m+n) >3 the last chlorine atom remains undisplaced and the alkoxy side-chains increase in length. This process may be called "internal polymerization" in order to distinguish it from a different polymerization process which, especially at higher temperatures, takes place in the presence of Lewis acids.[8–10] The latter reaction can be quite effectively minimized by keeping the temperature below 5° but the extent of the "internal polymerization" is also dependent upon the temperature and the maximum chain length will not under such conditions exceed five units. As the equation (3) indicates the reaction product is a mixture of isomeric and homologous compounds and because all attempts for separation of the components by crystallization, distillation, extraction, etc. failed, the most valuable information was obtained by hydrolyzing the mixture and identi-



$$FeCl_3 + (m+n)\ O\langle CH_2 \atop CH_2 \rangle \longrightarrow ClFe\langle (OCH_2CH_2)_mCl \atop (OCH_2CH_2)_nCl \quad (3)$$

(1) Presented before the Division of Organic Chemistry at the 132nd Meeting of the American Chemical Society, New York, N. Y., September 1957.

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(4) M. S. Malinovskii and M. K. Romantsevich, *Sbornik Statei Obshchei Khim.*, **2**, 1366–1369 (1953); J. B. Rust and L. Spialter, U. S. Patent 2,511,013 (1950); D. J. Worsfold and A. M. Eastham, *J. Am. Chem. Soc.*, **79**, 897 (1957).

(5) W. I. Patnode and R. O. Sauer, U. S. Patent 2,381,137 (1945).

(6) J. D. Edwards, W. Gerrard, and M. F. Lappert, *J. Chem. Soc.*, 1470 (1955); 348 (1957); D. J. Worsfold and A. M. Eastham, *J. Am. Chem. Soc.*, **79**, 900 (1957).

(7) No such intermediate was ever isolated in several attempts; the epoxy ring seems to be too reactive to permit stability. Analogous compounds derived from tetrahydrofuran and BCl_3 have been isolated (see reference 6).

(8) See for example K. H. Meyer, *High Polymers*, Vol. IV, Interscience Publishers, Inc., New York, N. Y., 1942, pp. 195–196 and the references mentioned there. The mechanism of this polymerization is still far from being fully understood but it can be assumed that since catalysts such as metal oxides or carbonates are also active it must be different from the "internal polymerization" suggested above.

(9) Petrochemicals Ltd., Belgian Patents 550,445 and 551,608 (1956); F. N. Hill, F. E. Bailey, and J. T. Fitzpatrick, Abstracts of Papers, 1T, 132nd Meeting of the American Chemical Society (1957).

(10) A quite different case of "internal polymerization" was discovered in the addition of acetals to olefin oxides; see O. C. Dermer and A. M. Durr, Jr., *J. Am. Chem. Soc.*, **76**, 912 (1954).

fying the resulting chlorohydrins. Table I shows typical results of the hydrolysis of $FeCl_3$-ethylene and propylene oxide reaction products.

TABLE I

PRODUCTS OF HYDROLYSIS OF ADDUCTS

Ratio of Reagents	% of $Cl(C_2H_4O)_nH$ or $Cl(C_3H_6O)_nH$ Produced				
	n = 1	n = 2	n = 3	n = 4	n > 4
$FeCl_3$ + 4 E.O.	23	31	27	12	7
$FeCl_3$ + 4 P.O.	34	32	15	10	—

Recently Worsfold and Eastham[4] suggested a rather different explanation for the formation of compounds derived from tin tetrachloride. The basic idea which was well supported by kinetic data represented the growing side chain as an ion which increased in length by reacting with additional molecules of ethylene oxide. Unfortunately, the termination step where the chloroalkoxy compound was supposed to be formed was only schematically presented without much regard for the distances between the carbonium ion and the chlorine-tin group; it is difficult to imagine how these two centers could come sufficiently close together to accomplish the suggested reaction.

Propylene oxide reacts very much like ethylene oxide; only the analysis of the products of hydrolysis is much more difficult owing to the presence of isomeric chlorohydrins (when n = 4, 16 isomers are possible). The reactivity of propylene oxide is much lower than that of ethylene oxide, as is evident in the by-product formation. 1,4-Dioxane is the chief by-product of the ethylene oxide reaction[11] but the corresponding dimethyldioxane is not formed in the propylene oxide reaction.

Solvents can have a very pronounced effect upon the nature of the reaction products. Ethers (and alcohols) take part in the reaction in a rather complicated fashion as a consequence of an extensive alkoxyl interchange. The hydrolysis of the

$$>Fe{-}OR + R_2'O \rightleftharpoons >Fe\begin{matrix}OR\\ \diagdown\\ \diagup\\ OR_2'\end{matrix} \rightleftharpoons >Fe{-}OR' + ROR'$$

reaction products then yields a mixture of chloro and hydroxy ethers instead of chlorohydrins. According to Meerwein and co-workers[12] a highly reactive oxonium compound is formed first; it apparently reacts further with the excess of the epoxide in a way similar to that indicated in Equation 3.

Aromatic solvents are to some extent alkylated by the epoxide[13] and 2-phenylethanol was actually identified among the products of the $FeCl_3$-ethylene oxide reaction when benzene was used as a solvent. Halogenated hydrocarbons seem to be most suitable as reaction media in spite of the fact that ferric chloride is insoluble in them and vigorous stirring is required to keep it in suspension.

The chloroalkoxyferric chlorides are extremely sensitive towards moisture and, when partially hydrolyzed, form amorphous solids possessing an extremely large surface area. Both unhydrolyzed and partially hydrolyzed compounds have been found to have surprising capacity for catalyzing the polymerization of alkylene oxides.[14]

EXPERIMENTAL

Reaction of ferric chloride with ethylene oxide. A suspension of 32.4 g. (0.2 mole) of anhydrous (sublimed) ferric chloride in 500 ml. of carbon tetrachloride which was previously dried over phosphorous pentoxide was placed in a dry 1000-ml. flask furnished with a stirrer, reflux condenser, and a gas dispersion tube. The system was cooled to −10° and a mixture (approx. 1:1) of nitrogen and ethylene oxide was introduced through the tube while the contents of the flask were vigorously stirred. Efficient stirring had to be maintained as long as there was any solid present to prevent the formation of a sticky cake. While the temperature was maintained between −10° and 0°, 36 g. (0.8 mole) of ethylene oxide was introduced within 6 hr. The mixture was then stirred 1 hr. at room temperature and filtered under nitrogen. The filtrate was distilled under reduced pressure to remove the solvent and about 1 ml. of 1,4-dioxane. The remaining dark brown (in thin layers bright yellow), viscous liquid (66 g.) was kept at 100° (0.1 mm.) for 10 min. and then *in vacuo* for 24 hr.

Hydrolysis of the ferric chloride-ethylene oxide reaction product. A solution of 170 g. (0.5 mole) of the reaction product in 500 ml. of carbon tetrachloride was mixed with 50 ml. of water and refluxed for 2 hr. on a steam bath. The brown precipitate was isolated by filtration (filtrate A), mixed with 100 ml. of water, heated on a steam bath for 24 hr., and again collected (filtrate B). Filtrate B was saturated with potassium carbonate (kept cool) and extracted twice with 50 ml. of ether. The ethereal extracts were combined with filtrate A, dried over potassium carbonate, and distilled. After the solvents were removed, the liquid (about 100 ml.) was transferred to a smaller flask and distilled at reduced pressure using 120-cm., helices-packed column operated at reflux ratio of 100:1. The individual fractions (see Table I) were analyzed (infrared spectra, refractive index, % of OH and Cl, mol. wt.) and compared with actual samples of the chlorohydrins. The total amount of recovered chlorohydrins was 155 g. (92%). The last fraction (n > 4 in Table I) was the distillation residue and consisted of a mixture of several extended chlorohydrins.

Reaction of ferric chloride with propylene oxide. The apparatus was the same as used for ethylene oxide. Propylene oxide (in 10% excess of the theoretical) mixed with an equal volume of carbon tetrachloride was added dropwise,

(11) A. Favorsky, *J. Russ. Phys.-Chem. Soc.*, **38**, 741 (1905); *Chem. Zentr.*, I, 15 (1907).

(12) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. prakt. Chem.*, **154**, 84 (1939).

(13) J. Colonge and P. Rochas, *Compt. rend.*, **223**, 403 (1945).

(14) M. E. Pruitt and J. M. Baggett, U. S. Patents 2,706,181 (1955); 2,706,182 (1955); 2,706,186 (1955).

the temperature being kept below 30° and the addition lasting 8 hr. The mixture was then stirred overnight. The solvent was removed in the same manner as above. the reaction product was a black (bright yellow in thin layers), viscous oil.

Anal. Calcd. for $C_{12}H_{24}Cl_3FeO_4$: Cl, 26.9 (ionic chlorine, 9.0); Fe, 14.2; mol. wt., 395. Found: Cl, 27.1 (ionic chlorine, 8.9); Fe, 14.5; mol. wt., 390.

Hydrolysis of the ferric chloride–propylene oxide reaction product. The procedure was the same as in the former case except that the iron-containing residue after being heated with water and filtered out was extracted with two 50-ml. portions of acetone. The acetone extract was then combined with the other filtrates. The amount of the ferric chloride–propylene oxide product was 197 g. (0.5 mole), and 130 g. (85% yield) of the chlorohydrins was isolated. The results of the fractional distillation of the mixture are summarized in Table II.

TABLE II

IRON-FREE COMPONENTS OF THE HYDROLYZED FERRIC CHLORIDE–PROPYLENE OXIDE REACTION PRODUCT

	No. of C_3H_6O Units in the Chlorohydrin			
	1	2	3	4
B.b., °C.	46–50	97–103	85–94	Residue
p, mm.	25	20	2	...
n_D^{25}	1.4370	1.4412	1.4440	1.4501
Mol. wt. calcd.	94.5	152.6	210.7	258.8
% OH calcd.	18.0	11.1	8.1	6.3
% Cl calcd.	37.5	23.3	16.8	13.2
Mol. wt. found	95	163	212	280
% OH found	17.5	10.7	8.2	5.9
% Cl found	37.8	22.8	17.0	13.1

FREEPORT, TEX.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF TENNESSEE EASTMAN COMPANY, DIVISION OF EASTMAN KODAK CO.]

Reaction of Ketene with Dialkyl Hydrogen Phosphites and Acylphosphonates

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Diethyl 1-acetoxyvinylphosphonate was obtained when a crude β-propiolactone—diethyl hydrogen phosphite reaction mixture containing excess diethyl hydrogen phosphite was treated with ketene. The structure of the diethyl 1-acetoxyvinylphosphonate was proved by reducing this compound to the known diethyl 1-acetoxyethylphosphonate. The enol form of diethyl acetylphosphonate is a probable intermediate in the reaction of diethyl hydrogen phosphite with ketene to form diethyl 1-acetoxyvinylphosphonate. The infrared spectra of the products obtained when diethyl acetylphosphonate is treated with ketene indicate that a lactone, probably the β-lactone of 3-diethylphosphono-3-hydroxybutyric acid, is formed in addition to diethyl 1-acetoxyvinylphosphonate.

In recent papers, the reaction of phosphites with lactones was described.[1,2] The phosphonates derived from the interaction of trialkyl phosphites with lactones were stable, distillable materials; however, those derived from the interaction of dialkyl hydrogen phosphites with lactones were rather sensitive to distillation, even at low pressures. For example, the reaction products from diethyl hydrogen phosphite and β-propiolactone included diethyl 3-hydroxypropionylphosphonate (I) and tetraethyl 1,3-dihydroxypropylidenediphosphonate (II).

$HOCH_2CH_2C(O)P(O)(OC_2H_5)_2$
I

$HOCH_2CH_2C(OH)[P(O)(OC_2H_5)_2]_2$
II

In an attempt to stabilize these products by acetylation, the crude diethyl hydrogen phosphite–β-propiolactone reaction mixture was treated with ketene. Although the product obtained was distillable, it did not prove to be the acetyl derivative of either I or II. Again, the higher boiling fractions were rather unstable to distillation at low pressures.

The distillable material was found to be diethyl 1-acetoxyvinylphosphonate (III). This product apparently was formed by reaction of ketene with excess diethyl hydrogen phosphite present in the reaction mixture, since good yields of III were obtained by reaction of pure diethyl hydrogen phosphite with ketene. This reaction was observed independently by Kennedy and Meaburn.[3] The formation of III could be explained by the following equation:

$$(C_2H_5O)_2P(O)H + CH_2{=}C{=}O \xrightarrow{BF_3} [CH_2{=}C(OH)P(O)(OC_2H_5)_2] \xrightarrow{CH_2{=}C{=}O} CH_2{=}C(OCOCH_3)P(O)(OC_2H_5)_2$$

IV

III

The postulated intermediate, IV, is the enol form of diethyl acetylphosphonate. This is a probable intermediate since carbonyl compounds are known to react readily with dialkyl hydrogen phos-

(1) R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, **78**, 4450 (1956).

(2) R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, **78**, 4453 (1956).

(3) J. Kennedy and G. M. Meaburn, *Chem. & Ind. (London)*, 930 (1956).

phites.[1,4–6] The enol, IV, formed *in situ* would be rapidly converted to the acetoxy derivative (III). To determine if IV is the intermediate, diethyl acetylphosphonate was treated with ketene under the same conditions used for the diethyl hydrogen phosphite–ketene reaction. The result was the formation of some III as well as the isomeric lactone (V). The presence of V was strongly suggested since

$$CH_3COP(O)(OC_2H_5)_2 + CH_2{=}C{=}O \xrightarrow{BF_3}$$

$$CH_2{=}C(OCOCH_3)P(O)(OC_2H_5)_2 + CH_3C(-O-CO-)CH_2-P(O)(OC_2H_5)_2$$

III V

the infrared spectra of the distillation fractions contained a carbonyl band at 5.45 μ, which is characteristic of a lactone structure. Also, the analyses were correct for $C_8H_{15}O_5P$ which is the molecular formula for both III and V. The reaction of ketene with carbonyl compounds to form lactones is well known.[7,8] It is likely, then, that the acetylphosphonate, in addition to enolizing to IV and then reacting with ketene to produce III, also reacted directly with ketene to form V.

Isomers III and V codistilled and were therefore difficult to separate by distillation. Also, much of the lactone probably decomposed during the initial distillation of the reaction mixture.

In the preparation of diethyl 1-acetoxyvinylphosphonate from diethyl hydrogen phosphite and ketene, the use of a solvent, such as toluene, was found advantageous. The reaction mixtures were easier to process and the yields of III were higher when a solvent was used. The attempted use of acetic anhydride instead of ketene was not successful.

The structure of III was proved by a catalytic reduction using Raney nickel to produce diethyl 1-acetoxyethylphosphonate (VI).

$$CH_2{=}C(OCOCH_3)P(O)(OC_2H_5)_2 + H_2 \xrightarrow{\text{Raney Ni}} CH_3CH(OCOCH_3)P(O)(OC_2H_5)_2$$

VI

The physical properties and infrared spectrum of VI obtained by reduction of III were identical with those of diethyl 1-acetoxyethylphosphonate prepared earlier by other methods.[9]

In addition, we prepared VI by treating diethyl 1-hydroxyethylphosphonate with acetic anhydride in pyridine.

$$CH_3CHOHP(O)(OC_2H_5)_2 + (CH_3CO)_2O \xrightarrow{\text{pyridine}} CH_3CH(OCOCH_3)P(O)(OC_2H_5)_2$$

EXPERIMENTAL

Diethyl 1-acetoxyvinylphosphonate (III). (*a*) *By reaction of ketene with crude diethyl hydrogen phosphite–β-propiolactone reaction mixture.* Diethyl hydrogen phosphite (110.4 g., 0.8 mole) and β-propiolactone (28.8 g., 0.4 mole) were mixed and heated at 150–173° with stirring for 17 hr. After 5 drops of boron fluoride etherate was added to the crude reaction mixture, ketene was bubbled in through a fritted glass disk while the flask was cooled externally with an ice-water bath. The temperature rose to a maximum of 80°. After 45 min., 49.4 g. of ketene had been absorbed by the reaction mixture. The crude mixture (a light yellow oil) was allowed to stand overnight, and was then distilled *in vacuo* through a 6-in. Vigreux column to obtain the following fractions: (*1*) 6.0 g., b.p. 25–95° (2.5 mm.), n_D^{20} 1.3978; (*2*) 13.6 g., b.p. 95–112° (2.6 mm.), n_D^{20} 1.4298; (*3*) 63.0 g., b.p. 112–125° (2.7–3.2 mm.), n_D^{20} 1.4344; (*4*) 23.4 g., b.p. 120–126° (1.9–3.5 mm.), n_D^{20} 1.4290. At this point, decomposition became excessive and the distillation was stopped. The residue was a dark, resinous material.

Redistillation of 50 ml. of fraction (*3*) through a 12-in. Vigreux column gave a forerun of 11 ml., b.p. 64–80° (0.9–0.3 mm.), n_D^{20} 1.4261, and 30 ml. of diethyl 1-acetoxyvinylphosphonate, b.p. 79–80° (0.3–0.4 mm.), n_D^{20} 1.4378.

Anal. Calcd. for $C_8H_{15}O_5P$: C, 43.24; H, 6.80; P, 13.94. Found: C, 43.21; H, 6.94; P, 13.95.

The infrared spectrum of this compound is compatible with III since it contains a terminal methylene band at 11.55 μ, a conjugated unsaturation band at 6.15 μ, a carbonyl band at 5.65 μ, and the usual phosphoryl and C—O—P bands. These bands are in complete agreement with those reported by Kennedy and Meaburn.[3]

(*b*) *By reaction of ketene with diethyl hydrogen phosphite.* Diethyl hydrogen phosphite (110.4 g., 0.8 mole) and 20 drops of boron fluoride etherate were dissolved in 110 ml. of toluene. Ketene was bubbled into the solution through a fritted glass disk. The temperature of the solution rose to 80°. At this point the temperature was moderated by external cooling, and the temperature was maintained in the 30–80° range by occasional cooling. Escaping ketene was returned to the reaction flask by means of a Dry Ice–cooled condenser. After 1 hr., 72.5 g. of ketene had been condensed in the reaction mixture (67.2 g. of ketene required). About 2 g. of anhydrous sodium carbonate was added to the solution and the material was distilled *in vacuo* through a 6-in. Vigreux column. A forerun boiling up to 97° (2.1 mm.) was removed, and then 71.7 g. (40.4%) of product distilling at 97–99° (2.0 mm.) was collected, n_D^{20} 1.4370. The infrared spectrum of this sample was identical with that obtained on the diethyl 1-acetoxyvinylphosphonate obtained in the previous experiment.

Diethyl 1-acetoxyvinylphosphonate (III) *and 3-diethylphosphono-3-hydroxybutyric acid, β-lactone* (V). Diethyl acetylphosphonate (18.0 g., 0.1 mole) and 10 drops of boron fluoride etherate were placed in 50 ml. of toluene, and ketene was introduced through a fritted glass disk, with stirring. After 30 min., 12 g. of ketene had condensed in the reaction mixture. The solution was then stirred for 2 hr. at 25° and finally heated on a steam bath for 15 min. The solvent was removed and the residue was distilled *in vacuo* through a 6-in. Vigreux column to obtain the following fractions: (*1*) 2.6 g., b.p. 60–79° (0.5–0.8 mm.), n_D^{20} 1.4262; (*2*) 4.2 g., b.p. 80–97° (0.8–1.4 mm.), n_D^{20} 1.4320; (*3*) 4.9

(4) W. E. Craig and W. F. Hester (to Rohm and Haas Co.), U. S. Patent **2,485,573** (1949).

(5) E. K. Fields (to Research Corp.), U. S. Patent **2,579,810** (1951).

(6) A. R. Stiles (to Shell Development Co.), U. S. Patent **2,593,213** (1952).

(7) F. E. Küng (to The B. F. Goodrich Co.), U. S. Patent **2,356,459** (1944).

(8) T. L. Gresham, J. E. Jansen, F. W. Shaver, and W. L. Beears, *J. Am. Chem. Soc.*, **76**, 486 (1954).

(9) R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, **79**, 1961 (1957).

g., b.p. 96–120° (1.2–1.8 mm.), n_D^{20} 1.4402 The distillation was stopped at this point because of decomposition. The residue was tarry. Fractions (1), (2), and (3) were combined and redistilled through a 6-in. Vigreux column to give the following fractions: (*1*) 4.6 g., b.p. 57–75° (0.7 mm.), n_D^{20} 1.4250 (diethyl acetylphosphonate); (*2*) 0.1 g., b.p. 75–84° (0.7 mm.), n_D^{20} 1.4322; (*3*) 1.2 g., b.p. 86–106° (0.7 mm.), n_D^{20} 1.4420; (*4*) 2.2 g., b.p. 109–112° (0.7–0.8 mm.), n_D^{20} 1.4430.

Anal. Calcd. for $C_8H_{15}O_5P$: C, 43.24; H, 6.80; P, 13.94. Found on fraction (3): C, 43.78; H, 7.13; P, 14.33.

The infrared spectra of fractions (*3*) and (*4*) indicated the presence of both diethyl 1-acetoxyvinylphosphonate and the β-lactone of 3-diethylphosphono-3-hydroxybutyric acid in addition to traces of diethyl acetylphosphonate.

Diethyl 1-acetoxyethylphosphonate (VI). (*a*) *From diethyl 1-acetoxyvinylphosphonate.* Diethyl 1-acetoxyvinylphosphonate (11.1 g., 0.05 mole) dissolved in 50 ml. of absolute ethyl alcohol was placed in a pressure bottle, and 5 g. of a suspension of Raney nickel in ethyl alcohol was added. Hydrogen was added until the pressure reached 45 p.s.i., and the temperature was raised to 57°. The reaction was continued at this temperature until 0.05 mole of hydrogen had been absorbed (2.5 hr.). The Raney nickel was removed by filtration and 0.2 g. of anhydrous sodium carbonate was added to the filtrate. The solution was then distilled *in vacuo* through a 6-in. Vigreux column. After the forerun had been removed up to a head temperature of 101° (3.0 mm.), 4.0 g. (35.7%) of diethyl 1-acetoxyethylphosphonate was collected at 101–102° (3.0 mm.), n_D^{20} 1.4265.

Anal. Calcd. for $C_8H_{17}O_5P$: C, 42.85; H, 7.64. Found: C, 42.47; H, 7.90.

The infrared spectrum of this sample of diethyl 1-acetoxyethylphosphonate was identical with that of this ester prepared by other methods.[9]

(*b*) *From diethyl 1-hydroxyethylphosphonate.* Acetic anhydride (40.8 g., 0.4 mole) and diethyl 1-hydroxyethylphosphonate[9] (36.4 g., 0.2 mole) were dissolved in 100 ml. of pyridine, and the solution was stirred for 24 hr. The reaction mixture was distilled *in vacuo* through a 6-in. column packed with glass helices. After the pyridine and forerun up to a temperature of 94° (1.8 mm.) had been removed, 26 g. (58%) of diethyl 1-acetoxyethylphosphonate was collected at 94–96° (1.8 mm.), n_D^{20} 1.4265.

Anal. Calcd. for $C_8H_{17}O_5P$: C, 42.85; H, 7.64; P, 13.82. Found: C, 43.09; H, 7.68; P, 14.04.

The infrared spectrum of this product was identical with that of this ester prepared by other methods.[9]

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

Steroids and Triterpenoids of Citrus Fruit. II. Isolation of Citrostadienol[1]

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Received November 4, 1957

Grapefruit peel oil was found to contain citrostadienol, a new doubly unsaturated steroidal alcohol. The isolation of this compound as well as of β-sitosterol and friedelin from orange peel oil is also reported.

In the first paper of this series we described the isolation of β-sitosterol and friedelin from grapefruit peel oil. Further investigation of the content of the nonvolatile unsaponifiable fraction of this oil has now revealed the presence of an additional compound called by us citrostadienol, $C_{30}H_{50}O \pm CH_2$,[2] m.p. 162–164°, $[\alpha]_D$ +24°.

This compound was first found in the β-sitosterol mother liquors. Later, it could be isolated directly by careful chromatography on alumina of the total crystalline material obtained from the unsaponifiable fraction of the peel oil. The quantity of the isolated citrostadienol amounted to only *ca.* 0.01% of the total. In order to obtain more of this compound large quantities of grapefruit peel oil were needed. Due to the difficulty in obtaining such quantities of this peel oil the more readily accessible orange peel oil was examined for its content of citrostadienol.

The isolation of a steroid from sweet orange (*Citrus Aurentium sinesis*) peel oil was reported already in 1900. Stephan[3] obtained from the peel of Italian sweet oranges a compound with m.p. 138° giving a Liebermann-Burchardt color.[4] A phytosterol with similar constants was isolated by Naves from Guinea oranges.[5] Matlack in an extensive study of the constituents of California orange peel oil succeeded in isolating two phytosterols melting at 139° and 150°, respectively (the acetates melted at 128° and 113.5–114°, respectively), and a "phytosterylin".[6] The compound with m.p. 139° later referred to as "sitosterol" possesses the physical constants of β-sitosterol, as is the case with the compounds isolated by Naves[5] and by Stephan.[3] The "phytosterylin" is most probably β-sitosterol glycoside.[7] This glycoside was found recently to be a constituent of orange juice.[8]

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(1) Presented in part at the 18th Meeting of the Chemical Society of Israel, 1955 (*cf. Bull. Res. Coun. Israel*, **5A**, 105 (1955). For Part I, see "Steroids and Triterpenoids of Grapefruit," Weizmann, Meisels, and Mazur, *J. Org. Chem.*, **20**, 1173 (1955).

(2) The distinction between the C_{29}, C_{30}, and C_{31} formulations cannot be made on the basis of the molecular weight determination by the *Rast* method or by C, H analyses.

(3) Stephan, *J. prakt. Chem.*, 62, 523 (1900).

(4) The molecular formula given for this compound, $C_{29}H_{48}O_2$, undoubtedly included water of crystallization. It is known that the plant 3β-hydroxy steroids may contain water of crystallization, which is removed only with difficulty.

(5) Naves, *Parfums France*, **10**, 181 (1932).

(6) Matlack, *J. Am. Pharm. Assoc.*, **18**, 24 (1928).

(7) Matlack, *J. Org. Chem.*, **5**, 104 (1940).

(8) Swift, *J. Am. Chem. Soc.*, **74**, 1099 (1952).

For examination of the orange (*Citrus Aurentium sinensis*) peel oil we used the procedure adopted previously for the grapefruit peel oil.[1] The non-volatile part of the orange oil was saponified and the unsaponifiable part treated with methanol. Concentration of the methanolic solution gave a crystalline precipitate, which was chromatographed on alumina. From the eluted fractions we isolated successively the following compounds: paraffins, friedelin, cerylalcohol, citrostadienol and β-sitosterol. Paraffins and ceryl alcohol have already been isolated and identified by former investigators.[6] Friedelin and β-sitosterol were identified by us by comparison with authentic samples.[1] The fractions which were eluted between pure citrostadienol and β-sitosterol gave mixed crystals of these two compounds, m.p. 150°, $[\alpha]_D$ ±0°, which could not be separated by crystallization. Acetylation of this material gave crystals with the constant m.p. 115°, $[\alpha]_D$ 10°. The separation of this mixture could be effected only through rechromatography on alumina. It is probable that the phytosterol melting at 150°, isolated by Matlack,[6] consists of a mixture of β-sitosterol and citrostadienol.

Citrostadienol gives a precipitate with digitonin. It forms a monoacetate, m.p. 145–146°, $[\alpha]_D$ 39°, and on oxidation yields a ketone, m.p. 147–148°, $[\alpha]_D$ 15° $\nu_{max.}$ 1715 cm^{-1}, no absorption maxima in the ultraviolet above 218 mμ, from which the alcohol can be regenerated by reduction with lithium aluminum hydride. Citrostadienol gives a violet-blue-green Liebermann-Burchardt coloration and reacts positively in the Tortelli-Jaffe reaction[9] and Fieser's selenium dioxide test.[10] It absorbs one molar equivalent of hydrogen on hydrogenation over platinum in acetic acid. If the above hydrogenation is carried out in the presence of hydrochloric acid, the substance absorbs two molar equivalents of hydrogen giving a fully saturated product.

The above described observations suggest that citrostadienol is a doubly unsaturated 3β-hydroxy steroid, one of the double bonds being located in the $\Delta^{7,8}$ or $\Delta^{8,9}$-position. On the other hand, the molecular rotation differences between citrostadienol, its acetate, and the corresponding ketone, resemble those of the tetracyclic triterpenes[11] rather than the steroids. It is interesting to note that the "α-sitosterols," which accompany β-sitosterol in other plants, show a similarity to citrostadienol in this respect.[12] The elucidation of the structure of citrostadienol is now in progress.

(9) *Cf.* Fieser and Fieser, *Natural Product Related to Phenanthrene*, third ed., Reinhold Publishing Co., 1949, pp. 100–101.

(10) Fieser, *J. Am. Chem. Soc.*, **75**, 4395 (1953).

(11) Barton, *J. Chem. Soc.*, 813 (1945).

(12) *Elsevier's Encyclopedia of Organic Chemistry*, Vol. 14 Supplement, Triterpenes, 1952, pp. 1307–10.

EXPERIMENTAL[13]

Isolation of citrostadienol from grapefruit peel oil. A. The The oil from the peel of grapefruit was treated as described in part I[1] yielding 17 g. of unsaponifiable crystalline product. This was crystallized twice from ether-methanol, the crystals were collected, and the mother liquors (8 g.) were combined, concentrated, and left for a few days in the cold. The crystals thus produced had m.p. 153–155° and gave positive Tortelli-Jaffe and Fieser selenium dioxide tests. Five crystallizations from ether-methanol afforded pure citrostadienol, m. p. 162–164° (*in vacuo* 167–168°), $[\alpha]_D$ +24°.

Anal. Calcd. for $C_{29}H_{48}O$: mol. wt., 413; C, 84.40; H, 11.72; for $C_{30}H_{50}O$: mol. wt., 427; C, 84.44; H, 11.81; for $C_{31}H_{52}O$: mol. wt., 441; C, 84.48; H, 11.89. Found: mol. wt., 450; C, 84.64; H, 11.61.

B. The unsaponifiable crystalline material (19 g.) obtained from another quantity of peel oil (6 kg.) was dissolved in 150 cc. of pentane-benzene mixture (9:1) and chromatographed on a column of 600 g. of alumina. The first fractions eluted with 3 l. of a mixture of pentane:benzene (9:1) were discarded. The next fraction eluted with 600 cc. of a benzene-ether mixture (9:1) gave 610 mg. of crystals, m.p. 153–156°, which after additional 5 crystallizations from ether-methanol gave plates, m.p. 160–162°, undepressed on admixture with the citrostadienol mentioned above. The fraction eluted next gave 900 mg. of plates, m.p. 142–148°, which after three crystallizations showed m.p. 148–150°, $[\alpha]_D$ ±0°. The melting point of this material could not be increased by additional crystallizations. Acetylation of this material with pyridine and acetic anhydride gave crystals of the acetate, m.p. 115°, $[\alpha]_D$ +10°. On hydrolysis with methanolic potassium hydroxide the starting material with m.p. 148–150° was recovered.

Further elution with 4 l. of benzene-ether (9:1) gave crystals, m.p. 139°, identified as β-sitosterol (mixture melting point, infrared spectrum).

Five hundred milligrams of the material with m.p. 148–150° was rechromatographed on alumina (15 g.). The fraction eluted with benzene-ether (9:1) gave crystals (150 mg.), m.p. 154–156°. Crystallization from ether-methanol gave citrostadienol, m.p. and mixed m.p. 162–164°. The fraction eluted next with the same solvent mixtures gave 200 mg. of β-sitosterol m.p. and mixed m.p. 139–140°.

Isolation of citrostadienol from orange peel. One kilogram of concentrated orange oil was distilled under reduced pressure at 80–120° (12–15 mm.).[14] The distillate consisted of limonene (450 g.). The rest was further distilled in high vacuum at 90–120° (0.5 mm.). The brown residue (460 g.) was then saponified with 2 l. of methanolic potassium hydroxide (3%) on the steam bath. The solution was concentrated *in vacuo* to a third of its volume, 3 l. of water was added and the neutral part extracted with ether. The ethereal extract was washed several times with water, dried, and evaporated. The dark unsaponifiable part was triturated with 2 l. of methanol and left in cold overnight. The crystalline product obtained (18.3 g.) was collected, dissolved in pentane, and chromatographed on alumina (6.00 g.).

The first fraction, eluted with 1400 cc. of pentane-benzene (9:1) mixture, gave 1.4 g. of crystals, m.p. 60–65°. This

(13) Melting points are uncorrected. Rotations were measured at 20° in chloroform solution in a 1 dm. tube and a concentration of 10 ± 2 mg./cc. Infrared spectra (Baird double-beam) were determined in chloroform solution. The microanalyses were carried out in our microanalytical department under the direction of Mr. E. Meier. We are indebted to Miss Rivka Shapira for her helpful technical assistance.

(14) We are indebted to the Citrus Products Manufacturers' Association, Tel-Aviv, Israel, for supplying us with this oil. It was obtained by concentration of the orange peel oil *in vacuo* and subsequent treatment with 80% ethanol.

material did not give a coloration with tetranitromethane, did not possess absorption in the ultraviolet, resisted treatment with hot sulfuric acid, and consisted of paraffins.[6]

The next fractions, eluted with 400 cc. of pentane-benzene (1:1) gave 500 mg. of needles, m.p. 223–250°. Crystallization from ethyl acetate and sublimation in high vacuum gave friedelin, m.p. 256–257°, $[\alpha]_D$ +20°.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.35; H, 11.70.

No depression of melting point was observed when mixed with an authentic specimen of friedelin. A comparison of the infrared spectra of this compound with an authentic sample showed complete indentity.

Further elution with 400 cc. of pentane-benzene (2:1) yielded a waxy material (550 mg.), m.p. 77–79°. This compound gave no coloration with tetranitromethane and did not show any appreciable absorption in the ultraviolet. The infrared spectrum possessed a hydroxyl band. It is probably identical with the ceryl alcohol previously isolated by Matlack from orange peel oil.[6]

Anal. Calcd. for $C_{26}H_{54}O$: C, 81.60; H, 14.20. Found: C, 81.85; H, 14.34.

The next fraction (1.4 g.), eluted with 500 cc. of benzene and 500 cc. of benzene-ether (9:1) gave crystals, m.p. 145–157°.

The last fraction of the chromatogram, eluted with 3 l. of benzene-ether (1:1) gave 5.5 g. of crystals, m.p. 132–138°. After crystallization from methanol the substance showed m.p. 139–140° and gave no depression on admixture with β-sitosterol. The infrared spectra of the two compounds showed complete identity.

The fractions with m.p. 145–157° were rechromatographed on 50 g. of alumina. Successive elution with 150 cc. of pentane-benzene (1:1) and 300 cc. of pentane-benzene (1:2) gave respectively 340 mg. of crystals with m.p. 157–161° and 930 mg. with m.p. 148–154°. The material with m.p. 157–161° was crystallized twice from ether-methanol to give citrostadienol, m.p. and mixed m.p. 162–164° $[\alpha]_D$ +24°. The material with m.p. 148–154° after another chromatography and crystallizations gave an additional 260 mg. of citrostadienol.

Citrostadienol acetate. Citrostadienol (200 mg.; m.p. 162–164°) was treated with 2 cc. of pyridine and 2 cc. of acetic anhydride and left overnight at room temperature. Isolation with ether and crystallization from absolute methanol gave citrostadienol acetate, m.p. 142–143° (145–146° *in vacuo*), $[\alpha]_D$ +43°.

Anal. Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08; $C_{32}H_{52}O_2$: C, 81.99; H, 11.18; $C_{33}H_{54}O_2$: C, 82.09; H, 11.27. Found: C, 81.73; H, 11.10.

Hydrolysis of the acetate. The acetate (100 mg.) was saponified with 100 cc. of methanolic potassium hydroxide (3%). Isolation from ether gave plates, m.p. 162–164°. No depression of melting point was observed when mixed with citrostadienol.

Oxidation of citrostadienol. A. Citrostadienol (150 mg.; m.p. 162–164°) was dissolved in 15 cc. of toluene, 5 cc. of cyclohexanone was added, and the mixture was distilled until 10 cc. of distillate had been collected in order to remove water. One gram of aluminum isopropoxide dissolved in 10 cc. of toluene was added dropwise to the boiling solution during 5 min., and the reaction mixture was refluxed for another 45 min. It was then cooled, water was added, and the solvents were removed by steam distillation. The resulting solid was collected by filtration and extracted with chloroform. Evaporation of the solvent gave a crystalline residue which was chromatographed on alumina (5 g.). Elution with pentane-benzene (9:1) gave 80 mg. of citrostadienone, which after crystallization from methanol showed m.p. 146–147°, $[\alpha]_D$ +15°.

Anal. Calcd. for $C_{29}H_{46}O$: C, 84.81; H, 11.29; $C_{30}H_{48}O$: C, 84.84; H, 11.39; $C_{31}H_{50}O$: C, 84.86; H, 11.49. Found: C, 84.61; H, 11.51.

B. A solution of 200 mg. of citrostadienol in 4 cc. of dry pyridine was added to a solution of chromium trioxide (200 mg.) in 4 cc. of pyridine. After being allowed to stand overnight at room temperature, water was added and the material was isolated with ethyl acetate. The residue (190 mg.) was chromatographed on 6 g. of alumina. The fraction eluted with pentane gave 85 mg. of crystals, m.p. 146–147°, $[\alpha]_D$ +15°, undepressed on admixture with the citrostadienone obtained above.

Citrostadienol from citrostadienone. A solution of 100 mg. of citrostadienone in 10 cc. of ether was added to 200 mg. of lithium aluminum hydride in 20 cc. of ether. After being refluxed for 1 hr., the mixture was decomposed with dilute sulfuric acid and ice. The material was isolated with ether and crystallized from ether-methanol to give 80 mg. of citrostadienol, m.p. and mixed m.p. 162–164°.

Hydrogenation of citrostadienol. A. Citrostadienol (30 mg.) in 10 cc. of acetic acid was hydrogenated in the presence of 10 mg. of platinum oxide. One molar equivalent of hydrogen was absorbed. The solid product showed coloration with tetranitromethane, gave positive Lieberman-Burchardt and Tortelli-Jaffe tests, and did not react in Fieser's selenium dioxide reaction.

B. Two drops of concentrated hydrochloric acid were added to a solution of 25 mg. of citrostadienol in 10 cc. of acetic acid and the solution was hydrogenated over 10 mg. of platinum oxide. Two molar equivalents of hydrogen were absorbed. The solid product showed no unsaturation in the tetranitromethane and Lieberman-Burchardt tests.

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REHOVOTH, ISRAEL

[CONTRIBUTION FROM THE INSTITUTE FOR CANCER RESEARCH AND LANKENAU HOSPITAL RESEARCH INSTITUTE]

Synthesis of Certain Hydroxycarboxylic Acids Related to Isocitric Acid[1]

MASATARO YAMASHITA[2]

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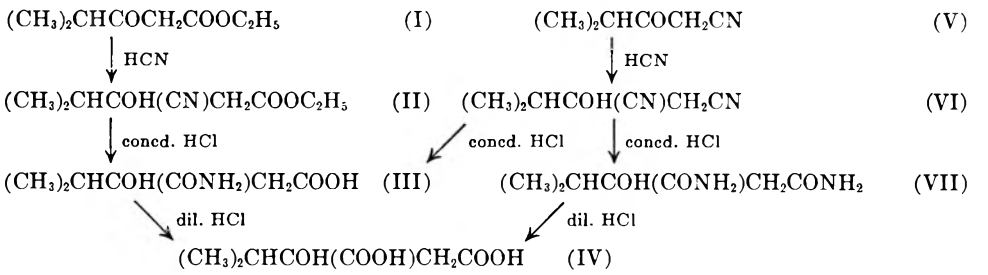
Syntheses of 2-hydroxy-2-isopropylsuccinic acid and 2-hydroxy-3-carboxyadipic acid are described.

2-Hydroxy-2-isopropylsuccinic acid and 2-hydroxy-3-carboxyadipic acid were proposed by Strassman *et al.*[3,4] as intermediates in the biosynthesis of leucine and lysine, respectively. These hydroxy acids were presumed to result from enzymatic condensation reactions analogous to citric acid formation from oxalacetic acid and acetyl coenzyme A. In order to appraise this hypothesis it was desirable to test these substances for biological activity,[5] and their synthesis is reported in the present communication.

2-Hydroxy-2-isopropylsuccinic acid. Ssemenow[6] reported the synthesis of this compound, having obtained a product melting at 165–166° by hydrolysis of 2-bromo-2-isopropylsuccinic acid. Darzens and Sejourné,[7] however, obtained a melting point of 139° for what they believed to be the same compound. Their method of preparation involved the hydrolysis of diethyl 2-isopropylsuccinate, prepared by condensation of ethyl 4,4-dimethyl-



glycidate with ethyl bromoacetate in the presence of zinc.

This compound was prepared by two straightforward procedures outlined below. In the first, ethyl isobutyrylacetate (I) was treated with hydrogen cyanide and, without isolation, the oily cyanhydrin (II) was hydrolyzed with concentrated hydrochloric acid. The product, 2-hydroxy-2-isopropylsuccinamic acid (III), m.p. 156–157°, was refluxed with dilute hydrochloric acid to yield 2-hydroxy-2-isopropylsuccinic acid (IV). An overall yield of 33% was obtained. The product, after repeated crystallization from ethyl acetate and petroleum ether, melted at 145–147°.

In the second procedure, isobutyrylacetonitrile (V), prepared by a modification of the method of Kroeker and McElvain,[8] was treated with hydrogen cyanide, and the resultant cyanohydrin (VI) was hydrolyzed with concentrated hydrochloric acid to yield 2-hydroxy-2-isopropylsuccinamide (VII), m.p. 195–197°, accompanied by small amounts of 2-hydroxy-2-isopropylsuccinamic acid (III). The diamide (VII) was hydrolyzed with dilute hydrochloric acid at 100° giving a 60% yield of 2-hydroxy-2-isopropylsuccinic acid (IV), m.p. 145–147° (not lowered by admixture with a sample prepared by the first method).

2-Hydroxy-3-carboxyadipic acid. Substances having this composition were described previously by Perlmutter,[9] in the form of a non-crystalline lactone, obtained by reduction and cleavage of quinolinic acid; and by Freudenberg and Geiger[10] who obtained the L-lactone melting at 110–111° by oxidation of methyl 3-acetyldihydroshikimate. In the present study, the hydroxy ester (XI) was obtained by reduction of triethyl 2-oxaloglutarate (X), prepared by condensation of diethyl glutarate (IX) with diethyl oxalate (VIII) according to a modification of the procedure of Gault.[11] On saponification, the free acid (XII) melting at 127–129° was obtained.

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(2) Research Fellow of the Women's Auxiliaries of the Institutes, on leave from Kinki University, Osaka, Japan.

(3) M. Strassman, L. A. Nocke, A. J. Thomas, and S. Weinhouse, *J. Am. Chem. Soc.*, **78**, 1599 (1956).

(4) M. Strassman and S. Weinhouse, *J. Am. Chem. Soc.*, **75**, 1680 (1953).

(5) The biological activities of these two compounds will be reported separately.

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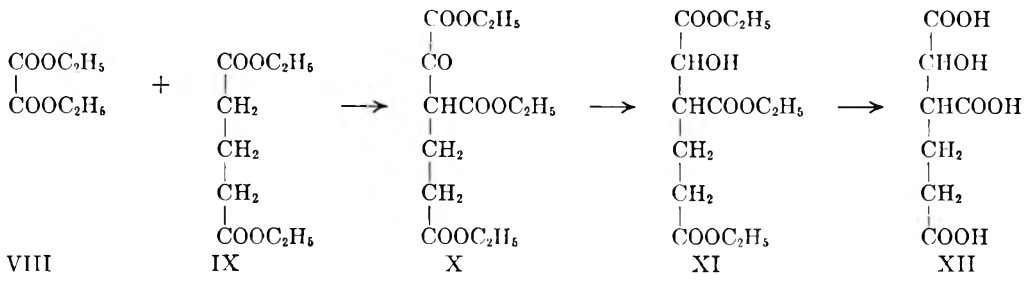
(8) E. H. Kroeker and S. M. McElvain, *J. Am. Chem. Soc.*, **56**, 1172 (1934).

(9) A. Perlmutter, *Monatsh.*, **13**, 842 (1892).

(10) K. Freudenberg and J. Geiger, *Ann.*, **575**, 145 (1952).

(11) M. H. Gault, *Compt. rend.*, **148**, 1113 (1909).



EXPERIMENTAL

2-Hydroxy-2-isopropylsuccinamic acid (III) *from ethyl isobutyrylacetate* (I). One and five-tenths g. (0.01 mole) of ethyl isobutyrylacetate,[12] and 0.98 g. (0.02 mole) of powdered sodium cyanide were stirred mechanically and cooled with ice while 1.7 ml. of concentrated hydrochloric acid was added dropwise. After stirring for 2 hr. at 0° the reaction mixture was extracted with ether, and the ether was removed by evaporation. The remaining oil (II) was added to 2 volumes of concentrated hydrochloric acid and the mixture was allowed to stand 48 hr. at room temperature. The reaction mixture was diluted with 2 volumes of water and extracted with ether continuously for 48 hr. Removal of the ether yielded 1 g. of crystals which on recrystallization from ethyl acetate, melted at 156–157°.

Anal. Calcd. for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00; neut. equiv., 175.18. Found: C, 48.08; H, 7.70; N, 7.95; neut. equiv., 174.

2-Hydroxy-2-isopropylsuccinic acid (IV) *from 2-hydroxy-2-isopropylsuccinamic acid* (III). One g. of 2-hydroxy-2-isopropylsuccinamic acid was refluxed in 6 ml. of *N* HCl for 3 hr. The product was evaporated to dryness under reduced pressure and extracted with ethyl acetate. The ethyl acetate solution was concentrated to a small volume, petroleum ether was added until the beginning of turbidity, and the mixture placed overnight in the refrigerator. The white crystals which deposited were recrystallized from ethyl acetate and petroleum ether; m.p. 145–147°, yield 0.5 g.

Anal. Calcd. for $C_7H_{12}O_5$: C, 47.72; H, 6.87; neut. equiv., 176.17. Found: C, 47.74; H, 6.89; neut. equiv., 176.

Isobutyrylacetonitrile (V) *from methyl isobutyrate and acetonitrile.* To 12.6 g. (0.2 mole) of sodium ethoxide was added a mixture of 23 ml. (0.2 mole) of methyl isobutyrate and 15 ml. (0.2 mole) of acetonitrile, and the mixture was heated for about 4 hr. at 115–120° with stirring, while the alcohol formed in the reaction was distilled off. The unchanged reactants were separated by fractional distillation and returned to the reaction flask, for additional refluxing for 4 hr., the alcohol being removed as before. This process was repeated until alcohol was no longer formed; total elapsed time was about 15 hr. The mixture was then acidified with ice water containing a slight excess of acetic acid and extracted with ether. The ether layer was washed with 5% sodium bicarbonate solution, dried over anhydrous sodium sulfate, the ether was evaporated, and the residual oil was distilled under diminished pressure, yielding 9 g. (45% of theory) of a light yellow oil, b.p. 102–104° at 12 mm.

2-Hydroxy-2-isopropylsuccinamide (VII) *and 2-hydroxy-2-isopropylsuccinamic acid* (III) *from isobutyrylacetonitrile* (V). To a mixture of 4.5 g. (0.04 mole) of isobutyrylacetonitrile and 3.9 g. (0.08 mole) of powdered sodium cyanide at 0° there was added dropwise 6.5 ml. of concentrated hydrochloric acid with stirring, and stirring was continued for 2 hr. at the same temperature after the addition of hydrochloric acid was completed. The reaction mixture was extracted with ether, washed with water, and the ether was removed by evaporation; the residual oil was added to 2 volumes of concentrated hydrochloric acid, and allowed to stand 48 hr. at room temperature. After addition of 2 volumes of water the hydrochloric acid solution was extracted with ether continuously for 80 hr. Evaporation of the ether yielded 2.5 g. of crystals, which after recrystallization from water, melted at 195–197°.

Anal. Calcd. for $C_7H_{14}N_2O_3$: C, 48.26; H, 8.10; N, 16.08. Found: C, 48.46; H, 8.23; N, 15.93.

Evaporation of the mother liquor yielded a small quantity of a product which, after repeated recrystallization from ethyl acetate, melted at 156–157° and did not lower the melting point of 2-hydroxy-2-isopropylsuccinamic acid obtained from ethyl isobutyrylacetate.

2-Hydroxy-2-isopropylsuccinamic acid (III) *and 2-hydroxy-2-isopropylsuccinic acid* (IV) *from 2-hydroxy-2-isopropylsuccinamide* (VII). One g. of 2-hydroxy-2-isopropylsuccinamide was refluxed 3 hr. with 6 ml. of *N* HCl and the reaction mixture was evaporated to dryness under diminished pressure. The residue was extracted with ethyl acetate and the solution concentrated. The crystals which deposited were recrystallized from ethyl acetate, yielding 0.8 g. of product which melted at 156–157° and did not depress the melting point of the monoamide described above.

One g. of 2-hydroxy-2-isopropylsuccinamide was refluxed 3 hr. with 12 ml. of *N* HCl and the reaction product was evaporated to dryness under diminished pressure. This procedure was repeated twice and the final residue was recrystallized twice from ethyl acetate and petroleum ether; the white crystals melting at 145–147°, obtained in a yield of 0.6 g., did not depress the melting point of the dicarboxylic acid obtained above.

Triethyl 2-oxaloglutarate (X) *from diethyl glutarate* (IX) *and diethyl oxalate* (VIII). To 3.4 g. (0.05 mole) of sodium ethoxide in 37 ml. of anhydrous ether there was added 7.3 g. (0.05 mole) of diethyl oxalate with stirring and cooling, and stirring was continued until most of the ethoxide dissolved; then, while cooling with ice water and stirring vigorously, 9.4 g. (0.05 mole) of diethyl glutarate was added. Stirring was continued until the solution became clear, when the color of the solution turned from yellow to red. After standing 3 days in the refrigerator, the reaction mixture was poured onto ice, the ether solution was separated, and the aqueous layer was washed with ether. The aqueous solution was acidified with a slight excess of 2*N* H_2SO_4 while cooling, and extracted with ether. The ether solution was shaken with a small amount of barium carbonate to remove a trace of sulfuric acid, dried over anhydrous sodium sulfate, filtered, and the ether was removed under reduced pressure yielding 12 g. (81% of theory) of a viscous light yellow liquid. This was undistillable, even under high vacuum (0.0003 mm.), as Gault reported.[11]

Similar results were obtained with potassium ethoxide. Following the procedure for synthesis of diethyl oxalosuccinate,[13] but using diethyl glutarate instead of diethyl succinate, the main product was 3,5-dicarbethoxycyclopentadione-1,2.[14]

2-Hydroxy-3-carboxyadipic acid (XII) *by reduction of triethyl 2-oxaloglutarate with hydrogen.* Three g. of triethyl

(12) H. Fischer, M. Goldschmidt, and W. Nüssler, *Ann.*, 486, 31 (1931).

(13) L. Friedman and E. Kosower, *Organic Syntheses*, 26, 42 (1946).

(14) W. Dieckmann, *Ber.*, 27, 965 (1894).

2-oxaloglutarate, 50 ml. of 95% ethanol, and 18 mg. of platinum dioxide were shaken in hydrogen under a pressure of 45 lbs./sq. in. at room temperature. The solution was filtered, evaporated under reduced pressure, and the light yellow residual oil was dissolved in 50 ml. of ether. The solution was washed 3 times with 5 ml. of 10% potassium carbonate solution to remove any unchanged compound, dried over anhydrous sodium sulfate, and evaporated under reduced pressure, yielding 2.8 g. of a residual oil having a fruit-like odor; on distillation, there was obtained a colorless liquid boiling at 140–141° (0.005 mm.) and a reddish oily residue.

Anal. Calcd. for $C_{13}H_{22}O_7$ (XI): Sapon. equiv., 96.8. Found: Sapon. equiv., 96.54.

Two and four-tenths g. of the undistilled triethyl 2-hydroxy-3-carboxyadipate was refluxed 2 hr. with 26.2 ml. (about an equivalent quantity) of 0.9*N* NaOH. The solution was acidified with a slight excess of *N* HCl, extracted continuously with ether for about 100 hr., and the ether solution was evaporated to dryness under reduced pressure. The residue was dissolved in water, and evaporated again to dryness to remove traces of hydrochloric acid. The 1.5 g. of residual sirup, after 3 days over phosphorus pentoxide in a vacuum desiccator, solidified. On repeated recrystallization from acetone and benzene, white crystals melting at 127–129° were obtained.

Anal. Calcd. for $C_7H_{10}O_7$: C, 40.78; H, 4.89; neut. equiv., 68.7. Found: C, 40.50; H, 4.88; neut. equiv., 68.3.

Reduction of triethyl 2-oxaloglutarate with sodium borohydride. To a solution of 5.1 g. of sodium borohydride in 25 ml. of water, a solution of 12 g. of triethyl 2-oxaloglutarate in 50 ml. of 70% methanol was added dropwise while stirring and cooling with ice water, and stirring was continued for 20 min. at room temperature. The reaction mixture was added to 2*N* H_2SO_4 to bring the *p*H to 3, filtered, evaporated at room temperature under vacuum, and extracted several times with ether after saturation with sodium chloride; then the ether solution was washed with 10% potassium carbonate solution until the latter gave a negative test for the carbonyl group with 2,4-dinitrophenylhydrazine, and dried over anhydrous sodium sulfate. Evaporation of the ether yielded 4.3 g. of oil. This was refluxed for 2 hr. with 17 ml. of *N* NaOH, neutralized with 17 ml. of *N* HCl with cooling, and the solution was evaporated to dryness under vacuum. The residue was extracted with acetone, the acetone solution was concentrated, and benzene was added until turbidity occurred. On standing overnight in the refrigerator crystals were precipitated which, after being recrystallized twice from acetone and benzene, melted at 127–129° and did not depress the melting point of the product obtained by catalytic reduction.

Trianilide of 2-hydroxy-3-carboxyadipic acid. Two-tenths g. of 2-hydroxy-3-carboxyadipic acid was neutralized with *N* NaOH, and the solution was evaporated to dryness and powdered. The dry sodium salt was heated 1 hr. at 150–160° with 1 ml. of aniline and 0.3 ml. of concentrated hydrochloric acid. After addition of 10 ml. of 2*N* HCl, the mixture was filtered, washed with water, and recrystallized 3 times from acetic acid; white crystals melting at 251° with decomposition were obtained in a yield of 0.15 g.

Anal. Calcd. for $C_{25}H_{25}N_3O_4$: C, 69.59; H, 5.84; N, 9.74. Found: C, 69.20; H, 5.92; N, 9.60.

Acknowledgment. The author wishes to thank Dr. S. Weinhouse for his valuable suggestions, and is indebted to the Research Laboratories of Takeda Pharmaceutical Industries, Ltd., Osaka, Japan, for some of the elementary analyses.

PHILADELPHIA, PENNA.

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

Synthesis of the Racemic and Optically Active Forms of α-Amino-γ-p-di(β-chloroethyl)aminophenylbutyric Acid[1]

HOWARD E. SMITH[2] AND J. MURRAY LUCK

Received November 7, 1957

In the continuing search for chemotherapeutic agents for the treatment of cancer, the DL-, D-, and L-α-amino-γ-*p*-di(β-chloroethyl)aminophenylbutyric acids were synthesized. Resolution of the intermediate α-acetamido-γ-*p*-nitrophenylbutyric acid as the (+)- and (−)-α-phenylethylamine salts led to the optically active isomers, the absolute configurations of which were tentatively inferred from their different degrees of biological activity; *i.e.* the L isomer caused a prompt transitory regression of a Cloudman malignant melanoma, S 91, in male mice while the D isomer caused only a barely perceptible brief regression.

Introduction. The carcinostatic and carcinolytic properties of nitrogen mustards, di(β-chloroethyl)-amino compounds, have been recognized for many years,[3] and recently the *p*-di(β-chloroethyl)amino-DL-, -D-, and -L-phenylalanines (I) have been prepared[4,5] and have displayed promising results in the treatment of certain types of tumors.[6] Interestingly, the L isomer, the absolute configuration of which was known by synthesis from L-phenylalanine,[4] showed a much greater ability to inhibit the growth of these tumors than did the D isomer.[6] This was one of the first examples of selectivity through optical isomerism with agents of this kind.

(1) A short summary of these syntheses has appeared previously (J. M. Luck, *Cancer Research*, 17, 1071 (1957), and the compounds have also been named 2-amino-4-*p*-di(2-chloroethyl)aminophenylbutyric acids.

(2) To whom inquiries concerning this communication should be sent. Present address: Organisch-Chemisches Laboratorium der E. T. H., Zurich, Switzerland.

(3) A rather complete survey of the nitrogen mustard literature may be found in J. W. Beattie and L. H. Howells, *Quart. J. Med.*, 23, 231 (1954).

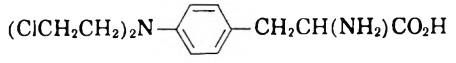
(4) F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954).

(5) F. Bergel, V. C. E. Burnop, and J. A. Stock, *J. Chem. Soc.*, 1223 (1955).

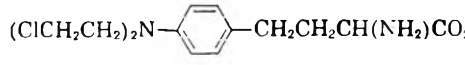
(6) F. Bergel and J. A. Stock, *Ann. Rep. Brit. Emp. Cancer Camp.*, 31, 6 (1953).

For further study of this selectivity of optical-isomers, it was desirable to determine the nature of the effect that would be produced in the carcinol static and carcinolytic properties of the *p*-di(β-chloroethyl)amino-DL-, -D-, and -L-phenylalanines by the interposition of an additional methylene group between the site of optical activity and the *p*-di(β-chloroethyl)aminophenyl moiety. With this in view the DL-, D-, and L-α-amino-γ-*p*-di(β-chloroethyl)aminophenylbutyric acids (II) were synthesized and their carcinostatic and carcinolytic properties studied and compared with those of the *p*-di(β-chloroethyl)amino-DL-, -D-, and -L-phenylalanines. The syntheses of the butyric acid derivatives are herein described while the details concerning their biological activities are presented elsewhere.[1]

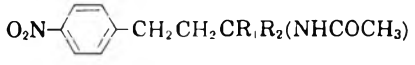
In Table I are presented the yields, physical properties, elemental analyses, and crystallization solvents for the DL-, D-, and L-α-amino-γ-*p*-di(β-chloroethyl)aminophenylbutyric acids and the intermediates encountered in their syntheses. Except as is noted in Table I, included with each compound is a number referring to a reference in the text wherein may be found the standard procedure used to obtain the compound in question. Any deviations from these procedures are fully discussed in the section below. Not included in Table I are the descriptions of the (+)- and (−)-α-phenylethylamine salts of the D- and L-α-acetamido-γ-*p*-nitrophenylbutyric acids (IIIb) since these are included in the experimental section with the description of the scheme for resolution of the racemic acid.



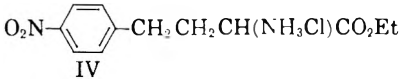
I



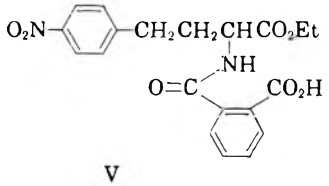
II



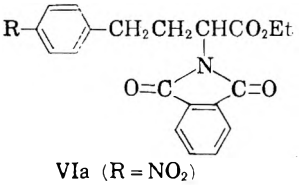
IIIa ($R_1 = R_2 = CO_2Et$)
IIIb ($R_1 = H$, $R_2 = CO_2H$)



IV



V



VIa ($R = NO_2$)
VIb ($R = NH_3Cl$)

DISCUSSION

The synthesis of the DL-, D-, and L-α-amino-γ-*p*-di-(β-chloroethyl)aminophenylbutyric acids(II) was accomplished by a route similar to that employed by Bergel, Burnop, and Stock[5] in the synthesis of the *p*-di-(β-chloroethyl)amino-DL-, -D-, and -L-phenylalanines (I). In this present work β-*p*-nitrophenylethyl bromide[7] was condensed[8] with diethyl acetamidomalonate[9] in the presence of sodium ethoxide to yield diethyl acetamido-(β-*p*-nitrophenylethyl)malonate (IIIa). Hydrolysis of the latter compound in aqueous sodium carbonate followed by decarboxylation on acidification with hydrochloric acid[5,10] gave the racemic α-acetamido-γ-*p*-nitrophenylbutyric acid (IIIb) which was resolved into its two enantiomorphs by fractional crystallization from ethanol of the (+)- and (−)-α-phenylethylamine salts. Of the five bases with which resolution was attempted only the two α-phenylethylamines gave crystalline salts while the salts of brucine, strychnine, and cinchonine were obtained as uncrystallizable oils.

It must be mentioned that the hydrolysis of diethyl acetamido-(β-*p*-nitrophenylethyl)malonate with aqueous sodium bicarbonate was much more rapid and was accompanied by greater decomposition than is usually reported[5,10] for this reaction. The reaction was found to be complete in six hours and after decarboxylation with acid the product could be obtained in a yield of seventy-eight percent. There was some decomposition during the hydrolysis and the crystalline product invariably had an orange color which was not easily removed by recrystallization from water (charcoal). Recrystallization of this colored material from ethyl acetate or chloroform-ethanol gave the compound as light yellow plates, the melting point of which was unchanged. If the heating period for hydrolysis was extended beyond six hours, extensive decomposition occurred and an inert atmosphere (nitrogen) over the reaction did not reduce the amount of decomposition. When the heating time was extended to twenty-four hours, the time required[5] for hydrolysis of diethyl α-acetamido-*p*-nitrobenzylmalonate, a very impure product in low yield was obtained.

After decomposition with aqueous sodium hydroxide of the α-phenylethylamine salts of the D- and L-α-acetamido-γ-*p*-nitrophenylbutyric acid, the D and L acids as well as the racemic modification

(7) E. L. Foreman and S. M. McElvain, *J. Am. Chem. Soc.*, 62, 1435 (1940).
(8) D. F. Elliott and C. R. Harington, *J. Chem. Soc.*, 1374 (1949).
(9) H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, 66, 350 (1944).
(10) N. F. Alberton, *J. Am. Chem. Soc.*, 72, 1396 (1950).

TABLE I

YIELDS, PHYSICAL PROPERTIES, AND ELEMENTAL ANALYSES FOR DL-, D-, AND L-α-AMINO-γ-p-DI-(β-CHLOROETHYL)AMINOBUTYRIC ACIDS AND INTERMEDIATES ENCOUNTERED IN THEIR SYNTHESES

Compound No. in Text	Isomer	Reference	Yield, %[a]	M.P., °C.[b]	$[\alpha]_D$, ±2°[c]	Crystallization Solvent	Crystal Form and Color	Formula	Elemental Analysis[d] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
IIIa		(8)	70[e]	117–119		Ethanol	Fine, colorless prism	$C_{17}H_{22}N_2O_7$	55.73	55.66	6.05	6.26
IIIb	DL	(5)(10)	78	158–160		Water	Light yellow plates	$C_{12}H_{14}N_2O_5$[f]	54.13	54.04	5.30	5.43
IIIb	D	[g]	64[h]	152–154	+36 (*c*, 1.23 in ethanol at 26°)	Water	Yellow plates	$C_{12}H_{14}N_2O_5$	54.13	54.08	5.30	5.27
IIIb	L	[g]	53[h]	152–153	−34 (*c*, 1.03 in ethanol at 26°)	Water	Large, light yellow needles	$C_{12}H_{14}N_2O_5$	54.13	53.96	5.30	5.24
IV	DL	(5)	91	174–176 (dec.)		Acetone-methanol	Fine, light yellow prisms	$C_{12}H_{17}ClN_2O_4$	49.91	50.03	5.94	6.06
IV	D	(5)	93	203–205 (dec.)	+41 (*c*, 2.00 in water at 26°)	Acetone-methanol	Fine, light yellow prisms	$C_{12}H_{17}ClN_2O_4$	49.91	49.92	5.94	6.19
IV	L	(5)	92	203–205 (dec.)	−43 (*c*, 2.03 in water at 26°)	Acetone-methanol	Fine, light yellow prisms	$C_{12}H_{17}ClN_2O_4$	49.91	49.75	5.94	6.02
V	DL	(4)	81	170		Benzene-acetone	Fine, colorless needles	$C_{20}H_{20}N_2O_7$	59.99	59.63	5.04	4.99
V	D	(4)	90	172–173	−31 (*c*, 2.43 in dioxane at 25°)	Benzene-acetone	Fine, colorless needles	$C_{20}H_{20}N_2O_7$	59.99	60.00	5.04	5.06
V	L	(4)	90	172–173	+30 (*c*, 2.66 in dioxane at 25°)	Benzene-acetone	Fine, colorless needles	$C_{20}H_{20}N_2O_7$	59.99	60.10	5.04	5.22
VIa	DL	(4)	83	99–100		n-Propanol	Light yellow prisms	$C_{20}H_{18}N_2O_6$	62.82	62.90	4.74	4.87
VIa	D	(4)	96	[i]	[j]	[i]	[i]	$C_{20}H_{18}N_2O_6$	62.82	[j]	4.74	[j]
VIa	L	(4)	90	[i]	[j]	[i]	[i]	$C_{20}H_{18}N_2O_6$	62.82	[j]	4.74	[j]
VIb	DL	(4)	78	179–183 (dec.)		Abs. ethanol	Light tan, amorphous	$C_{20}H_{21}ClN_2O_4$	61.77	61.66	5.45	5.41
VIb	D	(4)	77	185–190 (dec.)	−8 (*c*, 0.68 in 50% aq. ethanol at 18°)	[k]	Colorless, amorphous	$C_{20}H_{21}ClN_2O_4$	61.77	61.80	5.45	5.27
VIb	L	(4)	75	188–182 (dec.)	+6 (*c*, 0.67 in 50% aq. ethanol at 18°)	[k]	Light tan, amorphous	$C_{20}H_{21}ClN_2O_4$	61.77	61.86	5.45	5.33
II	DL	(4)	12	154–155 (dec.)	[l]	Methanol	Colorless, amorphous	$C_{14}H_{20}Cl_2N_2O_2$	52.67	52.37	6.32	6.04
II	D	(4)	17	156–159 (dec.)	+29 (*c*, 0.87 in 2*N* HCl at 26°)	Methanol	Colorless, amorphous	$C_{14}H_{20}Cl_2N_2O_2$	52.67	52.45	6.32	6.16
II	L	(4)	20	155–158 (dec.)	−32 (*c*, 0.86 in 2*N* HCl at 26°) −12 (*c*, 0.57 in methanol at 26°)	Methanol	Light tan, amorphous	$C_{14}H_{20}Cl_2N_2O_2$	52.67	52.44	6.32	6.10

[a] Based on the appropriate compound appearing immediately above in the table or as otherwise noted. [b] Melting points were obtained by the capillary method and are uncorrected. [c] Path lengths of one decimeter. [d] Elemental analysis by Miss M. A. DaRooge, Wayne State University, Detroit 2, Mich. [e] Based on β-*p*-nitrophenylethylbromide. [f] Neutral equivalent. Calcd.: 266. Found: 266, 264. [g] This procedure is described in the experimental section of this communication. [h] Based on DL-IIIb. [i] Obtained as an uncrystallizable oil. [j] Not determined. [k] Not purified by crystallization. [l] One sample identical in all respects with others had m.p. 166–169° (dec.).

were converted by hydrolysis in 6*N* hydrochloric acid and then esterified in 2*N* ethanolic hydrogen chloride to the DL-, D-, and L-α-amino-γ-*p*-nitrophenylbutyrate hydrochlorides (IV). The free amino group in each substance was then reblocked *via* the α-*o*-carboxybenzamido compounds (V) as the α-phthalimido group (VIa). The introduction of this blocking group was necessary since subsequent intermediates were to be treated with phosphorus oxychloride; and under the conditions of the reactions, the optically active α-acetamido compounds would be racemized whereas the α-phthalimido derivatives maintain their optical integrity.[4] The racemic ethyl α-phthalimido-γ-*p*-nitrophenylbutyrate was obtained as a crystalline solid but the optically active isomers could not be made to crystallize and were obtained as oils which after washing with sodium bicarbonate and water had infrared absorption spectra identical with that of the pure, crystalline, racemic compound. The *p*-nitro group of each isomer was then reduced in methanol–ethyl acetate to the *p*-amino function with hydrogen over platinum (platinum hydroxide on calcium carbonate), and the reduced compounds isolated as the ethyl DL-, D-, and L-α-phthalimido-γ-*p*-aminophenylbutyrate hydrochlorides (Vb). The racemic form was reprecipitated from hot ethanol as a slightly hygroscopic, amorphous, light tan solid while the optically active isomers were purified by thorough washing with dry ether and were also obtained as slightly hygroscopic, amorphous solids.

The ethyl DL-, D-, and L-α-phthalimido-γ-*p*-aminophenylbutyrate hydrochlorides were then converted by the elegant method of Bergel and Stock[4] to the respective α-amino-γ-di(β-chloroethyl)aminophenylbutyric acids(II) employing in turn diethylamine, ethylene oxide, phosphorus oxychloride, 6*N* hydrochloric acid, and aqueous sodium acetate. The pure amino acids were obtained after two reprecipitations from hot methanol as amorphous, colorless or light tan solids with appearances, physical properties, and infrared absorption spectra[11] quite similar to the *p*-di(β-chloroethyl)amino-DL-, -D-, and -L-phenylalanines (I). The crude butyric acid derivatives were heavily contaminated with sodium chloride and their purification was difficult due to their reluctant solubility in hot methanol, their reluctant reprecipitation on cooling the solvent, and the coprecipitation of sodium chloride. It must be noted that the yield in this last reaction is low (12 to 20%) not only because of the difficulties in the purification of the crude material but also because of the inherent difficulties in the hydroxyethylation and chlorination reactions. No special effort was made to improve these yields.

When the carcinostatic and carcinolytic properties of the two optically active isomers of II were studied,[1] one was found more active in its ability to induce a prompt, transitory regression of Cloudman malignant melanoma, S 91, in dba/1 male mice and was tentatively assigned, in analogy to *p*-di(β-chloroethyl)amino-L-phenylalanine, the L absolute configuration. The other isomer, to which was assigned the D absolute configuration, was about one-fifth as active as its enantiomorph at the same dosage level. With the absolute configurations of II indicated by biological activity, the absolute configurations of the intermediate compounds (IIIa through VIb) were assigned by inference, since the reactions in going from IIIa to II proceed with retention of configuration at the asymmetric center.[4,5] It should be pointed out, however, that the assignments of absolute configuration are tentative and a final decision must be based on a chemical transformation of one of the optically active compounds listed in Table I to a substance of established configuration. Applying the conclusion of Lutz and Jirgensons,[12] that for optically active α-amino acids, the specific rotation of the L isomer becomes more positive with increasing acid concentration, it is indicated that possibly the configurations of the optically active α-amino-γ-*p*-di-(β-chloroethyl)aminophenylbutyric acids are opposite to that which we have inferred from the biological tests (*cf.* II in Table I).

EXPERIMENTAL[13]

D-α-*Acetamido-γ-p-nitrophenylbutyric acid* (+)-α-*phenylethyleneamine salt.* To 18.8 g. of DL-α-acetamido-γ-*p*-nitrophenylbutyric acid (0.0707 mole) dissolved in 300 ml. of hot 95% ethanol was added 8.55 g. of (+)-α-phenylethylamine[14] (0.0707 mole) dissolved in 50 ml. of hot 95% ethanol and the mixture was allowed to cool slowly overnight at room temperature. On cooling light yellow plates were deposited and after filtration there was obtained 20.3 g. (70.5% of the total) of crystalline material with $[\alpha]_D^{27}$ +15 ± 1° (*c*, 1.17 in methanol). Two recrystallizations of this mixture from 300 ml. of 95% ethanol gave 8.5 g. of the D-α-acetamido-γ-*p*-nitrophenylbutyric acid (+)-α-phenylethylamine salt (62%) as light yellow plates with $[\alpha]_D^{21}$ +44 ± 2° (*c*, 0.96 in methanol) and m.p. 204–208° (dec.), the rotation of which was not altered by further recrystallization from ethanol. Reworking of the mother liquors pro-

(11) Infrared absorption spectra of the three isomers of II were obtained using a Perkin-Elmer Model 12c infrared spectrophotometer with sodium chloride optics and in general had bands in agreement with the assigned structure, *i.e.* (Nujol mull) 2.97 μ (w), NH; 6.2–6.3 μ (s), $COO^{\ominus}$ and aromatic ring; 6.60 μ (s) aromatic ring. The infrared spectra of the three isomers of I were obtained in the same way with material supplied by Dr. J. A. Stock and with other samples of these substances synthesized in these laboratories and also had bands in agreement with the assigned structures, *i.e.* (Nujol mull) 3.00 μ (w) NH; 6.22 μ (s), aromatic ring 6.34 μ (s), $COO^{\ominus}$; 6.65 μ (s), aromatic ring. All spectra, however, had a very weak band appearing at 5.80 to 5.86 μ which is unassigned or perhaps could be assigned to presence of a small amount of the unionized carboxylic acid group.

(12) O. Lutz and B. Jirgensons, *Ber.*, 63, 448 (1930).

(13) Melting points and elemental analyses were obtained as is indicated in Table I.

(14) A. W. Ingersoll, *Org. Syntheses*, **Coll. Vol. II**, 506 (1943).

duced an additional 0.8 g. of the salt with rotation and melting point identical with those above and this material was added to the main portion. The total yield was 68% for this diastereoisomer.

Anal. Calcd. for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50. Found: C, 62.12; H, 6.52.

L-α-*Acetamido-γ-p-nitrophenylbutyric acid* (+)-α-*phenylethylamine salt.* During the isolation of D-α-acetamido-γ-*p*-nitrophenylbutyric acid (+)-α-phenylethylamine salt from 18.8 g. of DL-α-acetamido-γ-*p*-nitrophenylbutyric acid (0.0707 mole) and 8.55 g. (+)-α-phenylethylamine (0.0707 mole) when the mother liquors were combined and evaporated to a small volume, two types of crystals were observed to form on cooling. One type was light yellow plates which were the D-α-acetamido-γ-*p*-nitrophenylbutyric acid (+)-α-phenylethylamine salt and very fine, long, almost colorless needles. By repeated recrystallizations from a minimum of 95% ethanol these two types of crystals were separated and there was obtained 1.4 g. of the L-α-acetamido-γ-*p*-nitrophenylbutyric acid (+)-α-phenylethylamine salt (10%) as fine, faintly yellow needles with $[\alpha]_D^{26}$ −38 ± 2° (c, 1.29 in methanol) and melting point 196–200° (dec.), the rotation of which was not changed by further recrystallization from ethanol.

Anal. Calcd. for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50. Found: C, 62.22; H, 6.63.

L-α-*Acetamido-γ-p-nitrophenylbutyric acid* (−)-α-*phenylethylamine salt.* The mother liquors from the isolation of 9.3 g. of the D-α-acetamido-γ-*p*-nitrophenylbutyric acid (+)-α-phenylethylamine salt and 1.4 g. of the L-α-acetamido-γ-*p*-nitrophenylbutyric acid (+)-α-phenylethylamine salt from 18.8 g. of the racemic acid (0.0707 mole) and 8.55 g. of the amine (0.0707 mole) were evaporated to dryness at reduced pressure (water pump) and there was obtained 16.3 g. of solid material. To this material suspended in 100 ml. of water was added concentrated aqueous sodium hydroxide until the solid was dissolved and the α-phenylethylamine was completely separated as an oil. The amine was removed from the aqueous solution by washing with three 60-ml. portions of ether. On acidification (*p*H 1) of the aqueous solution with concentrated hydrochloric acid, the partially resolved acid separated as a crystalline solid; and after cooling overnight at 0°, 10.8 g. (0.0406 mole) was collected by filtration. To the acid dissolved in 170 ml. of hot 95% ethanol was added 4.91 g. of (−)-α-phenylethylamine[13] (0.0406 mole) dissolved in 30 ml. of hot 95% ethanol, and the solution was allowed to cool slowly overnight at room temperature. On cooling light yellow plates were deposited and after filtration and one recrystallization from 95% ethanol, there was obtained 8.2 g. of the L-α-acetamido-γ-*p*-nitrophenylbutyric acid (−)-α-phenylethylamine salt (67% corrected for the L-α-acetamido-γ-*p*-nitrophenylbutyric acid (+)-α-phenylethylamine salt obtained above) as light yellow plates with $[\alpha]_D^{26}$ −44 ± 2° (*c*, 1.23 in methanol) and m.p. 203–207° (dec.), the rotation of which was not altered by further recrystallization from ethanol.

Anal. Calcd. for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50. Found: C, 62.10; H, 6.68.

D-α-*Acetamido-γ-p-nitrophenylbutyric acid* (IIIb). To 52.2 g. of the D-α-acetamido-γ-*p*-nitrophenylbutyric acid (+)-α-phenylethylamine salt (0.135 mole) suspended in 300 ml. of water was added concentrated aqueous sodium hydroxide until the solid was completely dissolved and the (+)-α-phenylethylamine was completely separated from the aqueous solution. The amine was removed by washing with three 200-ml. portions of ether and, on acidification (*p*H 1) of the aqueous solution with concentrated hydrochloric acid, the organic acid precipitated. After cooling the mixture overnight at 0°, filtration, and recrystallization, there was obtained 33.3 g. of D-α-acetamido-γ-*p*-nitrophenylbutyric acid (92.8%) with properties as shown in Table I.

L-α-*Acetamido-γ-p-nitrophenylbutyric acid* (IIIb). In the same way as with its enantiomorph, 26.5 g. of the L-α-acetamido-γ-*p*-nitrophenylbutyric acid (−)-α-phenylethylamine salt (0.0684 mole) was decomposed with aqueous sodium hydroxide to 14.2 g. of L-α-acetamido-γ-*p*-nitrophenylbutyric acid (78.9%) with properties as shown in Table I.

Acknowledgment. We are indebted to Professor F. Bergel and Dr. J. A. Stock of the Chester Beatty Research Institute for Reference samples of the *p*-di-(β-chloroethyl)amino-DL-, -D-, and -L-phenylalanines and to Dr. C. L. Stevens of Wayne State University for providing the elemental analysis. This work was supported by a research grant-in-aid (CH-40) from the American Cancer Society to J. Murray Luck.

DETROIT, MICH.

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

Santonin and Related Compounds. XVI.[1] C-Methylation of the Δ⁴-3-Octalone Systems[2]

MASAITI YANAGITA, MINORU HIRAKURA, AND FUJIO SEKI

Received November 18, 1957

The reaction of 9-methyl-Δ⁴-3-octalone (I) with methyl iodide and potassium *tert*-butoxide readily yielded the 4,4,9-trimethyl ketone (II), as the chief product. In addition, 2,4,4,9-tetramethyl (III) and 4,9-dimethyl ketone (IV) were both obtained in minute amounts. Similar methylation of the dimethyl ketone (IV) proceeded much less readily leading to lower yield of the trimethyl ketone (II). A possible explanation is offered for these methylation reactions.

As described in the preceding paper of this series,[1] it became necessary to introduce one methyl group into the 4-position of Δ⁴-3-octalone compounds. It had been previously reported[3] that the direct methylation of either Δ⁴- or Δ⁵-cholesten-3-one with

(1) Part XV, M. Yanagita, S. Inayama, M. Hirakura, and F. Seki, *J. Org. Chem.*, **23**, 690 (1958).

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

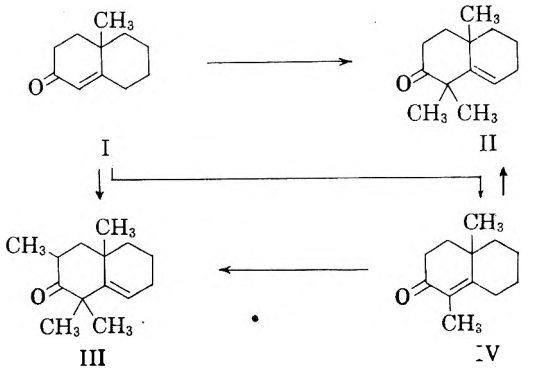
(3) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Am. Chem. Soc.*, **76**, 2852 (1954).

methyl iodide and potassium *tert*-butoxide in *tert*-butyl alcohol readily afforded the 4,4-dimethyl derivative in good yield. As our model experiment, the methylation of 9-methyl-Δ^4-3-octalone (I) with these reagents was explored.

Since this work was initiated, several papers[4] have appeared describing similar dimethylation of the Δ^4-3-octalone systems in steroids and others, in some of which but unrewarding efforts[4b,d,e] to prepare the 4-monomethyl derivative by this procedure have been mentioned. It seems of interest to compare the methylation of the Δ^4-3-ketosteroids with that of the simplest analog such as I.

9-Methyl-Δ^4-3-octalone (I) was treated with 3 equivalents of potassium *tert*-butoxide and excess of methyl iodide in *tert*-butyl alcohol at refluxing temperature for 5 min. On chromatographic separation of the crude product on alumina, the expected 4,4,9-trimethyl ketone (II) was in 46% yield obtained, which was characterized as a 2,4-dinitrophenylhydrazone ($\lambda_{max}^{CHCl_3}$ 369.5 mμ, log ϵ 4.24). The evidence for the structure (II) was based on the analysis of the hydrazone derivative and on the lack of the ultraviolet absorption band corresponding to the α,β-unsaturated ketone.[5]

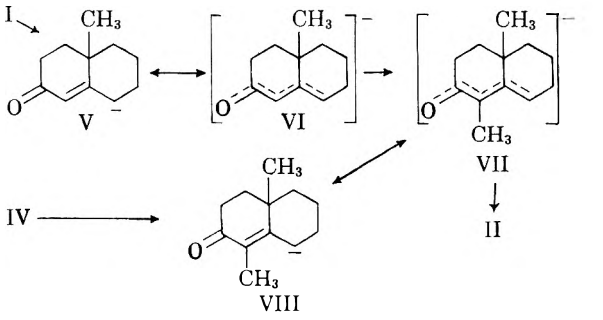
The more readily eluted fraction gave a small amount of an oil, which formed a 2,4-dinitrophenylhydrazone different from the same derivative of the trimethyl ketone (II). The analytical figures of the hydrazone showed that this oily ketone possibly possesses the tetramethyl structure III. This assignment was supported by the ultraviolet absorption band ($\lambda_{max}^{CHCl_3}$ 370 mμ, log ϵ 4.35) of the hydrazone, which is practically identical with that of the same derivative of II. From the later elution, the desired 4,9-dimethyl-Δ^4-3-octalone (IV), along with the starting material (I), was isolated in a small amount, as the 2,4-dinitrophenylhydrazone.



Hoping to raise the yield of the dimethyl ketone (IV), the methylation of I was effected by employing one equivalent of potassium *tert*-butoxide. However, it did not improve the yield of IV and gave chiefly II in 25% yield. The use of two equivalents of potassium *tert*-butoxide resulted only in a better yield of II.

From the present and earlier works,[4b,d,e,g] it may be deduced that ready methylation of the Δ^4-3-octalone systems by the above procedure normally does not proceed through the dimethyl ketone (IV). To examine this deduction, the methylation of IV was carried out with two equivalents of potassium *tert*-butoxide under similar conditions. Expectedly, the methylation took place much less readily than that of I, and refluxing of the solution required 7 hr. for completion of the reaction. There was obtained, together with traces of III, the trimethyl ketone II in a rather low yield.

During this investigation, an improvement was made in preparation of the dimethyl ketone IV, which was hitherto obtained by the condensation of 2-methylcyclohexanone and diethylaminopentan-3-one methiodide with sodamide in ether.[6] Use of the free Mannich base in place of its methiodide with sodium at higher temperature, as reported for the preparation of I,[7] was found to raise the yield of IV from 46% to 65–74%. This provided a more simple and economical method for preparing IV.



On the basis of the foregoing results, a possible explanation is proposed for the formation of the trimethyl ketone II from I or IV. Extraction of a proton at the 4-position by a base may give the carbanion V, for which a resonating structure VI can be written. The electrophilic attack by methyl cation on VI would give the dimethyl anion VII, which would be immediately converted to II by further methylation. It may be assumed that in the

(4) (a) G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 2998 (1955). (b) G. D. Meakins, O. R. Rodig, *J. Chem. Soc.*, 4679 (1956). (c) W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb, B. Sturgeon, *J. Chem. Soc.*, 4490 (1956). (d) J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *J. Chem. Soc.*, 753 (1957). (e) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, 22, 602 (1957). (f) J. D. Cocker and T. G. Halsall, *Chem. & Ind. (London)*, 1275 (1956). (g) F. Sondheimer and Y. Mazur, *J. Am. Chem. Soc.*, 79, 2906 (1957). *Cf.* since the preparation of this manuscript was completed, N. W. Atwater has announced in his communication to the Editor [*J. Am. Chem. Soc.*, 79, 5315 (1957)] that direct methylation of the Δ^4-3-ketosteroids with the same reagents under the suitable conditions gave a satisfactory yield of the 4-monomethyl derivate.

(5) During the later stages of this investigation, F. E. King, C. F. Ritchie, and C. J. Timmons [*Chem. & Ind. (London)*, 1230 (1956)] reported the preparation of the trimethyl compound (II) by the similar method, but no experimentation was described.

(6) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952).

(7) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, 22, 291 (1957).

carbanion VIII from the dimethyl ketone IV, the electron release properties of the methyl group at the 4-position would suppress the distribution of π-electrons of the Δ^4-double bond to the carbon at the 3-position, preventing VIII from assuming the mesomeric form VII. This may account for the considerable difficulty encountered in the methylation of IV, compared with that of I.

EXPERIMENTAL[8]

All temperatures were uncorrected.

Methylation of 9-methyl-Δ^4-3-octalone (I) *by methyl iodide.* (*a*) *With 3 equivalents of potassium tert-butoxide.* To a paste of potassium *tert*-butoxide prepared from 1.20 g. of potassium metal and 15 cc. of *tert*-butyl alcohol was added a solution of 1.64 g. of the ketone (I) in 2 cc. of benzene. Methyl iodide (6.0 g.) was added, with stirring, to the deep brown solution at room temperature, and was heated to reflux for 5 min. The solution faded in color and became completely neutral to the litmus paper. After removal of potassium salt by filtration, the reaction was evaporated under reduced pressure. The residual oil was dissolved in ether, and washed successively with dilute hydrochloric acid, aqueous sodium carbonate, and water. A brown oil from the dried ether solution was fractionated to a colorless oil (1.52 g.), b.p. 137–147° at 22 mm., which was chromatographed on alumina (30 g.). Each fraction was eluted with 20 cc. of the solvent: fractions 1–6, petroleum ether; fractions 7–11, petroleum ether–ether (1:1); fraction 12, ethanol.

Fractions 2–3 gave an oil (0.83 g.) which was again chromatographed on alumina (25 g.). Early elution with petroleum ether yielded 0.30 g. of an oil, consisting mainly of the tetramethyl ketone (III). It formed a 2,4-dinitrophenylhydrazone (0.43 g., 77%), melting in the range of 162–175°. Recrystallization from ethanol–ethyl acetate gave orange plates, m.p. 177.5–178°; $\lambda_{max}^{CHCl_3}$ 370 mμ (log ϵ 4.35).

Anal. Calcd. for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.06; H, 6.78; N, 14.80.

The later elution with petroleum ether and elution with petroleum ether–ether furnished 0.47 g. of the trimethyl ketone (II), white leaflets, m.p. 31.5–32.5°. It formed quantitatively a 2,4-dinitrophenylhydrazone, m.p. 156–158°, which was recrystallized from ethanol to yellow plates, m.p. 159–160°; $\lambda_{max}^{CHCl_3}$ 369.5 mμ (log ϵ 4.24).

Anal. Calcd. for $C_{19}H_{24}N_4O_4$: C, 61.27; H, 6.48; N, 15.05. Found: C, 61.18; H, 6.28; N, 15.16.

Fractions 4–7 yielded 0.24 g. of the trimethyl ketone (II), m.p. and mixed m.p. 31–32° (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 159–160°).

Fraction 8 gave 0.29 g. of crystals contaminated with a little oil. On rechromatography on alumina (8 g.) as described above, an additional 0.16 g. (total 46%) of the trimethyl ketone (II), m.p. and mixed m.p. 31.5–32.5° (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 159–160°). The later elution with petroleum ether–ether furnished 0.03 g. of an oil (IV), forming a red 2,4-dinitrophenylhydrazone (0.05 g.). Recrystallization from glacial acetic acid gave red plates, m.p. 196–198°, undepressed on admixture with the same derivative, m.p. 198–199°, of the dimethyl ketone (IV) reported previously.[7,9]

Fraction 9 furnished 0.07 g. of IV (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 197–198°).

Fractions 10–12 gave only traces of an oil which was not examined.

(8) Microanalyses were by Miss C. Shibuya, and the ultraviolet measurements by Miss M. Suzuki.

(9) M. Yanagita and R. Futaki, *J. Org. Chem.*, 21, 949 (1956).

(*b*) *With one or two equivalents of potassium tert-butoxide.* As described in (*a*), the ketone (I, 0.50 g.) was treated with methyl iodide (0.50 g.) and potassium *tert*-butoxide prepared from 0.12 g. (1 equivalent) of potassium metal and 5 cc. of *tert*-butyl alcohol. The crude product, b.p. 124–131° at 13 mm., amounted to 0.38 g., which was chromatographed on alumina (10 g.). The trimethyl ketone (II, 0.15 g., 25%), m.p. and mixed m.p. 31–32°, was obtained from the elution with petroleum ether. A fraction eluted with petroleum ether–ether furnished a small amount (15 mg.) of the dimethyl ketone (IV) (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 195–197°). The starting ketone (I, 0.10 g.) was recovered from the later elution, which was identified as its 2,4-dinitrophenylhydrazone,[10] m.p. and mixed m.p. 169°, after recrystallization from ethanol–ethyl acetate.

The ketone (I, 0.50 g.) was similarly treated with methyl iodide (1 cc.), potassium metal (0.24 g., 2 equivalents), and *tert*-butanol (10 cc.). The crude product (0.39 g.), b.p. 92–102° at 4 mm., was chromatographed on alumina (10 g.), as described above. There was obtained 0.255 g. (38%) of II, m.p. and mixed m.p. 31.5–32.5°.

4,9-Dimethyl-Δ^4-3-octalone (IV). This was prepared by effective variation of the earlier method[6] similarly as described for the preparation of I.

Sodium metal (0.8 g.) was added, in small pieces, to 40.5 g. of 2-methylcyclohexanone under stirring at room temperature (exothermic). After sodium dissolved, 25.0 g. of diethylaminopentan-3-one was added, and the mixture under stirring was slowly heated to 130–140° (oil bath temperature). Soon the separated diethylamine began to reflux. This temperature was maintained for 3 hr. The reaction mixture, consisting of two layers, was acidified with 10% hydrochloric acid and ice, and was extracted with ether. The ether solution was washed with aqueous sodium carbonate, then with water, and dried. A yellow oil from the ether solution was fractionated to the unchanged starting ketone (20.7 g.), and 21.0 g. of the crude octalone (IV), a colorless oil, b.p. 102–116° at 2 mm. Redistillation of the latter fraction afforded 19.5 g. (69%) of IV, b.p. 104–107° at 2 mm.; n_D^{20} 1.5256. Reported,[6] b.p. 99–100° at 1 mm.; n_D^{20} 1.5260.

It formed quantitatively the 2,4-dinitrophenylhydrazone,[6,7] m.p. and mixed m.p. 197–198° (after recrystallization from ethanol).

Methylation of 4,9-dimethyl-Δ^4-3-octalone (IV) *with methyl iodide.* This was carried out by a similar procedure as described above for I. To a paste of potassium *tert*-butoxide prepared from 0.44 g. (2 equivalents) of potassium metal and 10 cc. of *tert*-butyl alcohol was added, dropwise, 1.00 g. of the dimethyl ketone (IV), followed by 5 cc. of methyl iodide. When the mixture was heated to reflux for 7 hr., it became neutral to litmus paper. The crude product, a yellowish oil (1.02 g.), was fractionated to 0.77 g. of a colorless oil, b.p. 106–111° at 4 mm., which was chromatographed on alumina (20 g.) and eluted with benzene. An oil (0.15 g.) from the early elution formed a mixture of 2,4-dinitrophenylhydrazones, which on mechanical separation by picking up and recrystallization from ethyl acetate afforded the derivative of II as yellow plates, m.p. and mixed m.p. 158–160°, and the derivative of III as orange plates, m.p. 173–174° and mixed m.p. 175–176°. The following elution gave the trimethyl ketone (II, 0.26 g., 24%), m.p. and mixed m.p. 31–32° (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 159°). The latter elution gave the unchanged starting ketone (IV, 0.17 g.).

SHINJUKU-KU, TOKYO, JAPAN

(10) E. C. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. IX. 3-Azabicyclo[3.3.1]nonane Derivatives[1]

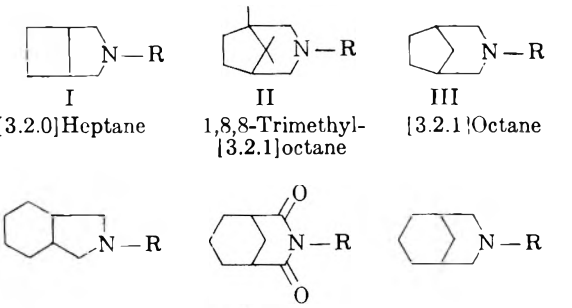
LEONARD M. RICE[2] AND CHARLES H. GROGAN[3]

Received December 2, 1957

Series of 3-alkyl and 3-dialkylaminoalkyl-3-azabicyclo[3.3.1]nonane-2,4-diones have been prepared from *cis*-hexahydroisophthalic anhydride and the corresponding alkyl and dialkylaminoalkylamines. These imides have been reduced to the corresponding 3-alkyl and 3-dialkylaminoalkyl-3-azabicyclo[3.3.1]nonanes and hydrochloride and mono- and bis-quaternary salts prepared for screening as hypotensive agents. These compounds exhibited only a low degree of hypotensive activity or were inactive. When compared to the very active compounds encountered in the closely related isoindole, 2-azabicyclo-[4.3.0]nonane series, this was quite an unexpected result and illustrates again the difficulties and pitfalls frequently encountered in structural-physiological activity predictions and correlation. In this case just changing the bridging in the bicyclic ring from the [4.3.0] to the [3.3.1] structure resulted in marked reduction or almost complete loss of hypotensive activity.

In continuation of our investigations of various bicyclic nitrogen heterocycles for use as one or both of the bridgehead groups in the formation of *alpha, omega* symmetrical and unsymmetrical bis-ammonium salts for screening in our hypotensive chemotherapy program, we have prepared derivatives in which the 3-azabicyclo[3.3.1]nonane nucleus is thus employed. Previous studies of this type of chemical structure have been concerned with such derivatives containing the 3-azabicyclo[3.2.0]heptane nucleus[4] (I), the 3-azabicyclo[3.2.1]octane nucleus[5,6] (II and III), and several variations including ring substitution and bridged modifications, of the 2-azabicyclo[4.3.0]nonane nucleus(IV).[7,8] This is the basic isoindole nucleus.

In these series of unsymmetrical bis-ammonium salts, the most effective combination was found to be either the dimethylaminoethyl or dimethylaminopropyl side chain in which the quaternizing group was also methyl. Not only the size of the bicyclic nucleus as well as ring substituents thereon but also the shape was found to affect the degree and duration of the hypotensive response obtained. This is reflected in the variation in response obtained by substituting on the bicyclic nucleus or by keeping the same number of atoms in the nucleus and changing the position of the bridging in the ring. This important factor, in addition to ring size, has also been noted by Cavallito *et al.*[9] in their review of hypotensive activity versus structural relationship of a large number of unsymmetrical bis-ammonium salts. It has been noted by them and by us that compounds having the same number of atoms comprising the entire bicyclic nucleus, and the common property of producing a good hypotensive response, but having different ring bridging (shape), differed greatly in toxicity, therapeutic index, and effectiveness by oral and parenteral routes.



I [3.2.0]Heptane

II 1,8,8-Trimethyl-[3.2.1]octane

III [3.2.1]Octane

IV [4.3.0]Nonane (Isoindole)

V [3.3.1]Nonane-2,4-dione R = H alkyl or dialkylaminoalkyl

VI [3.3.1]Nonane VIa, R = Alkyl VIb, R = Dialkylaminoalkyl

Unsymmetrical as well as symmetrical *alpha, omega* bis-ammonium salts containing the isoindole nucleus, IV, 2-azabicyclo[4.3.0]nonane, and the many modifications of it prepared and screened by us, in general possessed hypotensive properties as a nucleus type. However, the degree and duration of this effect, toxicity and therapeutic index, as well as the therapeutic value in humans, of these compounds varied quite widely with variations in ring substituents and additional bridging of the basic isoindole nucleus to form tricyclic rings with an additional oxygen[10] or methylene bridge.

Because of the broad general hypotensive activity encountered with many series of compounds containing this ring system, we were interested in varying the bridging in the compound to ascertain its effect on physiological activity. To this end we

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(4) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, 22, 1100 (1957).

(5) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, 22, 185 (1957).

(6) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, 22, 1223 (1957).

(7) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, 75, 4911 (1953).

(8) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, 77, 616 (1955).

(9) C. J. Cavallito, A. P. Gray, and T. B. O'Dell, *Arch. intern. pharmacodynamie*, 101, 38 (1955).

(10) C. H. Grogan and L. M. Rice, U. S. Patent 2,807,624 (1957).

TABLE I

3-DIALKYLAMINOALKYL-3-AZABICYCLO[3.3.1]NONANE-2,4-DIONES

	Substituent	Formula	B.P., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{20}
1	Dimethylaminoethyl	$C_{12}H_{20}N_2O_2$	95–105	0.1	64.25	64.43	8.99	8.82	12.49	12.47	1.5030
2	Dimethylaminopropyl	$C_{13}H_{22}N_2O_2$	112–117[a]	0.07	65.51	65.55	9.31	9.11	11.76	12.06	1.5019
3	Diethylaminoethyl	$C_{14}H_{24}N_2O_2$	105–115	0.1	66.63	66.77	9.59	9.63	11.10	11.30	—
4	Diethylaminopropyl	$C_{15}H_{26}N_2O_2$	118–124	0.1	67.63	67.74	9.84	9.84	10.52	10.69	—

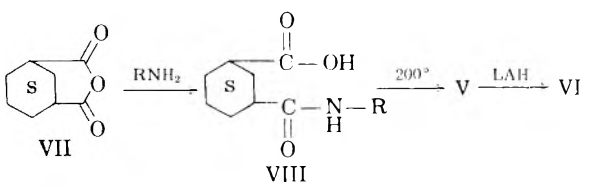
DERIVATIVES OF COMPOUNDS ABOVE

	Hydrochloride Formula	Hydrochloride M.P., °C.	Hydrochloride Chlorine, % Calcd.	Hydrochloride Chlorine, % Found	Methiodide Formula	Methiodide M.P., °C.	Methiodide Iodine, % Calcd.	Methiodide Iodine, % Found
1	$C_{12}H_{21}ClN_2O_2$	195–196	13.60	13.49	$C_{13}H_{23}IN_2O_2$	213–214	34.65	34.52
2	$C_{13}H_{23}ClN_2O_2$	183–184	12.90	13.14	$C_{14}H_{25}IN_2O_2$	224–225	33.37	33.65
3	$C_{14}H_{25}ClN_2O_2$	145–147	12.28	12.20	$C_{15}H_{27}IN_2O_2$	163–164	32.18	32.40
4	$C_{15}H_{27}ClN_2O_2$	118–119	11.71	11.83	$C_{16}H_{29}IN_2O_2$	114–116	31.08	30.95

[a] M.P., °C. 34–35. From ligroin.

have now prepared unsymmetrical bis-ammonium salts containing the 3-azabicyclo[3.3.1]nonane nucleus, VI, which contains the exact number of total atoms in the bicycle as the isoindoles, IV, but differs only in the bridging in the bicycle. The results of this study were quite unexpected since it was found that by simply changing the bridging from [4.3.0] to [3.3.1] in the azabicyclononane nucleus there resulted compounds that were either inactive or possessed a very low activity when administered either orally or parenterally. The toxicities of these compounds did not differ greatly from some of the corresponding members of the perhydroisoindoline series.

The synthesis of compounds containing the 3-azabicyclo[3.3.1]nonane nucleus was achieved by employing *cis*-hexahydroisophthalic anhydride as the key starting material. Hexahydroisophthalic acid was prepared by catalytic hydrogenation of dimethyl isophthalate followed by separation of the calcium salts of the *cis* and *trans* isomers according to the method of Skita *et al.*[11] The acid was converted to the anhydride by treatment with acetyl chloride. Hexahydroisophthalic anhydride, VII, was treated with various primary alkyl and dialkylaminoalkylamines to obtain the corresponding amic acids, VIII, which readily yielded the corresponding 3-azabicyclo[3.3.1]-2,4-diones (imides), V, on cyclization at 200° for 4 hr. All imides thus prepared were readily isolated as colorless oils by distillation *in vacuo*, with the exception of the imide in which R was hydrogen. Typical examples of the dialkylaminoalkyl imides and their hydrochloride and methonium salts are given in Table I.



These imides were all readily reduced by means of lithium aluminum hydride in ether solution to yield the corresponding bicyclic bases, VI, in good yields. These bases and their dihydrochloride and bis-methonium salts are listed in Table II. Conversion of the bases to their dihydrochlorides and monomethiodides occurred readily at room temperature. The monomethiodides are also listed in Table II. However, as in the case of the 3-azabicyclo[3.2.1]octanes, the introduction of the second methonium group could only be achieved with difficulty. It was necessary to heat the bases in a bomb tube at 100° in order to effect bisquaternization.

The hypotensive activity of these compounds was evaluated on dogs by both the cannulation technique and femoral artery puncture in the intact animal.[12] When the dialkylaminoalkyl hexahydroisophthalimides were employed as either the hydrochloride or methiodide, no activity was encountered. The dihydrochlorides of the 3-dialkylaminoalkyl-3-azabicyclo[3.3.1]nonanes were also inactive. The mono- and bis-quaternary methonium salts of these bases surprisingly were either inactive or showed only a low order of activity. Thus, by bringing about such a simple change in structure as that reported herein, changing the bridging from [4.3.0] to [3.3.1] in the azabicyclononane nucleus, while retaining identical N substituents, resulted in a change in hypotensive activity from very great and therapeutically useful in humans to practically inactive in the present series of compounds.

EXPERIMENTAL

3-Methyl-3-azabicyclo[3.3.1]nonane-2,4-dione. A total of 30.0 grams of a 25% aqueous solution of methylamine

(11) A. Skita and R. Rössler, *Ber.*, **72**, 265 (1939).

(12) W. E. O'Malley, G. Winkler, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc., Sci. Ed.*, 46, 346 (1957),

TABLE II

3-DIALKYLAMINOALKYL-3-AZABICYCLO[3.3.1]NONANES

	Substituent	Formula	B.P., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{20}
1	Dimethylaminoethyl	$C_{12}H_{24}N_2$	59–62	0.3	73.41	73.56	12.32	12.24	14.27	14.20	1.4870
2	Dimethylaminopropyl	$C_{13}H_{26}N_2$	68–70	0.2	74.22	74.32	12.46	12.54	13.32	12.91	1.4843
3	Diethylaminoethyl	$C_{14}H_{28}N_2$	73–76	0.1	74.94	75.18	12.58	12.44	12.48	12.74	—
4	Diethylaminopropyl	$C_{15}H_{30}N_2$	75–78	0.1	75.56	75.80	12.68	12.86	11.76	11.93	—

DERIVATIVES OF COMPOUNDS ABOVE

	Dihydrochloride Formula	M.P., °C.	Chlorine, % Calcd.	Chlorine, % Found	Monomethiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found	Dimethiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found
1	$C_{12}H_{26}Cl_2N_2$	275–276	26.33	26.17	$C_{13}H_{27}IN_2$	218–220	37.52	37.41	$C_{14}H_{30}I_2N_2$	239–240	52.86	52.95
2	$C_{13}H_{28}Cl_2N_2$	278–279	25.03	25.05	$C_{14}H_{29}IN_2$	213–214	36.02	36.20	$C_{15}H_{32}I_2N_2$	257–258	51.36	51.70
3	$C_{14}H_{30}Cl_2N_2$	197–198	23.85	23.56	$C_{15}H_{31}IN_2$	174–175	34.65	34.38	$C_{16}H_{34}I_2N_2$	221–222	49.89	49.94
4	$C_{15}H_{32}Cl_2N_2$	205–207	22.55	22.78	$C_{16}H_{33}IN_2$	133–134	33.37	33.43	$C_{17}H_{36}I_2N_2$	214–216	48.60	48.81

(excess) was added with cooling and stirring to 30.8 g. (0.2 mole) of *cis*-hexahydroisophthalic anhydride contained in a 250-ml. round-bottom flask. When the initial reaction had subsided, the solution was heated to boiling. After all water had boiled off the temperature was slowly raised to 240°. The product was distilled *in vacuo* at 82–86° at 0.5 mm., and melted at 59–60°, yield 18 g. (54%).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.88; H, 7.87; N, 8.58.

3-Butyl-3-azabicyclo[3.3.1]nonane-2,4-dione. The butyl homolog was prepared in essentially the same manner except that the reaction mixture was heated at 180° for several hours and then distilled *in vacuo*, b.p. 95–104° at 0.1 mm., m.p. 34–36°.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.57; H, 9.06; N, 6.90.

3-Azabicyclo[3.3.1]nonane-2,4-dione (hexahydroisophthalimide) was prepared as with the methyl analog except that concentrated aqueous ammonia was employed and the crude product recrystallized from petroleum ether or water-acetone. The product sublimed on heating to 80°.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.89; H, 7.19; N, 9.07.

3-Dimethylaminopropyl-3-azabicyclo[3.3.1]nonane-2,4-dione. A total of 31 g. (0.3 mole) of dimethylaminopropylamine was added in one lot to 46.2 g. (0.3 mole) of *cis*-hexahydroisophthalic anhydride contained in a 100-ml. round bottom flask. There was an immediate exothermic reaction and a homogeneous melt was obtained on stirring. After the initial reaction had subsided, the temperature was slowly raised to 180–200° and maintained for 4 hr. The product was distilled *in vacuo* to yield 43 g. (60%), b.p. 127–140° at 0.5 mm. Redistillation of the crude material yielded analytically pure material, 35 g. (49%), b.p. 112–117° at 0.07 mm., m.p. 34–35° from ligroin, n_D^{20} 1.5019.

Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.55; H, 9.11; N, 12.06.

The *hydrochloride* was formed in isopropyl alcohol with alcoholic-HCl and precipitated with dry ether, m.p. 183–184°.

The *methiodide* was readily formed in isopropyl alcohol at room temperature on treatment with excess methyl iodide, m.p. 224–225°.

3-Dimethylaminopropyl-3-azabicyclo[3.3.1]nonane. Lithium aluminum hydride, 16 g., was dissolved in 800 ml. of anhydrous ether in a two-liter, three-necked reaction flask equipped with dropping funnel, stirrer, and condenser, and protected from atmospheric moisture. A solution of 32 g. (0.13 mole) of 3-dimethylaminopropyl-3-azabicyclo[3.3.1]-nonane-2,4-dione in 400 ml. of anhydrous ether was dropped in just fast enough to maintain gentle reflux of the ether. The reaction mixture was stirred an additional hour and then decomposed by dropwise addition of water added so as to maintain reflux of the ether. A 10-ml. excess of water was added and the mixture stirred for one hour and filtered with rapid suction. The inorganic precipitate was washed with three portions of ether which were combined with the filtrate and dried over anhydrous sodium sulfate. The ether was stripped off and the residue distilled *in vacuo* to yield 23 g. (81%) of product boiling at 68–70° at 0.2 mm., n_D^{20} 1.4843. The *dihydrochloride* was prepared in the usual manner, m.p. 278–279°.

The *monomethiodide* was prepared by allowing the base to stand at room temperature overnight with slightly more than one equivalent of methyl iodide in absolute methanol. Precipitation with dry ether and recrystallization from methanol-ether gave a product with m.p. 213–214°. The *dimethiodide* was prepared by heating 8 ml. of methyl iodide, 20 ml. of methanol, and 4 ml. of the base in a bomb tube in a boiling water bath for 4 hrs. After cooling the product was precipitated by adding acetone and refrigeration. Recrystallization from either isopropyl alcohol or ethanol gave a product with m.p. 257–258°.

3-Methyl-3-azabicyclo[3.3.1]nonane. This compound was prepared in a manner analogous to that employed for the dimethylaminopropyl derivative. Employing 14 g. (0.084 mole) of 3-methyl-3-azabicyclo[3.3.1]nonane-2,4-dione there was obtained 9 g. (77%) of product, b.p. 85° at 38 mm. or 175° at 760 mm.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06. Found: C, 77.67; H, 12.49; N, 10.20.

The *hydrochloride* was prepared in the usual way and recrystallized from isopropyl alcohol–ethyl acetate and melted at 211–213°.

Anal. Calcd. for $C_9H_{18}ClN$: Cl, 20.18. Found: Cl, 19.92.

The *methiodide* was prepared in refluxing acetone with an excess of methyl iodide and recrystallized from methanol–ethyl acetate, m.p. 234–235°.

Anal. Calcd. for $C_{10}H_{20}IN$: I, 45.14. Found: I, 45.07.

WASHINGTON 7, D. C.

[CONTRIBUTION FROM ORGANIC RESEARCH DEPARTMENT, ABBOTT LABORATORIES]

Reactions of Some Ester Alkaloids and Related Synthetic Compounds with the Phenyl Grignard Reagent

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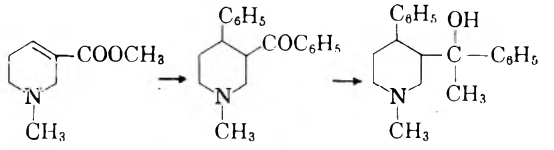
Received December 12, 1957

Reactions of arecoline (I), cocaine (VI), the methyl ester of anhydroecgonine (IX), and pilocarpine (XIII) with phenylmagnesium bromide have been carried out and the products have been subjected to further transformations. In addition, the two stereoisomeric 3-aceto-1,4-dimethyl-4-hydroxypiperidines (XI) and three simple imidazole esters XVI, XVII, and XVIII have been treated similarly. The stereochemistry of several of the products is discussed and their preliminary pharmacological assay is reported.

In order to prepare a number of basically substituted benzhydrols for examination in connection with their pharmacological activity on the central nervous system, it seemed appropriate to use as starting materials, suitably substituted alkaloids which possess physiological activity in their own right. Arecoline was chosen as one alkaloid which fulfilled these requirements. Treatment of arecoline (I) with excess phenylmagnesium bromide in refluxing ether gave a 36% yield of a solid base, m.p. 115–116°, which was not the expected carbinol, but rather an isomeric ketone II formed by both simple and conjugate addition to the unsaturated ester. The ketonic nature of the product was established by infrared analysis, and by the fact that reaction with methylmagnesium iodide led to a carbinol IV, m.p. 86–87°. Furthermore, when II was treated with concentrated hydrobromic acid



I II, cis III, trans IV, cis V, trans

in an attempt to effect cyclodehydration to the corresponding pyridindene derivative,[1] the only product isolated (72% yield) was an isomeric ketone III, m.p. 62–63°. That compounds II and III bear a *cis-trans* relationship to each other becomes obvious from Zimmerman's[2] experience in the analogous cyclohexane series. He found that the main kinetically favored product formed in the reaction of phenyl Grignard reagent with 1-benzoylcyclohexene is *cis*-1-benzoyl-2-phenylcyclohexane; but that, when equilibrium conditions are permitted, the *cis* isomer is converted quantitatively to the thermodynamically more stable *trans* form. Also, in accord with his findings we observed that compound II decolorizes a solution of bromine in hot glacial acetic acid whereas the isomeric III does not. Thus, with considerable confidence, the higher melting isomer II can be assigned the *cis* configuration and the lower melting III the *trans*. It follows that the two carbinols IV, m.p. 86–87°, and V, m.p. 142–143°, although bearing an inverse melting point relationship with respect to II and III, actually maintain the same steric relationship, for if steric integrity had not been maintained during the addition of methyl Grignard reagent, only one product or at least the same mixture of products would have been obtained from both II and III. The fact that only one of the two possible racemic mixtures was obtained in each case is interesting but not unexpected. It is also of interest to note the incidental observation that the infrared absorption band of the carbonyl group in the *cis* ketone II is at 5.88μ whereas that of the *trans* ketone III is at a significantly longer (5.92μ) wave length.

In addition to the hydrobromic acid treatment already mentioned, other methods were used in attempting to cyclodehydrate the *cis* ketone II. Treatment either with refluxing 65% sulfuric acid or with polyphosphoric acid led to III as the only isolable product. From anhydrous hydrogen fluoride at room temperature II was recovered unchanged. Aluminum chloride in tetrachloroethylene led only to destruction of the material.

Two publications pertinent to the present work appeared during and after its completion. Lyle, Perlowski, and Lyle[3] treated arecoline (I) with phenyllithium and obtained a 74% yield of the expected 1-methyl-1,2,5,6-tetrahydro-3-pyridyldiphenyl carbinol. Plati, Ingberman, and Wenner[4] treated arecoline with phenylmagnesium bromide at −10° and obtained a 73% yield of a mixture of the two stereoisomeric modifications of 1-methyl-3-carbomethoxy-4-phenylpiperidine formed by 1,4-addition of one mole of the Grignard reagent. However, no assignment of configuration could be made in their case. In view of the low yield (36%) of II obtained in our work, their results indicate that III must have also been formed in considerable

(1) See J. T. Plati and W. Wenner, *J. Org. Chem.*, **20**, 1412 (1955) and earlier references.

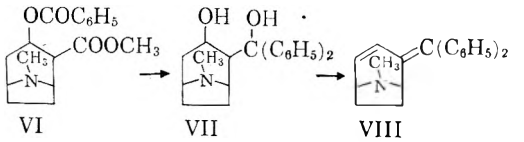
(2) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

(3) G. G. Lyle, E. F. Perlowski, and R. E. Lyle, *J. Org. Chem.*, **21**, 423 (1956).

(4) J. T. Plati, A. K. Ingberman, and W. Wenner, *J. Org. Chem.*, **22**, 261 (1957).

amounts although none was actually isolated from residues of the Grignard reaction. Their work also indicates that the ketone II must arise from primary 1,4-addition of the Grignard reagent to the conjugated ester system.

Attention was next directed to the reaction of cocaine VI with phenylmagnesium bromide. When a large excess of the Grignard reagent was used,

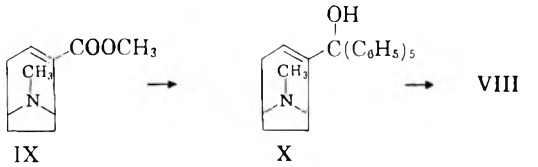


VI VII VIII

the expected glycol VII was isolated in 51% yield as a solid base, m.p. 185–186°. It was further characterized by conversion to a quaternary methomethyl sulfate and by dehydration to the diene VIII. Attempts to effect selective elimination of the tertiary hydroxyl group failed. When the glycol VII was distilled under reduced pressure either with or without added iodine as a catalyst, it was recovered unchanged. When it was distilled from potassium bisulfate or treated with a refluxing solution of hydrochloric acid in acetic acid, only the diene VIII was obtained as a yellow oil, b.p. 201–203° (2.5 mm.). This behavior is readily accounted for by the fact that initial elimination of the tertiary hydroxyl would yield a ring-substituted allylic carbinol which could be expected to dehydrate as readily as the tertiary carbinol. It is interesting to note the radical change in specific rotation observed in going from the glycol VII ($[\alpha]_D^{27}$ −23.5°) to the diene VIII ($[\alpha]_D^{30}$ +548°). Compound VII undoubtedly possesses the same conformation as cocaine which has been elucidated by others.[5]

The diene VIII was further characterized by conversion to a quaternary methiodide, m.p. 281–282° dec., by pK_a measurements and by its ultraviolet absorption spectrum. The pK_a values (measured by potentiometric titration in aqueous methanol) of compounds VI, VII, and VIII are, respectively, 7.6, 7.5, and 7.3. If, even in violation of Bredt's rule, one of the two double bonds were at the bridgehead, the pK_a of the resulting vinylamine would be expected to be much lower rather than of the same order as the pK_a values observed for the two reference substances. Furthermore, the ultraviolet absorption spectrum of VIII in ethanol shows a broad band in the region, 281–283 mμ typical of the 1-phenylbutadiene system[6] and practically identical with the absorption at 281 mμ reported[3] for the analogous diene formed by dehydration of the carbinol obtained by the addition of phenyllithium to arecoline.

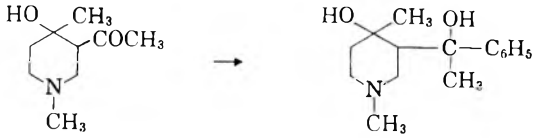
In order to prepare compounds in the tropane series analogous to those obtained from arecoline (I), the methyl ester (IX) of anhydroecgonine was prepared. The literature[7] reports the direct Fischer-esterification of anhydroecgonine by methanol in 70% yield. In the present work only poor yields of IX could be secured by this method. However, a 62% yield of the ester was finally obtained by refluxing the acid in a mixture of methanol and ethylene dichloride in the presence of Amberlite XE-156 resin. Treatment of IX with phenylmagnesium bromide gave a mixture of basic products from which no pure substance could be isolated. How-



IX X

ever, when phenyllithium was substituted for the Grignard reagent a 56% yield of the carbinol X, m.p. 209–210°, was obtained, which showed no carbonyl absorption in the infrared. The compound was characterized further by quaternization and by dehydration to a yellow oil which gave a quaternary methiodide identical in infrared spectrum and specific rotation to the methiodide previously obtained from the diene VIII.

The two synthetic stereoisomers of 3-aceto-1,4-dimethyl-4-hydroxypiperidine (XI), obtained by Mannich and Ball[8] from the reaction of acetone with formaldehyde and methylamine, seemed to provide suitable structures for the purpose of this work. Accordingly, both the α-form of XI, m.p. 130°, and the β-form, m.p. 85–86°, were treated with phenyl-



XI, α and β XII, α and β

magnesium bromide in refluxing benzene. The corresponding glycols XII were obtained in 45% and 11% yields, respectively. The greater reactivity of the α-ketone was further evinced by a tendency, not shown by the β-isomer, to react exothermically during the initial phase of the Grignard reaction. These facts, taken together with the lower melting point of the β-isomer, point to the presence of an intramolecular hydrogen-bonded structure in the latter form, involving the hydroxyl hydrogen and the carbonyl oxygen. The infrared spectra of the two isomers are also consistent with this designation. The α-form, at 0.7% concentration in carbon tetrachloride, shows two hydroxyl

(5) O. Kovacs, G. Fodor, and G. Weiss, *Helv. Chim. Acta*, **37**, 892 (1954).

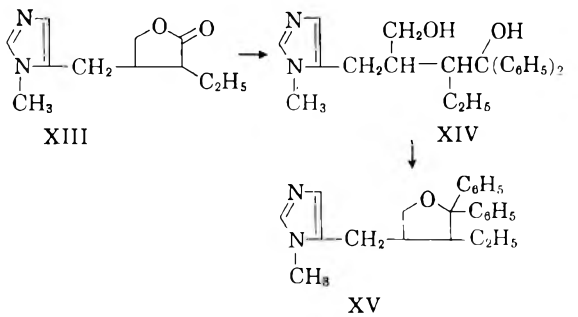
(6) E. A. Braude, E. R. H. Jones, and E. S. Stern, *J. Chem. Soc.*, 1087 (1947).

(7) P. S. Ugryumov, *J. Gen. Chem.* (*U.S.S.R.*), **14**, 997 (1944). *Chem. Abstr.*, **39**, 4616 (1945).

(8) C. Mannich and G. Ball, *Arch. Pharm.*, **264**, 65 (1926).

absorption bands of equal intensity at 2.82μ and 2.88μ. Dilution to 0.1% concentration reduces the intensity of the 2.88-μ band relative to the 2.82-μ band. This indicates that the former band represents absorption by an intermolecularly hydrogen-bonded hydroxyl group which decreases in importance with dilution relative to the non-bonded hydroxyl absorption at 2.82μ. In the β-isomer, on the other hand, only a single more intense band at 2.89μ is in evidence; and, in accord with expectation for intramolecularly hydrogen-bonded hydroxyl absorption, the intensity of this band relative to other absorption does not diminish with dilution nor does non-bonded, hydroxyl absorption (*ca.* 2.8μ) appear. Slight differences in carbonyl stretching frequencies (5.87μ for the β-isomer and 5.85μ for the α-form) also fall in line with the assumption of a greater degree of hydrogen-bonding in the lower melting (β) isomer. Construction of scale models of the two forms reveals that, although the six-membered hydrogen-bonded ring is achievable in the case where the hydroxyl and acetyl are *trans* to each other, the *cis* form lends itself much more readily to such interaction. These circumstances would seem to justify tentative assignment of the *trans* conformation to the higher melting (α) isomer and the *cis* conformation (OH and $COCH_3$ on the same side of the ring) to the lower melting (β) form. Finally, it should be noted that from each of the two forms of XI, as in the preparation of the carbinols IV and V, only one of two possible racemic forms of XII was isolated.

The lactone ring of pilocarpine (XIII) also seemed to provide a suitable functionality for reaction with the Grignard reagent. During the course of the present work, Pourrat[9] reported the reaction of phenylmagnesium bromide with pilocarpine to give the glycol XIV in 70% yield as a solid base, m.p. 290°. However, it was not characterized further. We also obtained the same glycol in 65% yield. It was converted to an optically active hydrochloride and dehydrated by the action of hydrochloric acid in acetic acid to the tetrahydrofuran XV, isolated as the hydrochloride. The structure of



XIII XIV XV

XV was indicated by the fact that its infrared spectrum showed no hydroxyl absorption and no sign of the presence of aliphatic unsaturation. Thus, XV bears a close structural relationship to pilocarpine in which the carbonyl oxygen atom has been replaced by two phenyl groups. It is interesting to note that, in going from XIII to XIV to XV, the specific rotations of the corresponding hydrochlorides in aqueous solution change from +91° to −145° to +156°.

Finally, the three synthetic imidazolecarboxylic esters, XVI, XVII, and XVIII were converted to the corresponding carbinols, XIX, XX, and XXI by treatment with phenylmagnesium bromide. An attempt to prepare the quaternary methiodide

XVI, R = R′ = H; R″ = CH_3
XVII, R = H; R′ = CH_3; R″ = CH_3
XVIII, R = R″ = CH_3; R′ = H

XIX, R = R′ = H
XX, R = H, R′ = CH_3
XXI, R = CH_3; R′ = H

of XX resulted in substitution at the nitrogen atom to give the quaternary salt of the corresponding *N*-methyl derivative.

Pharmacology. Most of the compounds prepared in this work were tested for antagonistic activity against the tremor-producing effects of Tremorine[10] in mice. Only compounds II and VIII were appreciably active, providing complete protection at subcutaneous doses of 10 and 20 mg./kg., respectively. It is interesting that III, the stereoisomer of II, provided only partial protection even at a dose of 50 mg./kg.

In the test for antagonism against acetylcholine-induced spasm of the isolated rabbit ileum only one tertiary amine, VIII, possessed appreciable activity of the order of one-tenth that of atropine. The quaternary salts of II, VIII, and X were, respectively, one-third, one-half, and one-third as active as atropine. All others tested were less than one percent as active.

EXPERIMENTAL

Reaction of arecoline (I) *with phenylmagnesium bromide. Preparation of II.* To a stirred solution of approximately 43 g. (0.24 mole) of phenylmagnesium bromide in 300 ml. of dry ether was added in several portions, 15 g. (0.06 mole) of powdered arecoline hydrobromide.[11] The mixture was stirred and heated under reflux for 2 hr. and allowed to stand overnight. To the stirred reaction mixture cooled in ice was added dropwise an aqueous solution of ammonium chloride. The ether layer was then separated and extracted with dilute hydrochloric acid. The acid extract was cooled in ice and made alkaline by the addition of a 40% aqueous potassium hydroxide solution. The precipitated oil was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an

(9) H. Pourrat, *Bull. soc. chim. France*, 827 (1955).

(10) G. Everett, L. Blockus, and I. Shepperd, *Science*, **124**, 79 (1956).

(11) Obtained from the Inland Alkaloid Co., Tipton, Ind.

oily residue which crystallized to a waxy solid (11 g.). Two recrystalllzations from cyclohexane gave 6 g. (36%) of pure II, m.p. 115–116°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57; N, 5.01; O, 5.74. Found: C, 81.52; H, 7.34; N, 5.07; O, 5.61.

The *methiodide* of II, m.p. 217–218° (dec.), was prepared by treatment of a sample of II with excess methyl iodide in methyl ethyl ketone followed by two recrystallizations of the resulting precipitate from aqueous ethanol.

Anal. Calcd. for $C_{20}H_{24}INO$: C, 57.01; H, 5.74; N, 3.32. Found: C, 57.18; H, 6.04; N, 3.30.

Isomerization of II *to* III. A mixture of 10 g. of compound II and 60 ml. of 48% aqueous hydrobromic acid was refluxed gently overnight and then poured into cold water. The mixture was made alkaline by the careful addition of excess solid sodium carbonate and the resulting oil was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an oil which solidified on trituration with hexane (Skellysolve B). Two recrystallizations from hexane gave 7.2 g. (72%) of compound III, m.p. 62–63°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57; N, 5.01; O, 5.74. Found: C, 81.72; H, 7.70; N, 4.83; O, 5.77.

III *Hydrochloride*, m.p. 230–231° (dec.), from ethanol-ether.

Anal. Calcd. for $C_{19}H_{22}ClNO$: C, 72.25; H, 7.02; N, 4.44. Found: C, 72.17; H, 7.13; N, 4.40.

Addition of methyl Grignard to the ketones II *and* III. *Preparation of* IV *and* V. To a stirred solution of methylmagnesium iodide prepared from 5.7 g. (0.04 mole) of methyl iodide and 1 g. (0.04 mole) of magnesium in 50 ml. of dry ether was added rapidly a solution of 7 g. (0.025 mole) of the *cis*-ketone II in 50 ml. of dry benzene. After heating under reflux for 2 hr. the reaction mixture was treated with aqueous ammonium chloride and worked up in the usual way (see the above procedure for the preparation of II). The crude product was recrystallized once from hexane (Skellysolve B) to give 5.3 g. (72%) of the *cis*-carbinol IV, m.p. 83–84°. Recrystallization of a sample once more for analysis raised the m.p. to 86–87°.

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.30; H, 8.59; N, 4.81.

In like manner from the *trans*-ketone III was obtained an 84% yield of the *trans*-carbinol V, m.p. 142–143° (from cyclohexane).

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.28; H, 8.54; N, 4.59.

Reaction of phenylmagnesium bromide with cocaine. Preparation of VII. To a stirred solution of 0.7 mole of phenylmagnesium bromide in 600 ml. of ether was added a solution of 0.088 mole of cocaine base (freed from 30 g. of the hydrochloride) in 500 ml. of dry ether. The mixture was stirred and heated under reflux for 18 hr. After cooling, a solution of 50 g. of ammonium chloride in 200 ml. of water was added dropwise to the stirred reaction mixture and the product was isolated in the usual way to give 15.4 g. (51%) of the glycol VII, m.p. 185–186° (from ethanol), $[\alpha]_D^{27}$ −23.5° (c = 0.04 g./ml.; $CHCl_3$), pK_a = 7.49 (by titration in aqueous methanol).

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 78.05; H, 7.79; N, 4.33. Found: C, 77.98; H, 7.72; N, 4.31.

The *quaternary methomethyl sulfate of* VII, m.p. 169–170°, was prepared by treating a sample of VII dissolved in methyl ethyl ketone with a slight excess of dimethyl sulfate, warming to about 40° for 1 hr., adding ether to the point of turbidity and cooling in an ice bath. The precipitated salt was recrystallized once from an isopropyl alcohol–ether mixture.

Anal. Calcd. for $C_{23}H_{31}NO_6S$: C, 61.45; H, 6.95; N, 3.12. Found: C, 60.90; H, 6.76; N, 3.06.

Dehydration of the glycol VII *to the diene* VIII. A mixture of 8.4 g. (0.026 mole) of the glycol VII, 18 ml. of concentrated hydrochloric acid, and 60 ml. of glacial acetic acid was heated under reflux for 2 hr. and then concentrated to dryness under reduced pressure. The residue was dissolved in water and made strongly alkaline with 40% aqueous sodium hydroxide. The precipitated oil was taken up in ether and dried over anhydrous sodium sulfate. Filtration and removal of the ether by distillation followed by two distillations of the residue under reduced pressure gave 4.5 g. of the diene VIII as a yellow oil, b.p. 201–203° (2.5 mm.), n_D^{25} 1.6338, $[\alpha]_D^{30}$ +548° (c = 0.04 g./ml.; $CHCl_3$), λ_{max} 282 mμ (ε = 17,800; 95% ethanol).

Anal. Calcd. for $C_{21}H_{21}N$: C, 87.76; H, 7.37; N, 4.87. Found: C, 87.94; H, 7.59; N, 4.91.

The methiodide of VIII was prepared by dissolving 1 g. of the diene in 50 ml. of methyl ethyl ketone, heating to reflux for 2 min. with 2 g. of methyl iodide and allowing to stand for 2 days. Recrystallization of the crude product from ethanol gave 0.7 g. of *VIII methiodide*, m.p. 281–282° dec., $[\alpha]_D^{26}$ +450° (c = 0.004 g./ml.; H_2O).

Anal. Calcd. for $C_{22}H_{24}IN$: C, 61.54; H, 5.63; N, 3.26. Found: C, 61.57; H, 5.86; N, 2.97.

Methyl ester of anhydroecgonine IX. A mixture of 13 g. (0.0638 mole) of anhydroecgonine hydrochloride,[7] 6.5 g. of Amberlite XE-156 resin, 50 ml. of dry methanol, and 175 ml. of ethylene dichloride was stirred and heated under reflux for 21 hr. The cooled reaction mixture was filtered and the filtrate was concentrated to dryness under reduced pressure. The residual glassy hydrochloride was treated with just enough saturated potassium carbonate solution to produce a fluid mixture which was then treated with solid anhydrous potassium carbonate to further salt out the somewhat water soluble base. The product was taken up in several portions of ether which were combined and dried over anhydrous sodium sulfate. Filtration, removal of the ether by distillation, and vacuum distillation of the residue gave 7.1 g. (62%) of IX, b.p. 124–126° (10 mm.) [Literature[7] reports b.p. 107° (7 mm.)], n_D^{25} 1.5006.

Addition of phenyllithium to IX. *Preparation of X*. A solution of phenyllithium was prepared by adding dropwise a solution of 42.4 g. (0.27 mole) of bromobenzene in 200 ml. of dry ether to a stirred suspension of 3.6 g. (0.52 mole) of lithium metal in 100 ml. of dry ether under an atmosphere of nitrogen. After stirring and heating under reflux for 2 hr., a solution of 8.1 g. (0.045 mole) of IX in 100 ml. of dry ether was added to the phenyllithium and the mixture was heated and stirred for 1 hr. longer. The cooled reaction mixture was then decomposed by the dropwise addition of 50 ml. of water and the solid which remained was collected by filtration. Two recrystallizations of the product from aqueous methanol gave 7.7 g. (56%) of the carbinol X, m.p. 209–210°, $[\alpha]_D^{29}$ −52.0° (c = 0.011 g./ml.; $CHCl_3$). The infrared spectrum of this material showed typical hydroxyl but no carbonyl absorption.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59; O, 5.24. Found: C, 82.37; H, 7.83; N, 4.57; O, 5.32.

Treatment of 1.5 g. of X with 0.6 g. of dimethyl sulfate in methanol gave, after two recrystallizations from dry ethanol, 1.1 g. of the *methomethyl sulfate of* X, m.p. 186–187°.

Anal. Calcd. for $C_{23}H_{29}NO_5S$: C, 64.01; H, 6.77; N, 3.25. Found: C, 63.96; H, 6.86; N, 3.27.

Dehydration of the carbinol X *to the diene* VIII. A 1.5-g. sample of the carbinol X was treated with a solution of 4 ml. of concentrated hydrochloric acid in 12 ml. of glacial acetic acid exactly as described above for the dehydration of the glycol VII. The crude diene base was treated directly with methyl iodide in the usual manner to give 0.4 g. of *VIII methiodide*, m.p. 275–276° (dec.).

Anal. Calcd. for $C_{22}H_{24}IN$: C, 61.54; H, 5.63; N, 3.26. Found: C, 61.63; H, 5.87; N, 3.16.

A mixture of this material with the methiodide, m.p. 281–282° (dec.), prepared from the diene VIII obtained by dehydration of VII, melted at 276–278° (dec.). Further proof of identity of these two materials comes from the fact that their infrared spectra in chloroform solution were qualitatively identical and their specific rotations (c =

0.021 g./ml. in $CHCl_3$) differed by only 2% (+443° and +450°).

Reaction of the hydroxyketones XI *with phenylmagnesium bromide. Preparation of the glycols* XII. A solution of phenyl Grignard reagent in ether was prepared in the usual way from 28.3 g. (0.18 mole) of bromobenzene and 4.3 g. (0.18 mole) of magnesium. The ether was then replaced by dry benzene and the stirred refluxing reagent was treated rapidly with a hot solution of 10 g. (0.0585 mole) of XI[8] in dry benzene. The reaction mixture was then heated under reflux overnight, cooled, and decomposed with aqueous ammonium chloride. The glycols XII were isolated in the usual manner in the form of solid free bases.

From the α-form of XI, m.p. 130°,[8] was obtained 6.6 g. (45%) of the *α-glycol XII*, m.p. 177–178° (from ethyl acetate).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.29; N, 5.61; O, 12.85. Found: C, 72.41; H, 9.17; N, 5.76; O, 12.54.

From the β-form of XI, m.p. 85–86°,[8] was obtained 1.6 g. (11%) of the *β-glycol XII*, m.p. 180–181° (dec.) (from ethyl acetate). A mixture of the α- and β-glycols melted at 155–160°.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.29; N, 5.61; O, 12.85. Found: C, 72.55; H, 9.11; N, 5.63; O, 12.94.

An attempt to increase the yield of the β-glycol XII by using toluene in place of benzene in the Grignard reaction led to essentially the same results. In addition to the poorer yield of addition product obtained from the β-isomer, the lower reactivity of this form as compared to the α-isomer was further indicated by the fact that the initial stage of the Grignard reaction of the α-form was exothermic. The β-isomer showed no such evidence of spontaneous reaction.

Reaction of pilocarpine (XIII) *with phenylmagnesium bromide. Preparation of* XIV. To a solution of phenylmagnesium bromide in ether prepared in the usual way from 37.7 g. (0.24 mole) of bromobenzene and 5.75 g. (0.24 mole) of magnesium was added in portions, 15 g. (0.06 mole) of powdered pilocarpine hydrochloride.[12] The mixture was stirred and heated under reflux overnight and decomposed as usual with aqueous ammonium chloride solution. The free base, insoluble in ether, was collected by filtration and gave, after recrystallization from dry ethanol, 14.3 g. (65%) of the glycol XIV, m.p. 285–288° (dec.). One recrystallization from dimethylformamide gave analytically pure XIV, m.p. 291–293° (dec.) (literature[9] reports m.p. 290°).

Anal. Calcd. for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.68. Found: C, 75.85; H, 7.71; N, 7.50.

XIV *Hydrochloride*, m.p. 137–139° dec. was recrystallized from an isopropyl alcohol–ether mixture. The specific rotation, $[\alpha]_D^{27}$, of the hydrochloride was −145° (c = 0.008 g./ml.; H_2O) whereas the $[\alpha]_D^{18}$ of pilocarpine hydrochloride is reported to be +91° (c = 0.02 g./ml.; H_2O).

Anal. Calcd. for $C_{23}H_{29}ClN_2O_2$: C, 68.90; H, 7.29; N, 6.98. Found: C, 68.78; H, 7.73; N, 6.85.

Dehydration of XIV *to* XV. A solution of 3.6 g. of the glycol XIV in 30 ml. of glacial acetic acid containing 10 ml. of concentrated hydrochloric acid was refluxed for 2 hr. The mixture was concentrated to dryness under reduced pressure, the residue was dissolved in water and the solution was made strongly alkaline with saturated aqueous potassium carbonate. The liberated base was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an oil which could not be crystallized. It was taken up in ether and treated with ethereal hydrogen chloride. Recrystallization of the resulting salt from an ethanol-ether mixture gave 2 g. of *XV hydrochloride*, m.p. 254–256°, $[\alpha]_D^{27}$ +156° (c = 0.01 g./ml.; H_2O).

Anal. Calcd. for $C_{23}H_{27}ClN_2O$: C, 72.14; H, 7.11; N, 7.32 Found: C, 72.10; H, 6.91; N, 7.40.

Reaction of imidazolecarboxylic esters with phenylmagnesium bromide. Preparation of the carbinol XX. A solution of approximately 54 g. (0.335 mole) of phenylmagnesium bromide in 300 ml. of ether was treated with 250 ml. of tetrahydrofuran and the ether was removed by distillation. To the hot Grignard solution was added 10 g. (0.065 mole) of powdered 4-carbethoxy-5-methylimidazole (XVII).[13] The mixture was stirred and refluxed for a few minutes and then about three-fourths of the solvent was removed under reduced pressure. To the cooled mixture, ether was added followed by excess of an aqueous ammonium chloride solution. The solid which remained undissolved was collected by filtration, the ether layer was separated and concentrated to dryness. The residual solid was combined with the original filter-cake and dissolved in excess aqueous hydrochloric acid. This solution was then made alkaline with aqueous potassium hydroxide and the liberated solid base [11.5 g., 67%, m.p. 182–184° (dec.)] was again collected by filtration. Several recrystallizations from isopropyl alcohol gave analytically pure carbinol XX, m.p. 186–187° (dec.).

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10; N, 10.60; O, 6.06. Found: C, 77.11; H, 5.89; N, 10.63; O, 6.35.

Heating under reflux for 4 hr. a mixture of 1.5 g. of XX, methyl ethyl ketone, and excess methyl iodide gave, after recrystallization from an isopropyl alcohol–ether mixture, 0.8 g. of the quaternary methiodide salt of the *N*-methyl derivative of XX, m.p. 223–224° (dec.) (from dry ethanol).

Anal. Calcd. for $C_{19}H_{21}IN_2O$: C, 54.29; H, 5.04; N, 6.67. Found: C, 54.25; H, 5.35; N, 6.56.

In a manner similar to the above procedure, addition of phenylmagnesium bromide to 4-carbomethoxyimidazole (XVI)[14] gave the *carbinol XIX* in 81% yield, m.p. 173–174° (dec.).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.64; N, 11.20; O, 6.39. Found: C, 76.56; H, 5.68; N, 10.88; O, 6.71.

Likewise, reaction of 4-carbomethoxy-2-methylimidazole (XVIII)[15] with the phenyl Grignard reagent led to the carbinol XXI in 78% yield, m.p. 200–201° (dec.) (from dry ethanol).

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10; N, 10.60; O, 6.06. Found: C, 77.30; H, 6.29; N, 10.44; O, 6.14.

Acknowledgment. Mr. E. F. Shelberg, Chief Microanalyst, Abbott Laboratories, was responsible for the elementary analyses. The infrared and ultraviolet spectra were kindly supplied by Mr. W. F. Washburn and Mr. F. E. Chadde of the Abbott Control Department, and the potentiometric titrations by Mr. Steve Ober of the Abbott Physical Chemistry Department. The physiological tests were carried out by Dr. Kao Hwang, Dr. G. M. Everett, and Mr. L. E. Blockus of the Abbott Pharmacological Research Department.

North Chicago, Ill.

(12) Obtained from Merck & Co., Inc., Rahway, N. J.

(13) O. Gerngross, *Ber.*, 45, 509 (1912).

(14) F. Pyman, *J. Chem. Soc.*, 109, 186 (1916).

(15) R. Fargher and F. Pyman, *J. Chem. Soc.*, 115, 1015 (1919).

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

Potential Purine Antagonists. XII. Synthesis of 1-Alkyl(aryl)-4,6-disubstituted Pyrazolo[3,4-*d*]pyrimidines[1]

C. C. CHENG AND ROLAND K. ROBINS[2]

Received December 23, 1957

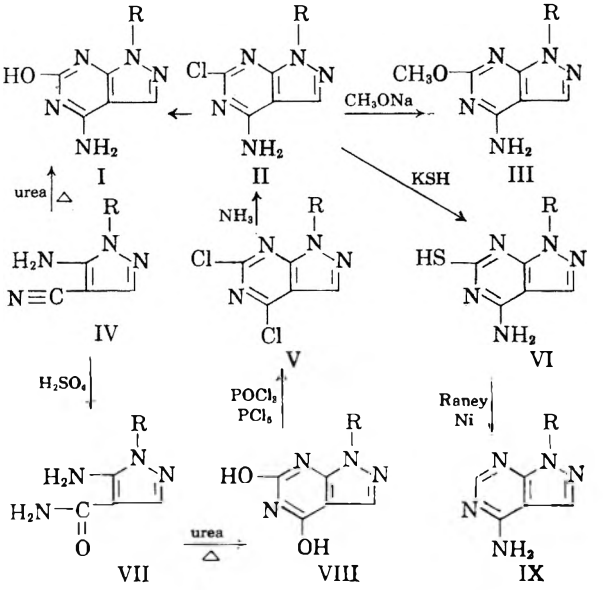
Various 1-alkyl(aryl)-4,6-disubstituted pyrazolo[3,4-*d*]pyrimidines were prepared *via* the corresponding 1-alkyl(aryl)-5-amino-4-cyanopyrazoles (IV). The urea fusion of the 1-alkyl(aryl)-5-aminopyrazole-4-carboxamide (VII) prepared from IV yielded the corresponding 1-alkyl(aryl)-4,6-dihydroxypyrazolo[3,4-*d*]pyrimidine (VIII) which was treated with phosphorus oxychloride and phosphorus pentachloride to yield the 4,6-dichloropyrazolo[3,4-*d*]pyrimidine (V). The replacement of the chlorine atoms of V was investigated and the position of substitution determined.

The report of the activity possessed by certain 1-methyl-4-substituted aminopyrazolo[3,4-*d*]pyrimidines and 4-hydroxy-6-aminopyrazolo[3,4-*d*]pyrimidine in the inhibition of the growth of certain experimental neoplasms *in vivo*[3] suggested further synthetic work be carried out in this series. This report is concerned with the preparation of certain 1-alkyl(aryl)-4,6-disubstituted pyrazolo[3,4-*d*]pyrimidines.

As previously described the general synthetic route to the pyrazolo[3,4-*d*]pyrimidines devised in this laboratory begins with a 5-amino-4-cyanopyrazole.[4-7] Hoggarth and Paget[8] have recently reported the preparation of 6-amino-4-methyl-pyrazolo(3,4-*d*)pyrimidine from the condensation of hydrazine and 4-alkylthiopyrimidines.

While the present investigation was in process, Schmidt and Druey[9] reported a synthesis of several pyrazolo[3,4-*d*]pyrimidines from 3-aminopyrazole-4-carboxylate in a manner similar to that utilized by Robins[4] who employed 3-aminopyrazole-4-carboxamide as a pyrazole intermediate. Schmidt and Druey[9] list 4,6-dihydroxy-1-phenylpyrazolo-[3,4-*d*]pyrimidine (III, R = C_6H_5) in a table and record the melting point as 297–298°. No experimental directions were reported for this preparation. This compound was prepared in our laboratory by the urea fusion of 5-amino-1-phenylpyrazole-4-carboxamide (VII, R = C_6H_5)[5] and found to possess a melting point of 372–373°. In a similar manner a number of 1-alkyl(aryl)-4,6-dihydroxypyrazolo-[3,4-*d*]pyrimidines (VIII) were prepared by heating the corresponding 1-alkyl(aryl)-4-aminopyrazole-

REACTION SCHEME I



carboxamides (VII)[5] with urea. In general the yields were good, and the crude 4,6-dihydroxypyrazolo[3,4-*d*]pyrimidine was utilized directly for further synthetic work. Fusion of a substituted urea such as *N*-methylurea or *N*-phenylurea with 4 - amino - 1 - methylpyrazole - 5 - carboxamide (VII, R = CH_3) gave 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (VIII, R = CH_3) instead of a 1-methylpyrazolo[3,4-*d*]pyrimidine substituted at nitrogen "5" or "7". Chlorination of VIII with phosphorus oxychloride in the presence of an excess of phosphorus pentachloride gave the corresponding 1-alkyl(aryl)-4,6-dichloropyrazolo[3,4-*d*]pyrimidine (V) in good yield. It is interesting to note that with V when R = H, these conditions for chlorination were unsuccessful, and special reaction conditions have previously[6] been found necessary for the preparation of 4,6-dichloropyrazolo[3,4-*d*]pyrimidine.

Treatment of V, R = CH_3, in 1*N* potassium hydroxide gave 6-chloro-4-hydroxy-1-methylpyrazolo-[3,4-*d*]pyrimidine (XI). Increased strength of the

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(2) Present address: Department of Chemistry, Arizona State College, Tempe, Ariz.

(3) Skipper, Robins, Thomson, Cheng, Brockman, and Schabel, *Cancer Research*, **17**, 579 (1957).

(4) Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

(5) Cheng and Robins, *J. Org. Chem.*, **21**, 1240 (1956).

(6) Robins, *J. Am. Chem. Soc.*, **79**, 6407 (1957).

(7) Cheng and Robins, *J. Org. Chem.*, **23**, 191 (1958).

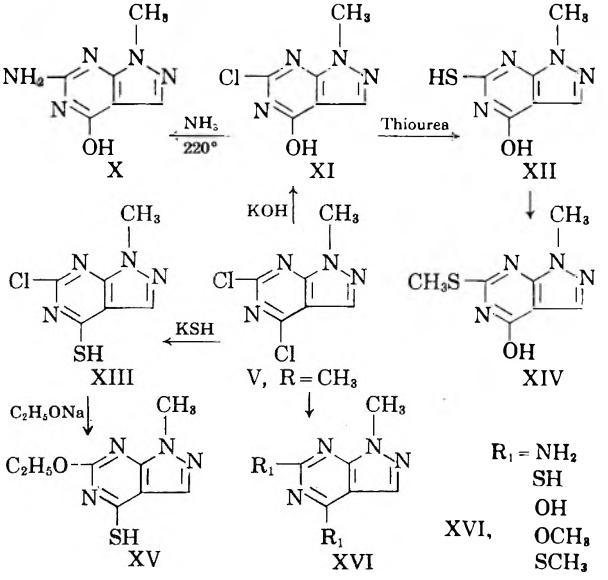
(8) Hoggarth and Paget, Brit. Patent, **716,327** [*Chem. Abstr.*, **49**, 5178a (1955)].

(9) Schmidt and Druey, *Helv. Chim. Acta*, **39**, 986 (1956).

base and longer reaction time did not hydrolyze the chlorine atom in position "6." Treatment of V, R = CH_3, with refluxing concentrated hydrochloric acid, however, readily gave the original dihydroxy derivative, VIII, R = CH_3. The selection replacement of the chlorine atoms in the 1-alkyl(aryl)-4,6-dichloropyrazolo[3,4-*d*]pyrimidines (V) was rather extensively investigated. As with 4,6-dichloropyrazolo[3,4-*d*]pyrimidine[6] selective nucleophilic replacement of the "4" chloro atom could be accomplished under relatively mild conditions. It would appear that the "4" chloro atom of V is more susceptible to nucleophilic replacement than the chlorine atom of the corresponding 1-alkyl(aryl)-4-chloropyrazolo[3,4-*d*]pyrimidine.[5] Thus, V, R = CH_3, reacted with alcoholic ammonia heated on the steam bath (70°) to give 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (II, R = CH_3) while 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine required heating in a bomb[5] with the same reagent to effect replacement of the chlorine atom in position "4."

The diamino derivative, XVI, $R_1 = NH_2$, was obtained from V, R = CH_3, and alcoholic ammonia heated to 180° in a bomb.

REACTION SCHEME II

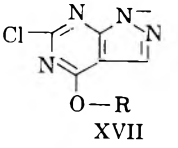


The structure of II, R = CH_3, was determined in the following manner. When II, R = CH_3, was refluxed with concentrated hydrochloric acid, 4-amino-6-hydroxy-1-methyl-pyrazolo[3,4-*d*]pyrimidine (I, R = CH_3) was formed in good yield. I, R = CH_3, was also synthesized by the fusion of urea and 5-amino-4-cyano-1-methylpyrazole (IV, R = CH_3).

Further proof of the structure assigned II, R = CH_3, was obtained as follows: 4-Amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (II, R = CH_3) was treated with 3 *N* potassium hydrosulfide in a bomb at 110° to give 4-amino-6-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (VI, R = CH_3). Raney Nickel dethiation converted VI, R = CH_3, to 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine (IX), which had been previously prepared[5] from 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine.

In general, the replacement of the second chlorine atom at position "6" was more difficult and required a higher temperature. Occasionally, however, the replacement of both chlorine atoms took place simultaneously. For example, the isolation of 6-chloro-4-dimethylamino-1-methylpyrazolo[3,4-*d*]pyrimidine and 6-chloro-4-(*p*-chloroanilino)-1-methylpyrazolo[3,4-*d*]pyrimidine under various experimental conditions was unsuccessful. In these two instances the 4,6-bis-substituted-amino derivatives were obtained exclusively.

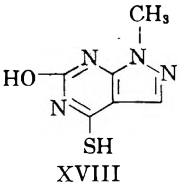
1-Alkyl(aryl)-4,6-dialkoxypyrazolo[3,4-*d*]pyrimidines were prepared from V, R = CH_3, and sodium alkoxides. It is interesting to note that in the case of 4,6-dichloropyrazolo[3,4-*d*]pyrimidine[6] a monosubstituted alkoxy derivative was obtained under carefully controlled conditions; but when the 1-position was substituted with an alkyl or aryl group, a disubstituted alkoxy derivative was obtained exclusively. This might possibly be explained in structure XVII by the acquisition of a negative charge by nitrogen at position "1" in the basic medium. Thus, the increase of electron density of the ring could hinder the nucleophilic displacement of the second chlorine atom. This type of deactivation would not be possible if position "1" were substituted with an alkyl or aryl group. The preparation of 4,6-dimercapto-1-methylpy-



XVII

razolo(3,4-*d*)pyrimidine (XVI, R_1 = SH) proceeded smoothly from V, R = CH_3, and thiourea in refluxing ethanol. Sodium methylmercaptide and V, R = CH_3, gave 1-methyl-4,6-bis(methylthio)-pyrazolo[3,4-*d*]pyrimidine (XVI, $R_1 = SCH_3$).

When 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (VIII, R = CH_3) was treated with phosphorus pentasulfide in pyridine, 6-hydroxy-4-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (XVIII) was obtained.


XVIII

The structure of XVIII was established since the isomer, 4-hydroxy-6-mercapto-1-methylpyrazolo-[3,4-*d*]pyrimidine (XII) was prepared from 5-amino-1-methylpyrazolo[3,4-*d*]pyrimidine-4-carboxamide (VII, R = CH_3) fused with thiourea.

Treatment of XI and thiourea in refluxing ethanol also gave XII, thus providing proof of the structure previously assigned XI. Careful methylation of XII with dimethylsulfate gave 4-hydroxy-1-methyl-6-methylthiopyrazolo[3,4-*d*]pyrimidine (XIV).

When 6-chloro-4-hydroxy-1-methylpyrazolo[3,-4-*d*]pyrimidine (XI) was treated with alcoholic ammonia at 220°, 6-amino-4-hydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (X) was obtained. Careful treatment of V, R = CH_3, with potassium hydrosulfide gave 6-chloro-4-mercapto-1-methylpyrazolo-[3,4-*d*]pyrimidine (XIII). The compound, XIII, was further treated with sodium ethoxide to yield 6-ethoxy-4-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (XV). This type of selective replacement of the chlorine atoms is further illustrated by the reaction of II, R = CH_3, and sodium methoxide to give 4-amino-6-methoxy-1-methylpyrazolo[3,4-*d*]-pyrimidine (III).

Similarly, V, R = CH_3, and sodium ethylmercaptide at room temperature gave 6-chloro-4-ethylthio - 1 - methylpyrazolo[3,4-*d*]pyrimidine (XIX) which in turn when treated with sodium ethoxide yielded XX.

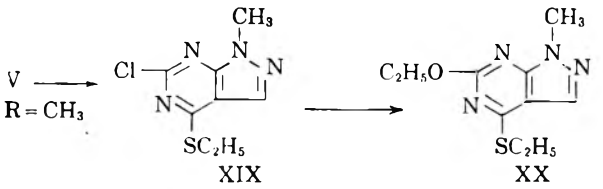


Table II lists the 1-alkyl(aryl)-6-chloro-4-(substituted amino)pyrazolo[3,4-*d*]pyrimidines prepared from V. Table III lists the 1-alkyl(aryl)-4,6-bis-(substituted amino)pyrazolo[3,4-*d*]pyrimidines prepared from V and the corresponding primary or secondary amines. By careful study of the reaction time and solvent, it was possible in most cases to effect mono- or disubstitution as desired. Table I lists a number of 1-alkyl(aryl)-4,6-disubstituted pyrazolo[3,4-*d*]pyrimidines which have been prepared in this study.

EXPERIMENTAL[10]

Preparation of 4,6-dihydroxy-1-methylpyrazolo[3,4-d]pyrimidine (VII, R = CH_3). *Method 1.* Fifty grams of 5-amino-1-methylpyrazolo-4-carboxamide[5] was fused with 100 g. of urea at 180–200° for 1 hr. The mixture melted in the beginning of the fusion; it then became mushy; finally, with continuous agitation, the reaction mixture solidified. The cooled solid mass was dissolved in 1 l. of hot, dilute potassium hydroxide. The solution was treated with charcoal and filtered. The boiling filtrate was acidified with glacial acetic acid. A white precipitate formed which was filtered and dried at 130° for 5 hr. to give 55 g. (93%) of white powder, m.p. >300°. This crude product was employed directly for chlorination to give 4,6-dichloro-1-methylpyrazolo[3,4-*d*]-pyrimidine (IV, R = CH_3). Ultraviolet absorption spectra showed this product to be above 90% pure. An analytically pure sample was obtained only by acid hydrolysis of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine (V, R = CH_3) as indicated in Method 2.

Method 2. Acid hydrolysis of 4,6-dichloro-1-methylpyrazolo-[3,4-d]pyrimidine (V, R = CH_3). Four grams of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine was suspended in 15 ml. of water. To this suspension was added 80 ml. of concentrated hydrochloric acid. The mixture was refluxed for 18 hr. A white precipitate resulted on cooling. The product was filtered and reprecipitated once from dilute alkaline solution by acetic acid to give white needles, m.p. >300°. The yield of pure 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]-pyrimidine (III, R = CH_3) was 2 g. (65%).

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.4; H, 3.6; N, 33.7. Found: C, 43.3; H, 3.6; N, 33.7.

Preparation of 4,6-dihydroxy-1-phenylpyrazolo[3,4-d]pyrimidine (VIII, R = C_6H_5). Fifty grams of 5-amino-1-phenylpyrazole-4-carboxamide[5] was fused with 100 g. of urea at approximately 200° until the fused mass solidified. The cooled melt was dissolved in dilute sodium hydroxide; the solution was treated with charcoal and filtered. The hot filtrate was acidified with glacial acetic acid and the white precipitate collected. The solid was washed with water and dried at 130° to yield 53 g. (94%) of white powder, m.p. >300°. A small amount of the product was recrystallized from 80% acetic acid to give long, white needles, m.p. 320–321° (copper block).

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.9; H, 3.5; N, 24.6. Found: C, 58.1; H, 3.6; N, 24.6.

Preparation of 4,6-dichloro-1-methylpyrazolo[3,4-d]pyrimidine (V, R = CH_3). One hundred grams of finely powdered 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine was mixed with 200 ml. of phosphorus oxychloride and 700 g. of phosphorus pentachloride. The mixture was refluxed for 28 hr. and the excess phosphorus oxychloride distilled at reduced pressure using a steam bath as a source of heat. The sirupy residue was poured, with vigorous stirring, onto 2 kg. of crushed ice. The cold, aqueous suspension was filtered and the filtrate extracted with chloroform. The chloroform extract, after being washed well with ice water until free of acid, was dried over anhydrous magnesium sulfate. The solvent was then distilled, and the residue solidified on cooling to yield 61 g. (50%) of tan solid, m.p. 82–85°. The product was recrystallized from absolute ethanol followed by a second recrystallization from heptane to give white needles, m.p. 87–88°.

Anal. Calcd. for $C_6H_4N_4Cl_2$: C, 35.5; H, 2.0; N, 27.6. Found: C, 36.0; H, 2.2; N, 27.6.

Preparation of 4,6-dichloro-1-phenylpyrazolo[3,4-d]pyrimidine (V, R = C_6H_5). Forty grams of 4,6-dihydroxy-1-phenylpyrazolo[3,4-*d*]pyrimidine was refluxed with a mixture of 160 g. of phosphorus pentachloride and 500 ml. of phosphorus oxychloride. The solution was refluxed for 2 hr. The excess phosphorus oxychloride was removed and the sirupy residue poured, with vigorous stirring, onto 1 kg. of crushed ice. The solution was extracted with chloroform, and the chloroform extract was washed and dried. A light-yellow solid remained after the distillation of the chloroform to yield 42 g. (90%), m.p. 120–122°. The product was recrystallized from heptane to give white needles, m.p. 126–127°.

Anal. Calcd. for $C_{11}H_6N_4Cl_2$: C, 49.8; H, 2.3; N, 21.1; Cl, 26.8. Found: C, 50.2; H, 2.4; N, 20.8; Cl, 26.6.

Preparation of 1-p-chlorophenyl-4,6-dichloropyrazolo[3,4-d]-pyrimidine. To 300 g. of phosphorus oxychloride and 60 g. of phosphorus pentachloride was added 27 g. of 1-*p*-chlorophenyl-4,6-dihydroxypyrazolo[3,4-*d*]pyrimidine (VIII, R = *p*-C_6H_4Cl). The solution was refluxed for 2.5 hr. and the excess phosphorus oxychloride removed under reduced pressure. The sirupy residue was poured on crushed ice and the solution kept cooled and stirred for 30 min. The precipitate was filtered and repeatedly washed with ice water and finally allowed to dry at room temperature. The crude

(10) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus, unless otherwise stated.

yield was 23.4 g., m.p. 140–142°. Recrystallization from *n*-heptane raised the melting point to 146–147°.

Anal. Calcd. for $C_{11}H_5N_4Cl_3$: C, 44.1; H, 1.7. Found: C, 44.4; H, 1.7.

Preparation of 4-amino-6-chloro-1-methylpyrazolo[3,4-d]-pyrimidine (II, R = CH_3). Ten g. of finely powdered 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine was added to 200-ml. of alcoholic ammonia. The mixture was then boiled gently on a steam bath to dryness. Another 200-ml. portion of alcoholic ammonia was added to the dry mass, and the solution was again evaporated to dryness. The residue was washed with cold water and recrystallized from 400 ml. of water to give white needles, m.p. 295–296°. The yield of 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine was 7 g. (78%).

Anal. Calcd. for $C_6H_6N_5Cl$: C, 39.3; H, 3.3; N, 38.2. Found: C, 39.3; H, 3.7; N, 38.6.

Preparation of 6-chloro-4-hydroxy-1-methylpyrazolo[3,4-d]-pyrimidine (IX). Five g. of 4,6-diehloro-1-methylpyrazolo-[3,4-*d*]pyrimidine (V, R = CH_3) was refluxed with 5 g. of potassium hydroxide and 1 g. of activated charcoal in 100 ml. of water for 3 hr. The solution was filtered and the hot filtrate acidified with glacial acetic acid. The precipitate was collected and reprecipitated to give white needles, m.p. 267–268°. The yield of 6-chloro-4-hydroxy-1-methyl-pyrazolo[3,4-*d*]pyrimidine (XI) was 4 g. (88%).

Anal. Calcd. for $C_6H_5N_4OCl$: C, 39.1; H, 2.7; N, 30.4. Found: C, 39.1; H, 3.1; N, 30.7.

Preparation of 4,6-diamino-1-methylpyrazolo[3,4-d]pyrimi-dine (XVI, R = CH_3). Ten g. of 4,6-dichloro-1-methyl-pyrazolo[3,4-*d*]pyrimidine was heated with 120 ml. of alcoholic ammonia in a bomb at 210° for 12 hr. The reaction mixture was evaporated to dryness, and the solid product was washed with a small amount of dilute alkali and then with water. Recrystallization from water gave small, white needles, m.p. >300°. The yield of 4,6-diamino-1-methyl-pyrazolo[3,4-*d*]pyrimidine was 2 g. (25%).

Anal. Calcd. for $C_6H_8N_6$: C, 43.8; H, 4.9. Found: C, 42.8, 44.8; H, 4.4, 5.1.

Preparation of 4,6-diamino-1-phenylpyrazolo[3,4-d]pyrimi-dine. Ten g. of V, R = C_6H_5, was added to 150 ml. of ethanol saturated with dry ammonia at 0°. The mixture was then heated at 190° in a bomb for 12 hr. The solvent was then evaporated and the residue washed with water and recrystal-lized from dilute ethanol to yield 6.3 g. of a white solid, m.p. 236–237°.

Anal. Calcd. for $C_{11}H_{10}N_6$: C, 58.3; H, 4.5; N, 37.5. Found: C, 58.0; H, 4.9; N, 38.0.

Preparation of 4-amino-6-hydroxy-1-methylpyrazolo[3,4-d]-pyrimidine (I, R = CH_3). *Method 1. Hydrolysis of 4-amino-6-chloro-1-methylpyrazolo[3,4-d]pyrimidine* (II, R = CH_3). A mixture of 12 g. of II, R = CH_3, and 100 ml. of concen-trated hydrochloric acid was refluxed for 10 hr. All the solid dissolved after 30 min. After 8 hr. of refluxing, the solution was cooled and the product filtered. Purification was accomplished by reprecipitation from a hot, dilute basic solution with glacial acetic acid to give 7 g. (64%) of white powder, m.p. >300°.

Anal. Calcd. for $C_6H_7N_5O_2$: C, 43.6; H, 4.3. Found: C, 43.4; H, 4.3.

Method 2. Fusion of urea and 5-amino-4-cyano-1-methyl-pyrazole (IV, R = CH_3). Twenty g. of IV, R = CH_3, was fused with 40 g. of urea at 200°. The mixture melted and then gradually formed a paste which finally solidified after stirring for 30 min. The crude product was purified by re-precipitation from a basic solution to yield 10.4 g. (34%). The ultraviolet absorption spectra at *p*H 1 and *p*H 11 was identical to that prepared by Method 1.

Preparation of 6-amino-4-hydroxy-1-methylpyrazolo[3,4-d]-pyrimidine (X, R = CH_3). A mixture of 7 g. of 6-chloro-4-hydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (XI) and 120 ml. of alcoholic ammonia was heated in a bomb at 220° for 12 hr. The reaction product was then evaporated to dryness. The residue was dissolved in dilute hydrochloric acid, the solution filtered, and the product reprecipitated by adding ammonium hydroxide to the hot filtrate to give 4.5 g. (72%) of white powder, m.p. >300°.

Anal. Calcd. for $C_6H_7N_5O$: C, 43.6; H, 4.3; N, 42.4. Found: C, 43.7; H, 4.5; N, 42.5.

Preparation of 6-hydroxy-4-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (X, R = CH_3). A solution of 30 g. of finely powdered 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine, 150 g. of phosphorus pentasulfide and 600 ml. of dry pyridine was refluxed for 12 hr. The excess pyridine was distilled under reduced pressure from a steam bath. The sirupy residue was heated with 4 l. of water for 5 hr. on the steam bath. The solid product was filtered and recrystallized from water to give 18 g. (55%) of a light-yellow solid, m.p. >310°.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.6; H, 3.3; N, 30.8. Found: C, 40.0; H, 3.3; N, 31.1.

Preparation of 4,6-dimercapto-1-methylpyrazolo[3,4-d]pyrim-idine (XVI, R_1 = SH). Ten g. of powdered 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine and 10 g. of thiourea were added to 150 ml. of absolute ethanol and the solution refluxed for 3 hr. The solid substance, which precipitated from the hot solution, was filtered and reprecipitated from dilute potassium hydroxide by glacial acetic acid to give 7.2 g. (74%) of light-yellow powder, m.p. 292–293°.

Anal. Calcd. for $C_6H_6N_4O_2$: C, 36.4; H, 3.1; N, 28.3. Found: C, 36.6; H, 2.9; N, 28.1.

Preparation of 4,6-dimercapto-1-phenylpyrazolo[3,4-d]py-rimidine. To a solution of 13 g. of thiourea, dissolved in 120 ml. of absolute ethanol, was added 10 g. of V, R = C_6H_5. The solution was refluxed for 4 hr. and then allowed to cool. The filtered product was dissolved in hot, dilute potassium hydroxide and precipitated with acetic acid to give 3.5 g. of product.

Anal. Calcd. for $C_{11}H_8N_4S_2$: C, 50.8; H, 3.1; N, 21.5. Found: C, 51.2; H, 3.3; N, 21.1.

Preparation of 1-alkyl(aryl)-6-chloro-4-substitutedamino-pyrazolo[3,4-d]pyrimidines. See Table II. The preparation of these derivatives can best be illustrated by the following examples:

6-Chloro-4-(o-chloroanilino)-1-methylpyrazolo[3,4-d]pyrimi-dine. Five g. of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimi-dine (V, R = CH_3) was mixed with 13 g. of *o*-chloroaniline in 150 ml. of absolute ethanol. The mixture was evaporated to dryness slowly on a steam bath. The residue was washed with a little cold ethanol and recrystallized from a mixture of 2-ethoxyethanol and water. The yield was 6.2 g. (86%) of small, white plates, m.p. 224–225°.

Anal. Calcd. for $C_{12}H_9N_5Cl_2$: N, 23.7. Found: N, 23.4.

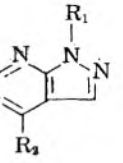
6-Chloro-4-(2',4'-dimethylanilino)-1-methylpyrazolo[3,4-d]-pyrimidine. Five g. of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]-pyrimidine (V, R = CH_3), 10 g. of 2,4-dimethylaniline, and 150 ml. of absolute ethanol were heated on a steam bath for 8 hr. The solution was then evaporated to dryness. The solid mass was washed with a little ether and recrystallized from ethanol to give 4 g. (57%) of white needles, m.p. 241°.

Anal. Calcd. for $C_{14}H_{14}N_5Cl$: C, 58.5; H, 4.9; N, 24.3. Found: C, 58.8; H, 4.7; N, 24.0.

6-Chloro-1-methyl-4-(1',1',3',3'-tetramethylbutylamino)-pyrazolo[3,4-d]pyrimidine. Five g. of 4,6-dichloro-1-methyl-pyrazolo[3,4-*d*]pyrimidine (V, R = CH_3), 15 g. of 1,1,3,3-tetramethylbutylamine, and 150 ml. of absolute ethanol were evaporated to dryness on a steam bath. The crude compound was recrystallized from benzene and ethanol to give 6.5 g. (72%) of white needles, m.p. 183–184°.

Anal. Calcd. for $C_{14}H_{22}N_5Cl$: C, 56.9; H, 7.5; N, 23.6. Found: C, 56.9; H, 7.7; N, 23.1.

6-Chloro-4-β-hydroxyethylamino-1-phenylpyrazolo[3,4-d]-pyrimidine. A mixture of 4,6-dichloro-1-phenylpyrazolo-[3,4-*d*]pyrimidine, 20 g. of ethanolamine, and 100 ml. of 50% methanol was boiled on a steam bath for 3 hr. A white precipitate formed gradually in the hot solution. The mix-ture was cooled and filtered, and the product was recrystal-

TABLE I 

SUBSTITUTED PYRAZOLO[3,4-*d*]PYRIMIDINES

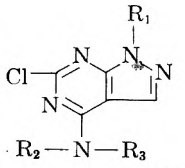
R_1	R_2	R_3	M.P. (°C.)	Yield (%)	U.v. Absorption λ_{max}, mμ pH 11	ϵ	λ_{max}, mμ Ethanol	ϵ	Recrystn.[a] Solvents	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	OH	OH	>300	93.0	247	12,600			E	43.4	3.64	33.7	43.3	3.60	33.7
					269	9,300									
CH_3	Cl	Cl	87–88	43.4			271	6,500	D	35.5	1.97	27.6	36.0	2.19	27.6
CH_3	OH	Cl	267–268	88.0	266	9,240			E	39.1	2.73	30.4	39.0	2.82	30.7
CH_3	OH	SH	>300	73.6	239	8,740			I	39.6	3.32	30.8	39.8	3.86	30.7
					278	11,600									
CH_3	SH	OH	>300	90.0	259	7,100	232	8,200	E	39.6	3.32	30.8	40.0	3.29	31.1
					331	17,100	262	6,550							
							300	6,500							
CH_3	SH	SH	292–293	73.7	240	19,800									
					325	19,800			E	36.4	3.05	28.3	36.6	2.94	28.1
CH_3	SH	Cl	223	45.5	237	16,200			E			27.9			27.1
					326	23,200									
CH_3	NH_2	Cl	295–296	77.5	266	10,500			A	39.3	3.30	38.2	39.3	3.70	38.6
CH_3	NH_2	NH_2	>300	24.8	276	10,200			A	43.8	4.90		42.8	5.12	
CH_3	OH	NH_2	>300	71.9	267	19,300			F	43.6	4.27	42.4	43.7	4.48	42.5
CH_3	NH_2	OH	>300	64.8	247	19,000			E and F	43.6	4.27		43.4	4.34	
					269	13,000									
CH_3	OCH_3	OCH_3	106	43.6	259	7,660			G	49.5	5.15	28.8	49.8	5.29	28.6
CH_3	SCH_3	SCH_3	100.5–101.5	87.8			249	15,800	G	42.5	4.45	24.7	42.2	4.53	24.3
							267	12,600							
							288	13,800							
CH_3	OC_2H_5	OC_2H_5	99–99.5	56.1	259	9,320			B			25.2			25.2
CH_3	SC_2H_5	SC_2H_5	61–62	79.7			242	13,000	C	47.2	5.55		47.0	5.62	
							291	10,200							
CH_3	SCH_3	Cl	144–145	53.8			289	12,400	H	39.3	3.29		39.7	3.51	
CH_3	OH	SCH_3	258–260	25.8	238	19,000									
					271	12,700			C	42.9	4.11	28.6	43.1	4.36	29.0
CH_3	NH_2	OCH_3	285–286	58.0			266	14,000	A	46.8	5.06		46.5	4.81	
CH_3	NH_2	SH	>310	49.4	238	14,800			E	39.8	3.89		39.7	3.82	
					288	23,000									
CH_3	SH	OC_2H_5	240	80.9	231	14,800	256	4,000							
					269	4,400	324	14,500	E	45.6	4.80		45.2	4.50	
					313	16,400									
CH_3	SC_2H_5	Cl	112–113	75.6			291	18,300	B	42.1	3.97		42.4	4.11	
CH_3	SC_2H_5	OC_2H_5	92–93.5	57.6			241	12,600	C	50.5	5.92		51.4	6.06	
							262	10,000							

TABLE I (*Continued*)

R_1	R_2	R_3	M.P. (°C.)	Yield (%)	U.v. Absorption λ_{max}, mμ pH 11	ϵ	U.v. Absorption λ_{max}, mμ Ethanol	ϵ	Recrystn.[a] Solvents	Analyses, % Calcd. C	H	N	Found C	H	N
CH_3	$OC_6H_4Br(p)$	Cl	152–152.5	59.8			261	22,900	C	42.5	2.40	16.5	42.4	2.49	16.4
CH_3	$OC_6H_4NO_2(p)$	Cl	180–180.5	31.4			271	10,700	C	47.2	2.64		47.3	2.76	
C_6H_5	OH	OH	320	94.0	239	25,300			I	58.0	3.53	24.6	58.1	3.57	24.6
C_6H_5	Cl	Cl	126–127	90.5			249	32,200	D	49.9	2.27	21.1	50.2	2.43	20.8
C_6H_5	OH	Cl	280–281	96.8	233	27,000			E	53.6	2.86	22.7	53.4	2.92	23.2
					275	13,800									
C_6H_5	SH	SH	230–232	35.8	238	24,200			E	50.8	3.10	21.5	51.2	3.25	21.1
					275	11,200									
					326	18,200									
C_6H_5	OCH_3	OCH_3	121–121.5	82.7			241	38,000	G	61.0	4.72	21.8	61.3	5.00	21.6
C_6H_5	OC_2H_5	OC_2H_5	93	70.6			222	23,800	B	60.1	5.37	18.7	60.5	5.39	18.7
							251	21,200							
							282	18,600							
C_6H_5	$OC_6H_4Br(p)$	Cl	128–129	33.0			240	34,000	B	50.9	2.52		50.7	2.74	
C_6H_5	NH_2	NH_2	236–237	73.9	274	13,500			C	58.3	4.45	37.5	58.0	4.62	37.6
p-ClC_6H_4	OH	OH	>300	73.0	242	19,800			E	50.3	2.68	21.4	50.7	2.40	21.6
					264	11,200									
p-ClC_6H_4	Cl	Cl	146–147	74.2			254	36,200	L	44.1	1.68		44.4	1.65	
p-ClC_6H_4	NH_2	OH	>300	33.3	246	22,200			E			26.8			26.8

[a] Recrystallization solvents: A, water; B, ethanol; C, ethanol and water; D, heptane; E, reprecipitated from dilute potassium hydroxide with acetic acid; F, reprecipitated from hydrochloric acid with ammonium hydroxide; G, methanol; H, toluene; I, acetic acid; L, benzene and heptane.

TABLE II



SUBSTITUTED 4-AMINO-6-CHLOROPYRAZOLO[3,4-*d*]PYRIMIDINES

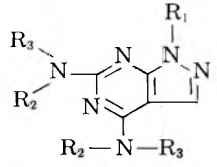
R_1	R_2	R_3	M.P. (°C.)	Yield (%)	U.v. Absorption λ_{max}, mμ Ethanol	ϵ	Recrystn.[a] Solvents	Analyses, % Calcd. C	H	N	Found C	H	N
CH_3	H	CH_3	239–240	51.4			C	42.6	4.05	35.2	42.8	4.38	35.1
CH_3	H	CH_2CH_3	211	44.2			C	45.6	4.75		45.3	4.64	
CH_3	H	$C(CH_3)_3$	162–163	42.4	284	10,500	J	50.3	5.85		50.9	4.92	
CH_3	H	$—(CH_2)_7CH_3$	87.5–88	66.0	284	10,000	L	56.9	7.52	23.6	56.6	8.03	23.4
CH_3	H	$C(CH_3)_2CH_2C(CH_3)_3$	183–184	89.5	285	19,200	K	56.9	7.52	23.6	56.9	7.74	23.1
CH_3	H	CH_2CH_2OH	238	95.0	282	15,500	G	42.2	4.44		42.2	4.34	
CH_3	H	$CH_2CH_2N(C_2H_5)_2$	89	58.5			G and H	51.0	6.78		51.3	6.67	

TABLE II (*Continued*)

R_1	R_2	R_3	M.P. (°C.)	Yield (%)	U.v. Absorption λ_{max}, mμ Ethanol	U.v. Absorption ε	Recrystn.[a] Solvents	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	H	$CH_2CH_2CH_2OCH(CH_3)_2$	117.5–119	43.0			G	50.8	6.40		50.3	6.05	
CH_3	H	$CH_2C_6H_5$	168	84.6	284	16,200	L	57.2	4.42		57.7	4.88	
CH_3	H	$CH_2C_6H_4Cl(p)$	201–202.5	74.3	283	17,600	B	50.7	3.60	22.7	51.2	3.74	23.0
CH_3	H	o-ClC_6H_4	224–225	85.6	285	15,900	M and A			23.7			23.4
CH_3	H	o-$CH_3C_6H_4$	235–237	37.2	284	20,000	B	57.1	4.43		57.2	4.38	
CH_3	H	$C_6H_3(CH_3)_2$(2,4)	241	56.5	284	20,400	B	58.5	4.91	24.3	58.8	4.67	24.0
CH_3	H	$C_6H_3(CH_3)_2$(2,5)	232	77.8	284	20,400	M	58.5	4.91	24.3	58.4	5.08	24.4
CH_3	H	$C_6H_3(CH_3)_2$(2,6)	242	70.7	283	14,600	B	58.5	4.91	24.3	58.6	4.98	24.0
CH_3	CH_2CH_3	C_6H_5	124–125	63.5	287	22,400	G	58.5	4.91		59.4	4.87	
CH_3	H	NH_2	>300	84.0	280	11,000	M	36.3	3.55		35.8	3.58	
C_6H_5	H	$CH_2CH_2CH_3$	186–187.5	64.5	242	34,000	C	58.5	4.91		58.5	5.20	
					292	17,100							
C_6H_5	H	$CH(CH_3)_2$	157–157.5	81.1	242	34,000	A and G	58.5	4.91		58.4	5.13	
					292	16,500							
C_6H_5	H	$C(CH_3)_3$	200–202	74.1	242	30,500	G	59.6	5.35	23.2	59.3	5.13	23.4
					291	16,200							
C_6H_5	H	$CH_2CH_2CH_2OCH(CH_3)_2$	129–130	69.0	243	32,600	G	59.4	5.83		60.0	6.10	
					291	16,600							
C_6H_5	H	CH_2CH_2OH	211.5–212.5	95.2	242	34,000	G	53.7	4.18	24.2	53.3	4.23	24.4
					291	18,900							
C_6H_5	H	2-Furfuryl	174–175.5	23.9	242	32,600	C	59.2	3.72		59.8	3.97	
					290	15,700							
C_6H_5	H	C_6H_5	281–284	66.0	245	29,800	M	63.6	3.77		64.0	3.89	
					307	27,200							
C_6H_5	H	$C_6H_3(CH_3)_2$(2,6)	218–219	83.5	243	33,600	B	65.4	4.62	20.0	65.4	4.83	20.0
					292	16,700							
C_6H_5	H	$C_6H_3(C_2H_5)_2$(2,6)	210–211.5	70.2	243	40,200	B	66.9	5.34		67.4	5.46	
					293	21,200							
C_6H_5	C_2H_5	C_6H_5	162–163.5	53.1	243	27,200	M and B	65.4	4.62		65.7	4.80	
					296	16,700							
C_6H_5	H	NH_2	>300	71.2	242	32,500	M	50.8	3.48		51.4	3.68	
					293	13,000							
C_6H_5	H	NHC_6H_5	268–269	56.4	243	46,000	M and B	60.6	3.90		60.3	4.02	
					291	17,600							

[a] Recrystallization solvents: A, water; B, ethanol; C, ethanol and water; G, methanol; H, toluene; J, methanol and water; K, benzene and ethanol; L, benzene and heptane; M, 2-ethoxyethanol.

TABLE III



SUBSTITUTED 4,6-DIAMINOPYRAZOLO[3,4-*d*]PYRIMIDINES

					U.v. Absorption				Re-crystn.[a]	Analyses, %					
					λ_{max}, mμ		λ_{max}, mμ			Calcd.			Found		
R_1	R_2	R_3	M.P. (°C.)	Yield (%)	pH 11	ε	Ethanol	ε	Solvents	C	H	N	C	H	N
CH_3	H	CH_2CH_3	140–141	57.2	232	35,200			C	54.5	7.32		54.6	7.12	
					261	12,000									
					283	13,600									
CH_3	CH_3	CH_3	128.5–129	92.3	240	30,400			G and A	54.5	7.32		54.5	7.45	
					286	10,500									
CH_3	H	$NHCH_3$	176	90.6					A	43.1	6.35	50.4	42.8	6.55	49.7
CH_3	H	C_6H_5	185–186	88.7	243	12,900			G	68.5	5.10		68.6	4.90	
					285	17,400									
CH_3	H	*o*-ClC_6H_4	161–161.5	80.0			270	32,000	M and A	56.2	3.66		56.0	3.82	
CH_3	H	*m*-ClC_6H_4	177–178.5	41.1			254	18,500	G	56.2	3.66		56.8	3.70	
							291	45,500							
CH_3	H	*p*-ClC_6H_4	202–204	48.1			255	18,500	B	56.2	3.66	21.8	56.2	3.70	22.0
							291	48,000							
CH_3	H	*p*-BrC_6H_4	201–202	21.5			255	17,600	B			17.7			17.6
							292	48,500							
CH_3	H	$C_6H_3(CH_3)_2$(2,4)	192.5–193.5	15.6			286	29,400	G and A	71.0	6.50		71.4	6.97	
CH_3	CH_3	C_6H_5	129–130	53.0			227	20,000	G	70.3	5.85		69.8	6.10	
							269	24,000							
C_6H_5	H	NH_2	217–219	50.4	368	21,000			B	51.6	4.72		51.6	4.80	
C_6H_5	H	$NHCH_3$	148–148.5	71.4			245	38,800	G and A	54.9	5.67	39.5	54.7	5.86	39.7
							293	18,200							
C_6H_5	H	$CH_2CH_2N(C_2H_5)_2.2HCl$	261–262.5		236	32,400	230	40,000	G	55.6	7.71		55.2	7.72	
					287	16,400	282	16,500							

[a] Recrystallization Solvents: A, water; B, ethanol; C, ethanol and water; G, methanol; M, 2-ethoxyethanol.

lized from methanol and water to give white, silky needles, m.p. 211.5–212.5°. The yield was 5.2 g. (95%).

Anal. Calcd. for $C_{13}H_{12}N_6OCl$: C, 53.7; H, 4.2; N, 24.2. Found: C, 53.3; H, 4.2; N, 24.4.

Preparation of 1-alkyl(aryl)-4,6-bis(substituted amino)-pyrazolo[3,4-d]pyrimidines. See Table III. The preparation of the bis-substituted amino derivatives can be illustrated by the following examples:

4,6-Bis(hydrazino)-1-phenylpyrazolo[3,4-d]pyrimidine. Six grams of 4,6-dichloro-1-phenylpyrazolo[3,4-*d*]pyrimidine was added to 60 g. of 70% hydrazine hydrate in 100 ml. ethanol. The mixture was boiled gently on the steam bath. A white precipitate appeared after 2 min. of heating and slowly redissolved with further heating. The solution was reduced to two thirds of its original volume, and the product crystallized on cooling. Recrystallization from ethanol gave 3 g. (51%) of glistening plates, m.p. 217–219°.

Anal. Calcd. for $C_{11}H_{12}N_8$: C, 51.6; H, 4.7. Found: C, 51.6; H, 4.8.

4,6-Bis(p-chloroanilino)-1-methylpyrazolo[3,4-d]pyrimidine. A solution of 8 g. of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]-pyrimidine and 15 g. of *p*-chloroaniline in 200 ml. of absolute ethanol was refluxed for 3 hr. A white precipitate appeared in the hot solution. The product was filtered and added to 100 ml. of ethanol containing 10 g. of potassium hydroxide. The mixture was boiled for 15 min. and filtered. To the filtrate was added 100 ml. of water, and the mixture was allowed to stand overnight. The product was filtered, washed with water, and recrystallized from 95% ethanol to give 7.3 g. (48%) of small, white needles, m.p. 202–204°.

Anal. Calcd. for $C_{18}H_{14}N_6Cl_2$: C, 56.2; H, 3.6; N, 21.8. Found: C, 56.2; H, 3.7; N, 22.0.

4,6-Bis(dimethylamino)-1-methylpyrazolo[3,4-d]pyrimidine. To 20 ml. of ethanol and 60 g. of 25% aqueous dimethylamine was added 10 g. of 1-methyl-4,6-dichloropyrazolo-[3,4-*d*]pyrimidine. The mixture was boiled gently on a steam bath to dryness. Another 40 g. of 25% aqueous methylamine was added, and the solution was again evaporated to dryness. The residue was recrystallized from aqueous methanol to give 10 g. (92.3%) of small, white needles, m.p. 128.5–129°.

Anal. Calcd. for $C_{10}H_{16}N_6$: C, 54.6; H, 7.3. Found: C, 54.5; H, 7.5.

Preparation of 4-amino-6-β-hydroxyethylamino-1-methylpyrazolo[3,4-d]pyrimidine. Seven g. of ethanolamine was added to 120 ml. of 2-ethoxyethanol containing 5 g. of 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (VI). The mixture was refluxed for 6 hr. Excess solvent was distilled off under reduced pressure and the sirupy residue poured into a beaker. To this crude product was added a little benzene followed by a few drops of methanol, and the residue solidified after a few minutes. The product was filtered and recrystallized from a mixture of benzene and methanol to give 3.4 g. (60%) of white crystals, m.p. 189–191.5°.

Anal. Calcd. for $C_8H_{12}N_6O$: C, 46.1; H, 5.8. Found: C, 46.1; H, 6.3.

Preparation of 4,6-bis(methylthio)-1-methylpyrazolo[3,4-d]-pyrimidine (XVI, R_1 = SCH_3). Four g. of 4,6-dimercapto-1-methylpyrazolo[3,4-*d*]pyrimidine was added to a mixture of 2 g. of potassium hydroxide, 10 g. of methyl iodide and 100 ml. of water. To this mixture was added, with stirring, 100 ml. of methanol. The solution was stirred for 30 min., and a white solid separated on standing. The product was filtered, washed with water, and dissolved in hot methanol. The solution was filtered, and to the filtrate was added 5 ml. of 1% potassium hydroxide solution. The product crystallized slowly as white plates and was filtered and washed with water to yield 4 g. (87.8%), m.p. 100.5–101.5°.

Anal. Calcd. for $C_8H_{10}N_4S_2$: C, 42.5; H, 4.5; N, 24.8. Found: C, 42.2; H, 4.5; N, 24.3.

Preparation of 4,6-dimethoxy-1-methylpyrazolo[3,4-d]pyrimidine (XVI, R_1 = OCH_3). To 6 g. of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine (VI, R = CH_3), dissolved in 50 ml. of methanol, precooled to 10°, was slowly added, with shaking, 50 ml. of a sodium methoxide solution (prepared by dissolving 2 g. of sodium in 50 ml. of methanol). The mixture was allowed to stand at room temperature for 30 min. with occasional shaking and finally heated for 10 min. on the steam bath. The sodium chloride was filtered, and 10 ml. of water was added to the filtrate. White needles separated after the solution was cooled. The product was filtered, washed with water, and recrystallized from methanol to give 2.5 g. (43.6%) of white needles, m.p. 106°.

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.5; H, 5.2; N, 28.8. Found: C, 49.8; H, 5.3; N, 28.6.

Preparation of 4-hydroxy-1-methyl-6-methylthiopyrazolo-[3,4-d]pyrimidine. To 7.2 g. (0.04 mole) of 4-hydroxy-6-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (XII) in 100 ml. of 2*N* potassium hydroxide solution was slowly added, with stirring, 5.1 g. (0.04 mole) of dimethylsulfate. The temperature was kept between 25–40°. The mixture was stirred for 1 hr. and then allowed to stand at room temperature for 48 hr. It was then acidified with glacial acetic acid to *p*H 5. A white substance was gradually formed. The product was filtered and recrystallized from a mixture of ethanol and water to give 2 g. (26%) of white needles, m.p. 258–260°.

Anal. Calcd. for $C_7H_8N_4OS$: C, 42.9; H, 4.1; N, 28.6. Found: C, 43.1; H, 4.4; N, 29.0.

Preparation of 4-amino-1-methyl-6-methoxypyrazolo[3,4-d]-pyrimidine (III, R = CH_3). To 100 ml. of methanol was added 5.5 g. of 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (II, R = CH_3). The mixture was added slowly to 100 ml. of methanol to which had previously been added 2 g. of sodium. The reaction mixture was allowed to stand at room temperature for 24 hr. followed by 30 min. of heating on a steam bath. Sodium chloride was filtered, and the product which separated from the cooled filtrate was recrystallized from water to give 3.1 g. (58%) of white needles, m.p. 285–286°.

Anal. Calcd. for $C_7H_9N_5O$: C, 46.8; H, 5.1. Found: C, 46.5; H, 4.8.

Preparation of 4-amino-6-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (VI, R = CH_3). A mixture of 8 g. of 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (II, R = CH_3) and 100 ml. of 3*N* potassium hydrosulfide was heated at 110° in a bomb for 8 hr. The solid potassium salt which appeared on cooling was filtered and dissolved in water. The resulting solution was acidified with glacial acetic acid and the solid product filtered and reprecipitated twice from potassium hydroxide solution with glacial acetic acid to give 3.9 g. (49%) of light-yellow precipitate, m.p. >310°.

Anal. Calcd. for $C_6H_7N_5S$: C, 39.8; H, 3.9. Found: C, 39.7; H, 3.8.

Preparation of 4-amino-1-methylpyrazolo[3,4-d]pyrimidine (IX, R = CH_3) *from 4-amino-6-mercapto-1-methylpyrazolo-[3,4-d]pyrimidine* (VI, R = CH_3). To 2.9 g. of 4-amino-6-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine, dissolved in 200 ml. of concentrated ammonium hydroxide, were added 1 l. of 95% ethanol and 20 g. of Raney Nickel. The mixture was refluxed for 48 hr., filtered, and the filtrate concentrated to 100 ml. White needles separated from the chilled solution. The product was filtered and recrystallized from ethanol to give 1.2 g. of 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine, m.p. 267–268°. This compound was identical to that product prepared from 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine,[5] as judged on the basis of mixed melting point data.

Preparation of 4-hydroxy-6-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (XII, R = CH_3). *Method 1.* Fifty-five g. of 5-amino-1-methylpyrazole-4-carboxamide was fused with 110 g. of thiourea at 210° for 2 hr. The fused product was dissolved in potassium hydroxide solution followed by reprecipitation with glacial acetic acid. The reprecipitation was repeated twice and 41 g. of white solid obtained, m.p. >300°.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.6; H, 3.3; N, 30.8. Found: C, 39.8; H, 3.9; N, 30.5.

Method 2. A mixture of 5.5 g. of 6-chloro-4-hydroxy-1-

methylpyrazolo[3,4-*d*]pyrimidine, 3 g. of thiourea, and 100 ml. of absolute ethanol was refluxed for 5 hr. The solid product was filtered and reprecipitated from dilute potassium hydroxide solution by glacial acetic acid to give 4.0 g. (73.6%) of white solid, m.p. >300°.

This preparation was found to be identical to the compound made by Method 1 on the basis of identical ultraviolet absorption spectra at *p*H 1 and *p*H 11.

Preparation of 6-chloro-4-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (XIV, R = CH_3). To 200 ml. of 0.5*N* potassium hydrosulfide was added 5 g. of finely powdered 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine. The mixture was stirred at 0° for 15 min. and then allowed to stand at room temperature for 2 hr. The mixture was filtered and the filtrate acidified with glacial acetic acid. Four and one-half grams (46%) of white solid was obtained, m.p. 223° (dec.).

Anal. Calcd. for $C_6H_5N_4SCl$: N, 27.9. Found: N, 27.7.

Preparation of 6-ethoxy-4-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (XV). To 100 ml. of absolute ethanol containing 2.0 g. of sodium was added 5.3 g. of powdered 6-chloro-4-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (XIII). The mixture was allowed to stir at room temperature for 1 hr. followed by 30 min. of heating on the steam bath. Sodium chloride was filtered and filtrate acidified with dilute acetic acid to give 4.5 g. (81%) of small, yellow plates, m.p. 240° (dec.).

Anal. Calcd. for $C_8H_{10}N_4S$: C, 45.6; H, 4.8. Found: C, 45.2; H, 4.9.

Preparation of 6-chloro-4-ethylthio-1-methylpyrazolo[3,4-d]-pyrimidine (XIX). Ten g. of finely powdered 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine was added to a solution of 12 g. of potassium hydroxide, 20 g. of ethylmercaptan, and 50 ml. of water. The mixture was stirred at room temperature for 3 hr. A white precipitate was obtained which was filtered and recrystallized from absolute ethanol to give 8.5 g. (76%) of white needles, m.p. 112–113°.

Anal. Calcd. for $C_8H_9N_4SCl$: C, 42.1; H, 4.0. Found: C, 42.4; H, 4.1.

Preparation of 6-ethoxy-4-ethylthio-1-methylpyrazolo[3,4-d]-pyrimidine (XX). Five g. of 6-chloro-4-ethylthio-1-methylpyrazolo[3,4-*d*]pyrimidine was added to 100 ml. of absolute ethanol containing 2.0 g. of dissolved sodium. The mixture was allowed to stand at room temperature for 5 hr. It was then warmed on a steam bath for 3 min. and filtered. White needles, m.p. 92–93°, were obtained from the cooled filtrate. The yield was 3.0 g. (58%).

Anal. Calcd. for $C_{10}H_{14}N_4OS$: C, 50.5; H, 5.9. Found: C, 50.4; H, 6.1.

TEMPE, ARIZ.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Condensations Involving the Metalation of the 3-Position of 3-Phenylphthalide by Means of Alkali Amides. Carbonation of Phthalide[1]

CHARLES R. HAUSER, MARVIN T. TETENBAUM, AND DAVID S. HOFFENBERG

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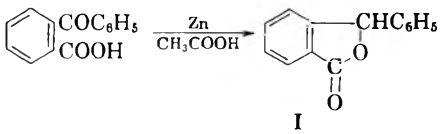
3-Phenylphthalide was metalated at its 3-position by means of an alkali amide in liquid ammonia, and the resulting alkali derivative was employed in several types of carbon-carbon condensations in this medium or in ether. These condensations included carbonation, benzylation, benzoylation, and conjugate addition. The structure of the acid obtained on carbonation was established by the Hofmann rearrangement of the corresponding acid amide. The ketone produced on benzoylation was cleaved by means of potassium hydroxide solution.

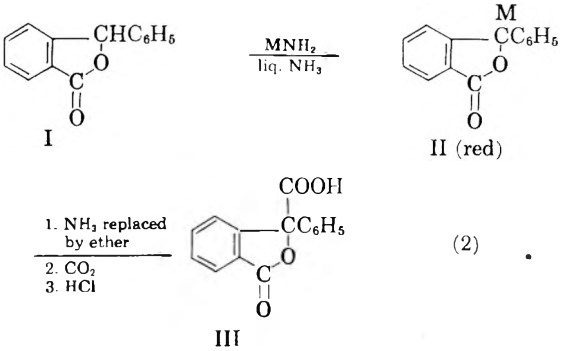
Although 3-phenylphthalide (I) is readily prepared by the reduction of *o*-benzoylbenzoic acid by means of zinc and acetic acid (Equation 1),[2,3] this active hydrogen compound appears not to have been employed previously in condensations involving the ionization of its 3-hydrogen (γ-hydrogen).



(1)

I

In the present investigation the 3-position of 3-phenylphthalide was metalated by means of alkali amides in liquid ammonia, and the resulting red alkali derivative employed in several types of carbon-carbon condensations. One of these reactions involved carbonation to form lactone acid III which was obtained in yields of 80–87% by means of potassium amide, sodium amide, or lithium amide (Equation 2, M = K, Na, or Li).



I II (red) III

(2)

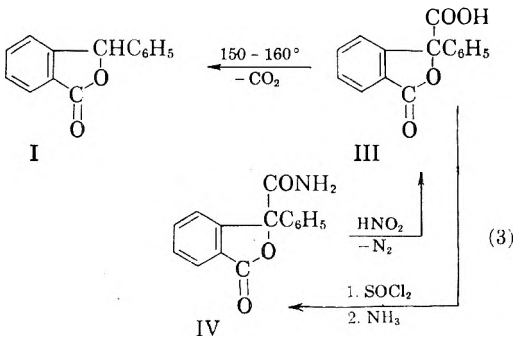
(1) Supported by the National Science Foundation.

(2) F. Ullmann, *Ann.*, 291, 23 (1896).

(3) Also, we have obtained a 48% yield of 3-phenylphthalide (I) along with a 25% yield of *o*-benzylbenzoic acid on reducing *o*-benzoylbenzoic acid with zinc-amalgam and hydrochloric acid (Clemmensen method). These two compounds were readily separated by means of sodium bicarbonate solution in which I was insoluble. Earlier workers [H. L. Bradlow and C. A. VanderWerf, *J. Am. Chem. Soc.*, 69, 1254 (1947)] have reported that, under certain conditions, this method produces *o*-benzylbenzoic acid in yields of 70–75%.

As indicated in Equation 2, the liquid ammonia over the red alkali derivative of 3-phenylphthalide (II) was replaced by ether before carbonation. The fact that intermediate salt II is stable during this interchange of solvents when its cation M is sodium or lithium as well as potassium is of interest, since only the potassium derivatives of di- and triphenylmethides are stable under similar conditions.[4] Such an interchange of solvents over the sodium and lithium derivatives of di- and triphenylmethides causes them to revert to sodium and lithium amides and di- and triphenylmethanes.[4] The greater stability of the sodium and lithium derivatives of 3-phenylphthalide (II = Na or Li) under these conditions appears to be ascribable to the presumably more weakly basic nature of 3-phenylphthalide carbanion (compared to di- and triphenylmethide carbanions).[4]

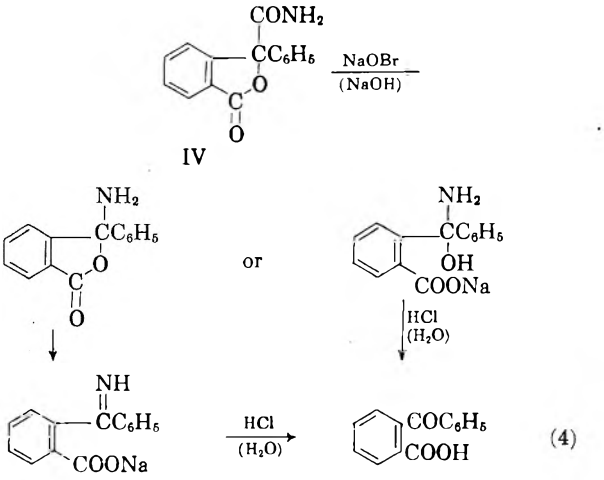
Although a sample of lactone acid III melting at 126–127° was isolated, this compound was generally obtained even after several recrystallizations as a white powder melting at 85–92°, which appeared to be essentially pure (see EXPERIMENTAL). Samples having either melting point were readily decarboxylated at 150–160° to form 3-phenylphthalide (I), and were converted to the corresponding amide (IV) from which lactone acid III was regenerated by means of nitrous acid (Equation 3).



(3)

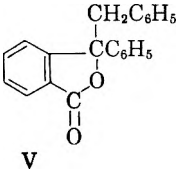
Since the carbanion of 3-phenylphthalide has several resonance structures involving the aromatic rings, its carbonation might conceivably have produced, instead of lactone acid III, a lactone acid having the carboxyl group attached to one of the aromatic rings. The corresponding lactone amide would then have the acid-amide group attached to the aromatic ring. That the lactone acid had structure III and the lactone amide, structure IV, was established by effecting the Hofmann rearrangement of the latter, which produced *o*-benzoylbenzoic acid in 89% yield (Equation 4).

Had the acid-amide group been attached to one of the aromatic rings, this rearrangement should have produced a relatively stable primary aromatic amine. No such amine was found.

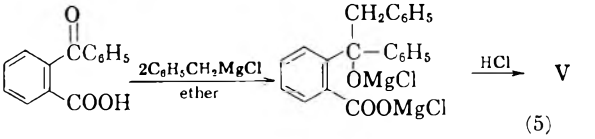


(4)

A second type of condensation of 3-phenylphthalide (I) involved its benzylation with benzyl chloride by means of sodium amide in liquid ammonia to form lactone V in 77% yield.

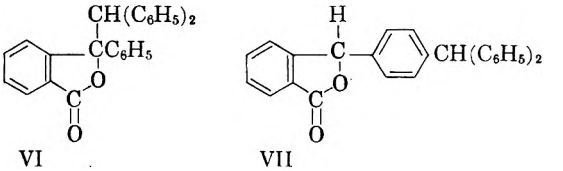


The structure of the benzylation product was established as V by an independent synthesis from *o*-benzoylbenzoic acid and excess benzylmagnesium chloride (Equation 5).[5]



(5)

Similarly, 3-phenylphthalide (I) was benzhydrylated with benzhydryl bromide by means of potassium amide. By analogy with the benzylation, the product would be assigned structure VI but this structure was not established. Its unexpectedly high melting point might suggest structure VII, or possibly still another isomer.

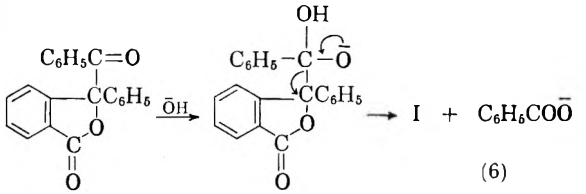


A third type of condensation of 3-phenylphthalide (I) involved its benzoylation with benzoyl chloride (after replacing the liquid ammonia with ether) to form lactone-ketone VIII in 74% yield. The structure of this product is supported by its cleavage by means of hot aqueous potassium hy-

(4) See C. R. Hauser, D. S. Hoffenberg, W. H. Puterbaugh, and F. C. Frostick, *J. Org. Chem.*, 20, 1531 (1955).

(5) W. R. Dunnavant in this laboratory performed this experiment (refluxed 20 hr.) to give a 20% yield of V, m.p. and mixed m.p. 103–104°.

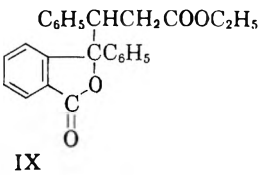
droxide to regenerate 3-phenylphthalide (95%) along with benzoic adid (93%). Such a cleavage would hardly be expected if the benzoyl group had been attached to the 3-phenyl ring. The mechanism of the cleavage presumably involves the attack of hydroxyl ion on the ketone carbonyl group and the elimination of the carbanion of 3-phenylphthalide (Equation 6). The alkali might also have opened (saponified) the lactone ring which would have been regenerated on acidification.



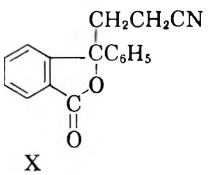
VIII

Lactone-ketone VIII reacted slowly with 2,4-dinitrophenylhydrazine reagent, losing the elements of water, to form a yellow product that was presumably the corresponding 2,4-dinitrophenylhydrazone. This reagent might possibly react with the lactone group,[6] but its preferential reaction with the ketone group of VIII should be expected.

A fourth type of condensation of 3-phenylphthalide (I) involved its conjugate addition to ethyl cinnamate and acrylonitrile. The structures of the products may be assigned tentatively IX and X, respectively.

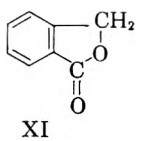


IX

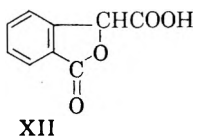


X

Carbonation of phthalide. Phthalide (XI) was carbonated to form lactone acid XII in 46% yield by means of potassium amide as described above for 3-phenylphthalide. Considerable resinous material was also obtained.



XI

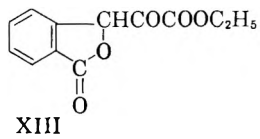


XII

However, an attempt to effect the benzylation of phthalide (XI) with benzyl chloride under the conditions that produced a good yield with 3-phenylphthalide was unsatisfactory, much resinous material being produced.

These results might indicate that the amide ion attacks not only the 3-hydrogen of phthalide to effect its ionization but also the carbonyl group resulting in the opening of the lactone ring, although the hydroxy-amide that should be formed from the latter reaction was not found. Hydroxide ion has been reported to attack the carbonyl group of phthalide (XI) to open the lactone ring.[7]

It should be mentioned that long ago Wislicenus[8] effected the acylation of phthalide (XI) with diethyl oxalate by means of sodium dissolved in ethanol to form lactone-ester XIII, but no yield was given.



XIII

EXPERIMENTAL[9]

3-Phenylphthalide (I). This compound was prepared by the method of Ullmann[2] employing 10 times the quantities of reactants.

A mixture of 100 g. (0.44 mole) of *o*-benzoylbenzoic acid, 200 g. (3.8 g.-atoms) of zinc dust, 200 ml. of water, and 800 ml. of glacial acetic acid was refluxed for 2 hr. The supernatant liquid was removed and allowed to cool. The white needles of the lactone, which soon precipitated, were collected on a funnel. More solid was precipitated by the addition of water to the filtrate. The combined solid was carefully added to a solution of sodium bicarbonate, and the resulting mixture was filtered. The solid was recrystallized from ethanol to give 71 g. (77%) of 3-phenylphthalide (I), m.p. 115–116° (reported m.p. 115–116°).[2]

Carbonation of 3-phenylphthalide (I) *to form lactone acid* III. To a stirred suspension of potassium amide[10] in 500 ml. of liquid ammonia was carefully added 21 g. (0.1 mole) of solid 3-phenylphthalide. The liquid ammonia was evaporated from the red solution on the steam bath as an equal volume of dry ether was added. The red ether solution was refluxed for 30 min., cooled, and excess crushed Dry Ice carefully added with stirring. When the excess Dry Ice had evaporated, water and ether were added. The alkaline aqueous layer was separated and combined with an alkali extract of the ether layer. After filtering to remove tarry material, the cooled solution was acidified with iced hydrochloric acid to precipitate a semisolid which soon almost completely solidified. After careful filtration, the solid was dissolved in chloroform, and ligroin (b.p. 60–90°) slowly added to precipitate 22 g. (87%) of 3-phenylphthalidecarboxylic acid (III) (white powder) melting at about 75°. Three more recrystallizations from the same solvents raised the melting point to 85–92° without much loss of the product. Further recrystallization generally failed to raise the melting point appreciably.

Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.86; H, 3.97. Found: C, 71.02; H, 4.08.

Although this product appeared to be essentially pure, a sample melting at 126–128° was isolated on two occasions by five or six recrystallizations from the chloroform-ligroin mixture.

Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.86; H, 3.97. Found: C, 70.86; H, 3.92.

(6) W. Wislicenus [*Ber.*, 20, 401 (1887)] reported that phthalide reacted with phenylhydrazine involving the opening of the lactone ring to form an alcohol-amide type of compound. Such an addition product was evidently not formed in our reaction of lactone-ketone VIII with 2,4-dinitrophenylhydrazine.

(7) J. Hessert, *Ber.*, 10, 1445 (1877); 11, 237 (1878).

(8) W. Wislicenus, *Ann.*, 246, 342 (1888).

(9) All melting points are uncorrected. Analyses are by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(10) See R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, 69, 2325 (1947).

Similar results were obtained employing sodium amide or lithium amide instead of potassium amide.

Samples of the product melting at 85–92° and at 126–128° were decarboxylated, on heating to 150–160°, to give high yields (89%) of 3-phenylphthalide (I), m.p. 115–116°.

Also, similar results were obtained in certain other reactions with samples having the two different melting points (see below).

Conversion of III *to lactone amide* IV. A solution of 5 g. of lactone acid III (m.p. 85–92° or 126–128°) in 40 ml. of thionyl chloride was refluxed for 30 min. and the excess of the reagent then distilled. The residue was cooled and carefully poured into 40 ml. of iced ammonium hydroxide solution to give, after recrystallization from ethanol, 4.3 g. (87%) of white 3-phenylphthalidecarboxylic acid amide (IV), m.p. 225–227°.

Anal. Calcd. for $C_{15}H_{11}O_3N$: C, 71.14; H, 4.37; N, 5.53. Found: C, 71.18; H, 4.31; N, 5.68.

Reaction of lactone amide IV *with nitrous acid.* This reaction was carried out by an adaptation of the method of Baker.[11]

To a mixture of 30 ml. of glacial acetic acid and 3 ml. of 70% sulfuric acid there was added 3.3 g. of lactone amide IV, and the solution cooled to 0°. A solution of 2 g. of sodium nitrite in 3 ml. of water was added dropwise, and the mixture gradually warmed to 50°. Water (70 ml.) was added to precipitate a white solid. After being cooled in an ice bath, the mixture was filtered, and the solid washed with cold sodium bicarbonate solution. There was obtained 2.7 g. (82%) of lactone acid III, m.p. 123–126°. A mixed melting point of this product with a sample of lactone acid III(m.p. 126–128°) was 125°.

Hofmann rearrangement of lactone amide IV. This reaction was carried out by the general method of Hoogewerff and Van Dorp.[12]

To an ice cold solution of sodium hypobromite, prepared from 3 ml. (0.06 g.-atom) of bromine and 12 g. (0.3 mole) of sodium hydroxide in 100 ml. of water, there was added with swirling 11.25 g. (0.05 mole) of the finely powdered lactone amide IV. The reaction mixture was warmed to 70–80° (solution was now complete) and kept there for 15–20 min. After cooling and filtering, the solution was acidified with 6*N* hydrochloric acid to give a dark oil, which solidified on cooling in a Dry Ice–carbon tetrachloride bath. The solid was dissolved in benzene (steam bath), and ligroin (b.p. 60–90°) was then added to precipitate an oil that quickly solidified. There was obtained 10 g. (89%) of *o*-benzoylbenzoic acid, m.p. 127°. This melting point was not depressed on admixture with an authentic sample of *o*-benzoylbenzoic acid.

Benzylation of 3-phenylphthalide (I) *to form lactone* V. To a stirred suspension of 0.1 mole of sodium amide[13] in 500 ml. of liquid ammonia was carefully added 21 g. (0.1 mole) of solid 3-phenylphthalide (I). The resulting dark red solution of the sodium derivative was stirred for 15 min., and 12.7 g. (0.1 mole) of benzyl chloride in an equal volume of anhydrous ether was added. The color was discharged, and a white precipitate was formed. After stirring for one hour, the liquid ammonia was evaporated on the steam bath as an equal volume of anhydrous ether was added. The resulting white suspension was refluxed for 30 min., cooled, and hydrolyzed with iced hydrochloric acid. The yellow ether layer was separated and combined with three ether extracts of the aqueous layer. After drying over Drierite, the ether was evaporated under reduced pressure on the steam bath to give 23 g. (77%) of white 3-benzyl-3-phenylphthalide (V) m.p. 99–102°. After two recrystallizations from ether, the product melted at 103–105°.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.94; H, 5.37. Found: C, 84.16; H, 5.66.

A 1-g. sample of this product was heated with 10 ml. of concentrated sulfuric acid on the steam bath for 30 min. the dark red mixture was cooled, and carefully poured onto ice. The resulting solution was extracted with ether overnight in a continuous liquid-liquid extractor. Evaporation of the yellow ethereal solution yielded 0.5 g. (40%) of an orange, water soluble powder that softened at 220° and decomposed at 240–250°. This product analyzed for a monosulfonated derivative of lactone V.

Anal. Calcd. for $C_{21}H_{16}O_5S$: C, 66.30; H, 4.24; S, 8.43. Found: C, 66.73; H, 4.26; S, 8.24.

Benzhydrylation of 3-phenylphthalide (I) *to form lactone* VII. To a stirred suspension of 0.1 mole of potassium amide[10] in 500 ml. of liquid ammonia was carefully added 21 g. (0.1 mole) of solid 3-phenylphthalide (I). The resulting dark red solution of the potassium derivative was stirred for 15 min., and 24.7 g. (0.1 mole) of benzhydryl bromide in an equal volume of anhydrous ether was added. The color was mostly discharged. After stirring for one hour, the liquid ammonia was evaporated on the steam bath as an equal volume of anhydrous ether was added. The resulting yellow-green mixture was refluxed for 30 min., cooled, and hydrolyzed with iced hydrochloric acid. The yellow ether layer was separated and combined with three ether extracts of the aqueous layer. After drying over Drierite, the ether was evaporated under reduced pressure on the steam bath to give a theoretical yield of white 3-benzhydryl-3-phenylphthalide (VII) m.p. 247–249°. After two recrystallizations from a mixture of chloroform and ether, the product melted at 252–252.5°.

Anal. Calcd. for $C_{27}H_{20}O_2$: C, 86.15; H, 5.36. Found: C, 85.94; H, 5.28.

Benzoylation of 3-phenylphthalide (I) *to form lactone-ketone* (VIII). The sodium derivative of 3-phenylphthalide (0.1 mole) was prepared in liquid ammonia as described above, and the ammonia evaporated as an equal volume of dry ether was added. The resulting red ethereal solution was stirred and refluxed for 30 min., and 14.1 g. (0.1 mole) of freshly distilled benzoyl chloride in an equal volume of anhydrous ether was then added, the color being discharged. After refluxing for one hour, the mixture was cooled and filtered. Evaporation of the ether on the steam bath under reduced pressure left 23 g. (74%) of 3-benzoyl-3-phenylphthalide (VIII), m.p. 102–104°. This melting point was not changed by three recrystallizations from ether.

Anal. Calcd. for $C_{21}H_{14}O_3$: C, 80.24; H, 4.49. Found: C, 80.16; H, 4.63.

A sample of this ketone was treated with 2,4-dinitrophenylhydrazine reagent for several days to give yellow crystals m.p. 193–194° after being recrystallized from ethanol. An analysis of these crystals agreed with that calculated for the 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{27}H_{18}O_6N_4$: C, 65.58; H, 3.67. Found: C, 65.62; H, 3.42.

Alkaline cleavage of lactone-ketone VIII. A 0.22-g. sample of this compound was refluxed with excess 40% aqueous potassium hydroxide for 2.5 hr. The resulting solution was cooled and acidified with cold 6*N* hydrochloric acid to precipitate a white solid which was collected on a funnel and washed thoroughly with hot water. The insoluble solid remaining on the funnel was 3-phenylphthalide (0.14 g., 95%), m.p. and mixed m.p. 116–117°. The aqueous filtrate was extracted with ether to give 0.08 g. (93%) of benzoic acid, m.p. and mixed m.p. 122°.

Conjugate addition of 3-phenylphthalide (I) *with ethyl cinnamate to form* IX. To a stirred solution of the sodium derivative of 3-phenylphthalide prepared from 0.1 mole each of sodium amide and the lactone I in 500 ml. of liquid ammonia, there was added 17.6 g. (0.1 mole) of ethyl cinnamate in an equal volume of anhydrous ether. After one hour, the liquid ammonia was replaced by ether, and the resulting suspension was refluxed for 30 min. The mixture

(11) R. H. Baker, *J. Am. Chem. Soc.*, **70**, 3858 (1948).

(12) See E. S. Wallis and J. F. Lane, *Org. Reactions*, III, 280 (1946).

(13) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 122 (1954).

was hydrolyzed with iced hydrochloric acid, and the ethereal layer, after being combined with several ether extractions of the aqueous layer, was dried over Drierite. The solvent was removed and the residue washed with ether to give 18.5 g. (48%) of lactone-ester IX, m.p. 150–153°. One recrystallization from ether raised the melting point to 155–156°.

Anal. Calcd. for $C_{25}H_{29}O_4$: C, 77.70; H, 5.74. Found: C, 77.56; H, 5.80.

Cyanoethylation of 3-phenylphthalide (I) *to form* X. To a stirred solution of the sodium derivative of 3-phenylphthalide prepared from 0.1 mole each of sodium amide and the lactone I in 500 ml. of liquid ammonia, there was added 5.3 g. (0.1 mole) of freshly distilled acrylonitrile in an equal volume of anhydrous ether. After stirring for 30 min., a few drops of excess acrylonitrile was added, causing the color to change from red to a deep, greenish black. After stirring for an hour longer, the liquid ammonia was replaced by ether during 15 min. on the steam bath. Some of the acrylonitrile appeared to polymerize. The reaction mixture was decomposed with iced hydrochloric acid, and the ethereal layer carefully separated and combined with several ether extracts of the aqueous layer. After drying over Drierite, the solvent was removed to leave 14.5 g. (56%) of lactonenitrile X, m.p. 176–180°. After two recrystallizations from ethanol, the product melted at 177–178°.

Anal. Calcd. for $C_{17}H_{13}O_2N$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.78; H, 4.80; N, 5.26.

Carbonation of phthalide (XI) *to form lactone acid* XII. This reaction was carried out as described above for 3-phenylphthalide (I), employing sodium amide. The intermediate sodium derivative which formed was deep orange. There was obtained, after recrystallization of the product from a mixture of chloroform and ligroin (b.p. 90–120°) and finally washing with cold ether, a 46% yield of 3-carboxyphthalide (XII) m.p. 152–153° (reported m.p. 150–151°).[14]

In an attempt to determine whether the amide ion was attacking the lactone ring, the phthalide was allowed to stir for 5 hr. with an equimolar portion of sodium amide before carbonation. Once again, an approximately 46% yield of acid XII was obtained along with considerable tar.

DURHAM, N. C.

(14) S. Ruhemann, *J. Chem. Soc.*, 2030 (1910).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Rearrangements of 2,6-Dimethyl- and 2,3,4,6-Tetramethylbenzyltrimethylammonium Ions with Sodium Amide and Reactions of the Products[1]

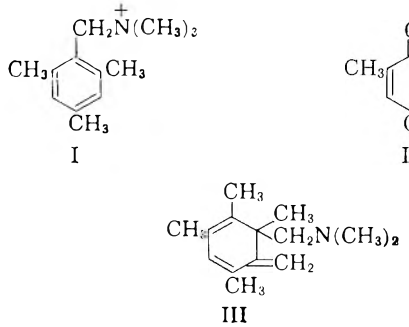
CHARLES R. HAUSER AND DONALD N. VAN EENAM

Received November 22, 1957

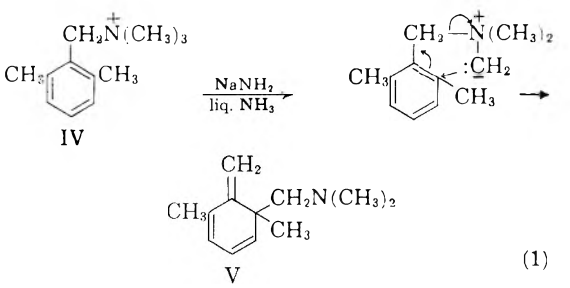
2,6-Dimethyl- and 2,3,4,6-tetramethylbenzyltrimethylammonium ions were rearranged by sodium amide in liquid ammonia to form corresponding *exo*-methylenecyclohexadieneamines which exhibited characteristic reactions of such compounds. The methiodide of each of these *exo*-methyleneamines was converted by sodium amide in liquid ammonia to another *exo*-methyleneamine which also exhibited certain of the characteristic reactions. Evidence is presented that the unsymmetrical 2,3,4,6-tetramethyl quaternary ion underwent only one of the two possible courses of rearrangement.

The 2,4,6-trimethylbenzyltrimethylammonium-ion (I) has previously[2] been rearranged by sodium amide in liquid ammonia to *exo*-methyleneamine II,[2] the methiodide of which was converted to another *exo*-methyleneamine (III)[3] on further treatment with this reagent.

The corresponding reactions have now been carried out with the 2,6-dimethyl- and 2,3,4,6-tetramethylbenzyltrimethylammonium ions. The former quaternary ion (IV) was rearranged by sodium amide in liquid ammonia to give *exo*-methyleneamine V, the mechanism being indicated in Equation 1. The ultraviolet absorption wave length maximum of the product agreed with the value calculated[4] for structure V.



I II III



IV V (1)

Similar to *exo*-methyleneamines II and III, V

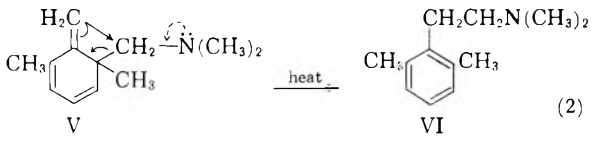
(1) Supported by the National Science Foundation.

(2) C. R. Hauser and D. N. Van Eenam, *J. Am. Chem. Soc.*, **79**, 5512 (1957).

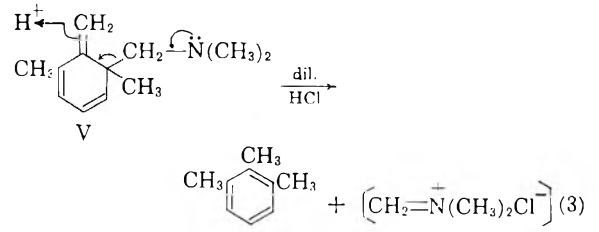
(3) C. R. Hauser and D. N. Van Eenam, *J. Am. Chem. Soc.*, **79**, 6280 (1957).

(4) For calculations of absorption maxima by Woodward's rules, see L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, third ed., Reinhold Publishing Corp., New York, N. Y., 1949, pp. 185–188.

readily underwent thermal isomerization to form β-arylethylamine VI (Equation 2). In fact some of this aromatic compound was generally produced in the distillation of *exo*-methyleneamine V which was isolated in yields ranging from 55 to 75%, depending on the distillation temperature.

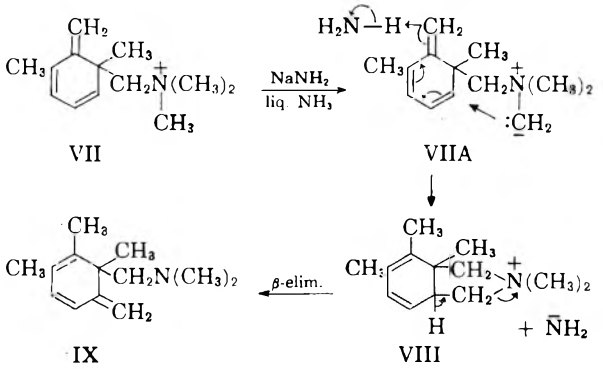


Also, similar to *exo*-methyleneamines II and III, V underwent an acid-induced decomposition to form an aromatic hydrocarbon, hemimellitene, and dimethylmethyleneiminium chloride (Equation 3).



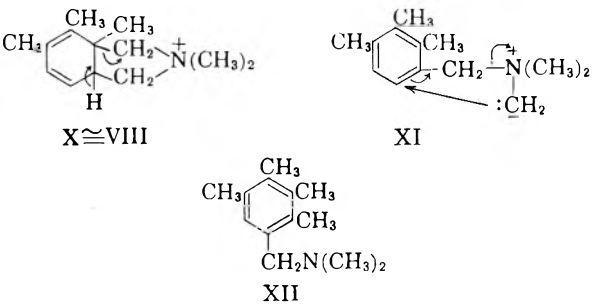
It should be mentioned that the starting quaternary ammonium ion undoubtedly had structure IV since it was synthesized by unequivocal reactions from 2,6-dimethylaniline (see Experimental).

The methiodide of *exo*-methyleneamine V, (Formula VII) was converted by sodium amide in liquid ammonia to another *exo*-methyleneamine (IX), the probable mechanism being indicated in Scheme A.

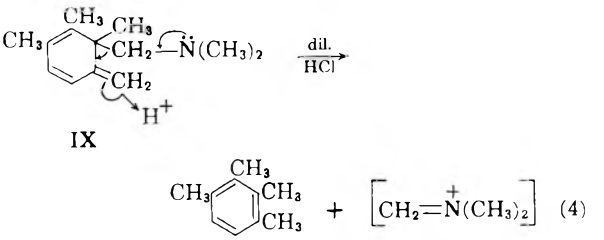


Scheme A

Evidence supporting this type of mechanism for the analogous conversion of the methiodide of *exo*-methyleneamine II to III has previously been discussed.[3] The conversion of VII to IX, like that of II to III, was accompanied by deep coloration. This might indicate the intermediate formation of carbanions in addition to carbanion VIIA. The present results show that the possible aromatization of intermediate quaternary ion VIII (indicated in X) does not occur since this would have formed quaternary ion XI which would have undergone the normal ortho substitution rearrangement to give tertiary amine XII. No such aromatic product was obtained.

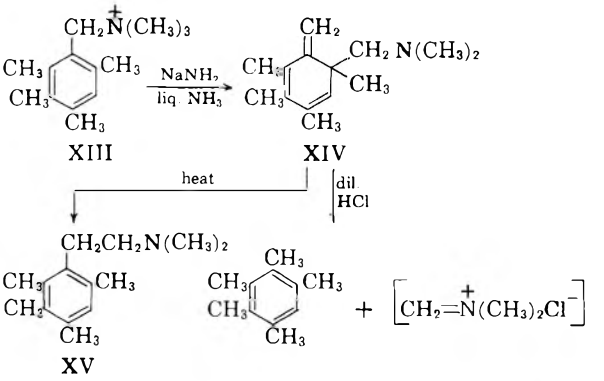


The structure of *exo*-methyleneamine IX was established not only by its ultraviolet absorption maximum but also by its conversion to prehnitene by dilute acid (equation 4).



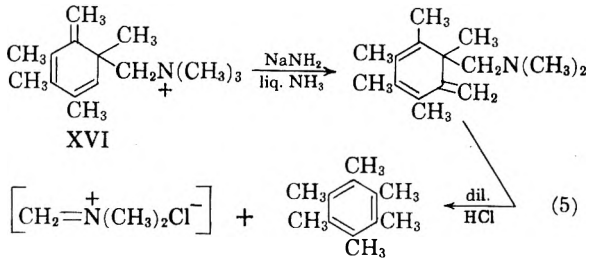
Although this acid-induced decomposition did not occur as readily as that of *exo*-methyleneamines II, III, and V, the aromatic hydrocarbon was obtained in high yield (85%). *exo*-Methyleneamine IX was also more stable toward heat than the other *exo*-methyleneamines, being largely recovered after heating to 150° for 5 min. At 200°, *exo*-methyleneamine IX was slowly converted to a mixture of products.

The other benzyl type quaternary ion studied in this investigation, the 2,3,4,6-tetramethylbenzyltrimethylammonium ion (XIII), was of interest because its unsymmetrical structure made possible two modes of rearrangement with sodium amide in liquid ammonia. Actually only one mode of rearrangement, that indicated in Scheme B to form *exo*-methyleneamine XIV, was realized, the methiodide of the product isolated melting sharply. The polyene structure of the product was established as usual by its ultraviolet absorption maximum and by the reactions represented in Scheme B.



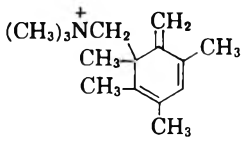
Scheme B

As might be expected, the methiodide of *exo*-methyleneamine XIV (formula XVI), on treatment with sodium amide in liquid ammonia followed by acid, produced hexamethylbenzene (Equation 5).



XVI (5)

The second possible mode of rearrangement of quaternary ion XIII would have formed *exo*-methyleneamine III which has previously been prepared from the methiodide of II.[3] Like *exo*-methyleneamine XIV, III undergoes thermal isomerization to β-arylethylamine XV and acid-induced decomposition to form pentamethylbenzene.[3] However, the product obtained from quaternary ion XIII was shown not to be *exo*-methyleneamine III by the refractive indices of the two amines and especially by the melting points of their methiodides. Moreover, whereas the product obtained from XIII was converted through its methiodide to hexamethylbenzene (Equation 5), the methiodide of *exo*-methyleneamine III (Formula XVII) failed to produce this aromatic hydrocarbon on similar treatment.[3]



XVII
(Methiodide of III)

It should be mentioned that the starting quaternary ammonium ion undoubtedly had structure XIII since it was synthesized by the chloromethylation of isodurene.

EXPERIMENTAL[5]

2,6-Dimethylbenzyltrimethylammonium iodide (IV). This quaternary ammonium salt was synthesized in four steps from 2,6-dimethylaniline.

Conversion of this amine (300 g., 2.48 moles) into 2,6-dimethylbenzonitrile was effected in 46% yield according to the general directions of Clarke and Read[6] for the synthesis of tolunitriles from the corresponding toluidines *via* the Sandmeyer reaction. The diazotized aniline was added with vigorous stirring to the cold cuprous cyanide solution with a layer of benzene on the surface. After the ensuing reaction, the solvent was removed, and the dark reddish brown solid was crystallized several times from ligroin (b.p. 60–90°) to afford 2,6-dimethylbenzonitrile (as white needles), m.p. 89–90° (reported m.p. 89–89.5°).[7]

This nitrile (1.13 moles) was reduced with 1.50 moles of lithium aluminum hydride in 2 l. of ether employing the procedure of Nystrom and Brown[8] for the reduction of *o*-tolunitrile. After stirring under reflux for 6 hr., the reaction mixture was decomposed by the addition of a 20% solution of sodium potassium tartrate. Distillation of the product *in vacuo* gave 99.7 g. (65%) of slightly impure 2,6-dimethylbenzylamine, b.p. 111–114° at 15 mm., n_D^{25} 1.5223, which was used without further purification for the following reaction.

Methylation of 2,6-dimethylbenzylamine was effected by the Eschweiler-Clarke procedure, employing the directions of Icke and Wisegarver[9] for the alkylation of β-phenylethylamine. From 98.0 g. (0.725 mole) of the amine, 190 g. of 88% formic acid, and 140 g. of 37% formalin solution (24-hr. reflux), there was isolated (second distillation) 96.1 g. (81%) of 2,6-dimethylbenzyldimethylamine, b.p. 104–106° at 15 mm., n_D^{25} 1.5087.

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.80; H, 10.72; N, 8.31.

The picrate, crystallized three times from 95% ethanol, melted at 164–165°.

Anal. Calcd. for $C_{17}H_{20}N_4O_7$: C, 54.04; H, 5.14; N, 14.28. Found: C, 54.23; H, 5.20; N, 14.00.

To a solution of 86.8 g. (0.532 mole) of this tertiary amine in 100 ml. of acetonitrile was added with swirling 100 g. (0.70 mole) of methyl iodide, the flask being cooled occasionally by immersion in an ice bath. After standing at room temperature for 2 hr. (some crystalline product separated), 1 l. of ether was added to precipitate the quaternary ammonium salt, which (after a second crystallization) was collected on a funnel, washed with ether, and dried *in vacuo*. There was obtained 156.7 g. (97%) of 2,6-dimethylbenzyltrimethylammonium iodide (IV), m.p. 156–157.5° (dec.), with darkening at 140°. Its picrate, following three crystallizations from water, melted at 131–132°.

Anal. Calcd. for $C_{18}H_{22}N_4O_7$: C, 53.20; H, 5.46; N, 13.79. Found: C, 53.32; H, 5.61; N, 13.67.

Rearrangement of IV *to 6-methylene-1,5-dimethyl-1-dimethylaminomethylcyclohexadiene-2,4* (V). This reaction was carried out with 30.5 g. (0.10 mole) of 2,6-dimethylbenzyltrimethylammonium iodide (IV) and 0.30 mole of sodium amide in 500 ml. of liquid ammonia essentially as described[2] for the corresponding rearrangement of 2,4,6-trimethylbenzyltrimethylammonium chloride (I), omitting steam distillation[10] of the crude reaction product. Ammonium chloride (10.7 g., 0.20 mole) was added to the purple colored reaction mixture after 3 hr. stirring, followed by the addition of 600 g. of Reagent Grade ether during the careful evaporation of the liquid ammonia on the steam bath. As soon as the ether began to reflux in the cold condenser the reaction mixture was cooled, filtered, and the solvent carefully distilled on the steam bath, the last traces being removed *in vacuo* at 35°. Distillation of the residual oil through a 40-cm. Podbielniak type column at a relatively low temperature afforded 10.3 g. (58%) of *exo*-methyleneamine V, b.p. 43–44° at 0.4 mm., n_D^{25} 1.5128.

(5) Melting and boiling points are uncorrected. Microanalyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ultraviolet absorption spectra were measured in 95% ethanol solution using a Warren Spectracord Model 3000 automatic-recording spectrophotometer.

(6) H. T. Clarke and R. R. Read, *Org. Syntheses*, **4**, 69 (1925).

(7) R. C. Fuson and co-workers, *J. Am. Chem. Soc.*, **62**, 2092 (1940).

(8) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3740 (1948).

(9) R. N. Icke and B. B. Wisegarver, *Org. Syntheses*, Coll. Vol. **3**, 723 (1955).

(10) In the isolation of *exo*-methyleneamine II, steam distillation was desirable in removing the product from polymeric material (see Ref. 2, note 26). However, in the present case the low content of high boiling polymer in the crude reaction mixture rendered steam distillation unnecessary.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.13; H, 10.80; N, 7.82. Ultraviolet absorption spectrum, calcd.[4] λ_{max} 308 mμ. Found: λ_{max} 309 mμ (3.8).

Also there was obtained from the above distillation 5.1 g. (29%) of the thermal isomerization product, aromatic amine VI, b.p. 63–65° at 0.4 mm., and 1.5 g. (9%) of polymeric residue.

In similar experiments the yield of *exo*-methyleneamine V varied from 55–75%, depending for the most part on the size of the run and the distillation temperature. Amine V, like other *exo*-methyleneamines, had a reasonably strong camphoric odor.

Thermal isomerization of V *to form β-(2,6-dimethylphenyl)-ethyldimethylamine* (VI). Crude *exo*-methyleneamine V, prepared from 21.4 g. (0.07 mole) of 2,6-dimethylbenzyltrimethylammonium iodide (IV) and 0.21 mole of sodium amide in 400 ml. of liquid ammonia, was thermally rearranged by distillation *in vacuo* at a higher temperature than employed above to yield 7.8 g. (63%) of β-(2,6-dimethylphenyl)ethyldimethylamine (VI), b.p. 116–118° at 10 mm., n_D^{25} 1.5077 (leaving a distillation residue of 4.0 g.).

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.31; H, 10.78; N, 7.84.

The picrate, recrystallized three times from 95% ethanol, melted at 135–136°.

Anal. Calcd. for $C_{18}H_{22}N_4O_7$: C, 53.20; H, 5.46; N, 13.79. Found: C, 53.39; H, 5.45; N, 13.86.

Reaction of exo-methyleneamine V *with hydrochloric acid to form hemimellitene.* To an ethereal solution of crude *exo*-methyleneamine V, obtained from the rearrangement of 0.10 mole of 2,6-dimethylbenzyltrimethylammonium iodide (IV) with 0.30 mole of sodium amide, was added all at once with vigorous shaking 250 ml. of cold 6*N* hydrochloric acid. After standing for 5 min., the ethereal layer was drawn off, washed with water, and dried, and the solvent was removed. The residue was distilled to give 8.9 g. (74%) of hemimellitene, b.p. 80–80.5° at 30 mm., n_D^{25} 1.5117 (reported b.p. 176° at 760 mm., n_D^{25} 1.5116).[11] The picrate of this hydrocarbon melted at 88.5–89.5° (from 95% ethanol) (reported m.p. 89.5°).[12]

When the aqueous acidified layer (containing dimethylmethyleneiminium chloride and basic products) was made alkaline with sodium hydroxide solution, strong fumes of formaldehyde and dimethylamine were detected,[2] and 2.1 g. of an oil (presumably aromatic amine VI, 12%) was isolated from the reaction mixture.

Rearrangement of exo-methyleneamine methiodide VII *to exo-methyleneamine* IX. Conversion of tertiary amine V into *exo*-methyleneamine methiodide VII was effected in 96% yield by the action of methyl iodide on V in acetonitrile solution. After crystallization from dry acetonitrile-ether and drying *in vacuo*, this salt[13] melted with decomposition at 128.5–130°.

To a stirred suspension of 0.26 mole of sodium amide in 500 ml. of liquid ammonia was added rapidly 27.3 g. (0.086 mole) of finely powdered methiodide VII, essentially as described[3] for the amide ion rearrangement of the methiodide of *exo*-methyleneamine II. After stirring for 1 hr. the deep, bright red reaction mixture was decomposed with excess ammonium chloride (color faded) and the ammonia replaced by Reagent Grade ether, followed by the addition of 25 ml. of 5*N* sodium hydroxide solution. The resulting mixture was rapidly steam distilled[10] and the distillate, after saturation with solid sodium carbonate and extraction with reagent grade ether, was worked up to give 10.9 g. (67%) of *exo*-methyleneamine IX, b.p. 52.5–54° at 0.5 mm., n_D^{25} 1.5108.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.62; H, 11.07; N, 7.31. Found: C, 81.66; H, 11.17; N, 7.35. Ultraviolet absorption spectrum, calcd.[4] λ_{max} 313 mμ. Found: λ_{max} 316 mμ (3.8).

The residue remaining after the steam distillation mentioned above consisted of 3.3 g. (20%) of polymeric material.

Also there was isolated 2.1 g. (12%) of what appeared to be the thermally isomerized amine. However, *exo*-methyleneamine IX was largely recovered after heating to 150° for 5 min. On heating 15.3 g. (0.09 mole) of IX at 200° for 2 hr. (Wood's metal bath, electrically controlled), there was obtained on distillation *in vacuo* 10.1 g. of a mixture of amines, b.p. 83–110° at 5 mm., and 3.5 g. of undistillable residue. This mixture was shown not to contain unreacted starting material by its failure to liberate prehnitene on treatment with hydrochloric acid (see below).

Reaction of exo-methyleneamine IX *with hydrochloric acid to form prehnitene.* To 5.74 g. (0.03 mole) of *exo*-methyleneamine IX was added all at once with stirring 25 ml. of 12*N* hydrochloric acid. The amine dissolved immediately with slight warming and within several minutes the solution became turbid. After standing at room temperature for 24 hr. (when an oily layer had separated on the surface) the reaction mixture was diluted with 100 ml. of water and extracted with ether. The ethereal extract was dried, the solvent removed, and the residue distilled to give 3.4 g. (85%) of prehnitene, b.p. 97–98° at 25 mm., n_D^{25} 1.5183 (reported b.p. 96.5° at 25 mm., n_D^{20} 1.5202.[14] The dinitro derivative of this hydrocarbon, after two recrystallizations from 95% ethanol, melted at 175–176° (reported m.p. 176–177°).[15] Formaldehyde was detected during the workup procedure.

2,3,4,6-Tetramethylbenzyltrimethylammonium chloride (XIII). α^2-Chloropentamethylbenzene, b.p. 114–117° at 5 mm. (reported b.p. 113–115° at 5 mm.),[16] was prepared in 83% yield from isodurene and monochloromethyl ether according to the directions of Varon and Bolle[17] for the chloromethylation of mesitylene.

Into a solution of 52.0 g. (0.284 mole) of this halide in 300 ml. of dry acetonitrile was slowly bubbled anhydrous trimethylamine for 1 hr. (some crystalline product separated). After standing at room temperature for an additional hour, 500 ml. of dry ether was added with swirling; the precipitated salt was collected on a funnel, washed with dry ether, and dried *in vacuo*. There was obtained 70.1 g. (quantitative) of 2,3,4,6-tetramethylbenzyltrimethylammonium chloride (XIII), m.p. 209–210° (dec.). The picrate of this hygroscopic compound melted at 164–165° after 3 crystallizations from water.

Anal. Calcd. for $C_{20}H_{26}N_4O_7$: C, 55.29; H, 6.03; N, 12.90. Found: C, 55.29; H, 6.13; N, 12.93.

Rearrangement of XIII *to 6-methylene-1,3,4,5-tetramethyl-1-dimethylaminomethylcyclohexadiene-2,4* (XIV). This reaction was carried out with 36.3 g. (0.15 mole) of 2,3,4,6-tetramethylbenzyltrimethylammonium chloride (XIII) and 0.45 mole of sodium amide in 500 ml. of liquid ammonia essentially as described[2] for the corresponding rearrangement of II. The lavender colored reaction mixture initially formed gradually changed to deep violet during 1 hr., this color persisting until ammonium chloride was added to the mixture after stirring for 3 hr. After replacing the ammonia with ether and steam-distilling the crude reaction product (see isolation of IX above), the distillate was processed to give, on distillation through a 40-cm. Podbielniak type column, 13.6 g. (44%) of *exo*-methyleneamine XIV, b.p. 62–62.5° at 0.4 mm., n_D^{25} 1.5240. (Compare *exo*-methyleneamine III,

(11) B. J. Mair and S. T. Schicktanz, *J. Research Nat. Bur. Standards*, 11, 665 (1933).

(12) O. L. Baril and E. S. Hauber, *J. Am. Chem. Soc.*, 53, 1087 (1931).

(13) Methiodide VII, which gradually darkened and partially decomposed on exposure to air, was used immediately for further reaction.

(14) L. I. Smith and O. W. Cass, *J. Am. Chem. Soc.*, 54, 1609 (1932).

(15) L. I. Smith and S. A. Harris, *J. Am. Chem. Soc.*, 57, 1289 (1935).

(16) R. C. Fuson and C. A. Sperati, *J. Am. Chem. Soc.*, 63, 2643 (1941).

(17) G. Varon and J. Bolle, *Compt. rend.*, 204, 1826 (1937).

n_D^{25} 1.5232[3]; see below for comparison of melting points of methiodides of XIV and III).

Anal. Calcd. for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.95; H, 11.39; N, 6.63. Ultraviolet absorption spectrum, calcd.[4] λ_{max} 318 mμ. Found: λ_{max} 321 mμ (3.9).

Also there was obtained from the above distillation 2.3 g. (8%) of the thermally rearranged product, aromatic amine XV, b.p. 88–89.5° at 0.4 mm., and 1.2 g. (4%) of undistillable residue. Considerable polymeric material (12.2 g., approximately 39%) remained from the steam distillation of XIV.

Thermal isomerization of XIV *to form β-(2,3,4,6-tetramethylphenyl)ethyldimethylamine* (XV). Crude *exo*-methyleneamine XIV, prepared from 19.3 g. (0.08 mole) of XIII and 0.24 mole of sodium amide, was thermally isomerized at 150° for 1 hr. to produce 7.4 g. (45%) of β-(2,3,4,6-tetramethylphenyl)ethyldimethylamine (XV), b.p. 90–90.5° at 0.5 mm., n_D^{25} 1.5163 (reported b.p. 88.5–89° at 0.45 mm., n_D^{25} 1.5162).[3] The picrate, recrystallized three times from 95% ethanol, melted at 178–179° (reported m.p. 179.5–180°).[3] Its melting point was not depressed on admixture with an authentic sample of the compound.

Reaction of exo-methyleneamine XIV *with hydrochloric acid to form pentamethylbenzene.* This reaction was carried out with an ethereal solution of crude *exo*-methyleneamine XIV (obtained from 0.07 mole of quaternary salt XIII and 0.21 mole of sodium amide) and 200 ml. of 6*N* hydrochloric acid as described for the acidic decomposition of V. The ethereal extract (containing neutral products) was steam-distilled, and the distillate worked up to yield 5.3 g. (51%) of pentamethylbenzene, m.p. 51–52°, after crystallization from absolute methanol (cooled to −78°). A mixed melting point determination with an authentic sample of this hydrocarbon, m.p. 52–53°, gave no depression in the melting point.

When the aqueous acidified extract (containing dimethylmethyleneiminium chloride) was made alkaline with sodium hydroxide solution, pungent fumes of formaldehyde were detected.

Rearrangement of the methiodide of exo-methyleneamine XIV *(Formula* XVI*) and acidic decomposition of its exo-methyleneamine product to form hexamethylbenzene.* Tertiary amine XIV (13.0 g., 0.063 mole), b.p. 62–62.5° at 0.4 mm., was converted into *exo*-methyleneamine methiodide XVI, m.p. 176–177° (dec.), in 98% yield by the action of 0.10 mole of methyl iodide on XIV in acetonitrile solution. The dissimilarity of this methiodide with that from *exo*-methyleneamine III [Formula XVII, m.p. 188–189° (dec.)][2] was demonstrated by the depression in melting point to 140–152° on admixture of these two quaternary ammonium salts.

To a stirred suspension of 0.19 mole of sodium amide in 300 ml. of liquid ammonia was added rapidly 21.2 g. (0.062 mole) of methiodide XVI, the resulting reddish violet colored reaction mixture being decomposed by the addition of ammonium chloride after 1 hr. The ammonia was replaced by ether, the suspension filtered, and the ethereal solution shaken with 200 ml. of 6*N* hydrochloric acid for 5 min. The two layers were separated. From the ether layer there was obtained 4.8 g. of impure hexamethylbenzene, m.p. 142–149°, which, after two crystallizations from ethanol afforded 4.2 g. (42%) of colorless hexamethylbenzene, m.p. 162–163°. This melting point was not depressed on admixture with an authentic sample of hexamethylbenzene, m.p. 162.5–164°.

From the aqueous hydrochloric acid layer (see above) there was obtained, on neutralization with sodium hydroxide and extraction with ether, 1.3 g. of unidentified material, b.p. 89–110° at 0.5 mm. (having a slight camphoric odor), and 2.7 g. of dark undistillable residue.

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT BERKELEY]

Unsaturated Four-Membered Ring Compounds. I. *cis*- and *trans*-1,2-Diiodobenzocyclobutene and Their Interconversion

FREDERICK R. JENSEN AND WILLIAM E. COLEMAN

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The reaction of α,α,α′,α′-tetrabromo-*o*-xylene with excess sodium iodide in ethanol gives two isomeric $C_8H_6I_2$ compounds. Evidence is presented which indicates these compounds are *cis*- and *trans*-1,2-diiodobenzocyclobutene. The stereochemical relationship of the isomers was assigned by dipole moment measurements. The *cis*-isomer (m.p. 150°) melts 87° higher than the *trans*-isomer (m.p. 63°). These compounds are readily interconverted by light in the presence of iodine in a free radical reaction, and by sodium iodide in ethanol in a reaction which is postulated to involve benzocyclobutadiene as an intermediate. At 30°, the equilibrium mixture contains 6% of the *cis*-isomer.

In his Inaugural Dissertation, Finkelstein reported the preparation of 1,2-dibromobenzocyclobutene (I) by refluxing sodium iodide with α,α,α′,α′-tetrabromo-*o*-xylene in ethanol solution.[1] Except for a brief reference to these results in connection with other work,[2] the details of this interesting reaction were not reported further until recently when Cava and Napier[3] reinvestigated and confirmed this preparation.

In this reaction an iodine-containing side product is produced which has been shown to be 1,2-diiodobenzocyclobutene (II). The same compound was also prepared in 70% yield by refluxing 1,2-dibromocyclobutene with ethanolic sodium iodide containing some iodine for eight days. As a side product in these reactions, a compound, $C_{16}H_{12}BrI_3$ (m.p. 135–136°), has been reported. The parent hydrocarbon, benzocyclobutene (III) was prepared by hydrogenolysis of (I) or (II).[3]

In attempting to prepare 1,2-diiodobenzocyclobutene directly by treating α,α,α′,α′-tetrabromo-*o*-xylene with a large excess of sodium iodide we obtained two isomeric $C_8H_6I_2$ compounds. This re-

(1) H. Finkelstein, Inaugural Dissertation, Strassbourg, 1910, carried out with J. Thiele.

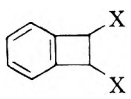
(2) H. Finkelstein, *Ber.*, **43**, 1532 (1910).

(3) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **78**, 500 (1956); M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **79**, 1701 (1957).

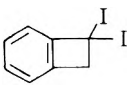
port concerns the assignment of structure to these two compounds and reactions for their interconversion.

Results. Heating $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene with excess sodium iodide in ethanol for 10 days produced two isomeric $C_8H_6I_2$ compounds in 80.9% yield. The low-melting isomer, prisms m.p. 63°, which comprised 91.6% of the mixture, has been postulated to be one of the two possible 1,2-diiodobenzocyclobutenes.[3] This compound was believed to be the *trans*-isomer on the basis of the instability expected for the *cis*-isomer.

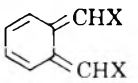
The other compound, needles m.p. 150° (8.4%), is an isomer as shown by elementary analyses and molecular weight determinations. Oxidation of this high-melting isomer with nitric acid gave a 74.1% yield of phthalic acid. There are three possible structures for this compound II, IV, or V. This compound does not add halogen when treated with bromine or iodine at room temperature.[4] Heating the high-melting isomer with maleic anhydride in benzene for 15 hr. produced no reaction. The recovered starting material (73.6%) contained some of the low-melting isomer.



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



IV



V, X = I
VI, X = Br

Reaction of the isomeric $C_8H_6I_2$ compounds with sodium iodide. The diiodides are interconverted by sodium iodide in refluxing ethanol. Small samples of each of the isomers were heated with alcoholic sodium iodide in the dark and the position of equilibrium determined by infrared analysis. Equilibrium was essentially obtained in 100 hr. and the equilibrium mixture contained about 9% of the high-melting isomer. In another experiment, a large sample of the low-melting isomer was heated with alcoholic sodium iodide in the dark for 8 days. The mixture was separated by recrystallization and found to contain 8.8% of the high-melting isomer (80% recovery).

In these reactions a small amount of decomposition occurred with the production of free iodine. In order to determine the cause of isomerization, samples were heated alone in ethanol and with added iodine.

Starting with the high-melting isomer, the pure compound was isomerized less than 3% and samples containing a little iodine were isomerized about 30% in the time necessary (92 hr.) for complete equilibration by sodium iodide. In another series of experiments the samples were heated 36 hr. A sample (0.037*M*) containing 0.5 mole per cent iodine was isomerized 7%, while a sample containing 63 mole per cent sodium iodide was isomerized 70%. Increasing the iodine concentration resulted in an increased amount of isomerization. The low-melting isomer is also isomerized by iodine or sodium iodide in refluxing ethanol.

All reactions were carried out in the dark, and the product compositions were determined by infrared analysis.

Interconversion of the $C_8H_6I_2$ compounds with light. Certain observations indicated that these isomers might be interconverted by light, and this was verified experimentally.

Since the infrared spectral changes are difficult to follow starting with the low-melting isomer, the majority of the studies were carried out with the high-melting isomer. The samples were dissolved in carbon disulfide solution. Although the effect of the solvent was not determined, the isomerizations also occur readily in carbon tetrachloride and hexane as solvents. The irradiation method was standardized in order to carry out semi-quantitative studies.

Both compounds were irradiated in order to determine the position of equilibrium. The compounds are equilibrated in about 4 hr. under the conditions of our experiments and the mixture contains about 6% of the high-melting isomer at 30°. In order to determine the conditions necessary for isomerization to occur, a series of experiments were carried out with the high-melting isomer. Initially, no isomerization occurred until iodine color was visible in the solution (about 5–10 min.). When a trace amount of iodine was added to the solution before starting the irradiation, the induction period no longer existed (Fig. 1). Removing the samples from the light source stopped the reactions. After allowing the samples to stand in the dark for 24 hr. the iodine color persisted, and placing the sample in the light source again caused the sample to isomerize further with no induction period. The effect of the iodine concentration on the rate of reaction was not studied in detail. Addition of copper, which caused the iodine color to disappear, essentially stopped the isomerization. The color of free iodine did not appear until the solution had been irradiated more than 24 hr. although the sample was partially decomposed. After prolonged irradiation, the surface of the copper became coated, the iodine color appeared, and the sample isomerized. During the period where no isomerization occurred, the sample was appreciably decomposed.

The changes observed in the infrared spectra during the isomerization of the low-melting isomer were small. In order to verify the results obtained by infrared analysis, a large sample was irradiated overnight in hexane and the isomers separated by recrystallization. The high-melting isomer ac-

(4) Although net addition of halogen does not occur when the isomers are treated with iodine or bromine, treatment of either $C_8H_6I_2$ compound with bromine converts it almost immediately to $C_8H_6Br_2$. The details of this and other reactions of these isomers will be reported in a future communication.

counted for about 6.8% of the recovered material.

Dipole moments of the isomeric diiodides. The dipole moments of the isomers were determined at 25° in benzene solution. The values obtained are for the low-melting isomer (m.p. 63°), $\mu = 1.84$ Debye, and for the high-melting isomer (m.p. 150°), $\mu = 2.51$ Debye.

Discussion. The high-melting isomer, $C_8H_6I_2$ m.p. 150°, must possess either structure II or IV on the basis that oxidation gives phthalic acid, it is nonreactive towards maleic anhydride,[3] and net addition of halogen does not occur upon treatment with bromine.[4]

The interconversion of the two isomers by iodide ion proceeds many times faster than the displacement reaction of iodide ion on cyclobutyl bromide.[5] The latter reaction has a half-life of about 120 days in acetone at 70° (initial concentrations 1 molar), whereas the equilibration is about complete in 100 hr. at 82°. Since this interconversion is catalyzed by iodide ions and proceeds readily in the dark, it is unlikely that it occurs by a process involving free radicals. The reaction probably does not proceed through carbonium ions since negligible amounts of ether are formed even after refluxing for 12 days in ethanol. A possible mechanism for the isomerization occurs through benzocyclobutadiene as an intermediate formed by elimination of iodine, which suggests that these compounds are *cis*- and *trans*-1,2-diiodobenzocyclobutene. These arguments have

been used previously to account for the iodide ion-catalyzed conversion of I to II.[3]

The interconversion of the isomers with iodine and heat in the dark was not studied in detail. The isomerization could conceivably proceed as a result of iodine serving as a Lewis acid to cause elimination, or through a reaction similar to that brought about by iodine and light. In the presence of sodium iodide, the small amount of iodine produced by decomposition is converted to sodium triiodide. In elimination reactions catalyzed by iodide ion, the triiodide ion is ineffective as a catalyst, and there is no reason to believe that it has an important function in the reactions given here.

The interconversion of these isomers by light in the presence of iodine can also be readily accounted for on the basis that they are *cis-trans* isomers. The observation that the reaction occurs with very low level illumination and other evidence strongly suggest that the reaction occurs by a chain process involving iodine atoms. Possible reaction schemes include the formation of benzocyclobutadiene as an intermediate. In the reaction scheme given here, chain terminating steps are not included.

(5) P. J. C. Fierens and P. Verschelden, *Bull. soc. chim. Belges*, 61, 427 (1952).

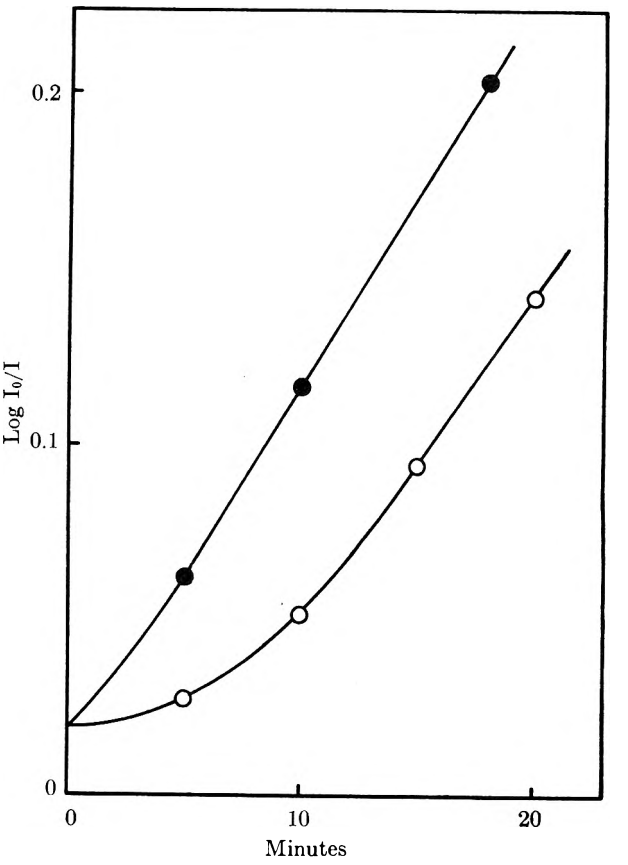
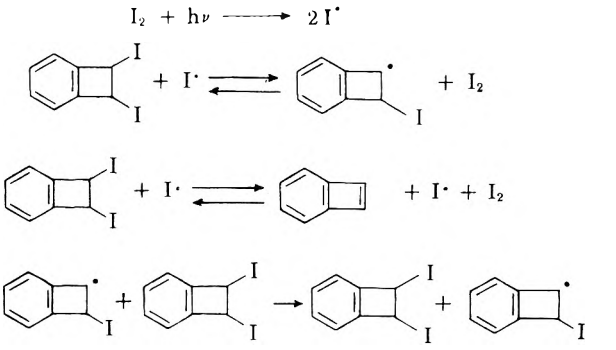


Fig. 1. Effect of added iodine on the rate of the light-catalyzed isomerization of *cis*-1,2-diiodobenzocyclobutene as shown by the formation of the 11.5 μ peak of the *trans*-isomer. Open circles, *cis*-isomer 0.5 g./5 ml. CS_2 solution; closed circles, *cis*-isomer 0.5 g./5 ml. CS_2 solution containing 0.003 g. iodine

It is very difficult to account for the interconversion of II and IV by iodide ions or light and iodine, and therefore it shall be assumed that these compounds are *cis*- and *trans*-1,2-diiodocyclobutene



(II). The chemistry of this system is unusual and it would be desirable to have final proof by independent synthesis of IV. Since the isomers are readily interconverted, it is difficult to fix the positions of the iodine atoms by chemical reactions.

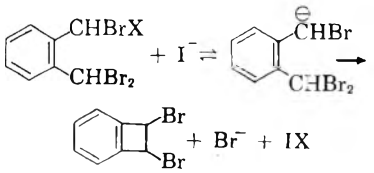
The position of equilibrium greatly favors the low-melting isomer which suggests that it is the *trans*-isomer since the iodine atoms might be expected to be badly crowded in the *cis*-compound.

Proof of this assignment was found from the dipole moment measurements.

The 87° higher melting point of the *cis*-isomer deserves some comment. Although the four membered ring might not be entirely planar in this molecule, nevertheless, it should have essentially a single-bend type structure. Such a structure could conceivably pack more favorably in the crystal lattice than that of the *trans*-isomer. The melting points of several esters of 3-aryl-2-isoxazoline-3,4-dicarboxylic acids, aryl—C(=N—O—CH(CO_2R)CH-(CO_2R), are higher for the *cis*- than for the *trans*-compounds.[6] These compounds also possess the single-bend type structure.

The known isomer of I, m.p. 52°, and *trans*-II, m.p. 63°, appear to be isomorphic since it is almost impossible to separate them by recrystallization. Also, the infrared spectra of I and *trans*-II have many similar features. For these reasons, it seems very likely that the known isomer of I is the *trans*-compound.

There is no evidence suggesting that isomerization of I occurs under the conditions of its preparation. It seems likely that the reaction of sodium iodide with $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene gives directly *trans*-I. Cava and Napier[3] have suggested that this reaction occurs through a 1,4-elimination to give VI as an intermediate. A reasonable pathway for conversion of VI to I would be through formation of the carbon-carbon bond in a one step process. In this reaction scheme, it might be expected that a considerable amount of the *cis*-isomer would be formed since in the transition state the substituent atoms are not fully opposed. However, the *cis*-isomer has not been isolated from the reaction mixture. The following mechanism might be expected to give predominantly the *trans*-isomer. A mechanism in which this over-all process occurs in a concerted fashion should also give predominantly



the *trans*-isomer since in these mechanisms the atoms would be nearly fully opposed in the transition states.

EXPERIMENTAL

cis- and trans-1,2-Diiodobenzocyclobutene. A mixture of 805 g. (5.4 moles) sodium iodide and 35 g. (0.21 mole) potassium iodide was refluxed with 2500 ml. absolute ethanol for 20 min. and then 700 ml. of ethanol was distilled. To this mixture was added 316 g. (0.75 mole) $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene,[7] and the mixture was refluxed for 10 days. The reaction vessel was carefully covered to exclude light and the solution was protected from moisture by a drying tube containing calcium sulfate. After cooling the mixture, 800 ml. methylene chloride was added and the resultant slurry was poured into 5000 ml. cold water. The water layer, which was nearly neutral, was titrated with sodium thiosulfate solution and 94% of the calculated amount (349 g.) was used. The solution was shaken to bring the iodine from the methylene chloride into the water later. The water layer was extracted three times with methylene chloride, the extractions were combined and the solvent was removed by flash distillation. The residue was distilled at 0.5 mm. (90–100°) and 224 g. was collected. Upon allowing to cool, two types of crystals, needles, and prisms, were observed. The mixture was separated by recrystallization from ether-hexane or heptane. Alternate fractions of each compound were taken, and if both types of crystals came down together, the mixture was taken back into solution. A total of 13 fractions were collected (216.1 g., 80.9%). Of this material, 18.2 g. (8.4%) was needles and 197.9 g. (91.6%) was prisms. We were unable to find any of the compound, $C_{16}H_{12}BrI_3$, reported previously as a side product in the reaction of 1,2-dibromocyclobutene with sodium iodide.[3]

The prisms (*trans*-1,2-diiodobenzocyclobutene, m.p. 62–63°) has been reported previously for essentially this same reaction.[3] The melting point of the needles [*cis*-1,2-diiodobenzocyclobutene, m.p. 150.1–150.8° (dec.)] depends on the rate of heating and whether or not the sample is exposed to strong light. The melting point reported was taken using a preheated bath and essentially in the dark. The melting point taken in the usual manner was 146–146.5°, although traces of impurities greatly lowered this value.

Anal. Calcd. for $C_8H_6I_2$: C, 26.99; H, 1.70; I, 71.31; mol. wt., 356. Found for the needles (m.p. 150.1–150.8°): C, 26.99; H, 1.82; I, 71.04; mol. wt., 334, 380 (isothermal distillation in carbon disulfide).

Oxidation of the high-melting diiodobenzocyclobutene. The diiodide (m.p. 150°, 1.198 g.) and concd. nitric acid (5 ml., d. 1.42) were added to a 20-ml. beaker, the beaker was covered and the temperature was slowly brought to 50° and maintained at this temperature for 30 min. The cover was removed and the cover and beaker sides were scraped down with a porcelain spatula. The mixture was then heated on a steam bath until all the iodine color had disappeared and the volume was 3 ml. The almost colorless solution was cooled in ice, the crystals were filtered with suction and washed twice with water. The phthalic acid was obtained in 74.1% yield (0.421 g.), m.p. 191–198° with the evolution of a gas.

Anal. Calcd. for $C_8H_6O_4$: C, 57.83; H, 3.71; neut. equiv., 83. Found: C, 57.36; H, 3.77; neut. equiv., 82.

A small sample of the phthalic acid was heated with acetic anhydride allowing the acetic acid formed to distill. The phthalic anhydride formed was sublimed, m.p. 128–129°.

Treatment of the high-melting diiodide with maleic anhydride. The high-melting diiodide (1.0 g.) was melted on a steam bath with maleic anhydride (3 g.). After heating the mixture for 3 hr., 75 ml. benzene was added and the mixture was refluxed for 15 hr. The flask was carefully covered to exclude light. The condenser was set for distillation, 40 ml. of benzene was distilled, 40 ml. water was added, and the remaining benzene was removed by steam distillation. The water solution was brought to a boil and filtered. The precipitate was washed twice more with 25-ml. portions of boiling water. The dried residue weighed 0.737 g. (74% recovery). An infrared spectrum revealed no carbonyl band, but did show, by the presence of a small band at 11.5 μ, that a small amount of isomerization had occurred to give the low-melting isomer.

(6) A. Quilico and P. Grunanger, *Gazz. chim. ital.*, 85, 1449 (1955).

(7) J. C. Bill and D. S. Tarbell, *Org. Syntheses*, 34, 82 (1954).

Treatment of the low-melting diiodobenzocyclobutene with sodium iodide. The diiodide (m.p. 63°, 15 g.) and sodium iodide (60 g.) were refluxed in 180 ml. absolute ethanol 8 days and the reaction mixture was worked up as before. Seven crops of crystals were obtained from heptane. A total of 12.13 g. of needles and prisms were isolated (81% recovery). Of this, 1.07 g. (8.8%) was the high-melting diiodide and 11.06 g. (91.2%) was the low-melting isomer.

In other experiments small samples were isomerized in refluxing ethanol in the presence of added sodium iodide, iodine, or alone. Light was carefully excluded during the heating periods. After cooling, the reaction mixture was poured into water and sodium sulfite was added until the iodine color disappeared. The compound was extracted with methylene chloride, the methylene chloride solution was washed with water, and the methylene chloride was removed under reduced pressure. The samples were dissolved in carbon disulfide and the isomer distribution was determined by infrared analysis using a Baird Associates double beam recording spectrophotometer and 0.1-mm. sodium chloride cells.

The concentration of the low-melting isomer was determined using the 11.5 μ-peak at a concentration 0.1 g./ml. CS_2 solution. The concentration of the high-melting isomer (at low concentrations) was determined using the 8.8-μ peak at a total concentration 0.5 g./ml. CS_2 solution with samples of the low-melting isomer in the reference beam. The calibration curve was made up using the same concentrations of the low-melting isomer in the reference and sample beams. Once the concentrations were approximately known, the unknown was determined using the concentration of the low-melting isomer in the reference beam approximately equal to that in the sample beam.

With initial concentrations of the high-melting isomer 0.071*M* and sodium iodide 0.041*M*, the concentration of the high-melting isomer was found to be 9.4% after 102 hr. With initial concentrations of the high-melting isomer about 0.03*M* and sodium iodide 0.02*M*, the concentration of the high-melting isomer was 37% after 36 hr. and 10.6% after 92 hr.

In experiments with the low-melting isomer, it was found that this compound is also isomerized by both iodine and sodium iodide in refluxing ethanol. Because the spectral changes in going from pure compound to the position of equilibrium are difficult to determine accurately, the reactions were not studied in detail. However, qualitatively the results indicated that this isomer is also isomerized faster by sodium iodide than by iodine. After heating the low-melting isomer (0.071*M*) for 102 hr. with sodium iodide (0.041*M*), the concentration of the high-melting isomer was 8.8%.

In refluxing ethanol, the best value for the concentration of the high-melting isomer at equilibrium is believed to be about 9%.

Light-catalyzed isomerizations of the 1,2-diiodobenzocyclobutenes. The irradiations were carried out using a 75-watt Sylvania flood lamp placed 5 inches from the soft glass volumetric flask which was used as the reaction vessel. The concentrations of the isomers were determined by infrared analysis of samples taken directly from the reaction flasks. All concentrations were 0.5 g./5 ml. CS_2 solution. The findings are given in Results.

The position of equilibrium was verified by irradiating 100 g. of the low-melting isomer in 500-ml. hexane for 12 hr. From the solution, 5.8 g. (6.8%) of the high-melting isomer and 80 g. (93.2%) of the low-melting isomer were obtained.

The best value for the concentration of the high-melting isomer at equilibrium (30°) is believed to be about 6%.

Dipole moment measurements. The measurements were carried out in dilute solution at 25°.[8] The dipole moments were calculated from the dielectric constants, densities, and refractive indices (Na_D line) of the solutions using a standard method.[9] The formulas used are:

$$P_{1,2} = C_1P_1 + C_2P_2 = [(\epsilon - 1)/(\epsilon + 2)][(C_1M_1 + C_2M_2)/d];$$
$$R_{12} = C_1R_1 + C_2R_2 = [(n^2 - 1)/(n^2 + 2)][(C_1M_1 + C_2M_2)/d];$$ and $$\mu_{298} = (0.2192)(P_2 - R_2)^{1/2}$$ Debye.

The dielectric constants were measured at four different concentrations. In the concentration range used, the values of P_2 found were essentially constant. The dipole measurement cell was placed in a constant temperature bath at 25°. The cell and a standard variable capacitor were connected in parallel in the tank circuit of a variable frequency oscillator operated at 950 K.C. The capacity changes in the cell were measured by determining the change in the standard capacitor necessary to restore the frequency of the oscillator to 950 K.C.

	Concentration Range (Mole Fraction)	P_2 (P_∞)	R_2 (R_D)	μ (Debye)
Needles, m.p. 150.1–150.8°	0.0242–0.00237	196 ± 3	64.3	2.51
Prisms, m.p. 62–63°	0.0368–0.00362	134 ± 2	63.8	1.84

Berkeley 4, Cal.

(8) We are indebted to Professor O'Konski for the use of the equipment for measuring the dielectric constants and for assistance in making the measurements.

(9) C. P. Smyth, *Physical Methods of Organic Chemistry*, A. Weissberger, editor, Second Edition, Vol. 1, Part II, Chapter 24, Interscience Publishers, Inc., New York, 1949.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

A Combined Analysis of Variance and Regression Treatment in the Evaluation of the Effects of Substituents on Reactivity[1]

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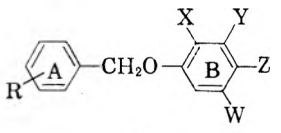
A technique is described for the statistical analysis of linear regression data. Particular emphasis is placed on tests of the hypotheses that a set of linear regressions have equal slope, or that a *significant* improvement is obtained by inclusion of an additional variable in a set of multiple regressions. As a most sensitive test of fit of data to a regression equation it is proposed to use the significance of the deviations from regression.

In the study of the effect of substituents on the reactivity of chemical compounds, a great deal of use is being made of linear regression,[2] and, to a lesser extent, of multiple regression involving two, and sometimes even more independent variables.[3] Owing to the relatively approximate nature of the correlations often observed and to the relative paucity of data usually available, although a good correlation is usually obvious, it is frequently difficult to evaluate adequately certain possible hypotheses: *e.g.* the hypotheses that various regression coefficients (slopes) differ, or that inclusion of a further independent variable results in a *significant* improvement of the fit. In an attempt to aid in the solution of some such problems we have utilized analysis of variance to provide statistical tests of significance.[4] The methods developed will be illustrated with several sets of data chosen from the literature.

Sets of linear regressions. An old set of data involving the rates of chlorination of a long series of variously substituted benzyl phenyl ethers (I)[5]



I

forms the simplest example. In these data the question arises whether the extent to which substituents in ring A affect the rate of chlorination depends on the substituents already present in ring B. Since the chlorination occurs only on ring B, the reaction behaves as a side chain reaction with respect to ring A, and effects of substituents in this ring can be treated by the use of the Hammett Equation (Equation 1) with good precision. A

$$\log k = Y_{ij} = \sigma_i\sigma_j + Y_{00} \qquad (1)$$

group of eight series of five compounds each was chosen in such a way that the same substituents in ring A recurred in each series, and each series was characterized by a different set of substituents in ring B.[6] The question posed then is equivalent to asking whether differences between the reaction constants (ρ-values) for these eight series are significant. Comparison of any pair of ρ-values and their standard deviations indicates no significant differences, but this comparison is not the most sensitive criterion as long as more than two ρ-values are available. An analysis of the total variance of the entire set of data will be used to obtain further information.

The total variance of each series having 5 degrees of freedom (DF) can be broken up into a contribution from the mean (1 DF) and from deviations from the mean (4 DF). The first of these terms is of little interest, but the latter one can be further divided into 1 DF due to regression and 3 DF due to deviations from regression. There is nothing unusual in this analysis, which is implied in the standard regression analysis, except the expression in the formalism of analysis of variance.

In the present example, we have, however, eight parallel series, and it is possible to add the corresponding terms from the analysis of each series to arrive at a composite analysis. This process is indicated in the first two columns of Fig. 1. The analysis of the over-all variance can be made, however, in terms of over-all terms, and a close correspondence in terms is observed; the third column in the "correlation diagram," Fig. 1, brings out this correlation. The eight individual degrees of freedom for deviations from individual series means split up into a single DF for deviation from the over-all mean, and 7 DF expressing the failure of the individual series means to coincide; in other words, measuring the average effect of substituents in ring B on the chlorination rates (in the customary terminology of analysis of variance, these 7 DF are referred to as "between series"). The eight

(1) Work supported by the Office of Ordnance Research, U. S. Army.

(2) (a) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, 1940, Chapter VII. (b) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(3) H. H. Jaffé, *Science*, **118**, 246 (1953); *J. Am. Chem. Soc.*, **76**, 4261 (1954).

(4) G. W. Snedecor, *Statistical Methods*, Iowa State College Press, Ames, Ia., 4th ed. 1946.

(5) B. Jones, *J. Chem. Soc.*, 2903 (1931); 1835 (1935); 1414 (1938); 267, 358 (1941).

(6) In three series, data for one substituent were missing, and were supplied using the Hammett Equation. Three DF were subtracted from the total number to account for this filling in of missing data.

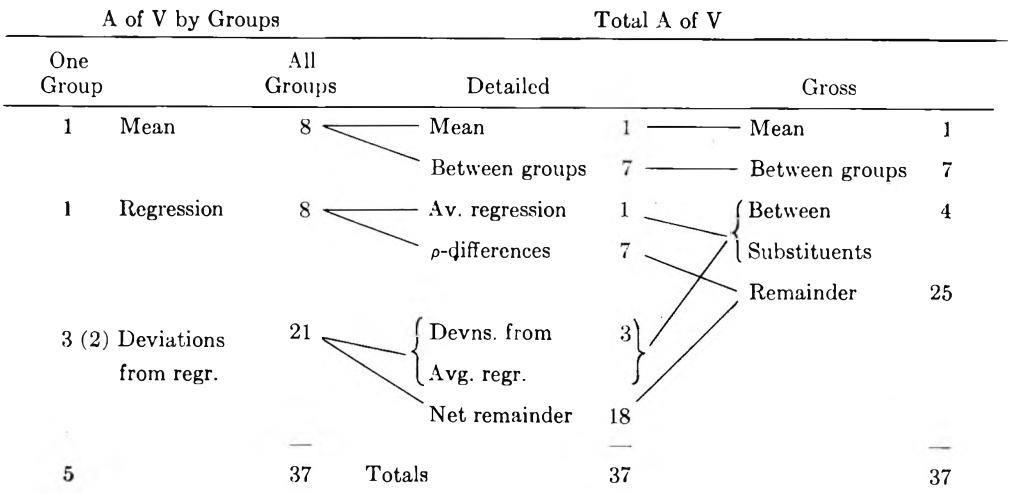


Fig. 1. Correlation diagram of degrees of freedom

DF for individual correlations can similarly be broken up into one DF for average correlation and 7 DF which measure the differences between the eight individual regression coefficients, *i.e.* between the eight ρ-values. The sum of squares for the average regression is most readily obtained by correlating the average of the eight individual rate constants (or rather their logarithms) with the corresponding sigma-values. Finally, the 21 DF for deviation from regressions contain three DF for deviations from the average regression, and the remaining DF are not specified in our model. A direct analysis of variance of the complete set of data (*cf.* right hand column of Fig. 1), divides the total variance into contributions from mean (1 DF), differences between series means (7 DF), between substituent means (4 DF), and a gross remainder (25 DF). The relations between the various terms in the third and fourth columns in Fig. 1 are readily apparent. Thus, the 4 DF for deviations from substituent means (in the fourth column) obviously contain 1 DF for average regression and 3 DF for deviations from it. Similarly, the 25 DF in the gross remainder contain the 7 DF for the differences in ρ-values, and then leave 18 DF of net remainder which are not otherwise identified in the present model. These 18 DF actually represent higher order interaction terms, and could conceivably be used for statistical tests, but, in the absence of duplicate rate data they are a measure of experimental error.

The computations of all the terms are performed readily, making free use of the principle of additivity of sums of squares, and are listed in Table I. Comparison of the mean square of the net remainder with the corresponding values for the various other types of variations shows that the effects due to substituents in either ring on the rate of chlorination, and the correlation are highly significant. The very high F values (variance ratios) are characteristic of analysis of variance of well known and readily observable effects. No statistical treatment was necessary to recognize these effects and failure to have attained large F values for these terms would have done more to throw doubt on the analysis than on the phenomena. The degrees of freedom for differences between ρ-values, however, turn out not to be significant (at the 95% level) so that it appears that ρ-values are not significantly affected by substituents in ring B. Further, we might have asked whether there exists a significant difference in ρ-values depending on the number and positions of the sites available for chlorination (some of the groups X, Y, Z, W in I are hydrogen atoms). Such a question could be examined by dividing the set of eight series in groups according to the nature and number of available sites, and calculating average regressions for each group. Comparison of the sum of the sums of squares for these separate groups with the overall average regression sum of squares then permits a test of significance of such differences. Such a procedure represents a division of the sum of squares corresponding to the 7 DF for ρ-value differences into portions between and within groups. In the present case the total sum of squares corresponding to these 7 DF is so small that, even if all of it were accounted for in a single degree of freedom, no significance would result. Consequently no such analysis is carried out, and it can be concluded that the number and type of sites available do not affect the ρ-values.

Sets of correlations with two independent variables. Tirouflet and co-workers[7] have recently measured the rates of alkaline hydrolysis of four 5-substituted phthalimides (II), of their conjugate bases, and of their *N*-methyl and *N*-ethyl derivatives. The authors suggest that the data may be correlated with the corresponding σ_p-values (σ-values for the para position), or slightly better with an average between the σ-values for meta and para position. Since the mechanism of the reaction most

(7) R. Dabard and J. Tirouflet, *Bull. soc. chim. France*, 565 (1957); J. Tirouflet, R. Dabard, and E. Laviron, *Bull. soc. chim. France*, 570 (1957).

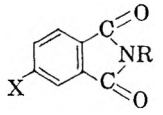
TABLE I

ANALYSIS OF VARIANCE OF THE RATES OF CHLORINATION OF SUBSTITUTED BENZYL PHENYL ETHERS (I)[a]

Source	D.F.	Sum of Squares	Mean Square	F^b
A: Total	37[c]	49.942083	—	
Mean	1	44.685732	—	
Between ring A substituents	4	3.092759	0.773190	6970**
Between ring B substituents	7	2.161072	0.308725	2780**
Gross remainder	25	0.002525	—	
B: Deviations from means for ring B substituents	29	3.095284	—	
Individual regressions	8	3.081962	0.385245	3470**
Deviations from individual regressions	21	0.013322	0.000634	5.71**
C: Deviations from means for ring B substituents	29	3.095284	—	
Average regression	1	3.081434	3.081434	2780**
Differences between ρ's	7	0.000528	0.000075	<1
Deviations from average regression	3	0.013850	0.004465	40**
Net remainder	18	0.001997	0.000111	—

[a] In each subtable the first entry is either contained in one of the preceding subtables, or is the sum of several terms in one of them. The remaining entries in each subtable are the breakdown of the entry in the first line. [b] One asterisk indicates significance at the 95%, a double asterisk, at the 99% level. [c] Corrected for data supplied by use of the Hammett Equation.

likely involves attack by OH^- on *one* of the carbonyl carbon atoms, the more reactive of the car-



II

bonyl groups, *i.e.* the one for which the σ-value is higher (more positive), should be the reactive group.[8] In this case, correlation with a single σ-value should be made with the larger one of the two values ($\sigma_>$), and correlations with two values should make use of the equation:

$$\log k = Y_{1j} = \sigma_> \rho_{1j} + \sigma_< \rho_{2j} + Y_{oj} \qquad (2)$$

When such an analysis is attempted it is again found, as expected, that the correlation, either with one or two independent variables, is excellent. But the critical question is whether a *significant* improvement can be achieved by the use of Equation 2 over the simple linear correlation, and whether there are significant differences between the regression coefficients for the four series of data.

The analysis of variance (*cf.* Table II) and the correlation diagram are analogous to the previous case. The only new feature involves the splitting of the 2 DF for multiple regression (either individual or average) into a DF for linear regression and a DF for improvement due to the inclusion of the second independent variable. Similarly, the differences between ρ-values are separated into differences in the linear regression ρ's, and additional differences due to the second set of ρ's. It should be noted, however, that the second set of differences as evaluated in Table II do not represent the differences in the ρ_2's in Equation 2. It is also possible to separate the variance due to multiple regression (either individual or average) into two parts, for ρ_1 and ρ_2 separately, and then the differences between corresponding values for individual and average regressions give the variance due to differences in ρ_1's and ρ_2's separately. This analysis is not carried out in the present case, since there seems no reason to expect such differences in one set of ρ's, but not in the other.

Table II shows that the differences between ρ-values for the various series are not significant but that Equation 2 produces a very appreciable improvement over the simple correlation. As in the previous case, one might have anticipated especially large differences between ρ-values for a particular series (the phthalimide conjugate bases, *e.g.*, might have been expected, due to the presence of the lone pair of electrons, to have a ρ-value different from the other 3 reaction series). Such a hypothesis can be tested most sensitively by examining correlations for average of groups believed to be similar. Again, if all the differences between slopes were concentrated in two degrees of freedom, the extreme situation possible, this term would not be significant. Hence the hypothesis is rejected with no need for computation of the division of the 6DF for slope differences. The uncertainties in the ρ_1- and ρ_2- values, owing to the small number of data available, are too large to make the actual values obtained of much interest. The average values, obtained in the present treatment, however, are better estimates than could have been obtained otherwise.

Sets with two-way correlations. Whenever reaction rates in a series of reactions satisfying the Hammett equation are determined at various temperatures, ρ-values can be calculated for each temperature. Hammett[2a] suggested long ago that ρ-values should be proportional to $1/T$, and much evidence has ac-

(8) Actually, probably some reaction must occur at both carbonyl groups, but the analysis of this situation is complicated since it involves additivity in k, not log k, and will not be attempted, particularly as long as data are not available for much longer series of substituents.

TABLE II

ANALYSIS OF VARIANCE OF RATES OF HYDROLYSIS OF SUBSTITUTED PHTHALIDES (II)[a]

Source	D.F.	Sum of Squares	Mean Squares	F^b
A: Total adjusted for mean	15	9.554063	—	
Between N-substituents	3	2.249285	0.749762	165**
Between ring A substituents	3	7.236849	2.412283	530**
Gross remainder	9	0.067929	—	
B: Deviations from means for N-substituents	12	7.304778	—	
Individual linear regressions	4	6.992836	1.748209	384**
Improvement by individual multiple regressions	4	0.298079	0.074520	16.4**
Deviations from individual multiple regressions	4	0.013863	0.003466	<1
C: Deviations from means for N-substituents	12	7.304778	—	
Average linear regression	1	6.961088	6.961088	1530**
Improvement by average multiple regression	1	0.275551	0.275551	60.5**
Differences between slopes	6	0.054276	0.009046	1.99
Deviations from average multiple regression	1	0.000210	0.000210	<1
Net remainder	3	0.013653	0.004551	—

[a] and [b] *cf.* Table I.

cummulated to indicate that this prediction was correct.[2b] However, owing to the large uncertainties usually accompanying ρ-values (with a median standard error of about $\pm$ 10%), this conclusion is based on the existence of rough trends, and significant differences are rarely demonstrated between any two ρ-values at two temperatures.[2b]

The analysis of variance technique developed permits ready demonstration of the significance of such differences. A series of reactions at four temperatures was chosen at random from our files and subjected to a combined analysis of variance and regression. The mathematical model implied by the correlation of rates on σ-values and on $1/T$ is given in Equation 3, where Y_{00} is an intercept in a

$$\log k = Y_{ij} = (\sigma - \bar{\sigma})\rho + (1/T - \overline{1/T})K + (\sigma - \bar{\sigma})(1/T - \overline{1/T})\alpha + Y_{00} \quad (3)$$

3-dimensional plot, and ρ, K and α are adjustable parameters. The last term represents the variation in individual ρ-values (for different temperatures) and in individual K-values (for different substituents). ρ and K in Equation 3 are the average values for the set of temperatures and substituents,

TABLE III

ANALYSIS OF VARIANCE OF THE RATES OF DISSOCIATION OF *t*-BUTYL PERBENZOATES AT VARIOUS TEMPERATURES[a,b]

Source	D.F.	Sum of Squares	Mean Squares	F^c
A: Total	19[d]	35.128856	—	
Mean	1	25.791747	—	
Between temperatures	3	8.027031	2.675677	2090**
Between substituents	4	1.242866	0.310717	243**
Gross remainder	11	0.067212	—	
B: Total adjusted for mean	18	9.337109	—	
Average regression on σ	1	1.240856	1.240856	969**
Average regression on 1/T	1	8.022765	8.022765	6260**
Average regression on σ/T	1	0.054355	0.051355	42**
Remainder	15	0.019133	0.001276	—
C: Deviations from means for substituents	15	1.310078	—	
Individual regressions on 1/T	4	1.293145	0.323286	173**
Deviations	11	0.014933	0.001357	<1
D: Deviations from means for substituents	15	1.310078	—	
Average regression on 1/T	1	1.240856	1.240856	665**
Deviations from average regression	3	0.002010	0.000670	<1
Variation in slopes	3	0.052289	0.017430	9.35**
Net remainder	8	0.014923	0.001865	—
E: Deviations from means for temperatures	14	8.094243	—	
Individual regressions on σ	5	8.082105	1.616421	1440**
Deviations	9	0.012138	0.001348	1.20
F: Deviations from means for temperatures	14	8.094243	—	
Average deviation on σ	1	8.022765	8.022765	7131**
Deviation from average regression	2	0.004266	0.002133	1.90
Variation in ρ's	4	0.059340	0.014835	13.2**
Net remainder	7	0.007872	0.001125	—

[a] *cf.* Table I. [b] A. T. Blomquist and I. A. Bernstein, *J. Am. Chem. Soc.*, **73**, 5546 (1951). [c] *cf.* Table I. [d] One value was extrapolated, using the Arrhenius equation, and consequently the total number of D.F.'s reduced by one.

TABLE IV

ANALYSIS OF VARIANCE OF THE RATES OF ALKALINE HYDROLYSIS OF SUBSTITUTED PHTHALIDES[a]

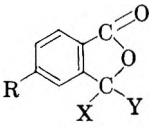
Source	D.F.	Sum of Squares	Mean Squares	F^b
A: Total	16	34.751698	—	
Mean	1	28.156289	—	
Between aromatic ring substituents	3	5.689432	1.896477	379*
Between methylene substituents	3	0.860946	0.286982	57*
Gross remainder	9	0.045031	0.005003	
B: Deviations from over-all means	15	6.595409	—	
Average regression on σ_i	1	5.668356	5.668356	1383*
Average regression on σ^*_j	1	0.834770	0.834770	183*
Regression on $\sigma_i\sigma^*_j$	1	0.022538	0.022538	3.88
Deviations	12	0.069565	0.00580	
C: Deviations from means for single methylene substituents	12	5.734463	—	
Individual regressions on σ_i	4	5.691818	1.422954	183*
Improvement of regression by inclusion of σ_i'	4	0.011261	0.002815	<1
Deviations from multiple regression	4	0.031084	0.007771	1.89
D: Deviations from means for single methylene substituents	12	5.734463	—	
Average regression on σ_i	1	5.668536	5.668536	1383**
Differences between ρ's	3	0.023282	0.007761	1.89
Improvement of average regression by inclusion of σ'_i	1	0.001837	0.001837	<1
Additional differences between and ρ's due to inclusion of σ'_i	3	0.009424	0.003141	<1
Deviations from average multiple regression	1	0.019059	0.019059	4.64
Deviations from regression on σ'_i	2	0.020896	0.010448	2.54
Net remainder	3	0.012325	0.004108	—
E: Deviations from aromatic ring substituents means	12	0.905977	—	
Individual regressions on σ_j^*	4	0.853579	0.213395	32**
Deviations from individual regressions on σ_j^*	8	0.053398	0.006675	1.47
F: Deviations from means for aromatic ring sub-substituents	12	0.905977	—	
Average regression on σ_j^*	1	0.834770	0.834770	183**
Differences between ρ^*	3	0.018809	0.006270	1.38
Deviations from average regression on σ_j^*	2	0.026176	0.013088	2.87
Net remainder	6	0.026222	0.004555	

[a] and [b] *cf.* Footnotes to Table I.

respectively. A significant contribution to the variance from α indicates significant differences between the individual ρ's and K's. But since the correlations are only approximate, it is still of interest to test deviations from average ρ- and K-values separately (Table III), and this procedure permits an answer to the question whether differences from the average regression and from the individual regressions, are significant.

In the present case, the last term in Equation 3 is highly significant, providing the demonstration that ρ-values change significantly with temperature. Although the mean square values for differences between ρ- and K-values, and for error, evaluated in two different ways do not agree accurately, the discrepancies are so small that they can be ascribed to accidental fluctuation.

Simultaneous multiple and linear regression. The rates of saponification of 2- and 5-substituted phthalides (III) reported by Tasman[9] provide the most complicated set of data we have treated by the present technique, although further extensions



III

should not produce any new difficulties. The effect of substituents in the aromatic ring in III should be expressable by a two parameter Hammett equation,[3] and the effect of X and Y might be expressed by the Taft equation.[10] Again the differences between ρ-values is of interest; *i.e.*, do 2-substituents affect the ρ-values? The mathematical model is rather complicated:

$$\log k = Y_{ij} = (\sigma_{pi} - \bar{\sigma}_{pi})\rho_1 + (\sigma_{mi} - \bar{\sigma}_{mi})\rho_2 + (\sigma^*_j - \bar{\sigma}_j^*)\rho^* + (\sigma_{pi} - \bar{\sigma}_{pi})(\sigma^*_j - \bar{\sigma}^*_j)\alpha_1 + (\sigma_{mi} - \bar{\sigma}_{mi})(\sigma^*_j - \sigma^*_j)\alpha_2 + Y_{oo} \quad (4)$$

The analysis, however, produces no new complications. When it appeared that the ρ_2 term produced no significant improvement, the α_2 term in

(9) A. Tasman, *Rec. trav. chim.*, 46, 653 (1927).

(10) R. W. Taft, Jr., in M. Newman, *Steric Effects in Organic Chemistry*. John Wiley and Sons, Inc., New York, 1956, Chapter 13, Section VI.

Equation 4 was also ignored. Again, the analysis is carried out in detail in order to segregate deviations from the various linear and multiple regressions from the remainder terms (Table IV). In this case it appears that, the linear regressions are again highly significant, the model

$$\log k = Y_{ij} = (\sigma_{pi} - \bar{\sigma}_{pi})\rho_1 + (\sigma^*_j - \sigma^*_j)^*\rho + Y_{oo} \quad (5)$$

is as satisfactory as the much more complicated model of Equation 4.

Discussion. Maybe the most striking features of Tables I–IV are the tremendous values of the variance ratios (F) for the differences in group means, and the manner in which the vast majority of the corresponding variances are accounted for by the simple linear regressions. As noted above, this fact is not surprising since the relations involved are well established and have long been apparent in extensive sets of data without recourse to more than the most rudimentary statistics. It is not a purpose of the present statistical technique to demonstrate their significance; rather, if they turned out not highly significant, the technique would be open to question.

Although more subtle, more important is the fact that in many cases deviations from regression (both individual, and when appropriate, average) are *not* significant. The search for a good criterion of "fit" to an empirical relation has gone on for a long time. It would appear that the fact that deviations from regression are not significant was the best possible criterion. Unfortunately, this criterion is rarely applicable to published data, since, in the analysis of a single regression, no DF remain to make such a test, unless data for duplicate determinations are available to provide an independent estimate of error. In the types of analysis presented in the present paper, also, it has been necessary to use higher order interactions as estimates of error; although these interactions probably provide a reliable estimate, an independent estimate of error would be preferable, since it would also permit the testing of these interactions. Unfortunately, it appears to have become customary *not* to publish duplicate values, except under special circumstances, or in a few instances to illustrate the type of reproducibility obtaine.

Finally, the method developed provides the most sensitive possible test of the significance of differences between regression coefficients (slopes) and of improvements due to inclusion of additional independent variables. The total amount of labor involved in the types of analyses outlined is negligible compared with the work involved in the accummulation of the experimental data. The most complicated of the analyses reported here can be completed with the use of a desk calculator in 1–2 hr.

CINCINNATI 21, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Reaction of β-Diketones with Peracids

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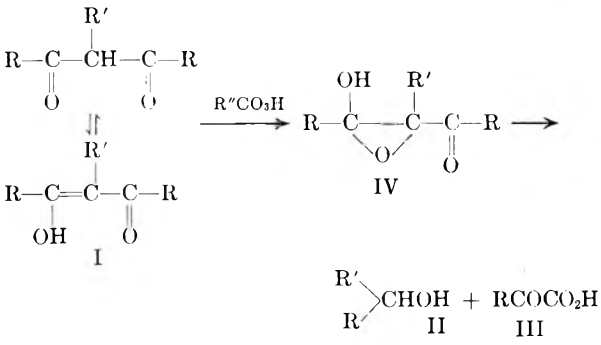
The reactions of 4-methyl-3,5-heptanedione and 3-benzyl-2,4-pentanedione with monoperphthalic acid have been studied. The heptanedione derivative yielded 4-hydroxy-4-methyl-3,5-heptanedione which underwent thermal isomerization to form the propionic acid ester of 2-hydroxy-3-pentanone. 3-Benzyl-2,4-pentanedione underwent a similar series of transformations.

In 1936 Boeseken and Jacobs reported[2] a study of the reaction of peracetic acid with a series of β-diketones and β-keto esters. The reaction, which occurred only with enolizable β-dicarbonyl compounds I, was said to yield an alcohol II and an α-keto acid III as shown in the accompanying equation when one equivalent of the peracid was employed. With an excess of the peracid a mixture of acids was obtained. In certain cases isolation of the supposed intermediates IV was also reported. Subsequently, a portion of the work claimed to yield the intermediates IV(R′ = H) was repeated by Karrer and co-workers, perbenzoic acid being used as the peracid to facilitate isolation of products.[3–5]



(1) Rohm & Haas Research Assistant, 1957.

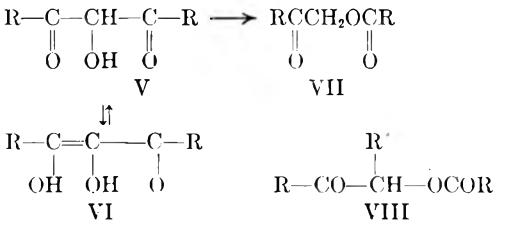
(2) J. Boeseken and J. Jacobs, *Rec. trav. chim.*, **55**, 804 (1936).

(3) P. Karrer, J. Kebrle, and R. M. Thakkar, *Helv. Chim. Acta*, **33**, 1711 (1950).

(4) P. Karrer, J. Kebrle, and U. Albers-Schonberg, *Helv. Chim. Acta*, **34**, 1014 (1951).

(5) P. Karrer, U. Albers-Schonberg, and J. Kebrle, *Helv. Chim. Acta*, **35**, 1498 (1952).

The products originally assigned structure IV,[2] were shown to be mixtures of the tautomeric forms V and VI of α-hydroxy-β-diketones.[6] Karrer and co-workers[3] also confirmed the previously reported[7] thermal rearrangement of the hydroxy diketone V (R = C_6H_5) to the ester VII and reported that the same isomerization occurred when a solution of the hydroxy diketone V (R = C_6H_5) was treated with sodium bicarbonate.



In other studies[8-10] the reactions of certain triacylmethane derivatives with peracids were reported to yield the α-acyloxy derivatives of β-dicarbonyl compounds, the products expected from a normal Baeyer-Villiger reaction. Thus, if the reaction of enolizable β-dicarbonyl compounds I were analogous, the expected products would be esters of the type VIII.

Consideration of these previous reports raises questions as to what are the expected products when enolizable β-dicarbonyl compounds I (especially where R′ ≠ H) react with peracids and, also, whether there is any justification for the formation of the cleavage products II and III in such reactions. In an effort to answer these questions the reactions of two β-dicarbonyl compounds IX and X with peracids have been studied.

In a preliminary study 4-methyl-3,5-heptanedione (IX) was allowed to react with peracetic acid in methylene chloride, the reaction being followed both by measurement of the optical density of the reaction mixture at 291 mμ (absorption attributable to the enol form XI of the diketone IX) and by vapor-phase chromatographic analysis. Although the enol content of the reaction mixture fell to a low level within 2 hr. complete consumption of the β-diketone IX required several days. These observations are in agreement with the contention of Boeseken and Jacobs that the enol form of the β-dicarbonyl compound reacts with the peracid. The only product which could be detected was propionic acid; presumably a part of the acetic acid present in the reaction mixture was also derived from the diketone IX. To facilitate the isolation of products, subsequent reactions employed an ether solution of monoperphthalic acid rather than peracetic acid. Even the latter reaction conditions did not eliminate the presence of extraneous by-products since the decomposition of monoperphthalic acid in pure ether resulted in the formation of a number of low molecular weight materials including ethanol, acetic acid, and ethyl acetate. Ether solutions of the diketone IX were allowed to react with one equivalent and with four equivalents of monoperphthalic acid at room temperature until the peracid content of each reaction mixture had fallen to 5% or less of its initial value. The reaction mixture obtained by the use of an excess of the peracid contained propionic aid and acetic acid as well as the ethyl esters of these two acids but no higher boiling materials and no 2-butanol (the expected cleavage product II according to the scheme of Boeseken and Jacobs). The reaction of the diketone IX with one equivalent of monoperphthalic acid afforded acetic and propionic acids accompanied by the unchanged diketone IX and a second high-boiling component subsequently shown to be 4-hydroxy-4-methyl-3,5-heptanedione (XII). Thus, it was apparent that the initial reaction product, the hydroxy diketone XII, reacted relatively rapidly with additional peracid. As in previous cases no 2-butanol, the cleavage product of the type II predicted by the general reaction scheme of Boeseken and Jacobs, could be detected in the reaction mixture.[11]

The initial reaction product, the hydroxy diketone XII, was quantitatively isomerized to the ester XIII when heated to 200°. Both compounds XII and XIII underwent facile hydrolytic cleavage in the presence of aqueous alkali to yield propionic acid (XIV), characterized as its *p*-bromophenacyl ester, and 2-hydroxy-3-pentanone (XV or the tautomeric keto alcohol XVI), characterized as its osazone. The infrared, ultraviolet, and nuclear magnetic resonance spectra of the initial reaction product were all consistent with structure XII. However, it must be noted that these data do not rigorously exclude the possibility that the product either has the epoxy alcohol structure IV or is an equilibrium mixture of structures XII and IV.

Reaction of 3-benzyl-2,4-pentanedione (X) with one equivalent of monoperphthalic acid in ether produced a mixture which could not be completely resolved either by fractional distillation or by vapor-phase chromatography. The mixture was shown to contain acetic and phenylacetic acids as well as 4-phenyl-2-butanone (presumably formed by hydrolytic cleavage of the starting diketone X)

(6) It is unlikely that small amounts of the epoxy alcohol IV (R = H), also a tautomer of structures V and VI, would have been detected if present.

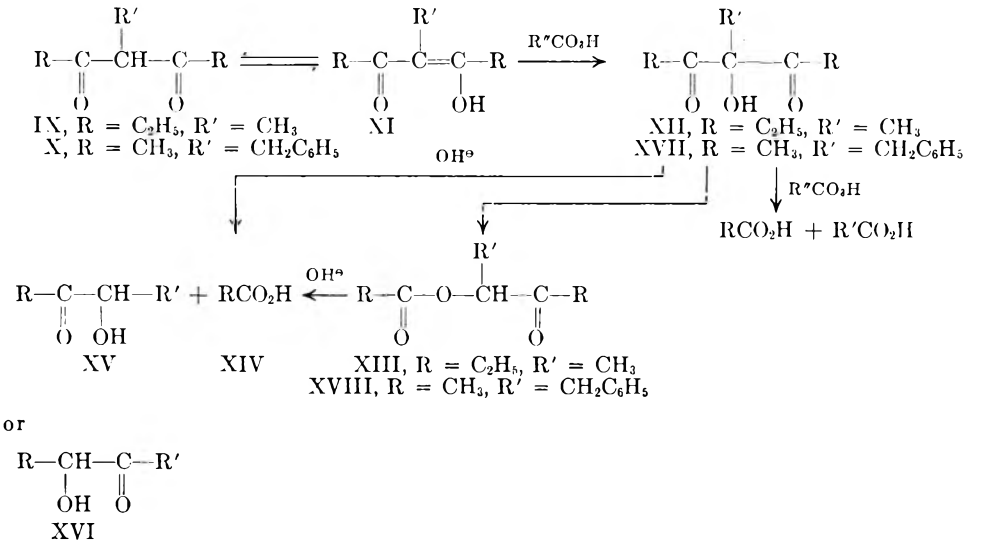
(7) A. H. Blatt and W. L. Hawkins, *J. Am. Chem. Soc.*, **58**, 81 (1936).

(8) C. H. Hassall, *Org. Reactions*, 9, 73 (1957).

(9) L. H. Briggs, C. H. Hassall, and W. F. Short, *J. Chem. Soc.*, 706 (1945).

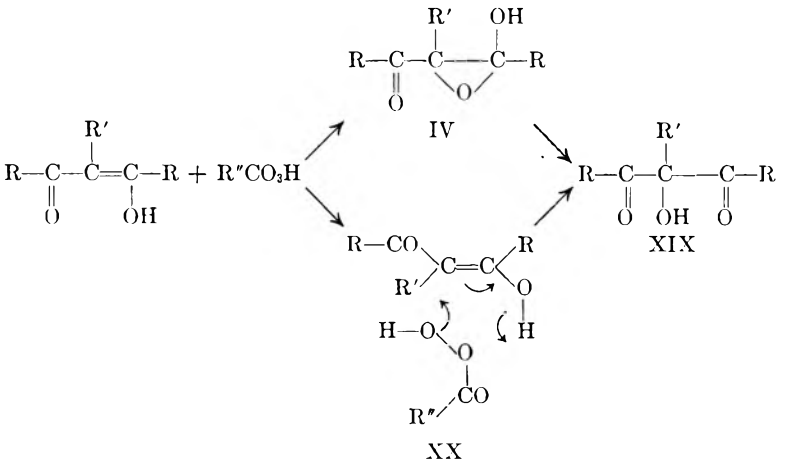
(10) C. H. Hassall, *J. Chem. Soc.*, 50 (1948).

(11) Since the hydroxy diketone XII was heated with substantial quantities of acetic, propionic, and phthalic acids during the distillation required for isolation of the reaction products, it does not seem reasonable to attribute the results reported by Boeseken and Jacobs to the acid-catalyzed rearrangement of hydroxy diketone XII or its tautomer IV in the acetic acid solution used by these workers.



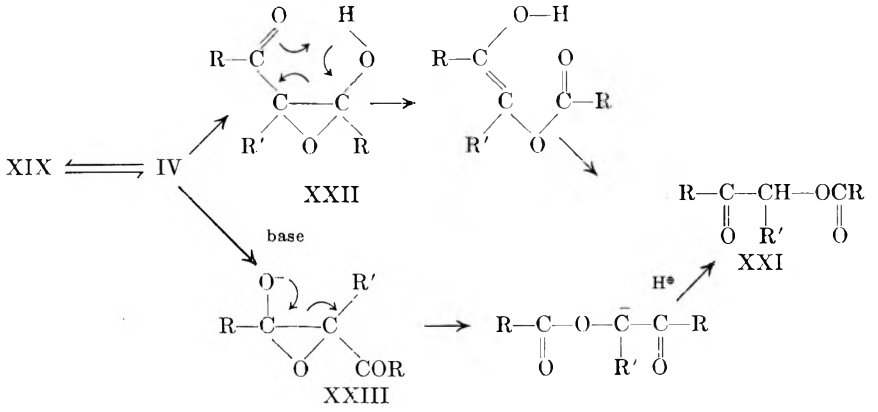
and a mixture of higher boiling materials. No benzylmethylcarbinol, one of the compounds which was reported[2] to be formed when the diketone X reacted with peracetic acid, could be detected in the reaction mixture. The infrared spectrum and chemical properties (*i.e.*, positive ferric chloride test, base-cleavage products) of the high boiling mixture isolated from the reaction were consistent with the presence of the starting diketone X and the hydroxy diketone XVII. Some of the ester XVIII may also have been present. After a portion of the mixture had been heated above 200°, the infrared spectrum of the resultant mixture was consistent with the presence of the starting diketone X and the ester XVIII. Hydrolytic cleavage of the crude product afforded acetic and phenylacetic acids plus 4-phenyl-2-butanone, characterized as its 2,4-dinitrophenylhydrazone, and 4-phenyl-3-hydroxy-2-butanone (XV or the tautomeric keto alcohol XVI), characterized as its osazone.

Thus, our results, like those of Karrer and coworkers,[3-5] indicate that enolizable β-dicarbonyl compounds react with peracids to yield α-hydroxy-β-dicarbonyl compounds. These initial reaction products, which are readily cleaved by further reaction with peracids, may be isomerized to esters of the type VIII by heat or bases;[3] alternatively, the initially formed hydroxy diketones may be cleaved by treatment with bases.[12] The formation of the hydroxy diketones XIX may be supposed to occur either by the intermediate formation of an epoxy alcohol IV[13] or by direct hydroxylation of the enol by a process such as that represented by XX. The rearrangement of the hydroxy diketones XIX to esters XXI may be most easily rationalized by processes involving the epoxy alcohol IV as an intermediate. For example, the thermal and base-catalyzed isomerizations might be represented as shown in formulas XXII and XXIII, respectively.



(12) The hydroxy diketones of type V, which can form stable enolate anions, would be expected to be relatively resistant to base cleavage compared with hydroxy diketones such as XII.

(13) This reaction is analogous to the reaction of enol esters and enol ethers with peracids. For examples and leading references see (a) C. L. Stevens and J. Tazuma *J. Am. Chem. Soc.*, **76**, 715 (1954); (b) P. D. Gardner, *J. Am. Chem. Soc.*, **78**, 3421 (1956).



EXPERIMENTAL[14]

4-Methyl-3,5-heptanedione (XII). A mixture of 170 g. (1.84 moles) of 3-pentanone and 600 g. (4.6 moles) of propionic anhydride was saturated rapidly with boron trifluoride gas, the temperature of the reaction mixture being kept below 10° by means of a Dry Ice–acetone cooling bath. After the resulting mixture had been allowed to stand overnight at room temperature, it was poured into a solution of 750 g. of sodium acetate trihydrate in 1500 ml. of water. The mixture was boiled under reflux for several hours and then cooled and extracted with ether. The ether extract was washed with saturated, aqueous sodium bicarbonate, dried over magnesium sulfate, and distilled through a 70-cm. Vigreux column. The diketone, b.p. 90.5–92.5° (16 mm.), n_D^{28} 1.4377 [lit. b.p. 95–97° (20 mm.),[15] 94–97° (20 mm.)[16]], amounted to 94 g. (36%). The ultraviolet spectrum[17] of the product has a maximum at 291 mμ (ε 1580) attributable to the presence of the enol form of the diketone. The infrared spectrum[18] has bands at 1725 and 1700 cm.$^{-1}$ (C=O of a non-enolized β-diketone) as well as a broad band at 1600 cm.$^{-1}$ attributable to an enolized β-diketone. The product reacted with cupric acetate to give a copper complex which crystallized from benzene as gray-green needles which partially melted with decomposition at temperatures ranging from 165–166° to 177–180° (lit. 176–178°,[15] 171–173°[16]). The position of the decomposition range was very dependent on the rate of heating of the melting point bath, the higher values being obtained when the sample was heated rapidly or placed in a bath at temperatures above 150°.

Anal. Calcd. for $C_{16}H_{24}O_4Cu$: C, 55.55; H, 7.58. Found: C, 55.63; H, 7.69.

Reaction of the diketone with 2,4-dinitrophenylhydrazine afforded *3,5-diethyl-1-(2,4-dinitrophenyl)-4-methylpyrazole* as orange needles, m.p. 93.5–94°, yield 82.5%. The infrared spectrum[19] of the product exhibited no band in the 3 μ region attributable to an N—H group and no band in the 6 μ region attributable to a carbonyl function.

Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.51; H, 5.49; N, 18.41.

Reaction of 4-methyl-3,5-heptanedione with peracetic acid. To a solution of 2.0 g. (0.014 mole) of the diketone in 20 ml. of methylene chloride was added 2.05 g. of a solution of 1.13 g. of sodium acetate trihydrate and 0.021 mole of peracetic acid in acetic acid. The resulting mixture was stirred at room temperature, aliquots being removed periodically for analysis. After 2 hr. the optical density of the reaction mixture at 291 mμ had fallen to 1% of its initial value. After 48 hr. vapor-phase chromatographic analysis indicated that a substantial amount of the ketone remained. An additional portion of peracetic acid, equivalent to the amount used initially, was added and the mixture was stirred for a total of fourteen days. At this time no β-diketone could be detected in the reaction mixture. The acidic and neutral components of the reaction mixture were separated by extraction with aqueous sodium hydroxide followed by appropriate manipulations. Only the reaction and extraction solvents were detected in the neutral fraction. The vapor-phase chromatogram of the acid fraction exhibited peaks attributable to acetic and propionic acids.

Reaction of 4-methyl-3,5-heptanedione with monoperphthalic acid. Procedure A. In an initial experiment 5.85 g. (0.0411 mole) of the diketone was treated with a solution of 0.0411 mole of monoperphthalic acid[20] in 100 ml. of ether and aliquots of the solution were removed periodically for iodometric titration. After 30 hr., at which time the peracid content of the mixture had fallen to 4% of its initial value, the bulk of the phthalic acid was filtered from the reaction mixture and the filtrate was distilled under reduced pressure. Analysis of the various fractions of the distillate by vapor-phase chromatography indicated the presence of acetic and propionic acids as well as the starting diketone and the major component of the mixture, subsequently shown to be 4-hydroxy-4-methyl-3,5-heptanedione. All four components were collected from the chromatogram and the three known compounds were identified by comparison of their infrared spectra with the spectra of authentic samples.

In a subsequent experiment a solution of 42.2 g. (0.297 mole) of the diketone and 0.393 mole of monoperphthalic acid in 1 l. of ether was allowed to stand at room temperature until the peracid content was negligible and then worked up as described previously. The high-boiling materials were fractionally distilled through an 18-in. spinning band column and each of the fractions collected was analyzed

(14) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined either with a Baird, Model B, or a Perkin-Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates. The vapor-phase chromatograms were obtained with 8 mm. × 215 cm. columns packed with suspensions of silicone oil, polyethylene glycol, or di-2-ethylhexyl sebacate on 50–80 mesh ground firebrick. The fractions, eluted with helium, were detected with a thermal conductivity cell.

(15) R. Levine, J. A. Conroy, J. T. Adams, and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 1510 (1945).

(16) B. M. Perfetti and R. Levine, *J. Am. Chem. Soc.*, **75**, 626 (1953).

(17) Determined as a solution in 95% ethanol.

(18) Determined in carbon tetrachloride solution.

(19) Determined as a suspension in a potassium bromide pellet.

(20) The peracid was prepared by the procedure of E. E. Royals and L. L. Harrell, Jr., *J. Am. Chem. Soc.*, **77**, 3405 (1955).

by vapor-phase chromatography. From these data the yields of the principle components were estimated to be: propionic acid, 11%[21]; 4-hydroxy-4-methyl-3,5-heptanedione, 32%; 4-methyl-3,5-heptanedione, 5% recovery; 3-keto-2-pentyl propionate (or its tautomer), 2%.[22] Redistillation of the appropriate fractions from the first distillation permitted the separation of 7.15 g. (15.2%) of the pure *4-hydroxy-4-methyl-3,5-heptanedione*, b.p. 93–95° (18 mm.), $n_D^{29.5}$ 1.4295.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.61; H, 9.09.

The infrared spectrum[18] of the product exhibits bands at 3450 cm.$^{-1}$ (O—H) and 1704 cm.$^{-1}$ with a slight shoulder at 1715 cm.$^{-1}$ (C=O of a non-enolized β-diketone). The ultraviolet spectrum[21] has maxima at 213 mμ (ε 750) and 304 mμ (ε 165). The nuclear magnetic resonance spectrum[23,24] has the following peaks (expressed as cycles per second relative to the proton resonance of water): a singlet at −5 sec.$^{-1}$ (O—H); a singlet at −150 sec.$^{-1}$ (CH_3 adjacent to a carbon atom not bonded to a hydrogen atom); a triplet with its center peak at −173 sec.$^{-1}$ (CH_3 adjacent to a CH_2); a series of 4 or 5 partially resolved peaks within the range −97 to −120 sec.$^{-1}$ (CH_2 adjacent to CH_3). It was not possible to decide whether or not the latter group of peaks represented two methylene groups in identical environments.

A solution of 3.0 g. (0.019 mole) of the hydroxy diketone in ether was shaken with about two equivalents of 10% aqueous sodium hydroxide. The aqueous phase was extracted with several additional portions of ether and concentrated to dryness under reduced pressure. A portion of the residual solid was neutralized and converted to the *p*-bromophenacyl ester in the usual way. The product, m.p. 64–65.5°, was shown to be identical with an authentic sample of *p*-bromophenacyl propionate both by a mixed melting point determination and by comparison of the infrared spectra of the two samples.

The combined ethereal extracts from the base-cleavage, which were shown to contain one component other than ether by vapor-phase chromatography, were dried over magnesium sulfate, concentrated and distilled. The product, 2-hydroxy-3-pentanone (or its tautomer), b.p. 56–57° (16 mm.), n_D^{29} 1.4174,[25] amounted to 0.95 g. (49%). The infrared spectrum[18] of the product has bands at 3510 cm.$^{-1}$ (O—H), 1715 cm.$^{-1}$ (C=O), and 1125 cm.$^{-1}$ (C—O of a secondary alcohol). The material exhibits no significant absorption in the ultraviolet region. A solution of 0.45 g. sample of the hydroxy ketone, 2 ml. of phenylhydrazine, and several drops of acetic acid in 10 ml. of water was refluxed for several hours and then cooled. When the crude material which separated was recrystallized from ethanol, the pure osazone of 2,3-pentanedione separated as yellow prisms, m.p. 162–163° [lit.[26] 161–162.5°], yield 0.604 g. (50%), which was shown to be identical with an authentic sample[27] both by a mixed melting point determination and comparison of the infrared spectra of the two samples.

A 1.0-g. sample of the hydroxy diketone XII, sealed in a Pyrex tube, was heated to 205–210° for 1 hr. The vapor phase chromatogram of the crude product exhibited only one major peak whose retention time differed only slightly from the retention time of the starting hydroxy diketone. Since a mixture of the starting material and the product was only partially resolved by vapor phase chromatography, a reliable estimate of how much, if any, of the starting hydroxy diketone remained was not possible. Distillation of the product afforded 3-keto-2-pentyl propionate, b.p. 90.5–91.5° (16 mm.), n_D^{30} 1.4173.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.58; H, 8.93.

The infrared spectrum[18] of the product has bands at 1735 cm.$^{-1}$ (C=O of an ester) with a shoulder at 1705 cm.$^{-1}$ (C=O of a ketone), 1185 cm.$^{-1}$ (C—O—C of an ester) with a very weak band at 3480 cm.$^{-1}$ attributable either to the O—H group of some unchanged hydroxy diketone present or to an overtone of the carbonyl band at 1735 cm.$^{-1}$ The material exhibits no significant absorption in the ultraviolet region.

An ether solution of the product was shaken with aqueous sodium hydroxide and the acid and neutral products were separated as described in the base-cleavage of the hydroxy diketone. The vapor phase chromatogram of the neutral product indicated the presence of a 2-hydroxy-3-pentanone (or its tautomer) shown to be identical with the product previously described by comparison of the infrared spectra of the two samples. The acidic fraction contained propionic acid accompanied by a small amount of acetic acid.

Procedure B. A solution of 1.46 g. (0.0103 mole) of 4-methyl-3,5-heptanedione and 0.0411 mole of monoperphthalic acid in 100 ml. of ether was allowed to stand at room temperature, the reaction being followed as described in Procedure A. After 240 hr., at which time the peracid content of the mixture had fallen to 5% of its initial value, the reaction mixture was worked up and analyzed as described in procedure A. The components other than ether and phthalic acid found in the mixture were acetic acid, ethyl acetate, propionic acid, and ethyl propionate.

3-Benzyl-2,4-pentanedione (XVII). To a solution of 50 g. (0.5 mole) of 2,4-pentanedione and 25 g. (0.4 mole) of potassium hydroxide in 100 ml. of water was added, dropwise and with stirring, 70 g. (0.55 mole) of benzyl chloride. After the addition was complete, the mixture was refluxed overnight with stirring and then cooled and extracted with ether. After the extract had been dried over magnesium sulfate and concentrated, distillation of the residue afforded 29.43–42.94 g. (31–45%) of the β-diketone, b.p. 110–112° (2 mm.), n_D^{31} 1.5313 [lit.[28] b.p. 143–146° (10 mm.)]. The infrared spectrum[18] has a band at 1700 cm.$^{-1}$ with a shoulder at 1725 cm.$^{-1}$ (C=O of a non-enolized β-diketone), as well as a broad band at 1605 cm.$^{-1}$ (enolized β-diketone). The ultraviolet spectrum[17] has a maximum at 290 mμ (ε 3500).

A 2.0-g. sample of the product was converted to its copper complex by reaction with cupric acetate. The copper complex separated from benzene as gray-green crystals, m.p.

(21) This yield is based upon the assumption that each mole of the diketone IX can yield two moles of propionic acid. The yield reported here is judged to be well below the actual amount of propionic acid produced since substantial quantities of the acid were lost as the solvent was distilled from the mixture. For this reason, no attempt was made to estimate the amount of acetic acid, ethanol, ethyl acetate, and ethyl propionate present in the initial fractions from the distillation.

(22) This ester, which appeared only in the latter fractions of the distillation, was apparently formed by thermal isomerization of the hydroxy diketone during the distillation. The properties of the pure material are described subsequently.

(23) Determined as a pure liquid.

(24) Determined with a Varian Associates high-resolution nuclear magnetic resonance spectrometer, Model V4300B.

(25) The properties reported for 2-hydroxy-3-pentanone are b.p. 63° (20 mm.) [M. D. Gauthier, *Compt. rend.*, **152**, 1100 (1911)] and b.p. 45–48° (11 mm.), n_D^{20} 1.4218 [E. Schmidt and A. Ascherl, *Ber.*, **58**, 356 (1925)]. The properties reported for 3-hydroxy-2-pentanone are b.p. 77° (35 mm.) [H. v. Pechmann and F. Dahl, *Ber.*, **23**, 2421 (1890)] and b.p. 59–59.5° (27 mm.) [E. Venus-Daniloff, *Bull. soc. chim.* (*France*), **43**, 582 (1928)].

(26) H. v. Pechmann, *Ber.*, **21**, 1411 (1888).

(27) Oxidation of 3-pentanone with an aqueous solution of selenium dioxide afforded a mixture of the starting material and 2,3-pentanedione which was treated with phenylhydrazine. The desired osazone, m.p. 161.5–163.5°, was isolated from the mixture by fractional crystallization.

(28) J. M. Sprague, L. J. Beckham, and H. Adkins, *J. Am. Chem. Soc.*, **56**, 2665 (1934).

187.5–188° (dec.) (lit.[29] 176°) yield 1.5 g. (55%). Because of the discrepancy in melting point values the composition of our sample was determined.

Anal. Calcd. for $C_{24}H_{26}O_4Cu$: C, 65.21; H, 5.93. Found: C, 65.30; H, 5.97.

A suspension of the pure copper complex in ether was shaken with 20% aqueous sulfuric acid. After the ether solution of the regenerated diketone had been dried and concentrated, distillation of the residue afforded the pure β-diketone, b.p. 97–98° (0.5 mm.), n_D^{30} 1.5300. The infrared spectrum of the product was essentially identical with the spectrum of the initial alkylation product indicating the absence of a significant amount of *O*-alkylated product.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.64; H, 7.64.

Reaction of 3-benzyl-2,4-pentanedione with monoperphthalic acid. After a solution of 42.9 g. (0.226 mole) of the diketone and 0.34 mole of monoperphthalic acid in 745 ml. of ether had been allowed to stand for seven days, the bulk of the phthalic acid was removed by filtration and the filtrate was concentrated. The entire residue was distilled under reduced pressure, the final fraction being taken at 119–122° (5 mm.). The vapor-phase chromatogram of the combined distillate indicated the presence of low-boiling components, several fractions of intermediate molecular weight, subsequently shown to be 4-phenyl-2-butanone, phenylacetic acid, and phthalic anhydride, and a mixture of high-boiling compounds which was not resolved in the chromatogram. Comparison of this chromatogram with the vapor phase chromatograms of authentic samples of benzylmethylcarbinol and benzyl methyl ketone demonstrated that no peak corresponding to either the ketone or the alcohol was present in the chromatogram of the reaction mixture. Fractional distillation of the crude product through an 18-in. spinning band column effected only partial separation of the mixture. The infrared spectrum[18] of the mixture of higher boiling components, 25.91 g., b.p. 82.5–86° (0.2 mm.), has a band at 3500 cm.$^{-1}$ (O—H) with a doublet at 1710 and 1735 cm.$^{-1}$ (nonenolized β-diketone).

A sample of the mixture, which gave a violet color with ethanolic ferric chloride indicating the presence of the starting diketone, was subjected to vapor-phase chromatography at 240° and the mixture of high-boiling components was collected. The infrared spectrum[18] of the mixture has a broad band at 1600 cm.$^{-1}$ (enolized β-diketone), a band at 1730 cm.$^{-1}$ (C=O of an ester) with a shoulder at 1700 cm.$^{-1}$ (C=O of a ketone) and a band at 1230 cm.$^{-1}$ (C—O—C of an ester).

An ether solution of the mixture of products from the reaction mixture was shaken with aqueous sodium hydroxide and the resulting neutral and acidic components were separated as previously described. The two neutral components, one of which corresponded to one of the components of the original reaction mixture, were separated by vapor phase chromatography. The infrared spectrum[18] of the first component eluted from the chromatogram has a band at 1725 cm.$^{-1}$ (C=O) and is essentially identical with the spectrum of an authentic sample[30] of 4-phenyl-2-butanone. The product was converted to its 2,4-dinitrophenylhydrazone which separated from ethanol as orange prisms, m.p. 125.8–127.2°. The material was shown by a mixed melting point determination and by comparison of infrared spectra to be identical with the 2,4-dinitrophenylhydrazone, m.p. 126–127.5° (lit.[31] 128–129°), prepared from an authentic sample[30] of 4-phenyl-2-butanone.

The infrared spectrum[18] of the second component eluted from the chromatogram has bands at 3550 cm.$^{-1}$ (O—H) and 1720 cm.$^{-1}$ (C=O). The product was characterized as its osazone, prepared as previously described, which crystallized from aqueous ethanol as pale yellow plates, m.p. 170–171.5°. The product was shown both by a mixed melting point determination and by comparison of infrared spectra to be identical with the osazone, m.p. 171–172.5° (lit.[32] 171–173°), prepared from an authentic sample[33] of 1-phenyl-2,3-butanedione.

Analysis of the mixture of acid components from the basic extraction by vapor-phase chromatography indicated the presence of acetic acid and a high boiling acid. The high boiling component which crystallized from petroleum ether as white plates, m.p. 75–76.5°, was shown to be identical with an authentic sample of phenylacetic acid both by a mixed melting point determination and by comparison of the infrared spectra of the two samples.

Benzylmethylcarbinol. Benzyl methyl ketone (10 g., 0.735 mole) was reduced with 2.1 g. (0.055 mole) of lithium aluminum hydride in 125 ml. of ether and the reaction mixture was worked up by the precipitation of the aluminum salts with a small amount of aqueous sodium hydroxide in the usual manner. The alcohol, collected at 103.5–104.5° (13 mm.), n_D^{29} 1.5171 [lit.[34] b.p. 125° (25 mm.), n_D^{20} 1.5190] amounted to 6.86 g. (69%).

CAMBRIDGE 39, MASS.

(29) G. T. Morgan and C. J. A. Taylor, *J. Chem. Soc.*, **127**, 797 (1925).

(30) Prepared by the procedure of Y. Chen and W. F. Barthel, *J. Am. Chem. Soc.*, **75**, 4287 (1953).

(31) G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953).

(32) T. I. Temnikova and V. A. Kropachev, *J. Gen. Chem.* (*U. S. S. R.*), **19**, a541 (1949).

(33) Prepared by the method of H. Moreau, *Ann. chim.* (*Paris*), [10] **14**, 339 (1930).

(34) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **105**, 1115 (1914); S. Winstein, M. Brown, K. C. Schreiber, and A. H. Schlesinger, *J. Am. Chem. Soc.*, **74**, 1140 (1952).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Electronic Effects and Rates in the Diels-Alder Reaction[1]

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A kinetic study has been made of the reactivities of a series of methyl esters of substituted phenylpropiolic acids with tetraphenylcyclopentadienone with the aim of defining the electronic effects of substituents on the rate of the Diels-Alder reaction. The reaction was followed by measuring the rate of evolution of carbon monoxide. The reactions were second order. The reaction products were isolated and characterized. The apparent ionization constants of the corresponding phenylpropiolic acids in 50% aqueous ethanol were also determined. A plot of log K/K_0 of the ionization of the *m*- and *p*-substituted phenylpropiolic acids against Hammett σ-constants gave a line whose slope was +0.69.

A plot of the logarithms of the rate constants against log K/K_0 gave a line whose slope was +1.10. Energies of activation for the reactions of the methyl esters of the *o*- and *p*-chlorophenylpropiolic acids were 18.2 and 18.9 Kcal/mole.

The significance of the results obtained is discussed.

It is well known that the Diels-Alder reaction is accelerated by electron-withdrawing groups in the dienophile and by electron-releasing groups in the diene. Few quantitative studies have been made because of experimental difficulties due to side reactions or to dissociation of the product. Notable are those of Barnstorff and Meek[4] who investigated the effect of nuclear substituents on the dienophilic reactivity of *N*-phenylmaleimide and of DeWitt, Lester, and Ropp[5] who measured the rate of reaction between *p*-substituted 1-phenyl-1,3-butadienes and maleic anhydride. Bickford, Hoffman, Heinzelman, and Fore[6] have recently reported on some electronic and steric effects in maleic anhydride but the substituents, CH_3 and Cl, were on the double bond.

A previous paper from these laboratories[7] reported a preliminary investigation of the Diels-Alder reaction between tetracyclone (tetraphenylcyclopentadienone) and substituted acetylenes. It was found that the reaction is favored by electron-withdrawing substituents, that side-reactions such as polymerization or copolymerization do not occur, and that the reaction is irreversible because a benzene ring is formed by decarbonylation of the intermediate adduct. These properties of the reaction permit a precise study of the kinetics of the Diels-Alder reaction. Based on a convenient time for the reaction and on the ease of introducing various groups into the phenylacetylene, the methyl esters of substituted phenylpropiolic acids were selected for study. The present paper reports on a kinetic study of the reactivities of a series of such methyl esters with tetracyclone with the aim of more specifically defining the electronic effects of substituent groups on the rate of the Diels-Alder reaction.

EXPERIMENTAL

A. Synthetic. Tetracyclone, m.p. 220–221° (rep. m.p. 219–220°), was prepared by the method of Johnson and Grummitt.[8]

The substituted phenylpropiolic acids were prepared by dehydrobromination of the corresponding cinnamic acid or ester dibromides with alcoholic potassium hydroxide essentially according to literature procedures.

Several methods were used for the esterification of these acids. Sulfuric acid in methanol was used for the esterification of phenylpropiolic acid. This method gave poor results with *p*-methoxyphenylpropiolic acid. However, dimethyl sulfate[9] gave satisfactory yields. Finally esterification with *N* HCl in methanol[10] was adopted as the standard esterification technique. The results are summarized in Table I.

Phenylcyclohexane, purchased from Distillation Products Industries, was purified according to Corson and Ipatieff,[11] b.p. 138.0–138.5° (32 mm.), n_D^{28} 1.5221 (rep. n_D^{20} 1.5254,[12] n_D^{25} 1.5190[13]).

B. Apparent ionization constants. A solution of about 0.75 mmole of the substituted phenylpropiolic acid, accurately weighed, in 50 ml. of 50 volume percent of aqueous ethanol was titrated potentiometrically under a nitrogen atmosphere with 0.1*N* NaOH. Ethanol was added during the titration to keep the composition of the solvent constant.

A Beckman Model G *p*H meter was used for the titration. The electrodes were Beckman #1190-42 and #1170.[14] The *p*H meter was standardized against aqueous buffer solution at *p*H of 5. Standardization was checked against aqueous buffer solution at *p*H of 2.

At the end of each titration, the electrodes were immersed in distilled water for one-half hour. The *p*H meter was

(1) Presented at the 132nd Meeting of the American Chemical Society, New York, N. Y., September 8 to 13, 1957, Abstracts, p. 32-P.

(2) Taken from the doctoral Dissertation of I. Benghiat presented to the Graduate Faculty of the Polytechnic Institute of Brooklyn, 1958.

(3) To whom inquiries should be directed.

(4) H. D. Barnstorff and J. S. Meek, 125th Meeting of the American Chemical Society, Kansas City, Mo., March 23 to April 1, 1954, Abstracts, p. 29-N.

(5) E. J. DeWitt, C. T. Lester, and G. A. Ropp, *J. Am. Chem. Soc.*, **78**, 2101 (1956).

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(7) J. J. Dudkowski and E. I. Becker, *J. Org. Chem.*, **17**, 201 (1952).

(8) J. R. Johnson and O. Grummitt, *Org. Syntheses*, Coll. Vol. III, 806 (1953).

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(10) P. Pfeiffer, *Ann.*, **411**, 148 (1916).

(11) B. B. Corson and V. N. Ipatieff, *Org. Syntheses*, Coll. Vol. II, 151 (1943).

(12) B. B. Corson and V. N. Ipatieff, *J. Am. Chem. Soc.*, **59**, 645 (1937).

(13) J. F. McKenna and F. J. Sowa, *J. Am. Chem. Soc.*, **59**, 471 (1937).

(14) *Cf.*, H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956).

TABLE I

PHYSICAL CONSTANTS OF METHYL ESTERS OF SUBSTITUTED PHENYLPROPIOLIC ACIDS

Substituent	Method of Prepn.[a]	M.P., °C. or B.P., °C. (mm.)	Yield, %	Analyses Carbon Calcd.	Carbon Found	Hydrogen, % Calcd.	Hydrogen, % Found	Other Elements, % Calcd.	Other Elements, % Found
None[b]	1	128 (4 mm.)	74						
m-CH_3	2	95 (0.6 mm.)[c]	69	75.84	75.92, 75.93	5.79	6.01, 6.23		
p-CH_3	2	68–70	86	75.84	76.12	5.79	5.79		
o-Cl	2	39.5–40	74	61.71	61.62	3.63	3.62	18.22	18.52
m-Cl	1	28–30	50					18.22	17.77
p-Cl	1	92–94	94					18.22	17.86
m-NO_2	2	51–52	18	58.54	58.51, 58.66	3.44	3.26, 3.42	6.83	6.54, 6.81
p-NO_2	2	112–113	100	58.54	58.44	3.44	3.53	6.83	6.73
m-OCH_3	2	124 (0.3 mm.)[d]	84	69.46	69.47, 69.35	5.30	5.65, 5.52		
p-OCH_3	1	45–47	20	69.46	69.44	5.30	5.33		
p-OCH_3	3	45	74						

[a] (1) Methanolic sulfuric acid; (2) methanolic hydrogen chloride[10]; (3) dimethyl sulfate.[9] [b] n_D^{22} 1.5628 (C. Moureau, P. T. Muller, and J. Varin, *Ann. chim.*, [9] **2**, 269 (1914), report n_D^{25} 1.5618). [c] n_D^{24} 1.5568. [d] $n_D^{24.5}$ 1.5663.

TABLE II

PHYSICAL CONSTANTS, APPARENT IONIZATION CONSTANTS (24°), AND SIGMA CONSTANTS OF SUBSTITUTED PHENYLPROPIOLIC ACIDS IN 50% ETHANOL (VOL.) AT 24°C. AND SPECIFIC RATE CONSTANTS OF THE ESTERS

Substituent	Found	Lit., M.P., °C.	Apparent pK_a	*p*H at Mid-Point[a]	K × 10^4	Sigma[b]	Specific Rate Constants of the Esters × 1000 (molal^{-1} sec.$^{-1}$)
None	136–137	135–136[c]	3.40	3.45	3.98	0.00	1.48
m-CH_3	135–136[d]	109.5[e]	3.44	3.48	3.63	−0.04	1.61
p-CH_3	148–149 dec.	150[f]	3.53	3.57	2.95	−0.13	1.25
o-Cl	134–135	132–133 dec.[f]	3.26	3.32	5.50	0.14	2.97
m-Cl	140–143	140–141[g]	3.15	3.23	7.08	0.25	2.87
p-Cl	192–194	192–193 dec.[h]	3.20	3.27	6.31	0.20	2.25
m-NO_2	143	143.7–144.4[h]	2.96	3.08	11.0	0.44	5.73
p-NO_2	202 dec.	201–202[i]	2.87	3.02	13.5	0.53	7.75
m-OCH_3	107–108	109[j]	3.36	3.41	4.37	0.04	1.73
p-OCH_3	139 dec.	141–143 dec.[k]	3.63	3.66	2.34	−0.23	1.19

[a] The *p*H at the half-neutralization point is recorded for comparison with the apparent pK_a values obtained using equation 1. [b] Log K_{ion} (substituted phenylpropiolic acid) −log $K°_{ion}$ (phenylpropiolic acid). [c] T. W. Abbott, *Org. Syntheses*, **Coll. Vol. II**, 515 (1943). [d] From CS_2. *Anal.* Calcd. for $C_{10}H_8O_2$: C, 74.99; H, 5.03; Neut. equiv., 160.2. Found: C, 75.03, 75.10, H, 4.85, 4.89; Neut. equiv., 162.6. [e] W. Müller, *Ber.*, **20**, 1212 (1887). [f] F. G. Baddar, L. S. Assal, and N. A. Doss, *J. Chem. Soc.*, 461 (1955). [g] M. M. Otto, *J. Am. Chem. Soc.*, **56**, 1393 (1934). [h] M. S. Newman and S. H. Merrill, *J. Am. Chem. Soc.*, **77**, 5549 (1955). [i] F. G. Baddar and L. S. Assal, *J. Chem. Soc.*, 1267 (1948). [j] J. I. Jones and T. C. James, *J. Chem. Soc.*, 1600 (1935). [k] E. Bergmann and A. Bondi, *Ber.*, **66**, 278 (1933).

recalibrated against aqueous buffer before each titration.

Apparent ionization constants were calculated using the equation[15]:

$$pK_a = pH - \log \frac{[salt] + [H^+]}{[acid] - [H^+]} \qquad (1)$$

In these calculations, corrections for liquid junction potentials were neglected; unit activities were assumed and *p*H readings were assumed to be equal to the logarithms of the reciprocals of the hydrogen-ion concentrations.

Two titrations were made on each acid at 24°. There was no change in pK_a values calculated at 30%, 50% and 70% neutralization. Maximum deviation of pK_a values between pairs of determinations was ±0.015 units. The results are listed in Table II. A plot of log K/K_0 of the ionization of the *m*- and *p*-substituted phenylpropiolic acids in 50% aqueous ethanol against Hammett sigma values showed the expected linearity. The slope of the line calculated by the method of least squares is +0.69 (see Fig. 1).

(15) S. Glasstone, *Textbook of Physical Chemistry*, Second Edition, D. Van Nostrand Co., Inc., New York, N. Y., 1946, p. 1003.

C. Kinetic measurements. The reaction was followed by measuring the rate of evolution of carbon monoxide.

1. Apparatus. The reaction flask was a 35-ml. or 50-ml. round bottom flask with a wide neck (20 mm. OD) which was 180 mm. long. The flask was fitted with a 19/38 tapered joint and a side arm of 1 mm. bore capillary tubing. A 13 mm. tube closed at the lower end and with a 19/38 tapered joint in the center extended to the bulb of the flask. A tungsten hook was sealed into the lower end of the tube. A sample cup (13 mm. OD × 19 mm. long) was fitted with a platinum loop so that it could be suspended from the tungsten hook.

The flask was supported in the constant temperature bath by means of a clamp which was attached to a shaking device. The sample cup dropped from the hook into the flask when operation of the shaker was started.

The capillary side arm of the reaction flask was connected to a cooling coil which in turn was connected (using capillary tubing) by way of a three-way stopcock to a Fisher Precision Hempel Gas Burette. One of the side arms of the three-way stopcock served as a vent to the atmosphere.

2. Kinetic experiments. A typical run was carried out as follows. Two millimoles of tetracyclone and 10 ml. of phenylcyclohexane were placed in the reaction flask. Three car-

borundum boiling chips were added. The flask was flushed with nitrogen. It was then stoppered with a 19/38 tapered cap and placed in the constant temperature bath. The side-arm of the flask was connected to the cooling coil. Twenty min. were allowed for the flask to reach the temperature of the bath (separate experiments had shown that 13 min. were adequate) with the flask vented to the atmosphere by way of the three-way stopcock. At the end of this time, the three-way stopcock was adjusted so that the flask was connected to the gas burette. Mercury was the confining liquid in the gas burette.

When the volume in the gas burette had remained constant for 0.5 hr., the cap on the reaction flask was replaced by the jointed tube and the pendant sample cup which contained 2 mmoles of the substituted methyl phenylpropiolate. After an additional 15 min., the initial volume was recorded and the timer and the shaker were started simultaneously. The sample cup dropped into the reaction flask when the shaker was started. Volume readings were taken at one-minute intervals initially, but at longer intervals at the reaction proceeded. Errors in volume readings were minimized by a preliminary equalization of the pressures of the system and the compensating tube just before the final reading was to be taken. Then the stopcock was closed again, the pressures were equalized exactly and the volume recorded. The reaction was followed to 80–94% completion. About 80 readings were taken during each run and used in the calculation of the specific rate constant. A portion of these readings for the reaction between tetracyclone (2 mmole) and methyl phenylpropiolate (2 mmole) in phenylcyclohexane (10 ml.) at 175.6° are shown for a typical run:

t, min.	Vol. CO, ml.	t, min.	Vol. CO, ml.
0.00	4.50	140.00	40.00
20.00	18.05	160.00	41.32
40.00	25.65	180.00	42.20
59.00	30.31	200.00	42.95
80.00	33.90	220.00	43.72
100.00	36.50	240.00	44.50
120.00	38.50	Infinity	53.50 (calcd.)

The rate constants for the Diels-Alder reaction of the esters are listed in Table II. Each rate constant is the average of two or more runs.

Rate constants are expressed in terms of molalities rather than molarities because of the uncertainty of the volume of the solution at 175.6°. Assuming that the density of the solution at 175.6° is the same as that of the phenylcyclohexane at 175.6° (0.82 g./ml.), the specific rate constants in units of sec.$^{-1}$ molar^{-1} are 10% greater than the specific rate constants (sec.$^{-1}$ molal^{-1}) reported in this study. This difference does not affect the relative values of the rate constants. The same values are found for the Hammett rho constant and for the energies of activation regardless of the concentration units used for the specific rate constants. An error in the energy of activation could result because the change of about 2% in the molar concentration due to the 30° change in temperature produces a corresponding error in the specific rate constant. The error in log k (from which energy of activation is derived) is less than the error in k.

The second order rate constants were obtained graphically from a plot of $1/V_\infty - V_t$ vs. t, where V_∞ is the final volume of carbon monoxide and V_t is the volume at time, t. Straight line relations were observed in all instances. V_∞ could not be determined conveniently experimentally because it increased slowly for several days. Accordingly, it was calculated from successive fractional lives by the following method.

3. Calculation of the final reading. In the second order reaction in which the reactants are present in equivalent amounts,

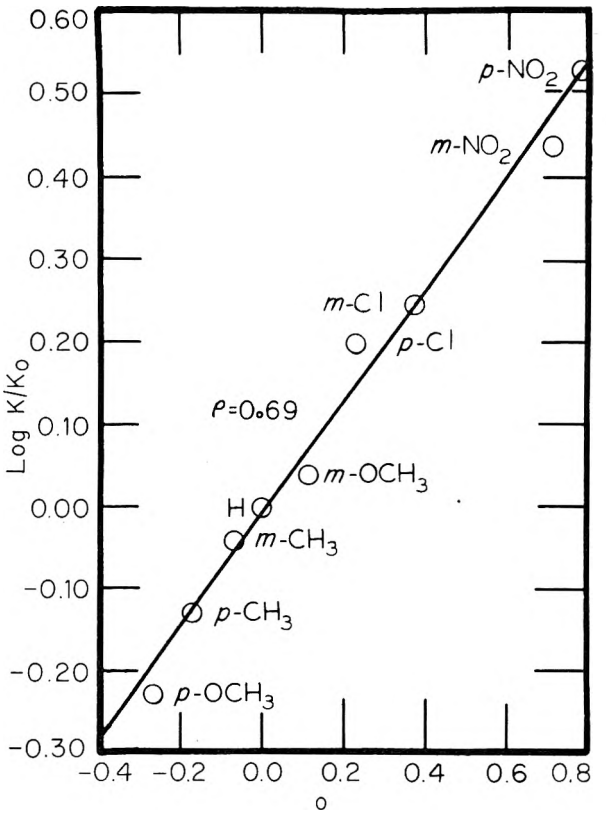


Fig. 1. Relationship between log K/K_0 for substituted phenylpropiolic acids and Hammett's σ-constants

$$kt = \frac{1}{c} - \frac{1}{c_0} = \frac{1}{x_\infty - x} - \frac{1}{x_\infty} \qquad (2)$$

where x is the amount by which the concentration of a product has increased since $t = 0$, and $x = 0$ at $t = 0$. Suppose x is experimentally known as a function of t over some limited time interval. Equation (2) will apply if the x, t axes are translated so that the experimental curve begins at the origin. Suppose that in the time interval $(0, t_1)$ the reaction concentration falls to the fraction α of its initial value, and in the interval (t_1, t_2) again falls to the same fractional amount so that $c_1 = \alpha c_0$, $c_2 = \alpha^2 c_0$, $x_1 = c_0(1 - \alpha)$, and $x_2 = c_0(1 - \alpha^2)$. Then $x_2/x_1 = 1 + \alpha$; and, from (2), $t_2/t_1 = 1 + 1/\alpha$. These relations may be used to evaluate x_∞ and hence k, as follows. For an arbitrarily chosen α, a value of t_1 is estimated from the graph. Then t_2 is calculated from the last equation. The corresponding value of x is read from the graph and is compared with $x_2 = x_1(1 + \alpha)$. Successive approximations of t_1 are made until consistent values are obtained. Now x_∞ is given by $x_1/(1 - \alpha)$ and values of k may be calculated from Equation 2.

In the present work x_∞ was calculated for $\alpha = 0.5$and checked for values of α equal to 0.6 and 0.7. The agreement was excellent.

4. Isolation of products. Methyl pentaphenylbenzoate was filtered from the reaction mixtures from several runs. The yield of ester, m.p. 341–342° (rep. m.p. 342°[7]) was 80.3%. An additional 18% of ester was obtained by concentration of the filtrates.

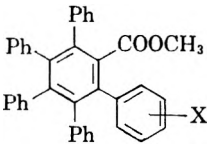
The remaining esters were prepared by heating one equivalent of tetracyclone with 1.1 equivalents of substituted phenylpropiolic ester at 175° overnight. The properties are recorded in Table III.

RESULTS

A plot of log K/K_0 of the ionization of the *m*- and

TABLE III

PHYSICAL PROPERTIES OF METHYL 2-ARYL-3,4,5,6-TETRAPHENYLBENZOATES



X	M.P., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Other Element, % Calcd.	Other Element, % Found
m-CH_3	306–307	88.00	87.95	5.83	6.09		
p-CH_3	297–298	88.00	87.88	5.83	5.91		
o-Cl	331–332	82.44	82.46	5.05	5.03	6.58	6.25
m-Cl	309–310	82.44	83.05	5.05	5.05	6.58	6.43
p-Cl	284–285	82.44	82.51	5.05	5.08	6.58	6.72
m-NO_2	260–261	80.86	81.21	4.95	5.04	2.49	2.40
p-NO_2	272–274	80.86	81.15	4.95	5.13	2.49	2.55
m-OCH_3	255–256	85.37	85.54	5.66	5.36		
p-OCH_3	256–257	85.37	85.70	5.66	5.62		

p-substituted phenylpropiolic acids in 50% aqueous ethanol against Hammett σ constants showed the expected linearity. The value of the constant obtained from the slope by the method of least squares was +0.69. The correlation coefficient,[16] r, was 0.99, the standard deviation,[16] s, was 0.03, and n was 9. Newman and Merrill[17] obtained a ρ constant of +0.81 from their measurements in 35% dioxane.

Our *relative* acid strengths, expressed as log K/K_0, correspond closely to those reported by Newman and Merrill[17] for these same acids in 35% aqueous dioxane.

The logarithms of the rate constants have been plotted against log K/K_0. The slope of the line calculated by the method of least squares is +1.10, with $r = 0.97$, $s = 0.07$, and $n = 9$ (see Fig. 2). Rates for the *o*-chloro ester were omitted in the calculation of the rho value.

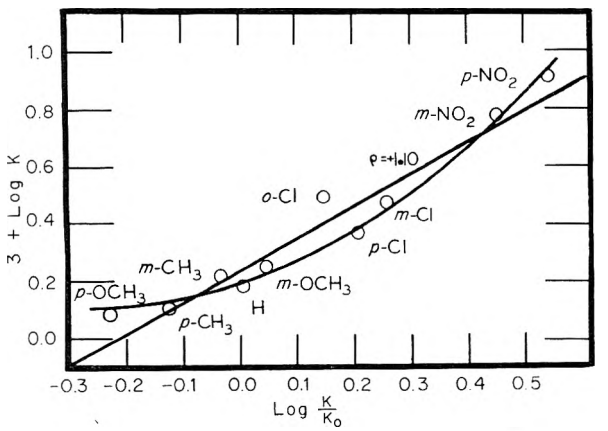


Fig. 2. Relationship between log k and log K/K_0 for substituted phenylpropiolic acids

Specific rate constants of the methyl esters of the *o*- and *p*-chlorophenylpropiolic acids were determined at three temperatures in order to permit calculation of the energies and entropies of activation. Results are shown in Table IV.

TABLE IV

SPECIFIC RATE CONSTANTS (MOLAL^{-1} SEC.$^{-1}$) AT VARIOUS TEMPERATURES FOR THE REACTION BETWEEN METHYL CHLOROPHENYLPROPIOLATES AND TETRACYCLONE

Subst.	*t*, °C.	1000 k
o-Cl	166.5	1.93
	175.6	2.97
	196.0	7.17
p-Cl	166.2	1.49
	175.6	2.25
	195.2	5.65

Energies and entropies of activation calculated from the data in Table IV are recorded in Table V. The entropy of activation was calculated in accordance with the usual equations[18]

$$k = Ae^{-E_a/RT} \quad \text{and} \quad A = e\frac{kT}{h}e^{\Delta S^{\ddagger}/R}$$

TABLE V

ENERGIES AND ENTROPIES OF ACTIVATION TETRACYCLONE WITH METHYL ESTERS OF *o*- AND *p*-CHLOROPHENYLPROPIOLIC ACID

	o-Cl	*p*-Cl
E_a, Kcal. mole^{-1}	18.2[a]	18.9[a]
$\log_{10}$ A, sec.$^{-1}$, molal^{-1}	6.3	6.6
$\Delta S^{\ddagger}$ at 175.6°C., e.u.[b]	−32.3	−31.3
$\Delta S^{\ddagger}$ at 175.6°C., e.u.[c]	−18.6	−17.6

[a] Correlation coefficients,[16] r, and standard deviations,[16] s; *o*-Cl, $r = 1.000$, $s = 0.00$, $n = 3$; *p*-Cl, $r = 0.996$, $s = 0.035$, $n = 3$. [b] Standard state of 1 molal solution. [c] Standard state of 1 mole per gram of solvent.

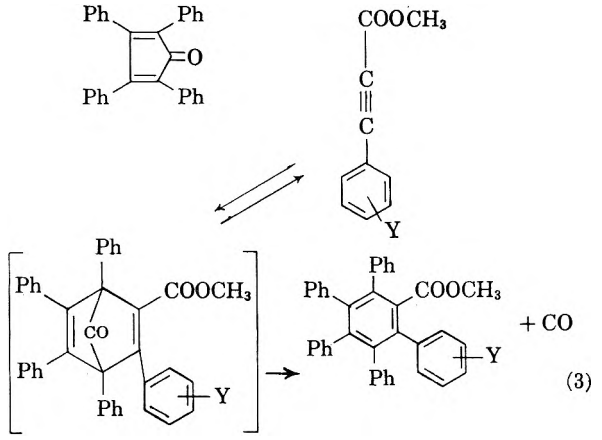
(16) H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953).

(17) M. S. Newman and S. H. Merrill, *J. Am. Chem. Soc.*, **77**, 5552 (1955).

(18) S. Glasstone, K. J. Laidler, and H. Eyring, *The Theory of Rate Processes*, McGraw-Hill Book Co., Inc., New York, N. Y., 1941, pp. 199, 417.

DISCUSSION

There is no drift in second-order rate constants in reactions followed up to 94% completion. This result is consistent with either the formation of the adduct in the rate-determining step, followed by rapid elimination of carbon monoxide, or the formation of the adduct by a rapid equilibrium followed by the elimination of carbon monoxide in the rate-determining step (Equation 3). These



(3)

two alternatives are kinetically indistinguishable by merely measuring the rate of evolution of carbon monoxide.[19] However, the first alternative is favored because the energies and entropies of activation of the reaction are comparable to those found in typical Diels-Alder reactions.[20] In the study of a Diels-Alder reaction in which hydrogen was eliminated from the adduct, Jarvie and Janz[21] also found that the kinetic parameters fell within the range for typical Diels-Alder association reactions. The absence of a marked difference in the entropies of activation found in this study from those of Diels-Alder reactions between simpler adducts is surprising in view of the presence of the phenyl groups in tetracyclone. This result, however, is in accordance with Wassermann's conclusion[22-24] that the transition state is non-planar.

The reactivities of the esters of the meta- and para-substituted phenylpropiolic acids are in the order expected from the values of the sigma constants of the corresponding acids. The positive sign means simply that the reaction is accelerated by electron-withdrawing substituents. The rates are in the same sequence as the corresponding sigma values except for *m*-CH_3 and *o*-Cl. With *m*-methyl the substituted ester is more reactive than the unsubstituted one. Jaffe[16] has noted that substituent constants may vary due to polarizability effects, and that occasionally, *m*-methyl substituents appear to be electron-attracting. In a study of the chlorination of *p*-(substituted benzyloxy)benzoic acids, Jones[25] found that the *m*-methyl group produced a greater acceleration of the reaction than the *p*-methyl group did.

With *o*-Cl the σ value is in line when compared with the unsubstituted ester. However, when compared with the *m*- and *p*-Cl compounds, it is out of line, being too rapid. Increases in the rate of acid hydrolysis[17] and in the rate of basic hydrolysis[26] of substituted phenylpropiolic esters have also been observed previously.

The points on the Hammett plot appear to exhibit a systematic curvature. Swain and Langsdorf[27] noted this curvature in polar reactions and attributed it to differences in the effectiveness of resonance interactions between the substituents and reacting center in the transition states. In the present study, the rate of reaction is greater than the expected value for both the *p*-nitro- and the *p*-methoxy- substituted esters. The effect observed here may be due to a solvent effect or to polarizability of the triple bond by strongly electron-attracting or electron-withdrawing groups. The curvature of the plot may be due to the electronegativity of the triple bond[28,29] resulting in unequal interactions with positive and negative substituents. This can be determined from a pending study of substituted cinnamic esters with tetracyclone. (Wolinski[30] reports that pentaphenylbenzoic acid is formed, presumably with the loss of both carbon monoxide and hydrogen, from the reaction between tetracyclone and cinnamic acid.)

DeWitt, *et al.*,[5] noted a curvature in a Hammett plot for the reaction between substituted 1-phenylbutadienes with maleic anhydride in dioxane. They attributed this curvature to the polarizability of the *p*-methoxy group. The Hammett rho value of the reaction at 25° was −0.685. Okamoto and Brown[31] showed that DeWitt's data fitted a plot of log *k* *vs.* σ^+ much better than a plot of log *k* *vs.* σ. (σ^+ is the substituent constant applicable to electrophilic reactions.) On the basis of this result, Okamoto and Brown concluded that the Diels-Alder reaction proceeds by the radical-ion-pair mechanism which was postulated by Woodward.[32]

(19) A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, John Wiley & Sons, Inc., New York, N. Y., 1953, pp. 179–182.
(20) Footnote 19, p. 101.
(21) J. M. S. Jarvie and G. J. Janz, *J. Phys. Chem.*, **60**, 1430 (1956).
(22) A. Wassermann, *J. Chem. Soc.*, 828 (1935).
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(31) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22**, 485 (1957).
(32) R. B. Woodward, *J. Am. Chem. Soc.*, **64**, 3058 (1942).

One would expect a correlation of the reactivity of the dienophile with Hammett (nucleophilic) σ values to go hand in hand with correlation of the reactivity of the diene with electrophilic σ^+ values. Moreover, reactions which are known to proceed by a free-radical mechanism have been correlated with the Hammett equation.[33] In some cases the substituent effects are quite large. The difference between a primary radical mechanism with secondary electronic effects on one hand and a radical-ion mechanism on the other is a matter of degree rather than of kind. Therefore, a clear-cut decision between them is not possible. This result is consistent with current interpretations of the electronic processes involved in a reaction proceeding through a cyclic transition state.

The reactivity of the *o*-chloro ester is greater than would be expected from the value of the sigma constant of the corresponding acid. The energies and entropies of activation for the *o*- and *p*-chloro esters are very similar and do not shed any light on the cause of this effect. Enhanced reactivities of the ortho derivatives were also noted by Newman and Merrill[17] for the esterification of substituted phenylpropiolic acids. Roberts and Carboni[26] found that the saponification rates of the *o*-esters are rather faster than would be expected from the rates and ionization constants of the *m*- and *p*-substituted acids although the rates of reaction of the *o*-acids with diphenyldiazomethane in ethanol and in dioxane fit the Hammett plot very well. The reason for the enhanced activities of the *o*-esters on the Diels-Alder reaction and in esterification and hydrolysis reactions is not known.

Acknowledgment. The authors are happy to express their appreciation to the Stauffer Chemical Company for making their facilities available for this investigation and to Mr. A. V. R. Crain for preparing the methyl *m*-chloro- and *p*-chlorophenylpropiolates.

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(33) J. E. Leffler, *The Reactive Intermediates of Organic Chemistry*, Interscience Publishers, Inc., New York, N. Y., 1956, pp. 238–241.

Notes

A department for short papers of immediate interest.

3-Hexyl- and 3-Octyladipic Acids[1,2]

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Received September 30, 1957

In the course of studies on the physical properties of liquids designed as potential lubricating oils, certain glycol ethers were prepared. The present report describes the preparation of two intermediates for glycols which were desired for these studies. Full details of their conversion to glycols and glycol ethers will be published elsewhere. The hexyl group is "normal" and the octyl group is derived from diisobutylene. Thus the octyl acid is 3-(2′,4′,4′-trimethylpentyl)adipic acid.

EXPERIMENTAL[3,4]

4-Hydroxycaprophenone was prepared from 129 g. (1.37 moles) of phenol, 186 g. (1.40 moles) of aluminum chloride, and 184 g. (1.37 moles) of caproyl chloride. The product distilled to give two fractions: (*1*) 2-hydroxycaprophenone, 98.2 g. (37.5%), b.p. 104–106°/1.0 mm. (reported 142–143°/10 mm.[5]); and (*2*) 4-hydroxycaprophenone, 91.5 g. (35%), b.p. 155–158°/1.0 mm. (reported 207–208°/10 mm.[5]).

4-Hexylphenol. Distillation of the product of Clemmensen reduction of 4-caprophenone afforded 91.5 g. (78%) of water-white 4-hexylphenol, b.p. 110–114°/1.0 mm. (reported 146–147°/10 mm.[5]).

4-Hexylcyclohexanol. The 4-hexylphenol was reduced using Raney nickel[6] at 150° and 100 atm. After an induction period of 15–30 min., the reduction started and proceeded rapidly, being complete in 3 hr. The catalyst was filtered off, and the alcohol (from the catalyst) was distilled out of the filtrate. The crude 4-hexylcyclohexanol was not purified but was converted directly to 3-hexyladipic acid, as described below.

3-Hexyladipic acid. A solution of 50% nitric acid (100 g., 0.80 mole) was heated nearly to boiling and 40 mg. of ammonium vanadate was added. The mixture was stirred and 44.0 g. (0.24 mole) of crude 4-hexylcyclohexanol was added slowly, the temperature being maintained at 60–65° by means of an ice bath. After complete addition the mixture was stirred for an additional hour and then was cooled. The acid formed a solid cake which was filtered off, washed with water to remove nitric acid and then was taken up in ether, washed thoroughly and was distilled at 176–179°/0.2 mm. to give 36.0 g. (65%) of 3-hexyladipic acid. Recrystallization from 70–90° petroleum ether afforded white plates, m.p. 71–72°.

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.62. Found: C, 62.84; H, 9.73.

4-Octylcyclohexanol. A 120 g. batch of 4-octylphenol[7] was hydrogenated at 150° and 1000 p.s.i. using a Raney nickel catalyst. There was obtained 100 g. (81%) of 4-octylcyclohexanol, b.p. 100–104°/0.3 mm.

3-Octyladipic acid. The oxidation of 4-octylcyclohexanol (100 g., 0.472 mole) was carried out as with 4-hexylcyclohexanol using 200 g. of 50% nitric acid and 95 mg. of ammonium vanadate. Upon completion of the reaction the mixture was placed in an ice bath and allowed to stand thus overnight. The nitric acid was decanted from the pasty mass which was then washed several times with water and dissolved in ether. The ethereal solution was thrice washed with water and was dried over magnesium sulfate. Evaporation afforded a yellow oil which rapidly solidified. Recrystallization from benzene yielded 3-octyladipic acid as colorless platelets, m.p. 133–135°, 68.5 g. An additional crop of 8 g. was obtained by concentration of the mother liquor to half its volume; thus the over-all yield was 76.5 g. (63%). Further recrystallization from cyclohexane-ethyl acetate raised the m.p. to 136–137°.

Anal. Calcd. for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 65.26; H, 10.03.

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(1) Work done under contract No. W-33-038-ac-21457, Project MX-982 between the Wright Air Development Center, U. S. Air Force, and the Engineering Research Institute of the University of Michigan.

(2) Abstracted from a portion of WADC Technical Report 53-45, June 1953. Released for publication by Mr. Harold Rosenberg, Senior Materials Laboratory, Directorate of Research.

(3) Melting points and boiling points are uncorrected.

(4) Microanalyses by Microtech Laboratories, Skokie, Ill.

(5) G. Sandelescu and A. Girard, *Bull. soc. chim.* (4), **47**, 1300 (1930).

(6) A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).

(7) Kindly supplied by Rohm & Haas Co., Philadelphia, Pa. The substance is prepared by alkylating phenol with diisobutylene.

Halogen Derivatives of 8-Aminoquinoline

EVERETT C. HURDIS

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In the course of work on the preparation of several new "ferroin" type oxidation-reduction indicators, it became of interest to synthesize certain trihalo-8-aminoquinolines. The specific derivatives desired were those in which all the available benzene ring positions (that is, positions 5, 6, and 7) are substituted by chlorine and/or bromine. Such derivatives have not heretofore been reported. However, it is known that the 5 and 7 positions, being strongly activated by the amino group, are easily halogenated directly.[1,2] Therefore, it was judged that the desired trihalo-8-

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(2) R. C. Elderfield and E. F. Claflin, *J. Am. Chem. Soc.*, **74**, 2953 (1952).

TABLE I

HALOGEN DERIVATIVES OF 8-AMINOQUINOLINE

Compound	M.P., °C.[a]	Nitrogen Calcd.	Nitrogen Found	Bromine Calcd.	Bromine Found	Chlorine Calcd.	Chlorine Found	Yield %
8-Amino-5,6,7-tribromoquinoline	154.5–155.5	7.36	7.38	62.94	62.66			81
8-Amino-5,7-dibromo-6-chloroquinoline	169–169.5	8.33	8.30	47.5	45.9	10.5	11.2	79
8-Amino-6-bromo-5,7-dichloroquinoline	160.5–161.5	9.60	9.57	27.4	26.6	24.3	23.9	77
8-Amino-5,6,7-trichloroquinoline	169–170	11.32	11.42			43.0	42.7	67
8-Amino-5,7-dichloroquinoline	125.5–126.5	13.15	13.54			33.28	33.36	60

[a] All melting points are corrected.

aminoquinolines would be readily preparable by direct bromination or chlorination of the known compounds 8-amino-6-bromoquinoline and 8-amino-6-chloroquinoline. Experimentally it proved possible to verify this prediction. 8-Amino-6-bromoquinoline and 8-amino-6-chloroquinoline were prepared by a modification of the method of Richter and Smith.[3,4] Bromination of these compounds in acetic acid solution yielded 8-amino-5,6,7-tribromoquinoline and 8-amino-5,7-dibromo-6-chloroquinoline respectively. By chlorination, using sulfuryl chloride in acetic acid solution, the 8-amino-6-bromoquinoline gave 8-amino-6-bromo-5,7-dichloroquinoline, while 8-amino-6-chloroquinoline gave 8-amino-5,6,7-trichloroquinoline. Convenient procedures were developed for these reactions, giving the desired compounds in satisfactory yields and high purity. Analytical and yield data for the individual compounds are listed in Table I.

The structures of these trihalo-8-aminoquinolines, as given, were assigned on the following basis: The pyridine ring in 8-aminoquinoline is known to be inert to halogenation under mild conditions. Thus, bromination[1] and chlorination[2] of 8-aminoquinoline have been found to give substitution only at the 5 and 7 (benzene ring) positions. In the work reported here, 8-amino-6-bromoquinoline and 8-amino-6-chloroquinoline were halogenated under very mild conditions, such as were used for 8-aminoquinoline.[1,2] Therefore, the assumption could be made, with considerable confidence, that again only the 5 and 7 positions were substituted and that 5,6,7-trihalo-8-aminoquinolines resulted.

Elderfield and Claflin[2] have reported the preparation of 8-amino-5,7-dichloroquinoline by the action of chlorine gas on 8-aminoquinoline. Their yield of crude product, m.p. 113–116°, was 31%. It was found that this compound could be prepared in greater yield and higher purity by using sulfuryl chloride for the chlorination. By this means a 60% yield of material, m.p. 125.5–126.5°, was obtainable. (Analytical data for 8-amino-5,7-dichloroquinoline are listed in Table I.) The 8-aminoquinoline used for preparing this compound was made in excellent yield by a convenient modification of the method of Woroschtzow and Kogan.[5]

(3) F. P. Richter and G. F. Smith, *J. Am. Chem. Soc.*, **66**, 396 (1944).

(4) G. F. Smith and F. P. Richter, *Phenanthroline and Substituted Phenanthroline Indicators*, G. Frederick Smith Chemical Company, Columbus, Ohio, 1944, pp. 12 and 13.

EXPERIMENTAL

8-Aminoquinoline. Woroschtzow and Kogan[5] reported the preparation of 8-aminoquinoline from 8-quinolinol in 89% yield. By modifying their method somewhat, the inconvenience of working with sulfur dioxide gas was avoided, and an even higher yield was obtained. A mixture of 145.2 g. (1 mole) of 8-quinolinol, 335 g. of ammonium sulfite monohydrate, 153 ml. of 28% aqueous ammonia, and 300 ml. of water was charged into a pressure vessel of 1300 ml. capacity. The mixture was heated with constant mechanical shaking for 7 hr. at 155°. The shaking was then continued while cooling the reactor to 25–35°. The crude product was removed by filtration, washed with water, dried, and vacuum distilled at 0.5 mm. gauge pressure. A 93% yield of material, m.p. 63–64°, was obtained.

8-Amino-6-bromoquinoline. 6-Bromo-8-nitroquinoline was prepared and reduced according to the directions of Richter and Smith[3,4] (starting with 1 mole of 4-bromo-2-nitroaniline). However, the steam distillation used by Richter and Smith to isolate the product was found to be very time-consuming because of the low volatility of 8-amino-6-bromoquinoline. The product was therefore isolated by the following more convenient procedure. After the stannous chloride reduction, the reaction mixture was poured into 3000 ml. of water and the solution neutralized by aqueous alkali. A solution of 675 g. of sodium hydroxide in 2250 ml. of water was added to dissolve the precipitated hydrous tin oxides. The precipitated crude product was then removed by filtration, dried, and extracted by several portions of hot benzene, totalling 1200 ml. Evaporation of the benzene, followed by recrystallization from hexane and finally vacuum distillation, gave material, m.p. 75–76°. The overall yield from 4-bromo-2-nitroaniline was 49%.

8-Amino-6-chloroquinoline. This compound was prepared from 4-chloro-2-nitroaniline by the same procedure used for 8-amino-6-bromoquinoline. The overall yield of 8-amino-6-chloroquinoline, m.p. 70–71°, was 50%.

Procedure for brominations. The amine (0.03 mole) was dissolved in 30 times its weight of acetic acid and the solution cooled to 15° in an ice water bath. A solution of 10.0 g. of bromine in 60 ml. of acetic acid was then added dropwise with constant mechanical stirring, keeping the temperature between 15° and 20°. After all the bromine had been added, the mixture was warmed to 25° and then poured into 750 ml. water. The small excess of bromine was destroyed by adding 0.3 g. of sodium bisulfite. The precipitate of crude product was removed by filtration, washed with water, dried and recrystallized from acetic acid.

Procedure for chlorinations. The amine (0.06 mole) was dissolved in 5 times its weight of acetic acid and the solution cooled to 10° in an ice water bath. A solution of 16.7 g. of

(5) N. N. Woroschtzow and J. M. Kogan, *Ber.*, **65**, 142 (1932).

sulfuryl chloride (3% excess) in 25 ml. of acetic acid was added slowly with constant mechanical stirring. The mixture was then warmed gradually to room temperature and finally was heated for 20 min. on the steam bath at 70–75°. The reaction mixture was then poured into a solution of 40 g. sodium acetate in 300 ml. water. The precipitate of crude product was removed by filtration, washed with water, dried and recrystallized from acetic acid.

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Some Observations on the Preparation of Salicylamide Esters of Acylated α-Amino Acids

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Acyl salicyclic acid esters frequently have been used as substrates in enzyme and non-enzyme catalyzed hydrolyses because of the ease with which such reactions may be followed spectrophotometrically.[1–8] However, these substrates when used in systems more alkaline than *p*H 5 will be present as the corresponding anions thus introducing a possible complication that would not be encountered with an uncharged substrate. Because of interest in the behavior of neutral as well as anionic substrates our attention was directed to the preparation of acyl esters of salicylamide whose spectral properties and those of the parent phenol[9,10] would be expected to be similar to those of salicyclic acid and its analogous esters.

The successful use of trifluoroacetic anhydride as a condensing agent in the synthesis of benzoyl-DL-phenylalanine α-naphthyl ester[11] suggested the use of this reagent for the preparation of the salicylamide esters of acetyl-DL- and L- and benzoyl-DL- and L-phenylalanine. While the two DL-compounds were obtained in good yield the attempted preparation of benzoyl-L-phenylalanine salicylamide ester gave a racemized product, even when the reaction was conducted at −20 to −30°. This result was not totally unexpected since it is known that many optically active α-acylamino acids are readily racemized in the presence of acetic or trifluoroacetic anhydride[12–16] presumably *via* an intermediate mixed anhydride and oxazolonium ion.[17–20]

The observations of Weygand *et al.*[14–16] and of Schallenberg and Calvin[21] relative to the preparation of optically active α-trifluoroacetamido acid chlorides and their use in the acylation of amines without attendant racemization led us to investigate the usefulness of such acid chlorides in the synthesis of the desired salicylamide esters.

Trifluoroacetyl-DL-phenylalanine was prepared by a procedure similar to that described by Weygand and Leising[15] and was converted to the acid chloride by treatment with phosphorus pentachloride. Reaction of the acid chloride with the sodium salt of salicylamide gave the DL-ester in good yield. However, when the above reaction sequence was repeated with L-phenylalanine a substantially racemized product was obtained.

In order to locate the point at which racemization had occurred the above synthesis was repeated, this time isolating each intermediate and determining its optical purity. As before,[14–17,21] it was found that trifluoroacetyl-L-phenylalanyl chloride could be prepared without difficulty but in contrast to previous experience with the reaction of this acid chloride with aniline,[15,21] its reaction with the sodium or triethylamine salt of salicylamide led to a substantially racemized product.

The absence of racemization in the preparation of trifluoroacetyl-L-phenylalaninanilide[21] and of trifluoroacetyl-L-alaninanilide[15] suggested the desirability of examining the reaction of trifluoroacetyl-L-phenylalanyl chloride with anthranilamide. Because of the poor yields obtained in the ammonolysis of methyl anthranilate,[22,23] the amide was prepared from *o*-nitrobenzamide by reduction

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(2) B. H. J. Hofstee, *Science*, **114**, 128 (1951).
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(5) B. H. J. Hofstee, *Biochim. Biophys. Acta*, **24**, 211 (1957).
(6) H. Brandenberger and R. Hanson, *Helv. Chim. Acta*, **36**, 900 (1953).
(7) H. Brandenberger and W. H. Weihe, *Helv. Chim. Acta*, **38**, 1347 (1955).
(8) The monovalent anion of salicylic acid has a prominent absorption band at 298–300 mμ that is absent in the corresponding ester.
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(16) F. Weygand and M. Reiher, *Ber.*, **88**, 26 (1955).
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with Raney nickel and hydrazine.[24] The reaction of trifluoroacetyl-L-phenylalanyl chloride with anthranilamide, in the presence of triethylamine, gave the desired L-amide in good yield. The synthesis of this latter compound was of importance not only in respect to the interpretation of the reaction of the above acid chloride with salicylamide, *vide ante*, but also because it may be inferred from the spectral properties of anthranilamide and acylated anthranilamides[25] that the spectra of the above amide and anthranilamide would be sufficiently different to permit the use of the former compound as a specific substrate in studies involving α-chymotrypsin where the extent of reaction is to be determined spectrophotometrically. It may be noted that Ellman[26] has found that the α-chymotrypsin-catalyzed hydrolysis of methyl acetyl-L-phenylalaninanthranilate, present in the DL-mixture, may be followed fluorometrically.

The reaction of trifluoroacetyl-L-phenylalanyl chloride with anthranilamide to give the L-amide and with salicylamide to give the DL-ester raises the question of whether racemization occurred during the formation of the ester or in a subsequent process. An attempt was made to answer this question by a proposed synthesis of methanesulfonyl-L-phenylalanine salicylamide ester through the intermediate methanesulfonyl-L-phenylalanyl chloride which might be expected to exhibit less tendency to form an oxazolonium chloride than the trifluoroacetyl derivative even though there is no evidence presently available that such a cyclic isomer can be formed from the latter compound. However, when the proposed synthesis was tested with DL-phenylalanine the yields were so unsatisfactory that no attempt was made to use the procedure for the preparation of the L-compound. Thus, while the point at which racemization occurred in attempted preparation of trifluoroacetyl-L-phenylalanine salicylamide ester remains unknown it should be noted that although phenolic esters would be expected to be subject to facile racemization Iselin *et al.*[27] recently have reported the preparation of the *p*-nitrophenyl esters of carbobenzoxy-L-leucine, carbobenzoxy-L-valine, and carbobenzoxy-*S*-benzyl-L-cysteine by the condensation of the appropriate acid with di-*p*-nitrophenyl sulfite in the presence of pyridine. The applicability of this latter procedure to the synthesis of optically active esters of salicylamide and various acylated α-amino acids is currently under investigation.

Bader and Kontowicz[28] reported the successful preparation of phenolic esters by simply heating the acid with phenol in the presence of polyphosphoric acid. The application of this procedure to the attempted synthesis of benzoylglycine salicylamide ester gave none of the desired product but instead benzoic acid, disalicylamide, and a compound $C_{16}H_{19}O_2N_2$ which appeared to arise from the condensation of 1 mole of benzoylglycine and 1 mole of salicylamide with the elimination of 3 moles of water. An attempted condensation of hydrocinnamic acid with salicylamide gave only disalicylamide, the dimer of α-hydrindone, *i. e.*, anhydrobishydrindone,[29] and α-truxene. It is known that disalicylamide may be obtained from salicylamide by reaction with phosphorus pentoxide[30] and in this study it was obtained in good yield using polyphosphoric acid in lieu of the anhydride. It also was found that anhydrobishydrindone was converted into α-truxene with the same reagent. Liebermann[31] and Kipping[29] prepared α-truxene by reaction of α-hydrindone with sulfuric acid and Kipping[29] also isolated anhydrobishydrindone from the reaction mixture. Since Snyder and Werber[32] obtained α-hydrindone and presumably α-truxene from the reaction of hydrocinnamic acid with polyphosphoric acid and 1-methylisoquinoline from the reaction of acetyl-DL-phenylalanine with the same reagent[33] it is clear that polyphosphoric acid offers little or no promise as a condensing agent for the preparation of phenolic esters of acylated α-amino acids because of side reactions involving the substituted phenol and acylated α-amino acid.

The reports of the usefulness of cyanomethyl esters[34–36] in peptide synthesis led to the attempted acylation of salicylamide with acetyl-DL-phenylalanine cyanomethyl ester. However, the desired product was not obtained. Similar results were observed in an attempt to extend the reaction of phenyldiazonium fluoroborate with acetic acid, to give phenyl acetate,[37] to the acylated α-amino acids and in an attempt to effect condensation of salicylamide and an acylated α-amino acid with

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dicyclohexylcarbodiimide.[38–43] In these latter three attempts no reaction was observed in the first and third and in the second only intractable products were formed, presumably arising from the reaction of the diazonium compound with acetonitrile or dimethylformamide which were used as solvents.

EXPERIMENTAL[44,45]

Benzoyl-DL-phenylalanine salicylamide ester. Acylation of 66 g. (0.40 mole) of DL-phenylalanine with 60 g. (0.43 mole) of benzoyl chloride under Schotten-Bauman conditions gave 82.4 g. (78%) of benzoyl-DL-phenylalanine, m.p. 179–182°, lit.,[46] m.p. 181–182°.

A mixture of 10 g. (.037 mole) of the above acid and 12 g. (.057 mole) of trifluoroacetic anhydride was warmed on a steam bath until a clear solution resulted. The excess trifluoroacetic anhydride was removed *in vacuo* and to the orange solution was added 5 g. (.037 mole) of salicylamide. The mixture was warmed on the steam bath for one hour, evaporated to dryness *in vacuo*, the residue washed with cold methanol and dried to give 10.4 g. (73%) of benzoyl-DL-phenylalanine salicylamide ester. Recrystallization from a mixture of dioxane and cyclohexane gave the desired ester, m.p. 198–199°.

Anal. Calcd. for $C_{23}H_{20}O_4N_2$: C, 71.1; H, 5.2; N, 7.2. Found: C, 71.0; H, 5.3; N, 7.2.

The compound gave a positive ferric hydroxamate test, was soluble in dimethylformamide and dioxane and insoluble in water, methanol, and ethanol.

Acetyl-DL-phenylalanine salicylamide ester. Acylation of 9 g. (.054 mole) of DL-phenylalanine with 19.2 ml. (0.21 mole) of acetic anhydride under Schotten-Bauman conditions gave 9.4 g. (84%) of acetyl-DL-phenylalanine, m.p. 152–155°.

The above product (.045 mole) was mixed with 12 g. (.060 mole) of trifluoroacetic anhydride and warmed on a steam bath to effect solution. The excess anhydride was removed *in vacuo*, 5 g. (.037 mole) of salicylamide added and the solution heated for ten minutes on a steam bath. Upon cooling a white solid precipitated. The solid was collected, washed with methanol, and dried to give 9 g. (76%) of acetyl-DL-phenylalanine salicylamide ester. Recrystallization from dimethylformamide gave the desired product, m.p. 208–209°.

Anal. Calcd. for $C_{18}H_{18}O_4N_2$: C, 66.2; H, 5.6; N, 8.6. Found: C, 66.3; H, 5.6; N, 8.7.

The compound gave a positive ferric hydroxamate test, was soluble in acetic acid, Methyl Cellosolve, and dimethylformamide, slightly soluble in acetonitrile and insoluble in water, ethanol, and methanol.

Attempted synthesis of acetyl-L-phenylalanine salicylamide ester using trifluoroacetic acid anhydride as a condensing agent. Acylation of 7.5 g. (.046 mole) of L-phenylalanine with 12 ml. (0.128 mole) of acetic anhydride under Schotten-Bauman conditions gave, after one recrystallization from water, 9.0 g. (94%) of acetyl-L-phenylalanine, m.p. 171–172°. Proceeding as described for the DL-compound 5 g. (.024 mole) of acetyl-L-phenylalanine gave 2.8 g. (37%) of ester, m.p. 207–208°. The low rotation initially observed disappeared upon recrystallization from dimethylformamide. When the recrystallized product was mixed with an authentic sample of the DL-compound the melting point was not depressed.

An attempt was made to conduct the above esterification at −40 to −50° but under these conditions the mixed anhydride was not formed as indicated by the fact that the solution never cleared. At −20° it appeared that the anhydride had formed since a clear solution resulted. Upon the addition of salicylamide the solution remained thick for an extended period. A small amount of racemic product was isolated.

Trifluoroacetyl-DL-phenylalanine salicylamide ester. Acylation of 20 g. (0.121 mole) of DL-phenylalanine with 18.8 ml. (0.119 mole) of trifluoroacetic anhydride as described by Weygand and Leising[15] gave 30.4 g. (95%) of crude trifluoroacetyl-DL-phenylalanine. Recrystallization from a mixture of benzene and hexane gave colorless crystals, m.p. 121–122°, lit.,[21] m.p. 125.6–126.8°. A solution of 5.2 g. (0.0191 mole) of the preceding acid in 100 ml. of dry ether was cooled in an ice-salt bath, an excess of phosphorus pentachloride added portionwise with vigorous shaking and the reaction mixture allowed to stand for three hours with intermittent shaking. The solvent was removed *in vacuo*, the residue washed with petroleum ether (30–60°), collected, and dried to give 4.5 g. (84%) of trifluoroacetyl-DL-phenylalanyl chloride, m.p. 96–98°, lit.[15] m.p. 99–100°.

A solution of 4.5 g. (0.0161 mole) of the above acid chloride in 50 ml. of dry benzene was added to a suspension of 2.4 g. (0.0161 mole) of the sodium salt of salicylamide in dry benzene and the resulting slurry was stirred vigorously at room temperature for twelve hours and at 50° for one hour. The solvent was removed *in vacuo*, the residue washed repeatedly with water, and dried to give 3.6 g. (59%) of the desired ester. Recrystallization from a mixture of ethanol and hexane gave a product, m.p. 223–224° with decomp.

Anal. Calcd. for $C_{18}H_{15}O_4N_2F_3$: C, 56.8; H, 4.0; N, 7.4. Found: C, 56.8; H, 3.9; N, 7.3.

The ester was soluble in hot ethanol and insoluble in water.

Attempted synthesis of trifluoroacetyl-L-phenylalanine salicylamide ester. To a solution of 10 g. (0.0605 mole) of L-phenylalanine in 100 ml. of dry benzene, contained in a 3-necked flask fitted with a mechanical stirrer, dropping funnel, and drying tube, was added with vigorous stirring 9.4 ml. (0.0595 mole) of trifluoroacetic anhydride. The reaction mixture was slowly warmed to 70° and then cooled to room temperature. The colorless solid was collected and dried to give 7.2 g. of trifluoroacetyl-L-phenylalanine, m.p. 117–119°. Removal of benzene and trifluoroacetic acid from the mother liquor gave an additional 4.9 g., m.p. 116–118°. The total yield was 12.1 g. (78%). Recrystallization from a mixture of benzene and hexane gave 10.4 g. of acid, m.p. 119–120°, lit.[21] m.p. 119.4–120.6°. $[\alpha]_D^{25}$ + 35.2 ± 0.6° (c, 2.6% in glacial acetic acid), lit.,[21] $[\alpha]_D^{25}$ + 36.4° (c, 0.4% in glacial acetic acid).

A solution of 7.2 g. (0.0276 mole) of the acid in 250 ml. of dry ether was treated in the usual manner with phosphorus pentachloride. Recrystallization of the crude product from a mixture of benzene and petroleum ether gave 6.5 g. (84%) of trifluoroacetyl-L-phenylalanyl chloride, m.p. 108–110°, lit.[21] m.p. 109.5–111.5°. $[\alpha]_D^{25}$ + 17.1 ± 0.4° (c, 3.3% in glacial acetic acid), lit.[21] $[\alpha]_D^{28.3}$ + 15.5° (c, 0.16% in glacial acetic acid).

Reaction of a solution of 6.5 g. (0.0232 mole) of the acid chloride in 250 ml. of benzene with 3.5 g. (0.0220 mole) of the sodium salt of salicylamide gave 7.6 g. (90%) of a compound m.p. 214.5–218° with decomp. Three recrystallizations from ethanol gave a compound with no optical rotation, m.p. 218–219°. The melting point was not depressed on admixture with an authentic sample of trifluoroacetyl-DL-phenylalanine salicylamide ester, m.p. 223–224°.

Anal. Calcd. for $C_{18}H_{15}O_4N_2F_3$: C, 56.8; H, 4.0; N, 7.4. Found: C, 56.8; H, 4.0; N, 7.2.

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Anthranilamide. Repeated reaction of 100 g. (0.66 mole) of methyl anthranilate with saturated methanolic ammonia over a 5-month period gave an oil. The oil was taken up in ether and hexane added to give 22.2 g. (27%) of anthranilamide, m.p. 108.5–111°, lit.,[22,23] m.p. 109–111°.

A mixture of 33.4 g. (0.2 mole) of *o*-nitrobenzoic acid and 43.6 g. (0.22 mole) of phosphorus pentachloride was shaken until reaction began, the semi-solid mass stirred vigorously and slowly heated to 40°, the deep brown solution cooled and added dropwise to 200 ml. of concd. ammonium hydroxide precooled in an ice-salt bath. The light brown solid was collected and dried to give 26.6 g. (80%) of crude *o*-nitrobenzamide. Recrystallization from methanol gave a product, m.p. 173–176°, lit.[47] m.p. 174–176°.

To a warm solution of 26.6 g. (0.16 mole) of the above amide and 16 g. (0.53 mole) of anhydrous hydrazine in 400 ml. ethanol was added a small amount of Raney nickel and the solution was heated for three hours. More Raney nickel was added and the solution heated under refluxing conditions for an additional 30 min. The catalyst was removed, the solution heated with Norit, filtered, and the solvent removed *in vacuo*. The resultant oil was cooled and the solid recrystallized from a mixture of ethanol and hexane to give 16.5 g. (77%) of anthranilamide, m.p. 109–110°, lit.[22,23] m.p. 109–111°.

Trifluoroacetyl-L-phenylalanine anthranilamide. Trifluoroacetyl-L-phenylalanine, $[\alpha]_D^{26}$ + 17.3 ± 0.3° (c, 2% in ethanol), $[\alpha]_D^{25}$ + 35.3 ± 0.4° (c, 2% in glacial acetic acid) was prepared as before. Three and two tenths g. (0.0123 mole) of the above acid was converted into the acid chloride as described above. The acid chloride was dissolved in dry ether, the ethereal solution added to 1.36 g. (0.01 mole) of anthranilamide in dry ether, 2 g. (0.02 mole) of triethylamine added, and the solution stirred at room temperature for 24 hr. The solution was freed of triethylamine hydrochloride and the ether removed *in vacuo*. Recrystallization of the residue from ethanol gave 1.86 g. (49%) of the desired amide, m.p. 191.5–192.0°, $[\alpha]_D^{25}$ −48.8 ± 0.8° (c, 1.3% in dimethylformamide).

Anal. Calcd. for $C_{18}H_{16}O_3N_3F_3$: C, 57.0; H, 4.3; N, 11.1. Found: C, 56.9; H, 4.2; N, 11.0.

Methanesulfonyl-DL-phenylalanine salicylamide ester. Acylation of 25 g. (0.152 mole) of DL-phenylalanine with 12 ml. (0.52 mole) of methanesulfonyl chloride as directed by Helferich and Grünert[48] gave 8.8 g. (0.036 mole) of product, m.p. 96–99°. Recrystallization of this substance from a 1:5 mixture of benzene and acetic acid gave 7.2 g. (19%) of methanesulfonyl-DL-phenylalanine, m.p. 101–102°, lit.,[48] m.p. 104°. Reaction of 7.2 g. of the above acid with an excess of phosphorus pentachloride gave methanesulfonyl-DL-phenylalanyl chloride, as a yellow oil, which was dissolved in 100 ml. of dry benzene. To this solution was added 3.9 g. (.0226 mole) of the sodium salt of salicylamide, the suspension vigorously stirred and heated at 40° overnight. The solid was collected, washed repeatedly with cold water, and recrystallized twice from a mixture of benzene and hexane to give 0.48 g. (1%) of the desired product, m.p. 153.8–155°.

Anal. Calcd. for $C_{17}H_{18}O_5N_2S$: C, 56.3; H, 5.0; N, 7.7. Found: C, 56.2; H, 5.4; N, 7.6.

Reaction of salicylamide with polyphosphoric acid. A mixture of 150 g. of polyphosphoric acid and 41.1 g. (0.3 mole) of salicylamide was heated on a steam cone for 24 hr. The deep red solution was diluted with 400 ml. of hot water, the remaining solid collected and dried *in vacuo*. A colorless crystalline solid separated from the filtrate on cooling. This solid proved to be salicylamide. Removal of most of the water gave a total of 24 g. of salicylamide. Thus, from the remaining 17.1 g. (0.125 mole) of salicylamide there was obtained 8.9 g. (54%) of disalicylamide. Three recrystallizations from hot water gave a product m.p. 188–190°, lit.[30] m.p. 197–199°.

Anal. Calcd. for $C_{14}H_{11}O_4N$: C, 65.4; H, 4.3; N, 5.5. Found: C, 65.4; H, 4.4; N, 5.5.

Reaction of hippuric acid with polyphosphoric acid. Reaction of 36 g. (0.2 mole) of hippuric acid with polyphosphoric acid in a manner analogous to that described above gave 26 g. of starting material. There also sublimed from the reaction mixture 4 g. of benzoic acid, m.p. 121–123°; anilide, m.p. 158–159.5°. Thus, based upon the unrecovered starting material, 65% of the hippuric acid was converted to benzoic acid.

Reaction of salicylamide and hippuric acid with polyphosphoric acid. A solution of 9 g. (0.05 mole) of hippuric acid and 10 g. (0.073 mole) of salicylamide in 150 g. of polyphosphoric acid was heated on a steam bath for 24 hr. during which time 2.1 g. of benzoic acid sublimed into the neck of the flask. The reaction mixture was diluted with water, and triturated with 5% aqueous sodium carbonate to give a brown clay-like friable mass. The dark brown solid was collected, dried, and powdered. Acidification of the aqueous sodium carbonate solution gave a small amount of disalicylamide, m.p. 186–189°. The brown solid was extracted with ethyl acetate, the solution filtered through 8 cm. of activated alumina, and the yellow filtrate evaporated to dryness to give 3.8 g. of a substance which was very slightly soluble in 5% aqueous hydrochloric acid, was readily oxidized by aqueous potassium permanganate, rapidly decolorized a solution of bromine in carbon tetrachloride, gave a negative ferric chloride test and a negative ferric hydroxamate test. Recrystallization of the crude product from ethanol gave light yellow needles, m.p. 131.5–132.5°.

Anal. Calcd. for $C_{16}H_{10}O_2N_2$: C, 73.3; H, 3.8; N, 10.7. Found: C, 73.1; H, 3.9; N, 10.5.

The ultraviolet spectrum of 4 mg. of the above substance in 100 ml. of chloroform was characterized by three peaks, *i.e.;* 247–248 mμ, $E_{1\,cm}^{1\%}$ 740; 264–265 mμ, $E_{1\,cm}^{1\%}$ 380 and 347–348 mμ, $E_{1\,cm}^{1\%}$ 90. Its chemical behavior, empirical formula, and ultraviolet and infrared spectra suggested that the compound was 4-phenylimidazolo[3,4-*b*]benzopyranone-2.

Reaction of salicylamide and hydrocinnamic acid with polyphosphoric acid. A mixture of 15 g. (0.10 mole) of hydrocinnamic acid and 20 g. (0.146 mole) of salicylamide in 150 g. of polyphosphoric acid was heated on a steam bath for 24 hr. Trituration of the green clay-like residue, resulting from dilution of the reaction mixture with water, with 5% aqueous sodium carbonate gave a green solid and a clear solution. The solution was acidified, the solid collected, and dried to give 10.2 g. (55%) of disalicylamide, m.p. 186–189°.

The green solid was extracted with ethyl acetate to give a yellow solution and a greenish yellow solid. Filtration of the solution through 8 cm. of activated alumina and removal of the solvent *in vacuo* gave 2.1 g. of a pale yellow compound, m.p. 140–143°. Recrystallization from ethyl acetate gave the dimer of α-hydrindone, called by Kipping[29] anhydrobishydrindone, m.p. 142–144°, lit.[29] m.p. 142–143°.

Anal. Calcd. for $C_{18}H_{14}O$: C, 87.8; H, 5.9. Found: C, 87.6; H, 5.9.

The greenish yellow solid remaining after extraction with ethyl acetate was recrystallized from tetrahydrofuran to give 4.4 g. of α-truxene, silky yellow needles, m.p. 376.1–378.0°, lit.,[29] m.p. 365–368°.

Anal. Calcd. for $C_{27}H_{18}$: C, 94.5; H, 5.3. Found: C, 94.2; H, 5.5.

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Certain Thiazolo-Benzimidazoles and Thiazino-Benzimidazoles

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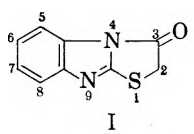
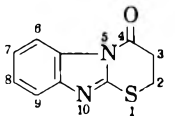
Since anthelmintic activity *in vitro* against *Fasciola hepatica* had earlier been recorded by Mackie and co-workers[1-3] in certain aralkylidene derivatives of 2-thioketo-4-oxothiazolidine and some derivatives of 2*H*-1,4-benzothiazin-3(4H)one, it appeared of interest to prepare the derivatives of the thiazolo[3,2-*a*]benzimidazol-3(2H)one (I) and the tetrahydro thiazinobenzimidazolones (II,III) of similar structures, with a view to testing of their anthelmintic activity against liver flukes, hookworms, and the ascaris infection in poultry and dogs.



I



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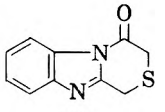

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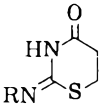
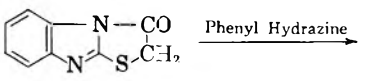
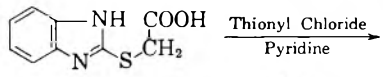


IVa R = -$COCH_3$
b R = -C_6H_5

The compound (I) was prepared by the method of Duffin and Kendall[4] by the cyclization of 2-benzimidazolyl thioglycollic acid with a mixture of pyridine and acetic anydride. The 5-substituted aralkylidenes of I were prepared by refluxing the thiazolidone with a slight excess of an appropriate aldehyde in the presence of glacial acetic acid and fused sodium acetate. On gentle warming with phenylhydrazine in glacial acetic acid, the thiazolo[3,2-*a*]benzimidazol-3(2H)one (I) was decomposed to the phenyl hydrazide of 2-benzimidazolylthioglycollic acid (V). Thionyl chloride in the presence of dry pyridine as catalyst, vigorously reacted with the 2-benzimidazolylthioglycollic acid to give a bronze colored product, to which a *trans*-thioindigoid type of structure VI has been assigned on the basis of the analysis and infrared spectra. This compound was insoluble in the usual organic solvents but could be crystallized from the boiling nitrobenzene. It had marked stability towards the boiling concentrated hydrochloric acid and the strong alkalies.



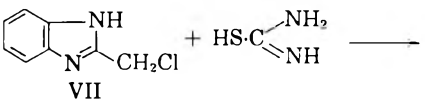
V



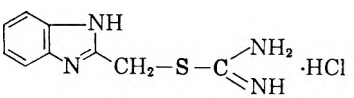
VI

The compounds II and III were prepared by the cyclization of the corresponding thioacids using a mixture of pyridine and acetic anhydride. The infrared spectra of these were identical in the 3–9 μ region, but showed dissimilarities in the region 9–14 μ. For the comparison of the anthelmintic activity, β-isothioureidopropionic and β-phenylisothioureidopropionic acids were also converted into their cyclized products (IVa,b) by a procedure similar to that used for the thiazolidone(I).

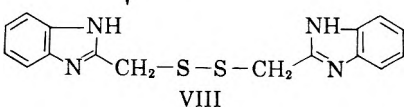
The reaction of 2-chloromethylbenzimidazole-(VII) with thiourea, led to the formation of the bis-(2-benzimidazolylmethyl) disulfide (VIII), presumably through the intermediate formation and the decomposition of the 2-benzimidazolylmethylisothiourea hydrochloride(IX)



VII



IX



VIII

The results of the biological testing of these compounds will be reported elsewhere.

EXPERIMENTAL

The following 5-aralkylidene derivatives of the thiazolidone(I) were prepared by refluxing I with a slight excess of the aldehyde in glacial acetic acid in the presence of fused sodium acetate. The derivatives were filtered, washed with a little hot water and dilute ethanol, and recrystallized from an appropriate solvent.

Reaction of phenylhydrazine with thiazolo[3,2-a]-benzimidazol-3(2H)one. A mixture of the thiazolidone (475 mg.) and phenylhydrazine (0.4 cc.) in glacial acetic acid (5 cc.) was heated for half an hour at 100° and then gently boiled for 5 min., cooled, and diluted with water. The precipitate recrystallized in needles from aqueous ethanol. Yield of the phenylhydrazide of 2-benzimidazolylthioglycollic acid was 380 mg., m.p. 191–192° (dec.).

Anal. Calcd. for $C_{15}H_{14}N_4OS$: C, 60.40; H, 4.69; N, 18.79. Found: C, 60.00; H, 4.69; N, 18.90.

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(1) A. Mackie and A. L. Misra, *J. Chem. Soc.*, 3919 (1954).

(2) A. Mackie and J. Raeburn, *Brit. J. Pharmacol.*, **7**, 219 (1952a).

(3) A. Mackie, G. M. Stewart, A. A. Cutler, and A. L. Misra, *Brit. J. Pharmacol.*, **10**, 7 (1955).

(4) G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 361 (1956).

TABLE I

Compound	M.P., °C.	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
Benzylidene[a]	216–217	$C_{16}H_{10}N_2OS$	69.05	68.95	3.59	4.31
Salicylidene[b]	214–215	$C_{16}H_{10}N_2O_2S$	65.30	65.38	3.40	3.54
Cinnamylidene[c]	234–235	$C_{18}H_{12}N_2OS$	71.05	71.03	3.94	3.94
Furfurylidene[d]	231–232	$C_{14}H_8N_2O_2S$	62.68	63.03	2.98	3.44
Vanillidene[d]	256–257 (dec.)	$C_{17}H_{12}N_2O_3S$	62.96	63.02	3.70	4.07
Anisalidene[e]	232–233	$C_{17}H_{12}N_2O_2S$	66.23	65.77	3.89	4.25
p-Nitrobenzylidene[d]	Above 300	$C_{16}H_9N_3O_3S$	59.44	59.85	2.78	2.67
p-Dimethylaminobenzylidene[f]	267–268 (dec.)	$C_{18}H_{15}N_3OS$	67.29	67.36	4.67	5.14

[a] Yellow plates from glacial acetic acid (Ref. 4 gives m.p. 219°). [b] Light grey plates from ethanol. [c] Yellow plates from glacial acetic acid. [d] Yellow needles. [e] Yellow prisms from the same solvent. [f] Orange prisms from ethanol (Ref. 4 gives m.p. 269°).

2-Carbamylmethylmercaptobenzimidazole. To 4.5 g. of 2-mercapto benzimidazole[5] in boiling 50 cc. of absolute ethanol, was added a solution of sodium ethoxide prepared by dissolving 0.8 g. of sodium in 15 cc. of absolute ethanol. After boiling the solution for 10 min., 2.82 g. of chloroacetamide was added and the contents refluxed for 0.5 hr. The alcohol was removed under reduced pressure and the residue recrystallized as prismatic rods from aqueous ethanol. The yield was 4.5 g., m.p. 206–207°.

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.17; H, 4.34; N, 20.29. Found: C, 52.30; H, 4.55; N, 19.97.

Ethyl N[1]*-acetyl-2-benzimidazolylthioglycollate* was prepared by refluxing ethyl 2-benzimidazolylthioglycollate with a 1:1 mixture of pyridine and acetic anhydride and crystallized in prismatic needles from ethanol, m.p. 118–119°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.11; H, 5.03; N, 10.07. Found: C, 56.31; H, 5.21; N, 10.30.

[$\Delta^{2,2'(3H,3'H)}$-Bithiazolo[3,2-a]benzimidazol]-3,3'-dione (VI). To 1 g. of anhydrous 2-benzimidazolyl thioglycollic acid[6] suspended in 4 cc. of dry benzene, 3.5 cc. of thionyl chloride was added drop by drop with stirring. On the addition of 1 cc. of dry pyridine, a vigorous reaction took place and the contents became dark red in color. After the initial reaction subsided, the contents were warmed on a water bath for about 10 min. and cooled, and the excess of thionyl chloride and benzene was pumped off. The residue was washed with a dilute solution of sodium carbonate and finally with water and dried. Recrystallization afforded 0.75 g. of bronze plates from boiling nitrobenzene, m.p. above 300°.

Anal. Calcd. for $C_{16}H_8N_4O_2S_2$: C, 57.44; H, 2.12; N, 14.89. Found: C, 57.48; H, 2.00; N, 15.13.

The compound was insoluble in the usual organic solvents and markedly stable toward the strong alkalies and concentrated hydrochloric acid. The infrared spectrum in a Nujol mull showed the characteristic maxima at 6.03 μ (C=O); 6.29 μ and 6.71 μ (C=C aromatic; 6.71 μ may be the C=N encountered in thiazoles) 10.25 μ and 10.38 μ (C=C trans). The absence of a band in the 3.70–4.00 μ region showed that the carboxyl group was not present.

Preparation of β-2-benzimidazolylthiopropionic acid. A mixture of 4.5 g. of 2-mercaptobenzimidazole, 3.27 g. of β-chloropropionic acid, 35 cc. of 2*N* sodium hydroxide and 10 cc. water was gently refluxed for 2 hr., filtered, cooled in an ice bath, and acidified with 2*N* hydrochloric acid to *p*H 4. The precipitated solid was filtered, washed with water, and dried. It was recrystallized as prismatic thick rods from aqueous ethanol (charcoal). The yield of the β-2-benzimidazolylthiopropionic acid was 3.7 g., m.p. 175–176° (with effervescence).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.28; H, 4.45; N, 12.98.

Preparation of 2H-m- thiazino[3,2-a]benzimidazol-4(3H)-one (II). A mixture of 1 g. of the above acid and a 10:1.5 mixture of pyridine and acetic anhydride was gently heated under reflux for 0.5 hr., cooled, diluted with ice cold water, the unreacted acid and acetic acid were neutralized with a dilute solution of sodium bicarbonate, and the residue filtered. It was recrystallized as colorless prismatic needles from aqueous ethanol. The yield of II was 690 mg., sintering at 143° and melting at 151–152°.

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.92; N, 13.72. Found: C, 58.60; H, 4.05; N, 13.67.

The infrared spectrum of the compound was determined in chloroform for the 2–7 μ region and in carbon disulfide for the 7–14 μ region. The characteristic maxima were 3.42 μ and 3.51 μ (CH_2), 5.97 μ (tertiary N, may also be C=N). There was no absorption in the 3.70–4.00 μ region (no carboxyl group).

Preparation of 2-benzimidazolyl methylthio acetic acid. 2-Sulfhydrylmethylbenzimidazole was prepared by the method of Hughes and Lions.[7] A mixture of 4.9 g. of the above mercaptan, 2.9 g. of monochloracetic acid, and 35 cc. of 2*N* sodium hydroxide was heated under reflux for 1 hr. on the water bath. The color of the liquid turned crimson red and then greenish brown. The solution was filtered, cooled, and neutralized with 2*N* hydrochloric acid to *p*H 4. A flocculent precipitate that separated became gummy. The yellow mother liquor was clarified with charcoal and on concentration *in vacuo* gave pale yellow crystals, which were recrystallized in plates from boiling water, yield, 1.9 g., m.p. 188–189°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.10; H, 4.92; N, 12.30.

Preparation of 1H-p-thiazino[4,3-a]benzimidazol-4(3H)-one (III). A mixture of the above acid 1.1 g. and a 10:1.5 cc. mixture of pyridine and acetic anhydride was allowed to reflux gently for 15 min., cooled, and worked up as before. The crude product was recrystallized first from aqueous ethanol and then in light yellow prismatic rods from benzene–light petroleum (40–60°). Yield of (III), 0.5 g., m.p. 104–105°.

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.92; N, 13.72. Found: C, 59.05; H, 4.17; N, 13.40.

The infrared spectrum of this compound was identical with that of II in the 3–9 μ region, and showed no bands in the 3.70–4.00 μ region but was dissimilar in the 9–14 μ region. The characteristic band at 13.15 μ may be due to the $-CH_2-S-CH_2-$ group.

(5) J. A. Van Allen and B. D. Deacon, *Org. Synthesis*, **30**, 56 (1950).

(6) J. G. Everett, *J. Chem. Soc.*, 3042 (1931).

(7) G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 209 (1938).

Cyclodehydration of β-isothioureido propionic acid. The acid was prepared using thiourea and β-propiolactone by the method of Gresham, Jansen, and Shaver.[8] Five grams of the above acid and 15 cc. of a mixture of acetic anhydride and pyridine (10:5) was gently refluxed for about 15 min. Most of the acid dissolved and the color of the liquid turned golden yellow. On cooling and leaving overnight, the crystals separated out, which were collected, washed with a small amount of ethanol (95%), and then finally recrystallized in colorless prismatic rods from boiling water. The yield of 2-acetylimino-1,3-thiazan-4-one (IVa), was 2.6 g., m.p. 198° (gradual decomposition).

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.86; H, 4.65; N, 16.27. Found: C, 42.15; H, 4.27; N, 15.72.

Cyclodehydration of β-phenylisothioureidopropionic acid. The acid was prepared from phenylthiourea and β-propiolactone by the method of Gresham and Shaver.[9] On the addition of 20 cc. of the acetic anhydride–pyridine mixture (11:5) to 7.9 g. of the above acid, dissolution took place with the evolution of heat. the deep yellow solution was warmed under reflux on a water bath for 30 min. and cooled, and the solid was filtered, washed with a dilute solution of sodium carbonate, and repeatedly crystallized from ethanol and finally in rectangular slender rods from benzene. The yield of 2-phenylimino-1:3-thiazan-4-one (IVb) was 4.8 g., m.p. 169–170°.

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.25; H, 4.85; N, 13.58. Found: C, 58.21; H, 5.29; N, 13.86.

The mother liquor from the ethanol crystallization on concentration deposited a solid, which crystallized in colorless needles from benzene, m.p. 139–140°. It was probably a mixture of the unreacted acid and the cyclized product.

Anal. Found: C, 56.90; H, 4.91; N, 13.00.

Reaction of 2-chloromethylbenzimidazole with thiourea. To a boiling solution of 1.5 g. of thiourea in 15 cc. of absolute ethanol, 3.3 g. of 2-ehloromethylbenzimidazole[10] was added. After a few minutes a thick crystalline mass of needles separated. The contents were refluxed for 5 hr., the needles gradually went into solution and the yellow prisms that separated, were filtered, recrystallized in pale yellow plates from aqueous ethanol. The yield of 2-benzimidazolylmethyl-isothiourea hydrochloride, (IX) was 0.58 g., m.p. 258–259°.

Anal. Calcd. for $C_9H_{11}N_4SCl,H_2O$: C, 41.45; H, 4.99. Found: C, 41.35; H, 4.62.

After removal of the yellow prisms, the ethanol mother liquor from the reaction was diluted with water and the precipitate crystallized in feathery pale yellow needles from aqueous ethanol and charcoal. Yield of the bis[2-(benzimidazolyl methyl)]disulfide (VIII), 0.5 g., m.p. 110–115°.

Anal. Calcd. for $C_{16}H_{14}N_4S_2.{}^1/_2H_2O$: C, 57.31; H, 4.47; N, 16.71. Found: C, 57.68; H, 4.23; N, 17.24.

Acknowledgment. The author is thankful to Dr. R. C. Shah, Assistant Director, National Chemical Laboratory, Poona (India), for his kind interest in this work, to Dr. (Mrs.) S. Dasgupta for infrared spectra, and to Dr. G. D. Shah for microchemical analysis.

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(8) T. L. Gresham, J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, **70**, 1001 (1948).

(9) T. L. Gresham and F. W. Shaver, U. S. Patent 2,563,034; *Chem. Abstr.*, **46**, 1594 (1952).

(10) A. Bloom and A. R. Day, *J. Org. Chem.*, **4**, 14 (1939).

A New Method for the Activation of Copper Chromium Oxide as a Reducing Catalyst

WILLIAM R. NES

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Copper chromium oxide, when prepared by the method of Adkins, Burgoyne, and Schneider,[1] will catalyze the reduction of carbonyl groups at room temperature but only after activation. This was originally accomplished through exposure of the catalyst to a high pressure (226 atm.) of hydrogen at 100°.[1] It has now been found that the same activation can be achieved simply by refluxing the copper chromium oxide in cyclohexanol for four hours. This is illustrated in Fig. 1. Hydrogenation of acetone to 2-propanol began at room temperature when copper chromium oxide was used which had been activated either essentially according to the previous procedure[1] (Curve C) or by the present method (Curve B), but, when the catalyst had not been activated by any means, a "critical temperature" of *ca.* 100° was required before hydrogenation would proceed (Curve A).

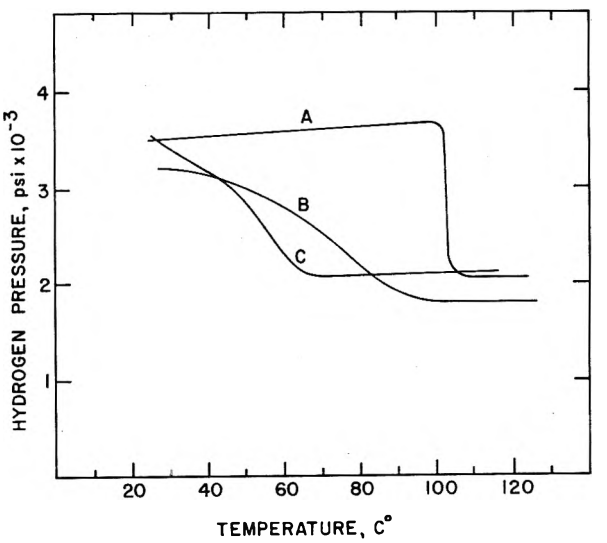

Fig. 1. The influence of temperature on the rate of hydrogenation of 20 ml. of acetone catalyzed by 6 g. of copper chromium oxide which had not been activated (Curve A), which had been activated by refluxing it in cyclohexanol (Curve B), and which had been activated by exposing it to 200 atm. pressure of hydrogen at 110° (Curve C)

The cyclohexanol which was used in the activation was simultaneously oxidized to cyclohexanone. The yield was 11% based on the isolation of cyclohexanone semicarbazone. No attempt was made to increase the percentage conversion of cyclohexanol to cyclohexanone, but it was found that under modified conditions certain steroidal alcohols could be oxidized to the corresponding ketones in a good

(1) H. Adkins, E. E. Burgoyne, and H. J. Schneider, *J. Am. Chem. Soc.*, **72**, 2626 (1950).

yield. Thus, when cholestan-3β-ol and 7,22-ergostadien-3β-ol were refluxed in xylene in the presence of three times their weight of copper chromium oxide, cholestan-3-one and 7,22-ergostadien-3-one were isolated in a 60–65% yield. This is believed to be the lowest temperature (139°) at which a copper chromium oxide catalyst has been found effective for the dehydrogenation of alcohols. This reaction is usually carried out in the vapor phase[2] above 300°, although liquid phase[3–5] oxidation of alcohols has been reported in the temperature range of 200-300°.

EXPERIMENTAL[6]

Hydrogenation experiments. The hydrogenations under high pressure were carried out in a stainless steel pressure vessel. Heating was accomplished with a jacket which allowed the rate of temperature increase to be the same in all cases. It was approximately 1°/min. Temperature and pressure changes were continuously recorded on automatic devices. The product of the various hydrogenations of acetone was identified as 2-propanol by its boiling point (80.5–81.8°) and index of refraction (n_D^{20} 1.3779). The used catalyst was always considerably more black in color than the catalyst which, in agreement with Adkins, *et al.*,[1] was a brownish black. The results of the hydrogenation experiments are summarized in Fig. 1.

Activation of copper chromium oxide. A mixture of 150 ml. of cyclohexanol and 6 g. of unactivated copper chromium oxide was refluxed with stirring under a stream of nitrogen for 4 hr. The jet-black catalyst was filtered off. From 10.0 g. of the filtrate was obtained 1.67 g. of cyclohexanone semicarbazone, m.p. 166–168°. The melting point was undepressed on admixture with an authentic sample. The recovered catalyst was washed with acetone and then used for the reduction of 20 ml. of acetone under 210 atm. pressure of hydrogen (Fig. 1, Curve B).

Oxidation of cholestan-3β-ol. A mixture of 2.0 g. of cholestan-3β-ol, 150 ml. of xylene, and 6.0 g. of unactivated copper chromium oxide was refluxed with stirring for 4 hr. The catalyst was filtered off and extracted with 200 ml. of hot ethanol. The combined filtrates were evaporated to dryness under reduced pressure. Chromatography of the residue on alumina and elution with ether afforded 1.34 g. (67%) of cholestan-3-one (λ_{max} 5.82 μ) which from methanol formed colorless microcrystals, m.p. 128–129°, $[\alpha]_D$ 42°. Lit.[7] m.p. 129–130°, $[\alpha]_D$ 40°.

Oxidation of 7,22-ergostadien-3β-ol. A mixture of 2.0 g. of 7,22-ergostadien-3β-ol, 150 ml. of xylene, and 6.0 g. of unactivated copper chromium oxide was refluxed with stirring under a stream of nitrogen for 2 hr. The catalyst was filtered off and extracted with 300 ml. of boiling ethanol The combined filtrates were evaporated to dryness under reduced pressure and the residue (1.7 g.) was chromatographed on alumina. The material which was eluted with ether was crystallized from ether-methanol and afforded 0.8 g. of 7,22-ergostadien-3-one as colorless flakes, λ_{max} 5.82 μ, m.p. 183–185°, $[\alpha]_D$ ±0°, Lit.[8] m.p. 182–183°, $[\alpha]_D$ 2°. Concentration of the mother liquor gave an additional 0.1 g. of the ketone (combined yield: 60% based on unrecovered starting material). Elution of the alumina with chloroform-ethanol and crystallization of the resulting steroid from ethyl acetate-methanol-water yielded 0.5 g. of starting material as colorless flakes, m.p. 182–183°, which readily formed a digitonide and possessed an infrared spectrum identical with authentic 7,22-ergostadien-3β-ol. The spectrum was quite different from that of samples (melting variously up to 203°) of the digitonin non-precipitable hydroxy compound (λ_{max} 2.76 μ) obtainable by allowing 7,22-ergostadien-3β-ol to react at 150° in the presence of copper chromium oxide under pressure of hydrogen.[9]

When 7,22-ergostadien-3β-ol was refluxed in xylene as described above with one particular batch of copper chromium oxide, instead of the ketone an "intermediate" was obtained by chromatography (alumina; elution with petroleum ether) which possessed neither hydroxyl nor carbonyl bands in the infrared, but which did possess a strong band at 9.03 μ. It was usually obtained in *ca.* 35% yield. It melted at 110–111° (from ether-methanol) and was converted to 7,22-ergostadien-3-one (m.p. 178–179°, λ_{max} 5.82 μ) simply by recrystallizing it from aqueous acetic acid. This compound was obtained on several occasions, but only with the one sample of catalyst. Other catalyst preparations gave the ketone directly. The structure of this material has not been elucidated.

Acknowledgment. The author is indebted to Mr. Robert B. Kostic and Mr. Allen Steele for their technical assistance in certain phases of this work. He also wishes to acknowledge the encouragement and advice of Dr. Erich Mosettig during the investigation.

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(2) See, for instance, R. E. Dunbar and M. R. Arnold, *J. Org. Chem.*, **10**, 501 (1945) and the references cited therein. This process has also been the subject of a number of patents, *e.g.*, T. Kritchevsky, U. S. Patent **2,462,107**, Feb. 22, 1949; *Chem. Abstr.*, **43**, 3841 (1949).

(3) L. P. Kyrides, W. Groves, and F. B. Zienty, U. S. Patent, **2,382,071**, Aug. 14, 1945; *Chem. Abstr.*, **40**, 90 (1946).

(4) O. J. Weinkauff, U. S. Patent **2,455,631**, Dec. 7, 1948; *Chem. Abstr.*, **43**, 1797 (1949).

(5) J. G. M. Bremner and D. G. Jones, British Patent **583,344**, Dec. 16, 1946; *Chem. Abstr.*, **41**, 2746 (1947).

(6) The infrared spectra were determined on a Perkin-Elmer double beam spectrophotometer by Mr. H. K. Miller and Mrs. Phyllis Smeltzer in CS_2. The melting points were determined on a Kofler block and are recorded as read. The rotations were determined at 20° in chloroform in 1–2% concentrations. The copper chromium oxide was prepared exactly according to the directions of Adkins, *et al.*[1]

(7) A. E. Lippman, E. W. Foltz, and C. Djerassi, *J. Am. Chem. Soc.*, **77**, 4364 (1955).

(8) A. Windaus and E. Auhagen, *Ann.*, **472**, 185 (1929).

(9) W. R. Nes and E. Mosettig, *J. Org. Chem.*, **18**, 276 (1953).

Oxidation of 3-Methylisoquinoline

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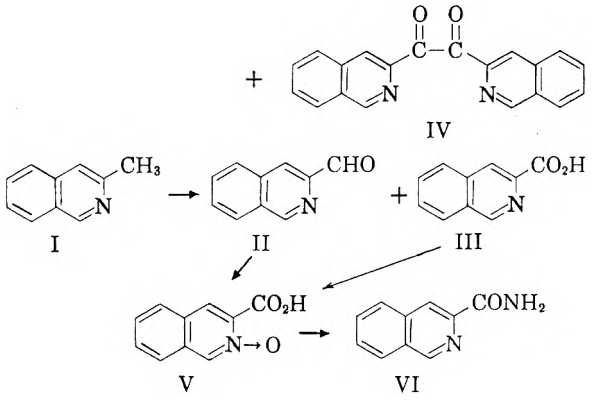
In connection with studies to be reported elsewhere we had the occasion to repeat the synthesis of 3-aminoisoquinoline from 3-methylisoquinoline (I)

(1) This work was supported in part by grant G-1090 of the National Science Foundation.

as described by Teague and Roe.[2] Because of two deviations from their experimental procedure we observed the formation of products not described by them. The first deviation consisted of carrying out the selenium dioxide oxidation of I to 3-isoquinolinecarboxaldehyde (II) under reflux rather than in an open vessel from which the water formed in the reaction (as well as some of the reactant and product) might escape. Under our conditions the temperature of the oxidation was 40–50° below that of Teague and Roe. Three substances were isolated from the reaction mixture. The first, II, was obtained in 25–37% yield (based on I consumed), which is about 10–20% lower than the yield reported by Teague and Roe. The second product was 3-isoquinolinecarboxylic acid (III), isolated only in trace amounts. The third product was di(3-isoquinolinyl)glyoxal (IV), which was obtained in about 3% yield. When the reaction was carried out under the conditions of Teague and Roe, the results were substantially as reported by them and none of the diketone (IV) was obtained.



The second deviation consisted of an attempt to eliminate the fractional distillation of the two solids, I and II. The crude mixed substances were oxidized with hydrogen peroxide in acetone solution, the amount of oxidant being based on an assumed yield equivalent to that of Teague and Roe. When the acetone-insoluble oxidation product was boiled with water, only a trace of the expected acid (III) was obtained. The principal product was 3-isoquinolinecarboxylic acid-2-oxide (V), obtained in 14% yield (based on I). The identity of this material was confirmed by comparison with a sample prepared by the oxidation of authentic III with hydrogen peroxide in acetic acid solution. Oxidation of purified II with hydrogen peroxide in acetone solution gave after treatment with boiling water only III and none of the N-oxide (V).

Ochiai[3] has shown that 4-nitropyridine-1-oxide may be converted to 4-nitropyridine by treatment with phosphorus trichloride. When V was treated with phosphorus trichloride, the N-oxide function was reduced and the carboxylic acid function converted to the acid chloride, for addition of the crude product to ammonium hydroxide gave 3-isoquinolinecarboxamide (VI) in 38% yield. The latter was identical with VI prepared by the procedure of Teague and Roe and could be converted to 3-aminoisoquinoline as described by them.

The infrared spectrum of IV in Nujol has fairly strong bands at 1694, 1674, 1642, 1617 and 1584 cm.$^{-1}$ Buehler and Edwards[4] have reported that 6,6′-dimethylquinaldil has bands at 1697, 1682, and 1651 cm.$^{-1}$ (medium unspecified), which may be regarded as partial support for the structural assignment made here. The origin of the several bands is obscure. Although benzil[5] has only a single ν(C=O) band at 1681 cm.$^{-1}$ (in chloroform), the proximity of the ring nitrogens to the carbonyl oxygens in IV may make certain conformations of the molecule more or less favorable, giving rise to rotational isomers. The skew structure assigned to compounds like IV[4,6] adds to the complexity of the system. Finally, the spectrum of IV has strong bands at 951, 758, 723, and 697 cm.$^{-1}$ The calculated combination tones derived from these fall at at 1709 (758 + 951), 1674 (723 + 951), 1648 (697 + 951), and 1581 (723 + 758) cm.$^{-1}$ Although the observed bands are of greater intensity than is usually associated with combination tones, Fermi resonance between a fundamental in the carbonyl region and one of the combination tones could result in the intensification of the latter.

In the infrared spectrum in Nujol of V the ν(O—H) band is broad and partially buried under the Nujol ν(C—H) bands near 2900 cm.$^{-1}$ The ν(C=O) band is quite broad (roughly 100 cm.$^{-1}$), centered at about 1675 cm.$^{-1}$ and has a spike at 1627 cm.$^{-1}$ Hydrogen bonding between the hydrogen atom of the carboxyl group and the oxygen atom of the *N*-oxide function is probably responsible for the broadening and shifting toward lower frequencies of these bands.

EXPERIMENTAL[7]

Oxidation of 3-methylisoquinoline. In a 500-ml., 3-necked round-bottomed flask fitted with a heating mantle, mechanical stirrer, thermometer, and water-cooled powder funnel 64.5 g. (0.45 mole) of 3-methylisoquinoline was heated with stirring to 180°. To the hot liquid 50 g. of selenium dioxide (freshly prepared and purified by sublimation) was added in 5-g. portions as rapidly as the reaction would allow. The temperature rose to 210°, refluxing began, and the temperature fell to 170° (increasing the heat input did not increase the temperature). About 15 min. was required for the addition. After an additional 15 min. of heating, the reaction mixture was cooled, then extracted with three 100-ml. portions of ether (with heating under reflux) giving extract A.

(2) C. E. Teague, Jr., and A. Roe, *J. Am. Chem. Soc.*, **73**, 688 (1951).

(3) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(4) C. A. Buehler and S. P. Edwards, *J. Am. Chem. Soc.*, **74**, 977 (1952).

(5) R. A. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).

(6) N. J. Leonard, R. T. Rapala, H. L. Herzog, and E. R. Blout, *J. Am. Chem. Soc.*, **71**, 2997 (1949).

(7) Melting points are corrected. Analyses are by Micro-Tech Laboratories, Skokie, Ill.

The oily residue was covered with water and the mixture was neutralized by addition of solid sodium carbonate and filtered, giving aqueous extract B. The residue (C) was a mixture of black metallic selenium and a yellow solid.

The ether extract A was dried over magnesium sulfate, filtered, and evaporated.[8] On the assumption that the yield of Teague and Roe[2] was realized in the oxidation step (*i.e.*, 30 g. of 3-isoquinolinecarboxaldehyde) the crude mixture of 3-isoquinolinecarboxaldehyde and 3-methylisoquinoline was dissolved in 300 ml. of acetone and 30 ml. of 30% hydrogen peroxide was added to the solution. The temperature rose to 45° and remained there for several hours. An additional 40 ml. of 30% hydrogen peroxide was added and the mixture was allowed to stand overnight. The fluffy white precipitate was collected by filtration, air-dried, and suspended in 350 ml. of water. The suspension was boiled for one hour, but the solids did not dissolve.[9] The mixture was filtered. Evaporation of the filtrate gave 0.3 g. of 3-isoquinolinecarboxylic acid, m.p. 164–166° (lit.[10] m.p. 167–168°). The solid was dissolved in dilute sodium hydroxide solution; the solution was treated with charcoal, filtered, acidified with acetic acid, and the resultant mixture was filtered. The pale cream colored solid remaining after air drying (14 g., m.p. 210–211°) was recrystallized from acetone, giving 12 g. of 3-isoquinolinecarboxylic acid-2-oxide, m.p. 211–211.5° dec.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: 63.97; H, 3.98; N, 7.25.

Extract B was treated with charcoal, filtered, and acidified with acetic acid. The resultant solid was recrystallized from water, giving 0.6 g. of 3-isoquinolinecarboxylic acid, m.p. 166–167°.

Residue C was extracted in a Soxhlet apparatus with pyridine. On chilling the pyridine in ice and filtering 2.0 g. of bright yellow needles, m.p. 320–321° dec. was obtained. A small sample (sufficient to form a saturated solution) was recrystallized twice from 25 ml. of pyridine giving 0.08 g. of di(3-isoquinolinyl)glyoxal, m.p. 322–323° dec.

Anal. Calcd. for $C_{20}H_{12}N_2O_2$: C, 76.91; H, 3.87; N, 8.97. Found: C, 77.19; H, 3.33; N, 8.65.

3-Isoquinolinecarboxylic acid-2-oxide. To a solution of 1.0 g. of 3-isoquinolinecarboxylic acid in 20 ml. of glacial acetic acid, 10 ml. of 30% hydrogen peroxide was added and the solution was heated for 2 hr. on the steam bath. On cooling and diluting with water pale tan needles precipitated and were collected and recrystallized from acetone, giving 0.4 g. of 3-isoquinolinecarboxylic acid-2-oxide, m.p. 211–211.5° dec., mixed melting point with product described above the same.

3-Isoquinolinecarboxamide. To 17.5 g. (0.093 mole) of 3-isoquinolinecarboxylic acid-2-oxide suspended in 150 ml. of chloroform, 26 ml. (*ca.* 0.3 mole) of phosphorus trichloride was added, and the mixture was heated for one hour under reflux on the steam bath (protected from moisture). The solid did not appear to dissolve, but did change in appearance. The solid was filtered off and added quickly to 200 ml. of concentrated ammonium hydroxide containing some crushed ice. A vigorous reaction took place and a pale cream colored solid deposited, which was collected by filtration and recrystallized (without drying) from dilute methanol, giving 6.0 g. (38%) of 3-isoquinolinecarboxamide, melting point and mixed melting point with an authentic sample[2] 212–213° (lit.[2] m.p. 213°).

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(8) Fractional distillation of the residue under reduced pressure in other experiments gave 9–13 g. (25–37%, based on 3-methylisoquinoline consumed in the reaction) of 3-isoquinolinecarboxaldehyde, b.p. 140–160° (10 mm.), m.p. 48.5–50.5° (lit.[2] m.p. 47°).

(9) This quantity of hot water will dissolve at least 25 g. of 3-isoquinolinecarboxylic acid.

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Rates of Reaction of *m*- and *p*-Substituted-1,2-Epoxyethylbenzenes with Thiosulfate in Aqueous Ethanol

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The observation[1] that β-halogen and other electron-withdrawing groups increase the rates of reaction of 1,2-epoxyalkanes with thiosulfate is in marked contrast to the effect of β-halogen in displacement reactions on haloalkanes by thiosulfate[2] and thiophenolate,[3] although alkyl substituents decrease the rates of both epoxides and halides.

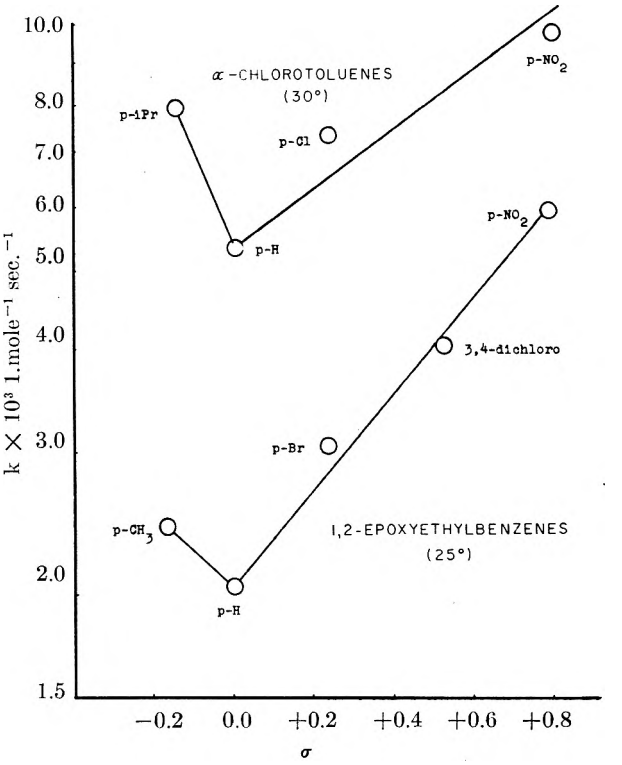

Fig. 1. Rates of reaction of 1,2-epoxyethylbenzenes and of α-chlorotoluenes with thiosulfate in 60% ethanol-40% water.

It was, therefore, of interest to compare the effect of substituents on rates of reaction of 1,2-epoxyethylbenzenes with that of *m*- and *p*-substituted-α-chlorotoluenes, in which substituents act predominently by electronic effects. It has been generally observed that both electron-withdrawing and electron-donating substituents increase the rate of reaction of α-chlorotoluenes with anions such iodide in

(1) W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

(2) K. Akagi, S. Oae, and M. Murakami, *J. Am. Chem. Soc.*, **78**, 4034 (1956).

(3) J. Hine and W. H. Brader, *J. Am. Chem. Soc.*, **75**, 3964 (1953).

acetone,[4] bromide in glycol diacetate,[5] alkoxides,[6,7] hydroxide in aqueous ethanol,[6] and thiosulfate in various solvents.[8] Comparison of the substituted 1,2-epoxyethylbenzenes with α-chlorotoluenes may raise the objection that attack by a nucleophile with a large steric requirement, such as thiosulfate, may take place considerably or even predominently at the primary carbon atom of the epoxide ring.[9] However, the rates of reaction of (2-chloroethyl)-benzene[10] and of α-chlorotoluene are similarly affected by substituents.

The rates of reaction of 4-methyl-, unsubstituted, 4-bromo, 3,4-dichloro-, and 4-nitro(1,2-epoxyethyl)-benzene with sodium thiosulfate in 60% ethanol-40% water at 25° have now been measured, by titration of the base liberated as a result of ring opening (Table I). The rates parallel those of the α-chlorotoluenes,[8] and are of the same magnitude if the temperature difference is taken into account.

TABLE I

RATES OF REACTION OF 3- AND 4-SUBSTITUTED (1,2-EPOXYETHYL)BENZENES WITH THIOSULFATE IN 60% ETHANOL-40% WATER AT 25°

Y—C_6H_4—CH(O)—CH_2[a] Y =	k × 10^3 l. Mole^{-1} Sec.$^{-1}$		Average
4-Methyl	2.40	2.40	2.40
	(2.68)	(2.73)	(2.71)[b]
	(2.03)	(2.03)	(2.03)[c]
4-Hydrogen	2.00	2.08	2.04
4-Bromo	3.06	3.07	3.07
3,4-Dichloro	4.27	4.10	4.19
4-Nitro	5.93	5.95	5.94

[a] (Oxide) = 0.033*M*, ($S_2O_3^=$) = 0.05*M*. [b] ($S_2O_3^=$) = 0.025*M*. [c] ($S_2O_3^=$) = 0.025*M*, ($NaNO_3$) = 0.087 molal; ionic strength of this solution equals that of 0.05*M* $S_2O_3^=$.

The procedure used was essentially that of Ross,[1] but the base was titrated continuously with 1*M* acetic acid using a Beckman Model K automatic titrator, which added increments of approximately 0.02 ml. of acid. The reference end point was slightly more basic than the ethanolic thiosulfate solution, but insufficiently basic to change the color of phenolphthalein. Although the solution was thus maintained faintly basic, the hydroxide ion concentration was too low to cause any appreciable amount of the competing reaction of glycol formation.

Consistent second-order rate constants were obtained over at least 60–65% completion. The specific rate of the 4-methyl compound depends on the thiosulfate concentration. Reduction of the thiosulfate concentration by one-half increases the rate constant slightly, which is consistent with the expected ionic strength effect. If the ionic strength of the diluted thiosulfate is brought up to the original value by the addition of sodium nitrate, the rate constant is decreased to slightly below the original value.

EXPERIMENTAL

Materials. The preparation of the epoxides has been previously described.[11] Each compound was redistilled before use. Commercial absolute ethanol was used directly to make the 60% ethanol-40% water (by volume) solvent mixture.

Rate measurements. A 100-ml. portion of 0.075*M* thiosulfate solution in 60% ethanol was pipetted into a 400-ml. beaker, brought to 25.0° and maintained at 25.0 ± 0.3° throughout the run. After adjusting the reference *p*H, a sample containing 0.005 mole of the epoxide in 50 ml. of solvent at 25° was added (time = 0). The volume of 1.09*N* acetic acid added from a microburet was periodically recorded. The amount of acid was in the range of 1.3-2.7 ml. at 60–65% completion, and this small dilution was neglected in subsequent calculations. Second-order rate constants were calculated from the equation $k = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$. The results of a typical run are shown in Table II.

TABLE II

RATE OF REACTION OF 4-BROMO(1,2-EPOXYETHYL)BENZENE WITH THIOSULFATE IN 60% ETHANOL-40% WATER AT 25°

Elapsed Time, Sec.	Vol. 1.09*N* Acid, Ml.	(RCl)[a]	k × 10^3 l. Mole^{-1} Sec.$^{-1}$
0	0.000	0.0333	
720	0.451	0.0300	3.02
1260	0.764	0.0277	3.00
1980	1.120	0.0251	3.03
2940	1.550	0.0220	3.12
3900	1.885	0.0196	3.10
5220	2.251	0.0169	3.08
6960	2.621	0.0142	3.05
			Av. 3.06 ± 0.04[b]

[a] Initial ($S_2O_3^=$) 0.0518. Concentrations in mole l.$^{-1}$ [b] Average deviation.

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(4) G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935); J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 236 (1936); A. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, **47**, 25 (1951).

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(8) R. Fuchs, *J. Am. Chem. Soc.*, **79**, 6531 (1957).

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Some Reactions of Benzyne and α-Naphthalyne[1]

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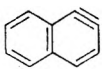
This report describes some reactions of bromobenzene with various nucleophilic reagents in the presence of sodium or potassium amide in liquid ammonia solution. These reactions assuredly occur *via* the benzyne mechanism.[3] Similar experiments were performed several years ago by Bergstrom and co-workers[4] and recently by Scardiglia and Roberts[5] and by Leake and Levine.[6]

Our experimental procedure was to add bromobenzene to a mixture of sodium or potassium amide and the relevant nucleophilic reagent in liquid ammonia. Bergstrom *et al.*[4] showed that many nucleophilic reagents are unreactive with halobenzenes in liquid ammonia unless an alkali metal amide is also present, and Roberts *et al.*[3] demonstrated that the function of the metal amide is to convert the halobenzene to benzyne (I)

I



II

which then reacts with the nucleophilic reagent. Thus our experiments, most of which are summarized in Table I, are essentially an exploration of the reactivity of benzyne.

Experiments 1, 2, and 3 in Table I show that thiophenoxide ion is reactive with benzyne. The same discovery has been made in other current investigations.[5,6] It should be noted that the metal amide was in considerable excess in these experiments, yet the benzyne intermediate combined with thiophenoxide ion to a greater extent than with amide ion. Thiophenoxide ion is evidently more reactive than amide ion with benzyne.

The two experiments (Expts. 4 and 5) with piperidine reagent differ in the metal amide used and in the results obtained. With sodium amide, 29% of *N*-phenylpiperidine was produced in addition to phenylamines resulting from combination of amide ion with benzyne. But with potassium amide no *N*-phenylpiperidine was formed; only phenylamines were obtained. It was noted that a precipitate formed when piperidine was added to a solution of potassium amide in liquid ammonia. The precipitate is presumably potassium piperidide; if so, the non-formation of *N*-phenylpiperidine is easily understood in terms of the potassium piperidide being effectively removed from the reaction system. Sodium piperidide is presumed to be soluble in liquid ammonia, although admittedly the formation of a new precipitate on addition of piperidine to a suspension of sodium amide in liquid ammonia would be hard to detect. The formation of *N*-phenylpiperidine in the sodium amide reaction is then explicable in terms of the solubility of sodium piperidide and the relative insolubility of sodium amide.

Phenylation of isobutyronitrile *via* benzyne (Expt. 6) is analogous to phenylation of acetonitrile and propionitrile as performed by Bergstrom and Agostinho.[4c]

It is remarkable that sulfide ion (Expt. 7) did not react with benzyne, especially in view of the high reactivity of thiophenoxide ion. Cyanide ion is also unreactive (Expt. 8). The objective of the experiment with chloroform (Expt. 9) was to see whether some product from the interaction of benzyne and dichlorocarbene[7] might be obtained. No such product was isolated.

The reaction of 1-bromonaphthalene, sodium thiophenoxide, and sodium amide was investigated. A 27% yield of mixed 1- and 2-naphthyl phenyl sulfides was obtained. The mixture of sulfides was oxidized and from the resulting mixture of sulfones both 1- and 2-naphthyl phenyl sulfones were isolated by fractional crystallization in yields, based on 1-bromonaphthalene, of 8.2% and 15.7%, respectively (total: 23.9%). Thus of the sulfones isolated, 34% was 1-naphthyl and 66% was 2-naphthyl phenyl sulfone.

This experment is significant in two respects. First, the fact that 2-naphthyl phenyl sulfide, a rearranged product, was formed gives assurance that the reaction in which it was generated proceeded by the elimination-addition mechanism, in this case *via* α-naphthalyne (II). The benzyne mechanism for reactions 1, 2, and 3 of Table I is thus further supported. Second, because the efficiency of the transformation of mixed sulfides to isolated sulfones was high, the ratio in which the two sulfones were obtained, 34:66, may be taken as representative of the rates of attachment of the thiophenoxide ion to the 1- and 2-positions of II, respectively. Within experimental error, the ratio is identical to the corresponding ratios pertaining to

(1) Financial assistance from the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

(2) American Enka Fellow, 1954–55; R. J. Reynolds Fellow, 1955–56. This note is based on the Ph.D. thesis of T. K. Brotherton, October, 1956.

(3) J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith, and C W. Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953); J. D. Roberts, D. A. Semenow, H. E. Simmons, and L. A Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

(4) (a) R. E. Wright and F. W. Bergstrom, *J. Org. Chem.*, **1**, 179 (1936); (b) R. A. Seibert and F. W. Bergstrom, *J. Org. Chem.*, **10**, 544 (1945); (c) F. W. Bergstrom and R. Agostinho, *J. Am. Chem. Soc.*, **67**, 2152 (1945).

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TABLE I

REACTIONS OF BENZYNE WITH VARIOUS REAGENTS IN LIQUID AMMONIA

Expt. No.	Amide Used[a] (moles per mole C_6H_5Br)	Other Reactant (moles per mole C_6H_5Br)	Yields (%) of Products Isolated[b] $C_6H_5NH_2$	$(C_6H_5)_2NH$	$(C_6H_5)_3N$	Others
1	Na (4)	C_6H_5SH (2)	10	12		52% of $(C_6H_5)_2S$
2	K (3)	C_6H_5SH (1)		Not sought		62% of $(C_6H_5)_2S$
3	Na (4)	C_6H_5SH (2) NaCN (8)	33			48% of $(C_6H_5)_2S$
4	Na (4)	Piperidine (2)	28	24	6	29% of $C_6H_5NC_5H_{10}$
5	K (4)	Piperidine (2)	55	2	13	
6	Na (3)	$(CH_3)_2CHCN$ (1)	29			23% of $C_6H_5(CH_3)_2CCN$ + 38% of $(CH_3)_2CH$-$CONH_2$
7	Na (4)	Na_2S (2)	33	48		
8	Na (2)	NaCN (2)	26	44	8	
9	Na (2)	$CHCl_3$ (1)	11	7	13	44% of C_6H_5Br

[a] Total amide used is listed, including that necessary to free the nucleophilic reagents from their conjugate acids. [b] See Experimental section for details.

the addition of other nucleophilic reagents to II.[8] All reagents attach to the 2-position of II about twice as fast as to the 1-position. It is remarkable that this ratio is virtually unaffected not only by steric effects in the reagent, as Huisgen and Zirngibl[8] have pointed out, but also by changes in the reagent as diverse as from phenyllithium to piperidide ion to thiophenoxide ion, by changes in reaction temperature as great as 140°, and by wide changes in the reaction medium.

Bromobenzene was heated with sodium amide at reflux in *tert*-butyl alcohol for 22 hours; 77% of bromobenzene was recovered and no products were isolated. Benzyne is evidently not formed in this system.

EXPERIMENTAL

Reactions summarized in Table I. In each experiment 15.7 g. (0.1 mole) of bromobenzene was used; the mole ratios of other reactants to bromobenzene are noted in Table I. In each experiment, the requisite amount of sodium or potassium metal was added to about 500 cc. of liquid ammonia in a three-necked round bottom flask equipped with a mechanical stirrer and an acetone-solid carbon dioxide condenser. A trace of ferric nitrate was added and the metal amide was allowed to form. The conjugate acid of the nucleophilic reagent under study was added in the amount noted in Table I. The bromobenzene was next added cautiously from a dropping funnel and the mixture was stirred for a period of from 30 minutes to several hours. An excess of ammonium chloride was then added and the ammonia was allowed to evaporate. The residue was separated into neutral, basic and acidic fractions by standard extraction techniques. Each fraction was submitted to distillation at reduced pressure or was examined by chromatography on alumina.

Aniline was isolated from the basic fraction and was recognized by its refractive index; the observed n_D^{25} ranged from 1.5786 to 1.5836 in various experiments. Diphenylamine was isolated from the neutral fraction and was recognized by its melting point, which ranged from 52–54° to 54–55° in various experiments, and by the observation of non-depression of mixed melting points with authentic samples. Triphenylamine was also isolated from the neutral fraction and was recognized by its melting point, which ranged from 123–125° to 129° in various experiments, and by the failure of mixed melting points with authentic samples to be depressed.

Diphenyl sulfide was isolated, in Expts. 1, 2 and 3, from the neutral fraction by distillation at reduced pressure; its identity was established by its boiling point (118–122°/4 mm., 120–130°/4–5 mm. and 101–103°/2 mm., respectively; lit.[9] 157–158°/16.5 mm.), by its refractive index (n_D^{18} 1.6326, n_D^{18} 1.6391 and n_D^{23} 1.6339, respectively; lit.[10] $n_D^{18.5}$ 1.635) and by oxidation (in the cases of Expts. 1 and 2) to diphenyl sulfone of m.p. 122–123°, not depressed on admixture with an authentic sample.

In Expt. 4, *N*-phenylpiperidine was isolated, as was aniline, by fractional distillation of the basic fraction. It had b.p. 92–96°/4–5 mm. and n_D^{24} 1.5619; authentic *N*-phenylpiperidine has b.p. 98°/5 mm. and n_D^{23} 1.5606.[11] Distillation of the basic fraction from Expt. 5 yielded only aniline; a trace of dark distillation residue had n_D^{25} 1.5799, quite different from the refractive index of *N*-phenylpiperidine.

α-Methyl-α-phenylpropionitrile was isolated by distillation of the neutral fraction from Expt. 6; it had b.p. 100–103°/12 mm. It was hydrolyzed by treatment with 90% sulfuric acid[12] to α-methyl-α-phenylpropionamide of m.p. 159.5–160° (lit.[12] 160–161°). Isobutyramide of m.p. 130–131°, not depressed on admixture with an authentic sample, was isolated from aqueous solutions in the separation of products from Expt. 6.

Reaction of 1-bromonaphthalene with sodium amide and sodium thiophenoxide in liquid ammonia. To 500 cc. of liquid ammonia in a three-necked flask equipped with a mechanical stirrer and an acetone-solid carbon dioxide condenser, 9.2 g. (0.4 mole) of sodium metal and a trace of ferric nitrate were added. When the formation of sodium amide was complete, 22 g. (0.2 mole) of thiophenol was introduced, and then 20.7 g. (0.1 mole) of 1-bromonaphthalene was added cautiously. The mixture was stirred for 3 hr., excess ammonium chloride was added, and the condenser was removed and the ammonia allowed to evaporate. The residue was separated into acidic, neutral, and basic fractions by standard extraction procedures. By distillation of the neutral

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(12) G. Darzens and A. Levy, *Compt. rend.*, **189**, 1287 (1929).

fraction, 6.2 g. of a yellow oil, b.p. 106–122°/3–4 mm., was obtained. The oil was dissolved in 125 cc. of acetic acid and then treated with 3 l. of a 5% potassium permanganate solution. After 1 hr. standing at room temperature, the mixture was treated with sulfur dioxide until the excess permanganate had been destroyed and it was then filtered. The solid collected on the filter melted at 69–91°. The solid was fractionally crystallized from ethanol. The early fractions consisted of grey plates of m.p. 115 ± 1°, but later fractions had much lower melting points and were therefore treated again with potassium permanganate. The resulting solid was fractionally crystallized, first from ethanol and then from an ethanol-ether mixture. The first fractions from ethanol were grey plates of m.p. 115 ± 1°, and the later fractions from ethanol-ether were tan crystals of m.p. about 99°. On recrystallization from ethanol, the lower-melting crystals yielded 2.2 g. of tan crystalline 1-naphthyl phenyl sulfone, m.p. 100.5–101.5° (lit.[13] 99.5–100.5°), and the higher-melting material furnished 4.2 g. of grey 2-naphthyl phenyl sulfone, m.p. 116.5–117.5° (lit.[13] 115–116°). Each sulfone gave a positive qualitative test for sulfur and a negative test for nitrogen, and a mixture of equal parts of the two sulfones melted at 77–111°. The final product composition was 34% 1-naphthyl phenyl sulfone and 66% 2-naphthyl phenyl sulfone, and the combined yield was 27%.

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Carbamates. I. From Monohydric Alcohols and Toluene-2,4-diisocyanate[1]

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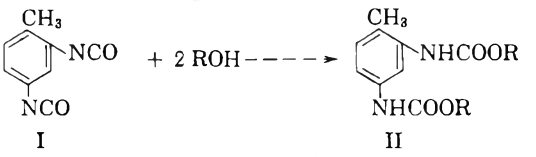
The reaction between an isocyanate and an alcohol to give the carbamate (urethan) is well known.[2] The early application of the reaction to the identification of alcohols was suggested by A. W. Hoffman[3,4] in 1885. The use of various isocyanates has appeared over the years, and a review was presented by Witten and Reid[5] in 1947. The formation of the dicarbamates from toluene-2,4-diisocyanate (or, 4-methyl-*m*-phenylene diisocyanate) has been reported for several of the monohydric alcohols.[6–9] This paper confirms compounds already presented and gives data for fifteen new ones.

Toluene-2,4-diisocyanate(I) reacts readily with monohydric alcohols to form the corresponding dialkyltoluene-2,4-dicarbamates(II).



I II

The reaction proceeds readily at room temperature for the lower, normal, primary alcohols with a definite evolution of heat. The higher, normal, primary alcohols (above eight carbon atoms) react less vigorously. Triethylamine in dry ether was employed as the catalyst for the higher alcohols, together with a heating process of 100° for a period of 4–6 hr. Tertiary butyl and tertiary amyl alcohols failed to give satisfactory derivatives.

The dialkyl toluene-2,4-dicarbamates are colorless, crystalline solids which are readily purified by crystallization from ethyl alcohol. The derivatives above ten carbon atoms show greater solubility in petroleum ether and can be crystallized from this medium.

The application of the dialkyl toluene-2,4 dicarbamates to the qualitative identification of monohydric alcohols offers a good spread of melting points when compared with the various series of carbamates.[5] The total data for the dicarbamates of the monohydric alcohols are presented in Table I.

EXPERIMENTAL

Materials. The toluene-2,4-diisocyanate was obtained from both Monsanto and Du Pont, and was fractionated *in vacuo*. A cut of not over 2° in range was used. Typical boiling ranges: 104–105° (5 mm.); 110–110.5°C. (9.5 mm.). The material was freshly distilled as used, and was stored and handled in a "dry box." The alcohols were obtained from Eastman, or Matheson, and were distilled after drying over Drierite; a cut of not over 0.5° was taken. The solid alcohols were recrystallized from petroleum ether or ethyl alcohol.

Preparation. Two and one-half milliliters (2.5 ml., 0.017 mole) of the diisocyanate were transferred to a test tube (dry box) which contained 0.035 mole of the given alcohol, and 2–3 drops of triethylamine in dry ether. The test tube carried a drying tube of calcium chloride for protection against moisture. The test tube and contents were heated in an oil bath from 4–6 hr. (higher alcohols were heated from 8–10 hr.) at 100°. (For purposes of qualitative identification, 2 ml. of the alcohol are heated on the boiling water bath for 1 hr. with 0.5 ml. of the diisocyanate.) The reaction mixture sets to a crystalline mass upon cooling. The lower members were recrystallized from ethyl alcohol (95%). The higher members were recrystallized from petroleum ether (35–60°). Usually, a highly crystalline product with a sharp melting point resulted after 4–5 recrystallizations. Each sample was dried under reduced pressure in a drying pistol prior to the analysis for nitrogen.

Physiological and herbicidal testing. Since a number of car-

(1) This paper was presented before the Organic Chemistry Section at the fall meeting of the American Chemical Society at Chicago, Sept. 6–11, 1953.

(2) J. H. Saunders and R. J. Slocombe, *Chem. Revs.*, **43**, 209 (1948).

(3) A. W. Hoffman, *Ber.*, **18**, 518 (1885).

(4) H. L. Snape, *Ber.*, **18**, 2428 (1885); see also: Fr. Gumpert, *J. prakt. Chem.* (2), **31**, 119 (1885); E. Knoevenagel and A. Schurenberg, *Ann.*, **297**, 148 (1897).

(5) B. Witten and E. Emmett Reid, *J. Am. Chem. Soc.*, **69**, 2470 (1947).

(6) R. Lussy, *Ber.*, **7**, 1263 (1874).

(7) W. Siefken, *Ann.*, **562**, 75 (1949); *Chem. Abstr.*, **44**, 109 (1950).

(8) N. G. Gaylord and J. J. O'Brien, *Rec. trav. chim.*, **741**, 218 (1955).

(9) J. A. Parker, J. J. Thomas, and C. L. Zeise, *J. Org. Chem.*, 22, 594 (1957).

TABLE I

DIALKYL TOLUENE-2,4-DICARBAMATES FROM CERTAIN MONOHYDRIC ALCOHOLS

Alcohol	Dicarbamate M.P. Lit., °C.	Dicarbamate M.P. Obsd., °C. (Uncorr.)	Formula	Nitrogen Calcd.	Nitrogen Found
Methyl	170–171[9]; 171[8]	170	$C_{11}H_{14}N_2O_4$	11.76	11.67
Ethyl	136.5[8]; 137[7]	135	$C_{13}H_{18}N_2O_4$	10.52	10.57[a]
n-Propyl		104	$C_{15}H_{22}N_2O_4$	9.52	9.66
Isopropyl	134[10]; 136[8]	134	$C_{15}H_{22}N_2O_4$	9.52	9.49
n-Butyl	80[9]	81	$C_{17}H_{26}N_2O_4$	8.69	8.66[a]
Isobutyl		120	$C_{17}H_{26}N_2O_4$	8.69	8.53
sec-Butyl	93[8]	89	$C_{17}H_{26}N_2O_4$	8.69	8.68
n-Amyl		89	$C_{19}H_{30}N_2O_4$	7.99	7.87
Isoamyl		76	$C_{19}H_{30}N_2O_4$	7.99	7.84
Neopentyl		132	$C_{19}H_{30}N_2O_4$	7.99	7.98[a]
n-Hexyl		83	$C_{21}H_{34}N_2O_4$	7.40	7.38
n-Heptyl		82	$C_{23}H_{38}N_2O_4$	6.89	7.03
n-Octyl	69[9]	69–70	$C_{25}H_{42}N_2O_4$	6.45	6.57[a]
n-Nonyl		72	$C_{27}H_{46}N_2O_4$	6.06	6.10
n-Decyl		72–73	$C_{29}H_{50}N_2O_4$	5.71	5.71[a]
n-Undecyl		61	$C_{31}H_{54}N_2O_4$	5.40	5.52[a]
n-Dodecyl	86[8]	87	$C_{33}H_{58}N_2O_4$	5.12	5.16
n-Tetradecyl		90	$C_{37}H_{66}N_2O_4$	4.65	4.67[a]
n-Hexadecyl	95–96[9]	93–94	$C_{41}H_{74}N_2O_4$	4.25	4.21[a]
n-Octadecyl		99.5–100	$C_{45}H_{82}N_2O_4$	3.92	3.89[a]
Cyclohexyl		158	$C_{33}H_{30}N_2O_4$	7.48	7.32
Benzyl		101–102	$C_{23}H_{22}N_2O_4$	7.18	7.11
β-Phenylethyl		129.5–130	$C_{25}H_{26}N_2O_4$	—	—

[a] Micro-Dumas by a commercial laboratory, others by macro-Kjeldahl.

bamates have been tested for carcinogenic activity,[11] as well as having been reported to show definite influence on experimental animal tumors,[12] six members of this series of carbamates (the dimethyl, diethyl, di-*n*-butyl, di-*sec*-butyl, di-*n*-decyl, and di-*n*-octadecyl) were submitted through the National Research Council (Chemical-Biological Coordination Center) to the National Cancer Institute for tumor chemotherapy against Sarcoma 37 in CAF1 mice. The results were negative. The herbicidal properties of certain carbamates[13–15] have attracted attention within recent years also. Certain members of the present series of dicarbamates are to be tested for herbicidal properties.

Acknowledgment. The author is grateful to Research Corp. for a Frederick Gardner Cottrell grant in support of this work; also, to the Monsanto Chemical Co. and to the E. I. Du Pont de Nemours & Co., Inc., for research samples of the diisocyanate. He is indebted to D. J. Leiter and his associates at the National Cancer Institute for the testing of carcinogenic activity. Special appreciation goes to former students who assisted in the work: John Gettleson, Robert Wyant, Malcolm Crew, Robert Pfeil, and Lloyd Horrocks.

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(10) Yu A. Baskakov and N. N. Mel'Nikov, *Zhur. Obshcheĭ Khim.*, **24**, 376 (1954); *Chem. Abstr.*, **48**, 8465 (1954).

(11) National Cancer Institute, *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, second edition, 1951, National Institutes of Health, Bethesda, Md., 35, 505.

(12) Haddow and Sexton, *Nature*, **157**, 500 (1946).

(13) D. H. Moore, D. K. George, V. O. Martin, and J. A. Garman, *J. Agr. Food Chem.*, **1**, 1154 (1953).

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(15) W. S. Shaw and C. R. Swanson, *Weeds*, **II**, 43 (1953).

A Synthesis of Aceanthrene

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Whilst the formation of 9,10-dihydrophenanthrene derivatives by the interaction of phenyllithium and 2,2′-dibromomethylbiphenyls has been fairly extensively studied,[1] the analogous formation of an ethane-bridge between the 1,8-positions of a naphthalene system has only been observed in one case, the synthesis of acenaphthene from 1,8-dibromomethylnaphthalene.[2] It seemed, therefore, worthwhile to add at least one more example.

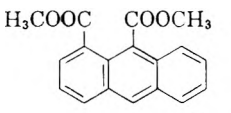
(1) See, also for literature, E. D. Bergmann and Z. Pelchowicz, *J. Org. Chem.*, **19**, 1383; 1387 (1954). G. Wittig and H. Zimmerman, *Ber.*, **86**, 629 (1953). O. M. Hall and E. E. Turner, *J. Chem. Soc.*, 1242 (1955). E. D. Bergmann and R. Ikan, *J. Am. Chem. Soc.*, **80**, 2081 (1958).

(2) E. D. Bergmann and J. Szmuszkowicz, *J. Am. Chem. Soc.*, **75**, 2769 (1951).

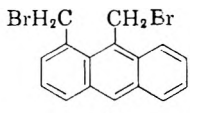
Dimethyl anthracene-1,9-dicarboxylate (I)[3] was reduced by lithium aluminium hydride to the corresponding diol and the latter converted into the dibromide (II). Treatment of II with phenyllithium gave aceanthrene (III) in 84% yield, the overall yield being 60%, calculated on the acid corresponding to I.

Aceanthrene (III) was identified by its m.p. and that of its picrate as well as by the absorption spectrum which was practically identical with that reported by Deno.[4]

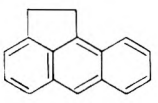
For the preparation of anthracene-1,9-dicarboxylic acid, the oxidation of aceanthrenequinone (IV) by means of hydrogen peroxide was employed for the sake of convenience. This method has been used for the oxidation of acenaphthenequinone[5] and benzil.[6]



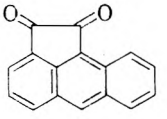
I



II



III



IV

EXPERIMENTAL

Aceanthrenequinone (IV) was prepared according to Liebermann and Zsuffa[7] from anthracene and oxalyl chloride in 58% yield. It was purified by sublimation and melted at 270°. The carbonyl absorption was observed at 1695 cm.$^{-1}$ (potassium bromide pellet).

Anthracene-1,9-dicarboxylic acid. When 6 ml. of 2*N* sodium hydroxide and 5 ml. of 30% hydrogen peroxide solution were added to a suspension of 1 g. of (IV) in 20 ml. of dioxane, an exothermic reaction set in which was kept under control by cooling with ice water. After 45 min., 50 ml. of water was added to the yellow solution and the acid precipitated by addition of dilute sulfuric acid. The yellow precipitate was filtered, washed with water, and dried. The yield was 1 g. (quantitative). The compound melted at 290° (this is probably the m.p. of the anhydride).[3]

Dimethyl anthracene-1,9-dicarboxylate (I). To a solution of 2.65 g. of the foregoing acid in 10 ml. of 2*N* sodium hydroxide, 2 ml. of dimethyl sulfate was added at 0° with stirring. After 1 hr., a yellow precipitate began to settle. With stirring, 1 ml. of dimethyl sulfate and 5 ml. of 2*N* sodium hydroxide and after a further hour, 0.5 ml. of dimethyl sulfate and 2.5 ml. of 2*N* sodium hydroxide were added, both at room temperature, and the stirring was continued for 1 further hour at room temperature and for 30 min. at 70°. The mass was cooled and the product filtered and recrystallized from isopropyl alcohol. The yellow needles of m.p. 149–150° were obtained in a yield of 2.5 g. (86%). The carbonyl absorption (potassium bromide pellet) was observed at 1700 cm.$^{-1}$

1,9-Dihydroxymethylanthracene. The solution of 2.2 g. of (I) in 50 ml. of benzene and 150 ml. of anhydrous ether was added to 1 g. of lithium aluminum hydride in 200 ml. of ether at 0°. Then the mixture was refluxed for 2 hr., cooled and decomposed with ice and dilute sulfuric acid. The organic layer was washed with water, sodium bicarbonate solution and water, dried and concentrated. After recrystallization from isopropyl alcohol, the product formed needles of m.p. 181–182°. The yield was 1.7 g. (95%).

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.7; H, 5.9. Found: C, 81.0; H, 5.7. IR spectrum (KBr pellet): 3200, 2900, 2800 cm^{-1}.

1,9-Dibromomethylanthracene (II). At 60°, 2.4 g. of phosphorus tribromide was added to the solution of 1.5 g. of the foregoing compound in 150 ml. of benzene, to which 3 drops of pyridine had been added. After 2 hr. at 55° (stirring), the mass was cooled, and water and ether was added. The organic layer was washed with sodium bicarbonate solution and water, dried and concentrated. The oily residue was triturated with petroleum ether and the solid product recrystallized from a mixture of benzene and petroleum ether. The yield was 2.1 g. (87%), the m.p. 138–139°.

Anal. Calcd. for $C_{16}H_{12}Br_2$: C, 52.8; H, 3.3. Found: C, 52.9; H, 3.5.

Aceanthrene (III). During 15 min., a solution of 1.8 g. of II in 20 ml. of dry benzene was added to a solution of phenyllithium, prepared from 0.033 g. of lithium and 0.8 g. of bromobenzene in 30 ml. of ether. The operation was carried out in an atmosphere of nitrogen. After 1 hr. at room temperature, 20 ml. of benzene was added and the mixture refluxed for 1 hr. The usual work-up yielded 0.8 g. (84%) of aceanthrene (III), which, after recrystallization from ethanol, formed yellow leaflets of m.p. 113–114°.[8,9]

Anal. Calcd. for $C_{16}H_{12}$: C, 94.1; H, 5.9. Found: C, 93.8; H, 5.6.

The *picrate*,[8,9] prepared in benzene solution and recrystallized from isopropanol, formed dark red needles of m.p. 120–121°.

Anal. Calcd. for $C_{22}H_{15}N_3O_7$: C, 61.0; H, 3.4. Found: C, 60.8; H, 3.4. Spectrum (in ethanol): 225 mμ (4.05); 256 mμ (4.14); 258 mμ (5.06); 355 mμ (3.50); 375 mμ (3.80); 395 mμ (3.56).

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(4) N. C. Deno, Dissertation, University of Michigan, 1948.
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(6) E. Weitz and A. Schefer, *Ber.*, **54**, 2327 (1921).
(7) C. Liebermann and M. Zsuffa, *Ber.*, **44**, 209 (1911).
(8) C. Liebermann and M. Zsuffa, *Ber.*, **44**, 852 (1911).
(9) L. F. Fieser and M. A. Peters, *J. Am. Chem. Soc.*, **54**, 4373 (1932).

Compounds Related to Podophyllotoxin. IX. 3,4-Methylenedioxyphenyllithium[1]

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The present communication is concerned with the preparation of 3,4-methylenedioxyphenyllithium, a reagent of interest in connection with work on the synthesis of picropodophyllin.

(1) Previous papers of this series will be found in *J. Am. Chem. Soc.*, **72**, 3318 (1950); **73**, 5555 (1951); **74**, 2959 (1952); *J. Org. Chem.*, **18**, 9 (1953); *J. Am. Chem. Soc.*, **76**, 315, 5890 (1954); **77**, 3674 (1955); *J. Org. Chem.*, **21**, 261 (1956).

Metalation of aromatic ethers is known to occur ortho to the ether group.[2] However, no report on the behavior of methylenedioxybenzene (1,3-benzodioxole) could be found, and, with the possibility in mind of metalation taking place at the para position, the reaction of this compound with butyllithium was tried. An uncomplicated metalation was not observed. Carbonation after exposure of methylenedioxybenzene to butyllithium either at room temperature or at reduced temperatures gave only colored water-soluble tars, from which no pure material was isolated. When, in place of carbon dioxide, acetic anhydride was used to trap the organolithium compound, only 1,2-diacetoxybenzene was obtained. Evidently, under the conditions employed, the hetero ring in methylenedioxybenzene suffers cleavage.[3]

Another approach to the desired organometallic compound makes use of the corresponding bromo compound. The reaction of methylenedioxybenzene with *N*-bromosuccinimide[4] provided a convenient source of 3,4-methylenedioxy-1-bromobenzene, in which the proper orientation was indicated by its conversion with cuprous cyanide to piperonylonitrile. Direct combination of 3,4-methylenedioxy-1-bromobenzene with metals failed, the compound reacting sluggishly if at all with magnesium[5] or with lithium. Carbonation after exposing the bromo compound to the action of ethereal butyllithium[6] at room temperature was also discouraging; a dark mixture was formed similar to that obtained in the metalation experiments. The same halogen-metal exchange at lower temperatures was more promising in that treatment with acetic anhydride led to a product provisionally considered to be 1,1 - bis(3',4' - methylenedioxyphenyl)ethylene. Eventually, halogen-metal interchange conditions giving 3,4-methylenedioxyphenyllithium in a practical manner were found. The results of carbonation after reaction of the bromo compound with butyllithium for ten minutes at −35° showed that the aryllithium was formed in yields of at least 60%. It may be anticipated that 3,4-methylenedioxyphenyllithium will prove useful in synthesis of compounds containing the methylenedioxyphenyl grouping.

EXPERIMENTAL[7]

Methylenedioxybenzene treated with butyllithium followed by acetic anhydride. Methylenedioxybenzene[8] (3.0 g. or 0.025 mole) in a flask fitted with a dropping funnel and an inlet through which nitrogen was passed was cooled by placing the flask in a −35° mixture of kerosene and solid carbon dioxide in a large Dewar flask. Fifty milliliters of an ethereal solution containing 0.025 mole of butyllithium[9] was added over a short period, and the mixture after being shaken once or twice was allowed to stand at −35° for 3 days.

Excess acetic anhydride (15 ml.) was added and the mixture was allowed to stand cold for 5 min. and then at room temperature for 6 hr. The ethereal reaction mixture was washed several times with water, was dried over magnesium sulfate, and was then warmed on the steam bath under moderate vacuum to remove volatile materials. Two crystallizations of the residue afforded 3.2 g. (67%) of 1,2-diacetoxybenzene, m.p. 63.2–65°. The melting point after admixture with authentic 1,2-diacetoxybenzene[10] having the same melting point was 64.0–65°.

To show that acetic anhydride alone has little effect, a solution of 3.0 g. of methylenedioxybenzene, 15 ml. of acetic anhydride, and 50 ml. of dry ether was allowed to stand at room temperature for 3 days. Distillation through a 6-inch Vigreux column permitted recovery of 2.7 g. (90%) of unchanged methylenedioxybenzene, b.p. 73–74° (23 mm.).

3,4-Methylenedioxy-1-bromobenzene. A mixture of 12.2 g. (0.10 mole) of methylenedioxybenzene, 18.8 g. (0.105 mole) of *N*-bromosuccinimide, and 50 ml. of chloroform was boiled for three hours. Solids were removed from the cooled mixture by filtration, and were washed with two small portions of cold chloroform. The combined chloroform solutions, after contact with magnesium sulfate, were concentrated by distillation on the steam bath. The residual 3,4-methylenedioxy-1-bromobenzene,[11] distilled twice through a small Vigreux column, weighed 18.4 g. (91%), boiled at 85–86° (1 mm.), and showed n_D^{25} 1.5778.

Anal. Calcd. for $C_7H_5O_2Br$: C, 41.82; H, 2.51. Found: C, 41.7; H, 2.5.

3,4-Methylenedioxybenzonitrile from 3,4-methylenedioxy-1-bromobenzene. A mixture of 2.01 g. (0.01 mole) of 3,4-methyl-

(2) H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 258 (1954). Also *cf.* W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948); D. Ginsburg and R. Pappo, *J. Am. Chem. Soc.*, **75**, 1094 (1953).

(3) For related opening of the methylenedioxybenzene ring *cf.* K. Ono and M. Imoto, *J. Chem. Soc. Japan*, **59**, 251, 359 (1938) [*Chem. Abstr.*, **32**, 9060 (1938)]; L. Helfer and M. Mottier, *14me. Congr. chim. ind., Paris*, 1934 [*Chem. Abstr.*, **29**, 6220 (1935)]; E. Späth and H. Quietensky, *Ber.*, **60**, 1882 (1927); A. H. Parijs, *Rec. trav. chim.*, **49**, 33 (1930); also see R. T. Arnold, N. Bortnick, and E. McMullen, *J. Am. Chem. Soc.*, **64**, 1410 (1942). Cleavage of simple ethers with alkyllithium reagents is discussed by H. Gilman, A. H. Haubein, and H. Hartzfeld, *J. Org. Chem.*, **19**, 1034 (1954).

(4) For a similar reaction *cf.* Ng. Ph. Buu-Hoï, *Ann.*, **556**, 1 (1944).

(5) Difficulty in formation of Grignard reagents from the analogously constituted 4-iodo and 4-bromoveratrole has been reported. V. Grignard (with Hua Chia Hsi), *Compt. rend.* **198**, 625, 2217 (1934); R. Willstätter, L. Zechmeister, and W. Kindler, *Ber.*, **57**, 1938 (1924).

(6) G. Jones and H. Gilman, *Org. Reactions* **6**, 339 (1951).

(7) Melting points and boiling points are uncorrected. The elementary analyses were performed by Dr. C. K. Fitz, 115 Lexington Avenue, Needham Heights 94, Mass.

(8) W. J. Gensler and C. M. Samour, *J. Org. Chem.*, **18**, 9 (1953).

(9) Prepared according to H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949), and analyzed according to H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.* **66**, 1515 (1944).

(10) *Cf.* G. Heller, P. Lindner, and H. Georgi, *Ber.* **56**, 1868 (1923); J. J. Sudborough and W. Thomas, *J. Chem. Soc.*, **87**, 1752 (1905).

(11) Previously prepared by T. G. H. Jones and R. Robinson, *J. Chem. Soc.*, **111**, 903 (1917), and by E. Mameli with E. Boi, *Atti reale accad. Lincei*, **15**, 101 (1906) [*J. Chem. Soc. Abstracts* **90**, i, 743 (1906)].

enedioxy-1-bromobenzene, 1.1 g. (0.012 mole) of cuprous cyanide, and 1 ml. of anhydrous pyridine was heated under reflux for 15 hr. using an oil bath at 210–225°. The contents of the reaction flask were stirred thoroughly with dilute aqueous ammonia and then with 25 ml. of benzene, and the resulting mixture was filtered through a sintered glass funnel. After extracting the aqueous layer of the filtrate several times with benzene, all the benzene fractions were combined and were concentrated on the steam bath. Crystallization of the residue from aqueous alcohol gave slightly pink needles, which after drying, weighed 0.84 g. (57%).

Anal. Calcd. for $C_8H_5O_2N$: C, 65.30; H, 3.43. Found: C, 65.5; H, 3.5.

The melting point, 90–91°, of this product corresponds more closely to the reported m.p. 94–95° for 3,4-methylenedioxybenzonitrile (piperonylonitrile)[12] than to the m.p. 80° for 2,3-methylenedioxybenzonitrile.[13]

3,4-Methylenedioxy-1-bromobenzene treated with butyllithium followed by acetic anhydride. An ether solution (60 ml.) containing 0.064 mole of butyllithium was added over a 5-min. period to 12.8 g. (0.064 mole) of 3,4-methylenedioxy-1-bromobenzene. The reaction mixture was blanketed with nitrogen and was held at −35°. After swirling the mixture briefly it was allowed to stand at −35° for another 5 min. Acetic anhydride (15 ml.) was added rapidly to the cold solution, which was then allowed to come to room temperature and to stand at room temperature for 2 days. Volatile materials were removed by distillation on the steam bath at water-pump pressures. Distillation of the residual oil through a 6-inch Vigreux column furnished some starting material [1.2 g., b.p. 104–105° (9 mm.), n_D^{25} 1.5791], an intermediate fraction (2–3 ml.), and finally a viscous yellow oil, b.p. 170–175° (1 mm.). Decomposition was evident, especially during the last part of the distillation when the bath temperature was raised to 270°, and much residue remained in the flask. The yellow oil on standing deposited crystals (0.53 g.) with m.p. 90.5–101°. Chromatography of this material in benzene solution using an alumina column gave colorless crystals (0.33 g.), m.p. 91–93°. Recrystallization from absolute alcohol brought the melting point to 92–93°.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.65; H, 4.51. Found: C, 70.5; H, 4.3.

This compound, tentatively considered to be 1,1-bis-(3′,4′-methylenedioxyphenyl)ethylene, absorbed bromine rapidly from a chloroform solution, contained no halogen, and showed absorption peaks at 299 mμ (log ε 3.85) and 269 mμ (log ε 3.83) in a 1×10^{-4} *M* alcoholic solution.

3,4-Methylenedioxy-1-bromobenzene treated with butyllithium followed by carbon dioxide. 3,4-Methylenedioxy-1-bromobenzene (14.1 g. or 0.070 mole) was treated as described above with 148 ml. of an ethereal solution containing 0.0705 mole of butyllithium. After a maximum exchange time of 10 minutes, the mixture was poured over a slurry of approximately 20 g. of crushed solid carbon dioxide in ether. The mixture was acidified with dilute hydrochloric acid, the ether layer was removed, and the aqueous layer extracted twice with ether. The combined ether solutions were dried over magnesium sulfate and then were warmed to remove solvent. Two crystallizations of the residual solid from 95% alcohol resulted in 7.0 g. (60%) of piperonylic acid, m.p. 226–227°. The melting point of this carbonation product admixed with authentic piperonylic acid was 225.8–227°.

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Some Derivatives of Biphenyl as Liquid Scintillator Solutes

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Previous studies of liquid scintillator solutes[1] have indicated the general principle that efficient solutes must contain three, and preferably four, aromatic rings linked to one another in chainlike fashion. We have screened a variety of compounds which may be regarded as derivatives of biphenyl in that each has only two distinct benzene rings joined directly (although some have fused rings as well). A few of these compounds have high relative pulse height values for such "small" molecules.

TABLE I

PRIMARY-SOLUTE RELATIVE PULSE HEIGHTS

No.	Compound	Relative Pulse Heights	Ref.
1.	2-Aminobiphenyl	0.16	[a]
2.	4-Benzylbiphenyl	<0.10	[b]
3.	2,2′-Dimethoxybiphenyl	0.14	[c]
4.	4,4′-Dimethoxybiphenyl	0.20	[d]
5.	2,2′-Dimethoxy-3,3′-dimethylbiphenyl	<0.10	[e]
6.	3,4-Benzocoumarin	<0.10	[a]
7.	*N,N,N′,N′*-Tetramethylbenzidine	0.28	[a]
8.	4,4′-Bistrimethylsilylbiphenyl	0.30	[e]
9.	*N*-(4-Biphenylyl)-aniline	0.63	[f]
10.	*N*-(*o*-Phenyldiphenylmethyl)-aniline	0.13	[g]
11.	2,3-Dimethoxyphenanthrene	0.14	[h]
12.	2-Aminophenanthrene	0.23	[i]
13.	3-Aminophenanthrene	0.20	[j]
14.	1,1′-Binaphthyl	0.87	[k]
15.	2,2′-Binaphthyl	0.25	[l]
16.	Perylene	0.24	[m]

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Previously tested hydrocarbons with a single phenyl-phenyl linkage include such compounds as biphenyl,[1a] fluorene,[1a] phenanthrene,[1b], and pyrene[1b] (0.10, 0.12, 0.16, and 0.21, respectively). Table I shows the remarkable value of 0.87 for 1,1′-binaphthyl along with 0.25 for 2,2′-binaphthyl and 0.24 for the closely related perylene. Some partially hydrogenated terphenyls and quaterphenyls having only two benzenoid nuclei also give surprisingly high values and will be reported later along with the corresponding aromatic compounds.

Included in Table I are a number of interesting functional derivatives of biphenyl. Among these are two solutes related to *p*-terphenyl (RPH 0.97[1b]). Previously[1e] we have reported a value of 0.16 for 4-biphenylyl phenyl ether. In Table I Compound 2, in which the three rings are separated by a $-CH_2-$ group, gives no response within the limits of our measuring system. Compound 9 with an —NH— function separating the rings shows a value of 0.63. The temptation to attribute this high value to resonance interaction between rings is discouraged by the low value of the corresponding oxygen compound. To date no theoretical explanation involving the hydrogen attached to the nitrogen separating the rings has been proposed, although there are other examples that lend appeal to this line of thought. Compare, for example, 4-biphenylyldiphenylamine[1f] (0.39) with Compound 9 and bis-4-biphenylylamine[1f] (0.95) with bis-4-biphenylylphenylamine[1f] (0.61). Even Compound 10, with little opportunity for any sort of interaction between the rings and the secondary amine function, affords a measurable response. In all of these cases consideration of the values of the oxygen analogs is discouraging in that the diaryl ethers have poor values and the phenolic hydroxyl group is known to be an undesirable function in all instances examined thus far.[1b]

The encouraging results for the dimethylamino and methoxy derivatives tested (Compounds 3,4,5,-7, and 11) seem to indicate that these functions give rise to enhanced scintillation in compounds which are otherwise poor solutes in spite of the fact that they have little, if any, effect on molecules which are otherwise good scintillators. The simple aminophenanthrenes are the first derivatives of this system reported, and the pulse heights (0.20 and 0.23) indicate good potential for this nucleus. Synthesis and examination of more complex derivatives will almost certainly be rewarding.

The values reported in Table I were measured in the pulse height analyzer previously described,[1b] and all were measured at a concentration of 3 g./l. in toluene. All values are relative to 2,5-diphenyloxazole which is assigned the arbitrary value of 1.00.

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Some Compounds in the Tri-*n*-hexylgermane Series

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Because the information in the literature on the higher aliphatic germanium compounds[1] is meager, a study of such types has recently been initiated in this laboratory. The preparations and physical properties of some compounds of the tri-*n*-hexylgermane series are reported herein, including tetra-*n*-hexylgermane, phenyltri-*n*-hexylgermane, tri-*n*-hexylbromogermane, bis(tri-*n*-hexylgermanium) oxide, tri-*n*-hexylchlorogermane, tri-*n*-hexyliodogermane and tri-*n*-hexylgermane.

Tetra-*n*-hexylgermane was prepared by the reaction of germanium tetrachloride with an excess of *n*-hexyllithium. Tri-*n*-hexylbromogermane was obtained directly from germanium tetrachloride and 3.3 equivalents of *n*-hexylmagnesium bromide, although the product obtained by this method cannot be completely freed of di-*n*-hexyldibromogermane. The ready displacement by bromide ion of the chloride ion from the expected initial product, tri-*n*-hexylchlorogermane, finds a parallel in the preparation of the corresponding iodide from either the chloride or the bromide by the action of sodium iodide in acetone solution. The high rate

$$R_3GeCl + NaI \longrightarrow R_3GeI + NaCl$$

of reaction of trialkylhalogermanes compared to tertiary butyl halides in bimolecular nucleophilic displacement reactions can be partially ascribed to the relative unimportance of steric hindrance at the large central germanium atom. Also, germanium is less electronegative than carbon.[2] This suggests a polarization of the alkyl-germanium bonds which would tend to lower the electron density at the central atom thereby speeding S_N2 reactions.

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TABLE I

PHYSICAL PROPERTIES OF TRI-*n*-HEXYLGERMANE COMPOUNDS

Compound[e]	B.P., °C at 0.5 mm.	n_D at t°	Den. at t°	Formula	Germanium % Calcd.	Germanium % Found
R_4Ge	158–161	1.4567/27	0.908/27	$C_{24}H_{52}Ge$	17.6	17.4 17.2
R_3GeBr	143–145	1.4763/27	1.117/26	$C_{18}H_{39}GeBr$[a]	17.8	17.8
$R_3GeC_6H_5$	160–165	1.4984/22	0.972/25	$C_{24}H_{44}Ge$	17.9	17.9 17.9
$(R_3Ge)_2O$	210–211[b]	1.4645/25	0.963/25	$C_{36}H_{78}Ge_2O$	21.6	21.8 21.9
R_3GeCl	138–139	1.4661/20	0.989/20	$C_{18}H_{39}GeCl$[c]		
R_3GeI	154–155	1.4935/26	1.188/26	$C_{18}H_{39}GeI$[d]		
R_3GeH	122–125	1.4565/21	0.917/25	$C_{18}H_{40}Ge$	22.1	22.4 22.4

[a] *Anal.* Calcd.: Br, 19.59. Found: Br, 21.8. This indicates a composition of 82% tri-*n*-hexylbromogermane and 18% di-*n*-hexyldibromogermane. [b] B.p. at 0.04 mm. gauge pressure. [c] *Anal.* Calcd.: Cl, 9.76. Found: Cl, 9.72. [d] *Anal.* Calcd.: I, 27.59. Found: I, 27.62. [e] R represents an *n*-hexyl group.

Pure tri-*n*-hexylchlorogermane was obtained by basic hydrolysis of the impure bromide, fractional distillation of the resulting oxide, and treatment of the oxide with concentrated hydrochloric acid. Tri-*n*-hexylbromogermane reacted with phenyllithium to give phenyltri-*n*-hexylgermane, and with lithium aluminum hydride to give tri-*n*-hexylgermane.

EXPERIMENTAL

Tetra-n-hexylgermane. *n*-Hexyllithium was prepared[3] by the addition over a two-hour period of 128 ml. (0.907 mole) of *n*-hexyl bromide in 100 ml. of anhydrous ether to a mixture of 13.9 g. (2.0 gram atoms) of lithium wire cut into pieces 5–10 mm. in length, and 400 ml. of anhydrous ether. A dry nitrogen atmosphere was maintained. The reaction was started at room temperature, then was cooled to −30° during the two-hour addition period, and finally was stirred at 0° for two hours more. The resulting solution was shown by the double titration procedure[4] to contain 0.62 mole of *n*-hexyllithium (68%). This was added to a solution of 14.8 ml. (0.13 mole) of germanium tetrachloride in 100 ml. of ether, at 0° (over a 1-hr. period) and then the mixture was stirred for two hours. Hydrolysis was effected with ice water, the layers were separated and the ether layer dried over magnesium sulfate, and the solvent was distilled. Fractional distillation of the residue through a Vigreux column gave 7.2 g. (14%) of product, b.p. 158–161° at 0.5 mm.

Anal. Calcd. for $C_{24}H_{52}Ge$: MR, 124.7. Found: MR, 123.9.

Tri-n-hexylbromogermane. To 19.4 ml. (0.17 mole) of germanium tetrachloride was added 0.56 mole of *n*-hexylmagnesium bromide obtained from 14.6 g. of magnesium and 84.4 ml. of *n*-hexylbromide. The suspension was filtered, and the liquid was distilled. First, solvent and unchanged *n*-hexyl bromide came over, followed by 28.0 g. (40%) of product, b.p. 143–145° at 0.5 mm.

Anal. Calcd. for $C_{18}H_{39}GeBr$: MR, 104.8. Found: MR, 103.1.

An additional 15.4 g. of material which boiled at 145–160° at 0.5 mm. appeared to be a mixture of tri-*n*-hexylbromogermane and tetra-*n*-hexylgermane.

Halogen analysis of halogermanes. A sample of the halogermane (0.2 g.) was weighed into a dry Erlenmeyer flask. This was heated nearly to boiling with 0.5 g. of calcium carbonate and 50 ml. of distilled water for 10 min. After the flask was cooled, the contents were titrated by the Mohr method against 0.1*N* silver nitrate solution using 0.05 g. of sodium chromate as an indicator. A blank containing calcium carbonate, sodium chromate, and water was titrated, and the volume of silver nitrate used was subtracted from the volume required by the sample.

Phenyltri-n-hexylgermane. A solution of 0.045 mole of phenyllithium in ether solution was added to 8.2 g. (0.02 mole) of tri-*n*-hexylbromogermane in 100 ml. of toluene. The ether was distilled until the vapor reached 110°, and the residue was refluxed overnight. The mixture, after hydrolysis and isolation by the method used for tetra-*n*-hexylgermane, gave 6.1 g. (75%) of product boiling at 160–165° at 0.5 mm.

Anal. Calcd. for $C_{24}H_{44}Ge$: MR, 121.1. Found: MR, 122.0.

Bis(tri-n-hexylgermanium) oxide. Fifteen g. of the higher boiling fraction of impure tri-*n*-hexylbromogermane was stirred for 0.5 hr. with 100 ml. of aqueous 10% potassium hydroxide solution cooled in ice. After the addition of 75 ml. of isopropyl ether, the organic layer was separated, washed with water, and dried. Distillation through a semimicro column gave 4.3 g. (35%) of a liquid, b.p. 210–211° at 0.04 mm.

Anal. Calcd. for $C_{36}H_{78}Ge_2O$: MR, 193.4. Found: MR, 192.8.

A total of 7.0 g. (57%) of product distilled over the range from 204–212° at 0.04 mm.

Tri-n-hexylchlorogermane. To concentrated hydrochloric acid (15 ml.) was added 3.6 g. of bis(tri-*n*-hexylgermanium) oxide, and the mixture was stirred for 30 hr. The product was extracted twice with hexane, and the combined extracts were dried over magnesium sulfate. Distillation afforded 2.62 g. (74%) of product boiling at 138–139° at 0.5 mm.

Anal. Calcd. for $C_{18}H_{39}GeCl$: MR, 102.0. Found: MR, 101.9.

Tri-n-hexyliodogermane. A solution of 7.5 g. of sodium iodide in 50 ml. of acetone was mixed with 2.6 g. of tri-*n*-hexylchlorogermane. Precipitation of sodium chloride began almost immediately. After overnight standing the addition of 50 ml. of hexane caused the unchanged sodium iodide to precipitate. The orange solid was separated by filtration during which contact with air was minimized. Distillation of the filtrate gave 1.8 g. (56%) of a colorless liquid, b.p. 154–155° at 0.5 mm.

Anal. Calcd. for $C_{18}H_{39}GeI$: MR, 109.8. Found: MR, 112.6.

This sample of tri-*n*-hexyliodogermane became brown after standing for several days.

Tri-n-hexylgermane. To 2 g. of lithium aluminum hydride dissolved in 75 ml. of anhydrous ether was added a solution

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

of 9.5 g. of tri-*n*-hexylbromogermane in 40 ml. of ether. The mixture was refluxed for 4 hr. and was allowed to stand overnight. Unchanged lithium aluminum hydride was then precipitated by the addition of 100 ml. of petroleum ether (b.p. 77–115°) followed by distillation of the ethyl ether. The solution was filtered and then distilled. After a forerun came over at 95–122° at 0.5 mm., 2.0 g. (26%) of product was collected, b.p. 122–125° at 0.5 mm.

Anal. Calcd. for $C_{18}H_{40}Ge$: MR, 97.1. Found: MR, 97.4.

The pure product does not evolve hydrogen at a noticeable rate when treated with dilute alcoholic potassium hydroxide solution, although triphenylgermane reacts readily. The infrared absorption spectrum shows a peak at 1980 cm.$^{-1}$ due to the Ge-H bond.

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Cleavage of the Silicon-Silicon Bond of Hexaphenyldisilane. IV[1]

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The silicon-silicon bond of hexaphenyldisilane is much more stable than the carbon-carbon bond of hexaphenylethane. Unlike the carbon analog, hexaphenyldisilane is not cleaved by oxygen,[3,4] iodine,[4] sodium in xylene or dioxane,[1c] or sodium amalgam in ether.[1c] Nevertheless, the silicon-silicon bond of hexaphenyldisilane has been cleaved by sodium-potassium alloy in ether,[1c,5] lithium in tetrahydrofuran,[1a] lithium and sodium in ethylene glycol dimethyl ether,[1b] potassium in di-*n*-butyl ether,[1c] and rubidium or cesium in ether.[5]

In an extension to the studies of the cleavage reactions of the silicon-silicon bond of hexaphenyldisilane, a number of other reagents have been studied. It was found that sodium cleaved the disilane in liquid ammonia. Although iodine does not react with hexaphenyldisilane,[4] bromine was found to effect slow cleavage of the silicon-silicon bond in carbon tetrachloride to give bromotriphenylsilane. For example, 33% of pure bromotriphenylsilane was isolated in a period of 42 hr., and a 55% yield of bromotriphenylsilane was formed in 6 days. This observation further demonstrates that the silicon-silicon bond of hexaphenyldisilane is more stable than the central carbon-carbon bond of hexaphenylethane since the latter compound reacts readily with iodine due to dissociation.

Hexaphenyldisilane has been treated with a number of oxidizing agents as well as lithium aluminum hydride, but no cleavage reaction of the silicon-silicon bond was observed. In most cases, a nearly quantitative recovery of the starting material was obtained. When chromic acid was employed, some oxidation occurred yielding a sirupy product.

EXPERIMENTAL[6]

Reaction of hexaphenyldisilane with bromine. A suspension containing 10 g. (0.019 mole) of hexaphenyldisilane, 3.4 g. (0.021 mole) of bromine, and 250 ml. of carbon tetrachloride was refluxed with constant stirring for 42 hr. The solvent and the unchanged bromine were removed by distillation to leave a solid residue (10.8 g.) melting at 100° to a turbid liquid. The crude product was boiled with 200 ml. of petroleum ether (b.p. 60–70°), filtered hot, and cooled. The insoluble solid (4.1 g.) melting at 346–354° was recrystallized from dioxane to give 3.6 g. (36%) of hexaphenyldisilane (mixed melting point). The filtrate was concentrated twice to collect 6.2 g. (47%) of solid melting at 115–118°. Two recrystallizations from petroleum ether (b.p. 60–70°) yielded 4.3 g. (33%) of crystals melting at 118–120°. A mixed melting point determination with an authentic specimen of bromotriphenylsilane was not depressed.

In a second experiment, the hexaphenyldisilane was allowed to react with bromine in refluxing carbon tetrachloride for 6 days. The reaction mixture was worked up according to the procedure described in the previous paragraph to give a 19% recovery of hexaphenyldisilane and a 65% yield of crude, and a 55% yield of pure bromotriphenylsilane.

Reaction of hexaphenyldisilane with sodium in liquid ammonia. Sodium, 0.35 g. (0.015 g.-atom), was cut into small pieces and dropped into about 50 ml. of liquid ammonia at −50°. To this deep blue solution thus formed there was added 2.6 g. (0.005 mole) of hexaphenyldisilane in one portion. The reaction mixture was stirred for 6 hr. at −50°. It was observed that some brown precipitate had formed although the color was somewhat masked by the deep blue color due to the excess sodium in liquid ammonia. The cooling bath was removed and ammonia was allowed to evaporate as the reaction mixture warmed to room temperature. A small amount of ethanol was added to the pale gray residue to destroy the excess sodium. Water was then added, and the mixture was filtered to give 1.6 g. of solid which softened at 120° but did not melt completely until 360°. This was boiled with a solution of benzene and ethanol and filtered hot. There was obtained, as the insoluble residue, 0.1 g. (4%) of hexaphenyldisilane (mixed melting point) melting at 360–362°. The filtrate was cooled to give 0.8 g. of solid melting at 150–200°. This was shaken with a small amount of cold ethanol and filtered to separate 0.4 g. of solid melting at 230–234°. One recrystallization from benzene raised the melting point to 233–235°. A mixed melting point determination with tetraphenylsilane was not depressed. The yield was 0.3 g. (9%). The ethanolic solution was evaporated to dryness, and the residue was recrystallized from petroleum ether (b.p. 60–70°) to give 0.4 g. (11%) of triphenylsilanol melting at 151–152°. Evaporation of the solvent from the

(1) (a) For Part III of this series see H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, **80**, 608 (1958); (b) for Part II see A. G. Brook and H. Gilman, *J. Am. Chem. Soc.*, **76**, 278 (1954); (c) for Part I see H. Gilman and T. C. Wu, *J. Am. Chem. Soc.*, **73**, 4031 (1951).

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(6) All melting points are uncorrected.

mother liquor after the removal of 0.8 g. of solid melting at 150–200°, resulted in 0.12 g. of colorless crystals melting at 163–167°. The infrared spectra of this slightly impure product and of hexaphenyldisilazane (the latter prepared by reaction of triphenylsilane with sodium in liquid ammonia[7]) are nearly identical, and a mixed melting point was not depressed.

Reaction of hexaphenyldisilane with chromic acid. Chromic acid solution was prepared by dissolving 5.0 g. of chromium trioxide in 5 ml. of water followed by the addition of 10 ml. of glacial acetic acid. This solution was added to 3.0 g. of hexaphenyldisilane, and the mixture was heated at 80–90° for 2 hr. with occasional shaking. The resulting dark green mixture was diluted with 100 ml. of water. Solid sodium carbonate was added to neutralize the reaction product until the addition of a small amount did not cause evolution of gases. Following filtration of the neutralized mixture there was obtained 2.7 g. (90%) of impure hexaphenyldisilane melting at 356–360°. It was boiled with petroleum ether (b.p. 60–70°) and filtered hot to separate 2.5 g. (83%) of purified hexaphenyldisilane. Only a trace of brown solid remained from the distillation of the filtrate.

In a second experiment, twice the amount of chromic acid was used, and the reaction mixture was refluxed for 48 hr. In this run, only a 48% yield of hexaphenyldisilane could be recovered. The aqueous solution was extracted with ether, from which a sirupy residue was obtained. Purification of this residue was unsuccessful.

Attempted reactions of hexaphenyldisilane with other oxidizing agents, and lithium aluminum hydride. Hexaphenyldisilane was treated with 30% hydrogen peroxide in refluxing glacial acetic acid for 24 hr. with no sign of reaction. It was also treated separately in refluxing solvent for 48 hr. with selenium dioxide in dioxane, nitric acid in water, periodic acid in benzene, and lead tetraacetate in acetic acid. In all cases no cleavage was observed while more than 90% of the unchanged disilane was recovered. Practically quantitative recoveries of hexaphenyldisilane were also obtained after it had been treated separately for 48 hr. with potassium permanganate in acetone, nitric oxide in ether, or lithium aluminum hydride in refluxing ether.

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Organoboron Compounds. VII. Alkylarylborinates

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Ethanolamine has proved to be a very useful reagent for the isolation and characterization of diarylborinic acids.[2] It reacts readily with the borinic acids, even in the presence of water, to yield air stable, sharp melting esters. As the boronic acids (also the boronate esters) and triarylborines do not behave in this manner, the borinates can be separated readily from reaction mixtures containing the three types of substances.

We now find that these techniques involving ethanolamine also provide a convenient means for isolating derivatives of the alkylarylboron-oxygen compounds. The preparation of three representative compounds, aminoethyl benzylphenylborinate (Ia), aminoethyl butylphenylborinate (Ib), and aminoethyl 1-methylheptylphenylborinate (Ic), are described in this note. In all cases the alkyl-boron bond was formed by reaction of the appropriate Grignard reagent with dibutyl benzeneboronate (II). Following hydrolysis the aminoethyl esters were precipitated by addition of ethanolamine. These esters are lower-melting and more soluble in

I II

I (a) R = $C_6H_5CH_2-$
(b) R = C_4H_9-
(c) R = $C_6H_{13}-\underset{H}{\overset{CH_3}{C}}-$

organic solvents than the previously described diarylborinates. The benzyl and butyl derivatives (Ia,b) have stood in vials in air over a year without change; however, the 1-methylheptyl derivative (Ic) is less stable. After a period of several months this compound melted over a range of several degrees at a lower temperature and a strong odor of octanol was noticed. All of the aminoethyl esters hydrolyzed very rapidly in dilute hydrochloric acid to give air sensitive substances (no doubt the free borinic acids since the aminoethyl esters could be regenerated by extraction of the acid with ether and reprecipitation with ethanolamine; however, crystalline borinic acids could not be obtained).

EXPERIMENTAL

Aminoethyl benzylphenylborinate. Benzylmagnesium bromide (55 cc. of 1.81*M* ether solution) was added over a period of 1 hr. to a stirred solution of 23.4 g. (0.1 mole) of dibutyl benzeneboronate in 175 cc. of ether. The initial temperature of the reaction mixture was −70°; after an hour of stirring the mixture was allowed to warm to room temperature and then hydrolyzed with dilute hydrochloric acid. The ether layer was then separated and to it was added 15 cc. of ethanolamine in 15 cc. of methanol. Up to this point a

(1) National Science Foundation Fellow, 1954.

(2) R. L. Letsinger and I. H. Skoog, *J. Am. Chem. Soc.*, 77, 2491, 5176 (1955). R. L. Letsinger and N. Remes, *J. Am. Chem. Soc.*, 77, 2489 (1955).

nitrogen atmosphere had been maintained; thereafter, the reaction products were handled in air without special precautions. The ether layer was mixed with 150 cc. of water and the ether removed at reduced pressure. A white precipitate of aminoethyl ester separated as the ether distilled. This material, after drying in a vacuum desiccator melted at 128–135° and weighed 19.9 g. (83%). The first crystallization from toluene gave a 96% recovery of ester melting at 139.5–141°, and the second recrystallization an 80% recovery of ester (over-all yield of purified material, 64%), m.p. 141–142°; neutralization equivalent, determined by titration with standard hydrochloric acid, 242; calcd. for $C_{15}H_{13}BON$, 239.

To prove the presence of the benzyl group in the molecule a 0.539-g. sample of the ester was oxidized with 2.5 g. of potassium permanganate in 50 cc. of water made alkaline with potassium hydroxide. After the initial exothermic reaction, an additional 2.5 g. of permanganate was added and the mixture warmed on a steam bath for 15 min. It was then cooled, decolorized with ethylene glycol, acidified, cleared of manganese dioxide with sodium hydrogen sulfite, and extracted with ether. The mixture of acids isolated from the ether was separated by sublimation to give benzoic acid (sublimate) m.p. 121–122°, 0.217 g. (80%); and benzeneboronic acid (residue) as the oxide, m.p. (193–197°), 0.079 g. (29%).

In another degradation 1.00 g. of ester was shaken with 3*N* hydrochloric acid and ether for several seconds to effect hydrolysis. The ether layer was evaporated on a steam bath to leave an oil which was warmed with 10 cc. of 5% potassium hydroxide solution. Air was passed through the solution for an hour then the mixture separated into neutral and organic acid products. From the acid portion was obtained 0.358 g. (70%) of benzeneboronic acid (m.p. 222–223°), proving the presence of a phenyl-boron linkage in the aminoethyl ester; and from the neutral fraction was isolated, following treatment with 3,5-dinitrobenzoyl chloride, 0.08 g. of benzyl 3,5-dinitrobenzoate, m.p. 111–113° (undepressed on mixture with an authentic sample).

Aminoethyl butylphenylborinate. By the procedure described for the benzyl compound 13.8 g. (71%) of aminoethyl butylphenylborinate m.p. 104–107°, was obtained from 0.103 mole of dibutyl benzeneboronate and 0.103 mole of *n*-butylmagnesium bromide. One recrystallization from toluene-hexane raised the melting point to 106–107° (12.2 g., 60% yield), and a subsequent recrystallization raised the melting point to 108–108.5°. As expected, aromatic C—H absorption was weak in the infrared whereas aliphatic C—H absorption was strong.

Anal. Calcd. for $C_{12}H_{20}BON$; C, 70.26; H, 9.83; N, 6.83; neut. equiv., 205. Found: C, 69.97; H, 9.42; N, 7.18; neut. equiv., 206 (C, H, and N analyses by H. Beck).

Mercuric chloride in ethanol cleaved 1.241 g. of the aminoethyl ester in ethanol to give 1.8 g. (95%) of phenylmercuric chloride. In another experiment, 0.92 g. of ester was hydrolyzed with hydrochloric acid, the reaction products taken up in ether and the ether evaporated. Sufficient oxidation had occurred that 0.2 g. (37%) of benzeneboronic acid could be isolated from the residue.

Aminoethyl 1-methylheptylphenylborinate. By the above procedure 23.5 g. of crude ester, m.p. 85–92°, was isolated from a reaction of 0.090 mole of dibutyl benzeneboronate with 0.090 mole of 1-methylheptylmagnesium bromide. Recrystallization from hexane that contained a small amount of benzene yielded 12.83 g. (55%) of the aminoethyl ester, m.p. 93–95°, neut. equiv. 258; calcd. for $C_{16}H_{28}BON$, 261. Acid hydrolysis of the aminoethyl ester in the presence of air yielded, as in the case of the butylphenylborinate, benzeneboronic acid, 0.153 g. (64%). The ease of oxidation of this mixed borinic acid points up the value of ethanolamine as a tool for working with this class of compounds.

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Acetylation of Amides with Ketene

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Although it has been demonstrated by several workers that amides can be acetylated with ketene, the number of such examples is rather limited. Rice and co-workers[1] prepared *N*-phenyldiacetamide by passing ketene into acetanilide at 140°. They suggested that *N*-acetylbenzamide was formed similarly from benzamide at 180° but that it decomposed into benzonitrile as the reaction progressed. Later, Padgham and Polya[2] isolated *N*-acetylbenzamide and diacetamide by passing ketene into molten benzamide and acetamide, respectively. The use of sulfuric acid as a catalyst in the formation of *N*-phenyldiacetamide from ketene and molten acetanilide was reported by Smirnova[3] and others.

In this present study seven amides, namely: acrylamide, methacrylamide, cyanoacetamide, *p*-toluamide, formamide, acetamide, and benzamide, have been successfully acetylated by ketene. Of these, the first four were treated with ketene for the first time. These reactions were carried out in a suitable solvent and in some cases in the presence of catalytic amounts of sulfuric acid. When sulfuric acid was used it was necessary to wash it from the reaction mixture as soon as possible after the reaction was completed. Continued contact with the catalyst in most instances caused decomposition of the acetylated product with a proportional decrease in yield. Monoacetyl derivatives were formed with the exception that formamide yielded *N*-formyldiacetamide. This triacylated ammonia is crystalline, a fact of interest in connection with Smirnova's[3] statement that triacetylammonia is a liquid. *N*-Acetylacrylamide and *N*-acetylmethacrylamide, prepared in the present study, are two additional new compounds reported for the first time, and their melting points are recorded. The melting point of cyanoacetamide is also recorded, as well as that of *N*-formyldiacetamide. The carbon, hydrogen, and nitrogen content of the latter is also reported in support of its identity.

EXPERIMENTAL

The ketene used was generated by the pyrolysis of acetone using the lamp previously described.[4] The amides were each individually placed in the gas absorption apparatus designed

(1) F. O. Rice, J. Greenberg, C. E. Waters, and R. E. Vollrath, *J. Am. Chem. Soc.*, **56**, 1760 (1934).

(2) D. N. Padgham and J. B. Polya, *Australian J. Sci.*, **13**, 113 (1951).

(3) N. V. Smirnova, A. P. Skoldinov, and K. A. Kocheshkov, *Doklady Akad. Nauk. S.S.S.R.* **84**, 737 (1952).

(4) R. E. Dunbar and L. L. Bolstad, *J. Org. Chem.*, 9, 219 (1944).

TABLE I

KETENE ACETYLATION PRODUCTS OF AMIDES

Amide	Solvent	Catalyst	M.P., °C. Obs.	M.P., °C. Lit.	Mol. Wt. Found	Mol. Wt. Calcd.	N % Found	N % Calcd.	Recryst. Solvent
Acetamide	Ligroin	H_2SO_4	79	78–79[a]	100	101	...	...	Acetone
Acrylamide	Ether	$CuSO_4$	200	...	...	...	12.3	12.4	Insol.
Benzamide	Benzene	H_2SO_4	114	115[b]	162	163	...	...	Ethanol
Formamide[c]	Ether + ethanol	H_2SO_4	107	...	130	129	10.5	10.8	Water
Methacrylamide	Ether	None	Dec. at 300	...	...	...	11.1	11.0	Ether
p-Toluamide	Benzene	H_2SO_4	145	147[d]	179	177	...	...	Acetone-H_2O
Cyanoacetamide	Benzene	H_2SO_4	115	...	126	126	22.0	22.2	Acetone

[a] W. Hentschel, *Ber.*, **23**, 2394 (1890). [b] C. E. Colby and F. D. Dodge, *Am. Chem. J.*, **13**, 1 (1891). [c] Product isolated was diacetyl formamide. *Anal.* Calcd. for $C_5H_7NO_3$: C, 46.5; H, 5.42. Found: C, 47.2% and H 5.50%. [d] G. Glock, *Ber.*, **21**, 2650 (1888).

by Bolstad and Dunbar,[5] together with a suitable solvent, and an acetylation catalyst[3] or a polymerization[6] inhibitor in one instance.

A typical acetylation is that of benzamide, which is described in detail. Exceptions to this procedure for other amides will be noted. A suspension of 3.6 g. (0.03 mole) benzamide and two drops of concentrated sulfuric acid in 70 ml. of benzene was agitated with a magnetic stirrer at room temperature while 0.03 mole of ketene was passed through the suspension. Care was taken to avoid any appreciable excess of ketene. The resulting product was soluble in the solvent. At the end of the run the solution was washed with 25-ml. portions of water until the washings were neutral to litmus, and the solvent was then allowed to evaporate at room temperature. The resulting product was recrystallized from a minimum amount of 95% ethanol. Yields were essentially quantitative except for mechanical loss in handling and recrystallizing the product. The molecular weights were determined by the Rast method[7] using camphor as the solvent. The nitrogen content was determined by the micro-Kjeldahl method.[8] Physical constants and other significant data are recorded in Table I.

Concentrated sulfuric acid proved to be a satisfactory catalyst for most of these acetylations. The unsaturated amides, however, when acetylated in the presence of sulfuric acid, formed gelatinous polymeric products. Methacrylamide was acetylated satisfactorily without any catalyst, but acrylamide had to be stabilized with copper sulfate. When acetamide was acetylated in hot ligroin it formed an oily insoluble product that was isolated with a separatory funnel, solidified at −5°, and was recrystallized from acetone. The diacetamide, contrary to most of the reaction products, was relatively stable at elevated temperatures.

Formamide was so insoluble in most inert organic solvents as to make acetylation nearly impossible even when the suspension was vigorously agitated. However, when the formamide was dissolved in an equal volume of ethanol, the resulting mixture was then found to be soluble in ether and the same could then be successfully acetylated. For this preparation 1.35 g. of formamide was, therefore, dissolved in 3 ml. of 95% ethanol and 70 ml. of anhydrous ether was then added. Ketene was then passed into the solution until two equivalents had been provided on the assumption that the ethanol would react with an equal amount of ketene. However, at the end of this period, the ketene was being absorbed so completely and readily that a third equivalent was provided. The crystalline product was isolated by permitting the solvent to evaporate at room temperature, and adding water to the remaining liquid. According to Smirnova and co-workers,[3] the literature regarding acetylated amides is "erroneous and contradictory." They report that triacetylammonia is a liquid at room temperature and leave the reader with the impression that this is the case with all similarly trisubstituted ammonias. It has been found, however, that treatment of formamide with excess ketene yielded a solid product with a molecular weight of 130 corresponding to the diacetyl derivative and a nitrogen content of 10.5%, also corresponding to the diacetyl derivative. Their conclusion is supported only by a nitrogen determination while this study reports not only the nitrogen percentage, but percentages of carbon and hydrogen, as well as molecular weight.

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(5) L. L. Bolstad and R. E. Dunbar, *Ind. Eng. Chem., Anal. Ed.*, **15**, 498 (1943).

(6) "Technical Bulletin Acrylamide," American Cyanamide Co., Petrochemical Department, New York, N. Y. (1956).

(7) A. Steyermark, *Quantitative Organic Microanalysis*, McGraw-Hill Publishing Co., New York, 1951, p. 82.

(8) T. S. Ma and G. Zuazaga, *Ind. Eng. Chem., Anal. Ed.*, **14**, 280 (1942).

Alkylations of Alkali Diphenylmethides with β-Diethylaminoethyl Chloride and Ethylene Oxide[1]

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Sodium diphenylmethide prepared from diphenylmethane and sodium amide in liquid ammonia has recently[2] been alkylated with alkyl halides in this medium to form hydrocarbons of the type $(C_6H_5)_2CHR$, where R is an alkyl group or a phenyl-substituted alkyl group.

This reagent has now been alkylated similarly with β-diethylaminoethyl chloride to form tertiary amine I in 83% yield (Equation 1).

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{NaNH_2} (C_6H_5)_2CHNa \xrightarrow{ClCH_2CH_2N(C_2H_5)_2} (C_6H_5)_2CHCH_2CH_2N(C_2H_5)_2 \quad (1)$$

I

(1) Supported by the Duke University Research Council.

(2) C. R. Hauser and P. J. Hamrick, Jr., *J. Am. Chem. Soc.*, **79**, 3142 (1957).

For convenience the commercially available hydrochloride salt[3] of β-diethylaminoethyl chloride was used. It was added to one equivalent each of sodium diphenylmethide and sodium amide, the latter base serving to liberate the amine.

The analogous potassium reagent was alkylated with this tertiary amine halide in ether to form amine I in 72% yield. The potassium diphenylmethide was prepared from diphenylmethane and potassium amide in liquid ammonia, and the ammonia replaced by ether before adding the halide.

Both of these procedures of alkylation of diphenylmethane with β-diethylaminoethyl chloride appear superior to those described previously employing sodium amide in toluene[4] and phenylsodium in benzene,[5] which have given amine I in yields of only 14% and 27% ,respectively.

Another type of alkylation of potassium diphenylmethide was realized in the present investigation with ethylene oxide in ether to form alcohol II in 78% yield (Equation 2).

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{KNH_2} (C_6H_5)_2CHK \xrightarrow[\text{2, } CH_2\text{—}CH_2 \text{ (O)}]{\text{1, } NH_3 \text{ replaced by ether}} (C_6H_5)_2CHCH_2CH_2OH \quad (2)$$

II

This introduction of the benzhydryl group into the molecule appears more convenient than the method employed previously, involving the reduction of β,β-diphenylpropionic acid[6] or its ethyl ester.[7]

The structure of alcohol II was established by converting it to hydrocarbon III through its benzenesulfonate (Equation 3a). Hydrocarbon III was independently synthesized from sodium diphenylmethide and ethylene chloride (Equation 3b). The details of the latter reaction will be published later.[8]

$$\text{II} \xrightarrow[\text{2, } C_6H_5SO_2Cl]{\text{1, } NaNH_2} (C_6H_5)_2CHCH_2CH_2OSO_2C_6H_5 \xrightarrow{(C_6H_5)_2CHNa} \quad (3a)$$

$$2(C_6H_5)_2CHNa \xrightarrow{ClCH_2CH_2Cl} (C_6H_5)_2CHCH_2CH_2CH(C_6H_5)_2 \quad (3b)$$

III

(3) The free β-diethylaminoethyl chloride has been observed to decompose slowly; see D. S. Breslow, R. S. Yost, H. G. Walker, and C. R. Hauser, *J. Am. Chem. Soc.*, 66, 1922 (1944). Presumably cyclization to form the cyclic quaternary ammonium chloride occurs; see E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, 1954, p. 357–8.

(4) O. Eisleb, *Ber.*, **74B**, 1438 (1941).

(5) G. Benoit, R. Delavigne, and F. Eliopoulo, *Ann. pharm. franc.*, 10, 185 (1952).

(6) E. D. Bergmann and Z. Pelchowicz, *Bull. soc. chim. France*, [5], **20**, 809 (1953).

(7) M. Protiva, *Chem. listy*, **45**, 20 (1951).

(8) P. J. Hamrick, Jr., C. F. Hauser, and C. R. Hauser, unpublished method.

EXPERIMENTAL

Alkylation with β-diethylaminoethyl chloride. To a stirred suspension of 0.2 mole of sodium amide in 500 ml. of commercial anhydrous liquid ammonia[9] was added 16.8 g. (0.1 mole) of diphenylmethane in an equal volume of anhydrous ether. The resulting orange-red mixture of sodium diphenylmethide and sodium amide was stirred for 15 min., and 17.2 g. (0.1 mole) of solid β-diethylaminoethyl chloride hydrochloride was added. After stirring 2 hr., the liquid ammonia was evaporated on the steam bath as an equal volume of anhydrous ether was added. The resulting gray, ether suspension was refluxed for 30 min., and then decomposed with ice water. The ethereal layer was separated and combined with an ether extract of the aqueous alkaline layer. The ethereal solution was dried over Drierite, and the solvent was removed. The residual oil was distilled *in vacuo* to give 22 g. (83%) of 1-diethylamine-3,3-diphenylpropane (I) as a colorless oil, b.p. 150–153° at 3 mm., n_D^{27} 1.5446; reported b.p. 160–165° at 4 mm.,[5] n_D^{25} 1.5438.[10]

When an ethereal suspension of 0.1 mole of potassium diphenylmethide[11] was treated with 0.1 mole of β-diethylaminoethyl chloride (freshly liberated from the hydrochloride salt),[3] there was obtained a 72% yield of amine I, b.p. 144–145° at 1 mm. The hydrochloride salt of the product melted at 142–143°; reported m.p. 143–144°.[4]

Alkylation with ethylene oxide. To a stirred solution of 0.2 mole of potassium amide in 500 ml. of liquid ammonia was added 33.6 g. (0.2 mole) of diphenylmethane in an equal volume of anhydrous ether, and the liquid ammonia was replaced by ether.[11] To the resulting orange-red suspension of potassium diphenylmethide in ether was added 8.8 g. (0.2 mole) of ethylene oxide in an equal volume of anhydrous ether, the color being discharged. After stirring for 90 min. the reaction mixture was cooled, and decomposed with iced hydrochloric acid. The ethereal layer was separated and combined with several ether extracts of the aqueous layer. After drying over Drierite, the solvent was removed. The residue was distilled *in vacuo* to give 9 g. of recovered diphenylmethane, and 33 g. (78%) of 3,3-diphenylpropanol-1 (II) as a viscous oil, b.p. 164–166° at 2.5 mm., 204–208° at 26 mm., n_D^{25} 1.5814; reported b.p. 203° at 25 mm.[6]

An ethereal solution of 0.1 mole of carbinol II was added to 0.1 mole of sodium amide in liquid ammonia, and the liquid ammonia was replaced by ether. After refluxing for several hours (to remove traces of ammonia) the resulting ethereal suspension of the sodium salt of the carbinol was treated with 0.1 mole of benzenesulfonyl chloride in ether (refluxed 1 hr.). The mixture was filtered, and the solvent was removed from the filtrate. The thick, residual oil was heated with water (steam bath) to hydrolyze unreacted benzenesulfonyl chloride and washed with water to remove benzenesulfonic acid. The resulting crude benzenesulfonate of carbinol II was dissolved in ether, and, after drying over Drierite, the solution was added to 0.1 mole of sodium diphenylmethide in liquid ammonia. The liquid ammonia was replaced by ether, and the resulting suspension (after refluxing 1 hr.) was decomposed with ice water. There was isolated from the ethereal layer 11 g. (66%) of recovered diphenylmethane and 11 g. (30%) of hydrocarbon III, m.p. 120–122° (recrystallized from ether). After recrystallization from ethanol, the melting point was 121–122°; reported m.p. 120–121.6°.[12] The melting point was not depressed on admixture with an authentic sample of III (m.p. 122–123°

(9) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(10) R. L. Clarke and A. Mooradian, *J. Am. Chem. Soc.*, **71**, 2826 (1949).

(11) See R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 2325 (1947).

(12) K. Scholtis, *Ann.*, **557**, 88 (1945).

recrystallized from ethanol) prepared from sodium diphenylmethide and ethylene chloride.[8]

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Fate of Selenium in the Isomerization of Oleic Acid

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Previous work in this laboratory on the selenium-catalyzed isomerization of *cis* -stilbene[2] and of *cis*-9-octadecenoic (oleic) acid[3] at 200° to their respective trans isomers established that the rate of conversion was essentially independent of the concentration of selenium at any particular initial concentration of selenium, despite the fact that the selenium slowly disappeared from the solid phase.

In the present paper, the fate of the selenium during the isomerization of oleic acid is examined and there are presented experimental data, consistent with the requirement that the concentration of the catalytically active species of selenium be essentially constant during the course of the isomerization.

EXPERIMENTAL

Three forms of the selenium catalyst are present during the isomerization of the oleic to elaidic acid at 200°: the original black, undissolved or bulk selenium; the active form of the selenium in solution, which on cooling, precipitates as the red modification; and the inactive species which remains in "solution" after cooling. In order to determine the approximate quantities of these three forms of selenium, pure oleic acid was heated to 200° for various time intervals using a fixed amount (0.2 weight percent) of black selenium powder.

Apparatus. The apparatus employed for the determinations consisted of a test tube reactor, equipped with an agitator passing through a glass-tube bearing in a rubber stopper, and having a side tube connected to a helium supply for maintaining an inert atmosphere. The reactor was heated by means of a salt bath controlled at 200° with a heating mantle connected through a variac to a Thermocap relay.

Procedure. The determinations were all carried out in the same manner. A typical experiment will be described:

Pure oleic acid, 40.017 g. was placed in the reactor and heated with stirring under a helium atmosphere. After the temperature had become adjusted to 200° ± 2°, the stopper was momentarily removed and 0.0800 g. of black selenium powder on a fragile glass boat was added. After replacing the stopper and starting agitation, the time was noted. After 12 minutes, the heating bath and agitator were quickly removed and a filter stick inserted. The contents of the reactor were quickly filtered while hot into a tared filter flask. The black selenium remaining in the reaction vessel was transferred to a weighed, fritted-glass, micro-filter funnel with the aid of petroleum ether. Since the material on the filter contained bits of glass from the weighing boat, it was necessary to dissolve the selenium in the weighed mixture with concentrated nitric acid and wash and dry and reweigh the filter funnel to obtain the true weight. Using this procedure it was determined that 0.0390 g. of black selenium powder was present. On cooling the oleic-elaidic acid mixture in the filter flask, red selenium precipitated. The mixture was diluted with petroleum ether and filtered through a weighed, fritted-glass micro-filter funnel. After washing with petroleum ether and drying, 0.0192 g. of red selenium was secured. The weight of "inactivated" selenium which remained in "solution" was 0.0218 g., by difference. The results are semi-quantitative but sufficiently accurate to allow appropriate conclusions.

RESULTS AND DISCUSSION

The results of measurements with 0.2 weight percent initial selenium at 200° are shown in Table I.

Disappearance of the solid catalyst is rapid until a certain concentration level of the active form is obtained; solution by complexing occurs thereafter only as it is needed to maintain this concentration level against an inactivation reaction occurring concomitantly.

The selenium which precipitates in the red form on cooling is believed to represent the active species of the catalyst. Table I shows that the concentration of this form at 200° increases rapidly and then remains essentially constant (within the limits of accuracy of the analytical method used) during the reaction or until all the undissolved black form has disappeared. These data are in agreement with the pseudo first-order rate equation found for the reversible selenium-catalyzed interconversion of oleic (cis) and elaidic (trans) acids:

$$-\frac{d[\text{Oleic}]}{dt} = k_1'[\text{Oleic}] - k_2'[\text{Elaidic}]$$

TABLE I

RATE OF SOLUTION OF SELENIUM IN PURE OLEIC ACID, 200°, 0.2% INITIAL SELENIUM

Heating Time, (Min.)	Percent of Total Selenium		
	Undissolved black	Precipitated red	Inactive (by diff.)
3	89.0	8.5	2.5
7	58.7	27.7	13.6
12	48.7	24.0	27.3
15	34.2	30.5	35.3
25	19.0	34.7	46.3
35	0.0	6.0	94.0

where the k′ values include a particular initial concentration of selenium. The rapid attainment of the (theoretically) constant value for the concentration of active selenium corresponds to the rapid equilibrium reaction between oleic acid and its pi complex with selenium, according to the mechanism previously advanced.[3]

The concentration of the inactive form of selenium increases at a constant rate giving essentially a straight line. This suggests that the inactivation reaction depends on the active species which is in constant concentration. Such an effect follows from the mechanism advanced previously, in which the inactivation of the catalyst was ascribed to an irreversible rearrangement of the pi complex to a new species presumably involving the formation of a carbon-selenium sigma bond.

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(2) J. D. Fitzpatrick and M. Orchin, *J. Org. Chem.*, 22, 1177 (1957).

(3) J. D. Fitzpatrick and M. Orchin, *J. Am. Chem. Soc.*, 79, 4765 (1957).

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Isolation of an Alkaloid, Annuloline, from the Roots of *Lolium Multiflorum*[1,2]

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The roots of the annual rye grass (*Lolium multiflorum*) have been known for some time to contain a brilliant blue fluorescing pigment.[5] Seed analysts are able to distinguish annual rye grass seed from the morphologically similar perennial variety (*L. perenne*) by viewing the roots of the 8-day old seedlings under long wave ultraviolet light; the perenne roots do not fluoresce.[6]

The extraction of the fresh roots of the seedlings obtained from about 100 lbs. of seed of *L. multiflorum* has enabled us to isolate and crystallize the fluorescent principle which appears to be a weakly basic alkaloid. The tentative empirical formula, $C_{20}H_{19}NO_4$, best satisfies the presently available data. It seems likely that there are three methoxyl groups present per formula weight.

A variety of organic solvents such as ethanol, methylene chloride, carbon tetrachloride, ether, benzene, and petroleum ether serve to extract this substance. Since it is both an extremely weak base and only sparingly soluble in water it cannot be readily extracted with hydrochloric acid. Having no acidic (or phenolic) groups it is not extractable with alkali. The pigment is strongly fluorescent. In petroleum ether it fluoresces with an intensity about 13 times that of quinine sulfate in 0.1 *N* sulfuric acid on a weight basis when compared in a model 12B Coleman fluorophotometer fitted with B-1 and PC-1 filters. It can be readily detected on filter paper by virtue of its fluorescence. In general it exhibits high mobilities on being chromatographed on paper with solvents of low water content. Acidification of solvents with hydrochloric acid or basification with ammonium hydroxide such as employed by Swain[7] as diagnostic procedures for discriminating between acidic (or enolic) and basic plant pigments did not influence the mobility of the pigment.

A hydrochloride can be obtained by the action of anhydrous hydrogen chloride on a solution of the alkaloid in ethanol or petroleum ether. The resulting salt is strongly acidic. Because the characteristic blue fluorescence of solutions of the alkaloid is not shown by the salt form it is possible to estimate from a plot of fluorescence vs. *p*H that the base is approximately 50% in the free form at *p*H 2.0.

By means of ultraviolet light as little as 0.01 mcg. of the alkaloid may be detected when applied to a 2-mm. diameter area on Whatman No. 1 filter paper. Exposure of the spot to fumes of hydrochloric acid abolishes the blue fluorescence and the spot now glows yellow-green. In sufficient amounts the hydrochloride is visible as a green-yellow spot in visible light. Fumes of ammonia reverse this change. This simple test serves to distinguish the alkaloid from a number of naturally occurring fluorescent substances such as methyl anthranilate, anthranilic acid, terthienyl, various coumarins, flavanoids, and alkaloids.

A characteristic property of this alkaloid is the marked decrease in fluorescence which occurs in its solution in petroleum ether on the addition of various oxygen-containing solvents such as methanol, ethanol, *n*-propanol, ether, and acetone. Ethanol is remarkably effective in this respect. However its presence does not significantly alter the ultraviolet absorption spectrum as obtained with a petroleum ether solution of the alkaloid. The possibility that the quenching phenomenon is due to the high dielectric constants of the materials used is unlikely since a concentration of 0.12*M* of methanol is sufficient to cause a 50% loss of fluorescence in petroleum ether.

Workers in New Zealand[8-12] have isolated and characterized an alkaloid from the aerial portion of *Lolium perenne* (perennial rye grass) which they have named, perloline. Following this precedent we offer the name "annuloline" for the alkaloid isolated from the roots of the annual rye grass. Perloline and annuloline are clearly different compounds on the basis of their chemical and physical properties, analyses, fluorescent colors, absorption spectra,

(1) Journal Paper No. 1205 of the Purdue Agricultural Experiment Station, Purdue University, W. Lafayette, Ind.

(2) A portion of this work is taken from the thesis submitted by J. R. B. in partial fulfillment of the requirements for the M.S. Degree, Purdue University, August, 1957.

(3) To whom inquiries should be sent.

(4) Present Address: Dept. of Chemistry, Ontario Agricultural College, Guelph.

(5) G. Gentner, *Prakt. Blätter Pflanzenbau u. Pflanzenschutz*, **6**, 166 (1929).

(6) U. S. Dept. of Agriculture, *Testing Agricultural and Vegetable Seeds*, Government Printing Office, Washington, D. C. (1952), pp. 103-104.

(7) T. Swain, *Biochem. J.*, **53**, 200 (1953).

(8) R. E. R. Grimmet and J. Melville, *New Zealand J. Sci. Technol.*, **24B**, 149 (1943).

(9) R. E. R. Grimmet and D. F. Waters, *New Zealand J. Sci. Technol.*, **24B**, 151 (1943).

(10) I. Reifer and N. O. Bathurst, *New Zealand J. Sci. Technol.*, **24B**, 155 (1943).

(11) F. B. Shorland, *New Zealand J. Sci. Technol.*, **24B**, 159 (1943).

(12) E. M. Clare and I. M. Morice, *New Zealand J. Sci. Technol.*, **27B**, 36 (1945).

and distribution. We have been unable to detect any annuloline in plants of *Lolium perenne*.

EXPERIMENTAL

Annuloline hydrochloride. Seed of *Lolium multiflorum* were germinated in lots of 350 grams on 47 × 51 cm. sheets of Whatman No. 1 filter paper. Water was supplied daily. The germination temperature varied between 22–25°. After 17 days the aerial portions of the seedlings were discarded and the roots together with the filter paper in which they were matted were extracted with petroleum ether (b.p. 62°–65°). Extraction was performed using 7–10 l. of solvent for each lot of roots and allowed to proceed for at least 24 hr. (with occasional stirring). The extraction was repeated 2–3 times with fresh solvent. The combined extracts from 2–3 lots of roots were concentrated to about 200–300 ml. After being stored for several days at −20° the concentrate was filtered through glass wool in order to remove the waxy solid which deposited. The concentrate was further reduced in volume to about 50 ml. and treated with anhydrous HCl whereupon crude annuloline hydrochloride was obtained as a yellow-gray ppt. The hydrochloride was triturated with about 5 ml. of ice cold absolute ethanol, the mixture centrifuged at 2° and the supernatant was discarded. The air dried product was further purified by trituration with 10–25 ml. of H_2O and extraction with a sufficient number of 50-ml. portions of petroleum ether to remove the alkaloid which was now in the form of the free base. The petroleum ether solution was concentrated to 50–100 ml. and treated with HCl gas as before. The hydrochloride was washed with cold absolute ethanol and dried, m.p. 174–177°.

Anal.[13] Calcd. for $C_{20}H_{20}NO_4Cl$: C, 64.30; H, 5.38; N, 3.75; Cl, 9.5. Found: C, 64.89; H, 5.28; N, 3.57; Cl, 8.57, 9.02.

Annuloline. The hydrochloride was converted to the free base by shaking its $CHCl_3$ solution with dilute alkali. The free base was obtained as a brown tar on removal of the $CHCl_3$. After prolonged cooling in an ice bath and stirring, followed by overnight storage at room temperature, the material became transformed into a microcrystalline yellow powder. Recrystallization from hot benzene to which petroleum ether had been added to produce incipient cloudiness yielded fragile, light-yellow narrow rectangles, occurring mainly in clusters; m.p. 105–106°, remelting at same temperature. The product was neutral and tasteless but possessing a pleasant spicy resinous odor. The ultraviolet spectrum in cyclohexane showed a maximum at 354 mμ (log $\epsilon = 4.48$) and a minimum at 285 mμ (log $\epsilon = 3.85$).

Anal. Calcd. for $C_{17}H_{10}NO(OCH_3)_3$: C, 71.20; H, 5.64; N, 4.15; $(OCH_3)_3$, 27.6. Found: C, 70.59; H, 5.65; N, 4.16; OCH_3, 26.1.

The methoxyl determinations[14] were made by the titrimetrie method described by Niederl and Niederl.[15] Since recovery of OCH_3 from vanillin standards was 92% of theory, the value shown for annuloline has been adjusted accordingly. Dioxymethylene groups were shown to be absent by the procedure of Gaebel.[16]

Annuloline picrate. A 1% ethanolic solution of annuloline hydrochloride was treated with a slight excess of a 1% ethanolic solution of picric acid. The yellow fibrous crystals were recrystallized from hot 80% ethanol, m.p. 216–218°. One mole of picric acid per atom of N was found colorimetrically.

Anal. Calcd. for $C_{20}H_{19}NO_4 \cdot C_6H_3N_3O_7$: C, 55.10; H, 3.89; N, 9.89. Found: C, 55.18; H, 3.86; N, 10.05.

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(13) Elementary analyses were performed by Huffman Microanalytical Laboratories, Wheatridge, Colo.

(14) The methoxyl and dioxymethylene tests were carried out by Mr. R. S. Karimoto of this laboratory.

(15) J. B. Niederl and V. Niederl, *Organic Quantitative Micro-analysis*, J. Wiley and Sons, Inc., New York (1938), pp. 187–193.

(16) G. O. Gaebel, *Arch. Pharm.*, **248**, 226 (1910).

The Neopentyl and Neophyl Systems in Peracid Oxidation of Ketones[1]

JAMES W. WILT AND ALBERT DANIELZADEH

Received December 10, 1957

The suggestion of Emmons and Lucas[2] that the migrating group in the Baeyer-Villiger ketone oxidation[3] normally is the one most stabilized by hyperconjugative electron release appears to be substantiated by their work. Thus, in all the alkyl methyl ketones they reported, the methyl group was never observed to migrate, while the other alkyl group present in each case was capable of such hyperconjugative electron release and gave an acetate ester, as indicated below.

$$CH_3COR \xrightarrow{CF_3CO_2OH} CH_3COOR \qquad (1)$$

The yields were excellent (mainly 70–90%).

We have investigated *neopentyl* methyl ketone and *neophyl* (β-phenylisobutyl) methyl ketone in this reaction, following closely the directions of Emmons and Lucas. These ketones give *neopentyl* and *neophyl acetates*, as shown below, with no detectable amounts of methyl or other alkyl esters.

$$CH_3COCH_2C(CH_3)_3 \xrightarrow[(CH_2Cl_2)]{CF_3CO_2OH} CH_3COOCH_2C(CH_3)_3 \quad (2)$$
$$(40\%)$$

$$CH_3COCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}C_6H_5 \xrightarrow[(CH_2Cl_2)]{CF_3CO_2OH} CH_3COOCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}C_6H_5^{*} \quad (3)$$
$$(39\%)$$

* Yield based on consumed starting ketone.

The yields are poorer, however, than those noted in Emmons' work.

Because the neopentyl and neophyl systems have *no* hyperconjugative electron release (indeed, these systems often rearrange to the tert-amyl and benzyldimethylcarbinyl systems in order to achieve such hyperconjugative stabilization), we believe the present work shows that this hyperconjugative ability is not necessary for migration. It seems from all the work reported thus far that *any* alkyl group migrates preferentially to methyl. Hyperconjugative electron release may, nevertheless, be im-

(1) Abstracted from the thesis of Albert Danielzadeh to be submitted to the Graduate School of Loyola University for the degree of Master of Science, February 1958.

(2) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(3) A. Baeyer and V. Villiger, *Ber.*, **32**, 3625 (1899) and other references to be found in the article cited in the previous footnote.

portant in determining the ease of oxidation and the yield of ester.

The retention of the neopentyl and neophyl skeletal systems in the product esters, with no indication of contamination by either tert-amyl or benzyldimethylcarbinyl acetates, incidentally affords support for the concerted (non-carbonium ion) type mechanism usually ascribed to this reaction.[4]

EXPERIMENTAL

Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The infrared spectra were determined on liquid samples on Perkin-Elmer Model 21 Infrared Spectrophotometers by Miss E. Godar of this laboratory and by the Anderson Physical Laboratory, Champaign, Ill. Melting and boiling points are uncorrected.

Materials. Trifluoroacetic anhydride was commercial material (Halogen Chemicals), used as received. *Hydrogen peroxide* (90%) was generously supplied by the Becco Chemical Division of the Food Machinery and Chemical Corp., Buffalo, N. Y. *Neopentyl methyl ketone* was prepared as reported[6] by the dichromate oxidation of diisobutylene (Eastman) [44% yield, b.p. 124–127°, n_D^{20} 1.404, d_4^{20} 0.800, 2,4-dinitrophenylhydrazone m.p. 97° (lit.[6] m.p. 100°)]. *Neophyl methyl ketone* was prepared as reported[7] by the addition of mesityl oxide to benzene under aluminum chloride catalysis (61% yield, b.p. 61–62° at 1 mm., n_D^{20} 1.5115, d_4^{20} 0.973 [lit.[7] b.p. 134° at 22 mm., d_{25}^{25} 0.972)]. The 2,4-dinitrophenylhydrazone was prepared in the usual fashion, m.p. 98.5–99°.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: N, 15.71. Found: N, 15.56.

Authentic *neopentyl acetate* was obtained by the esterification of commercial neopentyl alcohol (Aldrich) in the usual manner with acetic acid and a trace of sulfuric acid [50% yield, b.p. 127°, n_D^{20} 1.390, d_4^{20} 0.855 (lit.[8] b.p. 127°, n_D^{20} 1.3893, d_4^{20} 0.8544)]. Authentic *neophyl acetate* was similarly obtained from neophyl alcohol[9] (60% yield, b.p. 105° at 5 mm., n_D^{20} 1.4959, d_4^{20} 1.008).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.38. Found: C, 75.17; H, 8.47.

The oxidation of neopentyl methyl ketone. A solution of peroxytrifluoroacetic acid was prepared by the dropwise addition of trifluoroacetic anhydride (37.8 g., 25.4 ml., 0.18 mole) to an ice cold solution of hydrogen peroxide (90%, 5.1 g., 4.1 ml., 0.15 mole) in methylene chloride (50 ml.). This solution was added dropwise over a 45-min. period to a stirred suspension of neopentyl methyl ketone (11.4 g., 0.1 mole) in methylene chloride (75 ml.) containing dry, finely powdered disodium hydrogen phosphate (65 g.). The exothermic reaction was controlled by the rate of addition and was completed by refluxing for 2 hr. after the addition was completed. The customary[2] work-up of the reaction mixture gave pure neopentyl acetate (5.25 g., 40% yield, b.p. 127–29°, n_D^{20} 1.390, d_4^{20} 0.863). The material gave a positive hydroxamic acid test for esters.

The infrared spectra of this product and authentic neopentyl acetate (see above) were identical, with indicative bands at 5.75s mμ (saturated ester C=O), 6.76m mμ (CH_2), 7.27s mμ (C_3≡C) and 8.05s mμ (acetate C—O—).

The oxidation of neophyl methyl ketone. A solution of peroxytrifluoroacetic acid was prepared as before, using double those amounts, and added as before to a solution of neophyl methyl ketone (35.2 g., 0.2 mole) in methylene chloride (150 ml.) containing dry, finely powdered disodium hydrogen phosphate (130 g.). Treatment of the reaction mixture in the usual fashion[2] gave neophyl acetate contaminated with much unchanged ketone (20 g., b.p. 90–100° at 4 mm., n_D^{20} 1.500, d_4^{20} 0.989). Purification was effected by means of Girard's reagent T in the usual manner [10] and furnished pure neophyl acetate [11.0 g., 28.5% yield (38.5% yield based on consumed ketone), b.p. 89–90° at 2 mm., n_D^{20} 1.4960, d_4^{20} 1.003]. This material was ketone free and gave a positive hydroxamic acid test for esters.

The infrared spectra of this product and authentic neophyl acetate (see above) were identical, with indicative bands at 5.76s mμ (saturated ester C=O), 6.75m mμ (CH_2), 7.26s mμ (C_3≡C) and 8.00–8.16s mμ (acetate C—O—), along with the expected peaks associated with aromatic unsaturation and mono-substitution.

Acknowledgment. We thank Miss E. Godar for certain of the infrared spectral measurements.

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(4) *Cf.* footnote 2 for leading references.

(5) E. H. Man, F. C. Frostick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **74**, 3229 (1952).

(6) L. Schmerling, *J. Am. Chem. Soc.*, **68**, 1650 (1946).

(7) A. Hoffman, *J. Am. Chem. Soc.*, **51**, 2542 (1929).

(8) O. R. Quayle and H. M. Norton, *J. Am. Chem. Soc.*, **62**, 1170 (1940).

(9) F. C. Whitmore, C. A. Weisgerber, and A. C. Shabica, Jr., *J. Am. Chem. Soc.*, **65**, 1469 (1943).

(10) As, for instance, described in L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath and Company, Boston, Mass., third edition (Revised) 1957, p. 89.

Configuration of Two Dinitroölefins

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Work by Freeman and Emmons[2] on the addition of dinitrogen tetroxide to acetylenes led them to assign *cis* and *trans* configurations to isomers of two pairs of dinitroölefins. Through calculations of dipole moments from dielectric constant measurements on two of these same compounds we can add evidence to confirm their assignment. Dipole moments of 5.79 D and 5.16 D were obtained for 3,4-dinitro-3-hexene, m.p. 31–32°, and 2,3-dinitro-2-butene, m.p. 28.0–28.5°, respectively, the isomers obtained from treatment of 1-chloro-1-nitro alkanes with alkali. Since the dipole moment of a nitro group in an alkane is about 3.3 D, the measurement constitutes strong evidence for the *cis* configuration in these compounds. Courtauld models of the *cis* isomers suggest that the two nitro groups may not be co-planar with the double bond. There is room for this interpretation in the values of the dipole moments, which are less than expected for *cis* nitro groups coplanar with the double bond.

A distorted *cis* structure for the two compounds is

(1) Taken from the M.S. thesis of T. E. Mead, Brown University, 1957.

(2) J. P. Freeman and W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 1712 (1957).

also consistent with the infrared spectra. A medium band at 1676 cm.$^{-1}$ in 3,4-dinitro-3-hexene and at 1686 cm.$^{-1}$ in 2,3-dinitro-2-butene was attributed in this laboratory to a C=C stretching vibration, a higher frequency than is common for this band. Two large nitro groups on either end of a double bond in the *cis* form would certainly twist the double bond and could cause an enhancement of its C=C frequency and an increase in its intensity.[3] This is in essential agreement with the interpretation given by Freeman and Emmons[2] for the two bands they found at 1667 cm.$^{-1}$ and 1676 cm.$^{-1}$ in the same compounds.

Additional evidence for a distorted *cis* configuration lies in a study of the ultraviolet spectra of the two dinitroölefins. The spectra of 2,3-dinitro-2-butene (λ_{max}, 219 mμ and ϵ, 5980) and 3,4-dinitro-3-hexene (λ_{max}, 219 mμ and ϵ, 5290) were very similar to the spectrum of 2-nitro-1-butene (λ_{max}, 223 mμ and ϵ, 1030). Actually the maximum for the K-bands (N→V) transitions appeared at only slightly lower wave lengths than in mononitroolefins.

The results in the ultraviolet measurements can be justified in the following way. K-bands for triply conjugated systems usually appear near 260 mμ but systems terminating in oxygen atoms are exceptional in that a shift to lower wavelengths occurs. An example is diacetylacetylene whose K-band appears at 236 mμ;[4] only one carbonyl group appears to enter into conjugation. A second argument rests on the statement that the wave length, λ, is proportional to the distance between charge centers in the excited state. In the *cis* configuration the separation of formally charged atoms is smaller than in the *trans* configuration. A third argument depends on the steric requirements of the conjugated system. In a *cis* structure steric inhibition of co-planarity should cause a hypsochromic effect,[5] that is, a shift in λ_{max} to lower wave lengths, as observed.

EXPERIMENTAL

cis-2,3-Dinitro-2-butene and cis-3,4-dinitro-3-hexene. The two dinitroölefins, *cis*-2,3-dinitro-2-butene, m.p. 28.0–28.5°, and *cis*-3,4-dinitro-3-hexene, m.p. 31–32°, were prepared by the method recently described in *Organic Syntheses*.[6] Infrared bands (melted on NaCl disks) for 2,3-dinitro-2-butene, cm.$^{-1}$: 3597 (m), 3003 (m), 1689 (m), 1558 (s), 1538 (s), 1435 (s), 1389 (s), 1346 (s), 1337 (s), 1217 (w), 1114 (m), 1028 (w), 969 (w), 885 (s), 821 (s).

For 3,4-dinitro-3-hexene, cm.$^{-1}$: 3067 (m), 3030 (shoulder), 1675 (w), 1555 (s), 1538 (s), 1458 (s), 1429 (s), 1348 (s), 1269 (w), 1202 (w), 1120 (m), 1056 (m), 959 (w), 896 (w), 815 (s), 804 (s).

Dipole moments of cis-2,3-dinitro-2-butene and cis-3,4-dinitro-3-hexene. Dielectric constants of benzene and carbon tetrachloride (Baker and Adamson Co., Inc., ACS Reagent Grade) solutions of the two dinitroölefins were determined at 100 kc/sec. using a capacitance-conductance bridge previously described.[7] The benzene was purified by the method of Nace and Turner.[8] Cell constants were calculated from capacitance measurements on carbon tetrachloride and cyclohexanol whose dielectric constants are accurately known.[9] The molar polarization and the dipole moments were then obtained by the method well described by Nace and Turner[8] except that the solute distortion polarization was taken as the molar refraction, calculated from atomic refraction values.

The following dipole moments were obtained: *m*-dinitrobenzene in benzene, 3.88 D[10]; 2,3-dinitro-2-butene in benzene, 5.16; in carbon tetrachloride, 5.16; 3,4-dinitro-3-hexene in benzene, 5.76; in carbon tetrachloride, 5.79.

TABLE I

MOLAR POLARIZATIONS IN CCl_4

Molality	Capacitance (Measured)	ϵ'	P_{12}
2,3-Dinitro-2-butene at 25.2°			
.00	54.244	2.235	...
.01	55.523	2.291	29.127
.03	57.759	2.388	30.615
.05	59.874	2.481	31.987
.07	61.924	2.571	33.258
.09	63.957	2.660	34.463
3,4-Dinitro-3-hexene at 26.0°			
.00	54.192	2.232	...
.01	55.703	2.298	29.263
.03	58.632	2.427	31.246
.05	61.638	2.558	33.148
.07	64.782	2.696	35.038
.09	67.862	2.830	36.771

Ultraviolet spectra of 2,3-dinitro-2-butene and 3,4-dinitro-3-hexene. Ultraviolet spectra were obtained with a Beckman Model DU Spectrophotometer in the region 210–320 mμ on 2,3-dinitro-2-butene and 2-nitro-1-butene and 210–350 mμ on 3,4-dinitro-3-hexene in 95% ethanol. The experimental data are given in the discussion above.

Acknowledgment. We are indebted to Dr. Donald J. Denney for advice in making the dielectric constant measurements.

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(3) R. C. Gore, American Cyanamid Co., Stamford, Conn., private communication.

(4) E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press, Inc., New York (1955), p. 148.

(5) Ref. 4, p. 170.

(6) D. E. Bisgrove, J. F. Brown, Jr., and L. B. Clapp, *Org. Syntheses*, **37**, 23 (1957).

(7) R. H. Cole and P. M. Gross, Jr., *Rev. Sci. Instr.*, **20**, 252 (1949).

(8) H. R. Nace and R. B. Turner, *J. Am. Chem. Soc.*, **75**, 4063 (1953).

(9) A. A. Maryott and E. R. Smith, *Natl. Bur. Standards Circ.* **514**, Aug. 10, 1951.

(10) C. P. Smyth, *Dielectric Behavior and Structure*, McGraw-Hill Book Co., Inc., New York (1955), p. 330 gives 3.89 D for *m*-dinitrobenzene.

Cyanoethylation of Aromatic Amides[1]

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Very little is known concerning the cyanoethylation of aromatic amides.[2] The one report indicates that benzamide is cyanoethylated to give *N*-β-cyanoethylbenzamide, m.p. 91–93°.[3] In our laboratory eleven different aromatic amides (Table I) were cyanoethylated in the presence of an excess of acrylonitrile and the products uniformly contained two cyanoethyl groups on the amide nitrogen, as shown by the following equation:

$$ArCONH_2 + CH_2{=}CHCN \longrightarrow ArCON(CH_2CH_2CN)_2$$

This was proved by analysis and by the fact that the *N*,*N*-di-β-cyanoethylbenzamide was identical to that produced by the reaction of benzoyl chloride on $HN(CH_2CH_2CN)_2$.[4]

EXPERIMENTAL[5]

The synthetic method given below is essentially the same for all the aromatic amides, and is based on a method by Galat.[6]

N,*N*,-*Di-β-cyanoethylnicotinamide.* In a three-neck 300-ml. flask equipped with a reflux condenser, a mechanical stirrer, and a separatory funnel, were placed 0.2 mole (24.4 g.) of nicotinamide and 100 ml. of acrylonitrile. This mixture was stirred, and cooled by means of an external cooling bath. Then 2.0 ml. of 40% benzyl trimethylammonium hydroxide (Triton B) was added, dropwise, over a 15-min. period.

After all the base had been added, the cooling bath was removed, and the mixture was allowed to gradually warm. The nicotinamide dissolved with the liberation of heat, which was controlled by external cooling. A precipitate formed, and stirring and cooling were continued for 10 min., and then the reaction mixture was neutralized with glacial acetic acid. The excess acrylonitrile was removed under reduced pressure.

After all the excess acrylonitrile had been removed, the yellow precipitate (33 g.) was separated by filtration. The product was crystallized repeatedly from hot water.

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TABLE I

N,N-Di-β-CYANOETHYL AMIDES

Starting Amide	Empirical Formula	M.P., °C.	Yield, %	% Nitrogen Calcd.	% Nitrogen Found
Benzamide	$C_{13}H_{13}N_3O$	110	77	18.48	18.41
Nicotinamide	$C_{12}H_{12}N_4O$	104	70	24.54	24.59
Isonicotinamide	$C_{12}H_{12}N_4O$	108	67	24.54	24.46
o-Toluamide	$C_{14}H_{15}N_3O$	83	62	17.42	17.42
p-Toluamide	$C_{14}H_{15}N_3O$	87	65	17.42	17.29
2-Furamide	$C_{11}H_{11}N_3O_2$	112	72	19.44	19.45
2-Naphthamide	$C_{17}H_{15}N_3O$	120	75	15.15	15.31
o-Chlorobenzamide	$C_{13}H_{12}ClN_3O$	83	70	16.06	16.28
3,4-Dichlorobenzamide	$C_{13}H_{11}Cl_2N_3O$	152	82	14.19	14.33
o-Iodobenzamide	$C_{13}H_{12}IN_3O$	99	66	11.92	12.17
m-Bromobenzamide	$C_{13}H_{12}BrN_3O$	83	62	13.73	13.73

(1) Taken from the M. S. thesis of Miss Romana Jonauskas.

(2) For leading reviews see (*a*) H. Bruson, *Org. Reactions*, Chapter 2 (1949) and (*b*) *The Chemistry of Acrylonitrile*, American Cyanamid Co. (1951), N. Y. 20, N. Y.

(3) I. G. Farbenind. A.G. Fr. Patent 877,120 (1942). When the reaction was run with essentially equimolar quantities of benzamide (2 moles) and acrylonitrile (2.26 moles) a 57% yield was obtained. No analytical figures were given. When the reaction was run between one mole of benzamide and 2.26 moles of acrylonitrile an oil was reported, and no physical constants nor analytical data were given.

(4) A. N. Kost, *Uchenye Zapiski Moskov. Gosudarst. Univ. im. M. V. Lomonosova*, No. 2, 141 (1947), *Chem. Abstr.*, **47**, 9906 (1953). It is interesting to note that *N*-β-cyanoethylbenzamide was reported by Goldberg and Kelly, *J. Chem. Soc.*, 1369 (1947), to melt at 96–98°, when prepared by the reaction of benzoyl chloride and β-cyanoethylamine. It would appear that the compound reported in reference 3 was a mixture of mono- and dicyanoethylated products.

(5) Microanalyses by Micro-Tech Labs., Skokie, Ill.

(6) A. Galat, *J. Am. Chem. Soc.*, **67**, 1414 (1945).

Sulfonylureas and Related Compounds

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Attempts in this laboratory to prepare hypoglycemic compounds based upon the structure of *N*-sulfanilyl-*N'*-*n*-butylurea, also known as BZ-55 or Carbutamide, have led to a series of new and active compounds. Marshall and Sigal[1] have reported upon the variations in the arylsulfonylureas. This note reports the preparation of some alkylsulfonylureas, and other varied compounds based upon the parent structure. The pharmacology[2] of these compounds will be reported elsewhere in the near future.

(1) F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958).

(2) The pharmacological testing was performed under the direction of Dr. M. Root.

TABLE I

$RSO_2NHCONHR'$

R	R'[a]	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	C_2H_5	170–171.5	$C_4H_{10}N_2O_3S$	28.92	6.07	16.86	28.92	6.02	16.65
CH_3	n-C_4H_9	106–107	$C_6H_{14}N_2O_3S$	37.11	7.27	14.43	37.02	7.40	14.67
CH_3	n-C_7H_{15}	123.5–124	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	46.01	8.50	11.76
n-C_3H_7	n-C_3H_7	125	$C_7H_{16}N_2O_3S$	40.38	7.75	13.46	40.32	7.91	13.59
n-C_3H_7	n-C_4H_9	114	$C_8H_{18}N_2O_3S$	43.25	7.99	12.30	43.45	8.20	12.49
n-C_3H_7	n-C_5H_{11}	105	$C_9H_{20}N_2O_3S$	45.98	8.49	11.84	46.19	8.47	12.04
n-C_3H_7	n-C_6H_{13}	97	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	48.35	9.09	11.37
n-C_4H_9	n-C_3H_7	43.0–43.5	$C_8H_{18}N_2O_3S$	43.22	8.16	12.60	43.25	7.99	12.30
n-C_4H_9	2-$CH_3OC_2H_5$	115–117	$C_8H_{18}N_2O_4S$			11.60			11.42
n-C_4H_9	n-C_4H_9	96–97	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.96	8.67	11.73
n-C_4H_9	i-C_4H_9	111–112	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	46.02	8.56	11.70
n-C_4H_9	2-C_4H_9	96–97	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.98	8.49	11.84
n-C_4H_9	t-C_4H_9	129–131	$C_9H_{20}N_2O_3S$			11.86			11.93
n-C_4H_9	1-HO-2-C_4H_8	Liquid	$C_9H_{20}N_2O_4S$			11.10			10.78
n-C_4H_9	$C_2H_5O_2CCH_2$[b]	109–110	$C_9H_{18}N_2O_5S$	40.59	6.81	10.51	40.91	6.81	11.28
n-C_4H_9	n-C_5H_{11}	91–92	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	48.26	9.07	11.10
n-C_4H_9	i-C_5H_{11}	76–77	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	48.27	8.75	10.82
n-C_4H_9	2-C_5H_{11}	87–89	$C_{10}H_{22}N_2O_3S$			11.19			11.14
n-C_4H_9	t-C_5H_{11}	82–84	$C_{10}H_{22}N_2O_3S$			11.19			11.51
n-C_4H_9	Cyclo-C_6H_9	131–132	$C_{10}H_{20}N_2O_3S$	48.39	8.12	11.28	48.60	8.55	11.47
n-C_4H_9	n-C_6H_{13}	91–93	$C_{11}H_{24}N_2O_3S$			10.59			10.40
n-C_4H_9	Cyclo-C_6H_{11}	139–140	$C_{11}H_{22}N_2O_3S$	50.38	8.45	10.65	50.55	8.65	10.43
n-C_4H_9	4-CH_3-2-C_5H_{10}	77–79	$C_{11}H_{24}N_2O_3S$			10.59			10.42
n-C_4H_9	n-C_7H_{15}	95–97	$C_{12}H_{26}N_2O_3S$			10.06			9.96
n-C_4H_9	2-C_7H_{15}	67–69	$C_{12}H_{26}N_2O_3S$			10.06			10.02
n-C_4H_9	3-C_7H_{15}	63–65	$C_{12}H_{26}N_2O_3S$			10.06			9.89
n-C_4H_9	p-$CH_3C_6H_4$[b]	118–120	$C_{12}H_{18}N_2O_3S$	53.32	6.71	10.37	53.54	6.79	10.64
n-C_4H_9	o-$CH_3OC_6H_4$[b]	164–165	$C_{12}H_{18}N_2O_4S$	50.30	6.33		50.48	6.53	
n-C_4H_9	p-$O_2NC_6H_4$[b]	184–185	$C_{11}H_{15}N_3O_5S$			13.33			13.40
i-C_4H_9	n-C_3H_7	142–144	$C_8H_{18}N_2O_3S$			21.61			12.91
i-C_4H_9	n-C_4H_9	107–109	$C_9H_{20}N_2O_3S$			11.86			12.15
i-C_4H_9	t-C_4H_9	133–135	$C_9H_{20}N_2O_3S$			11.86			11.89
CH_2=$C(CH_3)CH_2$—	n-C_3H_7	162–163	$C_8H_{16}N_2O_3S$	43.63	7.32		43.91	7.13	
CH_2=$C(CH_3)CH_2$—	n-C_4H_9	118–120	$C_9H_{18}N_2O_3S$			11.96			11.98
2-C_4H_9	n-C_4H_9	106–107	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.86	8.55	11.82
i-C_4H_9	i-C_5H_{11}	101–103	$C_{10}H_{22}N_2O_3S$			11.19			10.92
i-C_4H_9	3-$CH_3OC_3H_6$	82–83	$C_9H_{20}N_2O_4S$			11.10			10.96
n-C_5H_{11}	n-C_3H_7	89–90	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	46.10	8.54	11.66
n-C_5H_{11}	CH≡C—CH_2—	143–145	$C_9H_{16}N_2O_3S$			12.00			12.01
n-C_5H_{11}	n-C_4H_9	98–99	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	47.89	8.61	11.35
n-C_5H_{11}	2-C_4H_9	115–117	$C_{10}H_{22}N_2O_3S$			11.19			11.10
n-C_5H_{11}	i-C_4H_9	106–108	$C_{10}H_{22}N_2O_3S$			11.19			11.18
n-C_5H_{11}	t-C_4H_9	94–96	$C_{10}H_{22}N_2O_3S$			11.19			11.09
n-C_5H_{11}	n-C_5H_{11}	88–89	$C_{11}H_{24}N_2O_3S$	49.99	9.15		50.04	9.25	
n-C_5H_{11}	i-C_5H_{11}	89–90	$C_{11}H_{24}N_2O_3S$	49.99	9.15	10.60	50.28	8.95	10.89
n-C_5H_{11}	$C_6H_5CH_2$—	161–162	$C_{13}H_{20}N_2O_3S$			9.85			9.61
i-C_5H_{11}	n-C_3H_7	148–149	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.86	8.48	11.65
i-C_5H_{11}	i-C_3H_7	106–107	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.88	8.61	11.65
i-C_5H_{11}	n-C_4H_9	113–114	$C_{10}H_{22}N_2O_3S$	47.97	8.86	11.19	47.94	8.86	11.00
i-C_5H_{11}	i-C_4H_9	159–160	$C_{10}H_{22}N_2O_3S$			11.19			11.23
i-C_5H_{11}	2-C_4H_9	117–119	$C_{10}H_{22}N_2O_3S$			11.19			11.03
i-C_5H_{11}	3-$CH_3OC_3H_6$	101–102	$C_{10}H_{22}N_2O_4S$			10.53			10.34
i-C_5H_{11}	1-Cl-2-C_4H_9	162–164	$C_{10}H_{21}ClN_2O_3S$	42.18	7.43	9.84	42.21	7.35	9.95
i-C_5H_{11}	n-C_5H_{11}	84–85	$C_{11}H_{24}N_2O_3S$	49.99	9.15	10.60	50.16	9.49	10.89
i-C_5H_{11}	i-C_5H_{11}	79–81	$C_{11}H_{24}N_2O_3S$	49.99	9.15	10.60	50.36	9.21	10.34
i-C_5H_{11}	2-C_5H_{11}	108–109	$C_{11}H_{24}N_2O_3S$	49.99	9.15	10.60	49.84	9.29	10.76
Cyclo-C_6H_9	n-C_3H_7	146–148	$C_9H_{18}N_2O_3S$	46.14	7.75		46.66	7.67	
Cyclo-C_6H_9	3-$CH_3OC_3H_7$	128–129	$C_{10}H_{20}N_2O_4S$	47.46	7.97	10.06	47.97	8.16	9.84
Cyclo-C_6H_9	n-C_4H_9	154–155	$C_{10}H_{20}N_2O_3S$	48.37	8.12		48.33	8.24	
Cyclo-C_5H_9	i-C_5H_{11}	139.5–140.5	$C_{11}H_{22}N_2O_3S$	50.37	8.45		50.47	8.37	
n-C_6H_{13}	3-$CH_3OC_3H_6$	71–73	$C_{10}H_{22}N_2O_4S$			10.52			10.66
Cyclo-C_6H_{11}	C_2H_5	145–146	$C_9H_{18}N_2O_3S$	46.14	7.75		46.01	7.61	
Cyclo-C_6H_{11}	n-C_3H_7	155.0–156.5	$C_{10}H_{20}N_2O_3S$	48.37	8.12		48.32	8.34	
Cyclo-C_6H_{11}	i-C_3H_7	151–152	$C_{10}H_{20}N_2O_3S$	48.37	8.12		48.50	8.35	
Cyclo-C_6H_{11}	n-C_4H_9	133–134	$C_{11}H_{22}N_2O_3S$	50.37	8.45		50.19	8.45	
Cyclo-C_6H_{11}	i-C_5H_{11}	121–123	$C_{12}H_{24}N_2O_3S$	52.16	8.75	10.14	52.36	8.93	10.00
Cyclo-C_6H_{11}	Cyclo-C_6H_{11}	145–147	$C_{13}H_{26}N_2O_3S$	54.15	8.39	9.72	54.29	8.65	9.50
n-C_8H_{17}	H	142–143	$C_9H_{20}N_2O_3S$	45.75	8.53	11.86	45.76	8.79	11.65

TABLE I (*Continued*)

R	R′[a]	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
n-C_8H_{17}	n-C_4H_9	74–75	$C_{13}H_{28}N_2O_3S$	53.40	9.65	9.58	53.80	9.86	9.53
n-$C_{10}H_{21}$	CH_3	103.5–104.5	$C_{12}H_{26}N_2O_3S$	51.78	9.42		52.13	9.69	
n-$C_{10}H_{21}$	C_2H_5	87–89	$C_{13}H_{28}N_2O_3S$	53.40	9.65		53.61	9.73	
n-$C_{10}H_{21}$	n-C_4H_9	90–92	$C_{15}H_{32}N_2O_3S$	56.22	10.07		56.13	10.01	
$C_6H_5CH_2$	n-C_3H_7	203–205	$C_{11}H_{16}N_2O_3S$	51.56	6.29		51.81	6.33	
$C_6H_5CH_2$	n-C_4H_9	161.0–161.5	$C_{12}H_{18}N_2O_3S$	53.32	6.71		53.29	6.87	
2-Thienyl	n-C_3H_7	141–143	$C_8H_{12}N_2O_3S_2$	38.69	4.87		38.69	4.79	
2-Thienyl	n-C_4H_9	151–152	$C_9H_{14}N_2O_3S_2$	41.22	5.38	10.68	41.24	5.54	10.29

[a] All compounds were made by procedure 1 except as noted. [b] Made by procedure 2.

TABLE II

$RSO_2NHCOOR'$

R	R′	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	C_2H_5	Oil	$C_4H_9NO_4S$	28.75	5.43	8.38	28.72	5.28	8.46
n-C_4H_9	C_2H_5	Oil	$C_7H_{15}NO_4S$	40.19	7.23	6.70	40.30	7.25	6.65
n-C_4H_9	n-C_3H_7	Oil[a]	$C_8H_{16}NO_4SNa$	39.18	6.58	5.71	39.18	6.67	5.64
n-C_4H_9	n-C_4H_9	46–48	$C_9H_{19}NO_4S$			5.90			6.08
n-C_4H_9	n-C_5H_{11}	Oil[a]	$C_{10}H_{20}NO_4SNa$			5.13			5.10
n-C_4H_9	n-C_6H_{13}	Oil[a]	$C_{11}H_{22}NO_4SNa$	45.98	7.72	4.87	45.75	7.86	5.02
n-C_5H_{11}	C_2H_5	Oil	$C_8H_{17}NO_4S$			6.28			6.35
n-C_5H_{11}	n-C_4H_9	Oil	$C_{10}H_{21}NO_4S$			5.57			5.63
n-C_5H_{11}	i-C_4H_9	73–75	$C_{10}H_{21}NO_4S$			5.57			5.42
Cyclo-C_5H_9	C_2H_5	Oil[b]	$C_8H_{15}NO_4S$	43.42	6.83		43.29	6.92	
n-C_6H_{13}	C_2H_5	Oil	$C_9H_{19}NO_4S$			5.90			5.74
Cyclo-C_6H_{11}	C_2H_5	81–83	$C_9H_{17}NO_4S$			5.96			6.22
n-$C_{10}H_{21}$	C_2H_5	46–48	$C_{13}H_{27}NO_4S$	53.21	9.27		53.35	9.31	
$C_6H_5CH_2$	C_2H_5	101–103	$C_{10}H_{13}NO_4S$			5.76			5.69
2-Thienyl	C_2H_5	80–81	$C_7H_9NO_4S_2$	35.75	3.86	5.96	35.98	3.64	5.89

[a] Analyses were made on the crystalline sodium salts which were purified by recrystallization from ethanol-acetone. [b] n_D^{25} 1.4795.

TABLE III[a]

$RSO_2NHCONR'R$

R	R′	R″	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
n-C_4H_9	CH_3	CH_3	Oil	$C_7H_{16}N_2O_3S$			13.46			13.53
n-C_4H_9	C_2H_5	C_2H_5	Oil	$C_9H_{20}N_2O_3S$	45.75	8.53		45.74	8.67	
n-C_4H_9	Morpholinyl		95	$C_9H_{18}N_2O_4S$	43.19	7.25		42.84	7.58	
n-C_4H_9	Piperidyl		37–38	$C_{10}H_{20}N_2O_3S$	48.37	8.12	11.28	48.27	8.39	11.09
n-C_4H_9	Pyrrolidyl		125	$C_9H_{18}N_2O_3S$	46.14	7.75	11.96	46.03	7.47	12.10

[a] Compounds were prepared by procedure 1 for Table I.

Replacement of the aryl group of the parent compound with an alkyl radical has resulted in the alkylsulfonylureas listed in Table I. The intermediate carbamates were all prepared by a general method[3] and many were not characterized due to the difficulty encountered in distillation. The carbamates characterized or analyzed are listed in Table II.

To complete this series several *bis* compounds were prepared: 1,6-bis(sulfonamido)hexane; 1,6-bis(*N*-carbethoxysulfonamido)hexane; 1,6-bis-(*N*-*n*-propylcarbamoylsulfonamido)hexane; 1,6-bis(*N*-isoamylcarbamoylsulfonamido)hexane; 1,6-bis(*n*-amylsulfonylureido)hexane; *N*,*N*′-bis(isoamylsulfonyl)urea. Secondary amines were also used in the reaction with the sulfonylcarbamates leading to a series of *N*,*N*′-disubstituted *n*-butylsulfonylureas as listed in Table III.

Variations in the basic sulfonylurea structure by replacement of each of the nitrogen moieties in turn by methylene gave the new compounds listed in Tables IV and V.

EXPERIMENTAL[4]

Preparation of the alkylsulfonylureas in Table I. Procedure 1.[3a] One molar part of the sulfonamide[5] was dissolved in

(3) (a) Haack, E. and Hagedorn, A., private communication. (b) J. R. Geigy A.-G., British Patent **538,884**, Aug. 20, 1941.

(4) The melting points are uncorrected.

(5) All sulfonamides were known compounds and were commercially available or prepared by literature methods.

TABLE IV

RSO_2NHCOR'

R	R'	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
n-C_4H_9	n-C_4H_9	61–62[a]	$C_9H_{19}NO_3S$			6.33			6.07
i-C_5H_{11}	n-C_3H_7	35–36[b]	$C_9H_{19}NO_3S$			6.33			6.08
p-$CH_3C_6H_4$	n-C_5H_{11}	63–65[c]	$C_{13}H_{19}NO_3S$	57.96	7.11	5.20	58.05	7.30	5.49

[a] B.p. 204–206° at 10 mm. Hg. [b] B.p. 200–201° at 10 mm. Hg. [c] Recrystallized from isopropyl ether–petroleum ether 60–90°.

TABLE V

RSO_2CH_2CONHR'

R	R'	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	n-C_4H_9	112–113	$C_{12}H_{17}NO_3S$	56.44	6.71	5.49	56.61	6.89	5.20
p-$CH_3C_6H_4$	n-C_3H_7	117–118	$C_{12}H_{17}NO_3S$	56.44	6.71	5.49	56.29	6.79	5.26
p-$CH_3C_6H_4$	n-C_4H_9	103–104	$C_{13}H_{19}NO_3S$	57.96	7.11		57.72	7.12	

about 10 molar parts of dry acetone and 1.2 molar parts of anhydrous finely divided potassium carbonate were added. With refluxing and stirring 1.2 molar parts of alkyl chlorocarbonate were added dropwise over a period of 1–2 hr. The mixture was then refluxed for 15 hr. with stirring, cooled, and filtered. The solid was dissolved in a minimum of water and acidified with concentrated hydrochloric acid. Ether extraction of the freed carbamate from the aqueous solution of salts and vacuum removal of the ether gave a 60–80% yield of the corresponding carbamate. Most of these compounds were viscous oils, which decomposed upon attempted distillation, and were used without further purification. A few representative samples of these carbamates are in Table II.

One molar part of the crude carbamate was dissolved in an excess of the appropriate amine forming a salt and the excess amine removed *in vacuo*. The residue was then pyrolyzed *in vacuo* at 128–130° for 2–3 hr. or until bubbling had ceased. The product was crystallized and then recrystallized from aqueous ethanol. Yield of the sulfonylurea was about 60%, ranging from 37% to 94% in some cases.

Procedure 2. One molar equivalent of the sulfonamide was treated with the appropriate isocyanate in nitrobenzene.[6]

Preparation of the acylsulfonamides in Table IV. The compounds were prepared in the same manner as the carbamates of Procedure 1 above. After reflux the acetone was removed *in vacuo* and the residue was dissolved in a minimum of water. Acidification of the resulting solution with hydrochloric acid precipitated the new compound. Recrystallization was from aqueous methanol. These new compounds are listed in Table IV.

Preparation of the α-arylsulfonyl-N-alkylacetamides. The N-alkyl-α-chloroacetamide[7] (0.1 mole) and sodium aryl sulfinate (0.11 mole) were refluxed in 60 ml. of anhydrous ethanol for 16 hr. The reaction mixture was then diluted with 60 ml. of boiling water and the product allowed to crystallize slowly from the mixture. The product was recrystallized from 50% aqueous ethanol. Yields were approximately 60%.

Preparation of the "bis" compounds. The following compounds were prepared by Procedure 1 for the alkylsulfonylureas: Starting sulfonamide, 1,6-bis(sulfonamido)hexane, m.p. 173–174°, yield 67% from 1,6-dibromohexane.[8] (*Anal.* Calcd. for $C_6H_{16}N_2O_4S_2$: C, 29.49; H, 6.60; N, 11.47. Found: C, 29.43; H, 6.66; N, 11.11). 1,6-bis(*N*-carbethoxysulfonamido)hexane, m.p. 84–85°, yield 73%. (*Anal.* Calcd. for $C_{12}H_{24}N_2O_8S_2$: C, 37.11; H, 6.23; N, 7.21. Found: C, 37.15; H, 6.24; N, 7.34). 1,6-bis(*N*-*n*-propylcarbamoylsulfonamido)hexane, m.p. 200–201°, yield 85%. (*Anal.* Calcd. for $C_{14}H_{30}N_4O_6S_2$: C, 40.57; H, 7.30; N, 13.52. Found: C, 40.73; H, 7.16; N, 13.33). 1,6-bis(*N*-isoamylcarbamoylsulfonamido)hexane, m.p. 194–195°, yield 94% (*Anal.* Calcd. for $C_{18}H_{38}N_4O_6S_2$: C, 45.76; H, 8.50; N, 11.88. Found: C, 45.90; H, 8.34; N, 11.73). 1,6-bis(*n*-amylsulfonylureido)hexane, m.p. 174–175°, yield 84% (*Anal.* Calcd. for $C_{18}H_{38}N_4O_6S_2$: C, 45.76; H, 8.50; N, 11.18. Found: C, 45.94; H, 8.53; N, 10.86).

Preparation of N,N'-bis(isoamylsulfonyl)urea. Ten grams (0.67 mole) of isoamylsulfonamide was dissolved in an excess of 10% sodium hydroxide. Phosgene was added slowly until a sample of the solution was acid to litmus paper. The product was extracted with benzene, the solvent removed *in vacuo* and the product (10 g., 91%) distilled (b.p. 138–140° at 1.5 mm. Hg).

Anal. Calcd. for $C_{11}H_{24}N_2O_5S_2$: C, 40.22; H, 8.36; N, 8.52. Found: C, 39.97; H, 8.46; N, 8.61.

Upon standing the liquid crystallized to a waxy solid melting at 35–36°.

Acknowledgment. The authors wish to express their appreciation for the microanalyses performed by H. L. Hunter, G. M. Maciak, and Miss G. Beckmann.

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(6) (a) H. Martin, R. Hirt, and A. Staub, U. S. Patent 2,371,178, March 13, 1945. (b) Haack, E., U. S. Patent 2,385,571, Sept. 25, 1945. (c) J. R. Geigy A.-G., Swiss Patent 215,241, Sept. 1, 1941. (d) J. R. Geigy A.-G., Swiss Patent 220,970, Aug. 1, 1942. (e) J. R. Geigy A.-G., Swiss Patent 260,201, July 16, 1947.

(7) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, 21, 145 (1915).

(8) Prepared by methods of T. B. Johnson, U. S. Patent 2,146,744, Feb. 14, 1939. Treatment of the resulting sulfonylchloride with anhydrous ammonia led directly to the bis-sulfonamide.

Some *N*-Arylsulfonyl-*N'*-alkylureas

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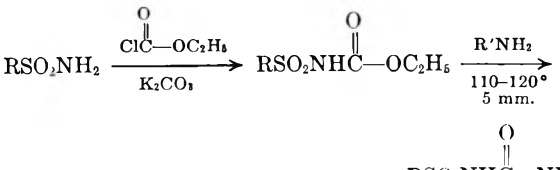
The clinical application of *N*-(*p*-aminophenylsulfonyl)-*N'*-*n*-butylurea (BZ 55, Carbutamide) as an effective oral agent for lowering blood sugar has been reported.[1] Insulin has been used very successfully for this purpose since its introduction thirty-five years ago but has the disadvantage that it must be given by injection. Although BZ 55 is effective only in selected cases of diabetes, it did seem to offer a partial answer to the problem of overcoming this disadvantage. The present study was undertaken to prepare additional compounds having hypoglycemic activity.

A number of derivatives (Table II) have been prepared according to the following reaction scheme.



The optimum temperature for the reaction between the amines and the sulfonylcarbamates (Table I) was found to be 110–120°. At higher temperatures (up to 150°) the reaction tended to produce varying amounts of the original sulfonamides.

Efforts to prepare a *p*-allyloxyphenyl derivative were unsuccessful because attempted chlorosulfonation of allyl phenyl ether did not yield the desired sulfonyl chloride.

Extensive comparative pharmacology has been carried out on several of the sulfonylureas and the detailed results of these studies will be reported elsewhere.

The most effective compound, when tested orally in dogs, was *N*-(*p*-chlorophenylsulfonyl)-*N'*-*n*-propylurea. The hypoglycemic effect of this compound is slightly more than twice that of BZ 55 tested under the same conditions. On the basis of these results, a number of derivatives were prepared in which the position or nature of the halogen was varied. Also, several dichloro and methyl chloro compounds were synthesized. None of these were as active as the original *p*-chlorophenyl derivative.

TABLE I

N-ARYLSULFONYLCARBAMATES

$RSO_2NHC(=O)—OC_2H_5$

R	Yield, %	M.P., °C.	Recryst. Solvent[a]	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_6H_5	84	108–110		$C_9H_{11}NO_4S$	[b]			
2-$CH_3C_6H_4$	57	121–123	$CHCl_3$–pet. ether	$C_{10}H_{13}NO_4S$	49.35	5.38	49.44	5.34
3-$CH_3C_6H_4$	70	66–68	$CHCl_3$–pet. ether	$C_{10}H_{13}NO_4S$	49.35	5.38	49.32	5.42
4-$(CH_3)_2CHC_6H_4$	75	[c]						
4-$CH_3OC_6H_4$	71	118–120	$CHCl_3$–pet. ether	$C_{10}H_{13}NO_5S$	46.32	5.06	46.60	5.35
4-$C_2H_5OC_6H_4$	90	98–100	EtOAc–pet. ether	$C_{11}H_{15}NO_5S$	48.34	5.54	48.30	5.53
4-(*n*-C_4H_9O)C_6H_4	72	69–71	EtOAc–pet. ether	$C_{13}H_{19}NO_5S$	51.82	6.36	51.94	6.47
2,4-$(CH_3O)_2C_6H_3$	82	155–157	C_6H_6–pet. ether	$C_{11}H_{15}NO_6S$	45.68	5.23	45.87	5.41
2-CH_3-4-$CH_3OC_6H_3$	45	128–130	Dil. ethanol	$C_{11}H_{15}NO_5S$	48.34	5.54	48.56	5.58
4-$CH_3SC_6H_4$	65	139–141	$CHCl_3$–pet. ether	$C_{10}H_{13}NO_4S_2$	43.65	4.76	43.83	4.94
4-BrC_6H_4	69[d]	88–90	EtOAc–pet. ether	$C_9H_{10}BrNO_4S$	35.04	3.27	35.31	3.53
2-ClC_6H_4	90	151–153	Dil. ethanol	$C_9H_{10}ClNO_4S$	41.00	3.86	41.32	3.84
4-ClC_6H_4	80	92–93	$CHCl_3$–pet. ether	$C_9H_{10}ClNO_4S$	41.00	3.86	41.56	3.87
					N, 5.32		N, 5.34	
2,4-$Cl_2C_6H_3$	40	136–137	C_6H_6–pet. ether	$C_9H_9Cl_2NO_4S$	36.24	3.04	36.45	3.30
3,4-$Cl_2C_6H_3$	67	115–117	Dil. ethanol	$C_9H_5Cl_2NO_4S$	36.24	3.04	36.51	3.32
2,5-$Cl_2C_6H_3$	74	151–153	Dil. ethanol	$C_9H_9Cl_2NO_4S$	36.24	3.04	36.47	3.39
3-Cl-4-$CH_3C_6H_3$	84	78–80	EtOAc–pet. ether	$C_{10}H_{12}ClNO_4S$	43.25	4.36	42.83	4.66
4-Cl-3-$CH_3C_6H_3$	84	87–89	EtOAc–pet. ether	$C_{10}H_{12}ClNO_4S$	43.25	4.36	42.93	4.23
					N, 5.05		N, 5.10	
4-FC_6H_4	88	91–93	EtOAc–pet. ether	$C_9H_{10}FNO_4S$	43.72	4.04	44.11	4.18

[a] The petroleum ether used was the fraction boiling at 60–71°. [b] O. C. Billeter, *Ber.*, **37**, 690 (1904). [c] Viscous oil did not crystallize and was used as such. [d] Yield based on sulfonamide actually consumed.

(1) J. D. Achelis and K. Hardebeck, *Deutsche med. Wochschr.*, 80, 1455 (1955); F. Bertram, E. Bendfeldt, and H. Otto, *Deutsche med. Wochschr.*, 80, 1452 (1955); H. Franke and J. Fuchs, *Deutsche med. Wochschr.*, 80, 1449 (1955).

TABLE II

ARYLSULFONYLUREAS

$$RSO_2NH—\overset{\overset{O}{\|}}{C}—NHR'$$

R	R′	Yield, %	M.P., °C.	Recryst. Solvent[a]	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_6H_5	n-C_3H_7	27	118–120	Dil. ethanol	$C_{10}H_{14}N_2O_3S$	49.58	5.82	49.83	5.83
C_6H_5	n-C_4H_9	62	130–132	Dil. ethanol	$C_{11}H_{16}N_2O_3S$	51.54	6.29	51.45	6.45
C_6H_5	iso-C_5H_{11}	63	120–122	Dil. ethanol	$C_{12}H_{18}N_2O_3S$	53.30	6.72	53.55	6.84
C_6H_5	C_6H_{11}[b]	33	185–186	Dil. ethanol	$C_{13}H_{18}N_2O_3S$	55.29	6.43	55.53	6.31
C_6H_5	3-$CH_3O(CH_2)_3$	55	110–112	Dil. ethanol	$C_{11}H_{16}N_2O_4S$	48.54	5.93	48.74	5.96
C_6H_5	3-$CH_3S(CH_2)_3$[c]	71	130–131	Dil. ethanol	$C_{11}H_{16}N_2O_3S_2$	45.81	5.59	46.07	5.24
2-$CH_3C_6H_4$	n-C_4H_9	52	159–161	Ethanol–pet. ether	$C_{12}H_{18}N_2O_3S$	53.30	6.72	53.68	6.47
3-$CH_3C_6H_4$	n-C_3H_7	18	108–110	Dil. ethanol	$C_{11}H_{16}N_2O_3S$	51.54	6.29	51.22	6.07
3-$CH_3C_6H_4$	n-C_4H_9	22	106–108	C_6H_6–pet. ether	$C_{12}H_{18}N_2O_3S$	53.30	6.72	53.68	6.90
4-$(CH_3)_2CHC_6H_4$	n-C_4H_9	62	130–132	C_6H_6–pet. ether	$C_{14}H_{22}N_2O_3S$	56.36	7.43	56.30	7.50
4-$CH_3OC_6H_4$	n-C_3H_7	22	120–122	Dil. ethanol	$C_{11}H_{16}N_2O_4S$	48.54	5.93	48.63	6.04
4-$CH_3OC_6H_4$	n-C_4H_9[d]	46	118.5–120	Dil. ethanol	$C_{12}H_{18}N_2O_4S$	50.30	6.34	50.68	6.38
4-$CH_3OC_6H_4$	iso-C_5H_{11}	38	125–127	Dil. ethanol	$C_{13}H_{20}N_2O_4S$	51.96	6.72	52.08	6.81
4-$CH_3OC_6H_4$	3-$CH_3O(CH_2)_3$	63	115–117	Dioxane–pet. ether	$C_{12}H_{18}N_2O_5S$	47.68	6.00	47.04	6.20
4-$C_2H_5OC_6H_4$	n-C_3H_7	53	177–178	Ethanol	$C_{12}H_{18}N_2O_4S$	50.30	6.34	50.08	6.50
4-$C_2H_5OC_6H_4$	n-C_4H_9	33	158–160	Dil. ethanol	$C_{13}H_{20}N_2O_4S$	51.96	6.72	52.09	6.91
4-(n-C_4H_3O)C_6H_4	n-C_3H_7	55	125–126	C_6H_6–pet. ether	$C_{14}H_{22}N_2O_4S$	53.48	7.05	53.76	7.09
2,4-$(CH_3O)_2C_6H_3$	n-C_3H_7	31	199–200	Dil. dioxane	$C_{12}H_{18}N_2O_5S$	47.68	6.00	47.95	6.00
2,4-$(CH_3O)_2C_6H_3$	n-C_4H_9	40	184–185	Dil. dioxane	$C_{13}H_{20}N_2O_5S$	49.33	6.37	49.57	6.35
2,4-$(CH_3O)_2C_6H_3$	iso-C_5H_{11}	25	172–174	Dil. dioxane	$C_{14}H_{22}N_2O_5S$	50.84	6.72	51.05	6.76
2,4-$(CH_3O)_2C_6H_3$	3-$CH_3O(CH_2)_3$	33	147–149	Dil. ethanol	$C_{13}H_{20}N_2O_6S$	46.96	6.06	47.12	5.75
2-CH_3-4-$CH_3OC_6H_3$	n-C_4H_9	45	163–165	Dil. ethanol	$C_{13}H_{20}N_2O_4S$	51.96	6.72	52.15	6.87
2-CH_3-4-$CH_3OC_6H_3$	C_6H_{11}	31	188–190	Dil. dioxane	$C_{15}H_{22}N_2O_4S$	55.20	6.78	54.95	6.85
4-$CH_3SC_6H_4$	n-C_3H_7	54	140–141	Dil. dioxane	$C_{11}H_{16}N_2O_3S_2$	45.81	5.59	45.82	5.67
4-$CH_3SC_6H_4$	n-C_4H_9	45	116–117	Dil. dioxane	$C_{12}H_{18}N_2O_3S_2$	47.66	6.00	47.94	6.50
4-$CH_3SC_6H_4$	C_6H_{11}	58	187–188	Dil. dioxane	$C_{14}H_{20}N_2O_3S_2$	51.20	6.13	51.09	6.29
4-BrC_6H_4	C_2H_5	68	147–149	Dil. ethanol	$C_9H_{11}BrN_2O_3S$	35.19	3.61	35.61	4.01
4-BrC_6H_4	n-C_3H_7	49	138–140	Dil. ethanol	$C_{10}H_{13}BrN_2O_3S$	37.38	4.08	37.40	4.11
4-BrC_6H_4	n-C_4H_9[e]	55	128–129	Dil. ethanol	$C_{11}H_{15}BrN_2O_3S$	39.45	4.52	39.64	4.64
2-ClC_6H_4	n-C_3H_7	37	176–178	Dil. ethanol C_6H_6–pet. ether	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.50	5.01

EXPERIMENTAL

Arylsulfonamides. The arylsulfonamides were all prepared by addition of the sulfonyl chloride[2] to a large excess of aqueous ammonium hydroxide. It was found to be advantageous to dissolve the solid sulfonyl chlorides in a volume of dioxane equal to their weight.

N-Arylsulfonylcarbamates.[3,4] To a mixture of 0.5 mole of the sulfonamide and 1.3 moles of anhydrous potassium carbonate in 600 ml. of reagent acetone was added, during 3 hr. with stirring, 0.66 mole of ethyl chlorocarbonate. The mixture was then stirred and refluxed for 18 hr., was allowed to cool, and was filtered. The solid residue was dissolved in about 1500 ml. of water. Any insoluble material was removed by filtration. If the amount was appreciable it was treated with more water. (Only in the case of the *p*-bromophenylsulfonylcarbamate was it impossible to dissolve almost all the material. In this one case a considerable amount of the starting sulfonamide was recovered.) The solution was acidified with concentrated hydrochloric acid. If the product did not crystallize readily, decantation of the acidic supernatant liquid and stirring the oily carbamate with water promoted crystallization. The crude product was used for reaction with the amines. Samples were purified for analysis.

N-Arylsulfonyl-N′-alkylureas.[3,5] A mixture of 0.1 mole of a *N*-sulfonylcarbamate and 0.3–0.4 mole of an alkylamine was shaken and, if necessary, warmed at about 80° until solution was complete. The excess amine was removed under reduced pressure and the residue was heated at 110–120° at a pressure of about 5 mm. for 6 hr. The product was first isolated by crystallization from dilute ethanol and was then purified from the solvents indicated in Table II.

(2) The arylsulfonyl chlorides which were not available commercially were prepared by chlorosulfonation. For general references on the sulfonyl chlorides and sulfonamides, see E. H. Huntress and F. H. Carten, *J. Am. Chem. Soc.*, **62**, 511, 603 (1940) and E. H. Huntress and J. S. Autentrieth, *J. Am. Chem. Soc.*, **63**, 3446 (1941).

(3) The method of preparation was essentially that which was kindly communicated to us by E. Haack and A. Hagedorn, C. F. Boehringer and Soehne, Mannheim-Waldhof, Germany.

(4) A similar method of preparation of a related carbamate is contained in British Patent 538,884 [*Chem. Abstr.*, **36**, 3512 (1942)].

(5) The preparation of this type compound has also been described in British Patent 604,259 [*Chem. Abstr.*, **43**, 1061 (1949)] using glycol monomethyl ether as a solvent.

TABLE II (*Continued*)

R	R′	Yield, %	M.P., °C.	Recryst. Solvent[a]	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2-ClC_6H_4	*n*-C_4H_9	64	164–166	Dil. ethanol	$C_{11}H_{15}ClN_2O_3S$	45.42	5.20	45.75	5.39
3-ClC_6H_4	*n*-C_3H_7	60	133–134	Dil. ethanol C_6H_6–pet. ether	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.73	4.95
4-ClC_6H_4	C_2H_5	73	144–146	Dil. ethanol	$C_9H_{11}ClN_2O_3S$	41.16	4.22	41.17	4.25
4-ClC_6H_4	*n*-C_3H_7	47	127–129	Dil. ethanol	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.48	4.84
4-ClC_6H_4	*iso*-C_3H_7	31	155–156	Dil. ethanol	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.56	4.63
4-ClC_6H_4	*n*-C_4H_9[e]	54	115–117	Dil. ethanol	$C_{11}H_{15}ClN_2O_3S$	45.42	5.20	45.70	5.23
4-ClC_6H_4	3-$CH_3O(CH_2)_3$	41	103–105	Dil. ethanol	$C_{11}H_{15}ClN_2O_4S$	43.06	4.93	43.16	5.08
4-ClC_6H_4	3-$CH_3S(CH_2)_3$	44	135–137	Dil. ethanol	$C_{11}H_{15}ClN_2O_3S_2$	40.88	4.66	40.84	4.81
2,4-$Cl_2C_6H_3$	*n*-C_4H_9	82	171–173	Dil. ethanol	$C_{11}H_{14}Cl_2N_2O_3S$	40.62	4.34	40.84	3.99
2,5-$Cl_2C_6H_3$	*n*-C_3H_7	48	201–203	C_6H_6–pet. ether	$C_{10}H_{12}Cl_2N_2O_3S$	38.60	3.89	38.66	3.91
2,5-$Cl_2C_6H_3$	*n*-C_4H_9	73	194–195	C_6H_6	$C_{11}H_{14}Cl_2N_2O_3S$	40.62	4.34	40.76	4.46
3,4-$Cl_2C_6H_3$	*n*-C_3H_7	62	144–146	Dil. ethanol	$C_{10}H_{12}Cl_2N_2O_3S$	38.60	3.89	38.78	3.86
3-Cl-4-$CH_3C_6H_3$	*n*-C_3H_7	41	132–133	Dil. ethanol	$C_{11}H_{15}ClN_2O_3S$	45.42	5.20	45.15	5.46
3-Cl-4-$CH_3C_6H_3$	*n*-C_4H_9	41	146–148	Dil. ethanol C_6H_6–pet. ether $NaHCO_3$ reppt.	$C_{12}H_{17}ClN_2O_3S$	47.26	5.62	47.60	5.53
4-Cl-3-$CH_2C_6H_3$	*n*-C_3H_7	44	142–144	Dil. ethanol C_6H_6–pet. ether	$C_{11}H_{15}ClN_2O_3S$	45.42	5.20	46.04	5.32
4-Cl-3-$CH_3C_6H_3$	C_2H_5	30	153–155	Dil. ethanol	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.21	4.71
4-FC_6H_4	*n*-C_3H_7	43	131–133	Dil. ethanol	$C_{10}H_{13}FN_2O_3S$	46.11	5.03	46.02	4.98
4-FC_6H_4	*n*-C_4H_9	52	103–104	Dil. ethanol	$C_{11}H_{15}FN_2O_3S$	48.16	5.52	48.41	5.75

[a] The petroleum ether used was the fraction boiling at 60–71°. [b] Since prepared in this study, this compound has been reported in Accepted German Patent Specification **F 18339 IVb/12o** (Dec. 27, 1956). [c] The required amine has been reported by W. Schneider, *Ann.*, **375,** 245 (1910). In this present work it was prepared by lithium aluminum hydride reduction of 3-methylmercaptopropionitrile [C. D. Hurd and L. L. Gershbein, *J. Am. Chem. Soc.*, **69,** 2328 (1947)] by the method of L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73,** 242 (1951). [d] Since prepared in this present investigation, this compound has been described in Accepted German Patent Specification **F 18136 IVb/12o** (Sept. 27, 1956). [e] This compound has since been reported independently in Accepted German Patent Specification **F 18659 IVb/12o** (Dec. 27, 1956).

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Steroid Epoxides

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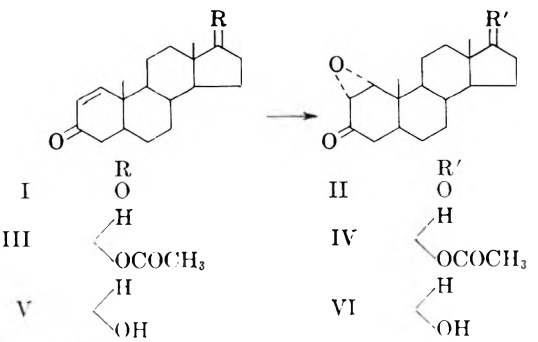
1α, 2α-Epoxyandrostane-3,17-dione (II),[1] a compound useful in the determination of the structure of ruscogenin,[2] was prepared from 1-androstene-3,17-dione (I)[3] by using alkaline hydrogen peroxide.[4] The same procedure was used in attempt to obtain the corresponding epoxide from 17β-acetoxy-1-androsten-3-one(III), but without success. Further attempts to obtain the epoxide of III were made using perbenzoic acid in chloroform solution and with peracetic acid in benzene. Modification[5] of the method used for the epoxidation of I yielded the



(1) *Cf.* P. Striebel and C. Tamm, *Helv. Chim. Acta*, **37,** 1094 (1954) for discussion of the configuration of 1,2-epoxides.

(2) W. R. Benn, F. Colton, and R. Pappo, *J. Am. Chem. Soc.*, **79,** 3920 (1957). For other references concerning the structure of ruscogenin see A. L. Nussbaum, F. E. Carlon, D. Gould, E. P. Oliveto, E. B. Hershberg, M. L. Gilmore, and W. Charney, *J. Am. Chem. Soc.*, **79,** 4814 (1957); D. Burn, B Ellis, and V. Petrow, *Proc. Chem. Soc.*, 119 (1959); H Lapin and C. Sannie, *Bull. soc. chim.*, 1552 (1955).

(3) A. Butenandt and H. Dannenberg, *Ber.*, **69,** 1158 (1936).

(4) P. L. Julian, W. Cole, E. W. Meyer, and B. M. Regan, *J. Am. Chem. Soc.*, **77,** 4601 (1955).

(5) The author gratefully acknowledges a suggestion by R. Pappo of our laboratories for this modification.

desired compound. This modified procedure required a relatively short reaction time for the formation of the epoxide, and the alkali concentration was less than that used for the preparation of compound II. 17β-Hydroxy-1α,2α-epoxyandrostan-3-one was obtained by this modified procedure or by the alkaline hydrolysis of the corresponding acetoxy derivative (IV).

The infrared absorption for the epoxide group was at 11.44 and 12.48 for the epoxide II, 11.42 and 12.52 for the epoxide IV, and 11.38 and 12.52 for the 17β-hydroxy-1α,2α-epoxyandrostan-3-one (VI). The ultraviolet spectra of the epoxides exhibited end absorption and at high concentrations the C_3-ketone group could be demonstrated.

EXPERIMENTAL[6]

1α,2α-Epoxyandrostane-3,17-dione (II). To a stirred solution of 1-androstene-3,17-dione (3 g.) in methanol (200 ml.) were added simultaneously and dropwise 4*N* sodium hydroxide (16.2 ml.) and 30% hydrogen peroxide (16.2 ml.). The mixture was maintained at 20° during the addition and stored overnight at 5°. The reaction mixture was diluted with water and extracted with benzene. The benzene solution was washed with 1% sodium hydroxide solution and then with water until the washings were neutral. The benzene solution was dried over anhydrous sodium sulfate, filtered, and the solvent removed under reduced pressure. The crystalline residue, still containing a small amount of benzene was dissolved in methylene chloride. On slow evaporation of the solvent, a crystalline solid was obtained. The solid was separated by filtration and washed with a small amount of methylene chloride. The yield was 2 g.; m.p. 246–247°; $[\alpha]_D$ +189° (1% in chloroform).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.61; H, 8.30; λ_{max}^{KBr} 5.76, 5.90, 11.42 and 12.48 μ.

17β-Acetoxy-1α,2α-epoxyandrostan-3-one (IV). To a stirred solution of III[7] (1.05 g.; m.p. 128–129°) in methyl alcohol (15 ml.) cooled to 10° was added 30% hydrogen peroxide (1 ml.). Then a 10% solution of sodium hydroxide (0.2 ml.) in methyl alcohol (5 ml.) was added. The temperature was kept between 15–20°. A crystalline precipitate was observed within 3 min. and after the reaction had proceeded for 10 min. the solid was separated by filtration and washed with methanol; yield was 300 mg.; m.p. 160–161°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.61; H, 9.04; λ_{max}^{KBr} 5.74; 5.78 (sh), 7.26, 9.56, 9.72, 11.42 and 12.52 μ.

The mother liquor was allowed to stand at 15–20° for 45 min. and diluted with water. The solid which deposited, was filtered, dried to constant weight (400 mg.) in a vacuum oven, and recrystallized from methanol. The yield from the latter material was 250 mg.; m.p. 157–158°.

Hydrolysis of 17β-acetoxy 1α,2α-epoxyandrostan-3-one (IV). To a solution of IV (250 mg.) in ethyl alcohol (10 ml.; 2B) was added 5*N* sodium hydroxide (0.5 ml.) and the solution heated to gentle reflux for 10 min. The reaction mixture became slightly turbid during the treatment. The mixture was cooled, diluted with water (50 ml.) and the aqueous layer decanted from the gummy residue which deposited on the sides of the flask. The gum was dissolved in methyl alcohol (5 ml.) and diluted with water (15 ml.). The filtered solid was dried to constant weight (220 mg.; m.p. 120–123°). The product was chromatographed over silica (45 g.). Elution was begun with benzene and followed by an ethyl acetate-benzene mixture (5.0-ml. fractions were collected). The first material eluted with 20% ethyl acetate was IV (70 mg.; m.p. 158–159.5°) followed by VI (90 mg.; m.p. 140–165°). Recrystallized from aqueous methyl alcohol gave pure IV (m.p. 160–161°); VI (m.p. 156–158°).

Anal. (VI) Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.09; H, 9.46; λ_{max}^{KBr} 2.87, 5.82, 9.43, 9.6, 10.78, 11.38, 12.51 μ.

17β-Hydroxy-1α,2α-epoxyandrostan-3-one (VI). To a stirred solution of V[7b] (0.9 g.; m.p. 152–153°) in methyl alcohol cooled to 10° was added 30% hydrogen peroxide (1 ml.). Then a 10% solution of sodium hydroxide in methyl alcohol (0.2 ml.) was added. The temperature was kept between 14–18°. After 10 min., the reaction mixture was diluted with water (45 ml.) and the solid that crystallized from the solution was separated by filtration and dried. The product (m.p. 157–158°) weighed about 700 mg. and was crystallized to constant m.p. from 90% methyl alcohol (m.p. 161–162°). This product showed no absorption in the 220–300 mμ region.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.95; H, 9.17; λ_{max}^{KBr} 2.86, 5.83, 9.44, 9.51, 10.78, 11.38 and 12.52 μ.

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(6) The author expresses his appreciation to Dr. R. T. Dillon and his staff on the analytical department of the G. D. Searle and Co. for the analytical data presented in this paper. The melting point determinations were observed on a Fischer-Johns block.

(7) (a) A. Butenandt and H. Dannenberg [*Ber.*, **71**, 1681 (1938)] describe this compound with a melting point 117–118°. (b) *Ber.*, **73**, 206 (1940).

Isomeric 2-Phenoxycyclopropanecarboxylic Acids[1]

J. H. LOOKER AND LOREN L. BRAUN

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Recently, a series of 2-aryloxycyclopropanecarboxylic acids was prepared by hydrolysis of the ethyl esters, initially formed through reaction of ethyl diazoacetate with a suitable arylvinyl ether.[2] In all cases only one acid was reported. The present communication describes the two theoretically possible diastereomeric 2-phenoxycyclopropanecarboxylic acids, as well as infrared spectra of the isomeric acids.

Although we employed the same reactants as Julia and Tchernoff,[2] our experimental procedure (similar to that of Burger and Yost[3]) differed from that of the French workers in several respects: reaction period, absence of copper catalyst, method for isolation of the ester, hydrolysis medium, and purification procedure. No attempt was made to obtain the pure diastereomeric ethyl esters, which were hydrolyzed in ethanolic sodium hydroxide.

(1) Abstracted from a portion of a thesis submitted by Loren L. Braun in partial fulfillment of the requirements for the Ph.D. degree, University of Nebraska, 1956.

(2) M. Julia and C. Tchernoff, *Bull. soc. chim. France*, 181 (1956).

(3) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).

TABLE I

INFRARED ABSORPTION MAXIMA[a,b] OF CYCLOPROPANECARBOXYLIC ACIDS

	Cyclopropanecarboxylic Acid[c]	2-Phenoxycyclopropanecarboxylic Acids	
		Acid A[d]	Acid B[d]
Carboxyl C=O[e]	1690 (1694 in CCl_4)	1683 (1692 in CCl_4)	1697 (1708 in CCl_4)
Carboxyl OH[e]	2560, 2670, 931	2630 (wk), 920	2550, 2685 (wk), 957
Oxide[e]	—	1257 (1224 ?)	1253 (1225 ?)
Aromatic:			
Phenyl C=C[e]	—	1602, 1589, 1496	1603, 1592, 1491
C—H out of plane deformation[e]	—	750, 687	756, 682
Methylene[e]	1460	1452	1450
Cyclopropyl[f]	1032	1051 or 1020	1032 or 1018

[a] Spectra were determined with a Perkin-Elmer Model 21 recording spectrophotometer. [b] Band locations are given in cm.$^{-1}$ Bands are of medium or strong intensity, except where otherwise indicated. Weak bands are denoted by (wk). [c] As pure liquid. [d] In KBr disks. [e] Band-structure correlations are in accordance with L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, N. Y., 1954, pp. 5–9. [f] Several workers have suggested that the cyclopropyl group displays a band in the region 1000–1020 cm.$^{-1}$ (Ref. e, pp. 27–28). The region 1000–1050 cm.$^{-1}$ has been suggested by V. A. Slabey [*J. Am. Chem. Soc.*, **76**, 3604 (1954)], and the region 1000–1040 cm.$^{-1}$ by F. R. Nelson, M. Maienthal, L. A. Lane, and A. A. Benderly [*J. Am. Chem. Soc.*, **79**, 3467 (1957)]. See, however, A. R. H. Cole [*J. Chem. Soc.*, 3807 (1954)], who states that a band at 1010 cm.$^{-1}$ is unreliable when oxygen functions are present. C. F. H. Allen, T. J. Davis, W. J. Humphlett, and D. W. Stewart [*J. Org. Chem.*, **22**, 1291 (1957)] have questioned the fact that the 2.3 μ or 9.8 μ (*ca.* 1020 cm.$^{-1}$) affords a clear indication of the presence or absence of the cyclopropyl group.

The diastereomeric acids obtained were then separated by fractional crystallization from water. The less soluble Acid A possessed a melting point of 113–113.7°, which is in reasonable agreement with the previously reported value of 112°.[2] The more soluble Acid B was obtained by benzene extraction of the aqueous mother liquors, and had a melting point of 135–137°. The latter acid apparently was not obtained by Julia and Tchernoff.[2] The yield of Acid A was roughly twice that of Acid B.

The method of synthesis, combustion analyses and negative results from two standard chemical tests for the ethylenic linkage indicate with reasonable certainty the structural nature and identity of Acids A and B. The infrared absorption spectra of the two acids, some of the more important bands of which are reported in Table 1, confirm the structural nature of the two acids. In addition, the acid carbonyl bands for the acids in carbon tetrachloride solution can be used to assign configuration by taking advantage of the generalization of Mohrbacher and Cromwell.[4] In accordance with the latter, Acid A has the lower carbonyl band frequency and is the *trans* isomer. Acid B, then, is assigned the *cis*-configuration. Acid A and cyclopropanecarboxylic acid in carbon tetrachloride solution have virtually identical carbonyl band frequencies, a fact which is interpreted as indicating less steric interaction between phenoxy and carboxyl groups in Acid A, the *trans* isomer, than in Acid B. This configurational assignment finds confirmation in our isolation of the more stable Acid A in considerably greater yield than Acid B, and in the isolation of Acid A as the sole reaction product by Julia and Tchernoff.[2]

(4) R. J. Mohrbacher and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 406 (1957).

Possible ring-closure of Acids A and B in polyphosphoric acid, under conditions which gave 8-bromo-1-benzo[*f*]chromanone from β-(6-bromo-2-naphthoxy)propionic acid,[5] was investigated. However, all ring-closure attempts were unsuccessful.

EXPERIMENTAL[6]

Phenylvinyl ether. This compound was prepared by the method of Lauer and Spielman.[7]

Ethyl diazoacetate. Ethyl diazoacetate was prepared by the general procedure of Womack and Nelson.[8]

2-Phenoxycyclopropanecarboxylic acids A and B. The procedure used to prepare these acids was similar to that of Burger and Yost[3] for synthesis of phenylcyclopropanecarboxylic acids A and B.

In a three necked flask, equipped with mechanical stirrer, reflux condenser, and dropping funnel, was placed a 30 g. (0.25 mole) quantity of phenylvinyl ether. To the stirred reaction mixture there was added, over a 15 hr. period, a solution of 57 g. (0.5 mole) of ethyl diazoacetate in 60 g. (0.50 mole) of phenylvinyl ether. The temperature was maintained at 146–154°. Gas evolution began with the addition of ethyl diazoacetate. The reaction mixture soon began to darken, and after 2 hr. was black. When addition of the diazoacetate solution was complete, the reaction mixture was distilled through a 24-inch Podbielniak column. Four fractions were collected at 6–10 mm.: (1) 51.8 g., b.p. 52–56°; (2) 2.5 g., b.p. 57–120°; (3) 1 g., b.p. 120–129°, and (4) 30 g., b.p. 129–140°.

Fractions 3 and 4 were combined and placed in a solution prepared by dissolving 8.8 g. of sodium hydroxide in a mixture of 11 ml. of water in 82 ml. of 95% ethanol. The alkaline mixture was heated under reflux for 9 hr., and then most of the alcohol was removed by distillation. The residue was

(5) L. L. Braun and J. H. Looker, *J. Am. Chem. Soc.*, **80**, 359 (1958).

(6) Melting points, observed in capillary tubes, are uncorrected.

(7) W. M. Lauer and M. A. Spielman, *J. Am. Chem. Soc.*, **55**, 1573 (1933).

(8) E. B. Womack and A. B. Nelson, *Org. Syntheses*, **Coll. Vol. 3**, 392 (1955).

diluted with a small volume of water and the resulting mixture acidified with concentrated hydrochloric acid. An oil separated, which solidified upon strong cooling of the mixture. The solid was collected by filtration and recrystallized from boiling water, of which about 2 l. were required. Several more recrystallizations from water yielded 6.5 g. (7.3%) of white, flaky crystals of Acid A, m.p. 110–113°. The combined mother liquors were extracted with benzene. The benzene extract was concentrated under reduced pressure, petroleum ether (b.p. 30–60°) added, and the resulting mixture permitted to stand in the refrigerator. The crystals which formed were recrystallized several times from water to give 3.0 g. (3.4%) of white crystals of Acid B, m.p. 134–137°. Repeated crystallization from water gave the analytically pure acids: Acid A, m.p. 113–113.7°; Acid B, m.p. 135–137°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.42; H, 5.65. Found: (for Acid A): C, 67.35; H, 5.67. (For Acid B): C, 67.58; H, 5.69.

Acid A in carbon tetrachloride did not decolorize 5% bromine in carbon tetrachloride. In acetone solution, Acid A gave no decoloration with a 2% solution of potassium permanganate. Acid B gave similar results with the preceding reagents. Phenylvinyl ether gave instantaneous decolorization with both reagents.

A 1-g. quantity of Acid A, m.p. 110–114°, was heated in 11.35 g. of polyphosphoric acid at 70–80° for 2 hr. with mechanical stirring and exclusion of moisture. The reaction mixture was poured into cold water and the resulting mixture extracted with benzene. The benzene solution was washed with 5% sodium bicarbonate and dried over anhydr. magnesium sulfate. Removal of the benzene revealed neither solid nor liquid residue. Acid B gave similar results with polyphosphoric acid.

Acknowledgment. The financial support of this investigation by the Research Corporation of New York is gratefully acknowledged.

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2,2-Diaryl-*p*-dioxanes

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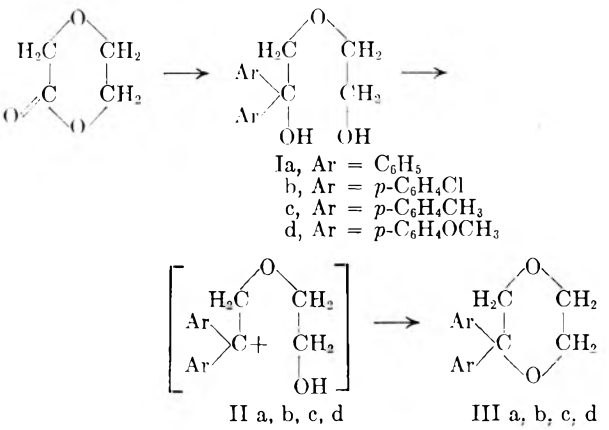
Two recent publications from our laboratory[1,2] have made use of 2,2-diphenyl-*p*-dioxane as the reference compound in proving structures. This note details the original synthesis of this and other 2,2-diaryl-*p*-dioxanes.

Treatment of *p*-dioxanone with the appropriate Grignard reagent resulted in the formation of fair yields of α,α-diphenyldiethylene glycol, Ia, α,α-di-*p*-chlorophenyldiethylene glycol, Ib, and α,α-di-*p*-tolyldiethylene glycol, Ic. These glycols were converted to dioxanes by treatment in benzene solution with anhydrous hydrogen chloride and calcium chloride at room temperature.



The ease of formation of the dioxane rings contrasts with the difficulty of closing similar 4-methylmorpholine rings with acid,[3] presumably because in the latter case the carbonium ion corresponding to II would have two positive charges. As would be expected from the proposed carbonium ion mechanism, Ib was not converted to the dioxane as easily as Ia or Ic. On the other hand, Id was not even isolated. Either the dioxane IIId was formed in solvent evaporation or under the extremely mild acid conditions of the hydrolysis of the Grignard reaction product with aqueous ammonium chloride, or it was a direct product formed before hydrolysis. Such direct formation of ethers from aliphatic lactones by treatment with Grignard reagents seems to be rare.[4]

When a butyl Grignard reagent was treated with *p*-dioxanone, a compound of correct composition for the expected glycol resulted, but starting material was recovered when ring closure to the dioxane was attempted by the method successfully employed for aromatic derivatives.

EXPERIMENTAL

p-Dioxanone. Small yields of this compound were obtained by each of the methods attempted.[5-7] None was satisfactory, and our modifications did not improve matters importantly. The compound was always distilled immediately before use in order to be certain that it was in the monomeric form. A convenient method for the laboratory preparation of this compound was found later in our laboratory, and has now been published.[2]

(1) R. K. Summerbell and Hans E. Lunk, *J. Am. Chem. Soc.*, **79**, 4802 (1957).

(2) R. K. Summerbell and Hans E. Lunk, *J. Am. Chem. Soc.*, **80**, 604 (1958).

(3) I. A. Geissman, M. Bassin, and E. V. Zeilberger, *J. Am. Chem. Soc.*, **73**, 5874 (1951).

(4) M. S. Kharasch and Otto Reinmuth, *Grignard Reactions of Non-metallic Substances*, Prentice Hall, New York, 1954, pp. 574–578.

(5) C. A. Bischoff and P. Walden, *Ber.*, **26**, 263 (1893); *Ann.*, **279**, 47 (1894).

(6) W. H. Carothers, C. L. Dorough, and F. J. Van Natta, *J. Am. Chem. Soc.*, 54, 771 (1932).

(7) R. W. McNamee and C. M. Blair, U. S. Patent 2,142,033, *Chem. Abstr.*, **33**, 2542 (1939).

α,α-Diphenyldiethylene glycol, Ia. To the Grignard solution resulting from the treatment of 12.2 g. (0.5 mole) of magnesium with 78.5 g. (0.5 mole) of bromobenzene in 200 cc. of ether was added with vigorous stirring, 15.2 g. (0.15 mole) of monomeric *p*-dioxanone dissolved in 50 cc. of dry benzene. The rate of addition was such as to cause gentle reflux. The reaction mixture was hydrolyzed with ice and aqueous ammonium chloride, and the product extracted with ether which was evaporated to yield 40.9 g. of crude product. Repeated recrystallization from water-ethanol gave 19.9 g. (51% yield) of a pure product, m.p. 109.0–109.2°.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02; mol. wt. 258. Found: C, 74.63; H, 7.29; mol. wt., ebullioscopic in benzene, 250.

α,α-Di-p-chlorophenyldiethylene glycol, Ib. Prepared as above from Grignard reagent from 0.15 mole of *p*-bromochlorobenzene and 0.07 mole of *p*-dioxanone. Product recrystallized from ethanol-water weighed 6.2 g. (0.019 mole), yield 27%, m.p. 108.5–109°.

Anal. Calcd. for $C_{16}H_{16}O_3Cl_2$: C, 58.73; H, 4.93. Found: C, 58.95; H, 4.80.

α,α-Di-p-tolyldiethylene glycol, Ic. Use of the Grignard reagent from *p*-bromotoluene as above gave a 26% yield of product recrystallized from water-ethanol, then from petroleum ether, m.p. 91–91.5°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.51; H, 7.74. Found: C, 75.48; H, 7.88.

2,2-Diphenyl-p-dioxane, IIIa. A solution of 0.903 g. (0.0035 mole) of Ia dissolved in 50 cc. of dry benzene to which 3 g. of anhydrous calcium chloride had been added was saturated with anhydrous hydrogen chloride and allowed to stand for 24 hr. The solvent was removed by aspirator and the product recrystallized from petroleum ether to give 0.251 g. (0.00105 mole) of white crystals, m.p. 119.5–120. Yield 30%.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.77; H, 6.65.

A melting point of 121° has been reported for 1,1-diphenylethylene glycol,[8] a conceivable product of this reaction. The latter was prepared and shown to be different from IIIa by mixed melting point.

2,2-Di-p-chlorophenyl-p-dioxane, IIIb. The product was recrystallized from absolute ethanol, m.p., 78–79°. Yield, 12%. Unchanged starting material recovered by evaporation of the solvent amounted to 77%.

Anal. Calcd. for $C_{16}H_{14}O_2Cl_2$: C, 62.2; H, 4.53. Found: C, 61.49; H, 4.77.

2,2-Di-p-tolyl-p-dioxane, IIIc. M.p., 94.2–95.5; yield, 30%.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.46. Found: C, 80.42; H, 7.55.

2,2-Di-p-anisyl-p-dioxane, IIId. When the preparation of 2,2-di-*p*-anisyldiethylene glycol from *p*-dioxanone and *p*-anisylmagnesium bromide was attempted, the product had a carbon content quite different from that of the glycol, but close to that of the corresponding dioxane. The yield was 54%. Repeated crystallization from ethanol, methanol, and petroleum ether gave a product of fair purity. A satisfactory analytical sample, obtained by sublimation, melted at 106.5–107.2°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.67. Found: C, 72.30; H, 6.90.

Acknowledgment. Thanks are given to the Abbott Foundation of Northwestern University for financial aid and to Union Carbide Chemicals Corp. for a small sample of *p*-dioxanone.

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(8) C. Paal and E. Weidenkaff, *Ber.*, **39**, 2063 (1906).

Unsaturated Fatty Acids. V. Preparation of α- and γ-Linolenic-1-C^{14} Acids[1]

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The decarboxylation-reconstitution technique developed[2] in this laboratory and employed[3,4] in the synthesis of oleic- and linoleic-1-C^{14} acids has now been applied to the problem of labeling two trienoic acids, α- (or the common) linolenic (all-*cis*-9,12,15-octadecatrienoic) and γ-linolenic (all-*cis*-6,9,12-octadecatrienoic), with C^{14} in the carboxyl group. Use of these labeled substances in studies of *in vivo* interconversions of polyunsaturated fatty acids has been described elsewhere.[5]

EXPERIMENTAL

All melting points are corrected. Reported *trans*-contents of olefinic substances, based on infrared absorption at 10.3μ, are considered to be within 5% of actual values.

Ultimate analyses were performed by Dr. A. Elek (Elek Micro Analytical Laboratories, Los Angeles) and infrared absorption analyses by Mr. Paul Kratz. Radioactivities were determined by Dr. J. F. Mead and by Mr. W. H. Slaton, Jr.

9,10,12,13,15,16-Hexabromostearic acid (α-I), m.p. 182.8–183.4°, was prepared by bromination of linseed oil fatty acids (kindly supplied by the Archer-Daniels-Midland Co.) essentially as described by McCutcheon,[6] except that butanone (16.5 ml. per g.) was found to be superior to dioxane as a crystallization solvent. Treating α-I in tetrahydrofuran with diazomethane in benzene gave *methyl 9,10,12,13,15,16-hexabromostearate*, m.p. 154.2–155.3° (recrystallized from butanone).

Anal. Calcd. for $C_{19}H_{32}Br_6O_2$: C, 29.56; H, 4.18; Br, 62.12. Found: C, 29.68; H, 4.16; Br, 62.18.

6,7,9,10,12,13-Hexabromostearic acid (γ-I) was obtained by bromination of the mixture of fatty acids produced by saponification of the oil extracted from seeds of the evening primrose, *Oenothera Lamarckiana*,[7] using a procedure developed by Dr. James F. Mead. In batches of about 300 g. each, 5 lbs. of dry seed (Vaughan Seed Co., Chicago) was crushed by shaking mechanically with porcelain balls (0.5–1 inch dia.) in 3 (dia.) by 10 inch tin cans for 3 hr. (Ball-mill treatment of the seeds was ineffective.) The crushed seeds were then steeped 48 hr. in 4 l. of light petroleum ether (30–60° or 60–70°), the mixture was filtered, and the dried filter cake was recrushed and reextracted twice. Evaporation of the combined yellow extracts (*in vacuo* under nitrogen) left 541 g. (23.8% by weight) of oil, which was refluxed

(1) This paper is based on work performed under Contract AT(04-1)-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles.

(2) D. R. Howton, R. H. Davis, and J. C. Nevenzel, *J. Am. Chem. Soc.*, **74**, 1109 (1952).

(3) D. R. Howton, R. H. Davis, and J. C. Nevenzel, *J. Am. Chem. Soc.*, **76**, 4970 (1954).

(4) J. C. Nevenzel and D. R. Howton, *J. Org. Chem.*, **22**, 319 (1957.)

(5) G. Steinberg, W. H. Slaton, Jr., D. R. Howton, and J. F. Mead, *J. Biol. Chem.*, **224**, 841 (1957); J. F. Mead and D. R. Howton, *J. Biol. Chem.*, **229**, 575 (1957).

(6) J. W. McCutcheon, *Org. Syntheses*, **22**, 82 (1942).

(7) T. Tsuchiya, *J. Chem. Soc. Japan*, **63**, 1085 (1942) [*Chem. Abstr*, **41**, 3754e (1947)].

40 min. in 2.8 l. of methanol (in which 1.6 g. of sodium had previously been dissolved), diluted with a solution of 250 g. of potassium hydroxide in 1.7 l. of methanol and 500 ml. of water, and let stand overnight under nitrogen at room temperature. Diluted with an equal volume of water and extracted with petroleum ether, the mixture yielded 2.65 g. (0.49% by weight) of unsaponified material. The aqueous phase was acidified and re-extracted with petroleum ether and the extracts washed with water, dried over magnesium sulfate, and freed of solvent *in vacuo* at 60–70°, giving 503.5 g. of mixed fatty acids, brown-orange semisolid at 4°. (Concentration of the more highly unsaturated fatty acids at this point by crystallization of the more saturated components from a 10% solution in acetone at −65°[8] resulted in somewhat lower yields of γ-I and no apparent advantage from the standpoint of purity of the product.) In two approximately equal batches, the mixed fatty acids were dissolved in 3 l. of dry ether containing 0.5 g. of 2,6-di-*tert*-butyl-*p*-cresol, cooled to 0°, treated with bromine until color persisted (about 85 ml. was required), and let stand in a refrigerator overnight. Filtered off, washed thoroughly with ether, and air-dried, the crude γ-I weighed 63.15 g. and melted at 192–196°; recrystallization from 1.4 l. of butanone gave 36.24 g. of pure γ-I, m.p. 200.0-200.8° (lit.[7,8] m.p. 196°).

The yield of this most insoluble of the four diastereoisomeric hexabromides produced in unknown relative amounts by *trans*-addition of bromine to γ-linolenic acid was 38.8%; reversed-phase-chromatographic analysis[9] of *Oe. Lamarckiana* seed oil fatty acids showed the presence of 1.4% stearic, 15.7% oleic and palmitic (unresolved), 75.7% linoleic, and 6.8% γ-linolenic acids.

A small sample of γ-I in tetrahydrofuran was treated with ethereal diazomethane to give *methyl 6,7,9,10,12,13-hexabromostearate*, small prisms from acetone, m.p. 170.5–171.5° (melt brown).

Silver hexabromostearates (II). The low solubility of the hexabromostearic acids necessitated use of special solvents in order to obtain high yields of silver salts of satisfactory purity. In a typical preparation of α-II, 15.16 g. (0.02 mole) of α-I was dissolved in 200 ml. of redistilled tetrahydrofuran and treated dropwise during 5–10 min. with a solution of ammoniacal silver nitrate prepared by diluting a solution of 3.40 g. (0.02 mole) of silver nitrate in 5 ml. of redistilled acetonitrile with 10 ml. of methanol and adding another of 0.02 mole of anhydrous ammonia in 13.7 ml. of methanol. The resulting white paste was stirred 30 min. and the solid filtered off, washed with 50 ml. each of tetrahydrofuran and methanol, and dried *in vacuo*, giving 16.67 g. (96.4%) of α-II of purity adequate for use in the Borodin degradation. Analyses of a number of such products indicated some coprecipitation of the free acid with the desired silver salt.

Anal. Calcd. for $C_{18}H_{29}AgBr_6O_2$: Ag, 12.47. Found: Ag, 11.48, 11.75, 11.59.

Similarly, 25.21 g. (33.3 mmol.) of γ-I gave a 98.5% yield of white γ-II containing 11.18% Ag.

Heptabromoheptadecanes (III). A stirred slurry of 24.93 g. (0.02883 mole) of α-II (dried *in vacuo* over P_2O_5) in 500 ml. of dry carbon tetrachloride was treated during about 30 min. under reflux with bromine until a slight excess was indicated by persistent color; 650 ml. of carbon dioxide was evolved (theory 646 ml.). After cooling, the mixture was filtered and the filter cake triturated with three 50-ml. portions of tetrahydrofuran to give 7.61 g. of soluble regenerated crude α-I and 6.1 g. (88%) of insoluble silver bromide. The reaction mixture filtrate was decolorized with aqueous sodium sulfite, washed free of mineral acid with water, dried over magnesium sulfate, and freed of solvent, leaving 13.0 g. of white semisolid residue which was taken up in 300 ml. of warm carbon tetrachloride and chromatographically resolved (in two batches) by passage through a 7.4 (dia.) × 26.0 cm. column of silicic acid. Carbon tetrachloride eluted a total of 9.29 g. (40.6%) of crude α-III. The more polar components of the mixture were eluted with acetone and titrated (in tetrahydrofuran) to estimate content of regenerated α-I. Semiquantitative analyses indicated formation of 9.5% (from α-II) of Simonini ester and of 41.8% of α-I. Recrystallization of the crude α-III from 125 ml. of acetone gave 4.87 g. of α-III, m.p., 154.6–155.6° which was recrystallized again (from 100 ml. of acetone) to give 4.095 g. of pure 1,8,9,11,12,14,15-(α)-III, m.p. 155.0–156.0°.

Anal. Calcd. for $C_{17}H_{29}Br_7$: C, 25.75; H, 3.69; Br, 7056. Found: C, 25.98; H, 3.66; Br, 70.30.

Exhaustive crystallization of a similarly prepared 4.39-g. sample of crude (CCl_4-eluted) α-III (shown by infrared examination to be free of C=O-group-containing components) left 1.69 g. (38.5%) of viscous yellow oil, about 1.5 g. of which was soluble in 25 ml. of boiling pentane. Chromatography of 0.51 g. of this pentane-soluble material on silicic acid gave 0.44 g. of oil (eluted readily by carbon tetrachloride, but not by at least 4.5 column volumes of pentane) which probably contains lower-melting stereoisomers of α-III but also (as shown by the following analyses) significant amounts of higher bromides presumably arising *via* substitution during the Borodin reaction.

Anal. Found: C, 24.57; H, 3.29; Br, 73.74.

In the preparation of 1,5,6,8,9,11,12-(γ)-III, attempts were made to avoid vexing solubility problems by use of the modified Borodin reaction of Rottenberg[10] in which a mixture of the *free* fatty acid and silver trifluoroacetate is used instead of the silver salt of the fatty acid. However, as will be discussed in greater detail elsewhere, this technique involves rather extensive and previously unrecognized side reactions. Essentially as described above in the preparation of α-III, 28.36 g. of γ-II (89.5% by Ag analysis) in 700 ml. of carbon tetrachloride was treated with bromine, permanent color being obtained when only about 60% of a molecular-equivalent amount had been added. Of the 21.4 g. of carbon tetrachloride–insoluble solid filtered from the reaction mixture, 15.5 g. was soluble in hot tetrahydrofuran and presumed to be regenerated γ-I. After it had been decolorized by shaking with aqueous sodium bisulfite, washed free of acid with water, and dried, the carbon tetrachloride solution of the other reaction products was chromatographed to give 7.25 g. (31.1% based on γ-II) of crude γ-III eluted from silicic acid with carbon tetrachloride; recrystallization from about 300 ml. of acetone gave 3.205 g. of γ-III, m.p. 184.0–184.6°. An analytical sample melted at 186.4–187.6°.

Anal. Calcd. for $C_{17}H_{29}Br_7$: C, 25.75; H, 3.69; Br, 70.56. Found: C, 25.84; H, 3.71; Br, 70.43.

In another experiment, after γ-III and related polybromohydrocarbons had been eluted from the silicic acid column with carbon tetrachloride, 3% tetrahydrofuran in carbon tetrachloride eluted a viscous oil, analysis of which approached consistency with that expected for the Simonini ester, 5,6,8,9,11,12-hexabromoheptadecyl 6,7,9,10,12,13-hexabromostearate.

Anal. Calcd. for $C_{35}H_{58}Br_{12}O_2$: Br, 65.25. Found: Br, 69.77.

Mother liquors from crystallization of various preparations of γ-III were combined, freed of solvent, extracted with pentane, and the pentane-soluble material chromatographed on silicic acid to give an oil eluted slowly by petroleum ether and rapidly by 20% carbon tetrachloride in petroleum ether. The infrared spectrum of the oil (in carbon tetrachloride) agreed well with another of crystalline γ-III (in potassium bromide pellet) and its analysis supported designation as isomeric γ-III (in contrast to evident over-bromination of similar material isolated in the α-series studies).

Anal. Calcd. for $C_{17}H_{29}Br_7$: Br, 70.56. Found: Br, 70.09.

1-Bromoheptadecatrienes (IV). A suspension of 5.0 g. of

(8) *Cf.* J. P. Riley, *J. Chem. Soc.*, 2728 (1949).

(9) *Cf.* J. F. Mead, *J. Biol. Chem.*, **227**, 1025 (1957).

(10) M. Rottenberg, *Helv. Chim. Acta*, **36**, 1115 (1953).

20-mesh zinc (preactivated by treating with concentrated aqueous hydrobromic acid) and 6.85 g. (8.64 mmol.) of α-III in 70 ml. of absolute ethanol was refluxed for 7 hr. (Remaining chunks of white solid were crushed after 50 min. of refluxing, and all α-III had dissolved in 90 min.; continued refluxing with zinc is probably responsible for the conversion of IV to bromine-free material and should therefore be avoided.) Isolated as described earlier in detail,[3] the product was distilled (short-path apparatus, at 0.01μ) to give 2.55 g. of oil, b.p. (bath temperature) 80–110°; from analysis of another product prepared in the same way and thus indicated to be contaminated with about 6.5% of bromine-free material, the yield of crude α-IV is estimated to be about 88%. Assuming the bromine-free contaminant to be heptadecatriene (produced by zinc reduction of IV) and hence more volatile than the desired product, the crude α-IV was freed of a small fraction, b.p. up to 116° (bath temperature) at 0.03μ, and the residue, predominantly all-*cis*-8,11,14-(α)-IV, n_D^{25} 1.4885, d^{25} 1.0134, analyzed and used in the preparation of α-linolenic-1-C^{14} acid.

Anal. Calcd. for $C_{17}H_{29}Br$: C, 65.17; H, 9.33; Br, 25.50. Found: C, 65.87; H, 9.34; Br, 24.80.

Infrared examination of a similar preparation of α-IV indicated the presence of 12% *trans* olefin (*i.e.*, on the average, one of the three double bonds in 12% of the material has the *trans* configuration), while ultraviolet absorption revealed 1.4% conjugated diene and 0.6% conjugated triene. The extent of double bond isomerization indicated by these analyses is typical of polyenes of this kind submitted to bromination-zinc-debromination.[11]

Similarly, refluxing 6.59 g. (8.31 mmol.) of γ-III with zinc in ethanol for 8.67 hr. (probably overly long—all γ-III had dissolved in 3.17 hr.) gave 2.1 g. of crude γ-IV; b.p. 120–135° (bath temperature) at 0.1μ. Analysis of the oil indicated the presence of 11.3% bromine-free material; yield of γ-IV is thus estimated to be 72%. Ultraviolet examination of this predominantly all-*cis*-5,8,11-(γ)-IV revealed the presence of 0.75% conjugated diene and 0.025% conjugated triene. Inasmuch as the bromine-free contaminant was expected to be inert in subsequent operations and to be easily and cleanly separable by chromatography from the ultimate fatty acid ester, no further effort was expended on purification of these samples of IV.

Zinc-debromination of a 350-mg. sample of chromatographically purified "*isomeric*" (oily) γ-III (see above) gave a product (twice distilled, but without fractionation) containing 96% γ-IV (by bromine analysis), possibly reflecting the benefit of a shorter reaction (5.5 hr.). The origin of this non-crystalline γ-III is perhaps most evidently explained on the basis of racemization (during the Borodin reaction) to give *erythro* vicinal dibromide groups which, with zinc, would yield *trans* double-bonds. It is therefore surprising that the sample of γ-IV prepared from this oily γ-III contained but 8–10% *trans* material. Conjugated polyenes were, however, present in comparatively large amounts (0.76% diene, 0.48% triene, and 0.21% tetraene).

In confirmation of the 5,8,11-structure of γ-IV, the material obtained by debromination of the oily γ-III was ozonized and the monocarboxylic acid fraction of the products shown by paper chromatography to consist solely of *n*-hexanoic acid. (The presence of small amounts of *n*-valeric acid would not have been detected under the conditions employed.)

Linolenic-1-C^{14} acids and methyl linolenates-1-C^{14}. Using techniques described in detail before,[3,4] 1.0783 g. (3.34 mmol.) of α-IV (97.2% by bromine analysis) was converted in 63% yield to the corresponding Grignard reagent, which was treated with 2.90 mmol. of carbon dioxide containing 1.993 mc. of C^{14}. By titration of an aliquot of the crude reaction product, formation of a 64% yield (based on Grignard) of acidic material was indicated. The ether-soluble fraction of the product was treated with excess diazomethane and the resulting material chromatographed on silicic acid–Celite (3:1 by weight), using a 3.4 (dia.) × 14.0 cm. column; successive column volumes of petroleum ether eluted 340 mg., 5 mg., and a trace of very weakly adsorbed material (heptadecatriene present in the α-IV and C_{34} hydrocarbon formed by Wurtz coupling during the formation of the Grignard reagent); 3% ether in petroleum ether eluted 10 mg., 320 mg., 80 mg., 10 mg., and a trace more of the desired ester; negligible amounts of material were eluted by 10% ether in petroleum ether; and acetone (two column volumes) eluted 70 mg. of strongly adsorbed material. The chromatographically pure ester, *methyl α-linolenate-1-C^{14}*, was obtained in 91% yield (based on acid determined by titration of the crude Grignard product) and found by spectroscopic examination to contain 8–12% *trans* material, 3.3% conjugated diene, 0.25% conjugated triene, and 0.5% conjugated tetraene; the ester is thus about 84% all-*cis*-9,12,15-linolenate. A 10.2-mg. sample of the substance was diluted with 849 mg. of corn oil, plated on lens paper, and counted (thin-window G.M. tube) to establish an activity of 2.01 mc./g. of the undiluted ester.

In the same way, 1.0519 g. (2.98 mmol.) of γ-IV (88.7% by bromine analysis) gave a 66% yield of Grignard, 1.83 mmol. of which was treated with 2.56 mmol. of active carbon dioxide (1.945 mc.) to give crude γ-linolenic-1-C^{14} acid (about 82% from Grignard by titration of an aliquot of the mixed products), converted with diazomethane in ether to the corresponding *methyl ester* (0.40 g. or 90% based on the acid, assay 3.55 mc./g.).

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(11) *Cf.* N. L. Matthews, W. R. Brode, and J. B. Brown, *J. Am. Chem. Soc.*, 63, 1064 (1941); and J. S. Frankel and J. B. Brown, *J. Am. Chem. Soc.*, 65, 415 (1943).

Synthesis and Reactions of *p*-Vinylphenylmagnesium Chloride

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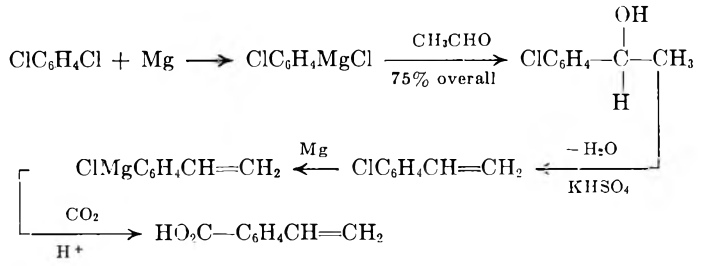
p-Chlorostyrene in tetrahydrofuran reacts smoothly with magnesium to form *p*-vinylphenylmagnesium chloride. The absence of polymer in the reaction may be attributed to controlled addition, the relative rapidity of the reaction with magnesium or to the stability of the coordination complex formed with the solvent. Under these conditions, monomer concentration remains low throughout the course of the reaction. The organometallic compound has been found to undergo typical Grignard reactions and thus provides a practical method for introducing the *p*-vinylphenyl group into a great variety of nuclei.

Carbonation of *p*-vinylphenylmagnesium chloride gave *p*-vinylbenzoic acid in 80% yield. *p*-Vinylbenzoic acid has been prepared from *p*-cyanostyrene[1] and from *p*-bromostyrene.[2] In the latter case, reaction of *p*-bromostyrene with magnesium

(1) C. S. Marvel and C. G. Overberger, *J. Am. Chem. Soc.*, 67, 2250 (1945).

(2) G. B. Bachman, C. L. Carlson, and M. Robinson, *J. Am. Chem. Soc.*, 73, 1964 (1951).

in diethyl ether gave *p*-vinylbenzoic acid in 15% yield on carbonation, accompanied by large quantities of polymer. The following reactions were involved in our synthesis:



p-Vinylphenyltriphenyltin was obtained in 78% yield by the reaction of *p*-vinylphenylmagnesium chloride with triphenyltin chloride in tetrahydrofuran.

In the reaction of *p*-vinylphenylmagnesium chloride with acetaldehyde, a 43% crude yield of *p*-vinylphenylmethylcarbinol was obtained, accompanied by considerable high-boiling, polymeric residue. Although an inhibitor was present, thermal polymerization apparently occurred during the distillation and molecular flash distillation is indicated.

EXPERIMENTAL

p-Chlorophenylmagnesium chloride.[3] Two gram atoms (48.6 g.) of magnesium was charged to a 3-necked flask equipped with thermometer, stirrer, addition funnel, and reflux condenser. The system was maintained under nitrogen. The reactor was heated to 35°C. Two moles (294.0 g.) of *p*-dichlorobenzene was dissolved in 500 ml. of tetrahydrofuran[4] and 20 ml. of this solution was added to the reactor. Ethyl bromide (2 ml.) initiated the reaction. The solution was added dropwise over a period of 2 hr., at a rate to maintain gentle reflux. The reaction mixture was then stirred for 2 hr. at reflux temperature. A yield of 90% by titration[5] was obtained.

p-Chlorophenylmethylcarbinol. To 2.0 moles of *p*-chlorophenylmagnesium chloride in 500 ml. of tetrahydrofuran at 15° was added 88.1 g. (2.0 moles) of acetaldehyde in 200 ml. of tetrahydrofuran over a period of 1 hr. The reaction mixture was stirred for 1 hr., followed by hydrolysis with dilute sulfuric acid. The organic layer was separated and the aqueous layer was extracted twice with 100-ml. portions of ethyl ether. After the solvent was stripped, the product was distilled *in vacuo*, yielding 235 g. *p*-chlorophenylmethylcarbinol b.p. 102–110°/3 mm., or 75%.

p-Chlorostyrene. The procedure described in *Org. Syn.*, **28**, 31 (1948) was employed for the dehydration of *p*-chlorophenylmethylcarbinol.

p-Vinylbenzoic acid. After 9.7 g. (0.4 g. atom) of magnesium was charged to a flask under nitrogen, 3 ml. of ethyl bromide in 5 ml. of tetrahydrofuran was added in order to activate the metal. The temperature rose to 60°. A solution of 27.6 g. (0.2 mole) of *p*-chlorostyrene in 50 ml. of tetrahydrofuran was introduced dropwise over a period of 35 min. at a rate to maintain gentle reflux. The reaction mixture was refluxed for 15 min. and stirred for 45 min. further without heating. The flask contents were cooled and poured on to crushed Dry Ice.

The carbonated mixture was acidified with dilute sulfuric acid; the layers were separated, and the aqueous layer was extracted with two 100-ml. portions of ethyl ether. The organic layer was added to excess base solution and the solvent boiled off. No appreciable base insoluble polymer was obtained. The basic solution was cooled, filtered, acidified, and filtered. The product was washed with cold water and dried to yield a crude acid melting at 138° (not sharply). Recrystallized from 20% ethanol it gave 23.8 g. of *p*-vinylbenzoic acid (80.4%). A sealed tube melting point showed rapid shrinkage and partial liquefaction at 142° with no clear melt. Its neutral equivalent was 152 (theory 148).

The product decolorized bromine in carbon tetrachloride. Oxidation with permanganate gave terephthalic acid which sublimed at *ca.* 305°. Microhydrogenation gave a hydrogen number of 153 (theory 148).

p-Vinylphenyltriphenyltin. To 0.2 mole of *p*-vinylphenylmagnesium chloride at 50° was added 62.0 g. (0.16 mole) of triphenyltin chloride in 150 ml. of tetrahydrofuran over a period of 45 min. The mixture was stirred for 90 min. during its cooling to room temperature. Then 0.5 g. of *p*-tertbutylcatechol was added to the reaction mixture followed by 200 ml. of 5% hydrochloric acid. The organic layer was separated and the aqueous layer extracted twice with 100-ml. portions of ethyl ether. The solvents were stripped off *in vacuo*, cold petroleum ether was added to the flask, and the crystalline product was filtered. A crude yield of 57.0 g. (or 78.5%) m.p. 102°, was obtained. The product was recrystallized twice from petroleum ether to m.p. 105.5–108.0°.

Anal. Calcd. for $C_{26}H_{22}Sn$: Sn, 28.19. Found: Sn, 26.18; % chlorine, negligible.

p-Vinylphenylmethylcarbinol. Acetaldehyde (8.8 g., 0.2 mole) in 100 ml. of tetrahydrofuran was added to 0.2 mole of *p*-vinylphenylmagnesium chloride over a period of 30 min. at 10°. The reaction mixture was stirred for 1 hr. further at 10°. *p*-Tertbutylcatechol (0.5 g.) was added to the flask and hydrolysis was effected by cautious addition of 150 ml. of 20% hydrochloric acid, maintaining temperature below 20°. The organic layer was separated and the aqueous layer extracted with a 100-ml. portion of ethyl ether. Solvents were stripped from the combined extracts and the crude product was distilled *in vacuo* to yield a fraction, b.p. 86–88°/1 mm. The yield was 12.8 g. or 43%; residue, 6.1 g., a dark red polymeric material. The product decolorized bromine in carbon tetrachloride rapidly. % Hydroxyl (acetylation), Calcd.: 11.5; Found: 9.8. The product was not purified further.

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(3) (a) H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, and R. Cserr, *J. Org. Chem.*, **22**, 1202 (1957); (b) H. Normant, *Compt. rend.*, **239**, 1510 (1954); (c) H. Normant, *Bull. soc. chim. France*, **1957**, 728.

(4) Purity of tetrahydrofuran is important; see ref. (3) (a).

(5) H. Gilman, E. A. Zollner, and J. B. Dickey, *J. Am. Chem. Soc.*, **51**, 1576 (1929).

Addition of Alcohols to Mesityl Oxide Using an Acid Ion Exchange Resin Catalyst

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The preparation of diacetone alcohol ethers from mesityl oxide and alcohols with basic and acidic catalysts has been reported.[1-6] Hoffman[1] prepared these ethers with a sulfuric acid catalyst and a reaction time of 12 days while the same reaction described by Halbig and Treibs[4] required only 12 hr. Acid ion exchange resins have been used by a number of investigators for catalyzing various reactions,[7,8] but the utilization of an acid resin for preparing ethers of diacetone alcohol is a new observation. Dowex 50, a sulfonic acid ion exchange resin, effectively catalyzed the formation of ethers of diacetone alcohol from mesityl oxide and alcohols. The advantages of this catalyst were the reaction time was greatly reduced, the yields were excellent, and the catalyst was easily separated from the reaction solution.

EXPERIMENTAL

The Dowex 50 was converted to the acid form with 3*N* hydrochloric acid, washed with water, and then methanol. Sufficient resin was put in a vertical Pyrex tube 90 cm. long, 19 mm. ID, so that there was a catalyst bed 71 cm. deep. The catalyst bed occupied a total volume of 200 ml. of which 155 ml. was resin beads and 45 ml. was void volume.

The temperature used for all experiments was 25°.

Preparation of 4-methoxy-4-methyl-2-pentanone. A stock solution of equal volumes of methanol and mesityl oxide (2.86 moles of methanol per mole of mesityl oxide) was used. In run 2 of Table 1, 1800 ml. (7.88 moles of mesityl oxide and 21.9 moles of methanol) of the stock solution was passed over the ion exchange resin at an average rate of 0.616 ml. per min. The effluent was first distilled using an efficient glass column at 200 mm. until all of the methanol (b.p. 35°) was removed. The pressure was then reduced to 40 mm. for the removal of the unreacted mesityl oxide (b.p. 42°) followed by 4-methoxy-4-methyl-2-pentanone, confirmed by infrared, b.p. 74°/40 mm., n_D^{25} 1.4159, d_{25} 0.900, (Lit.[1] d_{25} 0.901).

In Table I the results of four runs made at varying feed rates are given.

Preparation of 4-ethoxy-4-methyl-2-pentanone. The same resin that was used above was used for this experiment after it was washed with ethanol. A solution composed of 24.9 moles of anhydrous ethanol and 9.7 moles of mesityl oxide was passed over the resin at a rate of 0.552 ml. per min. The reaction solution was then distilled at 170 mm. until all of the ethanol (b.p. 45°) was removed and then at 40 mm. for the mesityl oxide removal followed by 20 mm. for the 4-ethoxy-4-methyl-2-pentanone, b.p. 67°/20 mm., n_D^{23} 1.4152, d_{25} 0.884 (lit.[1] d_{25} 0.886). A 37 g. high boiling residue remained. A recovery of 7.04 moles of mesityl oxide and 2.19 moles of ether represented a conversion of 27% and a yield of 82% based on unrecovered mesityl oxide.

TABLE I

Run No.	Feed Rate, Ml./Min.	Volume of Stock Soln., Ml.	High Boiling Residue, G.	Mesityl Oxide % Conv.	Mesityl Oxide % Yield[a]
1	0.377	1585	35	57.0	88.2
2	0.616	1800	28	56.6	93.7
3	1.29	1800	27	46.5	94.0
4	2.41	1800	28	40.9	94.0

[a] Based on unrecovered mesityl oxide.

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(1) A. Hoffman, *J. Am. Chem. Soc.*, **49**, 530 (1927).
(2) A. Hoffman, U. S. Patent **1,729,255**.
(3) C. W. Simms, U. S. Patent **1,823,704**.
(4) P. Halbig and A. Treibs, U. S. Patent **2,217,167**.
(5) B. P. Geyer and S. A. Ballard, U. S. Patent **2,413,822**.
(6) J. B. Tindall, U. S. Patent **2,430,436**.
(7) F. Helfferich, *Angew. Chem.*, **66**, 241 (1954).
(8) F. C. Nachod and J. Schubert, editors, *Ion Exchange Technology*, Academic Press, Inc., New York, 1956, pp. 279–284.

Reaction of Alkyl and Aryl Silicon Isocyanates with Amines

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Silicon tetraisocyanate and alkyl and arylsilicon isocyanates have been extensively studied by Forbes and Anderson,[2,3] and by Eaborn.[4] Although it is known that silicon tetraisocyanate reacts with water to form silica no study has been made of the reaction of silicon isocyanates with primary and secondary aliphatic and aromatic amines.[5]

(1) For reprints: 3267 57th Avenue S.W., Seattle 16, Wash.
(2) G. S. Forbes and H. H. Anderson, *J. Am. Chem. Soc.*, **62**, 761 (1940); *J. Am. Chem. Soc.*, **66**, 1703 (1944); *J. Am. Chem. Soc.*, **67**, 1911 (1945); *J. Am. Chem. Soc.*, **69**, 1241 (1947); *J. Am. Chem. Soc.*, **70**, 1043, 1222 (1948).
(3) H. H. Anderson, *J. Am. Chem. Soc.*, **66**, 934 (1944); *J. Am., Chem. Soc.*, **72**, 193, 196, 2761(1950); *J. Am. Chem. Soc.*, **75**, 1576 (1953).
(4) C. Eaborn, *Nature*, **165**, 685 (1950).
(5) Incidentally to another study, Anderson reacted aniline with silicon tetraisocyanate, *n*-butylsilicon triisocyanate, diphenylsilicon diisocyanate, *n*-propylsilicon triisothiocyanate, diethylsilicon diisothiocyanate, and triethylsilicon isothiocyanate, but did not characterize the products, where formed. See H. H. Anderson, *J. Am. Chem. Soc.*, **73**, 2351 (1951).

We wish to report that reaction of amines with silicon isocyanates of the above type results in cleavage of the isocyanate group from the silicon atom with formation of theoretical yields of the corresponding monosubstituted urea.

Silicon tetraisocyanate and isocyanates of empirical formula $R_xSi(NCO)_y$, where R is methyl or phenyl and x and y are 1, 2, or 3, were prepared by reaction of R_xSiCl_y with silver (iso)cyanate in anhydrous benzene.[2,3] Treatment of these isocyanates either alone or in anhydrous benzene with allylamine, diallylamine, aniline, benzylamine, *o*- or *p*-toluidine, produced theoretical yields of the corresponding urea. In every case the NCO: NH_2 ratio was 1:1. No evidence was obtained for the formation of ureidosilanes, and the fate of the silicon-containing moiety was not determined.[6]

EXPERIMENTAL

Allylurea from phenylsilicon triisocyanate. In a typical reaction, phenylsilicon triisocyanate (2.31 g., 0.01 mole) was added, dropwise, to a well-stirred mixture of allylamine (1.71 g., 0.03 mole) in anhydrous benzene (10 ml.). After the initial strongly exothermic reaction had moderated the mixture was heated on the steam bath for 2 hr., then allowed to cool. The white solid was washed thoroughly with benzene, yield 3.94 g. (98%). Recrystallization from isopropyl alcohol gave a white crystalline product of m.p. 85.0°. The mixed melting point of this product with authentic allylurea was undepressed.

Anal. Calcd. for $C_4H_8N_2O$: N, 28.0. Found: N, 27.9.

Similarly, allylurea was produced by reaction of allylamine with silicon tetraisocyanate, methylsilicon triisocyanate, dimethylsilicon diisocyanate, trimethylsilicon isocyanate, and diphenylsilicon diisocyanate.

Products of reaction with other amines. Reaction of aniline, benzylamine, diallylamine, *o*-, and *p*-toluidines with the above silicon isocyanates produced 95–100% yields of, respectively, phenylurea, benzylurea, *N,N*-diallylurea, *o*-, and *p*-tolylurea, which gave undepressed mixed melting points with the authentic ureas and analyzed correctly for nitrogen.

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(6) Further work is in progress to determine the nature of the silicon-containing fragment.

Disulfides

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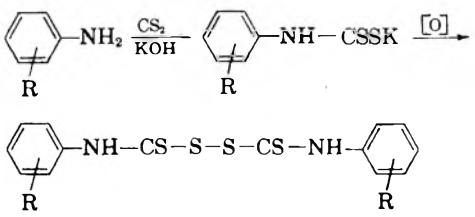
Chemotherapeutic activity can be conceived as due to the interference of the agent in the progression of the parasites metabolic reaction. This interference takes the form of inactivation or displacement of a metabolite essential to the parasite (*a*) by oxidizing a substance that requires to be reduced, (*b*) by molecular combination forming an inactive product, or (*c*) by competition with an enzyme associated with the essential metabolite.[1-3]

It was reported by Srinivasan[4] that paludrine can inhibit the oxygen uptake of the malarial parasite. He is of the opinion that the drug acts through inhibition of the activity of some —SH groups essential for the respiration of the parasite.

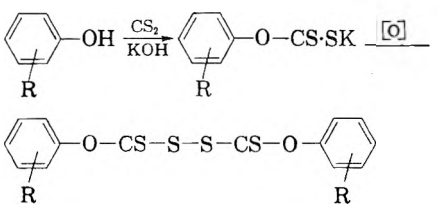
It was, therefore, decided to prepare some —S—S— compounds as potential antimalarials, since these compounds might be active by oxidizing some of the —SH groups essential to the parasite. The potency of thiuramdisulfides as bacterial poisons as well as the antimalarial activity exhibited by them in experimental malaria led us to prepare some analogous disulfides.

These compounds were made by first treating various amines with carbon disulfide in presence of aqueous potassium hydroxide and then oxidizing the thiocarbamido derivative with sodium nitrite, methyl alcohol, and hydrochloric acid.



o-, *m*-, *and p*-Aminobenzoic acids and the three aminobenzene sulfonic acids were thus treated to give the corresponding bisaryl thiuram disulfides.

The dixanthogens are a class of compounds closely related in structure and hence it was decided to prepare some derivatives of this type to study their effect in experimental malaria. The preparation of these compounds follows a similar route, different phenol carboxylic and phenol sulfonic acids being used instead.



These compounds were quite active in inhibiting the respiration of *Plasmodium gallinaceum in vitreo*, using the Warburg technique. However, only diphenylxanthogen-*p,p'*-disulfonic acid and *N,N'*-diphenylthiuram disulfide-*p,p'*-disulfonic acid were active *in vivo* against *P. gallinaceum* in chicks. Detailed pharmacological data will be published elsewhere.

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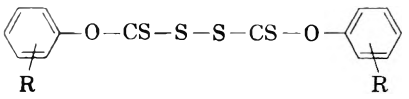
EXPERIMENTAL

Bis(o-carboxyphenyl)xanthogen. Seven grams of salicylic acid, 4 g. of carbon disulfide, 6 g. of potassium hydroxide, and 250 ml. of water were heated on the water bath for six hours. To the yellow solution was added a solution of 3 g. sodium nitrite, 3 ml. methyl alcohol, and under good cooling and stirring 10 ml. of concentrated hydrochloric acid. The precipitated product was collected and crystallized from water.

The procedure was essentially the same for the preparation of the rest of the compounds listed in the tables.

TABLE I

DISULFIDES

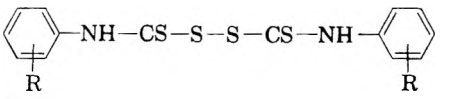


R	M.P., °C.	Yield, %	Formula	S Found	S Required
H[a]	182–183	60	$C_{14}H_{10}O_2S_4$	38.02	37.90
2—COOH	154–155	66	$C_{16}H_{10}O_6S_4$	30.14	30.01
3—COOH	198–200	70	$C_{16}H_{10}O_6S_4$	30.21	30.01
4—COOH	339–340	60	$C_{16}H_{10}O_6S_4$	30.18	30.01
2—SO_3H	360–dec.	48	$C_{14}H_{10}O_8S_6$	42.51	42.70
3—SO_3H	360–dec.	56	$C_{14}H_{10}O_8S_6$	42.34	42.70
4—SO_3H	360–dec.	40	$C_{14}H_{10}O_8S_6$	42.50	42.70
4—Cl[a]	128	70	$C_{14}H_8Cl_2O_2S_4$	30.54	30.70

[a] Crystallized from alcohol.

TABLE II

DISULFIDES



R	M.P., °C.	Yield, %	Formula	N Found	N Required
H[a]	183	66	$C_{14}H_{12}N_2S_4$	8.39	8.42
2—COOH	236–238	75	$C_{16}H_{12}N_2O_4S_4$	6.51	6.60
3—COOH	224.5	57	$C_{16}H_{12}N_2O_4S_4$	6.80	6.60
4—COOH	238–240	57	$CL_6H_{12}N_2O_4S_4$	6.39	6.60
2—SO_3H	360–dec.	53	$C_{14}H_{12}N_2O_6S_6$	5.39	5.36
3—SO_3H	360–dec.	49	$C_{14}H_{12}N_2O_6S_6$	5.42	5.36
4—So_3H	360–dec.	65	$C_{14}H_{12}N_2O_6S_6$	5.51	5.36
4—Cl[a]	100	70	$C_{14}H_{10}Cl_2N_2S_4$	6.58	6.90

[a] Crystallized from alcohol.

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Communications TO THE EDITOR

3-Pyridylphosphonic Acid[1]

Sir:

On the basis of the apparent relation of the bacteriostatic activity of various antagonists of *p*-aminobenzoic acid to the electronegativity of sulfone and similar (XO_2) groups, Bell and Roblin[2] predicted that compounds of the phosphanilic acid type (X = P) should show activity similar to the sulfonamides. Indeed, phosphanilic acid,[3] (*p*-aminophenyl)phosphonous acid[4] and several substituted phosphanilamides[5] possess significant antibacterial activity while in a series of esters and ester amidates of phosphanilic acid only slight inhibition was observed.[6] Since 3-pyridinesulfonic acid and its amide are niacin antagonists,[7] 3-pyridylphosphonic acid has now been prepared in the hope that the analogy between sulfonic and phosphonic acids would hold also in this series.

This expectation has not been fulfilled. *Lactobacillus arabinosus*, which requires niacin or niacinamide for growth, was cultured in Difco niacin assay medium.[8] With increasing ratios of 3-pyridylphosphonic acid to either of these essential metabolites (maximum ratio 10^4:1) no inhibition or stimulation of growth was observed. This suggests that 3-pyridylphosphonic acid does not interfere with the incorporation of niacin into coenzyme systems. That the biosynthesis of niacin is not affected either was shown by experiments with two organisms which synthesize their own niacin requirements. *Mycobacterium smegmatis* and *M. tuberculosis* var. BCG, grown in Proskauer and Beck medium, were indifferent to concentrations up to 1,000 μg./ml. of 3-pyridylphosphonic acid.

The method of synthesis of 3-pyridylphosphonic acid was the decomposition of 3-pyridyldiazonium fluoborate[9] with phosphorus trichloride at a lower temperature than described for analogous cases,[10] and under controlled conditions of isolation. A suspension of the diazonium fluoborate[9] from 18.9 g. (0.201 mole) of 3-aminopyridine in 240 ml. of ethyl acetate was cooled to −10° and treated gradually with 18.9 ml. (29.6 g., 0.215 mole) of phosphorus trichloride and 3.9 g. (0.027 mole) of cuprous bromide. After the exothermic reaction was complete, 75 ml. of water was added, the mixture was concentrated under reduced pressure to 50 ml., and treated with excess saturated barium hydroxide solution. After the mixture was filtered, barium ions were precipitated with the exact amount of sulfuric acid, and the halide ions were precipitated with saturated silver lactate solution. Barium sulfate and silver halide were filtered, the filtrate was concentrated to 50 ml. and decolorized with Darco, and 800 ml. of dioxane was added to turbidity. The cloudy suspension was allowed to crystallize at 4°. The crude 3-pyridylphosphonic acid (4.4 g., 13.8%, m.p. 249–253°) was recrystallized by dissolving in a minimum of hot water, adding ethanol to turbidity, and cooling slowly. The colorless prisms (calcd. for $C_5H_6NO_3P$: C, 37.74; H, 3.81; neut. equiv., 79.6. Found: C, 37.31; H, 4.04; neut. equiv., 79.5) had m.p. 258–260° (corr.).

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