Syntheses of Hormones from 5,6-Dichloro Steroids. I. Addition of Chlorine to Pregnenolone Acetate

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Chlorine has been added to pregnenolone acetate to give in 84% yield a dichloride assigned the $5\alpha,6\beta$-configuration. The chlorination is readily effected by bubbling chlorine into a benzene solution of pregnenolone acetate containing a small amount of pyridine. Small amounts of an isomeric dichloride, assigned the $5\alpha,6\alpha$-configuration, and of a 7-hydroxypregnenolone acetate are also formed.

Reichstein's Substance S ($17\alpha,21$-dihydroxy-4-pregnene-3,20-dione) has been the target of many syntheses, particularly since it can be converted by suitable microbiological processes into the 11-oxygenated cortical hormones.[1] Because of the availability of 3β-hydroxy-5-pregnen-20-one from sapogenins and soya sterols, we became interested in the conversion of this steroid into Substance S.

Our intent was to introduce the 17α-hydroxyl group *via* the general method of Gallagher,[2] involving peracid treatment of the enol acetate of the 20-ketone; subsequent bromination and metathesis with acetate would introduce oxygen at position 21. In several of these operations, competing reactions at the 5,6 double bond were anticipated. We indeed found that 5,17-pregnadiene-$3\beta,20$-diol diacetate[3] on treatment with peracid or bromine showed virtually no evidence of selectivity between the 5,6 and the 17,20 double bonds. It seemed essential to protect the 5,6 double bond prior to enol acetylation. Ideally, this protecting group should serve to advantage in the final transformation to a Δ^4-3-keto derivative.

Addition of bromine was attractive; however, 5,6-dibromo-3β-acetoxypregnan-20-one was found to suffer loss of bromine at the elevated temperature required for enol acetylation.[4] Moreover, 5,6-dibromides are prone to undergo mutarotation.[5] For these reasons protection by the addition of chlorine was investigated, and proved admirably suited in all respects. The addition of chlorine to 3β-acetoxy-5-pregnen-20-one I forms the subject of the remainder of this paper.[6] The further conversion of the dichloride to Reichstein's Substance S and related hormones is described in the subsequent papers.[7]

The addition of chlorine to the 5,6 double bond of sterols has been investigated by many workers,

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(1) For references to published syntheses of Reichstein's Substance S and to its microbiological transformations see H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 820 (1956).

(2) T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

(3) L. F. Fieser and Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 1840 (1949).

(4) At the time this work was done, the method of enol acetylation at room temperature of D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones, and T. Walker, *J. Chem. Soc.*, 747 (1954), had not been published.

(5) For a discussion of the mutarotation of 5,6-dibromides, see D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 1066 (1950).

(6) Certain details of the chlorination of pregnenolone acetate I and the further transformation to Reichstein's Substance S have already been described: F. A. Cutler and J. M. Chemerda, U. S. Patents 2,786,856-7 (March 26, 1957), 2,884,417 (Apr. 28, 1959).

(7) F. A. Cutler, Jr., J. F. Fisher, and J. M. Chemerda, *J. Org. Chem.*, **24**, 1626 (1959); F. A. Cutler, Jr., L. Mandell, J. F. Fisher, D. Shew, and J. M. Chemerda, *J. Org. Chem.*, **24**, 1629 (1959).

notably Wallis[8] and Barton.[9] The presence of the ketone function in our case could well be expected to cause complication, and indeed such proved to be the case.

Our initial experiments involved treating solutions of pregnenolone acetate I in chloroform at low temperatures with a slight excess of chlorine dissolved in carbon tetrachloride. A dichloride II,[10] m.p. 199.5–201°, was obtained in yields up to about 60%. It regenerated the starting pregnenolone acetate on treatment with chromous chloride or zinc dust. By analogy with the work of Barton, Miller, and Young[9] it has been assigned the structure $5\alpha,6\beta$-dichloro-3β-acetoxypregnan-20-one. As shown in the subsequent papers,[7] this compound is well suited to the synthesis of Substance S.

An immediate objective was to improve the procedure both in yield and workability. The use of antimony trichloride as catalyst as described by Barton[9a] and the N-chlorosuccinimide–hydrogen chloride couple[11] also gave yields of II of the order of 50–60% and were not further explored. The obvious formation of hydrogen chloride under our original conditions suggested chlorination of the ketonic side chain as the principal side reaction. It was felt that a base would serve to inhibit side chain chlorination by combining with the hydrogen chloride as it was formed and minimize enolization. When our original conditions were modified by adding a mole of pyridine, the yield of II was increased to 73.5%. The procedure was complicated by the formation of an insoluble complex of pyridine and chlorine.

In an experiment designed to produce the $5\alpha,6\alpha$-dichloride, pregnenolone acetate was treated with iodobenzene dichloride[12] in dry, refluxing benzene. The product, obtained in 56% yield, proved to comprise largely the same $5\alpha,6\beta$-dichloride observed before.[13]

This unexpected result led us to explore extensively the use of benzene as the solvent for the direct chlorination at room temperature. Initial experiments were directed toward determining the optimum amount of pyridine to be added to the benzene. The results are summarized in Table I. As can be seen, the optimum molar ratio of pyridine to pregnenolone acetate is in the range 0.3 to 0.5, giving first crop yields of II of the order of 77–80%.

It was then found that it was not necessary to add chlorine as a solution, but that chlorine gas could be merely bubbled into the solution of the steroid and pyridine in benzene until the yellow color just persisted. The benzene–steroid ratio was found to play a peculiar role in that at dilutions below 32 ml. per gram, erratic and lower yields were obtained. There was some indication that the efficiency with which the chlorine was distributed into the solution was involved. In large scale work it was found useful to employ a dilution principle: a solution of pregnenolone acetate and pyridine in benzene was introduced alternately with chlorine gas into benzene containing pyridine. In this manner it was possible to use a total benzene to steroid ratio of 12 ml. per gram. The yield of II obtained in several crops was 84%.

The benzene used in these experiments was dried over sodium. With benzene deliberately made wet with sufficient water to form a second phase during the chlorination, the yield was reduced to 42%.

The use of a number of solvents other than benzene in the chlorination was investigated; none was found superior to benzene. The results are tabulated in Table II.

Chromatography of the mother liquor solids from the chlorination of pregnenolone acetate led to the isolation of small amounts of two by-products. The first (III) proved to be an isomeric dichloride. On treatment with zinc in acetic acid it regenerated pregnenolone acetate. However, unlike the major isomer, it resisted the action of chromous chloride. Thus, this minor isomer differs only in configuration, the major isomer having the chlorine atoms disposed in a *trans* axial–axial relationship which facilitates reductive elimination.

Further light was shed on the configuration by comparison of the rate of dehydrochlorination by potassium hydroxide in refluxing dioxane-methanol. In the earlier work with the $5\alpha,6\beta$- and $5\alpha,6\alpha$-dichlorocholesteryl benzoates[8,9] it was shown that the $5\alpha,6\alpha$-isomer dehydrochlorinated faster than did the $5\alpha,6\beta$-isomer. In our series we have found that the minor isomer dehydrochlorinated some six times as fast as the major isomer. We have therefore assigned the $5\alpha,6\alpha$-configuration to the minor isomer III. The $5\beta,6\alpha$ and $5\beta,6\beta$ structures are not ruled out, but such dichlorides have never been isolated in other series. In this connection it may be noted that Barton[5] has shown that the $5\beta,6\alpha$-dibromide of cholesteryl benzoate dehydrobrominates even more slowly than the $5\alpha,6\beta$-isomer.

(8) C. J. Berg and E. S. Wallis, *J. Biol. Chem.*, **162**, 683 (1946); D. E. A. Rivett and E. S. Wallis, *J. Org. Chem.*, **15**, 35 (1950).

(9) (a) D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 370 (1950); (b) D. H. R. Barton, E. Miller, and H. T. Young, *J. Chem. Soc.*, 2598 (1951).

(10) This same dichloride has also been obtained by the catalytic hydrogenation of 5,6-dichloro-3β-acetoxy-16-pregnen-20-one; J. M. Chemerda, U. S. Patent **2,739,162** (March 20, 1956). Also P. L. Julian and W. J. Karpel, U. S. Patent **2,696,490** (Dec. 7, 1954), describe a reaction of a dichloride of pregnenolone acetate without giving details of its preparation or its properties.

(11) *Cf.* J. B. Ziegler and A. C. Shabica, *J. Am. Chem. Soc.*, **74**, 4891 (1952).

(12) Barton[9] has shown that this reagent produces the $5\alpha,6\alpha$-dichloride of cholesterol benzoate.

(13) The circumstances under which iodobenzene dichloride leads to the same products as elemental chlorine have recently been discussed by L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **80**, 1723 (1958).

The formation of a $5\alpha,6\alpha$-dichloride may be rationalized by noting that when the A-ring takes a boat form, the 3β-acetoxy group may participate at position 5 in the opening of the initial $5,6\alpha$-chloronium ion.[14] Subsequent attack by chloride at position 5 would lead to the $5\alpha,6\alpha$-isomer.
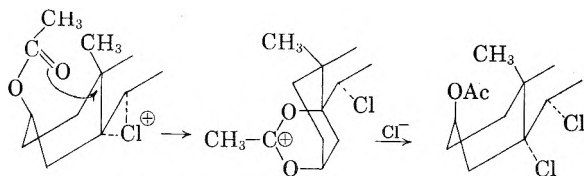
The second by-product in the chlorination was a 7-hydroxylated pregnenolone acetate IV, apparently arising by action of the alumina used in the chromatography on an allylic chloride.[15]
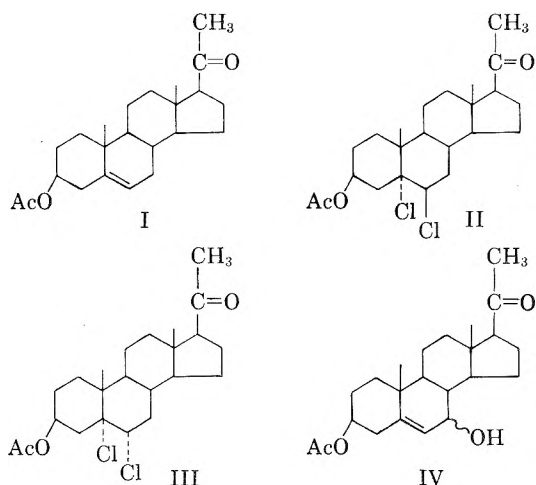
The hydroxyl group was indicated by infrared analysis and by acetylation. On oxidation with chromium trioxide, an α,β-unsaturated ketone was obtained whose spectral characteristics and melting point agree with those of the known[16] 7-ketopregnenolone acetate.[17]

In conclusion we may note that our experience in forming 5,6-dichlorides has been found in these

laboratories to have rather general application. Details of the chlorination of other Δ^5-steroids in inert solvents containing a tertiary amine have recently been disclosed by another laboratory.[19]

EXPERIMENTAL

Melting points were measured on samples in open capillaries with total immersion thermometers and are not corrected. Rotations were measured in chloroform, except as noted, and at concentrations of about 1 g. per 100 ml.

Reaction of 5,17-pregnadiene-3β,20-diol diacetate. (a) *With perbenzoic acid.* Eight grams (20 mm.) of 5,17-pregnadiene-3β,20-diol diacetate[3] (mixed isomers, m.p. 126–138.5°, $[\alpha]_D^{24}$ $-53.5°$) was dissolved in 67.1 ml. of 0.298M (20 mm.) perbenzoic acid in benzene. The solution was held at 27–30° for 30 min. at which time a test for peracid was negative. The solution was washed with sodium hydroxide solution and water, dried, and evaporated under reduced pressure. The residual sirup was dissolved in 100 ml. of ethanol and saponified by adding a solution of 4.0 g. of sodium hydroxide in 50 ml. of water. After an hour at 25–30°, a crop of crystals (1.67 g., m.p. about 220–250°) was collected. The filtrate was diluted with ether (500 ml.) and the aqueous layer was separated. The ether layer was washed with four 100-ml. portions of 5% sodium chloride solution and evaporated to dryness. Trituration of the residue with ether gave 3.64 g. of crystals, m.p. 187–206°. Specimens of both portions of crystals were chromatographed on 20 parts of acid-washed alumina, giving in each case many fractions with wide melting-point ranges. No pure products were identified.

(b) *With bromine, then perbenzoic acid.* To a stirred solution of 4 g. (10 mm.) of 5,17-pregnadiene-3β,20-diol diacetate in 75 ml. of chloroform at $-60°$ was added 25.5 ml. (10 mm.) of 0.392M bromine in chloroform. The bromine was rapidly consumed. The solution was allowed to warm to 0° and 38.7 ml. (11 mm.) of 0.284M perbenzoic acid in benzene was added. The solution was allowed to stand overnight, then was washed with three 100-ml. portions of cold 0.5N sodium hydroxide and three 100-ml. portions of water. Evaporation of the solvent and slurrying of the residue in 30 ml. of hot methanol gave after chilling 2.46 g. of solid, m.p. 155–160° dec. This material was evidently 5,6,17-tribromo-3β-acetoxypregnan-20-one (lit.[3] m.p. 167–168° dec.), for on treatment with sodium iodide it formed in good yield 17-bromo-3β-acetoxy-5-pregnen-20-one as plates, m.p. 146.5–149° (lit. 147–148°[20]; 146–148°[21]). Thus, attack by an equimolar amount of bromine was not selective.

Attempts to use pregnenolone acetate dibromide. (a) Pregnenolone (10 g.) was treated with one molar equivalent of bromine in chloroform and after removal of solvent, the residue was treated with acetic anhydride (300 ml.) containing 3 g. of p-toluenesulfonic acid at the boiling point with slow distillation as described by Gallagher.[22] The distillate was found to contain bromide ion. Further processing with perbenzoic acid and hydrolysis with sodium hydroxide at room temperature gave only dark amorphous materials, even after zinc debromination.

(b) Pregnenolone acetate (20 g.) in chloroform (200 ml.) at $-60°$ was treated with 38.5 ml. of 1.45M bromine in chloroform and gave after recrystallization from ethyl acetate 13.7 g. (47%) of 5,6-dibromo-3β-acetoxypregnan-20-one, m.p. 144–148.5° dec. A solution of dibromide (11.09

(14) *Cf.* J. B. Ziegler and A. C. Shabica[11] and D. H. R. Barton, E. Miller, and H. T. Young.[9b]

(15) The similar hydrolysis of 7-bromocholesterol benzoate by action of alumina during chromatography was first observed by J. A. K. Buisman, W. Stevens, and J. v. d. Vliet, *Rec. trav. chim.*, **66**, 83 (1947). The reaction has been used in preparative work by H. J. Ringold, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 3318 (1952) and by R. H. Lenhard and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 989 (1956). The latter two groups have shown that principally the 7α-hydroxy configuration is obtained.

(16) W. Logemann and P. Giraldi, *Gazz. chim. ital.*, **81**, 548 (1951); W. Klyne, *J. Chem. Soc.*, 3449 (1951).

(17) Two alternate structures were considered, namely the Δ^4-6-ketone and the Δ^5-4-ketone. An estimate[18] of the absorption expected of these *cisoid* chromophores is log ϵ 3.8 and 3.5 respectively, much below that observed, log ϵ 4.13.

(18) H. Dannenberg, *Abhandl. preuss. Akad. Wiss.*, **21**, 3 (1939); L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 191.

(19) Glidden Company, Brit. Patent **778,334** (July 3, 1957); *Chem. Abstr.*, **52**, 2106 (1958).

(20) H. Heusser, C. R. Engel, P. T. Herzig, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 2229 (1950).

(21) P. L. Julian and W. J. Karpel, *J. Am. Chem. Soc.*, **72**, 362 (1950).

(22) C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher, *J. Am. Chem. Soc.*, **70**, 1837 (1948).

g.) and 1.2 g. of *p*-toluenesulfonic acid monohydrate in 48 ml. of acetic anhydride was heated 5 hr. on the steam bath, and yielded after the usual work-up a black amorphous enol acetate. This was treated with 156 ml. of 0.276*M* perbenzoic acid in benzene at room temperature for 4 hr., at which time an equimolar amount of peracid had been consumed. The solution was washed with alkali and water and evaporated. The residue was debrominated with sodium iodide and then hydrolyzed with sodium hydroxide in ethanol-water at room temperature. Multiple recrystallizations from ethanol finally afforded 0.525 g. of 3β,17α-dihydroxy-5-pregnen-20-one, m.p. 258–268° (lit.[23] 271–273°).

Chlorination of pregnenolone acetate. (a) *In chloroform at* −60°. To a stirred solution of 25 g. of pregnenolone acetate in 940 ml. of chloroform at −60° was added over a period of a minute 116 ml. of 0.63*M* chlorine in carbon tetrachloride. The colorless reaction mixture was concentrated to dryness *in vacuo*, and flushed with acetone. The residue was dissolved in 180 ml. of boiling acetone and 100 ml. was distilled off. After chilling, the suspension of crystals was filtered. After washing with cold acetone and drying, the 5α,6β-*dichloro-3β-acetoxypregnan-20-one II* weighed 17.8 g. (59.4%); m.p. 194–197°; [α]$_D$ +6.0°.

Pure 5α,6β-dichloro-3β-acetoxypregnan-20-one is obtained by additional recrystallization from acetone or methanol; m.p. 199.5–201° (bath was heated at 6° per minute, insertion at 190°; at slower rates and with more preheating, slight decomposition was observed); [α]$_D^{25}$ +6.5° (chloroform); −4.2° (benzene).

Anal. Calcd. for $C_{23}H_{34}Cl_2O_3$: C, 64.33; H, 7.98; Cl, 16.51. Found: C, 64.42; H, 8.11; Cl, 16.33.

(b) *In chloroform containing pyridine at* −60°. To a stirred solution of 25 g. of pregnenolone acetate and 6 ml. of pyridine in 940 ml. of chloroform at −60° was added 79 ml. of 0.93*M* chlorine in carbon tetrachloride. A white crystalline precipitate formed (evidently a complex between pyridine and chlorine since it also formed in the absence of steroid) which gradually dissolved as the reaction mixture was allowed to warm to 15°. The solution was then washed successively with 200 ml. of 10% hydrochloric acid, 200 ml. of 5% sodium carbonate solution and two 200-ml. portions of water. Further processing as described above gave 22 g. of II (73.5%), m.p. 193–197°, [α]$_D$ +7.0°.

(c) *With antimony trichloride as catalyst.* To a solution of 50 g. of pregnenolone acetate in 1875 ml. of chloroform containing 0.5 g. of anhydrous antimony trichloride was added 268 ml. of 0.55*M* chlorine in carbon tetrachloride, keeping the temperature between −60 and −55°. The reaction mixture was washed with three 200-ml. portions of dilute hydrochloric acid, three 200-ml. portions of 10% sodium carbonate solution, and three 200-ml. portions of water. The chloroform extract was then worked up as described above, giving 32.15 g. (53.6%) of II, m.p. 195–198°.

(d) *With N-chlorosuccinimide-hydrogen chloride.* Pregnenolone acetate (10 g.) was dissolved in 100 ml. of chloroform and the solution was saturated with hydrogen chloride at room temperature. The solution was then cooled to −10° and a slurry of 4.15 g. of *N*-chlorosuccinimide in 80 ml. of chloroform was added, keeping the temperature at about −10°. The reaction mixture was washed to neutrality with water and worked up as previously described, yielding 6.45 g. (53.8%) of II, m.p. 193–195°.

(e) *With iodobenzene dichloride.* Five grams of pregnenolone acetate was dissolved in 150 ml. of reagent-grade benzene and the solution was dried by distilling off 50 ml. of benzene at atmospheric pressure. To the hot solution was added 3.88 g. of iodobenzene dichloride with shaking. After 5 min. the yellow reaction mixture gave a negative starch-iodide test. The solution was allowed to reflux for 30 min. during which the yellow color disappeared. The solution was concentrated under reduced pressure, and the resi-

due was recrystallized from 25 ml. of methanol; yield, 3.38 g. (56.4%), m.p. 174–190°. Further recrystallization from methanol gave material whose infrared spectrum was identical with that of II.

(f) *In benzene containing pyridine.* To a stirred solution of 10 g. (28 mm.) of pregnenolone acetate in 320 ml. of benzene (dried over sodium) containing an amount of pyridine indicated in Table I was added 25.4 ml. (28 mm.) of 1.1*M* chlorine in carbon tetrachloride. The reaction was run at room temperature. After discharge of the yellow color, the solution was washed with 250 ml. of 5% hydrochloric acid and 200 ml. of water. After evaporation of the benzene, the residue was crystallized by dissolution in 100 ml. of acetone, distillation of 75 ml. of acetone, and chilling. The yields (first crop) and melting points are given in Table I.

TABLE I

EFFECT OF PYRIDINE ON CHLORINATION IN BENZENE

Pyridine, Ml.	Moles Pyridine per Mole Pregnenolone Acetate	Yield, %	Melting Point, °C.
0.0	0.00	55.2	194.5–197
0.1	0.04	58.2	193.5–196
0.5	0.22	77.5	192–195
0.6	0.27	76.5	196–197
0.65	0.29	79.4	196–198
0.8	0.35	77.5	196–198
1.2	0.53	80.0	195–198
2.4	1.06	75.4	195–196.5

(g) *Using dilution principle.* Chlorine gas was bubbled into a stirred solution of 3.5 ml. of pyridine in 600 ml. of anhydrous benzene until a definite yellow color was obtained. A small portion of a solution of 100 g. of pregnenolone acetate and 3.5 ml. of pyridine in 600 ml. of anhydrous benzene was added from a dropping funnel, discharging the yellow color. Another portion of chlorine was bubbled in to definite excess, followed by another portion of steroid solution until the color was discharged. The cycles were repeated until all the steroid had been added and chlorine was in excess. The solution was washed successively with dilute sodium thiosulfate solution, dilute hydrochloric acid, and with water. The product was isolated from acetone as described previously to give 91.0 g. (76%) of II, m.p. 196–200.5°. The residue from the liquor on crystallization from 60 ml. of acetone afforded a second crop of 7.14 g., m.p. 191–195°. On further concentration a third crop was obtained which after recrystallization from acetone amounted to 1.35 g.; m.p. 192–196.5°. The total direct yield (99.49 g.) corresponds to 83%. A final residue of 15.7 g. was obtained and was chromatographed as described hereafter.

(h) *Comparison of solvents.* These experiments were run using the following proportions: 10 g. of pregnenolone acetate, 320 ml. of solvent, and 0.7 ml. of pyridine. Chlorinations were conducted at room temperature and worked up as described in (f) or (g). The first crop yields are recorded in Table II. The dichloride obtained generally melted in the range 195–200°.

Isolation of by-products in chlorination of pregnenolone acetate. The mother liquor residue amounting to 15.7 g., which resulted from the chlorination of 100 g. of pregnenolone acetate as described earlier, was chromatographed over 350 g. of acid-washed alumina and eluted with mixtures of ether and light petroleum ether. From the 5% ether-petroleum ether eluate there was obtained 1.79 g. more of II (total, 84.5%). From the 35% ether-petroleum ether cuts after evaporation and crystallization from methanol, there was obtained 1.7 g. of 5α,6α-*dichloro-3β-acetoxy-*

(23) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, 24, 828 (1941).

TABLE II
EFFECT OF SOLVENT ON CHLORINATION

Solvent	Method[a]	Yield
Benzene, sodium-dried	G	77.7%
Benzene plus 10 ml. water	G	42.3[b]
1,1,1-Trichloroethane	G	73.8
Chlorobenzene	S	71.5
Carbon Tetrachloride	S	61.7
Cyclohexane[c]	S	61.9
Dimethylformamide	S	42.5

[a] In experiments labeled "G," chlorine was added as the gas to slight excess; in those labeled "S," an equivalent amount of chlorine dissolved in about 11 ml. of carbon tetrachloride was added. [b] This material melted at 180–189°. [c] Sixty ml. of benzene was present in this run.

pregnan-20-one (III), m.p. 174–175°; mixed m.p. with II, 151–171°.

Anal. Calcd. for $C_{23}H_{34}Cl_2O_3$: C, 64.33; H, 7.98; Cl, 16.51. Found: C, 63.77; H, 8.23; Cl, 16.36.

From the ether eluate there was obtained by concentration and recrystallization from ether 1.7 g. of *3β-acetoxy-7-hydroxy-5-pregnen-20-one* (IV), m.p. 193–195°. The infrared spectrum showed bands at 2.81 (hydroxy), 5.79 (acetate), 5.90 (carbonyl), and 6.00 μ (double bond).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.11; H, 9.34.

Acetylation of 50 mg. of IV in 2 ml. of pyridine and 2 ml. of acetic anhydride overnight at room temperature gave after precipitation with water and recrystallization from methanol 40 mg. of *3β,7-diacetoxy-5-pregnen-20-one*, m.p. 207–210°. The infrared spectrum showed the absence of hydroxyl bands and the presence of ester carbonyl at 5.80 μ and of ketonic carbonyl at 5.9 μ.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.63; H, 8.85.

Oxidation of IV was carried out as follows: To a solution of 0.1 g. of IV and 0.2 ml. of water in 2 ml. of glacial acetic acid at 5° was added 1.0 ml. of a solution prepared by dissolving 0.27 g. of chromium trioxide in 0.5 ml. of water and 9.5 ml. of glacial acetic acid. Concentrated sulfuric acid (0.015 ml.) was added and the reaction mixture was stirred at 5° for 90 min., then at room temperature overnight. The steroid was then precipitated by the addition of water and recrystallized from methanol, to give 20 mg. of 7-ketopregnenolone acetate, m.p. 149–151°.[24] The infrared spectrum showed bands at 5.79 (acetoxyl carbonyl), 5.86 (C-20 carbonyl) and 5.99 and 6.1 μ (conjugated carbonyl bands). The ultraviolet spectrum showed $\lambda_{max}^{methanol}$ at 235 mμ, ε 13,450.

Reactions of 5α,6β-dichloro-3β-acetoxypregnan-20-one II. (a) *With zinc.* Five grams of II was dissolved in 100 ml. of glacial acetic acid. To the stirred solution was added 10 g. of zinc dust in portions over 2.5 hr., beginning at 35° and increasing finally to 80°. The mixture was filtered and the zinc cake was washed with 100 ml. of acetic acid. Water (800 ml.) was added to the combined filtrate. The suspension was chilled and the pregnenolone acetate was collected, washed with water and dried; yield, 4.0 g. (96%); m.p. 148–149.5°.

(b) *With chromous chloride.* To a solution of 500 mg. of II in 100 ml. of acetone at room temperature was added 40 ml. of chromous chloride solution.[25] The reduction was virtually instantaneous. The acetone was then removed under reduced pressure, additional water (200 ml.) was added, and the mixture was chilled and filtered. The pregnenolone acetate was washed and dried; yield, 0.41 g. (98%); m.p. 145–148°.

(c) *With potassium hydroxide.* To a solution of 0.5 g. (1.17 mm.) of II in 50 ml. of dioxane (purified by distillation over sodium) was added a solution of 0.5 g. of potassium hydroxide in 25 ml. of methanol. The solution was heated at the reflux temperature for 1 hr., after which the steroid was precipitated by the addition of water (300 ml.) and filtered off. The filtrate and washings were acidified with nitric acid and the chloride ion, as determined by titration by the Volhard method, amounted to 0.17 me.

Reactions of 5α,6α-dichloro-3β-acetoxypregnan-20-one III. (a) *With zinc.* A solution of 0.24 g. of III in 5.2 ml. of glacial acetic acid was heated on the steam bath and three 0.3 g.-portions of zinc dust were added at 20-min. intervals with shaking. The mixture was filtered and the zinc cake was washed with a small amount of acetic acid. The combined filtrate was diluted with water (about 30 ml.) and after chilling, the crystals of pregnenolone acetate were collected, washed with water and dried; weight, 0.19 g. (95%); m.p. 142–144.5°. There was no depression in melting point on admixture with authentic pregnenolone acetate and the infrared spectra were identical.

(b) *With chromous chloride.* To a solution of 50 mg. of III in 35 ml. of acetone was added 30 ml. of chromous chloride solution.[25] The solution was refluxed for 30 min., then concentrated under reduced pressure to remove acetone. The residue was extracted into chloroform and the chloroform extract was washed with water and then concentrated to dryness under reduced pressure. Recrystallization of the residue from methanol afforded 40 mg. of unreduced starting material, m.p. 168–175° alone and 172–175° when mixed with III.

(c) *With potassium hydroxide.* To a solution of 0.5 g. (1.17 mm.) of III in 36 ml. of purified dioxane was added a solution of 0.4 g. of potassium hydroxide in 18 ml. of methanol. The solution was heated at the reflux temperature for 1 hr. The steroid was precipitated by the addition of water and filtered off. The filtrate and washings were acidified with nitric acid and the chloride ion was determined to be 1.13 me.

RAHWAY, N. J.

(24) W. Logemann and P. Giraldi, *Gazz. chim. ital.*, 81, 548 (1951), give m.p. 152–153°; W. Klyne, *J. Chem. Soc.*, 3449 (1951), gives m.p. 151–153°.

(25) Prepared as described by G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, 72 4077 (1950).

Syntheses of Hormones from 5,6-Dichloro Steroids.
II. Introduction of 17α-Hydroxyl

FRANK A. CUTLER, JR., JAMES F. FISHER, AND JOHN M. CHEMERDA

Enol acetylation of 5α,6β-dichloro-3β-acetoxy-pregnan-20-one followed by treatment with peracetic acid and hydrolysis has given 5α,6β-dichloro-3β,17α-dihydroxy-pregnan-20-one in 80% yield. The peracid–enol acetate reaction is shown to be bimolecular and its rate constant is greater than those observed with the mono- and dienol acetates of 3α-acetoxypregnane-11,20-dione.

In the preceding paper[1] we described the addition of chlorine to 3β-acetoxy-5-pregnen-20-one and indicated that the product, 5α,6β-dichloro-3β-acetoxypregnan-20-one (I), obtained in 84% yield, was useful in the synthesis of Reichstein's Substance S. In the present paper we wish to record our experience in introducing the 17α-hydroxy group via the general method of Gallagher[2] involving preparation of the enol acetate II, epoxidation with peracid, and hydrolysis of the epoxide III to 5α,-6β-dichloro-3β,17α-dihydroxypregnan-20-one IV. Certain details of this work have already appeared in the form of patents.[3]
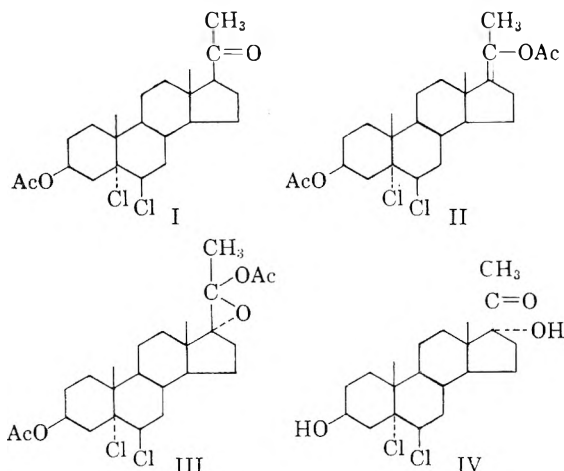
When the enol acetylation of I was attempted by the original method[4] involving continuous distillation of acetic anhydride at atmospheric pressure in the presence of p-toluene sulfonic acid, some loss of halogen was observed. However, at steam bath temperature loss of halogen did not occur. Crude kinetic experiments indicated that the enol acetylation was essentially complete in a few hours. The enol acetate II was ordinarily not isolated in solid form, but could be chromatographed to give crystalline material; however, most cuts were broad melting, suggesting mixed cis and trans isomers. The initial fraction, m.p. 158–161.5°, may be one isomer in nearly pure form.[5]

The epoxidation of the enol acetate was effected with perbenzoic acid,[3] monoperphthalic acid,[3] and peracetic acid. Of these, peracetic acid was the most convenient because of its commercial availability.[6] A procedure for its direct use is described in the Experimental.

It was also possible to extract peracetic acid into benzene in a simple manner and to study the epoxidation in some detail. The crystalline enol acetate, even though an apparent mixture of isomers, was useful in this work. We were gratified to find that merely determining the amount of peracid consumed as a function of time afforded data which responded well to kinetic analysis. When the data are plotted in conformity with a bimolecular reaction between the enol acetate and peracetic acid, it is found that a straight line is obtained to over 80% conversion, as may be seen from Fig. 1. The second-order rate constant in benzene at 27° is found to be 4.1 l./mole-hour.

It became of interest to compare this rate with those of two other enol acetates: 3α,20-diacetoxy-17(20)-pregnen-11-one (V),[7] and 3α,11,20-triacetoxy-9(11),17(20)-pregnadiene (VI).[9] Each of these was allowed to react with peracetic acid in benzene at 27° and again second-order kinetics were fol-

(1) F. A. Cutler, Jr., L. Mandell, D. Shew, J. F. Fisher, and J. M. Chemerda, J. Org. Chem., 24, 1621 (1959).

(2) T. H. Kritchevsky and T. F. Gallagher, J. Biol. Chem., 179, 507 (1949).

(3) F. A. Cutler and J. M. Chemerda, U. S. Patents 2,786,856–7 (Mar. 26, 1957), 2,884,417 (Apr. 28, 1959).

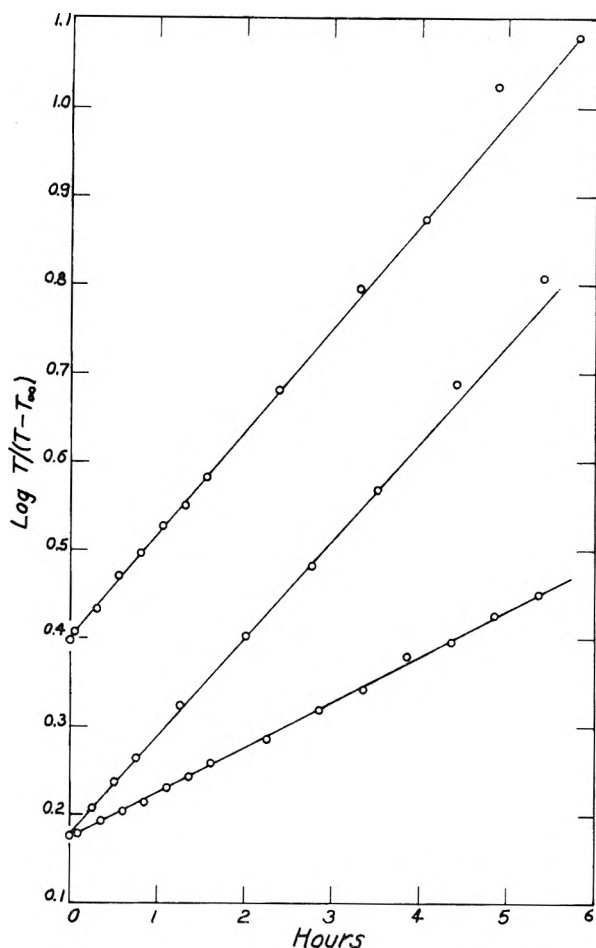(4) C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher, J. Am. Chem. Soc., 70, 1837 (1948).

(5) Enol acetylation of 5,6-dichloro-3β-acetoxypregnan-20-one in the presence of ketene has been reported to give an enol acetate melting at about 155°; A. Middelbeek, E. M. De Graaf, and P. Modderman, German Patent 1,021,844 (June 12, 1958).

(6) Treatment of steroidal enol acetates with commercial 40% peracetic acid in the presence of sodium acetate has been described by Anderson et al.[7] Its use without the addition of base to neutralize the sulfuric acid present has also been described.[8]

(7) H. V. Anderson, E. R. Garrett, F. H. Lincoln, Jr., A. H. Nathan, and J. A. Hogg, J. Am. Chem. Soc., 76, 743 (1954).

(8) E. P. Oliveto and E. B. Hershberg, J. Am. Chem. Soc., 76, 5167 (1954).

(9) T. H. Kritchevsky, D. L. Garmaise, and T. F. Gallagher, J. Am. Chem. Soc., 74, 483 (1952).

Fig. 1. Second-order curves for reaction of peracetic acid with enol acetates in benzene at 27°. Upper curve, with 3α,11,20-triacetoxy-9(11),17(20)pregnadiene (VI); middle curve, with 5α,6β-dichloro-3β,20-diacetoxy-17(20)pregnene (II); lower curve, with 3α,20-diacetoxy-17(20)pregnen-11-one (V)

V   VI
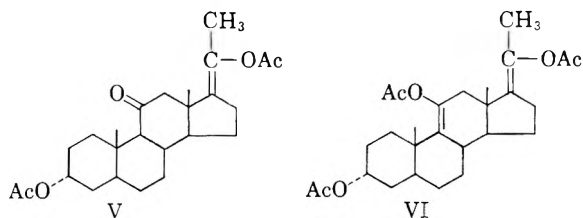
lowed, based on the consumption of one mole of peracid.[10] The data are likewise plotted in Fig. 1. The specific rate constants are 1.95 and 2.5 l./mole-hour for V and VI, respectively. Apparently the enol acetylation of the 11-carbonyl slightly increases the rate of reaction at 17(20). In each case the rate of reaction is considerably lower than with II.

(10) Had the dienol acetate VI reacted appreciably at the 9(11) double bond, considerable deviation from a straight line would have resulted. Moreover, Anderson et al.,[7] have shown that treatment of VI with peracetic acid gives after hydrolysis a 78.5% yield of 3α,17α-dihydroxypregnane-11,20-dione, demonstrating that attack was limited largely to the 17(20) double bond. Hydrolysis of our product at the termination of the run confirmed this.

Since simple second-order kinetics are observed in the epoxidation of enol acetates, it follows that the reaction is not catalyzed by the by-product acid produced.[11] The reaction is kinetically similar to that between simple olefins and peracids.[12] The reaction probably involves direct attack by the peracid on the 17(20)-double bond rather than prior dissociation of peracid into OH^+ and RCO_2^-.[13]
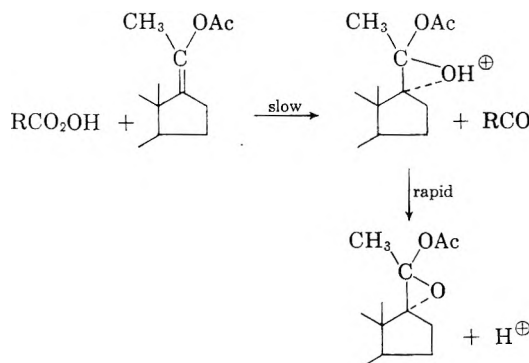
The direct product III of the epoxidation was not fully characterized. Its melting range indicated that it was a mixture of isomers. Attempts to hydrolyze III at room temperature with potassium hydroxide were complicated by solubility problems. These could be overcome by hydrolyzing instead with potassium bicarbonate in aqueous methanol at the reflux temperature. The product, 5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one (IV) proved to be an easily isolated, stable compound. By operating without isolation of intermediates, it was possible to convert I to IV in 80% yield. No loss of halogen was observed at any point.

EXPERIMENTAL[14]

5α,6β-Dichloro-3β,20-diacetoxy-17(20)-pregnene (II). The enol acetylation was conducted in a 250-ml. three-neck round-bottom flask fitted with an agitator and thermometer and connected through a spray trap to a condenser and receiver. Ten g. of 5α,6β-dichloro-3β-acetoxypregnan-20-one (I), 1.34 g. of p-toluenesulfonic acid monohydrate, and 52.5 ml. of acetic anhydride were charged to the flask and the solution was heated on the steam bath to 97–98°. A vacuum of 10–11 in. was applied to the receiver to eliminate air from the system and the reaction was maintained at this tempera-

(11) The Baeyer-Villiger cleavage of ketones with peracids constitutes an example in which the reaction is catalyzed by the acid produced; M. F. Hawthorne and W. D. Emmons, *J. Am. Chem. Soc.*, 80, 6398 (1958).

(12) J. Böeseken and J. Stuurman, *Rec. trav. chim.*, 56, 1034 (1937).

(13) C. G. Overberger and R. W. Cummins, *J. Am. Chem. Soc.*, 75, 4250 (1953), regard the bimolecular oxidation of organic sulfides to sulfoxides with perbenzoic acid as a nucleophilic attack on a cyclic hydrogen-bonded form of the peracid with elimination of molecular benzoic acid. A similar mechanism could prevail in the present case rather than the indicated stepwise elimination of the acid as its ions.

(14) Melting points were measured with total immersion thermometers and are not corrected.

ture and vacuum for 2 hr.[15] The vacuum was then increased to 25–26 in. until slow, continuous distillation occurred, while the batch temperature was maintained at 90–94°. Distillation was continued under these conditions for 2.5 hr., leaving a sirup. A 29-in. vacuum was applied for 10 min. followed by pumping at about 50° with an oil pump in order to remove most of the residual acetic anhydride. The dark gummy residue was dissolved in 150 ml. of benzene and the benzene solution was cooled, washed with two 50-ml. portions of cold 10% sodium carbonate solution and 50 ml. of water. Halogen ion was not detectable in the washes. The benzene solution was concentrated to dryness under reduced pressure, finally with the use of an oil pump. The crude amorphous enol acetate was ordinarily used in the next step without further purification.

Crystalline enol acetate was obtained as follows: A solution of the foregoing amorphous enol acetate in 11 ml. of benzene and 110 ml. of light petroleum ether was chromatographed over 220 g. of acid-washed alumina. Crystalline material first appeared in the 5 to 1 petroleum ether: benzene eluates and after crystallization from methanol melted at 158–161.5° and showed $[\alpha]_D^{25}$ −36.5° (c = 1, chloroform); −64° (c = 1, benzene).

Anal. Calcd. for $C_{25}H_{36}Cl_2O_4$: C, 63.69; H, 7.70; Cl, 15.04. Found: C, 64.14, 64.36; H, 7.50, 8.00; Cl, 14.51.

Later chromatographic fractions were progressively lower melting (to about 140–146°) but their infrared spectra were only slightly different from the spectrum of the initial material.

Preparation of 5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one (IV). (a) *Using monoperphthalic acid.* To the amorphous enol acetate (23.2 mm.) prepared as described hereinbefore was added 45.5 ml. of 0.777M monoperphthalic acid (150% of that theoretically required) in ethyl acetate.[16] The solution was allowed to stand overnight at room temperature.[17] The solution was washed free of peracid with four 50-ml. portions of cold 1N sodium hydroxide and to neutrality with water. No ionic halogen was detectable in the washes. Backwashing with ethyl acetate was necessary to avoid losses. Evaporation of the ethyl acetate and trituration with methanol left a crystalline residue of epoxide III, not purified further. A specimen was found to melt at 130–160° and probably is a mixture of isomers.

The crude epoxide was suspended in 210 ml. of methanol and a solution of 6.46 g. of potassium bicarbonate in 21 ml. of water was added. The mixture was heated to reflux, complete dissolution occurring in 5 min. Reflux was continued for 3 hr. more, the entire operation being carried out under a nitrogen atmosphere. Water (84 ml.) was added slowly, crystallization occurring. The methanol was removed under reduced pressure, and the suspension was chilled and filtered. No ionic halogen was observed in the filtrate. The crude product after washing and drying weighed 9.0 g.; m.p. 188–194° (dec.). The material was dissolved in 680 ml. of boiling benzene, filtered from traces of colored material, and concentrated at atmospheric pressure

until approximately 80 ml. of solvent remained, crystallization occurring in the process. After chilling, the product was collected, washed with benzene, and dried; weight, 7.28 g. (77.5% from I); m.p. 199–204° (dec.). For analysis the compound was recrystallized from benzene and melted at 201–206° (dec.) (bath heated at 6° per min.; insertion at 190°); $[\alpha]_D^{21}$ −72° (c = 1, chloroform).

Anal. Calcd. for $C_{21}H_{32}Cl_2O_3$: C, 62.52; H, 8.00; Cl, 17.58. Found: C, 63.07; H, 8.07; Cl, 17.36, 17.69.

(b) *Using peracetic acid.* The enol acetylation was conducted on five-fold the scale described earlier. The benzene solution of the enol acetate after the washes with sodium carbonate solution and water was concentrated to a volume of 345 ml. The solution was cooled to 10° and 14.6 g. of anhydrous sodium sulfate (powder) and 4.1 g. of sodium bicarbonate were added. The suspension was stirred for about 3 min. at 10° and 29 ml. of commercial 40% peracetic acid[18] was added slowly, maintaining the temperature at 10°. The mixture was then allowed to warm to 20° and was stirred for about 18 hr. at 20–23°. The mixture was then cooled to 10° and a cold solution of 12.4 g. of sodium bisulfite and 20.7 g. of sodium hydroxide in 104 ml. of water was slowly added, keeping the temperature below 23°. After the addition, the mixture was stirred further for 15 min. The mixture was transferred to a separatory funnel with the aid of additional benzene and water and the benzene phase was separated and washed with two 100-ml. portions of water. Evaporation of the benzene left a sirupy residue which was hydrolyzed in a mixture of 625 ml. of methanol, 35 g. of potassium bicarbonate, and 115 ml. of water for 2 hr. The crude product was slurried in 460 ml. of boiling benzene to give after chilling 37.8 g. (80.5%) of 5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one (IV), m.p. 202–205° (dec.).

Kinetic experiments. General. It was convenient in this work to express the second-order rate expression in the following form:

$$\log T/(T - T_\infty) = 0.4343(1 - 1/r)Mkt + \log r$$

where T represents ml. of thiosulfate solution required to titrate iodometrically an aliquot of the reaction mixture, T_∞ represents T at infinite time, r represents the initial ratio of peracid to enol acetate, and M is the initial molarity of the peracid. If second-order kinetics are obeyed, a plot of $\log T/(T - T_\infty)$ against time (t) gives a straight line from whose slope the rate constant k may be calculated:

$$k = \frac{(\text{slope})}{0.4343(1 - 1/r)M}$$

In practice T_∞ could not be determined precisely from experiment, and was calculated instead from the titration at zero time, T_0, by the following equation:

$$T_\infty = T_0(r - 1)/r$$

Temperature was maintained at 27 ± 0.5° during the runs.

Preparation of peracetic acid solution.[19] A suspension of 10 g. of anhydrous sodium sulfate (powder)[20] and 10 g. of sodium bicarbonate in 100 ml. of benzene was cooled with stirring to 5°. Commercial 40% peracetic acid (8.4 ml.) was added and the mixture was stirred for 5 min. at 5°.[21] The benzene layer containing the peracetic acid was immediately decanted through glass wool. The molarity of the peracetic acid was determined by adding 2 ml. to a solution of sodium iodide (about 3 g.) and acetic acid (1–2 ml.) in water (about 25 ml.) and titrating the liberated iodine

(15) In studies of the enol acetylation in which the rotation of aliquots was observed with time, it was found that the enol acetylation was essentially complete under these conditions after two hours. Analysis of the data from a kinetic viewpoint was difficult because of color at high conversions. The reaction appeared to be pseudo first order in steroid, as was found by Anderson, *et al.*[7] The rate was also found to be roughly proportional to the concentration of catalyst. These findings are in accord with the mechanism of enol acetylation proposed by Barton *et al.* [D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones, and T. Walker, *J. Chem. Soc.*, 747 (1954)].

(16) Prepared by a modification of the method of M. A. Stahmann and M. Bergmann, *J. Org. Chem.*, 11, 586 (1946).

(17) The second-order rate constant for this reaction in ethyl acetate at 25° was estimated from a kinetic study to be 1.35 l./mol.-hr.

(18) From Buffalo Electro-Chemical Co., Buffalo, N. Y.

(19) We are indebted to Dr. H. E. Mertel of these laboratories for this procedure.

(20) Granular sodium sulfate gives poorer results..

(21) Longer times lead to lower final molarity.

with 0.1N sodium thiosulfate. The molarity was generally about 0.2. Aliquots in the kinetic runs were titrated in a similar manner.

Kinetic run with 5α,6β-dichloro-3β,20-diacetoxy-17(20)-pregnene (II). A specimen of II obtained by chromatography and melting at 140–150° was dissolved in the required amount of peracetic acid in benzene solution. The initial molarity of the peracetic acid was 0.187 and the peracid:enol acetate ratio, r, was 1.5. The titration data are plotted in Fig. 1. Excellent linearity is observed to over 80% conversion at 3.5 hr. The upward deviation beyond that time reflects lack of blank corrections. From the slope of the line (0.111 unit per hour) the rate constant, k, is calculated to be 4.1 l./mol.-hr.

Kinetic run with 3α,20-diacetoxy-17(20)-pregnen-11-one (V). A specimen of V melting at 118–125° (lit.,[7] 130.5–131.5°) was used. The initial molarity of the peracetic acid was 0.182 and r was 1.5. Small blank corrections were applied after 3 hr. A straight line (Fig. 1) is obtained for more than 5 hr. (72% conversion). From the slope (0.0515) the rate constant, k, is calculated to be 1.95 l./mol.-hr.

Kinetic run with 3α,11,20-triacetoxy-9(11),17(20)-pregnadiene (VI). A specimen of VI melting at 196–200° (lit.,[9] 200–201°) was used. The initial molarity of the peracetic acid was 0.181 and r was 2.5 to allow for possible reaction at both double bonds. Small blank corrections were applied throughout the run. Linearity (Fig. 1) is good through 4 hr. (77% conversion) and fair to 5.8 hr. (86% conversion). The slope (0.118) gives a rate constant, k, of 2.5 l./mol.-hr.

After 22 hr. total time, the steroid remaining was recovered and hydrolyzed to give 3α,17α-dihydroxypregnane-11,20-dione, m.p. 200.5–205°, in 85% yield.


Syntheses of Hormones from 5,6-Dichloro Steroids. III. Progesterone, 17α-Hydroxyprogesterone, and Reichstein's Substance S Acetate

FRANK A. CUTLER, JR., LEON MANDELL, JAMES F. FISHER, DANIEL SHEW, AND JOHN M. CHEMERDA

5α,6β-Dichloro-3β,17α-dihydroxypregnan-20-one has been converted to Substance S acetate in 72% yield by bromination at position 21, metathesis to the 21-acetoxy derivative, oxidation to the 3-ketone, and dechlorination with chromous chloride. Progesterone and 17α-hydroxyprogesterone have likewise been prepared by dechlorination of the appropriate ketones.

In the preceding papers of this series[1,2] the addition of chlorine to pregnenolone acetate and conversion of the dichloride to 5α, 6β-dichloro-3β, 17α-dihydroxypregnan-20-one (I) were described. In the present paper we wish to discuss the conversion of I to Reichstein's Substance S acetate, and to indicate some of the other transformations possible with various intermediate compounds.
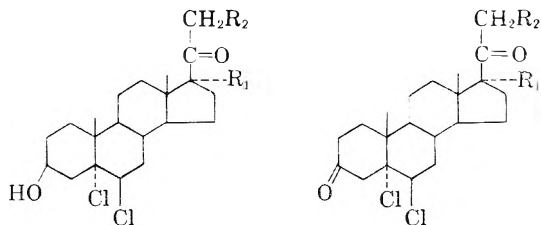
I. R₁ = OH, R₂ = H   IV. R₁ = OH, R₂ = OAc
II. R₁ = OH, R₂ = Br   IX. R₁ = OH, R₂ = H
III. R₁ = OH, R₂ = OAc VII. R₁ = R₂ = H
VI. R₁ = R₂ = H
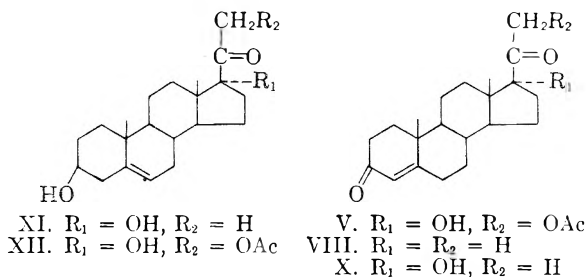
XI. R₁ = OH, R₂ = H
XII. R₁ = OH, R₂ = OAc

V. R₁ = OH, R₂ = OAc
VIII. R₁ = R₂ = H
X. R₁ = OH, R₂ = H

The bromination of I was carried out in hot chloroform with 1.12 moles of bromine and afforded in 92% yield crude 21-bromide II which was easily purified by recrystallization from methanol. Small amounts of the 21,21-dibromide were also isolated.

The pure 21-bromide II gave the corresponding 21-acetoxy compound III in good yield on treatment with potassium acetate in refluxing acetone. However, for practical purposes, the acetoxylation was better carried out in the presence of sodium iodide[3] and a small amount of acetic acid.[4] The

(1) F. A. Cutler, Jr., L. Mandell, D. Shew, J. F. Fisher, and J. M. Chemerda, *J. Org. Chem.*, (Paper I).

(2) F. A. Cutler, Jr., J. F. Fisher, and J. M. Chemerda, *J. Org. Chem.*, (Paper II).

(3) G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4081 (1950).

latter procedure is efficient with crude 21-bromides, which normally contain traces of 21,21-dibromides. This was emphasized in an experimental sequence in which I was treated with 1.85 moles of bromine; the product, in spite of being largely the 21,21-dibromide, was acetoxylated in 73.7% yield to the *mono-acetoxy* compound III. Apparently the combination of acetic acid and sodium iodide serves to reduce the additional halogen rather selectively. When applied to ordinary crude II, the procedure gave a nearly quantitative yield of III. It is to be noted that in this operation, sodium iodide does not cause elimination of halogen from the 5,6-position as is the case with 5,6-dibromides.[5]

Attempts to oxidize the 3-hydroxyl of III with *N*-bromoacetamide met with failure. Normally this reagent would be expected to attack a 3β-hydroxyl of an A/B: *trans* steroid.[6] Apparently the 5,6-dichloro functionality exerts an influence at the 3-position.[7] However, oxidation with chromium trioxide was successful, giving the 3-ketone IV in 85% yield.

The removal of halogen from IV to give Substance S acetate (V) was first attempted with zinc dust in acetic acid, but only poor yields of V were obtained. In order to conserve material, the corresponding sequence leading to progesterone was studied as a model.

5α,6β - Dichloro - 3β - acetoxypregnan - 20 - one was hydrolyzed with potassium bicarbonate in aqueous methanol to the 3-alcohol VI. This in turn was oxidized with chromium trioxide to the 3-ketone VII. Treatment of VII with zinc dust under a variety of conditions gave only poor yields of progesterone (VIII); infrared spectra indicated the formation of hydroxylated products. Similar difficulties have been observed in attempts to debrominate the corresponding 5,6-dibromopreg-

nane-3,20-dione. In this instance Julian, *et al.*[8] found that chromous chloride was a much more efficient reagent. Treatment of VII with chromous chloride was found to give excellent yields of progesterone provided that the intermediate 5-pregnene-3,20-dione[9] was isomerized with acid.

Application of the chromous chloride technique to IV gave Substance S acetate in 94% yield. The entire sequence from 3β-acetoxy-5-pregnen-20-one to Substance S acetate proceeded in about 48% yield.

It was also possible to prepare 17α-hydroxy-progesterone (X) from I by oxidation with chromium trioxide to the ketone IX and reduction by chromous chloride. In this instance, oxidative cleavage to the 17-ketone was a serious side reaction.

Reduction of I and III with chromous chloride also constitutes a convenient synthesis of 3β, 17α-dihydroxy-5-pregnen-20-one (XI) and of 21-acetoxy - 3β,17α - dihydroxy - 5 - pregnen - 20 - one (XII), respectively, as indicated in the experimental.

EXPERIMENTAL[10]

21-Bromo-5α,6β- dichloro-3β,17α - dihydroxypregnan-20-one (II). To a solution of 16.12 g. (0.04 mole) of 5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one[2] (I) in 480 ml. of reagent chloroform (stabilized with about 0.75% ethanol) at 46–48° was added below the surface 116 ml. of 0.387M bromine in chloroform (0.0448 mole) over a period of 40 min., after the initial uptake had been established. The colorless solution was washed with 200 ml. of 10% sodium bicarbonate solution and concentrated under reduced pressure with a minimum of heat. The semicrystalline residue was slurried in 48 ml. of methanol, and after chilling the crystals were collected, washed with 16 ml. of cold methanol and dried; weight 17.7 g. (91.8%); m.p. about 185° (dec.). This material was suitable for the next step. The analytical specimen was prepared by recrystallization from methanol and decomposed at about 190°. The decomposition point of II depended greatly on rate of heating and extent of preheating. The rotation was $[\alpha]_D^{29}$ −22.8°.

Anal. Calcd. for $C_{21}H_{31}BrCl_2O_3$: C, 52.30; H, 6.48; AgX/Cmpd., 0.982. Found: C, 52.36; H, 6.76; AgX/Cmpd., 0.986.

Evaporation of the original methanol mother liquor and wash and recrystallization of the residue from acetonitrile afforded 0.37 g. of the *dibromide*, decomposing at 183–188°.

Anal. Calcd. for $C_{21}H_{30}Br_2Cl_2O_3$: AgX/Cmpd., 1.180. Found: 1.174.

21-Acetoxy-5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one (III). (a) *From crude* II. Ten grams of crude 21-bromide II was dissolved in 120 ml. of acetone and 12.3 g. of anhydrous potassium acetate, 3.8 ml. of glacial acetic acid and 5.88 g. of sodium iodide were added in that order. The mixture was refluxed with agitation for 4 hr., the initial yellow iodine color fading completely during this time. Water (200 ml.) was added and the acetone was removed by distillation, finally

(4) Rosenkranz, *et al.*[3] in replacing 21-bromide by acetate *via* the 21-iodide have prepared potassium acetate by the reaction of potassium bicarbonate and acetic acid immediately before use, and found it to be superior to reagent anhydrous potassium acetate. This was confirmed in related work and the difference was traced to incomplete neutralization; adding a small amount of acetic acid to runs with reagent potassium acetate now gave equivalent results. F. A. Cutler, Jr., and W. E. Guenther, unpublished observations.

(5) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. Ryden, *J. Am. Chem. Soc.*, 71, 3574 (1949); P. L. Julian and W. J. Karpel, *J. Am. Chem. Soc.*, 72, 362 (1950).

(6) H. Reich and T. Reichstein, *Helv. Chim. Acta*, 26, 562 (1943).

(7) Advantage was taken of this inertness to oxidation to provide an alternate synthesis of I. 5α,6β-Dichloropregnane-3β,17α,20-triol, conveniently prepared by the action of lithium aluminum hydride on 5α,6β-dichloro-16α,17α-oxido-3β-hydroxypregnan-20-one, on oxidation with *N*-bromoacetamide or chlorine gave I. F. A. Cutler, Jr., U. S. Patent 2,811,522 (Oct. 29, 1957). This procedure has the advantage that the 20-carbonyl need not be protected as a ketal prior to reduction of the oxide by lithium aluminum hydride. P. L. Julian, E. W. Meyer, and I. Ryden, *J. Am. Chem. Soc.*, 71, 756 (1949).

(8) P. L. Julian, W. Cole, A. Magnani, and E. W. Meyer, *J. Am. Chem. Soc.*, 67, 1728 (1945).

(9) U. Westphal and J. Schmidt-Thomé, *Ber.*, 69, 889 (1936).

(10) Melting points were measured with total immersion thermometers and are not corrected. Rotations were measured in chloroform at concentrations of about one gram per 100 ml.

under reduced pressure, whereupon the product separated as bulky fibers. After chilling, the product was collected, washed with water and dried; weight, 9.4 g. (98.3%); m.p. 192–195° (dec.). This material was sufficiently pure for the next step.

The analytical specimen was prepared by recrystallization from acetonitrile; m.p. 191–193.5° (dec.); $[\alpha]_D^{25}$ −19.8°. The decomposition point varied considerably with the rate of heating and extent of preheating.

Anal. Calcd. for $C_{23}H_{34}Cl_2O_5$: C, 59.86; H, 7.43; Cl, 15.37. Found: C, 59.60; H, 7.18; Cl, 15.36.

(b) *From pure II.* A mixture of 0.32 g. of II (analytical specimen), 1.0 g. of anhydrous potassium acetate, and 25 ml. of acetone was stirred and heated at the reflux temperature for 4 hr. Water (50 ml.) was added and the acetone was removed under reduced pressure. The solid was collected, washed with water and dried; weight, 0.29 g. (95%); m.p. 188–192° (dec.); infrared spectrum identical with that of pure III.

(c) *From dibromide.* Ten grams (0.0248 mole) of I dissolved in 300 ml. of chloroform was brominated in the manner described for the preparation of II using 118 ml. of $0.39M$ bromine solution (0.046 mole). The dibromide crystallized directly from the reaction mixture and after a cooling period, was collected, washed with cold chloroform and dried; weight, 9.28 g.; m.p. 190–198° (dec.). This was slurried in 100 ml. of boiling acetonitrile and collected after cooling; weight, 7.36 g.; m.p. 190–198° (dec.). Two grams of the latter material was acetoxylated in 100 ml. of acetone containing 2.08 g. of potassium acetate, 0.985 g. of sodium iodide, and 0.625 ml. of glacial acetic acid for 4 hr. at the reflux temperature. During this period the yellow iodine color rapidly formed and largely remained. The crude 21-acetoxy compound III was isolated in the usual way and recrystallized from 23 ml. of acetonitrile to give 1.21 g. (73.7% from dibromide) of III; m.p. 189–191° (dec.), undepressed on admixture with III; infrared spectrum identical with that of pure III.

In another experiment which differed from the preceding experiment in that the sodium iodide was withheld for 2 hr., a complex mixture of products resulted.

5α,6β-Dichloro-17α,21-dihydroxypregnane-3,20-dione   21-acetate (IV). Five grams of crude III was dissolved in 110 ml. of glacial acetic acid and 11 ml. of water was added to depress the freezing point. The solution was cooled to 5°. Meanwhile, a solution of chromium trioxide (2.16 g.) in water (2 ml.) and acetic acid (to a total volume of 25 ml.) was prepared. A 12.5 ml. portion of the solution was added to the steroid solution with stirring over 5 min., keeping the temperature at about 5°. Then 0.605 ml. of concentrated sulfuric acid was added over 8 min., keeping the temperature near 5°. The mixture was stirred further at 0–5° for 80 min., during which time crystallization of the product occurred. The mixture was then shaken with chloroform (250 ml.) and water (400 ml.). The aqueous phase was separated and extracted again with 50 ml. of chloroform. The combined chloroform solution was washed successively with 250 ml. of water, three 250-ml. portions of 2.5% sodium bicarbonate solution and 250 ml. of water, back-washing with chloroform as necessary. The chloroform solution was concentrated to dryness under reduced pressure, while the internal temperature was kept below 30°. The residue was triturated with a small amount of ether, transferred to a funnel, washed with minimum quantities of ether and dried. The white product weighed 4.248 g. (85%) and melted at about 190° (dec.). Such material is suitable for conversion to Substance S acetate.

Samples of this compound have been stored without serious deterioration for several months at room temperature. There is some tendency toward spontaneous loss of hydrogen chloride. For analysis the compound was recrystallized from ethyl acetate. It then decomposed at 202°; $[\alpha]_D^{25}$ −7.6°.

Anal. Calcd. for $C_{23}H_{32}Cl_2O_5$: C, 60.13; H, 7.02; Cl, 15.44. Found: C, 60.79; H, 6.77; Cl, 15.63.

Substance S acetate (V). A solution of chromous chloride was first prepared as follows[11]: Zinc dust (400 g.) was amalgamated by shaking with 400 ml. of water containing 32 g. of mercuric chloride and 20 ml. of concentrated hydrochloric acid. The aqueous phase was decanted and 800 ml. of water, 80 ml. of hydrochloric acid and 200 g. of chromic chloride were added. Carbon dioxide was bubbled through the mixture to provide agitation and prevent reoxidation by air. When the solution was blue, it was ready for use.

To a solution of 9.21 g. of IV in 650 ml. of boiling acetone was added in a slow stream 740 ml. of chromous chloride solution. The resulting mixture was then concentrated under reduced pressure until the acetone was removed. The resulting suspension was chilled, filtered, and the product washed with water until the washes were colorless and neutral. The crude product gave a negative Beilstein halogen test and showed λ_{max}^{MeOH} 241 mμ (ϵ = 13,000). To complete the isomerization of the double bond, the crude product was dissolved in 370 ml. of boiling acetone and 9 ml. of $1N$ sulfuric acid in acetone was added. The solution was boiled down to a volume of 135 ml. during 9 min. The solution was then chilled, and the crystals were collected, washed with cold acetone, and dried to constant weight *in vacuo* at room temperature; weight, 6.84 g. (88%); m.p. 235–240°; λ_{max}^{MeOH} 241 mμ (ϵ = 16,600)[12]; infrared spectrum identical with that of authentic Substance S acetate. The material gave a scarlet color in concentrated sulfuric acid.

From the acetone mother liquors there was obtained by concentration and recrystallization, an additional 0.47 g. (6%) of Substance S acetate, m.p. 237–241°, bringing the total yield to 94%.

5α,6β-Dichloro-3β-hydroxypregnan-20-one (VI). A mixture of 5 g. of 5α,6β-dichloro-3β-acetoxypregnan-20-one,[1] 3.7 g. of potassium bicarbonate, 160 ml. of methanol, and 12 ml. of water was heated at reflux for 1 hr. The resulting solution was concentrated under reduced pressure to 40 ml. and diluted with 150 ml. of water. After cooling, the crystals were collected, washed and dried. The material weighed 4.32 g. and melted at 154–157° after a transition at about 90° (hydrate?).

The analytical specimen was recrystallized from a mixture of petroleum ether, ethyl ether, and acetone, and melted at 160–160.5°.

Anal. Calcd. for $C_{21}H_{32}Cl_2O_2$: C, 65.12; H, 8.32; Cl, 18.31. Found: C, 64.85; H, 8.21; Cl, 18.30.

5α,6β-Dichloropregnane-3,20-dione (VII). The oxidation of VI was carried out by essentially the same procedure used to prepare IV. From 3 g. of VI there was obtained 2.55 g. (85%) of VII, whose melting point depended on the rate of heating. When heated in the usual way from room temperature, it decomposed at 129–131°. However, if a specimen was placed in a bath held at 140°, 40 seconds elapsed before decomposition occurred. On storage for a day at room temperature, the material turned pink and began to lose hydrogen chloride.

For analysis the material was recrystallized from acetone-ether with no significant change in melting point.

Anal. Calcd. for $C_{21}H_{30}Cl_2O_2$: C, 65.45; H, 7.85; Cl, 18.40. Found: C, 66.23; H, 7.70; Cl, 18.05.

Progesterone (VIII). (*a*) *By zinc dust.* To a solution of 1 g. of VII in 20 ml. of glacial acetic acid maintained at 40–45° was added 2.0 g. of zinc dust in small portions over 90 min. with continuous agitation. The mixture was filtered and the zinc cake was washed with 20 ml. of acetic acid. The combined filtrate and wash was diluted with 160 ml. of water and chilled. The flocculent precipitate was collected,

(11) G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950).

(12) Reported, m.p. 239–241°; ϵ_{2410} 17,400 (methanol). B. A. Koechlin, T. H. Kritchevsky, and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 189 (1951).

washed, and dried; weight, 0.68 g.; m.p. 137–173°; Beilstein halogen test, negative. The infrared spectrum showed peaks at 2.93 (hydroxyl), 5.89 (carbonyl), 6.03 (conjugated carbonyl), and 6.19 μ (carbon–carbon double bond), but no acetate bands. Numerous variations in the above procedure gave similar poor results.

(b) *By chromous chloride.* To a solution of 500 mg. of VII in 100 ml. of acetone at room temperature was slowly added 40 ml. of chromous chloride solution. Reduction was virtually instantaneous, as judged by color. Water (200 ml.) was added and the acetone was removed under reduced pressure. The resulting suspension of crystals was chilled and filtered, yielding 400 mg. (98%) of material giving a negative Beilstein halogen test and melting at 140–155° after softening at 115°.[13] To complete the isomerization of the double bond, 100 mg. of the material was dissolved in 2 ml. of ethanol and 6 drops of *N* sulfuric acid in ethanol was added. The solution was refluxed for 6 min., then diluted with water. The progesterone was collected, washed, and dried; yield, 90 mg.; m.p. 120.5–122°, undepressed on admixture with authentic material; infrared spectrum identical with that of authentic material.

17α-Hydroxyprogesterone (X). The oxidation of 5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one (I) was carried out essentially as described for the preparation of IV. The yield of crude 5α,6β-dichloro-17α-hydroxypregnane-3,20-dione (IX) was 60–70%, and the material decomposed unsharply in the range 145–170°. Chromous chloride reduction in refluxing acetone gave a halogen-free product whose infrared spectrum showed at peak at 5.78 μ, indicating that the oxidation product had contained a considerable amount

of 17-ketone due to cleavage of the side chain. Isomerization with a trace of acid followed by recrystallization from methanol gave 17α-hydroxyprogesterone, m.p. 219–222° (lit.,[14] 222–223°). The yield from I was about 30%.

3β,17α-Dihydroxy-5-pregnen-20-one (XI) was prepared in 80% yield by the reduction of 5 g. of I in 500 ml. of acetone with 400 ml. of chromous chloride solution. Recrystallized from methanol, the material melted at 262–268° (lit.,[15] 271–273°).

3β,17α,21-Trihydroxy-5-pregnen-20-one 21-acetate (XII). Reduction of 10 g. of III in 250 ml. of acetone with 500 ml. of chromous chloride solution by heating for 5 min. at the reflux temperature afforded 8.0 g. (94%) of crude XII. This was recrystallized twice from acetonitrile, the first time involving a charcoal treatment, then from methanol, and finally again from acetonitrile to give 3.96 g. of XII, m.p. 209–213° (lit.,[16] 211–213°). Acetylation of XII with acetic anhydride in pyridine gave the 3,21-diacetate, m.p. 196–199° (lit.,[16] 195°).

(13) 5-Pregnene-3,20-dione is reported[9] to melt at 158–160°.

(14) J. v. Euw and T. Reichstein, *Helv. Chim. Acta,* 24, 879 (1941).

(15) P. Hegner and T. Reichstein, *Helv. Chim. Acta,* 24, 828 (1941).

(16) J. Heer and K. Miescher, *Helv. Chim. Acta,* 34, 359 (1951).


Potential Anticancer Agents.[1] XXIV.
Tetrahydroquinazoline Analogs of Tetrahydrofolic Acid. II.

Joseph DeGraw, Leon Goodman, Ruth Koehler, and B. R. Baker

A variety of 6-substituted 5,6,7,8-tetrahydroquinazolines were prepared in which the substituents at 2 and 4 were mercaptohydroxy, dihydroxy, dichloro, diamino, and bis(benzylamino). The use of the dichloro-, diamino-, and bis(benzylamino)-5,6,7,8-tetrahydroquinazolines in synthetic schemes designed to prepare intermediates for the synthesis of 5,8-dideaza-5,6,7,8-tetrahydroaminopterin, is described.

In a preceding work of this series[2] the synthesis of 5,8-dideaza-5,6,7,8-tetrahydrofolic acid (I) was described. The key compound in the synthesis of
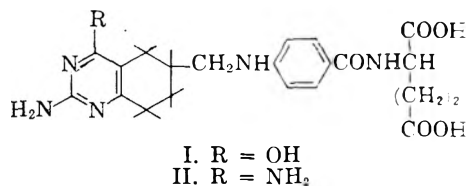
I. R = OH
II. R = NH₂

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series, *cf.* E. J. Reist, P. A. Hart, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.,* 81, 5176 (1959).
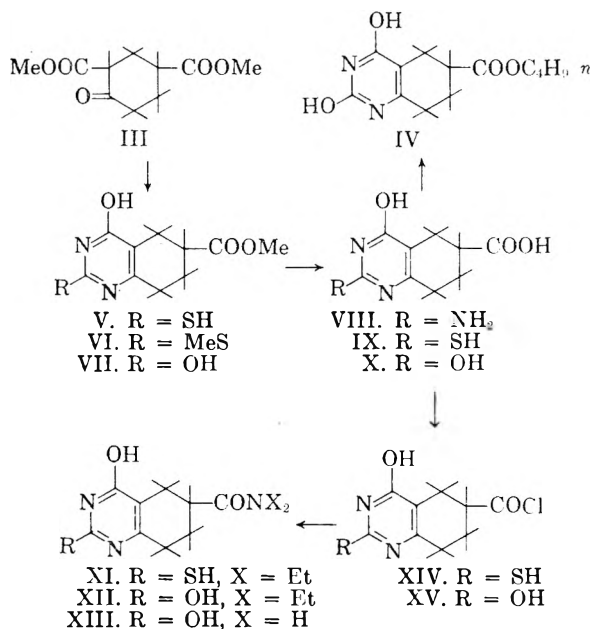
(2) R. Koehler, L. Goodman, J. DeGraw, and B. R. Baker, *J. Am. Chem. Soc.,* 80, 5779 (1958).

I was 2-amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxylic acid (VIII). In the course of that work a number of other substituted 5,6,7,8-tetrahydroquinazolines were prepared and, subsequent to that work, many more such compounds have been synthesized as part of an attempted synthesis of 5,8-dideaza-5,6,7,8-tetrahydroaminopterin (II), the 4-amino analog of I. Although the work has not achieved the synthesis of II, the interesting chemistry involved prompts a description of the observations.

Condensation of dimethyl 4-oxo-1,3-cyclohexanedicarboxylate (III)[2] with thiourea proceeded readily in the presence of sodium methoxide to give a good yield of methyl 5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylate (V). In contrast with the condensation of III with

guanidine, there was no evidence for the presence of the 6-carboxylic acid (IX) in the product. When the crude product from the condensation of III and thiourea was saponified, the acid IX was isolated as a chromatographically homogeneous solid in 87% over-all yield. The acid (IX) was converted to the acid chloride (XIV) with thionyl chloride and a trace of pyridine and XIV, in turn, was converted in low yield to the diethylamide (XI).

The ester (V) was converted to the 2-methylthio derivative (VI) by means of dimethyl sulfate in methanolic sodium methoxide. Compound VI was unstable in 0.1 M hydrochloric acid and slowly changed to, presumably, the 2,4-dihydroxytetra-hydroquinazoline ester (VII). This was shown by the coincidence of the ultraviolet absorption spectra of VI and the 2,4-dihydroxy acid (X) after the dilute acid solution of VI had stood for about 20 hr.
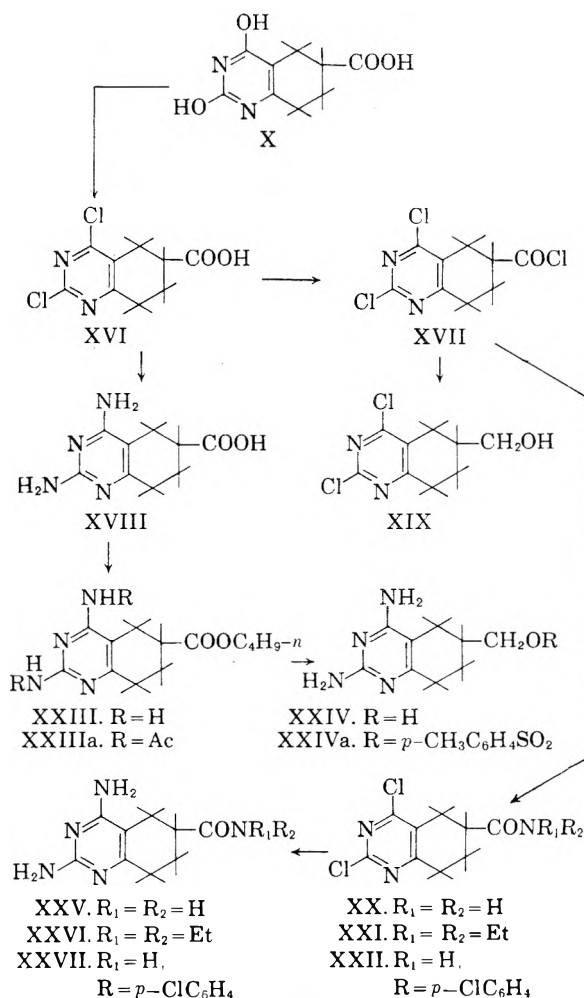

III

IV

V. R = SH
VI. R = MeS
VII. R = OH

VIII. R = NH₂
IX. R = SH
X. R = OH

XI. R = SH, X = Et
XII. R = OH, X = Et
XIII. R = OH, X = H

XIV. R = SH
XV. R = OH

Although it is known that 2-alkylthio groups on a pyrimidine ring are hydrolyzed in hot acid,[3] the mildness of the hydrolytic conditions for VI is surprising.

The condensation of III with urea in the presence of sodium methoxide gave a mixture of products which was converted to the 2,4-dihydroxy acid (X) in fair yield by a further treatment with aqueous alkali. Attempted isolation of the direct product of the urea condensation, the methyl ester (VII), from the condensation mixture was unsuccessful. However, the acid (X) was converted to the crystalline n-butyl ester (IV) in high yield. Conversion of the acid (X) to the acid chloride (XV) was accomplished with thionyl chloride and a trace of pyridine. The crude acid chloride was

converted to the diethylamide (XII) and to the carboxamide (XIII).

Two routes leading to the diaminotetrahydroquinazoline ring system, of which II was the desired end product, were visualized. Chlorination of the aminohydroxy acid (VIII) to the 2-amino-4-chloro acid, followed by amination to the diamino acid (XVIII), appeared to be one practical sequence, and chlorination of the dihydroxy acid (X) to the dichloro acid (XVI), followed by amination to XVIII, seemed to represent a second method. However, attempts to achieve the chlorination of VIII using phosphoryl chloride and a variety of conditions gave heterogeneous products, while chlorination of X with phosphoryl chloride proceeded smoothly and gave a good yield of the crystalline dichloro acid (XVI). Amination of XVI with ethanolic ammonia at 150° gave the diamino acid (XVIII) as a chromatographically homogeneous solid. The acid (XVIII) could be converted to the n-butyl ester (XXIII) in good yield, but a number of attempts to convert the ester (XXIII) to amides were unsuccessful. The ester (XXIII) was smoothly acetylated with acetic

X

XVI

XVII

XVIII

XIX

XXIII. R = H
XXIIIa. R = Ac

XXIV. R = H
XXIVa. R = p-CH₃C₆H₄SO₂

XXV. R₁ = R₂ = H
XXVI. R₁ = R₂ = Et
XXVII. R₁ = H,
    R = p-ClC₆H₄

XX. R₁ = R₂ = H
XXI. R₁ = R₂ = Et
XXII. R₁ = H,
    R = p-ClC₆H₄

(3) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **29**, 492 (1903); H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, **32**, 349 (1904); T. B. Johnson and A. W. Joyce, *J. Am. Chem. Soc.*, **37**, 2151 (1915).

(4) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 3164 (1955).

anhydride to the diacetamido ester (XXIIIa); the N-acetyl groups represented, possibly, blocking groups for some other contemplated transformations using diaminotetrahydroquinazoline derivatives. The butyl ester (XXIII), either as the free base or as the p-toluenesulfonic acid salt, was reduced to the diamino-6-hydroxymethyl compound (XXIV) by means of the sodium borohydride-aluminum chloride reagent first reported by Brown and Subba Rao[4] and used previously in the reduction of butyl 2-amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxylate.[2] However, compound XXIV was not useful as a precursor for II. A number of attempts to convert XXIV to the 6-chloromethyl compound by means of thionyl chloride were unsuccessful, as were a variety of attempts to form the 6-bromomethyl compound with hydrogen bromide and hydrogen bromide-sulfuric acid combinations. The p-toluenesulfonate ester (XXIVa) of XXIV could be prepared but in such low yield that the approach to II through the tosylate was not practical. This same situation also was true for the preparation of the 6-p-toluenesulfonate ester of 2-amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinemethanol.[2]

The diamino acid (XVIII) could not be converted to an acid chloride by means of thionyl chloride under a variety of conditions. Alternately, however, a number of amides were prepared in good yield from the acid chloride (XVII) of the dichloroacid (XVI). The carboxamide (XX) was prepared from XVII in ammonia-saturated acetonitrile at 0°, the diethylamide (XXI) was prepared in refluxing methylene chloride, and the p-chloroanilide (XXII) was prepared in methylene chloride in the presence of pyridine at room temperature. Under these conditions there was no tendency for replacement of the ring chlorines of XVII. Ammonolysis of the amides (XX, XXI, and XXII) in ethanol at 150° gave good yields of the diamino amides (XXV, XXVI, and XXVII, respectively). As expected, no amide interchange occurred.
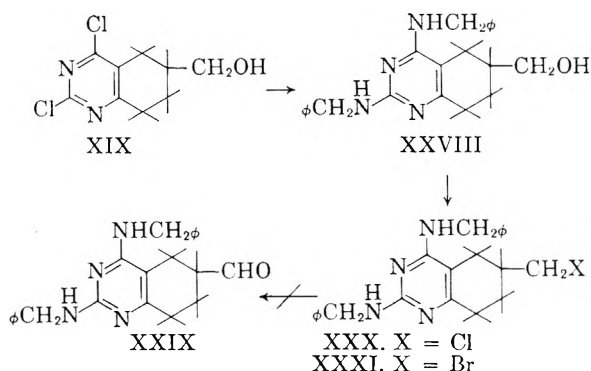
The lability of the ring chlorines of XVI under acid conditions was demonstrated in several attempts to prepare esters of XVI. The use of ethanesulfonic acid and butyl alcohol gave the dihydroxy butyl ester (IV) and the reaction of the acid chloride (XVII) with methanol gave replacement of the ring chlorines by methoxyl. When pyridine was used as an acid acceptor in the reaction of XVII with methanol, the product could not be purified.

The acid chloride (XVII) was reduced to the 6-hydroxymethyl compound (XIX) with sodium borohydride in diglyme[5] at −20°. At this temperature ring dechlorination and reduction of the pyrimidine ring were minimized and fair yields of XIX could be isolated. The reduction of the dichloro acid (XVI) with the sodium borohydride-aluminum chloride combination was unsuccessful. A

number of attempts were made to oxidize XIX to the 6-aldehyde, which, in turn, could probably be ammonolyzed to 2,4-diamino-5,6,7,8-tetrahydro-6-quinazolinecarboxaldehyde, a probable precursor for II. The chromic acid-pyridine reagent of Poos,[6] et al., gave only tars and no reaction was observed with the sodium dichromate-acetic acid method of Friedman.[7] Attempts to reduce the acid chloride (XVII) to the dichloro aldehyde by the Rosenmund method or with lithium tri-t-butoxyaluminum hydride[8] were unsuccessful. The latter method gave mostly alcohol (XIX), even at −75°.

The utility of 2,4-bis-(benzylamino)-5,6,7,8-tetrahydro-6-quinazolinemethanol (XXVIII) in the preparation of precursors of II was next investigated on the assumption that the benzyl groups could be removed at a later step in the synthesis. The alcohol (XXVIII) was prepared in high yield by the treatment of dichloro alcohol (XIX) with benzylamine at 150°. Thionyl chloride readily con-

verted the alcohol (XXVIII) to the chloromethyl compound (XXX) and phosphorus tribromide converted XXVIII to the bromomethyl compound (XXXI). Reaction of the bromomethyl derivative (XXXI) with N-(p-aminobenzoyl) glutamic acid (PABGA) or the dimethyl ester of PABGA gave crude products which did not contain the desired precursors of II and which could not be purified to any well-defined compounds. Reaction of XXXI with p-aminobenzoic acid (PABA) gave a product which was insoluble in both acid and base and therefore could not have been the simple product of alkylation of PABA.

Two attempts were made to prepare 2,4-bis(benzylamino)-5,6,7,8-tetrahydro-6-quinazolinecarboxaldehyde (XXIX), whose reductive coupling with PABGA might be expected to give the dibenzyl precursor of II.[9] Reaction of the bromo compound (XXXI) with pyridine N-oxide and treatment of

(5) The dimethyl ether of diethylene glycol.

(6) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, J. Am. Chem. Soc., 75, 422 (1953).

(7) Dr. L. Friedman, New York University, private communication.

(8) H. C. Brown and R. F. McFarlin, J. Am. Chem. Soc., 78, 252 (1956).

(9) M. Sletzinger, D. Rheinhold, J. Grier, M. Beachem, and M. Tischler, J. Am. Chem. Soc., 77, 6365 (1955).
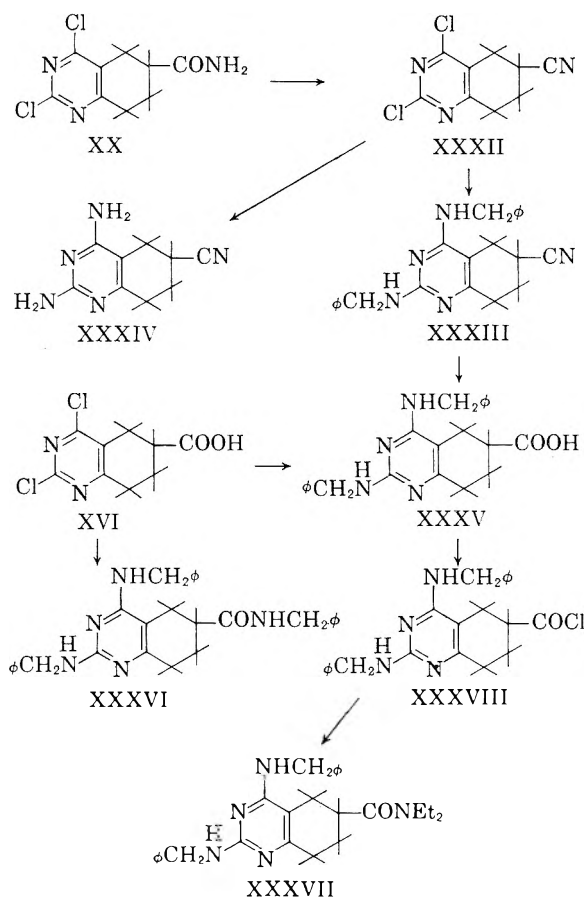
the crude product with aqueous sodium hydroxide[10] failed to give any aldehyde. Hydrogenation of the bis(benzylamino) nitrile (XXXIII) in the presence of N,N'-diphenylethylenediamine according to the method of Plieninger[11] resulted in the uptake of about 80% of the theoretical amount of hydrogen but acid treatment of the residue, the supposed imidazolidine, gave no aldehyde. The nitrile (XXXIII) was prepared by conversion of the dichloro amide (XX) to the dichloro nitrile (XXXII) with phosphoryl chloride and reaction of the nitrile (XXXII) with ethanolic benzylamine at 150°. Reaction of the dichloro nitrile (XXXII) with alcoholic ammonia at 150° gave the diamino nitrile (XXXIV). However, the synthesis of 2,4-diamino-5,6,7,8-tetrahydro-6-carboxaldehyde has been successful and will be reported in a future paper.

In order to investigate the utility of the benzyl group as a blocking group in reactions directed toward the synthesis of II, the bis(benzylamino) acid (XXXV) was prepared by mild treatment of the dichloro acid (XVI) with benzylamine, or by hydrolysis of the dibenzyl nitrile (XXXIII). Extended treatment of the dichloro acid (XVI) with benzylamine gave another compound whose infrared spectrum suggested it to be the bis(benzylamino) benzylamide (XXXVI). The bis(benzyla-

mino) acid (XXXV) with thionyl chloride gave the acid chloride (XXXVIII) which, without purification, was converted to the diethylamide (XXXVII). Attempts to remove the benzyl groups from XXXVII by hydrogenation to give the diamino amide (XXV) were unsuccessful; there was no hydrogenolysis of the benzyl groups but only reduction of the pyrimidine ring when platinum oxide was used as the catalyst. A number of cases have been reported where benzylamino groups do not undergo hydrogenolysis.[12]

EXPERIMENTAL[13]

Methyl 5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylate (V). A mixture of 2.14 g. (10 mmoles) of dimethyl 4-oxo-1,3-cyclohexanedicarboxylate (III), 1.20 g. (16 mmoles) of thiourea, and 16 ml. of methanolic 1 M sodium methoxide was heated under reflux for 3 hr. Water (40 ml.) was added, the solution was acidified with acetic acid, and the resulting precipitate was collected, washed with water, and air-dried to give 1.75 g. (73%) of product, m.p. 273–274°. A portion of the crude product was recrystallized from ethyl alcohol-N,N-dimethylformamide and again from N,N-dimethylformamide to give white crystals, m.p. 269–271°; $\lambda_{max(\mu)}^{KBr}$ 2.94 and 3.15 (NH, OH), 5.78 (ester C=O), 6.05 and 6.42 (pyrimidine ring), 8.25 (ester C—O—C); $\lambda_{max(m\mu)}^{pH\ 1}$ 275 (ϵ 25,200). On paper chromatography in either solvent A or C the product showed a single spot with R_{Ad} 1.67 and R_{Ad} 1.59, respectively.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S$: C, 50.0; H, 5.00. Found: C, 49.6; H, 5.13.

5,6,7,8-Tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylic acid (IX). A mixture containing double the amounts of reagents used in the preparation of V was heated under reflux for 3 hr., then allowed to stand overnight. After 5 ml. of 50% aqueous sodium hydroxide had been added, the mixture was refluxed 1.5 hr. The heavy precipitate that formed

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(13) Boiling and melting points are uncorrected; the latter were obtained with the Fisher-Johns Apparatus. Paper chromatography was done by the descending technique, usually on Whatman No. 1 paper, and the spots were detected by visual examination under ultraviolet light. Adenine was used as a standard and the spots were located relative to R_{Ad} 1.00. These solvent systems were used: A,[14] methyl Cellosolve-H_2O (9:1); B,[15] 5% aqueous Na_2HPO_4 (no organic phase); C,[16] n-BuOH—HOAc—H_2O (5:2:3); D, n-BuOH—$2N$NH$_4$OH; E,[17] H_2O sat'd. n-BuOH; F,[18] benzene-Skellysolve C—MeOH—H_2O (3.3:6.7:8:2); when Schleicher & Schuell acetylated paper was used, solvent system G,[19] benzene-MeOH-H_2O (2:6:1) was employed.

Infrared absorption assignments for the common functional groups were made in accordance with the data of Bellamy;[23] those of the substituted pyrimidine rings were made according to the consistent bands noted in a given series (*i.e.*, diamino, dihydroxy, dichloro, etc.) in this and in the previous paper.[2]

(14) A. E. Bender, *Biochem. J.*, **48**, xv (1951) (Proc. Biochemical Society).

(15) C. E. Carter, *J. Am. Chem. Soc.*, **72**, 1835 (1950).

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

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

(18) I. E. Bush, *Biochem. J.*, **50**, 370 (1952).

(19) T. Wieland and W. Kracht, *Angew. Chem.*, **69**, 172 (1957).

(10) W. Feeley, W. Lehn, and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).

(11) H. Plieninger and B. Kiefer, *Ber.*, **90**, 617 (1957).

dissolved upon the addition of 30 ml. of water. The cooled solution was adjusted to pH 4 with concentrated hydrochloric acid; the odor of hydrogen sulfide was noticeable. The precipitate was collected, washed with water, and dried to give 3.94 g. (87%) of product, m.p. >300°. A portion of this product (0.20 g.) was dissolved in 4 ml. of saturated aqueous sodium bicarbonate and the solution filtered. The filtrate was acidified with acetic acid to give 0.14 g. (61%) of product, m.p. >300°; $\lambda_{max(\mu)}^{KBr}$ 2.94 and 3.15 (NH, OH), 3.75–3.85 (OH of COOH, SH), 5.77 (shoulder, C=O of carboxyl), 5.95 and 6.40 (pyrimidine ring); $\lambda_{max(m\mu)}^{pH\ 1}$ 217 (ϵ 13,700), 278 (ϵ 19,700). On paper chromatography in solvent A the product showed a single spot with R_{Ad} 1.24.

Anal. Calcd. for $C_9H_{10}N_2O_3S$: C, 47.8; H, 4.42; N, 13.3. Found: C, 47.4; H, 4.53; N, 12.4, 12.3.

N,N-Diethyl-5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxamide (XI). A suspension of 0.23 g. (1 mmole) of 5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylic acid (IX) in 4 ml. of anhydrous ether, 1.46 ml. (0.02 mole) of thionyl chloride, and 0.02 ml. of pyridine was stirred overnight. After addition of 20 ml. of anhydrous ether, the precipitate was collected and washed with two 5-ml. portions of ether. The crude acid chloride (XIV) was added to a solution of 0.32 g. (4.2 mmoles) of diethylamine in 6 ml. of reagent acetone and the resulting suspension was stirred for 2.5 hr. The mixture was evaporated to dryness *in vacuo* and the residue was washed with 10 ml. of water and air-dried to give 0.11 g. (40%) of a dark brown solid, m.p. 272–276°. Both paper chromatography and infrared spectrum indicated this material to be essentially the same as the purified product described below. The crude product (0.10 g.) was recrystallized from ethyl alcohol and water to give 0.09 g. of a tan solid which, in turn, was dissolved in 15 ml. of saturated sodium bicarbonate solution, decolorized with Norit, and reprecipitated with 0.1 M hydrochloric acid to yield 0.04 g. (16% over-all yield) of solid, m.p. 286.5–287°; $\lambda_{max(\mu)}^{KBr}$ 2.90 and 3.19 (NH, OH), 6.12 (amide C=O and pyrimidine ring). On paper chromatography in solvent A the product showed a single spot with R_{Ad} 1.37.

Anal. Calcd. for $C_{13}H_{19}N_3O_2S$: C, 55.5; H, 6.76; N, 14.9. Found: C, 55.3; H, 6.90; N, 14.9.

Methyl 5,6,7,8-tetrahydro-4-hydroxy-2-(methylthio)-6-quinazolinecarboxylate (VI). To a stirred solution of 0.25 g. (1.0 mmole) of methyl 5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylate (V) in 1.05 ml. of methanolic 1 M sodium methoxide was added dropwise 0.13 g. (1.0 mmole) of dimethyl sulfate. After the solution had stood 10 minutes the white solid which had precipitated was collected and washed. The crude product was treated with hot aqueous sodium bicarbonate solution to remove unchanged V and there remained 0.10 g. (40%) of crude VI, m.p. 271–274°. The analytical sample was obtained by recrystallization from methanol-*N,N*-dimethylformamide (2:3), m.p. 277–280°; $\lambda_{max(\mu)}^{KBr}$ 2.95 (OH), 5.78 (ester C=O), 6.11 and 6.50 (pyrimidine ring), 8.18 (ester C—O—C). In the ultraviolet, fresh solutions of VI gave the following results: $\lambda_{max(m\mu)}^{pH\ 1}$ 230 (ϵ 9590), 253 (ϵ 10,600), 270–275 (ϵ 9670); and $\lambda_{max(m\mu)}^{pH\ 13}$ 218 (ϵ 16,100), 252 (ϵ 9750), 270–275 (ϵ 7050). After standing 3 days the acid solution gave $\lambda_{max(m\mu)}^{pH\ 1}$ 207 (ϵ 9840), 266 (ϵ 8440), which is in good agreement with the acid spectrum of X (*vide infra*); there was essentially no change in the alkaline solution. On paper chromatography in solvents A or C, the product showed a single spot with R_{Ad} 1.65 or 1.72, respectively.

Anal. Calcd. for $C_{11}H_{14}N_2O_3S$: C, 52.0; H, 5.51; N, 11.0. Found: C, 52.3; H, 5.63; N, 11.0.

5,6,7,8-Tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylic acid (X). A mixture of 4.28 g. (0.02 mole) of dimethyl 4-oxo-1,3-cyclohexanedicarboxylate (III), 1.92 g. (0.032 mole) of urea, and 32 ml. of 1 M sodium methoxide was refluxed 3-2/3 hr., then allowed to stand overnight. After the addition of 5 ml. of 50% sodium hydroxide, the reaction mixture was refluxed for 2 hr. Then 30 ml. of water was added and

the solution was acidified with 6 M hydrochloric acid with cooling. The resulting white precipitate was filtered and washed with water to give 2.34 g. (55.7%) of product, m.p. >300°. An analytical sample was obtained by solution of the crude product in saturated aqueous sodium bicarbonate filtration, and reprecipitation with acetic acid (over-all yield 31%), m.p. >300°; $\lambda_{max(\mu)}^{KBr}$ 2.90 and 3.15 (NH, OH), 5.79 (carboxyl C=O and pyrimidine C=O), 6.05 (pyrimidine C=O); $\lambda_{max(m\mu)}^{pH\ 1}$ 207 (ϵ 10,700), 267 (ϵ 9300); $\lambda_{max(m\mu)}^{pH\ 13}$ 217 (ϵ 12,700), 275 (ϵ 6300). On paper chromatography in solvents A or C, the product showed a single spot at R_{Ad} 1.02 or 1.00, respectively.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.4; H, 4.76; N, 13.3. Found: C, 51.9; H, 4.78; N, 13.3.

A large-scale run employing 500 g. of ketone (III) gave 270 g. (55.4%) of dihydroxyacid (X).

Butyl 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylate (IV). A mixture of 0.5 g. (2.4 mmoles) of 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylic acid (X), 0.57 g. (3 mmoles) of *p*-toluenesulfonic acid monohydrate, and 25 ml. of butyl alcohol was refluxed 3.25 hr., then allowed to stand overnight at room temperature. The addition of 20 ml. of saturated aqueous sodium bicarbonate gave 2 layers and a suspended solid. The solid was filtered from the liquid phases, washed with 5 ml. of aqueous sodium bicarbonate solution and with water, and air-dried to give 0.13 g. of product, m.p. 260–265°. The two layers in the filtrate were separated. The upper layer was washed with 10 ml. of saturated aqueous sodium bicarbonate, then with 10 ml. of water, then concentrated to dryness *in vacuo*. The residue was suspended in 10 ml. of water and filtered to give 0.36 g. of product, m.p. 265° (total yield 78%). An analytical sample was obtained by heating 0.30 g. of crude product in 3 ml. of saturated aqueous sodium bicarbonate solution. The solid was removed by filtration, washed with 10 ml. of water, then recrystallized from *N,N*-dimethylformamide-water to give white crystals, m.p. 273–274°; $\lambda_{max(\mu)}^{KBr}$ 2.89 and 3.15 (NH, OH), 5.76 (ester C=O), 5.87 and 6.00 (pyrimidine C=O), 8.43 (ester C—O—C). On paper chromatography in solvent A, the product gave a single spot at R_{Ad} 1.51.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.6; H, 6.76; N, 10.5. Found: C, 58.4; H, 6.90; N, 10.5.

N,N-Diethyl-5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxamide (XII). To a suspension of 0.21 g. (1 mmole) of 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylic acid (X) in 4 ml. of anhydrous ether containing 0.02 ml. of pyridine was added 1.46 ml. (0.02 mole) of thionyl chloride. The mixture, protected from moisture, was stirred 5 hr., then 10 ml. of ether was added. The solid was collected on a filter, washed 2 times with 10-ml. portions of ether, and added immediately to 6 ml. of acetone containing 0.45 ml. (4.2 mmoles) of diethylamine. After being stirred for 1.5 hr. and standing overnight, the reaction mixture was concentrated *in vacuo*. To the residue was added 10 ml. of water. The insoluble solid was collected on a filter, washed with water, and air-dried; yield 0.21 g. (81%), m.p. >300°. The crude product was washed with 3 ml. of saturated sodium bicarbonate solution and with 5 ml. of cold water, then recrystallized from 35 ml. of hot water to give 0.12 g. (48%) of white crystals.

Anal. Calcd. for $C_{13}H_{19}N_3O_3 \cdot H_2O$: C, 55.1; H, 7.42. Found: C, 55.3; H, 7.16.

When the material was redried at 140° in high vacuum, the anhydrous amide was obtained, $\lambda_{max(\mu)}^{KBr}$ 2.90 and 3.19 (NH, OH), 5.80 and 6.12 (amide C=O and pyrimidine C=O). On paper chromatography in solvents A or C, the product showed a single spot at R_{Ad} 1.35 and 1.44, respectively.

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.9; H, 7.17; N, 15.9. Found: C, 59.0; H, 7.38; N, 16.1.

5,6,7,8-Tetrahydro-2,4-dihydroxy-6-quinazolinecarboxamide (XIII). The acid chloride (XV) was prepared from 0.50 g. (2.4 mmoles) of 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quin-

azolinecarboxylic acid (X), 5 ml. of thionyl chloride, and 0.27 ml. of pyridine according to the procedure detailed for the preparation of XII. The crude acid chloride was suspended in 12 ml. of reagent acetone and the suspension was saturated with dry ammonia during 20 min. The mixture was concentrated to dryness *in vacuo* and the residue was washed with 10 ml. of water and air-dried to yield 0.47 g. (94%) of a solid which failed to melt at 300°. Paper chromatography indicated that the crude product was contaminated with the 6-carboxylic acid (X). The crude product was extracted with 15 ml. of saturated sodium bicarbonate solution and the residue, which was insoluble in organic solvents, was dissolved in 3 ml. of cold 10% aqueous sodium hydroxide, decolorized with Norit, and reprecipitated with 6 M hydrochloric acid. The solid was extracted with 3 ml. of hot saturated aqueous sodium bicarbonate solution, filtered, washed with water, and air-dried to yield 0.24 g. (48%) of solid, m.p. >300°; $\lambda_{max(\mu)}^{KBr}$ 2.90 and 3.15 (NH, OH), 5.86 and 6.05 (amide C=O and pyrimidine C=O). On paper chromatography in solvent C the product gave a single spot with R_{Ad} 0.52 but with some streaking from the origin.

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.7; H, 5.26; N, 20.1. Found: C, 51.5; H, 5.45; N, 19.9.

2,4-Dichloro-5,6,7,8-tetrahydro-6-quinazolinecarboxylic acid (XVI). A mixture of 10.0 g. (48 mmoles) of 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylic acid (X) and 200 ml. of phosphoryl chloride was heated under reflux for 2.5 hr. Most of the phosphoryl chloride was evaporated at 50° using a water pump vacuum and the sirupy residue was poured, with stirring, over 250 g. of ice and water. Stirring was continued for 30 min. to hydrolyze any acid chloride and the resulting fine suspension was filtered. The filtrate was extracted with 50 ml. of chloroform and the filtered solid was extracted with two 50-ml. portions of chloroform, filtering each time. The combined chloroform extracts were combined, dried over magnesium sulfate, and evaporated to leave 7.0 g. (61%) of crude product. This was recrystallized from 50 ml. of benzene-chloroform (2:1) to give 5.52 g. (47%) of product, m.p. 158-160, and a second crop of 0.54 g. (5%) of product, m.p. 161-164°. The analytical sample was obtained by further recrystallization, m.p. 159-160°; $\lambda_{max(\mu)}^{KBr}$ 5.77 and 5.90 (carboxyl C=O), 6.45 and 6.55 (aromatic pyrimidine); $\lambda_{max(m\mu)}^{95\% EtOH}$ 218 (ϵ 8000), 267 (ϵ 5100), $\lambda_{max(m\mu)}^{pH 13}$ 218 (ϵ 8500), 268 (ϵ 6000). On paper chromatography in solvent D, the product showed a single spot at R_{Ad} 0.97.

Anal. Calcd. for $C_9H_8Cl_2N_2O_2$: C, 43.7; H, 3.26; N, 11.3. Found: C, 43.9; H, 3.09; N, 11.3.

A large-scale run employing 270 g. of the dihydroxy acid (X) gave 284 g. (88.5%) of dichloro acid (XVI).

2,4-Diamino-5,6,7,8-tetrahydro-6-quinazolinecarboxylic acid (XVIII). To 10 ml. of absolute ethyl alcohol, previously saturated with dry ammonia at 0°, was added 1.00 g. (4.0 mmoles) of dichloro acid (XVI) and the solution was heated at 150° for 15 hr. in a stainless steel bomb. The bomb was cooled and the solution was transferred and evaporated *in vacuo*. The residue was dissolved in 35 ml. of water, the solution was extracted with 5 ml. of chloroform, and the pH of the solution was adjusted to 6–7 with 6 M hydrochloric acid. Upon standing, 0.49 g. (58%) of crystals deposited and were collected. These were redissolved in 1 M hydrochloric acid, the solution was decolorized with Norit, and, after filtration and neutralization of the filtrate, 0.15 g. (18%) of pure XVIII, m.p. >300°, was obtained as a crystalline solid; $\lambda_{max(\mu)}^{KBr}$ 2.98 and 3.12 (NH$_2$, NH), 6.00 (carboxyl C=O and NH$_2$), 6.35 (pyrimidine ring); $\lambda_{max(m\mu)}^{pH1}$ 273 (ϵ 7000); $\lambda_{max(m\mu)}^{pH 13}$ 285 (ϵ 6400). On paper chromatography in solvent D, the product moved as a single spot with R_{Ad} 0.40.

Anal. Calcd. for $C_9H_{12}N_4O_2 \cdot 1/2H_2O$: C, 49.8; H, 6.04; N, 25.8. Found: C, 49.9; H, 5.67; N, 25.8.

A large-scale run employing 100 g. of dichloro acid (XVI) gave 67.8 g. (80.4%) of diamino acid (XVIII).

Butyl 2,4-diamino-5,6,7,8-tetrahydro-6-quinazolinecarboxylate (XXIII). A mixture of 1.00 g. (4.8 mmoles) of diamino

acid (XVIII), 1.3 g. (12 mmoles) of ethanesulfonic acid, and 32 ml. of butyl alcohol was heated to boiling and 20 ml. of distillate was collected during 1.5 hr. The solution was cooled to 50° and poured into 25 ml. of saturated sodium bicarbonate solution. The butyl alcohol layer was separated, washed with an equal volume of water, and dried over magnesium sulfate. The filtrate was evaporated *in vacuo* to leave 0.90 g. of residue, which was extracted with 20 ml. of benzene leaving 0.71 g. (56%) of XXIII, m.p. 160-163°. Previously, by using *p*-toluenesulfonic acid, an analytical sample had been obtained after recrystallization from ethyl alcohol, m.p. 162-163°; $\lambda_{max(\mu)}^{KBr}$ 2.87, 2.98, and 3.15 (NH), 5.75 (ester C=O), 6.15 (NH$_2$), 6.30 and 6.93 (pyrimidine ring), 8.55 (ester C—O—C); $\lambda_{max(m\mu)}^{95\% EtOH}$ 286 (ϵ 7100), $\lambda_{max(m\mu)}^{pH 1}$ 274 (ϵ 7100).

Anal. Calcd. for $C_{13}H_{20}N_4O_2$: C, 59.1; H, 7.63; N, 21.2. Found: C, 58.7; H, 7.54; N, 21.5.

A mixture of 10.0 g. (48 mmoles) of diamino acid (XVIII), 21.9 g. (0.11 mole) of *p*-toluenesulfonic acid (monohydrate), and 350 ml. of butyl alcohol was heated to boiling and 235 ml. of distillate collected. The solution, upon chilling, deposited 21.4 g. (100%) of product, which was recrystallized from 200 ml. of 95% ethyl alcohol to give 14 g. (66%) of the *p*-toluenesulfonic acid salt of XXIII, m.p. 203-206°. The analytical sample had m.p. 204-206°; $\lambda_{max(\mu)}^{KBr}$ 2.95 and 3.15 (NH), 5.76 (ester C=O), 5.95-6.10 and 6.60 (pyrimidine ring), 8.2-8.5 (ester C—O—C and sulfonate ion), 9.65 and 9.85 (sulfonate ion).

Anal. Calcd. for $C_{20}H_{28}N_4O_5S$: C, 55.1; H, 6.46; S, 7.35. Found: C, 55.2; H, 6.40; S, 7.37.

Butyl 2,4-diacetamido-5,6,7,8-tetrahydro-6-quinazolinecarboxylate (XXIIIa). A mixture of 0.50 g. (1.9 mmoles) of butyl ester (XXIII) and 4.0 ml. of acetic anhydride was heated for 10 minutes on the steam bath, complete solution resulting. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in 10 ml. of chloroform. The chloroform solution was washed with 5 ml. of saturated sodium bicarbonate solution and 10 ml. of water and was dried over magnesium sulfate. Evaporation of the chloroform *in vacuo* gave a white residue which was recrystallized from 5 ml. of benzene to yield 0.55 g. (83%) of product, m.p. 160-162°. A second recrystallization from benzene gave the analytical sample, m.p. 163-165°; $\lambda_{max(\mu)}^{KBr}$ 3.05-3.15 (NH), 5.80 (ester C=O), 6.00 (amide C=O), 6.30 and 6.70 (pyrimidine ring), 8.30 and 8.45 (ester and amide C—O); $\lambda_{max(m\mu)}^{95\% EtOH}$ 230 (ϵ 23,800), 282 (ϵ 7530).

Anal. Calcd. for $C_{17}H_{24}N_4O_4$: C, 58.6; H, 6.94; N, 16.1. Found: C, 58.9; H, 7.11; N, 16.3.

2,4-Diamino-5,6,7,8-tetrahydro-6-quinazolinemethanol (XXIV). To 13.0 ml. of diglyme,[5] previously dried by distillation over lithium aluminum hydride, cooled to 0–5°, was 1.0 g. (7.5 mmoles) of anhydrous aluminum chloride and the mixture was stirred until the salt had dissolved. Sodium borohydride (0.85 g., 23.6 mmoles) was added and the mixture was stirred until almost all the hydride had dissolved. A suspension of 1.0 g. (3.8 mmoles) of butyl ester (XXIII) in 10 ml. of dry diglyme was added dropwise and with good stirring over a period of 15 minutes, while the temperature was maintained below 20°. The resulting solution was stirred at room temperature for 50 minutes and was poured over 50 g. of ice. The aqueous solution was acidified with 1.0 ml. of concentrated sulfuric acid, adjusted to pH 5 with 5.0 ml. of 10% aqueous sodium hydroxide, and evaporated to dryness *in vacuo* at about 60°. The residue was powdered and extracted with boiling methanol for 4 hr. in a Soxhlet apparatus. The methanol extract was evaporated to dryness *in vacuo* and the residue (2.0 g.) was dissolved in 15 ml. of water, the solution filtered, and the filtrate adjusted to pH 10 with saturated sodium carbonate solution. The solution was chilled and the crystalline product, 0.49 g. (67%), was collected and recrystallized from water to give the analytical sample, m.p. 260-270° (dec.); $\lambda_{max(\mu)}^{KBr}$ 2.95 (NH, OH), 6.15 and 6.30 (pyrimidine ring), 9.55 (alcohol C—O); $\lambda_{max(m\mu)}^{pH 1}$ 274 (ϵ 7580), $\lambda_{max(m\mu)}^{pH 13}$ 285 (ϵ 7500). On paper

chromatography in solvent C, the product showed a single spot at R_{Ad} 0.83.

Anal. Calcd. for $C_9H_{14}NO$: C, 55.6; H, 7.27; N, 28.8. Found: C, 55.7; H, 7.29; N, 28.2.

2,4-Diamino-5,6,7,8-tetrahydro-6-quinazolinylmethyl p-toluenesulfonate (XXIVa). To a suspension of 0.50 g. (2.6 mmoles) of diamino alcohol (XXIV) in 3 ml. of dry pyridine was added dropwise and with stirring a solution of 0.60 g. (3.2 mmoles) of p-toluenesulfonyl chloride in 2 ml. of dry pyridine. The solution was stirred 10 minutes more until complete solution was attained, the temperature reaching 35°, and was cooled and poured into 30 ml. of water. To the aqueous solution was added 10% aqueous sodium hydroxide until the color changed from yellow to pink (pH 9–10). On chilling, 0.06 g. (6.7%) of product precipitated, m.p. 186–188°. It was recrystallized from 4 ml. of absolute ethanol to give the analytical sample, m.p. 188–192°; $\lambda_{max(\mu)}^{KBr}$ 2.91–3.06 and 6.19 (NH_2), 6.35–6.40 and 6.95 (pyrimidine ring), 7.41, 8.43 and 8.53 (O-sulfonate), 12.30 (v-disubstituted phenyl).

Anal. Calcd. for $C_{16}H_{20}N_4O_3S$: C, 55.2; H, 5.78; S, 9.21. Found: C, 55.1; H, 6.82; S, 8.28.

There was insufficient sample for further purification.

2,4-Dichloro-5,6,7,8-tetrahydro-6-quinazolinecarboxamide (XXIX). A mixture of 0.50 g. (2.0 mmoles) of dichloro acid (XVI) and 3.0 ml. of phosphoryl chloride was heated under reflux for 1.8 hr. The solution was evaporated *in vacuo* and the residue was dissolved in 4.0 ml. of dry acetonitrile. This solution was added dropwise, with stirring, to 3.0 ml. of acetonitrile which had been saturated with ammonia at 0°. The solution was allowed to stand at room temperature for 15 hr. and was evaporated *in vacuo*. The residue was dissolved in 15 ml. of water and the pH adjusted to 9 with 10% aqueous sodium hydroxide. The precipitate, 0.44 g. (88%), m.p. 210–225°, was collected, washed with water, and dried.[20] After several recrystallizations from ethyl alcohol–methanol (7:1), the analytical sample was obtained, m.p. 220–225°; $\lambda_{max(\mu)}^{KBr}$ 2.95, 3.00, 3.15 and 6.17 (NH), 6.00 (amide C=O), 6.43–6.50 (pyrimidine ring); $\lambda_{max(m\mu)}^{95\% EtOH}$ 218 (ϵ 9800), 267 (ϵ 6230). On paper chromatography in solvent E, the product showed a single spot with R_{Ad} 2.0.

Anal. Calcd. for $C_9H_4Cl_2N_3O$: C, 43.9; H, 3.69; Cl, 28.8. Found: C, 44.2; H, 3.89; Cl, 28.6.

2,4-Dichloro-N,N-diethyl-5,6,7,8-tetrahydro-6-quinazolinecarboxamide (XXI). The dichloro acid chloride (XVII) was prepared as in the preparation of XX from 1.05 g. (4.1 mmoles) of XVI and 6.0 ml. of phosphoryl chloride. It was dissolved in 5 ml. of dry methylene chloride and the solution was cooled to 0–5°. A solution of 2.0 ml. (27 mmoles) of diethylamine in 2 ml. of methylene chloride was added dropwise during 5 minutes and the resulting solution was heated at reflux for 1 hr., allowed to stand at room temperature for 15 hr., and evaporated to dryness *in vacuo*. Water (15 ml.) was added to the gummy residue, which then solidified on standing. The aqueous mixture was adjusted to pH 9 with 10% aqueous sodium hydroxide and the precipitate was collected and washed with water to give 1.27 g. (100%), m.p. 108–109°. Recrystallization from benzene-hexane (1:1) gave the analytical sample, m.p. 109–110°; $\lambda_{max(\mu)}^{KBr}$ 6.10 (amide C=O), 6.45–6.50 (pyrimidine ring); $\lambda_{max(m\mu)}^{95\% EtOH}$ 267 (ϵ 5300). On paper chromatography in solvent F, the product moved as a single spot with R_f[21] 0.85.

Anal. Calcd. for $C_{13}H_{17}Cl_2N_3O$: C, 51.7; H, 5.68; Cl, 23.5. Found: C, 51.5; H, 5.67; Cl, 23.4.

2,4,4'-Trichloro-5,6,7,8-tetrahydro-6-quinazolinecarboxanilide (XXII). The dichloro acid chloride (XVII) was pre-

pared in the usual way from 0.50 g. (2.0 mmoles) of XVI and was dissolved in 2 ml. of methylene chloride. This solution was added dropwise to an ice-cold solution of 0.50 g. (3.9 mmoles) of p-chloroaniline in 2 ml. of dry pyridine, the resulting solution was allowed to stand 15 hr. at room temperature and was poured over 20 g. of ice. The aqueous mixture was extracted with 15 ml. of chloroform and the chloroform solution was washed with 10 ml. of saturated sodium bicarbonate solution and then with 0.5 M hydrochloric acid until the washings remained acidic. On chilling the chloroform solution, 0.50 g. of product, m.p. 97–104°, crystallized and was collected. The mother liquors were evaporated *in vacuo* and the residue was recrystallized from 3 ml. of chloroform yielding 0.15 g. more of crude XXII and giving a total crude yield of 87%. Several recrystallizations of the crude product from methanol-water gave the analytical sample, which showed a double melting point of 88–96° and 164–166° and had $\lambda_{max(\mu)}^{KBr}$ 3.05 (NH), 5.98 (amide C=O), 6.25 and 6.67 (aryl), 6.50 (NH and pyrimidine ring), 12.00 (p-disubstituted phenyl); $\lambda_{max(m\mu)}^{95\% EtOH}$ 252 (ϵ 23,800). On paper chromatography in solvent G, the product showed a single spot at R_{Ad} 1.23.

Anal. Calcd. for $C_{15}H_{12}Cl_3N_3O$: C, 50.6; H, 3.39; Cl, 29.8. Found: C, 50.6; H, 3.62; Cl, 29.4.

2,4-Diamino 5,6,7,8-tetrahydro-6-quinazolinecarboxamide (XXV). To 15 ml. of absolute ethyl alcohol previously saturated with ammonia at 0° was added 1.0 g. (4.2 mmoles) of dichloro amide (XX) and the mixture was heated at 150° for 15 hr. in a stainless steel bomb. The cooled solution was transferred and evaporated *in vacuo*. Water (10 ml.) was added to the residue and the pH was adjusted to 1 with concentrated hydrochloric acid. The solution was filtered, the filtrate was brought to pH 9–10 with 10% sodium hydroxide and chilled, giving 0.55 g. (66%) of product, m.p. >300°. This was recrystallized from N,N-dimethylformamide-water (1:1) to give the analytical sample, m.p. >300°; $\lambda_{max(\mu)}^{KBr}$ 2.95 (NH), 6.00 (amide C=O), 6.20–6.35 (NH_2, NH and pyrimidine ring); $\lambda_{max(m\mu)}^{pH 1}$ 272 (ϵ 7230), $\lambda_{max(m\mu)}^{pH 7}$ (ϵ 6280). On paper chromatography in solvent C, the product showed a single spot with R_{Ad} 1.20.

Anal. Calcd. for $C_9H_{13}N_5O$: C, 52.2; H, 6.32; N, 33.8. Found: C, 51.7; H, 6.15; N, 32.8.

2,4-Diamino-N,N-diethyl-5,6,7 8-tetrahydro-6-quinazolinecarboxamide (XXVI). A mixture of 1.0 g. (3.4 mmoles) of dichloro amide (XXI) in 10 ml. of absolute ethanolic ammonia (saturated at 0°) was heated at 150° for 10 hr. in a stainless steel bomb. The cooled solution was transferred, evaporated *in vacuo*, and the residue was dissolved in 5 ml. of water. The solution was filtered and the filtrate adjusted to pH 10 with saturated sodium carbonate solution. The precipitate, 0.59 g. (68%), was collected and was recrystallized from water to give the analytical sample, which showed a crystal transition at 70–75° and a double melting point of 115–118° and 231–234°; $\lambda_{max(\mu)}^{KBr}$ 3.00 (NH), 6.10 (amide C=O and pyrimidine ring), 6.90 (pyrimidine ring); $\lambda_{max(m\mu)}^{95\% EtOH}$ 285 (ϵ 7250). On paper chromatography in solvent C it showed a single spot with R_{Ad} 1.14.

Anal. Calcd. for $C_{13}H_{21}N_5O$: C, 59.3; H, 8.04; N, 26.6. Found: C, 59.1; H, 8.09; N, 26.3.

2,4-Diamino-4'-chloro-5,6,7,8-tetrahydro-6-quinazolinecarboxanilide (XXVII). The dichloro anilide (XXII), 1.0 g. (2.9 mmoles) was ammonolyzed by the procedure used for the preparation of XXVI except that the time of heating was 15 hr. The solution was evaporated *in vacuo* and the residue was dissolved in 10 ml. of water. The solution was brought to pH 10–11 with 10% aqueous sodium hydroxide and warmed on the steam bath for 10 minutes. After it had stood 3 hr. at room temperature, the mixture was filtered and the precipitate washed with water to give 0.48 g. (55%) of product, which was recrystallized from 4 ml. of N,N-dimethylformamide–water (4:1) to give 0.44 g. (50%) of product, m.p. 285–286°; $\lambda_{max(\mu)}^{KBr}$ 2.95–3.00 (NH), 5.92 (amide C=O), 6.05 (NH_2), 6.30 and 6.70 (aryl), 6.50 (NH and pyrimidine ring), 6.95 (pyrimidine ring), 12.15 (p-disub-

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(20) In a later preparation, the precipitate was triturated with 1 M hydrochloric acid to remove traces of ring aminated material and gave 40 g. (90%) of product, m.p. 225–227°.

(21) Adenine does not move in solvent F and so no R_{Ad} value is possible.

stituted phenyl). On paper chromatography in solvent C, the product showed a single spot with R_{Ad} 1.27.

Anal. Calcd. for $C_{15}H_{16}ClN_6O$: C, 56.7; H, 5.08; Cl, 11.2. Found: C, 56.6; H, 5.29; Cl, 11.2.

2,4-Dichloro-5,6,7,8-tetrahydro-6-quinazolinemethanol (XIX). A mixture of 10.0 g. (40.5 mmoles) of dichloro acid (XVI) and 50 ml. of phosphoryl chloride was heated under reflux for 2 hr., evaporated *in vacuo*, and the residue dissolved in 50 ml. of dry diglyme.[5] The solution was added dropwise during 25 minutes to a suspension of 3.0 g. (78 mmoles) of sodium borohydride in 50 ml. of dry diglyme, cooled to $-40°$ in a Dry Ice, carbon tetrachloride–chloroform (95:5) bath. The temperature was maintained at -20 to $-15°$ during the addition, then was stirred 5 minutes longer at that temperature and poured into a mixture of 300 ml. of saturated sodium bicarbonate solution and 200 g. of ice. The resulting solution was extracted with 250 ml. of chloroform, the chloroform was washed with 250 ml. of water and was dried over magnesium sulfate. Evaporation of the chloroform *in vacuo* left 6.4 g. of oil which was taken up in 100 ml. of chloroform and the solution washed with 20 ml. of saturated sodium bicarbonate solution and 100 ml. of water, then dried over magnesium sulfate. Evaporation of the chloroform *in vacuo* left 4.9 g. (52%) of a viscous oil which crystallized on standing but which resisted further purification efforts. It had $\lambda_{max(\mu)}^{film}$ 2.92 (OH), 6.50 (pyrimidine ring), 9.30 (alcohol C—O), and $\lambda_{max(m\mu)}^{95\% EtOH}$ 218 (ϵ 7200), 267 (ϵ 4700).

Anal. Calcd. for $C_9H_{10}Cl_2N_2O$: C, 46.6; H, 4.33; Cl, 30.5. Found: C, 46.8; H, 4.82; Cl, 28.2, 28.3.

Compound XIX was unstable and lost hydrogen chloride slowly on standing at room temperature.

2,4-Bis(benzylamino)]-5,6,7,8-tetrahydro-6-quinazoline-methanol (XXVIII). To a solution of 3.28 g. (14.1 mmoles) of dichloro alcohol (XIX) in 18 ml. of absolute ethyl alcohol was added 10 ml. (90 mmoles) of benzylamine and the mixture was heated at 150° for 15 hr. in a stainless steel bomb. The cooled solution was transferred, evaporated *in vacuo*, and to the residue was added 25 ml. of water. The aqueous mixture was extracted with 25 ml. of chloroform, the chloroform solution was dried over magnesium sulfate and evaporated *in vacuo*. The residue was carefully triturated with 25 ml. of hexane and the undissolved solid was recrystallized from 18 ml. of benzene-hexane (5:1), yielding 4.17 g. (79%) of product, m.p. 130–131°; $\lambda_{max(\mu)}^{KBr}$ 2.90 (OH), 3.05 (NH), 6.30 (aryl and pyrimidine ring), 6.60 (aryl, pyrimidine ring, and NH), 9.35 (alcohol C—O), 13.60 and 14.30 (monosubstituted phenyl).

Anal. Calcd. for $C_{23}H_{26}N_4O$: C, 73.8; H, 7.00; N, 15.0. Found: C, 73.8; H, 7.28; N, 14.7, 14.9.

2,4-Bis(benzylamino)-6-(chloromethyl)-5,6,7,8-tetrahydro-quinazoline (XXX). To 3.0 ml. of thionyl chloride was added 0.30 g. (0.80 mmole) of bis-(benzylamino) alcohol (XXVIII) and the mixture was heated under reflux for 2 hr., evaporated *in vacuo* to about 1 ml., and poured over 10 g. of ice. The mixture was extracted with 10 ml. of chloroform, the chloroform solution was washed with 5 ml. of saturated sodium bicarbonate solution and 5 ml. of water, and dried over magnesium sulfate. The solution was evaporated *in vacuo* to give 0.25 g. (80%) of product, m.p. 138–140°, which was recrystallized from 2 ml. of benzene to give 0.15 g. (48%) of the analytical sample, m.p. 141–142°; $\lambda_{max(\mu)}^{KBr}$ 2.95 and 3.10 (NH), 6.27 (aryl and pyrimidine ring), 6.45–6.60 (aryl, pyrimidine ring, and NH), 13.55–13.70 and 14.30 (monosubstituted phenyl).

Anal. Calcd. for $C_{23}H_{25}ClN_4$: C, 70.4; H, 6.42; Cl, 9.04. Found: C, 70.9; H, 6.35; Cl, 9.38.

2,4-Bis(benzylamino)-6-(bromomethyl)-5,6,7,8-tetrahydro-quinazoline (XXXI). A mixture of 1.0 g. (2.7 mmoles) of bis-(benzylamino) alcohol (XXVIII) and 5 ml. of phosphorus tribromide was heated with stirring for 2.5 hr. at 90–100°. The solution was cooled and poured into 50 g. of ice and the resulting solution stirred for 15 minutes. The solution was extracted with 25 ml. of chloroform, which was

washed with 15 ml. of saturated sodium bicarbonate solution and then 20 ml. of water, and dried over magnesium sulfate. The chloroform solution was evaporated *in vacuo* to give 0.80 g. of white solid, which was recrystallized from 6 ml. of benzene-hexane (9:1) to give 0.68 g. (58%) of product, m.p. 140–143°. A further recrystallization gave the analytical sample, m.p. 140–143°; $\lambda_{max(\mu)}^{KBr}$ 2.90, 3.10 and 6.50 (NH), 6.25–6.30 and 6.60 (aryl and pyrimidine ring), 13.50 and 14.50 (monosubstituted phenyl); there was no alcohol C—O band near 9.30.

Anal. Calcd. for $C_{23}H_{25}BrN_4$: C, 63.3; H, 5.77; N, 12.8. Found: C, 63.2; H, 5.66; N, 13.1.

2,4-Dichloro-5,6,7,8-tetrahydro-6-quinazolinecarbonitrile (XXXII). A mixture of 2.4 g. (10.0 mmoles) of dichloro amide (XXIX) and 12 ml. of phosphoryl chloride was heated under reflux for 2 hr. The solution was evaporated *in vacuo* and 15 ml. of cold water was added to the residue. The aqueous solution was extracted with 20 ml. of chloroform and the extract was washed with 15 ml. of saturated sodium bicarbonate solution, then 15 ml. of water, and dried over magnesium sulfate. The chloroform solution was evaporated *in vacuo* leaving 2.18 g. of residue, which was recrystallized from 12 ml. of benzene-hexane (1:1) to yield 1.77 g. (80%) of product, m.p. 108–109°; $\lambda_{max(\mu)}^{KBr}$ 4.50 (C≡N), 6.45 and 6.55 (pyrimidine ring).

Anal. Calcd. for $C_9H_7Cl_2N_3$: C, 47.4; H, 3.09; Cl, 31.1. Found: C, 47.4; H, 3.28; Cl, 31.4.

2,4-Bis(benzylamino)-5,6,7,8-tetrahydro-6-quinazolinecarbonitrile (XXXIII). To 5 ml. of a 35% solution of benzylamine in absolute ethyl alcohol was added 0.50 g. (2.2 mmoles) of dichloro nitrile (XXXII) and the mixture was heated at 150° for 9 hr. in a stainless steel bomb. The cooled solution was transferred and evaporated *in vacuo* and the residue was thoroughly triturated with 20 ml. of water, then with 20 ml. of hexane. The undissolved solid was recrystallized twice from toluene–ethyl alcohol (5:1) to give 0.30 g. (37%) of product, m.p. 212–214°; $\lambda_{max(\mu)}^{KBr}$ 3.00 and 3.10 (NH), 4.50 (C≡N), 6.25–6.30 (aryl and pyrimidine ring), 6.50 (NH and pyrimidine ring), 13.65 and 14.30 (monosubstituted phenyl).

Anal. Calcd. for $C_{23}H_{23}N_5$: C, 74.8; H, 6.28; N, 19.0. Found: C, 75.0; H, 6.29; N, 18.9.

2,4-Diamino-5,6,7,8-tetrahydro-7-quinazolinecarbonitrile (XXXIV). A mixture of 0.70 g. (3.1 mmoles) of dichloronitrile (XXXII) and 7 ml. of absolute ethanolic ammonia solution (saturated at 0°) was heated for 15 hr. at 150° in a stainless steel bomb. The cooled solution was transferred, evaporated *in vacuo*, and the residue stirred in 10 ml. of 0.1 *M* hydrochloric acid for 1 hr., most of the material remaining undissolved. The mixture was filtered and the filtrate adjusted to pH 10 with 10% aqueous sodium hydroxide, giving 0.10 g. of white solid. The acid-insoluble material was stirred with aqueous sodium hydroxide (pH 11), the mixture filtered, and the solid washed thoroughly with water, yielding 0.35 g. of solid. The total of the crude solids (0.45 g.) was extracted with 2 ml. of hot N,N-dimethylformamide and the undissolved solid collected to give 0.28 g. (48%) of product, m.p. >290°; $\lambda_{max(\mu)}^{KBr}$ 2.95 and 3.20 (NH), 4.50 (C≡N), 6.02 and 6.18 (NH₂), 6.35 and 6.90 (pyrimidine ring). On paper chromatography in solvent C, the product moved as a single spot with R_{Ad} 0.90.

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.1; H, 5.86; N, 37.0. Found: C, 57.2; H, 6.00; N, 37.4, 37.7.

2,4-Bis-(benzylamino)-5,6,7,8-tetrahydro-6-quinazolinecarboxylic acid (XXXV). (A) A mixture of 0.50 g. (1.4 mmoles) of bis-(benzylamino) nitrile (XXXIII) and 4 ml. of 25% aqueous sulfuric acid was refluxed for 15 hr. The mixture was made basic with 10% aqueous sodium hydroxide until complete solution resulted (pH ~12) and the product was reprecipitated with 0.5 *M* sulfuric acid by adjusting the pH to 4–5. The solid, 0.47 g. (90%) was recrystallized several times from N,N-dimethylformamide–water; the various recrystallization products showed widely variable melting points, 152–156°, 214–219° and 168–195°. The sample for

analysis had m.p. 168–195° and $\lambda_{max(\mu)}^{Nujol}$ 3.05 and 6.40 (NH), 3.6–3.9 (broad carboxyl OH), 5.95 (carboxyl C=O),[22] 6.05 (pyrimidine ring), 13.30 and 14.35 (monosubstituted phenyl). On paper chromatography in solvent C, the product moved as a single spot with R_{Ad} 1.50.

Anal. Calcd. for $C_{23}H_{24}N_4O_2$: C, 71.1; H, 6.23; N, 14.4. Found: C, 70.2; H, 6.29; N, 14.1.

(B) A better method of preparation of XXXV was available by the reaction of 0.50 g. (2.0 mmoles) of dichloro acid (XVI) with 2 ml. of benzylamine, the mixture heated for 17 hr. on the steam bath. Water (10 ml.) was added to the residue along with enough 10% aqueous sodium hydroxide to dissolve all the solid. The basic solution was extracted with two 10-ml. portions of ethyl ether and was neutralized with glacial acetic acid. The precipitate, 780 mg. (100%), was washed and dried and shown to be identical with the acid from the nitrile hydrolysis by identical infrared spectra[23] and paper chromatographic behavior.

When the mixture of dichloro acid (XVI) and benzylamine was refluxed for 3 hr., a solid product was obtained whose infrared spectrum suggested that it was the bis-(benzylamino) benzylamide (XXXVI). After recrystallization from ethyl alcohol the compound melted at 169–170°; $\lambda_{max(\mu)}^{KBr}$ 2.95–3.05 (NH), 6.05 (amide C=O), 6.32 (aryl and pyrimidine ring), 6.56–6.68 (aryl, pyrimidine ring and NH), 13.68 and 14.33 (monosubstituted phenyl). There was no broad carboxyl OH absorption in the 3.5 to 4.0 μ region and the intensity of the 13.7 and 14.3 μ bands was greater than in the acid (XXXV) spectrum. The material was not otherwise characterized.

2,4-Bis-(benzylamino)-N,N-diethyl-5,6,7,8-tetrahydro-6-quinazolinecarboxamide (XXXVII). A mixture of 3.0 g. (7.8 mmoles) of bis(benzylamino) acid (XXXV) and 7 ml. of thionyl chloride was heated under reflux for 45 minutes.

The mixture was evaporated *in vacuo* and two 5-ml. portions of benzene were separately evaporated *in vacuo* from the residue. The final residue was dissolved in 20 ml. of methylene chloride and added dropwise to a stirred solution of 9 ml. of diethylamine in 10 ml. of methylene chloride. After the mixture had stood overnight, it was evaporated *in vacuo* and 25 ml. of water was added to the residue. The aqueous mixture was extracted with 25 ml. of methylene chloride, the organic solution was washed with 20 ml. of 0.1 *M* aqueous sodium hydroxide and two 20-ml. portions of water and was dried over magnesium sulfate. Evaporation of the methylene chloride solution left 3.1 g. of residue, which was recrystallized from 10 ml. of benzene to give 1.7 g. (50%) of product, m.p. 82–90°. A small amount of material was recrystallized from benzene-hexane (9:1) to give a solid, m.p. 82–85°; $\lambda_{max(\mu)}^{KBr}$ 3.00 and 6.52 (NH), 6.14 (amide C=O), 6.30 (aryl and pyrimidine ring), 6.89 (pyrimidine ring), 13.60 and 14.30 (monosubstituted phenyl). This material was not analytically pure.

Anal. Calcd. for $C_{27}H_{33}N_5O$: C, 73.1; H, 7.50; N, 15.8. Found: C, 74.1; H, 7.53; N, 15.3.

Attempts to cleave the benzyl groups of XXXVII by hydrogenolysis to give the diamino amide (XXV) were unsuccessful. The use of platinum oxide as catalyst gave an excessive uptake of hydrogen but infrared examination of the product showed no loss of benzyl groups. The use of 5% palladium-on-charcoal led to no uptake of hydrogen.

(22) When the spectrum was run in KBr, the acid carbonyl occurred at 6.05 μ.

(23) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley, New York, N. Y., 1958.

Potential Anticancer Agents.[1] XXVI. Synthesis of Nucleosides Derived from D-Fructose

ELMER J. REIST, PHILLIP A. HART, AND B. R. BAKER

The reaction of chloromercuri derivatives of purines with the appropriately blocked derivatives of D-fructose has been utilized to synthesize 9-α-D-fructofuranosyladenine (II) and 9-β-D-fructopyranosyladenine (III). The stereochemistry of these ketose nucleoside condensations is discussed.

As part of an intensive program on the synthesis of C′-methyl- and C′-hydroxymethylpentofuranosyl nucleosides, the syntheses of a number of C_5′-methylpentofuranosyl nucleosides have been reported from this Laboratory.[2–6] A logical continuation of this work involves the syntheses of C_1′-methyl- and C_1′-hydroxymethyl nucleosides (I, R + H or OH). As the majority of the naturally occurring nucleosides contain the β-D-ribofuranose configuration,[7] it was most desirable to prepare the C_1′-substituted nucleosides in which the sugar

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series, *cf.* W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) E. J. Reist, L. Goodman, R. R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 3962 (1958).

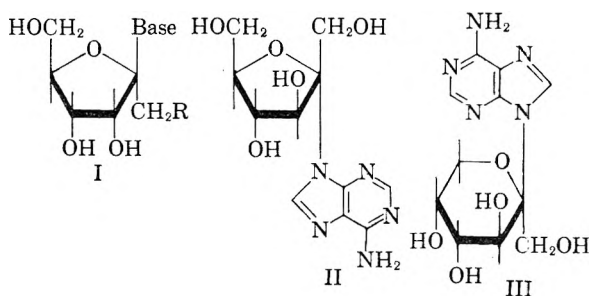(3) E. J. Reist, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 5775 (1958).

(4) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, 23, 1753 (1958).

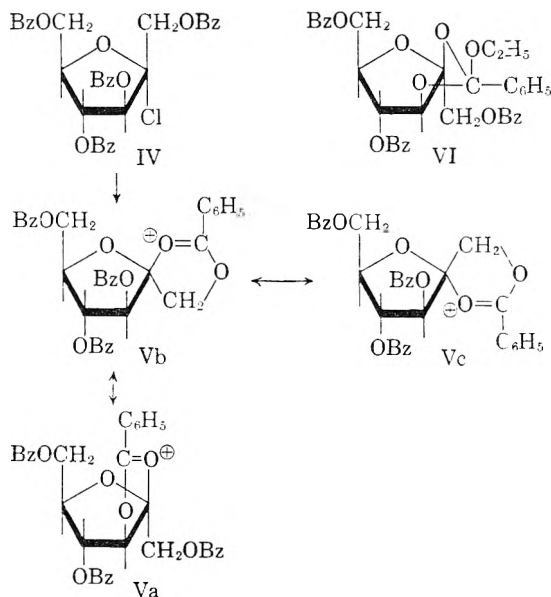(5) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, 23, 1757 (1958).

(6) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, 23, 1958 (1958).

(7) R. S. Tipson, "Advances in Carbohydrate Chemistry," Vol. I, Academic Press, Inc., New York, N. Y., 1945, p. 193.

possessed the β-configuration and which maintained the stereochemistry of D-ribofuranose at the remaining carbon atoms of the sugar moiety. The requisite sugar for nucleosides of this type is D-allulose (D-psicose). Because at the inception of this work there had been no cases reported of the use of ketose sugars in nucleoside condensations[8] and because D-allulose is very difficultly available, it seemed logical to initiate model studies of a nucleoside condensation which utilized a readily available ketose sugar such as D-fructose. The syntheses and stereochemistry of 9-α-D-fructofuranosyladenine (II) and 9-β-D-fructopyranosyladenine (III) are the subjects of this paper.

Normally, the condensation between a heavy metal salt of a purine or pyrimidine and an acylated glycosyl halide will form a nucleoside with a C_1'-C_2' *trans* configuration, regardless of the original configuration at C_1-C_2.[9] This result has been attributed[9] to a neighboring group participation by the 2-acyl group *via* an ortho ester ion which then reacts with the purine moiety to give the

trans nucleoside. As in the aldose sugars there is only one acyloxy group vicinal to the reactive center, the stereochemical directive influence is relatively simple. In the case of the ketose sugars, however, the situation is more complex, for there are now two vicinal acyloxy groups, both of which should be capable of forming an ortho-ester ion. In addition, the C_1 group can be either α or β with respect to C_2. Thus, there is the possibility of three ortho-ester ions (Va, b, and c) with which to contend. Structures Va and Vb would be expected to yield the α-nucleoside, whereas Vc should yield the β-nucleoside.

Ness and Fletcher[10] reported that the reaction of 1,3,4,6 - tetra - O - benzoyl - α - D - fructofuranosyl bromide[11] with ethanol and zinc oxide gave a 50% yield of a material which they identified as 1,4,6 - tri - O - benzoyl - 2,3 - O - (1 - ethoxybenzylidene)-β-D-fructofuranose (VI). A structure of this type could only have arisen from reaction of the ethanol with Va. Assuming from this information that Va is the favored ortho-ester ion, it is reasonable to expect that condensation of the halo sugar (IV) with a purine should give predominantly the α-nucleoside.

When the chloro sugar (IV) was condensed with chloromercui-6-benzamidopurine in the usual fashion,[2] a yield of 17% of crude nucleoside was obtained upon regeneration of the picrate. This crude nucleoside had a rotation $[\alpha]_D$ +42.6° (1% in water) and could be easily recrystallized from absolute ethanol to give a crystalline nucleoside with $[\alpha]_D$ +46.8° (1.03% in water). The close agreement in rotation between the crude and purified nucleosides indicates that only one anomer was formed. The positive value of the rotation suggests that the nucleoside has the α-configuration. This is further borne out by comparison with the rotations of the glycosides of fructofuranose. Thus, methyl α-D-fructofuranoside tetraacetate has a rotation $[\alpha]_D$ +88.1° (chloroform),[12] whereas methyl β-D-fructofuranoside tetraacetate has a rotation $[\alpha]_D$ −26.2° (methanol).[13]

In the case of fructopyranose, presumably the same arguments should hold true. Certainly, it would appear that three different ortho-ester ions (VIIIa, b, and c) are possible. Ions VIIIa and b should favor the formation of an α-nucleoside, whereas VIIIc should favor β-nucleoside formation. Although the bromo sugar exists in the β-configuration[14] (on the basis of rotation) and the

(8) A recent communication by W. Schroeder and W. Hoeksema, *J. Am. Chem. Soc.*, **81**, 1767 (1959) reported the synthesis of 6-amino-9-D-psicofuranosylpurine, as part of the structure proof of an antibiotic which has marked antibacterial and antitumor activity *in vivo*.

(9) B. R. Baker, Ciba Foundation Symposium on "The Chemistry and Biology of Purines," J. and A. Churchill Ltd., London, 1957, pp. 120–130.
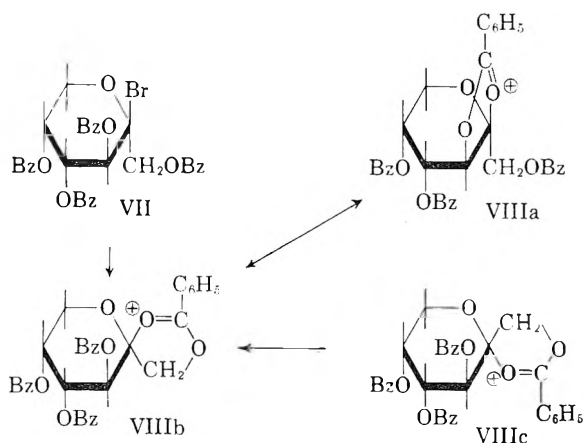
(10) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 1001 (1956).

(11) B. Helferich and L. Bottenbruch, *Ber.*, **86**, 651 (1953), assumed from the rotation of this bromo sugar that it was an α-D-halide.

(12) C. B. Purves and C. S. Hudson, *J. Am. Chem. Soc.*, **59**, 49 (1937).

(13) H. H. Schlubach and E. Bartels, *Ann.*, **541**, 76 (1939).

(14) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **75**, 2169 (1953).

ortho-ester ion VIIIc is the one that can form initially, one cannot necessarily expect that the β-nucleoside would be the sole product of the reaction, since the ortho-ester ions (VIII) can equilibrate.

Condensation of the bromo sugar (VII) with chloromercuri-6-benzamidopurine in the usual fashion[2] gave, on regeneration from the picrate, a 50% yield of crude amorphous nucleoside III which had a rotation $[\alpha]_D$ $-75°$ (1% in methanol). Treatment of this crude nucleoside with hot absolute ethanol caused the crystallization of the β-anomer, which had a rotation of $[\alpha]_D$ $-171°$ (1% in water). As the crude nucleoside was free of adenine, as shown by paper chromatography, it seems most likely that the very large change in rotation between the crude and recrystallized nucleoside indicates the presence of large amounts of α-nucleoside in the crude product. On the basis of the rotational values reported for various α- and β-fructopyranosides,[15] a rough estimate can be made that the crude nucleoside from the condensation is an approximately equal mixture of the α and β forms. This is further borne out by the fact that a 43% recovery of crystalline nucleoside III was obtained from crude III.

The formation of anomerically pure nucleoside in the furanose condensation from the halo sugar (IV), while pyranosyl bromide (VII) gave an anomeric nucleoside mixture, is somewhat surprising. That the pyranose condensation gave a mixture of anomers can only be interpreted on the basis of participation by the C_1 benzoate to give the ortho-ester ions VIIIb and VIIIc, the latter reacting with the purine to form the β-anomer. The complete absence of isolable amounts of the β-furanose nucleoside suggests that either the ortho-ester ion Vc did not form in appreciable amounts, or if it did, there was some factor, possibly the steric hindrance of the 3-benzoate, which prevented reaction between Vc and the purine base.

On the basis of the present information, it is not possible to draw any conclusions as to the relative effects of ortho-ester ions from C_3 versus C_1 benzoate. However, further work in progress on other appropriate ketose sugars should do much to clarify the stereochemistry of these condensations and afford a possible chemical proof of the configuration of the products.

EXPERIMENTAL[16]

9-α-D-*Fructofuranosyladenine* (II). To a mixture of 2.0 g. (3.35 mmoles) of 1,3,4,6-tetra-O-benzoyl-D-fructofuranose[17] in 60 ml. of anhydrous ether which had been saturated with dry hydrogen chloride at 0° was added 2.25 ml. of acetyl chloride. The solution was stored at 0° for 2 days, by which time the tetrabenzoate had dissolved. The solution was concentrated to dryness *in vacuo* at 30° and the last traces of acetic acid were removed by the addition and removal *in vacuo* of two 5-ml. portions of dry benzene to yield the chloro sugar IV as a white foam whose infrared absorption spectrum showed the essential absence of hydroxyl absorption at 2.9 μ; $[\alpha]_D^{30}$ $+8.8 \pm 2.8°$ (0.89% in methylene chloride).

A solution of IV in 200 ml. of dry xylene was condensed with 1.82 g. of chloromercuri-6-benzamidopurine[18] in the usual manner.[2] Evaporation of the organic phase gave 2.3 g. of crude blocked II as a foam; λ_{max}^{film} 3.25 μ (NH), 5.77 μ (benzoate C=O), 7.9 μ (O=C—O), 9.0 μ and 9.75 μ (C—O—C). A solution of 2.3 g. of blocked II in 45 ml. of reagent methanol and 4.2 ml. of N methanolic sodium methoxide was heated at reflux for 40 minutes. The solution was neutralized with Dowex 50(H), the resin was removed by filtration, and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in 25 ml. of water and extracted with two 15-ml. portions of ether. The aqueous phase was concentrated to dryness *in vacuo* and the residue was dissolved in 18 ml. of methanol and treated with 18 ml. of 10% methanolic picric acid. After the mixture had stood for 1 hr. at 0°, the amorphous picrate was filtered and then washed with cold methanol. The free nucleoside was regenerated by treating a suspension of the above picrate in 20 ml. of water with a total of 1.0 g. of Dowex 2(CO₃) added in small portions with stirring over 1 hr. After the picrate had all dissolved, the resin was removed by filtration and the aqueous filtrate was concentrated to dryness *in vacuo* to yield 0.17 g. (17%) of an off-white solid which showed one spot at R_{Ad} 0.43 in solvent A and R_{Ad} 1.68 in solvent B; $[\alpha]_D^{31}$ $+42.6°$ (1% in water). Recrystallization from absolute ethanol gave white crystals, m.p. 234–235° (dec.); $[\alpha]_D^{31}$ $+46.8 \pm 3.1°$ (1.03% in water).

(15) C. P. Barry and J. Honeyman, "Advances in Carbohydrate Chemistry," Vol. VII, Academic Press, Inc., New York, N. Y., 1952, p 86.

(16) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions. Paper chromatograms were run with water-saturated butyl alcohol (solvent A) and 5% aqueous sodium phosphate (solvent B) by the descending procedure on Whatman No. 1 paper. The spots were located by visual examination with an ultraviolet lamp. Adenine was used as a standard and spot locations were expressed as R_{Ad} units, with adenine at 1.00.

(17) P. Brigl and R. Schinle, *Ber.*, 67, 127 (1934). We wish to thank Dr. H. G. Fletcher, Jr., of the National Institutes of Health for supplying seed crystals of 1,3,4,6-tetra-O-benzoyl-D-fructofuranose.

(18) Prepared from mercuric chloride and 6-benzamidopurine as described for chloromercuri-2,6-diacetamidopurine.[19]

(19) B. R. Baker and K. Hewson, *J. Org. Chem.*, 22, 950 (1957).

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.5; H, 5.08; N, 23.6. Found: C, 44.5; H, 5.17; N, 23.4.

9-β-D-Fructopyranosyladenine (III). A solution of 8.2 g. of 1,3,4,5-tetra-O-benzoyl-D-fructopyranosyl bromide (VII)[14] in dry xylene was treated with 8 g. of chloromercuri-6-benzamidopurine and the nucleoside was isolated through the picrate as described for 9-α-D-fructofuranosyladenine (II) to yield 1.7 g. (46%) of a pale yellow foam which showed one spot at R_{Ad} 0.20 in solvent A and R_{Ad} 1.63 in solvent B; [α]D −75 ± 3° (1% in methanol).

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.5; H, 5.08; N, 23.6. Found: C, 43.8; H, 5.63; N, 21.6.

Treatment of 1.4 g. of this material with 20 ml. of hot ethanol caused crystallization to take place. Recrystalliza-

tion from absolute ethanol gave 0.6 g. (16%) of material, m.p. 227–228° (dec.); [α]D −171 ± 4° (1% in water).

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.5; H, 5.08; N, 23.6. Found: C, 44.6; H, 5.12; N, 23.7.

Tetrazole Analogs of Amino Acids[1]

J. M. McMANUS[2,3] AND ROBERT M. HERBST

The synthesis of analogs of several amino acids in which the carboxyl group is replaced by the acidic 5-tetrazolyl group is described. Tetrazole analogs of glycine, D,L-alanine, β-alanine, D,L-phenylalanine and D,L-tryptophan have been prepared. With the exception of the tryptophan analog each was prepared by at least two independent methods. Apparent dissociation constants of the tetrazole analogs were determined and are comparable to those of the respective amino acids. The tetrazole analogs were further characterized as phenylureas and as acetyl and benzoyl derivatives.

Numerous examples of metabolite antagonism have been noted for compounds that bear various relationships to the naturally occurring α-amino acids. One of the most thoroughly investigated is phenylalanine. Various changes in its structure have transformed phenylalanine into an inhibitor of bacterial growth. Among the changes sufficient to interfere with the nutritional effect of this amino acid are introduction of an amino group[4] or a fluorine atom[5] in the *para* position of the benzene ring. Substitution of certain heterocyclic rings for the phenyl group, such as 2-pyridyl,[6] 2-thienyl,[7] 2-furyl,[8] and 2-pyrryl,[9] has also resulted in analogs which exhibit specific antagonism for phenylalanine. 5-Methyltryptophan[10] and β-3-indolylacrylic acid[11] act as antimetabolites for tryptophan. The changes necessary to develop antimetabolite

activity are not restricted to any one portion of the amino acid structure. Analogs of glycine, alanine, valine, and leucine with the sulfonic acid residue replacing the carboxyl group have shown specific inhibition of the utilization of these amino acids as measured by interference with bacterial growth.[12]

In view of the acidic character of the 5-substituted tetrazoles it has been suggested that analogs of biologically active carboxylic acids in which the carboxyl group is replaced by a 5-tetrazolyl group might interfere with the normal utilization of the respective carboxylic acids.[13] Tetrazole analogs of 3-indolylacetic acid and 2,4-dichlorophenoxyacetic acid antagonize the plant growth regulatory effects of these compounds,[14,15] and there are indications that the tetrazole analog of nicotinic acid will prevent growth of certain bacteria.[16]

These observations have encouraged us to prepare analogs of several amino acids in which the 5-tetrazolyl group replaces the carboxyl group. Analogs of glycine, D,L-alanine, β-alanine, D,L-phenylalanine and D,L-tryptophan are described in the following. The synthesis of each 5-amino-

(1) Based on the doctoral thesis submitted to Michigan State University in 1958 by James M. McManus.

(2) White Laboratories Fellow, 1956–1958.

(3) Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

(4) J. H. Burckhalter and V. C. Stephens, *J. Am. Chem. Soc.*, **73**, 56 (1951).

(5) D. E. Atkinson, S. Melvin, and S. W. Fox, *Arch. Biochem. Biophys.*, **31**, 205 (1951).

(6) E. M. Langsford, Jr., and W. Shive, *Arch. Biochem. Biophys.*, **38**, 347 (1952).

(7) V. duVigneaud, H. McKennis, S. Simmonds, K. Dittmer, and G. B. Brown, *J. Biol. Chem.*, **159**, 385 (1945).

(8) D. A. Clark and K. Dittmer, *J. Biol. Chem.*, **173**, 313 (1948).

(9) W. Herz, K. Dittmer, and S. J. Cristol, *J. Am. Chem. Soc.*, **70**, 504 (1948).

(10) T. F. Anderson, *Science*, **101**, 565 (1945).

(11) P. Fildes, *Biochem. J.*, **32**, 1600 (1938).

(12) H. McIlwain, *J. Chem. Soc.*, 75 (1941).

(13) R. M. Herbst, *Essays in Biochemistry*, S. Graff, Ed., John Wiley and Sons, Inc., New York, 1956, pp. 141–155.

(14) J. M. McManus and R. M. Herbst, *J. Org. Chem.* In press.

(15) R. M. Hamilton, A. Kivilaan, and J. M. McManus, *Plant Physiol.* In press.

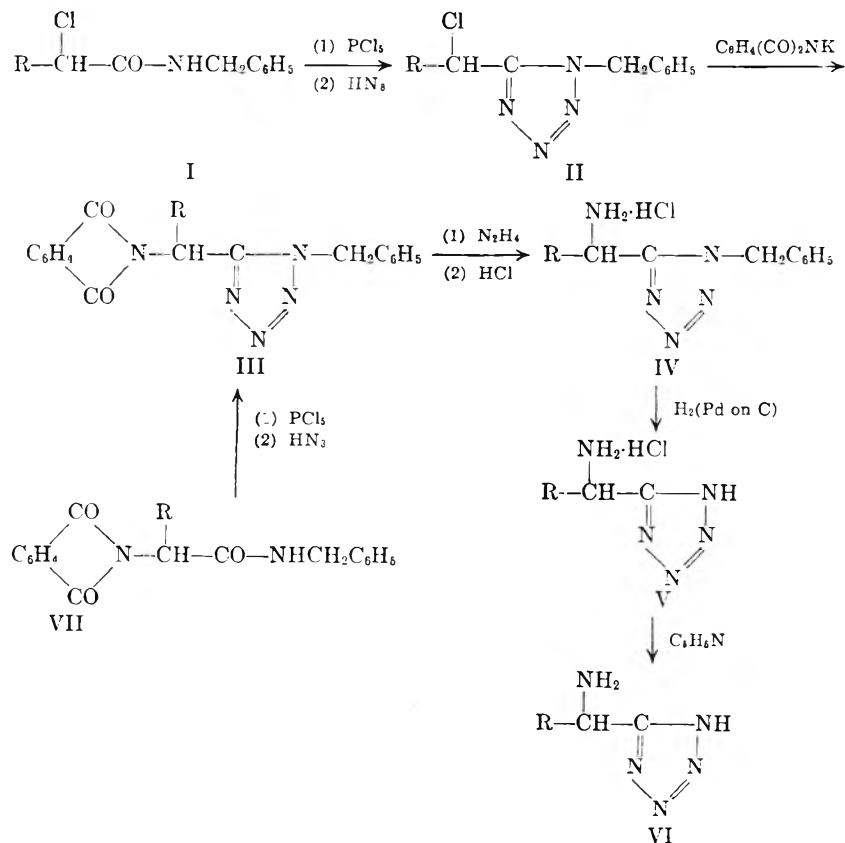(16) J. M. McManus and R. M. Herbst, *J. Org. Chem.* In press.

alkyltetrazole, with the exception of the tryptophan analog, was accomplished by two different methods so as to corroborate structures by independent syntheses. Three general synthetic approaches have been developed.

Scheme A employs the initial formation of a 1-benzyl-5-α-haloalkyltetrazole (II) from an *N*-benzyl-α-haloamide ·(I) using the von Braun procedure.[17] Interaction of II with potassium phthalimide gave a 1-benzyl-5-α-phthalimidoalkyltetrazole (III) which upon removal of the phthalyl group by treatment with hydrazine[18,19] gave the hydrochloride of a 1-benzyl-5-α-aminoalkyltetrazole (IV). Removal of the benzyl group by hydrogenolysis[20] gave the hydrochloride of a 5-α-aminoalkyltetrazole (V) from which the free amino acid analog (VI) was obtained by treatment with pyridine in absolute ethanol. In cases where the basicity of the amino group was too great to permit the latter type of exchange, silver oxide in aqueous suspension was used to liberate the free amino acid analog. Because of the severe irritation of mucous membranes caused by the α-haloalkyltetrazole (II), it was advantageous to use an alternate sequence of reactions; the *N*-benzyl-α-

phthalimidoamide (VII) was formed first and converted into the tetrazole (III) by treatment successively with phosphorus pentachloride and hydrazoic acid.

Scheme A permits the formation of the tetrazole ring by an unequivocal procedure from an *N*-substituted amide and formation of the final product by a series of unambiguous reactions.

Scheme B provides a method for converting an amino acid into its tetrazole analog. The phthalyl derivative of the amino acid is converted successively into the acid chloride and amide. Dehydration of the latter gave the α-phthalimidonitrile (VIII). Using the general procedure of Behringer and Kohl[21] for the preparation of 5-substituted tetrazoles, VIII was converted into the 5-α-phthalimidoalkyltetrazole (IX) by treatment in refluxing tetrahydrofuran with aluminum azide formed *in situ* from aluminum chloride and sodium azide. The procedure of Behringer and Kohl for isolation of the tetrazoles was modified. Tetrahydrofuran was displaced from the reaction mixture by distillation while the volume was kept constant by addition of water. The aluminum salt of the tetrazole separated from the aqueous

medium and was decomposed, after resuspension in fresh water, by warming with dilute hydrochloric acid. Removal of the phthalyl moiety gave the α-aminoalkyltetrazole hydrochloride (V)

(17) E. K. Harvill, R. M. Herbst, and E. C. Schreiner, *J. Org. Chem.*, **17**, 1597 (1952).

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

(19) J. C. Sheehan and V. S. Frank, *J. Am. Chem. Soc.*, **71**, 1856 (1949).

(20) L. Birkofer, *Ber.*, **75**, 429 (1942).

(21) H. Behringer and K. Kohl, *Chem. Ber.*, **89**, 2648 (1956).

from which the free amino acid analog (VI) was liberated with pyridine or silver oxide. This route opens the possibility of starting with an optically active amino acid and preparing the optically active tetrazole analog of the same configuration.

VIII

IX
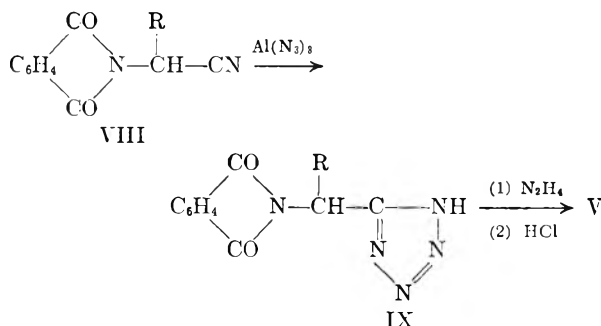
After completion of this work a procedure for the conversion of nitriles into 5-substituted tetrazoles by interaction with lithium azide or ammonium azides in dimethylformamide was described.[22]

Scheme C is an adaptation of a procedure used for the preparation of a number of amino acids. Ethyl acetamidocyanoacetate was alkylated and the resulting nitrile (X) treated with aluminum azide in tetrahydrofuran to form the 5-substituted tetrazole (XI). The latter was converted into the amino acid analog (VI) either by stepwise or by a single step hydrolysis and decarboxylation. The former procedure was used to provide a logical sequence of intermediates after which the latter technique was employed for preparative purposes. This route offers a process closely analogous to that used for the synthesis of many amino acids differing only in the conversion of the cyano group to the 5-tetrazolyl rather than to the carboxyl group.

X

XI
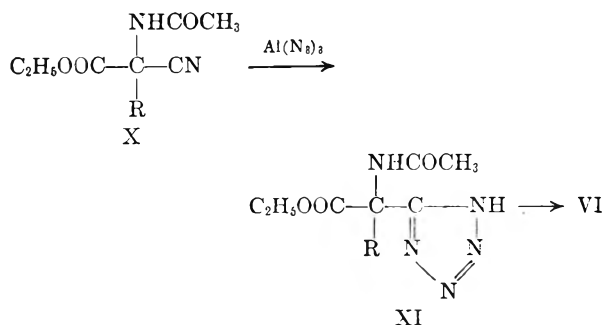
5-α-Aminomethyltetrazole (VI, R=H), the glycine analog, was prepared following both *Schemes A* and *B*. The sequence of reactions involved in *Scheme B* was initiated with phthalimidoacetonitrile (VIII, R=H) prepared from potassium phthalimide and chloroacetonitrile. As glycine is optically inactive, the pursuit of *Scheme B* from the

amino acid offered no advantage. The hydrochloride (V, R=H) of this compound has been described by Behringer and Kohl[21] but its behavior as a glycine analog apparently was not recognized.

The D,L-alanine anlog, D,L-5-α-aminoethyltetrazole (VI, R=CH$_3$) was synthesized from α-bromopropionyl bromide using *Scheme A* and from D,L-alanine using *Scheme B*. So as to avoid handling the α-halotetrazole, the modified sequence involving N-benzyl-α-phthalimidopropionamide (VII, R=CH$_3$) was followed.

5-β-Aminoethyltetrazole, the β-alanine analog, was prepared according to *Schemes A* and *B*. As potassium phthalimide caused dehydrohalogenation of N-benzyl-β-bromopropionamide, the sequence of steps in *Scheme A* was modified to the extent of preparing N-benzyl-β-phthalimidopropionamide by interaction of β-phthalimidopropionyl chloride and benzylamine Subsequent steps of *Scheme A* were followed without change. *Scheme B* was shortened by preparation of β-phthalimidopropionitrile from phthalimide and acrylonitrile[23] rather than from the amino acid. The hydrochloride of the β-alanine analog has been described as a potential histamine antagonist[21,24]; however, its amphoteric character was not noted.

The D,L,-phenylalanine analog, 5-α-amino-β-phenylethyltetrazole (VI, R=C$_6$H$_5$CH$_2$), was prepared following *Schemes B* and *C*. The intermediate, ethyl α-acetamido-α-5-tetrazolyl-β-phenylpropionate (XI, R=C$_6$H$_5$CH$_2$) obtained in *Scheme C* was converted into the amino acid analog both by stepwise degradation and by a single step hydrolysis and decarboxylation.

The analog of D,L-tryptophan, 5-α-amino-β-3-indolylethyltetrazole (VI, R=3-indolylmethyl), was prepared only by *Scheme C*. The intermediate ethyl α-acetamido-α-5-tetrazolyl-β-3-indolyl propionate (XI, R=3-indolylmethyl) was converted into the amino acid analog by stepwise hydrolysis and decarboxylation.

The tetrazole analogs are very similar to the corresponding amino acids in both physical and chemical properties. The glycine, D,L-alanine, and β-alanine analogs are soluble in water, aqueous acids and alkalies. The phenylalanine and tryptophan analogs are only slightly soluble in water but readily soluble in dilute, aqueous acids and alkalies. All of the analogs are insoluble in acetone, ethanol and non-polar solvents. All have high melting points and all decompose at the melting point which may vary with the rate of heating. Using methods applicable to the characterization of amino acids permitted the preparation of phenylureas and of acetyl and benzoyl derivatives. The benzoyl derivatives and phenylureas melted with gas evolution. The benzoyl derivative of D,L-alanine exhibited a double melting point; after

(22) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).

(23) A. Galat, *J. Am. Chem. Soc.*, **67**, 1414 (1945).
(24) C. Ainsworth, *J. Am. Chem. Soc.*, **75**, 5728 (1953).

melting at 176–177° it solidified and on continued heating remelted at 199–200°. Although this behavior has not been investigated, the possibility that bicyclic compounds such as tetrazoloimidazoles are formed on melting, analogous to the formation of azlactones and hydantoins from acylamino- and phenylureido acids, respectively, is not without merit.

Potentiometric determination of the dissociation constants of the 5-aminoalkyltetrazoles served to emphasize the analogy with amino acids. Apparent pK_1 values were obtained by titrating the aminoalkyltetrazoles with standard hydrochloric acid; pK_2 values were taken from titration curves with standard alkali. Inspection of the pK_1 values given in Table I shows that the tetrazolyl group is slightly weaker as an acid than the carboxyl group of the corresponding amino acid. This result could be anticipated from comparison of the apparent acidic dissociation constants of 5-alkyltetrazoles and the corresponding carboxylic acids.[25] Examination of the pK_2 values of the alkylaminotetrazoles indicates that the basicity of the amino group is lower than that of the amino group in the corresponding amino acids. Both pK_1 and pK_2 values decrease in the same order observed for the corresponding amino acids.[26]

TABLE I

APPARENT DISSOCIATION CONSTANTS OF SOME 5-AMINO-ALKYLTETRAZOLES AND CORRESPONDING AMINO ACIDS IN AQUEOUS SOLUTION AT 25°

Tetrazole	Apparent		Amino Acid[a]	Apparent	
	pK_1	pK_2		pK_1	pK_2
5-Aminomethyl	2.62	8.54	Glycine	2.34	9.60
5-α-Aminoethyl	2.63	8.77	D,L-Alanine	2.34	9.69
5-β-Aminoethyl	3.99	9.58	β-Alanine	3.60	10.19
5-α-Amino-β-phenylethyl	1.93	8.18	D,L-Phenylalanine	1.83	9.13

[a] The pK values for the amino acids were taken from reference 26.

EXPERIMENTAL[27]

Preparation of the Glycine Analog. 1-Benzyl-5-chloromethyltetrazole (II, R = H) was prepared from *N*-benzylchloroacetamide[28] in benzene solution by interaction successively with phosphorus pentachloride and hydrazoic acid.[17] The compound is a rather severe irritant of mucous membranes and must be handled with considerable care.

1-Benzyl-5-phthalimidomethyltetrazole (III, R = H). A mixture of 21 g. (0.1 mole) of 1-benzyl-5-chloromethyltetrazole and 21 g. (0.114 mole) of potassium phthalimide

(25) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

(26) E. J. Cohn and J. T. Edsall, Proteins, Amino Acids and Peptides, Reinhold Publishing Corp., New York, 1943, p. 84.

(27) Microanalyses were done on all compounds by Micro-Tech Laboratories, Skokie, Illinois. Melting points were done in open capillaries and are not corrected.

(28) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **20**, 685 (1915).

was refluxed in 250 ml. of dry xylene for 5 hr. The hot suspension was filtered; the product crystallized from the filtrate on cooling, yield 26.4 g. (83%), m.p. 132–133° after recrystallization from toluene.

Anal. Calcd. for $C_{17}H_{13}N_5O$: C, 63.9; H, 4.1; N, 21.9. Found: C, 64.1; H, 4.2; N, 22.2.

1-Benzyl-5-aminomethyltetrazole hydrochloride (IV, R = H). The technique of Ing and Manske[18] as modified by Sheehan and Frank[19] was adapted to this case. A suspension of 10.6 g. of 1-benzyl-5-phthalimidomethyltetrazole in 120 ml. of absolute ethanol was treated with 33 ml. of 1*M* hydrazine hydrate in ethanol and the mixture stirred at reflux temperature for 3 hr. After evaporation of the solvent the residue was heated with 75 ml. of 2*N* hydrochloric acid for 10 minutes at 50°. The suspension was filtered and the filtrate evaporated to dryness. The residue was recrystallized from aqueous isopropyl alcohol, yield 4 g. (53%), m.p. 228–229°.

Anal. Calcd. for $C_9H_{12}ClN_5$: C, 47.9; H, 5.4; Cl, 15.7; N, 31.0. Found: C, 48.1; H, 5.3; Cl, 15.7; N, 31.2.

5-Aminomethyltetrazole (VI, R = H). A solution of 10.5 g. of 1-benzyl-5-aminomethyltetrazole hydrochloride in a mixture of 200 ml. of absolute ethanol and 30 ml. of water was shaken with 2.5 g. of 5% palladium on charcoal at an initial pressure of 47 p.s.i. The temperature of the reaction mixture was kept at 60° during the hydrogenolysis. After separation of the catalyst, evaporation of the solvent left 6.2 g. (97%) of crude hydrochloride which was dissolved in 100 ml. of absolute ethanol and treated with 3.6 g. of pyridine. On chilling the glycine analog separated slowly from the solution, yield 3.8 g. (85%). The product was recrystallized by dissolution in a small amount of water and addition of sufficient absolute ethanol to give a 95% ethanol solution; the glycine analog crystallized slowly on standing overnight in a refrigerator, m.p. 267° with decomposition.

Anal. Calcd. for $C_2H_5N_5$: C, 24.2; H, 5.1; N, 70.7. Found: C, 24.5; H, 5.2; N, 70.6.

The hydrochloride of this product has been described by Behringer and Kohl.[21]

Phthalimidoacetonitrile (VIII, R = H) was prepared from potassium phthalimide and chloroacetonitrile in dimethylformamide, yield 64%, m.p. 127.5–128.5°. Sonn and Falkenheim[29] report m.p. 124–125° for this compound prepared from the same reagents in xylene.

Anal. Calcd. for $C_{10}H_6N_2O_2$: N, 15.1. Found: N, 15.3.

5-Phthalimidomethyltetrazole (IX, R = H). A suspension of 46.5 g. of phthalimidoacetonitrile and 50 g. of sodium azide in 100 ml. of dry tetrahydrofuran was treated at room temperature with 35 g. of anhydrous aluminum chloride dissolved in 300 ml. of the same solvent. After the mixture was refluxed for 24 hr. with continuous stirring, tetrahydrofuran was removed by distillation while the volume was kept constant by the gradual addition of water. After the aqueous suspension cooled, the aluminum salt was filtered off, resuspended in 450 ml. of water and 50 ml. of concentrated hydrochloric acid, and stirred at room temperature for 1 hr. The crude product was filtered from the chilled suspension, yield 50.6 g. (89%), m.p. 233.5–235° with decomposition. The pure product was obtained by recrystallization from ethanol–ethyl acetate mixture, m.p. 234–235° with decomposition.

Anal. Calcd. for $C_{11}H_9N_5O_2$: C, 52.4; H, 3.1; N, 30.6. Found: C, 52.4; H, 3.0; N, 30.8.

5-Aminomethyltetrazole (VI, R = H). A suspension of 45.8 g. of 5-phthalimidomethyltetrazole in 300 ml. of absolute ethanol was treated with 200 ml. of 1*M* hydrazine hydrate in ethanol. The mixture was stirred at reflux temperature for 3 hr., chilled overnight, and filtered. The solid was suspended in 450 ml. of 2*N* hydrochloric acid and warmed at 50–55° for 15 minutes. The precipitate was filtered from the cooled solution and the filtrate evaporated to dryness under reduced pressure. The residue of 5-aminomethyltetrazole

(29) A. Sonn and S. Falkenheim, *Ber.*, **55**, 2975 (1922).

hydrochloride (23.6 g.) was treated with pyridine in absolute ethanol and the product recrystallized as in the previous example to give 14.6 g. (74%) of the free glycine analog, m.p. 268.5° with decomposition. The product was identical with the material prepared according to *Scheme A*.

5-Acetamidomethyltetrazole, aceturic acid analog, was prepared from VI (R = H) by heating in glacial acetic acid with acetic anhydride. The residue left upon evaporation of the solvent under reduced pressure was recrystallized from amyl acetate, m.p. 159.5–161°.

Anal. Calcd. for $C_4H_7N_5O$: C, 34.0; H, 5.0; N, 49.6. Found: C, 34.2; H, 4.9; N, 49.6.

5-Benzamidomethyltetrazole, hippuric acid analog, was prepared from VI (R = H) in aqueous alkaline solution by treatment with benzoyl chloride. The product was recrystallized from water, m.p. 229.5–230° with decomposition.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.2; H, 4.5; N, 34.5. Found: C, 53.4; H, 4.6; N, 34.3.

N-Phenyl-N′-(5-tetrazolylmethyl)urea was prepared by shaking an aqueous, alkaline solution of VI (R = H) with phenyl isocyanate and isolating the product in the manner usual for phenylureido acids. Recrystallization from water gave the pure product, m.p. 194.5–195° with decomposition.

Anal. Calcd. for $C_9H_{11}N_6O$: C, 49.5; H, 4.6; N, 38.5. Found: C, 49.6; H, 4.8; N, 38.5.

Preparation of the D,L-Alanine Analog. N-Benzyl-α-bromopropionamide was prepared from α-bromopropionyl bromide and benzylamine in benzene solution in 52% yield, m.p. 91.5–92.5°, previously reported m.p. 93.5–94.5°.[30]

Anal. Calcd. for $C_{10}H_{12}BrNO$: Br, 33.0; N, 5.8. Found: Br, 33.1; N, 6.0.

N-Benzyl-α-phthalimidopropionamide (VII, R = CH_3). A mixture of 22.2 g. of potassium phthalimide and 24.2 g. of *N*-benzyl-α-bromopropionamide in 75 ml. of dimethylformamide was heated on a steam bath for 1 hr. with continuous stirring. The mixture was diluted with 100 ml. of chloroform and 250 ml. of water. The organic layer was separated and the aqueous layer washed with 50 ml. of chloroform. The combined chloroform solutions were washed with 0.2N sodium hydroxide and water, the solvent removed by evaporation and the residue recrystallized from toluene, yield 18 g. (59%), m.p. 141–142°.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2; N, 9.1. Found: C, 70.1; H, 5.3; N, 9.2.

1-Benzyl-5-α-phthalimidoethyltetrazole (III, R = CH_3). A suspension of 6.2 g. of *N*-benzyl-β-phthalimidopropionamide in 100 ml. of dry benzene was treated at room temperature with 4.2 g. of powdered phosphorus pentachloride. A clear solution formed after stirring the mixture for several minutes. Stirring was continued for 2 hr. when 20 ml. of a benzene solution containing 2.78 g. of hydrazoic acid was added. A colorless precipitate started to separate quickly, but stirring was continued for 2 hr. at room temperature and then for 2 hr. at reflux temperature. The precipitate that separated on chilling the solution was filtered off and washed with water, yield 5.9 g. (88%), m.p. 147°. The product was recrystallized from toluene, m.p. 146–147°.

Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.9; H, 4.5; N, 21.0. Found: C, 65.0; H, 4.5; N, 20.9.

1-Benzyl-5-α-aminoethyltetrazole hydrochloride (IV, R = CH_3) was prepared from 1-benzyl-5-α-phthalimidoethyltetrazole by treatment with hydrazine in ethanol as described for the lower homolog (IV, R = H). The crude hydrochloride was recrystallized several times from isopropyl alcohol, yield 60%, m.p. 184–184.5°.

Anal. Calcd. for $C_{10}H_{14}ClN_5$: C, 50.1; H, 5.9; Cl, 14.8; N, 29.2. Found: C, 50.0; H, 5.9; Cl, 14.9; N, 29.2.

5-α-Aminoethyltetrazole (VI, R = CH_3). A solution of 0.5 g. of 1-benzyl-5-α-aminoethyltetrazole hydrochloride in a mixture of 65 ml. of absolute ethanol and 10 ml. of water was shaken with 0.5 g. of 5% palladium on charcoal at 50–

55° and an initial hydrogen pressure of 40 p.s.i. Isolation of the tetrazole followed the procedure described for the glycine analog, yield 110 mg., m.p. 267–268° with decomposition. The product is identical with the material obtained according to *Scheme B* as described in the succeeding paragraphs.

α-Phthalimidopropionamide. A stirred suspension of 68.5 g. of phthalyl-D,L-alanine[31] in 500 ml. of benzene was treated with 61.3 g. of thionyl chloride. The mixture was heated with stirring on a steam bath until a clear solution formed. After cooling to 15° ammonia gas was bubbled into the solution until precipitation was complete. The solid was filtered off, dried, suspended in 1 l. of water, filtered and dried again, yield 46.5 g. (64%) of crude product, m.p. 209–210°. Radde[32] reported m.p. 211–212° for this compound. The crude material was used in the next step.

α-Phthalimidopropionitrile (VIII, R = CH_3) was prepared by dehydrating 44.5 g. of the crude amide by heating for 10 min. in 200 ml. of pyridine with 120 ml. of benzenesulfonyl chloride. The reaction mixture was cooled, poured into water and the solid that separated was recrystallized from methanol, m.p. 136–138°, yield almost quantitative. Radde[32] reported m.p. 139–140° for this product.

5-α-Phthalimidoethyltetrazole (IX, R = CH_3). From 49.3 g. of α-phthalimidopropionitrile by interaction with aluminum azide in tetrahydrofuran as described for the glycine analog (IX, R = H), 54.3 g. (91%) of crude product, m.p. 229–231° with decomposition, was obtained. The analytical sample was recrystallized from aqueous ethanol, m.p. 230–231° with decomposition.

Anal. Calcd. for $C_{11}H_9N_5O_2$: C, 54.3; H, 3.7; N, 28.8. Found: C, 54.3; H, 3.8; N, 28.8.

α-Aminoethyltetrazole (VI, R = CH_3). From 37.1 g. of 5-α-phthalimidoethyltetrazole by treatment with hydrazine in ethanol, 20 g. of crude hydrochloride was obtained in a manner analogous to that described for the glycine analog. Treatment of the crude hydrochloride with pyridine in ethanol, followed by recrystallization from water by addition of ethanol, gave the D,L-alanine analog in 40% over-all yield, m.p. 272–273° with decomposition. There was no depression of the mixture melting point with the material prepared following *Scheme A*.

Anal. Calcd. for $C_3H_7N_5$: C, 31.9; H, 6.2; N, 61.9. Found: C, 31.8; H, 6.1; N, 62.1.

5-α-Acetamidoethyltetrazole was prepared from 5-α-aminoethyltetrazole with acetic anhydride in glacial acetic acid. It was recrystallized from amyl acetate, m.p. 145–145.5°.

Anal. Calcd. for $C_5H_9N_5O$: C, 38.7; H, 5.9; N, 45.1. Found: C, 38.7; H, 5.7; N, 45.1.

5-α-Benzamidoethyltetrazole was obtained from the free alanine analog in aqueous, alkaline solution on treatment with benzoyl chloride. The product was recrystallized from water, m.p. 176–177° followed by solidification and remelting at 199–200° on continued heating.

Anal. Calcd. for $C_{10}H_{11}N_5O$: C, 55.3; H, 5.1; N, 32.2. Found: C, 55.5; H, 5.1; N, 32.4.

N-Phenyl-N′-(α-5-tetrazolylethyl)urea formed from the alanine analog in aqueous, alkaline solution on shaking with phenyl isocyanate. The derivative was recrystallized from water, m.p. 184–185° with decomposition.

Anal. Calcd. for $C_{10}H_{12}N_6O$: C, 51.7; H, 5.2; N, 36.2. Found: C, 51.9; H, 5.4; N, 36.2.

Preparation of the β-Alanine Analog. N-Benzyl-β-phthalimidopropionamide. Phthalyl-β-alanine was prepared in 91% yield from β-alanine and phthalic anhydride as described by Gabriel.[31] The acid chloride, m.p. 105–106.5°, was prepared in 91% yield from the acid on treatment with thionyl chloride in benzene solution. Gabriel[33] reported m.p. 107–108° for the acid chloride. β-Phthalimidopropionyl chloride (38.6 g.) was added in small portions during 20

(30) S. Kushner, R. I. Cassell, J. Morton, and J. H. Williams, *J. Org. Chem.*, 16, 1283 (1951).

(31) S. Gabriel, *Ber.*, **38**, 630 (1905).
(32) E. Radde, *Ber.*, **55**, 3174 (1922).
(33) S. Gabriel, *Ber.*, **41**, 242 (1908).

minutes to a stirred and cooled solution of 34.9 g. of benzyl-amine in 500 ml. of dry benzene. When interaction was complete the solid was filtered off, dried and digested with 750 ml. of water for 2 hr. The insoluble amide was filtered off and dried, yield 50.9 g., m.p. 194–197°. Recrystallization from absolute ethanol gave 41 g. (82%) of pure product, m.p. 198–199.5°; the analytical sample was crystallized again from absolute ethanol, m.p. 198–198 5°.

Anal. Calcd. for $C_{18}H_{19}N_2O$: C, 70.1; H, 5.2; N, 9.1. Found: C, 70.0; H, 5.0; N, 9.2.

1-Benzyl-5-β-phthalimidoethyltetrazole. N-Benzyl-β-phthal-imidopropionamide (35.1 g.) was treated with phosphorus pentachloride in dry benzene. It was necessary to warm and stir the mixture at 60° for 2 hr. to bring about complete interaction as evidenced by the formation of a homogeneous solution. The imidyl chloride solution was treated with hydrazoic acid as in previous examples. The tetrazole had an appreciable solubility in benzene; concentration of the benzene mother liquors was essential to insure maximum recovery. The product was recrystallized from toluene, yield 25.5 g. (67%), m.p. 156.5–158°. The analytical sample was recrystallized again from toluene, m.p. 159–159.5°.

Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.9; H, 4.5; N, 21.0. Found: C, 65.0; H, 4.3; N, 21.2.

1-Benzyl-5-β-aminoethyltetrazole hydrochloride was prepared from 1-benzyl-5-β-phthalimidoethyltetrazole by treatment with hydrazine in ethanol solution by the same techniques employed for the other analogs. The yield of crude hydrochloride was 75%. Recrystallization from aqueous isopropyl alcohol gave the pure hydrochloride, m.p. 138.5–139.5°.

Anal. Calcd. for $C_{10}H_{14}ClN_5$: C 50.1; H, 5.9; Cl, 14.8; N, 29.2. Found: C, 49.9; H, 6.0; Cl, 15.0; N, 29.0.

5-β-Aminoethyltetrazole hydrochloride was prepared by hydrogenolysis of 1-benzyl-5-β-aminoethyltetrazole hydrochloride as described for the other analogs. After crystallization from ethanol-ether the yield of hydrochloride was 37%, m.p. 127.5–129°.

Anal. Calcd. for $C_3H_8ClN_5$: C, 24.1; H, 5.4; Cl, 23.7; N, 46.8. Found: C, 24.1; H, 5.5; Cl, 23.5; N, 46.7.

This compound was prepared by Behringer and Kohl,[21] m.p. 132°, and by Ainsworth,[24] m.p. 128–129°. The same product was obtained following the sequence of *Scheme B* as described in the succeeding paragraphs.

5-β-Phthalimidoethyltetrazole. β-Phthalimidopropionitrile, prepared from acrylonitrile and phthalimide,[23] was treated with aluminum azide in tetrahydrofuran. The product was isolated from the reaction mixture by the modified technique described for the comparable derivative of the glycine analog (IX, R = H), yield 94%, m.p. 249.5–250.5° with decomposition after recrystallization from ethanol-ethyl acetate mixture.

Anal. Calcd. for $C_{11}H_9N_5O_2$: C, 54.3; H, 3.7; N, 28.8. Found: C, 54.3; H, 3.9; N, 29.0.

Behringer and Kohl[21] report m.p. 241° for this intermediate.

5-β-Aminoethyltetrazole hydrochloride was obtained from the phthalyl derivative by treatment with hydrazine in ethanol solution, yield 84%, m.p. 130–132°. The product is identical with the material obtained from 1-benzyl-5-β-aminoethyltetrazole hydrochloride.

5-β-Aminoethyltetrazole. A solution of 7.45 g. of the hydrochloride in 65 ml. of water was stirred in a dark place for 24 hr. with 6.1 g. of powdered silver oxide. The resulting suspension was filtered, the filtrate saturated with hydrogen sulfide and the silver sulfide removed by filtration. After treatment with Norite the clear filtrate was evaporated to a small volume. Dilution with acetone precipitated the amino acid analog which was further purified by dissolving in a small volume of water and again precipitating with acetone, yield 3.0 g. (58%), m.p. 223–224° with decomposition.

Anal. Calcd. for $C_3H_7N_5$: C, 31.9; H, 6.2; N, 61.9. Found: C, 32.1; H, 6.3; N, 62.0.

5-β-Acetamidoethyltetrazole was prepared from the β-alanine analog by treatment with acetic anhydride in glacial acetic acid. The product was crystallized from amyl acetate, m.p. 202–203°.

Anal. Calcd. for $C_5H_9N_5O$: C, 38.7; H, 5.9; N, 45.1. Found: C, 38.8; H, 6.1; N, 45.3.

5-β-Benzamidoethyltetrazole was obtained by shaking an aqueous, alkaline solution of the β-aminoethyltetrazole with benzoyl chloride. The product was recrystallized from water, m.p. 200.5–201° with decomposition.

Anal. Calcd. for $C_{10}H_{11}N_5O$: C, 55.3; H, 5.1; N, 32.2. Found: C, 55.1; H, 5.2; N, 32.3.

Ainsworth[24] reports m.p. 206° for this derivative.

N-Phenyl-N'-(β-5-tetrazolylethyl)urea was prepared by shaking an aqueous, alkaline solution of the β-aminoethyl-tetrazole with phenyl isocyanate. The product separated on acidification of the clear, alkaline solution and was recrystallized from aqueous ethanol, m.p. 199–199.5° with decomposition.

Anal. Calcd. for $C_{10}H_{12}N_6O$: C, 51.7; H, 5.2; N, 36.2. Found: C, 51.9; H, 5.4; N, 36.3.

Preparation of the D,L-*Phenylalanine Analog.* α-Phthal-imido-β-phenylpropionyl chloride was prepared from phthalyl-D,L-phenylalanine[19] by treatment with phosphorus penta-chloride in benzene suspension, yield 97%, m.p. 134–136°. Sheehan and Frank[19] report m.p. 124–126° for the acid chloride.

α-Phthalimido-β-phenylpropionitrile (VIII, R = benzyl) was prepared by converting the acid chloride into amide with aqueous ammonia and treating the amide with benzene-sulfonyl chloride in pyridine as recommended by Peterson and Niemann.[34]

5-(α-Phthalimido-β-phenylethyl)tetrazole (IX, R = benzyl) was prepared from 8.1 g. of α-phthalimido-β-phenylpro-pionitrile, 6.5 g. of sodium azide and 4.4 g. of anhydrous aluminum chloride in 75 ml. of dry tetrahydrofuran. The reaction and isolation followed the technique described for other examples. The yield of tetrazole was 9.2 g. (95%), m.p. 212.5–213° with decomposition after crystallization from ethyl acetate.

Anal. Calcd. for $C_{17}H_{13}N_5O_2$: C, 63.9; H, 4.1; N, 21.9. Found: C, 64.0; H, 4.4; N, 22.2.

5-(α-Amino-β-phenylethyl)tetrazole (VI, R = benzyl) was prepared from the phthalyl derivative (IX, R = benzyl) by treatment with hydrazine in ethanol solution. The free amino acid analog was obtained by adjusting its solution in dilute hydrochloric acid to pH 5, yield 82%, m.p. 271–272° with decomposition. Mixture melting point with the analytical sample prepared according to *Scheme C* as described in the following paragraphs was not depressed.

Ethyl α-acetamido-α-cyano-β-phenylpropionate (X, R = benzyl) was prepared from ethyl acetamidocyanoacetate and benzyl chloride as described by Albertson and Tullar.[35]

Ethyl α-acetamido-α-5-tetrazolyl-β-phenylpropionate (XI, R = benzyl) *and 5-(α-amino-β-phenylethyl)tetrazole* (VI, R = benzyl) were both prepared from 67.8 g. of the cyano-propionate (X, R = benzyl), 50 g. of sodium azide and 34.1 g. of anhydrous aluminum chloride in 550 ml. of tetra-hydrofuran. After the stirred reaction mixture was refluxed for 24 hr., the tetrahydrofuran was displaced with water as previously described. The suspended aluminum salt was filtered off and dried. The filtrate was acidified to Congo red and cooled overnight (Caution: hydrazoic acid liberated) and the crystallizate separated by filtration, yield 8 g. of crude ester (XI, R = benzyl). Recrystallization from ethanol gave the pure ester, m.p. 147.5–148.5°.

Anal. Calcd. for $C_{14}H_{17}N_5O_3$: C, 55.4; H, 5.7; N, 23.1. Found: C, 55.4; H, 5.4; N, 23.1.

The aluminum salt was refluxed with 450 ml. of concentrated hydrochloric acid for 3 hr. and the mixture evaporated

(34) P. E. Peterson and C. Niemann, *J. Am. Chem. Soc.*, **79**, 1389 (1957).

(35) N. F. Albertson and B. F. Tullar, *J. Am. Chem. Soc.*, **67**, 502 (1945).

almost to dryness under reduced pressure. The residue was taken up in 250 ml. of 95% ethanol and treated with 30 g. of pyridine. The amino acid analog crystallized from the solution on chilling overnight, yield 26 g. Recrystallization from water gave pure 5-(α-amino-β-phenylethyl)tetrazole, m.p. 270.5–271.5° with decomposition.

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.1; H, 5.9; N, 37.0. Found: C, 56.9; H, 6.0; N, 37.2.

The amino acid analog was also prepared by refluxing 2 g. of the tetrazolylpropionate (XI, R = benzyl) with 25 ml. of concentrated hydrochloric acid. The hydrolyzate was brought to pH 6 by addition of aqueous ammonia to precipitate the aminoalkyltetrazole. After recrystallization from water the product was identical with the material described in the preceding paragraph, yield 0.9 g. (72%), m.p. 276–277° with decomposition on rapid heating.

α-Acetamido-α-5-tetrazolyl-β-phenylpropionic acid. A suspension of 1.5 g. of the ester (XI, R = benzyl) in a solution of 0.8 g. of sodium hydroxide in 16 ml. of water was boiled for 1 hr. The solution was filtered and acidified (pH 2–3) with dilute hydrochloric acid. The product separated slowly on chilling after crystallization was initiated. It was recrystallized from tetrahydrofuran by addition of petroleum ether, m.p. 110° with gas evolution followed by solidification and remelting at 224–225° on continued heating.

Anal. Calcd. for $C_{12}H_{13}N_5O_3$: C, 52.4; H, 4.8; N, 25.5. Found: C, 52.7; H, 5.0; N, 25.6.

5-(α-Acetamido-β-phenylethyl)tetrazole. The tetrazolylpropionic acid derivative (20 mg.) described in the preceding paragraph was heated at 170° for a few minutes then recrystallized from water, m.p. 226°.

The same compound was prepared by acetylation of the amino acid analog (VI, R = benzyl) with acetic anhydride in glacial acetic acid solution. After recrystallization from aqueous ethanol the acetyl derivative melted at 224.5–225.5°.

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.1; H, 5.7; N, 30.3. Found: C, 57.2; H, 5.8; N, 30.2.

5-(α-Benzamido-β-phenylethyl)tetrazole was prepared by treating an aqueous, alkaline solution of the amino acid analog (VI, R = benzyl) with benzoyl chloride and recrystallizing the product from aqueous ethanol, m.p. 234–235° with decomposition.

Anal. Calcd. for $C_{16}H_{15}N_5O$: C, 65.5; H, 5.2; N, 23.9. Found: C, 65.5; H, 5.0; N, 24.0.

N'-Phenyl-N'-(α-5-tetrazolyl-β-phenylethyl)urea formed when an aqueous, alkaline solution of the amino acid analog (VI, R = benzyl) was shaken with phenyl isocyanate. The product was recrystallized from aqueous ethanol, m.p. 188–189.5° with decomposition.

Anal. Calcd. for $C_{16}H_{16}N_6O$: C, 62.3; H, 5.2; N, 27.3. Found: C, 62.4; H, 5.2; N, 27.4.

Preparation of the D,L-*Tryptophan Analog. Ethyl α-acetamido-α-cyano-β-3-indolylpropionate* was prepared by alkylation of ethyl acetamidocyanoacetate with gramine according to Albertson and Tullar.[35]

Ethyl α-acetamido-α-5-tetrazolyl-β-3-indolylpropionate (XI, R = 3-indolylmethyl). A solution of 13.3 g. of anhydrous aluminum chloride in 200 ml. of dry tetrahydrofuran was added to a stirred suspension of 19.5 g. of sodium azide in 50 ml. of the same solvent. After heating the stirred mixture under reflux for 1 hr. and then cooling to room temperature, 29.9 g. of ethyl α-acetamido-α-cyano-β-3-indolylpropionate

was added. The temperature was slowly raised to the boiling point and maintained there for 24 hr. with stirring. The mixture was then diluted with 150 ml. of water, cooled to 5° and acidified by slow addition during 20 min. with cooling of 50 ml. of concentrated hydrochloric acid. The entire mixture was poured into 300 ml. of ether, the organic layer separated, and the aqueous portion extracted with 100 ml. of 1:1 ether–tetrahydrofuran. The combined organic layers were washed with 100 ml. of water and dried over sodium sulfate. Removal of the solvent under reduced pressure left a residue that was recrystallized from chloroform to give the product, yield 11 g. (32%). A second crystallization from chloroform gave the analytical sample, m.p. 183.5–185° with decomposition.

Anal. Calcd. for $C_{16}H_{18}N_6O_3$: C, 56.1; H, 5.3; N, 24.6. Found: C, 56.0; H, 5.3; N, 24.5.

α-Acetamido-α-5-tetrazolyl-β-3-indolylpropionic acid was obtained by hydrolysis of 6.8 g. of the ester (XI, R = 3-indolylmethyl) with a solution of 3.2 g. of sodium hydroxide in 32 ml. of water at reflux temperature for 3 hr. The hydrolyzate was treated with Norit and the clear solution was acidified with 8.4 ml. of concentrated hydrochloric acid. Crystallization of the product was initiated while cooling the solution. On recrystallization from water the product separated as a dihydrate, m.p. 153–155° with decomposition.

Anal. (Air dried) Calcd. for $C_{14}H_{14}N_6O_3 \cdot 2H_2O$: N, 24.0. Found: N, 24.1, 23.9. (Dried at 100° *in vacuo*) Calcd. for $C_{14}H_{14}N_6O_3$: N, 26.7. Found: N, 26.7.

5-(α-Acetamido-β-3-indolylethyl)tetrazole was formed when 7.4 g. of the propionic acid derivative just described was heated in 200 ml. of boiling water for 2.5 hr. The hot solution was treated with Norite. The product crystallized on cooling the filtrate, yield 5.8 g. (91%). Recrystallization from water gave the analytical sample, m.p. 223–223.5° with decomposition.

Anal. Calcd. for $C_{13}H_{14}N_6O$: C, 57.8; H, 5.2; N, 31.1. Found: C, 57.9; H, 5.3; N, 31.2.

5-(α-Amino-β-3-indolylethyl)tetrazole (VI, R = 3-indolylmethyl). A solution of 1.3 g. of the acetyl derivative in 16 ml. of water containing 1.3 g. of sodium hydroxide was boiled under reflux for 12 hr. Concentrated hydrochloric acid (2.7 ml.) was added to the hot solution followed immediately by aqueous ammonia sufficient to adjust the acidity to pH 5 rapidly. Crystallization was initiated as the solution cooled, yield 0.8 g. (70%). A single crystallization from water gave the analytical sample, m.p. 268.5–269° with decomposition.

Anal. Calcd. for $C_{11}H_{12}N_6$: C, 57.9; H, 5.3; N, 36.8. Found: C, 57.8; H, 5.5; N, 36.9.

Determination of Apparent pK Values. Potentiometric titrations of the 5-aminoalkyltetrazoles were done at 25 ± 1° using a Beckman pH Meter, Model H-2. Solutions of 0.2–0.3 g. of the tetrazoles in 100–125 ml. of water were titrated with 0.1 *N* sodium hydroxide and 0.1 *N* hydrochloric acid. pK values were taken from large scale plots of the region of half neutralization on each leg of the curves. In each case the titration curves exhibited the form typical for an amino acid. The pK_1 and pK_2 values for the aminoalkyltetrazoles and the comparable amino acids are recorded in Table I.

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5-Aroyltetrazoles[1]

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Two synthetic avenues to 5-aryltetrazoles (IV) are described. In the first (Method A) an α-bromo-α-phenoxyacetophenone is converted to IV by treatment with excess sodium azide in glacial acetic acid. A plausible reaction scheme is suggested. In Method B, an aryl-5-tetrazolylcarbinol (VIII), obtained from the interaction of the corresponding mandelonitrile acetate and aluminum azide in tetrahydrofuran, is oxidized to IV with sodium dichromate in aqueous sulfuric acid. The latter method has been extended to the preparation of 5-acetyltetrazole. 5-Benzoyltetrazole (IVa) and its oxime readily undergo the Schmidt reaction and the Beckmann rearrangement, respectively. Wolff-Kishner reduction of IVa affords 5-benzyltetrazole while a photochemical reduction of IVa leads to the corresponding pinacol. The addition of phenylmagnesium bromide to IVa gives diphenyl-5-tetrazolylcarbinol.

The dependence of the acid dissociation constant of a 5-substituted tetrazole on the nature of the substituent and its analogy with the carboxylic acid has recently been reviewed by Herbst.[2] On the basis of a suggestion contained in this same review, several 5-tetrazolyl analogs of physiologically and pharmacologically active carboxylic acids have been synthesized and assayed for analogous or antagonistic activity.[3,4] The results were somewhat disappointing to the extent that no appreciable activity in either sense was detected.

The importance of α-keto acids in the citric acid cycle as well as in a variety of other biochemical transformations stimulated our interest in 5-tetrazolyl analogs of such intermediates as potential growth antagonists. The present communication discloses two approaches to 5-aroyltetrazoles, analogs of arylglyoxylic acids, and the properties of this class of tetrazole derivatives.

The decomposition of 2-azido-3-(2H)benzofuranones(2-azidocoumaranones) in glacial acetic acid containing excess sodium azide yields 5-(*o*-hydroxybenzoyl)-tetrazoles.[5] It was suggested that the reaction involves the intermediate formation of *o*-hydroxybenzoylcyanides as direct precursors of the ketones. However, the results of a recent study in this laboratory on the course of the reaction between

aroylcyanides and sodium azide tend to vitiate this hypothesis.[6] Nevertheless, the method constitutes the sole approach to 5-aroyltetrazoles which carry no additional function attached to the heterocycle.[7a,b]

An extension of this method to open chain analogs of 2-azidocoumaranone would circumvent the inherent limitation of simultaneous introduction of an *ortho* hydroxyl function in the 5-aroyltetrazole and, thereby, broaden the scope of the synthesis. Accordingly, it was found that α-bromo-α-phenoxyacetophenone[8] (IIa), on treatment with sodium azide in acetone, affords the corresponding azide (IIIa) in 80% yield. Decomposition of IIIa in glacial acetic acid and in the presence of excess sodium azide gave a solid with properties conforming to 5-benzoyltetrazole (IVa). Alternatively, the entire reaction sequence may be telescoped by simply refluxing IIa with excess sodium azide in glacial acetic acid (Method A). This modification gave IVa in 40% yield, based on α-phenoxyacetophenone, and is applicable to the conversion of α-phenoxy-*p*-bromo- (Ib) and α-phenoxy-*p*-nitroacetophenone (Ic) to the corresponding 5-aroyltetrazole (IVb and c) (*cf.* Table I). However, an attempt to prepare 5-acetyltetrazole from phenoxyacetone by this method was unsuccessful.

Recently, Boyer and Straw demonstrated that the pyrolysis of α-azidocarbonyl compounds leads to the decomposition of the azido group with rearrangement to α-iminocarbonyl compounds.[9] Moreover, in all possible cases hydrogen migration occurred exclusively.

By analogy, a rearrangement accompanying the decomposition of IIIa would lead to phenyl benzoylformimidate (V). Moreover, the conversion of
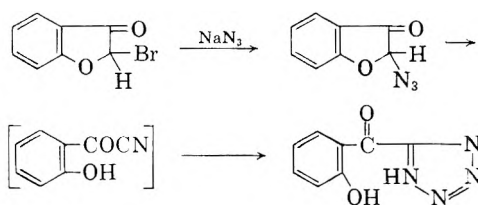
(1) This work was supported in part by research grant CY-2903 from the National Cancer Institute, Public Health Service and in part by an institutional grant from the American Cancer Society, Southeastern Michigan Division.

(2) R. M. Herbst in Graff's *"Essays in Biochemistry,"* Wiley and Sons, New York, 1956, p. 141.

(3) C. van de Westeringh and H. Veldstra, *Rec. trav. chim.*, 77, 1107 (1958).

(4) B. Brouwer-van Straaten, D. Solinger, C. van de Westeringh, and H. Veldstra, *Rec. trav. chim.*, 77, 1129 (1958).

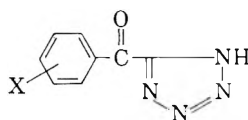(5) K. Fries and K. Saftien, *Ber.*, 59, 1246 (1926).

(6) J. P. Horwitz, B. E. Fisher, and A. J. Tomasewski, *J. Am. Chem. Soc.*, 81, 3076 (1959).

(7) Indirect syntheses of 1-phenyl-5-tetrazolylmethyl ketone have been described by (a) E. K. Harvill, R. M. Herbst, and E. G. Schreiner, *J. Org. Chem.*, 17, 1597 (1952) and (b) C. R. Jacobson and E. D. Amstutz, *J. Org. Chem.* 19, 1652 (1954).
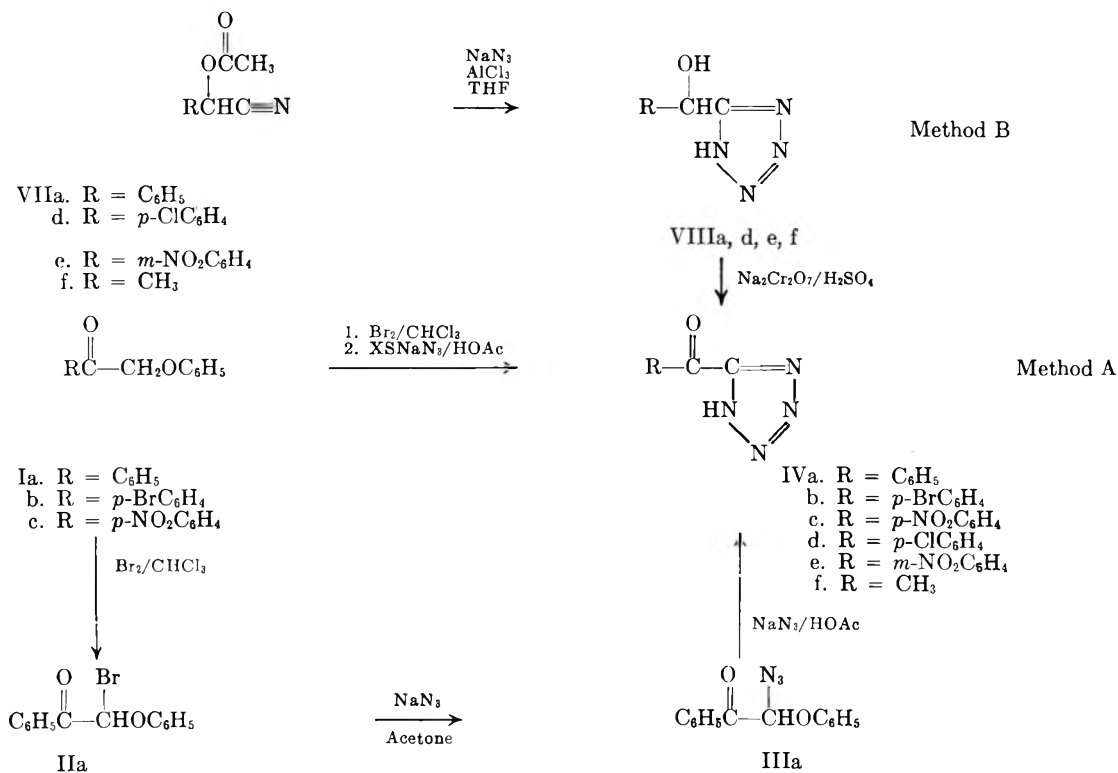
(8) E. B. Knott, *J. Chem. Soc.*, 4099 (1952).

(9) J. H. Boyer and D. Straw, *J. Am. Chem. Soc.*, 75, 1642 (1953).

TABLE I

5-AROYLTETRAZOLES

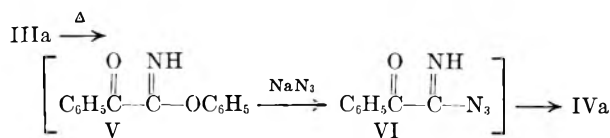| X	M.P.[a]	Method of Synthesis	Yield,[b,c] %	$\lambda_{max.},$[d] Mμ	Log ϵ	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	140–141	A	40	261	4.10	$C_8H_6N_4O$	55.17	3.47	32.17	55.34	3.48	32.10
		B	78									
p-Cl	174–175	B	75	270	4.14	$C_8H_5N_4OCl$	46.05	2.42	26.87	46.29	2.43	27.16
p-Br	176–177	A	50	272	4.12	$C_8H_5N_4OBr$	37.97	1.99	22.14	38.15	2.22	22.44
p-NO$_2$	161–163[d]	A		271	4.18	$C_8H_5N_5O_3$	43.84	2.30	31.96	43.91	2.46	32.14
m-NO$_2$	131–132	B	75	245	4.29	$C_8H_5N_5O_3$	43.84	2.30	31.96	44.13	2.45	31.83

[a] All of the tetrazoles were recrystallized from benzene. [b] Yield by Method A is based on the phenoxyacetophenone. [c] Yield by Method B is based on the aryl-5-tetrazolylcarbinol. [d] Spectra determined in 95% ethanol with a Cary Model 11 recording spectrophotometer.

VIIa. R = C$_6$H$_5$
d. R = p-ClC$_6$H$_4$
e. R = m-NO$_2$C$_6$H$_4$
f. R = CH$_3$

Method B

VIIIa, d, e, f

Na$_2$Cr$_2$O$_7$/H$_2$SO$_4$

Ia. R = C$_6$H$_5$
b. R = p-BrC$_6$H$_4$
c. R = p-NO$_2$C$_6$H$_4$

1. Br$_2$/CHCl$_3$
2. XSNaN$_3$/HOAc

Method A

IVa. R = C$_6$H$_5$
b. R = p-BrC$_6$H$_4$
c. R = p-NO$_2$C$_6$H$_4$
d. R = p-ClC$_6$H$_4$
e. R = m-NO$_2$C$_6$H$_4$
f. R = CH$_3$

NaN$_3$/HOAc

Br$_2$/CHCl$_3$

C$_6$H$_5$C—CHOC$_6$H$_5$ (O, Br)
IIa

NaN$_3$ / Acetone

C$_6$H$_5$C—CHOC$_6$H$_5$ (O, N$_3$)
IIIa

this ester to the corresponding imidyl azide (VI) by sodium azide followed by cyclization would account for the formation of IVa by a plausible reaction scheme.[10]

The oxidation of aryl-5-tetrazolylcarbinol aryl-5-tetrazolylcarbinols (VIII) with sodium dichromate in aqueous sulfuric acid provided an alternative route to IV. Thus, mandelonitrile acetate (VIIa), on

IIIa $\xrightarrow{\Delta}$ [C$_6$H$_5$C—C—OC$_6$H$_5$ (O, NH) $\xrightarrow{NaN_3}$ C$_6$H$_5$C—C—N$_3$ (O, NH)] $\longrightarrow$ IVa
   V   VI

treatment with aluminum azide in anhydrous tetrahydrofuran, affords phenyl-5-tetrazolylcarbinol (VIIIa).[11]

Oxidation of VIIIa with sodium dichromate gave 5-benzoyltetrazole (IVa) in 77% yield. This method (B) was successfully extended to the preparation of
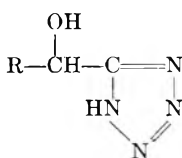
(10) Syntheses of 5-substituted tetrazoles from imino esters and sodium azide are relatively uncommon since the same transformation may be accomplished with the more readily accessible nitrile or cyanamide. However, all such reactions involve the intermediate formation of an imidyl azide which readily undergo ring closure in acetic acid, cf. F. Benson, Chem. Rev., 41, 1 (1947).

(11) H. Behringer and K. Kohl, Chem. Ber., 89, 2648 (1956) report an 80% yield for this transformation. In our hands, the yield of reasonably pure VIIIa never exceeded 50%.

TABLE II

Substituted-5-tetrazolylcarbinols

$$\begin{array}{c} OH \\ | \\ R-CH-C=N \\ \diagup \diagdown \\ HN \quad N \\ \diagdown \diagup \\ N \end{array}$$

R	M.P.	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
			Analyses					
C$_6$H$_5$	159–160^a	48	...	...	...	...	...	...
p-ClC$_6$H$_4$	188–189^b	38	45.62	3.35	26.60	45.83	3.52	27.12
m-NO$_2$C$_6$H$_4$	171–172^c	31	43.44	3.19	31.82	43.47	3.49	32.03
CH$_3$	133–134^c	39	31.57	5.30	49.10	31.72	5.37	49.57

^{a} Lit. m.p. 159. See ref. 11. ^{b} Recrystallized from a mixture of ethyl acetate and petroleum ether (65–110°). ^{c} Recrystallized from ethyl acetate.

5-(p-chlorobenzoyl)- (IVd) and 5-(m-nitrobenzoyl)-tetrazole (IVe) (Table II). Similarly the interaction of lactonitrile acetate (VIIf) and aluminum azide gave methyl-5-tetrazolylcarbinol (VIIIf), the analog of lactic acid. Oxidation of VIIIf in the usual manner provided the corresponding analog of pyruvic acid, 5-acetyltetrazole (IVi), though in relatively low yield (20%). On the other hand reagents such as potassium permanganate, manganese dioxide, and chromic anhydride all failed to accomplish this oxidation.

The 5-aroyltetrazoles are colorless acidic solids which are soluble in aqueous alkali, alkali carbonates, and bicarbonates. They dissolve in warm (60–70°) polyphosphoric acid and are recovered unchanged on dilution with water. However, they are degraded to benzoic acids (IX) by the action of hot, 70% sulfuric acid. All of the 5-aroyltetrazoles exhibit prominent absorption maxima in the region of 245 mμ – 272 mμ (cf. Table I).

The interaction of IVa and excess phenylmagnesium bromide gave diphenyl-5-tetrazolylcarbinol (X) in 64% yield. A Wolff-Kishner reduction of IVa afforded 5-benzyltetrazole (XI) in 76% yield whereas a photochemical reduction of IVa in isopropyl alcohol produced 1,2-bis(5-tetrazolyl)-1,2-diphenyl-1,2-ethanediol (XII) in 70% yield. The correctness of structure XII is indicated by elementary analysis and infrared data (no carbonyl absorption, strong hydroxyl absorption at 2.93μ and 3.03μ).

The principal product of a Schmidt reaction on IVd in polyphosphoric acid proved to be 5-tetrazolecarbox(p-chloroanilide) (XIIIb). The course and extent of migration was established from the observation that hydrolysis of the crude reaction product with concentrated hydrochloric acid followed by acetylation gave p-chloroacetanilide in 75% yield. The reaction mixture yielded, in addition, a small quantity (ca. 7%) of p-chlorobenzoic acid which might be attributed to the migration of the 5-tetrazolyl group. However, in view of the

ease with which IVd is degraded by mineral acid it is highly probable that the formation of IX stems from the presence of unreacted IVd in the crude amide.
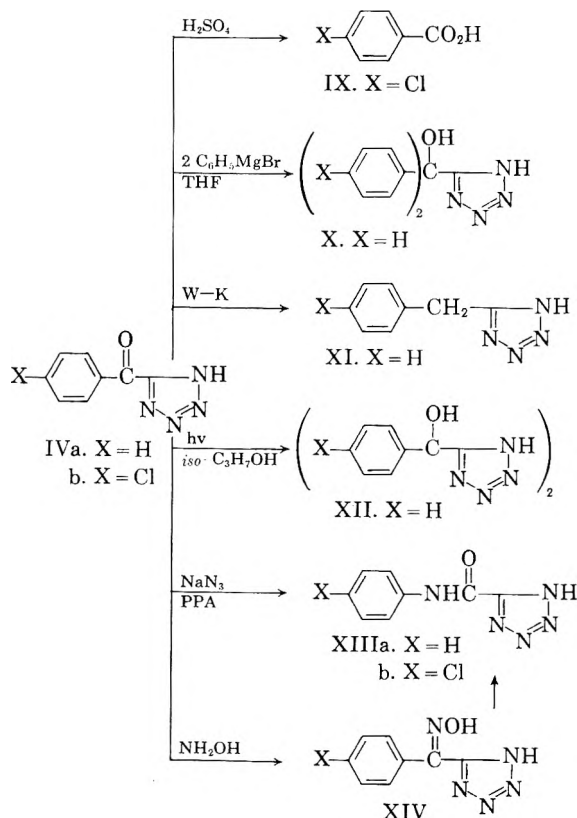
A Schmidt reaction on IVa was observed to pursue a similar course. Thus, successive hydrolysis and acetylation of the initial reaction product gave acetanilide in 66% yield. However, no benzoic acid was detected in this case. Moreover, recrystallization of the crude reaction product in a subsequent experiment gave 5-tetrazolecarboxanilide (XIIIa) in 51% yield.

The oximation of IVa yielded a single isomer (XIV) which was subjected to a Beckmann rearrangement. The product, obtained in 50% yield, was identical with XIIIa. Apparently, the more stable of the two possible oximes is that in which the hydroxyl group is *syn* to the tetrazole ring.

A more efficacious route to 5-acetyltetrazole (IVf) and its homologs is currently under investigation. Accordingly, a discussion of the properties of IVf is deferred until a broader spectrum of 5-acyltetrazoles has been examined. However, it seems pertinent to report at this time that methyl-5-tetrazolyl-carbinol (VIIIf) is an acceptable substrate for lactic dehydrogenase, as determined by histochemical methods.

EXPERIMENTAL[12]

Phenoxyacetophenones (I). The procedure used for the preparation of Ia is that described by Yates *et al.*[13] The extension of this method to the synthesis of Ib and c required only the substitution of benzene for ether as the solvent.

α-Phenoxy-4-bromoacetophenone (Ib). Off-white plates from methanol (50% yield), m.p. 92–93°.

Anal. Calcd. for $C_{14}H_{11}O_2Br$: C, 57.75; H, 3.81; Br, 27.45. Found: C, 57.80; H, 3.82; Br, 27.48.

α-Phenoxy-4-nitroacetophenone (Ic). Yellow plates from 95% ethanol (35% yield), m.p. 114–115°.

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.45. Found: C, 65.48; H, 4.44; N, 5.49.

α-Bromo-α-phenoxyacetophenones (II). The bromoethers were prepared according to the method of Knott.[8] In accord with the prior report, it was observed that IIa, m.p. 68–70° (lit. m.p. 72°), is an unstable solid and recrystallization leads to a considerable loss of product. Therefore, upon completion of the bromination of Ib and c in chloroform, the solvent was removed under reduced pressure and the residue, IIb or IIc, was used directly in the synthesis of the ketone (IV) (*vide infra*).

α-Azido-α-phenoxyacetophenone (IIIa). To a solution of 5.8 g. of IIa (0.02 mole) in 40 ml. of acetone diluted with 15 ml. of water was added 1.3 g. of sodium azide (0.02 mole) and the mixture heated to boiling and held at this temperature for 3 min. The clear solution was quickly cooled to room temperature and poured on ice. The product was collected and recrystallized from aqueous ethanol to give 3.3 g. of a white solid, m.p. 79–81°. An additional 0.7 g. of material, m.p. 75–80°, was deposited from the filtrate on standing; total yield 80%. Two recrystallizations from 95% ethanol provided an analytical sample in the form of white needles, m.p. 83–84°.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.51; H, 4.35; N, 16.71.

5-Aroyltetrazoles (IV) *Method A.* The conversion of Ib to 5-(p-bromobenzoyl)-tetrazole (IVb) without isolation of the corresponding intermediates, IIb and IIIb, is presented as an example typical of the method. To a solution of 8.7 g. of Ib (0.03 mole) in 40 ml. of chloroform, cooled to 0° by an external salt-ice mixture, was added, dropwise with stirring, a solution of 5.3 g. of bromine (0.033 mole) in 12 ml. of chloroform. The temperature of the reaction mixture was maintained at 5–8° during the course of bromination. The solvent was next removed *in vacuo* and the residue dissolved in 50 ml. of glacial acetic acid to which 6.0 g. of sodium azide (0.092 mole) was added. The mixture was slowly brought to reflux and maintained at this temperature for 1.5 hr. The inorganic salts were removed by filtration, and the filtrate was evaporated in a stream of air to a thick paste. To this dark residue was added 50 ml. of water, followed by sufficient 10% sodium hydroxide to render the oily mixture alkaline. The tarry alkali-insoluble material was removed by filtration through Celite and the filtrate acidified with concentrated hydrochloric acid. The mixture was then placed in a refrigerator for 24 hr. and the product collected, wt. 3.8 g. (50% yield), m.p. 167–171°. Two recrystallizations from a mixture of benzene and ethyl acetate gave colorless plates, m.p. 176–177° (*cf.* Table I for analysis).

Alternate synthesis of IVa from IIIa. A solution of 2.5 g. of IIIa (0.01 mole) in 25 ml. of glacial acetic acid, containing 2.5 g. of sodium azide (0.039 mole) was carefully brought to boiling and then gently refluxed for 2 hr. Using the same procedure described above for the isolation of IVb, there was obtained 1.0 g. (58% yield) of 5-benzoyltetrazole, m.p. 138–140°. A single recrystallization from benzene gave white plates, m.p. 140–141°.

Mandelonitrile acetates (VIId and e). Of the α-acetoxy-propionitriles employed in this work, only VIId and e, to our knowledge, have not, previously, been described.

To a cold solution of 42.3 g. of p-chlorobenzaldehyde (0.3 mole) in 150 ml. of glacial acetic acid was added, with stirring and intermittent cooling to maintain a temperature of approximately 25° C., 27.3 g. of potassium cyanide. The solution was, then, treated with 66.0 g. of acetic anhydride (0.65 mole) and the mixture heated to 60° with stirring for 0.5 hr. The dark solution was poured on ice and the resulting oil extracted with ether. The extract was washed successively with a saturated solution of sodium bicarbonate and water, then dried over magnesium sulfate. Distillation gave 49.0 g. (78%) yield of product, b.p. 104–107°/0.5 mm (m.p. 31–32°). Redistillation gave a water-white product, b.p. 121–122°/0.6 mm.

Anal. Calcd. for $C_{10}H_8NClO_2$: C, 57.29; H, 3.86. Found: C, 57.49; H, 3.98.

The same procedure applied to m-nitrobenzaldehyde affords a solid product when the reaction mixture is poured on ice. The crude material was dissolved in 95% ethanol, treated with Norit, and on cooling, VIIIe was deposited in the form of white needles, yield 82%, m.p. 75–76°.

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66. Found: C, 54.47; H, 3.64.

Methyl- and aryl-5-tetrazolylcarbinols (VIII). The procedure described by Behringer and Kohl[11] for the preparation of VIIIa from mandelonitrile acetate was extended to the present study. The conversion of VIId to VIIId is presented as a typical example of this transformation.

A solution of 13.5 g. of anhydrous aluminum chloride in 150 ml. of dry tetrahydrofuran was added, all at once, to a suspension of 19.5 g. of sodium azide (0.3 mole) in 50 ml. of tetrahydrofuran. The mixture was stirred at room temperature for 1 hr., then, a solution of 21.0 g. of p-chloromandelonitrile acetate (0.1 mole) in 50 ml. of tetrahydrofuran was introduced, and the yellow suspension stirred under gentle reflux for 20 hr. The reaction vessel was cooled externally with an ice-salt bath, acidified with 75 ml. of 6N hydrochloric acid, and, then, evaporated to dryness *in vacuo*. The dry residue was triturated with three-250 ml. portions of hot acetone and the filtered extract evaporated to dryness *in vacuo*. The light tan residue crystallized from a mixture of ethyl acetate and petroleum ether (65–110°), wt. 8.0 g. (38% yield), m.p. 183–188°. Two recrystallizations from this same solvent provided an analytical sample, m.p. 188–189°.

5-Aroyltetrazoles IV. *Method B.* The oxidation of VIII was effected in each case with a solution of sodium dichromate in dilute sulfuric acid. The conversion of VIIIa to IVa is considered typical. A suspension of 9.0 g. of finely divided VIIIa (0.05 mole) in 55 ml. of 2N sulfuric acid containing 9.0 g. of sodium dichromate dihydrate (0.03 mole) was carefully heated to 80–85° with vigorous stirring and held at this

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(12) All melting points are uncorrected. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(13) P. Yates, D. G. Farnum, and G. H. Stout, *J. Am. Chem. Soc.*, **80**, 196 (1956).

temperature for 0.5 hr. The reaction mixture was cooled, the product was collected and crystallized from benzene, wt. 6.5 g. (77% yield), m.p. 137–138°, alone or when admixed with a sample of IVa prepared by Method A.

5-Acetyltetrazole (IVf). To a solution of 4.5 g. of sodium dichromate dihydrate (0.015 mole) in 27 ml. of 3N sulfuric acid was added 5.0 g. of the carbinol (VIIIf) (0.044 mole). The mixture was vigorously stirred while the temperature was carefully raised to 75–80° and maintained for 0.5 hr. The solution was evaporated to dryness *in vacuo* and the residue triturated with three 50-ml. portions of hot acetone. Evaporation of the acetone left a colorless sirup which was subjected to vacuum sublimation. The sublimate was recrystallized from a mixture of ether–petroleum ether (60–110°) to give 1.0 g. (20% yield) of product in the form of small white needles, m.p. 89–90°.

Anal. Calcd. for $C_3H_4N_4O$: C, 32.14; H, 3.60; N, 50.00. Found: C, 32.25; H, 3.67; N, 50.64.

Acid degradation of IVd. A solution of 250 mg. of IVd (1.2 mmoles) was suspended in 10 ml. of 70% sulfuric acid and the mixture refluxed for 0.5 hr. The cooled solution was diluted with 30 ml. of water, extracted with ether, and the extract dried over magnesium sulfate. Evaporation of the ether left a residue which crystallized from aqueous ethanol, wt. 160 mg. (85% yield), m.p. 240–241° alone or when admixed with an authentic sample of *p*-chlorobenzoic acid.

Diphenyl-5-tetrazoylcarbinol (X). A solution of 7.5 g. of IVa (0.043 mole) in 50 ml. of dry tetrahydrofuran was added, dropwise with stirring, to a solution of phenylmagnesium bromide, prepared from 33.8 g. of bromobenzene (0.22 mole) and 5.3 g. of magnesium (0.22 g. atom) in 200 ml. of anhydrous ether. The reaction mixture was stirred under reflux for 1 hr. and, then, poured on a mixture of ice and sulfuric acid. The ether phase was drawn off and the aqueous layer extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, then, concentrated to a crystalline mass under reduced pressure. Crystallization from a mixture of ether–petroleum ether (65–110°) gave 7.0 g. (64% yield) of product, in the form of colorless needles, m.p. 172–174° dec.

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.80; N, 22.21. Found: C, 66.83; H, 5.14; N, 22.78.

5-Benzyltetrazole (XI). A solution of 3.48 g. of IVa (0.02 mole) in 50 ml. of diethylene glycol containing 1.68 g. of potassium hydroxide (0.03 mol.) and 5 ml. of 85% hydrazine hydrate was refluxed for 2 hr., the water being removed by a take-off condenser. The reflux period was continued until the evolution of nitrogen subsided (ca. 1.5). The glycol was removed *in vacuo*, the residue dissolved in water and acidified with concentrated hydrochloric acid. The reaction mixture was chilled and the product collected, wt. 2.12 g., m.p. 122–124°. A second crop, wt. 0.35 g., m.p. 122–123°, was deposited from the filtrate on standing. The combined solids, amounting to 2.47 g. (76% yield), were crystallized from benzene to give colorless needles, m.p. 125–126° (lit.[14] 125.5–126°).

1,2-Bis(5-tetrazolyl)-1,2-diphenyl-1,2-ethanediol (XII). A solution of 3.48 g. of IVa (0.02 mole) in 200 ml. of isopropyl alcohol, contained in a quartz flask, was placed in a window of the laboratory. After two weeks the solid, which began to appear after the third day, was collected, wt. 1.5 g., m.p. 181–182° dec. The filtrate was returned to the window for a total elapsed time of 30 days and a second crop of material, wt. 1.0 g., m.p. 181–182° dec., was obtained; total yield 2.5 g. (71%).

(14) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

Anal. Calcd. for $C_{16}H_{14}N_8O_2$: C, 54.85; H, 4.03; N, 31.99. Found: C, 54.65; H, 4.02; N, 31.99.

5-Tetrazolecarboxanilide (XIIIa). To a suspension of 1.80 g. of IVa (0.01 mol.) in 25 g. of polyphosphoric acid was added, all at once, 2.0 g. of sodium azide (0.03 mol.) and the mixture heated to 55–60° for 2.5 hr. The semisolid mass was diluted with a mixture of ice and water and the solid collected. The crude product was twice recrystallized from aqueous ethanol to give 1.0 g. (51% yield) of anilide in the form of pale yellow needles, m.p. 219–220° dec. The product was dissolved in 10% sodium hydroxide, treated with Norit and reprecipitated by the addition of concentrated hydrochloric acid. The solid was collected and recrystallized from aqueous ethanol to give colorless needles, m.p. 220–221° dec.

Anal. Calcd. for $C_8H_7N_5O$: C, 50.79; H, 3.73; N, 37.02. Found: C, 50.96; H, 3.95; N, 36.70.

A sample of the crude amide (0.7 g.), obtained according to the procedure described above was refluxed for 1 hr. with 20 ml. of 70% sulfuric acid. The solution was extracted with three portions of ether. No solid remained on evaporation of the dried extract. The aqueous phase was made alkaline with 50% sodium hydroxide and extracted with three portions of benzene. Evaporation of the dried extract left an oily residue which was suspended in 10% sodium hydroxide and treated with 1.0 ml. of acetic anhydride. The mixture was chilled and the product collected, wt. 0.33 g. (2.45 mmoles), m.p. 110–112°, alone or when admixed with acetanilide. The crude reaction product, therefore, contained, at least, 66% XIIIa.

Beckmann rearrangement of 5-benzoyltetrazole oxime (XIV). The preparation of the oxime (87% yield, m.p. 219–220°) was carried out in the usual way.

Anal. Calcd. for $C_8H_7N_5O$: C, 50.78; H, 3.73; N, 37.02. Found: C, 50.80; H, 3.98; N, 37.59.

A mixture of 700 mg. of the oxime (3.7 mmoles) in polyphosphoric acid, prepared from 20 g. of phosphorus pentoxide and 12 ml. of 85% *ortho* phosphoric acid, was heated at 100° for 4 hr. Ice was then added to the cooled mixture and the product collected. The filter cake was dissolved in aqueous sodium carbonate, treated with Norit, and the filtrate was acidified. The product was collected, wt. 250 mg., m.p. 214–216°. The filtrate was extracted with three portions of chloroform and the dried extract was evaporated to dryness *in vacuo* to give an additional 110 mg. of product (total yield 51%), m.p. 215–216°. A mixed melting point with the product of the Schmidt reaction showed no depression.

Schmidt reaction on IVd. To a suspension of 2.09 g. of ketone (IVd) (0.01 mol.) in 25 g. of polyphosphoric was added, portionwise over a period of 6 hr., 2.0 g. of sodium azide (3.01 mmoles) at a temperature of 55–60°. The mixture was diluted with ice and the product collected, wt. 1.93 g. The crude amide (1.93 g.) was suspended in 100 ml. of concentrated hydrochloric acid and the mixture refluxed for 24 hr. A solid was deposited, on cooling, which was combined with a small amount of material which had sublimed into the condenser, wt. 180 mg., m.p. 230–240° (with sublimation). Two recrystallizations from aqueous alcohol gave shiny plates, m.p. 240–241° which failed to depress the melting point of *p*-chlorobenzoic acid.

The original acid filtrate was evaporated to dryness, the residue made alkaline with 10% sodium hydroxide and treated with 3 ml. of acetic anhydride. The solid was collected and sucked dry, wt. 1.16 g., m.p. 174–177° (lit., *p*-chloroacetanilide, 176–177°). Accordingly, it is concluded that the crude product of rearrangement contains at least 75% 5-tetrazolecarbox(*p*-chloroanilide) (XIIIb).

Oxygen Heterocycles. A New Isoflavanone from *Sophora japonica*, L.

HIROSHI SUGINOME

From *Sophora japonica*, L. there has been isolated a new isoflavanone, $C_{16}H_{12}O_6$, which has been named sophorol. By spectroscopic and degradative experiments it was shown that sophorol is either 2′,7-dihydroxy-4′,5′-methylenedioxyisoflavanone or 2′,7-dihydroxy-5′,6′-isoflavanone. The former is preferred on the basis of phytochemical ground. Attention is called to the structural similarity with known naturally occurring isoflavanone, ferreirin, and homoferreirin. Sophorol is unique in that it is first example of optically active isoflavanone.

Since the structure of chrysin was elucidated by Kostanecki in 1893 numerous flavone and isoflavone coloring matters in various oxidation states have been found in nature.[1] It is, however, only recently that some simple isoflavanones have been discovered in the vegetable kingdom. Padmakstein[2] from *Prunus puddum* and ferreirin as well as homoferreirin[3] from *Ferreirea spectabilis* are first examples of isoflavanone.

In the present studies examination of the coloring principle of the heartwood of *Sophora japonica*, L.[4] led to the isolation of a new phenolic ketone. The writer wishes now to record that this compound is a new member of this class. It was obtained in pale yellow needles approximately in 0.02–0.5% yields from dry heartwood by ethanol extraction, followed by petroleum ether treatment. In reference to the source of this new compound, the name "sophorol" is suggested for this phenolic ketone.

Analyses of sophorol and molecular weight determination of its *O*-dimethyl derivative agree most closely with the molecular formula $C_{16}H_{12}O_6$. It is optically active, giving a value of $[\alpha]_D^{15}$ 9.5

in dry acetone and $[\alpha]_D^{16}$ −13.6 in absolute ethanol. The phenolic character of sophorol was suggested by its solubility in aqueous sodium carbonate and hydroxide and insolubility in aqueous sodium hydrogen carbonate, to yield yellow orange solutions. Alcoholic solution of sophorol gives no color with ferric chloride.[6] The presence of two phenolic hydroxyl groups was shown by the preparation of the *O*-dimethyl ether with methyl iodide–potassium carbonate in acetone or methylsulfate-caustic alkali. The same ether was also produced with ethereal diazomethane. On acetylation under various conditions sophorol gave an uncrystallizable product. On the other hand, sophorol oxime readily afforded a crystalline triacetate. Thus, it might be inferred that acetylation of sophorol was accompanied, in addition to the acetylation, by a side reaction in which carbonyl group participated (*vide infra*.) Indication of a reactive carbonyl group in sophorol was afforded by the formation of an oxime. *O*-dimethylsophorol also forms an oxime and 2,4,-dinitrophenylhydrazone. By the positive color tests[7] for a methylenedioxyl group the indication for two further oxygen atoms was added. Beroza's modified procedure[8] of a spectrophotometric method[9] for the determination of combined formaldehyde with chromotropic-sulfuric acids gave 0.58 and 0.63 mole of combined formaldehyde for the sophorol and *O*-dimethylsophorol respectively, showing the presence of one methylenedioxyl group.[10] Above mentioned methylenedioxyl

1) (a) F. Mayer and A. H. Cook, *The Chemistry of Natural Coloring Matters*, Reinhold, 2nd Printing, New York, 1947.

(b) T. R. Seshadri, *Annual Review of Biochemistry*, **20**, 487 (1951).

(c) H. Erdtman, *Progress in Organic Chemistry*, Butterworths, London, 1952, J. W. Cook, ed., Vol. I, pp. 31, 37.

(d) T. A. Geissman and Hinreiner, *Botan. Rev.*, **18**, 77 (1952).

(e) W. K. Warburton, *Quart. Revs.*, **8**, 67 (1954).

(2) N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 202 (1952).

(3) F. E. King and K. G. Neill, *J. Chem. Soc.* 4752 (1952).

(4) Order Leguminocea. *Sophora japonica*, L. is chiefly known by the existence of many anthoxanthins[5] in its flower buds and fruits. Its heartwood has a dark brown appearance.

(5) Ref. (2) (b) pp. 183, 188, 196. Also see J. F. Couch, J. Naghiski, and C. F. Krewson, *J. Am. Chem. Soc.*, **74**, 424 (1952), (for Rutin); J. Rabate, *Bull. soc. chim. biol.*, **22**, 565 (1940). K. Freudenberg, H. Knauber, and F. Cramer, *Ber.*, **84**, 44 (1951), (for Sophoraflavonoloside); G. Zemplen, R. Bognar, *Chem. & Ind. (London)*, 518 (1954), (for Sophoricoside); G. Zemplen and R. Bognar, *Ber.*, **75**, 482 (1942); R. Bognar, *Magyar Kem. Lapja*, **4**, 519 (1949), *Chem. Abstr.* 8104 (1952), (for Sophorabioside).

(6) It has been observed that in general 6.7. or 4′ hydroxyls in flavones are lacking in a ferric chloride color reaction. L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3136 (1951).

(7) A. Labat, *Bull. soc. chim. France*, **5**, 745 (1909); K. Weber and B. Tollens, *Ann.*, **299**, 318 (1898); G. O. Gaebel, *Arch. Pharm.*, **248**, 225 (1910).

(8) M. Beroza, *Anal. Chem.*, **26**, 1970 (1954).

(9) C. E. Bricker and H. R. Johnson, *Ind. Eng. Chem. Anal. Ed.*, **17**, 400 (1945).

(10) Beroza has shown that pinoresinol acetate which contained no methylenedioxyl groups gave 0.79 equiv. of formaldehyde, probably being due to the formation of primary alcohol groups which upon hydrolytic scission produce formaldehyde (see Ref. 8). However, in present experiments it was verified that the γ-pyranone nucleus in the isoflavanone gives no noticeable formaldehyde, under Beroza's condition, using 7,2′,4′-trimethoxyisoflavanone.
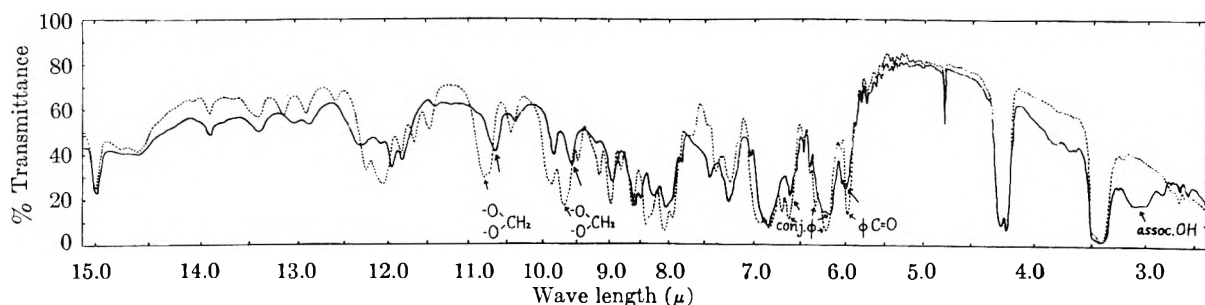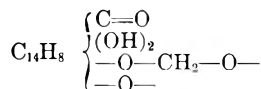
Fig. 1. Infrared spectra of sophorol (———) and O-dimethylsophorol (———); Nujol paste

group was also detected by infrared spectra. According to L. H. Briggs *et al.*,[11] —C—O—C—O—C— group attached to the aromatic ring exhibits 12 major bands associated with this group. Among them, particularly those within the range from 1047 to 1025 cm.$^{-1}$ and from 938 to 919 cm.$^{-1}$ are diagnostic for the methylenedioxy group.

The spectra of sophorol, O-dimethylsophorol and its hydrolyzed product (VII) show the corresponding strong bands for the methylenedioxyl group in 1044 (sophorol) 1032 (O-dimethyl) 1032 (hydrolyzed product VII) 939 (sophorol) 925 (O-dimethyl) 929 cm.$^{-1}$ (hydrolyzed product VII). Thus, the one remaining inert oxygen atom is probably present in the ether system. On the basis of above evidences the functional groups of sophorol can be symbolized as follows.

$$C_{14}H_8 \begin{cases} C=O \\ (OH)_2 \\ -O-CH_2-O- \\ -O- \end{cases}$$

Infrared[12] *and ultraviolet spectra.* The infrared spectra of sophorol and O-dimethylsophorol in Nujol mull are shown in Fig. 1.

The maxima are as follows (cm.$^{-1}$): (a) Sophorol 3333∼3195 (associated phenolic hydroxyl) 1661 (carbonyl conjugated with phenyl) 1618, 1575, 1508 (conjugated phenyl) 1340, 1239, 1163, 1116, 1044, 1015, 948, 843, 675.

(b) O-dimethylsophorol (cm.$^{-1}$): 1672, 1575, (CO—C = C— in a six membered ring) 1603, 1506 (conjugated phenyl) 1353, 1258, 1236, 1190, 1160, 1114, 1092, 1044, 1032, 1013, 966, 927, 836, 822, 675.

The absence of absorption near 3 μ in O-dimethylsophorol shows the lack of any alcoholic hydroxyl in sophorol.

The examination of the ultraviolet absorption spectra of sophorol and O-dimethylsophorol in ethanol and aqueous caustic solution gave valuable information. The absorption curves are shown in Fig. 2.

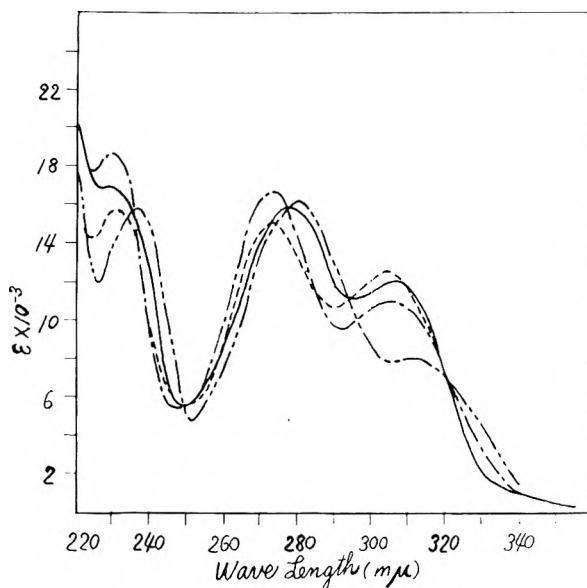It was found that the spectra of these two compounds were strikingly similar to those of 7-

Fig. 2. Ultraviolet spectra of sophorol (———), O-dimethylsophorol (—·—·—), 2',7-dimethoxy-3',4'-methylenedioxyisoflavanone (– – – –), and 7'-hydroxy-3',4'-methylenedioxyflavanone (—··—··—); solvent ethanol

hydroxy (methoxy) 2- or 3-phenyl chromanone derivatives.[13,14] Furthermore, the ultraviolet absorption spectrum of sophorol showed a marked red shift in aqueous 0.1N sodium hydroxide solution (Fig. 3). These characteristic spectral properties are those[15] of resacetphenone chromophore, as exactly to be shown in Fig. 3.

Consequently it seemed reasonably certain that sophorol contains a partial formula (I).
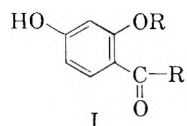
I

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(11) L. H. Briggs, L. D. Colebrook, H. M. Fales, and W. C. Wildman, *Anal. Chem.*, **29**, 904 (1957).

(12) The writer is indebted to Mr. A. Fujino and Mr. M. Yamaguchi of Osaka City University for these spectra.

(13) B. Skarzynski, *Biochem. Zeit.*, **301**, 150 (1939). The ultraviolet spectra of 7-hydroxyisoflavanone and specimen of 7-hydroxy-3',4'-methylenedioxyflavanone were kindly supplied by Dr. S. Hishida and Dr. N. Inoue of Tohoku University.

(14) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 871 (1953).

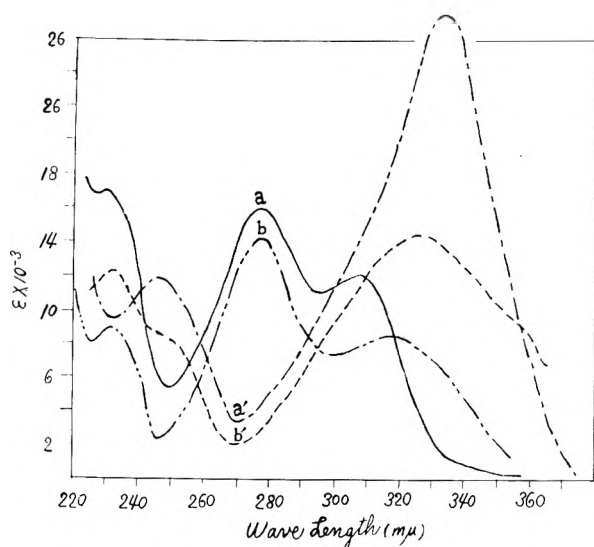(15) R. A. Morton and Z. Sawires, *J. Chem. Soc.*, 1052 (1940).

Fig. 3. Ultraviolet spectra: (a) sophorol. (b) resaceto-phenone (solvent ethanol). (a') sophorol (solvent 0.12N aqueous NaOH). (b') resacetophenone (solvent 0.1N aqueous NaOH).

On the basis of above spectroscopic and analytical proof isoflavanone or flavanone structure for sophorol may be reasonably considered. In consistency with these facts sophorol contains no aliphatic double bonds since O-dimethylsophorol resists oxidation by potassium permanganate in acetone even when heated to boiling for several hours.

It is well known that flavones, flavonols, flavanones, 3-methoxyflavones, and isoflavones each show the characteristic color reactions,[16,31] by sodium amalgam or magnesium-hydrochloric reduction. Further, it has been shown that isoflavanone ferreirin also gave characteristic color on reduction by sodium amalgam.[3] Although sophorol did not give the characteristic color by sodium amalgam reduction, O-dimethylsophorol afforded a feeble pink color by treatment with same reagent. The Wilson boric acid test[17] for both compounds gives no color reaction. These color reactions suggest that sophorol is an isoflavanone, but not a flavanone.

The simplest method of differentiation between an isoflavanone (II) and flavanone (III) is the examination of the products of mild alkaline degradation, since the former furnishes an O-hydroxydesoxybenzoin (IV)[3] with loss of carbon probably as formaldehyde, while a flavanone leads to an O-hydroxychalcone (V).[18]
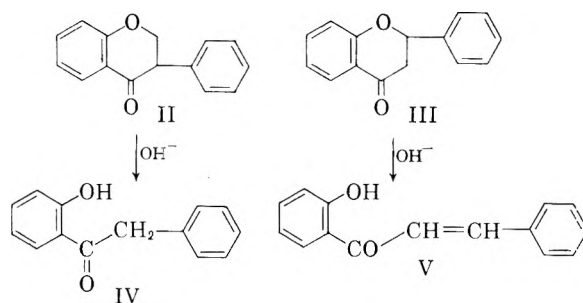
The schema of degradation concerning sophorol and O-dimethylsophorol is revealed to be as indicated in VII–IX.
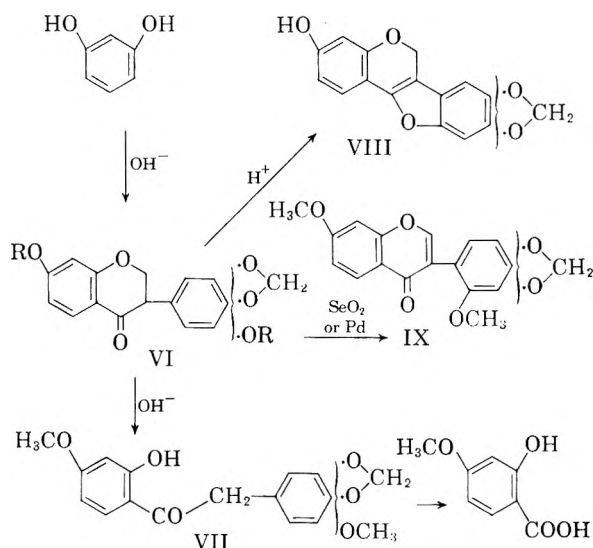
On being fused with alkali in a nitrogen atmosphere, dimethylsophorol undergoes extensive degradation of the molecule and gives rise to resorcinol which fact is presumably due to the part structure (I). With prolonged treatment by hot 20% alcoholic potassium hydroxide in a nitrogen stream, O-dimethylsophorol yielded a saturated phenolic ketone $C_{17}H_{16}O_6$ (VII) which was isolated from neutral fraction as sole product. This compound exhibited an intense ferric reaction in alcohol and still kept two methoxyl groups as well as a positive methylenedioxyl color test. The ketone was evidently stable to the further action of alcoholic caustic potash. The ultraviolet absorption curve of this ketone closely resembles that of O-dimethylsophorol and it is clear that the main chromophoric system of the latter is unaffected by the alkaline degradation (Fig. 4).

This ketone gives a green color with nitric acid. This is property of certain hydroxyacetophenone derivatives and its methyl ethers.[19] The Zimmermann test[20] for active methylene and Weygand

(16) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 2157 (1949). Wolfrom, Benton, Gregory, Hess, Mohan, and Morgan, *J. Am. Chem. Soc.*, 61, 2832 (1939). M. Shimizu, *J. pharm. chem. Japan*, 1329 (1951).

(17) C. W. Wilson, *J. Am. Chem. Soc.*, 61, 2303 (1939).

(18) S. Fujise, *J. Chem. Soc. Japan.*, 497 (1929).

(19) Rao and Seshadri, *Proc. Ind. Acad. Sci.*, A 30, 30 (1949).

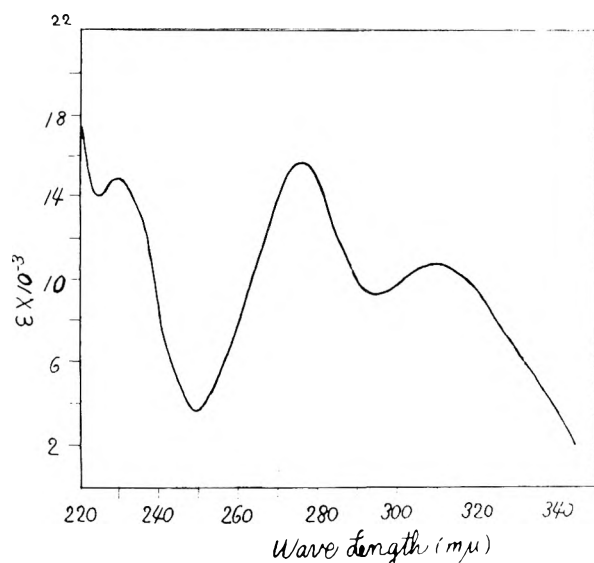(20) W. Zimmermann, *Zeit. physiol. chem.*, 233, 257 (1935).

Fig. 4. Ultraviolet spectrum of hydrolyzed product (VII) of O-dimethylsophorol; solvent ethanol

test[21] for endiol also were positive. Further, this ketone formed the precipitation of 2,4-dinitrophenylhydrazone and showed a strong infrared band, being due to a hydrogen-bonded carbonyl of O-hydroxyacetophenone,[22] at 1639 cm.$^{-1}$ (Fig. 5).

this desoxybenzoin derivative from the alkaline degradation product, flavanone structure for sophorol was excluded entirely and parent O-dimethylsophorol and sophorol are formulated as in (VI) R = CH_3, R = H, respectively.

Attempts to clarify the relative positions of the substituents in the side phenyl group of above ketone (VII), by oxidation with permanganate under various conditions were unsuccessful. Thus, the oxidation of this ketone with aqueous permanganate in boiling acetone gave only a phenolic acid as the product. It was identified as 4-methoxysalicylic acid by comparison with authentic specimen, thus only confirming the presence of the chromophoric group (I) in the molecule.

When treated with boiling diluted sulfuric acid for 2 hours sophorol was converted to form a compound which is designated "anhydrosophorol" and was indifferent to carbonyl reagents. The lack of carbonyl group in this substance was confirmed by the disappearance of infrared absorption band at 1661 cm.$^{-1}$ in original material. Analytical data are in agreement with a molecular formula $C_{16}H_{10}O_5$, showing the elimination of one molecule of water. The ultraviolet absorption spectrum of anhydrosophorol in ethanol is markedly different from that of sophorol. The change of the spectra of
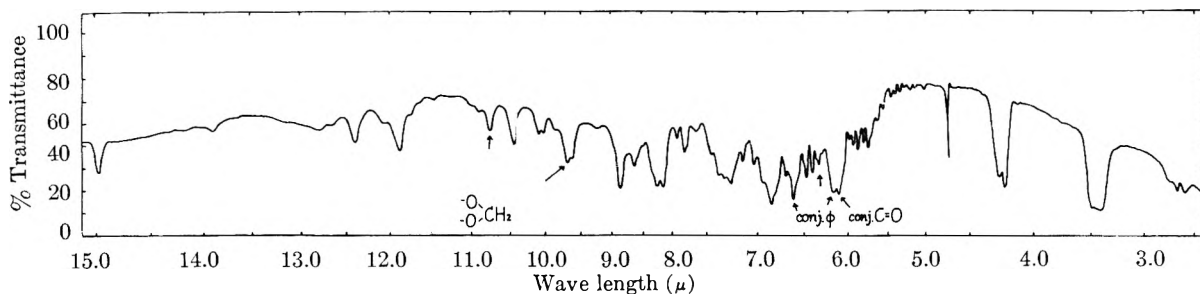

Fig. 5. The infrared spectrum of hydrolyzed product (VII) of O-dimethylsophorol; Nujol paste

These facts may be explained by giving partial formula (VII) for this ketone.[23] By the isolation of

(21) F. Weygand and E. Csendes, Ber. 85, 45 (1952).

(22) H. L. Hergert and E. F. Kurth, J. Amer. Chem. Soc., 76, 1622 (1953).

(23) In early degradative experiments, somewhat impure material was submitted to alkaline degradation. In this case the ketone $C_{17}H_{16}O_5$ was isolated in place of ketone $C_{17}H_{16}O_5$, and the former was identified as 2',4',4-trimethoxy-2-hydroxydesoxybenzoin. This result led to the suspicion that the dimethylsophorol might be identical with 2',4',7-trimethoxyisoflavanone which had already been derived in optically active form from homopetrocarpin, one of the minor constituents of Pterocarpus santalinus, by Robertson, (see Ref. 31). Thus, the DL-2',4',4-trimethoxyisoflavanone was synthesized through the catalytic hydrogenation of the corresponding isoflavone with Adams' catalyst; it showed the melting point 128° ∼ 131°. The melting point of O-dimethylsophorol was depressed by mixing with a synthetic product. Therefore, 2',4',7-trimethoxyisoflavanone formula for the dimethylsophorol was excluded. By above mentioned results, though it might be supposed that the above isoflavanone existed in crude sophorol, unfortunately attempts for isolation of this substance were unsuccessful.

sophorol into anhydrosophorol is similar to that observed on the conversion of rotenone into the corresponding enol acetate.[24] (Fig. 6).

Similar example is found in the change of spectra of isoflavanone to isoflav-3-en[14] (Fig. 7). Consequently, it is probable that the change of spectrum which occurred with dehydration of sophorol is due to acid-catalyzed cyclodehydration giving a coumarone ring system. In fact, the disappearance of carbonyl band in infrared spectrum of anhydrosophorol will support the above conversion. It is therefore almost certain that phenolic hydroxyl in the side phenyl nucleus of sophorol occupies position 2'. Apparently similar examples of this reaction have been recorded by Spetz[25] and Laforge,[26] who found that 2'-hydroxydesoxybenzoins were

(24) R. S. Cahn, R. F. Phipers, and J. J. Boam, J. Chem. Soc., 513, 734 (1938).

(25) Åke Spetz, Acta. Chem. Scand., 10, 1422 (1956).
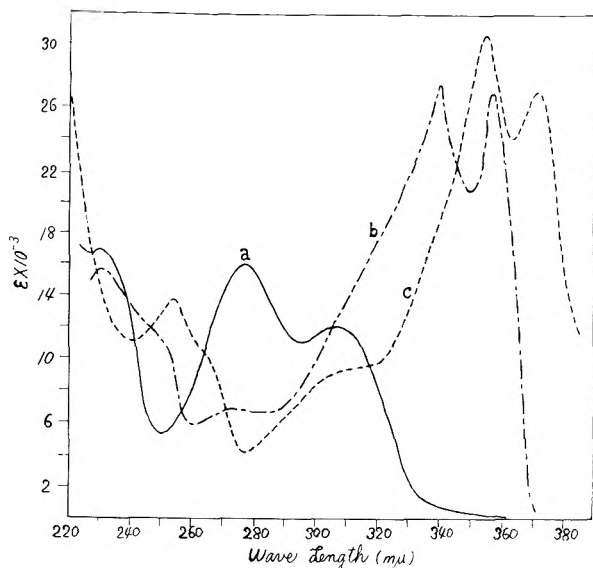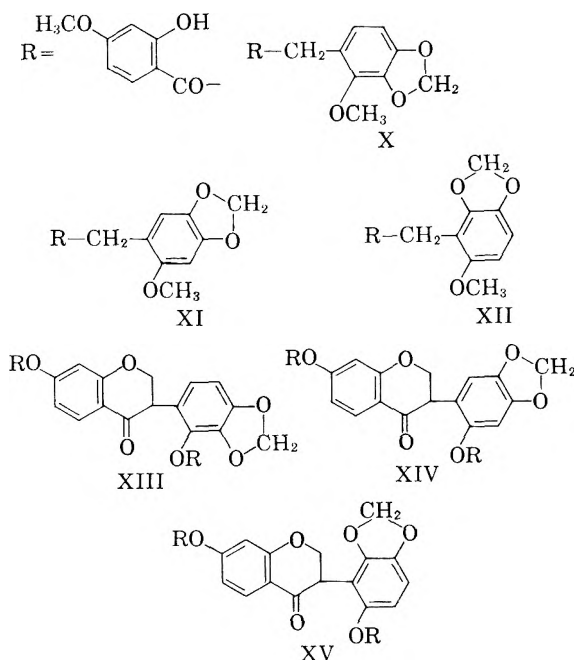
(26) F. B. Laforge, J. Am. Chem. Soc., 55, 3040 (1933).

Fig. 6. Ultraviolet spectra of sophorol (curve a), anhydrosophorol (VIII) (curve b), and acetylrotenone (curve c); solvent ethanol
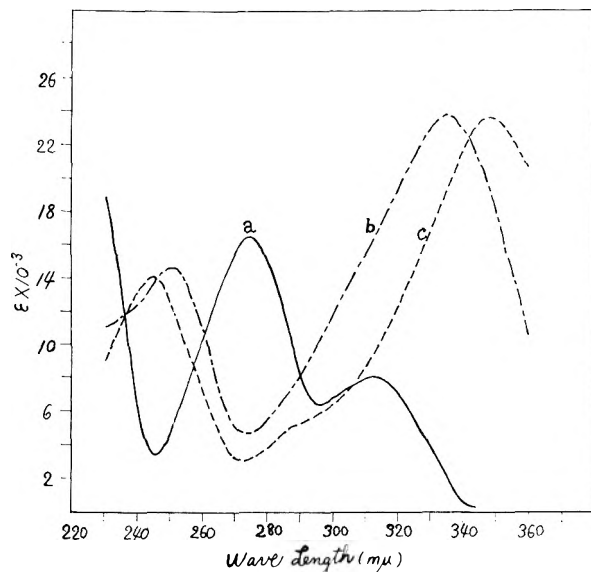

Fig. 7. Ultraviolet spectra of 4',7-dimethoxyisoflavanone (curve a), 4',7-dimethoxyisoflav-3-en (curve b), and 7-methoxy-3-p-methoxyphenylcoumarin (curve c) (from a paper of R. B. Bradbury and D. E. White)

readily dehydrated to the corresponding coumarones when treated with strong acids. On the basis of these results three formulas (X), (XI), (XII), and (XIII), (XIV), (XV), may be considered for a ketone (VII) and the parent dimethylsophorol respectively.

The isoflavone which corresponds to formula (XIII) has already been synthesized by Robertson and Whalley in the course of the elucidation of the structure of pterocarpin.[27] Furthermore, the active

form of the corresponding isoflavanone has been derived from pterocarpin by hydrogenolysis followed by methylation of hydroxyl and oxidation[28] (ultraviolet spectrum, Fig. 2). Thus, the conversion of O-dimethylsophorol to the corresponding isoflavone was attempted. When O-dimethylsophorol was treated with palladized charcoal and cinnamic acid as hydrogen acceptor[29] at about 200° in nitrogen stream, a new ketone, $C_{18}H_{14}O_6$, (IX) was obtained. The same substance was obtained also by selenium dioxide oxidation[30] in amyl alcohol. The isoflavone structure of the new ketone was evident from the appearance of a red color upon reduction with sodium amalgam followed by acidification. The same color reaction was not shown with magnesium and HCl.[31] Further, the new ketone had melting point 203-5°, being very similar to that of synthetic 2', 7-dimethoxy-3', 4'-methylenedioxyisoflavone, (m.p. 203°). However, the melting point of synthetic isoflavone,[27] kindly provided by Dr. W. B. Whalley through the courtesy of Professor A. Robertson, depressed on admixture with the ketone $C_{18}H_{14}O_6$. The ultraviolet absorption spectra of both isoflavone and 2',4',7-trimethoxyisoflavone is shown in Fig. 8.

Therefore, formula XIII is definitely excluded, and dimethylsophorol must be either XIV or XV.

(27) A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1440 (1954). The ultraviolet absorption maximum of 2',7-dimethoxy-3',4'-methylenedioxyisoflavone (Fig. 8) are as follows. λ_{max} (alcohol) 247, 295, inflection 304 mμ (ϵ; 25680, 11610, and 10870).

(28) A. McGookin, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 787 (1940). Precious specimen of 2',7-dimethoxy-3',4'-methylenedioxyisoflavanone which was derived from pterocarpine was provided by Dr. W. B. Whalley. The ultraviolet spectrum; λ_{max} (ethanol) 231, 273, and 304 mμ (ϵ; 15850, 15120, and 12640).

(29) T. Kubota, *J. Chem. Soc. Japan*, 604 (1939).

(30) N. Narasimhachari and T. R. Seshadri, *Proc. Ind. Acad. Science*, **35**, Sec A. 202, (1952).

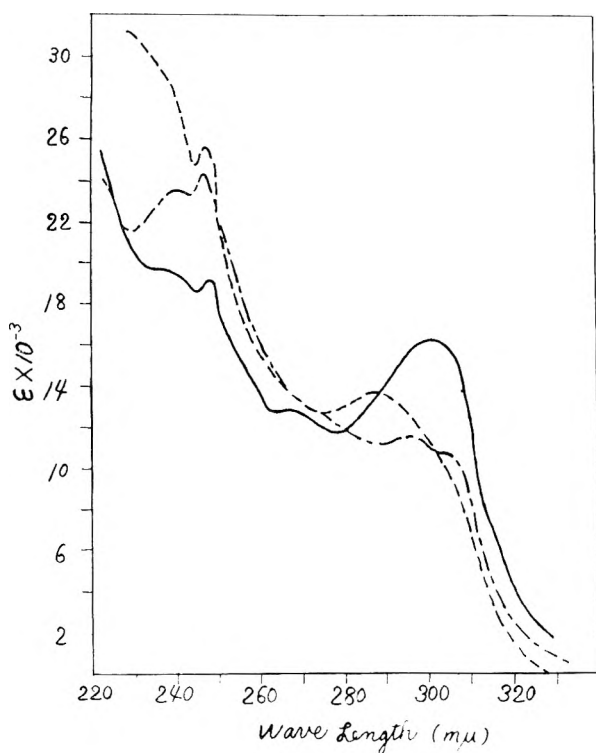(31) S. H. Harper, *J. Chem. Soc.*, 595 (1942). Wolfrom, *J. Am. Chem. Soc.*, **63**, 1248 (1941).

Fig. 8. Ultraviolet spectra of 2',7-dimethoxy-3',4'-methylendioxyisoflavone (— — — —), 2',4',7-trimethoxyisoflavone (—·—·—) and selenium oxidation product $C_{18}H_{14}O_5$ (IX) (————); solvent ethanol

Though no definite proof can be given so far for the constitution of the new ketone the phytochemical evidence, the nonexistence of any naturally occurring 2',5',6'-trisubstituted flavone, favors the formula XIV. Furthermore, it is of interest to note that formula XIV contains the essential core of rotenoide.[32] By analogy with rotenone and pachyrhizon,[32b] of the remaining alternatives, the present writer prefers formula XIV R' = OCH_3 for dimethylsophorol. Therefore, sophorol should be considered to be formulated as formula XIV, R = H. The occurrence of 2'-hydroxyisoflavanones, ferreirin, homoferreirin,[3] and sophorol, in nature is of interest in connection with the biogenesis[33] of pterocarpin and homopterocarpin. It is considered that the formation of anhydrosophorol from sophorol suggests a possible synthetic route for pterocarpin and homopterocarpin. Further, sophorol is unique in that it is optically active isoflavanone. Synthetic work about sophorol and related compounds is now in progress.

(32) (a) A. A. Morton, The Chemistry of Heterocyclic Compounds, McGraw-Hill, New York, 1946, p. 172.

(b) H. Bickel and H. Schmid, Helv. Chim. Acta, 36, 664 (1953). Also see Sir. R. Robinson, The Structural Relations of Natural Products, Oxford University Press, 1955, p. 43.

(33) J. A. Ballantine and W. B. Whalley, J. Chem. Soc., 3225 (1956).

EXPERIMENTAL[34]

Isolation and purification of sophorol. The ground heartwood of *Sophora japonica*, L. (3.0 kg.) was extracted with ethanol (9.1) at room temperature for 2–4 days. The deep red extract was then concentrated to about 200 ml. under diminished pressure. After the solution was shaken with petroleum ether (200 ml. × 4) brown solid (9.3 g.–33.5 g.) deposited during 1–2 weeks.

When the deposited solid was digested with boiling diluted methanol (methanol-water 1:1) hot methanolic solution separated a crude sophorol. It was treated with a small volume of warm benzene. From a soluble part in warm benzene the solvent was distilled off. Residual light brown solid (0.5–10 g.) was recrystallized repeatedly from diluted acetone, yielding colorless plates m.p. 178.5–179°. After drying under vacuum the melting point of this compound rose to 180–181°.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 65.68; H, 4.69; in a sample dried at 100–110° *in vacuo:* C, 67.67, 67.33; H, 4.41, 4.58.

This material is soluble in aqueous sodium hydroxide and had the positive color tests for a methylenedioxyl group, but detailed examination for the constitution was deferred. After the part insoluble in warm benzene was crystallized repeatedly from diluted acetone a pure sophorol separated as slightly pale yellow short needles, m.p. 215° (slight decomp.) (0.6–15 g.).

Anal. Calcd. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found: (sample dried at 100–110° *in vacuo*) C, 64.18, 63.96, 63.91; H, 4.40, 4.37, 4.24.

Light absorption in ethanol (Fig. 2), λ_{max} 230, 277, and 307.5 mμ (ϵ: 16950, 15950, and 12090); in aqueous 0.1N NaOH solution (Fig. 3) λ_{max} 246 and 332 mμ (ϵ: 11950, 27570) $[\alpha]_D^{1.5}$ 9.5 (acetone), $[\alpha]_D^{1.6}$ −13.6 (absolute ethanol). Combined formaldehyde determination[8] 0.58. Purified material from diluted acetone shown 0.6% methoxyl content by Zeizel determination, being due to the trace of impurity. However, it was difficult to remove this completely by recrystallization. Sophorol dissolved readily in acetone, ethylacetate, dioxane, and the simple alcohols, sparingly in chloroform, benzene, and did not dissolve in water. It gave neither ferric reaction in alcohol nor precipitate with alcoholic lead tetraacetate. It did not give characteristic color reaction with magnesium–hydrochloric acid or on sodium amalgam reduction. Alkaline solution of sophorol developed red color by application of *p*-diazobenzenesulfonic acid. Sophorol gave a yellow orange solution in concentrated sulfuric acid. The solution became a green color with a drop of 5% alcoholic gallic acid but the color reaction with phloroglucin–sulfuric acid for combined formaldehyde was very sluggish. It dissolved to yellow in aqueous 2N sodium hydroxide and darkened in air. Sophorol reduced an ammoniac silver nitrate and Fehling's solution with heating on the water bath.

Sophorol O-dimethyl ether. (a) *With diazomethane.* Sophorol (2 g.) in acetone (20 cc.) was treated with an ethereal solution of diazomethane (from nitrosomethylurea 3.2 g.) and set aside overnight. Evaporation under diminished pressure and recrystallization of the crystalline residue from diluted acetone yielded O-dimethylsophorol (0.7 g.) as optically inactive colorless short needles, m.p. 136–138°.

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91; Mol. wt., 328; $2OCH_3$, 18.9. Found: in a sample dried *in vacuo* at 100–110°: C, 65.25, 65.66; H, 4.73, 4.85; $2OCH_3$, 22.24; Mol. wt., 326 (Rast).

Light absorption (Fig. 2) λ_{max} (alcohol) 230, 273, and 306 mμ (ϵ: 18830, 16650, and 11030). O-dimethylsophorol dissolved readily in acetone, dioxane, and the simple alco-

(34) Melting points uncorrected. The ultraviolet absorption spectra were measured on either a Beckman Model D.U. spectrophotometer or on a Shimazu spectrophotometer in alcohol.

hol, moderately in benzene, and did not dissolve in water. It dissolved in concentrated sulfuric acid to yellow and gave a blue color with one drop of 5% alcoholic gallic acid solution indicative of a methylenedioxyl group. Combined formaldehyde determination[8,9] 0.63. When alcoholic solution of O-dimethylsophorol was reduced by sodium amalgam, pink color was gradually developed. Magnesium-hydrochloric acid reduction did not give the same color. O-dimethylsophorol was insoluble in 2N alkali and did not react with acetylating agents. It can be distilled at 260–270° (bath temp.) under 0.5 mm. The 2,4-dinitrophenylhydrazone slowly deposited from sulfuric alcoholic 2,4-dinitrophenylhydrazine solution. On recrystallization from diluted alcohol and acetic acid it formed red orange crystals, m.p. 180–181° (decomp.).

Anal. Calcd. for $C_{24}H_{20}O_9N_4$: N, 11.02. Found: N, 9.62.

The isomerization of O-dimethylsophorol (84 mg.) was tried in 1 ml. of acetic acid with 0.3 ml. of concentrated hydrochloric acid on the steam bath for 1 hr., but the original compound was recovered unchanged.

(b) *With methyl iodide.* Sophorol (0.50 g.), in dry acetone (10 cc.), was refluxed for 6 hr. with methyl iodide (2.5 cc.) and anhydrous potassium carbonate (1.5 g.). After isolation from the acetone liquor, O-dimethylsophorol (0.27 g.) crystallized from diluted acetone in colorless needles m.p. 136–138° and was identical to the product isolated in procedure (a).

(c) *With methylsulfate.* Thirty per cent aqueous sodium hydroxide solution was added dropwise to a mixture of sophorol (2 g.) and methyl sulfate (20 cc.) in methanol (40 cc.). After the violent reaction took place, solution became a greenish yellow and then formed precipitation. The solution was diluted with water, then set aside overnight. Next day resultant precipitation was washed and crystallized from diluted acetone, giving a O-dimethylsophorol, m.p. 136–138°.

O-Dimethylsophorol oxime. Sophorol dimethyl ether (100 mg.) and hydroxylamine hydrochloride (50 mg.) were heated on the water bath for 2 hr. in anhydrous pyridine (0.5 cc.) and absolute ethanol (0.5 cc.). When the solvent was evaporated and diluted with water, the oxime (70 mg.) separated. Recrystallized from diluted methanol, it formed colorless crystals decomposing at 194–195.5°.

Anal. Calcd. for $C_{18}H_{17}O_6N$: N, 4.08. Found: N, 3.34.

Sophorol oxime. Oximation of sophorol (100 mg.) as described for the O-dimethyl derivative gave the oxime (80 mg.). It was recrystallized from water, decomposing at 204°.

Anal. Calcd. for $C_{16}H_{13}O_6N$: N, 4.44. Found: N, 4.00.

Sophorol oxime triacetate. Sophorol oxime (200 mg.) in pyridine (1.2 cc.) was acetylated with acetic anhydride (2 cc.) by a standard procedure. After repeated crystallizations from diluted acetone it crystallized in beautiful colorless leaflets, and melted at 163.5–165.5°, not dissolving in aqueous sodium hydroxide.

Anal. Calcd. for $C_{22}H_{19}O_9N$: C, 59.86; H, 4.34; N, 3.17. Found: C, 61.30; H, 4.69; N, 2.99.

Potash fusion of O-dimethylsophorol. O-Dimethylsophorol (2.0 g.) was thoroughly mixed with finely powdered potassium hydroxide (20 g.) and heated in a nitrogen stream from 50° to 250° for 20 min., and then in 250–270° for 30 min. (bath temp.).

After cooling, the melt was dissolved in water; the resulting solution was acidified with diluted sulfuric acid and extracted with three 100-ml. portions of ether.

The ethereal solution was extracted with three 50-ml. portions of 5% sodium hydrogen carbonate (Fraction A), and then two 50-ml. portions of 2N aqueous sodium hydroxide (Fraction B), successively. No noticeable residue was obtained from evaporation of mother ether liquor.

Fraction A was acidified with diluted sulfuric acid, and the resinous product (606 mg.), was extracted with three 50-ml. portions of ether; it gave no recognizable compound. Fraction B was acidified with diluted sulfuric acid and

extracted with three 50-ml. portions of ether. The solution was washed with a small volume of water and the solvent distilled off. On vacuum distillation at 220–240°/10⁻² mm., residual red brown phenolic fraction yielded resorcinol (325 mg.). On recrystallization from ether–petroleum benzine it melted at 110–111° which was identical in every way with authentic specimen.

The alkaline hydrolysis of O-dimethylsophorol. O-Dimethylsophorol (1 g.) in alcohol (20 cc.), containing potassium hydroxide (5 g.) and water (5 cc.) was boiled under reflux in an atmosphere of nitrogen for 5 hr.

After alcohol was removed in vacuum the residue was diluted with water (25 cc.) and extracted with three 100-ml. portions of ether. Evaporation of the washed and dried ethereal liquor gave a yellow oily product (738 mg.), which gradually solidified. On distillation at 205–240° (bath temp.)/0.03 mm. this product yielded pale yellow distillate (440 mg.) which solidified quickly. After repeated crystallization from diluted acetone the distillate gave a ketone (VII) in colorless silky needles, m.p. 120–123°, having an intense reddish-brown ferric reaction in alcohol and not dissolving in cold aqueous sodium hydroxide. It dissolved in nitric acid to green color. Its yellow sulfuric acid solution gave a green color with a drop of 5% alcoholic gallic acid solution. The alcoholic solution gave an orange colored precipitation with alcoholic sulfuric 2,4-dinitrophenylhydrazine solution.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10; 2OCH₃, 19.6%. Found: C, 65.15; H, 5.59; OCH₃, 22.3%.

Ultraviolet spectrum, (Fig. 4); combined formaldehyde determination,[8,9] 0.64. The mother alkaline layer in ether extraction was saturated with carbon dioxide and extracted with three 50-ml. portions of ether. Evaporation of the solvent yielded residue (142 mg.) which exhibited intense ferric reaction, but no homogeneous compound could be obtained.

Oxidation of the ketone (VII). Potassium permanganate (1.25 g.) in water (50 cc.) was added under reflux dropwise during 4 hr. to the foregoing ketone (699 mg.) in acetone (30 cc.). Next day, the mixture was cleared with sulfur dioxide, and extracted with ether. The oily residue left on evaporation of the extract was redissolved in ether (50 cc.) and agitated with three successive portions of 5% sodium hydrogen carbonate (20 cc. each). Acidification of the combined sodium hydrogen carbonate extracts gave 2-hydroxy-4-methoxy benzoic acid which was isolated with ether of three 100-ml. portions and purified by crystallization from hot water, forming needles (11 mg.), m.p. and mixed m.p. 153°, identified by comparison with an authentic specimen.

Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80; OCH₃, 18.5. Found: C, 57.26; H, 4.90; OCH₃, 19.2.

Evaporation of the washed and dried ethereal mother liquor remaining after the separation of 2-hydroxy-4-methoxybenzoic acid gave a resinous product (702 mg.). After washing with ether repeated crystallization from diluted ethanol yielded a product of 20 mg. in pale brown prisms, m.p. 170–172°, having an intense reddish-brown ferric reaction in alcohol and not dissolving in aqueous cold 2N-sodium hydroxide. It dissolved to pink color in concentrated sulfuric acid. Further investigations on this compound were prevented by lack of material.

Dehydrogenation of O-dimethylsophorol. (a) *With selenium dioxide.* O-Dimethylsophorol (245 mg.) and selenium dioxide (300 mg.) were refluxed in amyl alcohol (10 cc.) for 12 hr. After selenium was removed and washed with ether, the filtrate and washings were collected. On being diluted with a little ether, a product (40 mg.) slowly deposited which melted at 190–198°. On repeated crystallizations from methanol the precipitate formed feeble pink-colored needles, m.p. 203–205° of dehydro-O-dimethylsophorol (IX). Ultraviolet absorption spectrum (Fig. 8).

Anal. Calcd. for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32; 2OCH₃, 19.0. Found: C, 66.45, 66.50; H, 4.40, 4.60; 2OCH₃, 19.9.

Reduction with sodium amalgam and acidification produced pink coloration. It gave no precipitation by addition

of Brady's reagent. Evaporation of mother liquor under diminished pressure left a residue (238 mg.).

On being purified from diluted acetone, original O-dimethylsophorol (57 mg.) was recovered unchanged.

(b) *With palladized charcoal and cinnamic acid.* O-Dimethylsophorol (300 mg.) and 30% palladized charcoal[35] (150 mg.) were heated in cinnamic acid (0.7 g.) under stream of carbon dioxide for 2.75 hr. at about 190–200°. The melt having intense odor of β-phenylpropionic acid was dissolved in ether. The residue insoluble in ether, containing catalyst was dissolved in acetone. After the catalyst was filtered off the removal of acetone yielded 45 mg. of residual solid. Recrystallization from diluted acetone gave the dehydro-O-dimethylsophorol in pale pink-colored needles m.p. 201–203°, identical with a specimen from selenium dioxide oxidation. From orange-colored ether solution the solvent was distilled off. After washing of residual solid with aqueous-2N-caustic alkali and water successively, residue (250 mg.) (m.p. 70–130°) was purified from diluted acetone, giving the original O-dimethylsophorol (50 mg.).

The synthesis of DL-7,2′,4′-*trimethoxyisoflavanone.* 7,2′,4′-Trimethoxyisoflavone (200 mg.), Adams' platinum oxide (20 mg.), and glacial acetic acid (12 cc.) were shaken under hydrogen at 1 atm. for 56 min., 1.3 moles of hydrogen being absorbed. After removal of catalyst and acetic acid (*in vacuo*), DL-7,2′,4′-trimethoxyisoflavanone was obtained as colorless needles, m.p. 128–130° (70 mg.) (from acetone-water).

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77; 3OCH_3, 29.6. Found: C, 68.20; H, 5.66; OCH_3, 29.0.

Ultraviolet absorptions; (Fig. 8) (alcohol) λ_{max} 229, 272, and 306 mμ (ϵ, 26800, 20000, and 10420).

The presence of a carbonyl group was confirmed by the infrared absorption spectrum, which showed a strong band at 1677 cm.$^{-1}$ in Nujol mull.

Anhydrosophorol (VIII). Sophorol (500 mg.) was heated under reflux with 4% sulfuric acid (50 ml.) for 2 hr. After the solution was cooled the deposited amorphous solid was collected by filtration, and recrystallized repeatedly from diluted ethanol (alcohol:water 3:2), giving anhydro-

sophorol (VIII) in colorless needles, m.p. 225–226° (decomp.), which darkened in a few days and gave a faint green ferric reaction in methanol. Original sophorol (200 mg.) was recovered unchanged from the filtrate.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57. Found: C, 67.89; H, 3.82.

Anhydrosophorol rapidly decolorizes potassium permanganate in acetone. This compound is easily soluble in acetone, dioxane, and soluble in alcohol, glacial acetic acid, ethyl acetate, while insoluble in water, chloroform, benzene, and light petroleum. It dissolves in hot aqueous 2N-sodium hydroxide but not in cold solution. Further, the compound reduces Tollens-reagent, and its warm alkaline solution develops red-orange color with diazobenzenesulfonic acid. The infrared spectrum showed a band at 3420 cm.$^{-1}$ (phenolic hydroxyl).

Durham test[36] *for O-dimethylsophorol.* When the crystals of O-dimethylsophorol were treated with a drop of concentrated nitric acid on a porcelain plate a red color developed, which quickly changed to green. The addition of a few drops of ammonia gave a violet color. On the other hand, when acetone solution of the compound was treated by Jones' method[37] a deep violet color was produced.

SAPPORO, JAPAN

(35) A. S. Pfau and P. A. Plattner, *Helv. Chim. Acta,* **23,** 781 (1940).

(36) S. H. Harper, *J Chem. Soc.,* 1100 (1939).

(37) H. A. Jones, *Ind. Eng. Chem. Anal. Ed.,* **5,** 75 (1933); S. H. Harper; *J. Chem. Soc.,* 595 (1942).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT AND OCEANOGRAPHIC INSTITUTE OF THE FLORIDA STATE UNIVERSITY]

Polycondensation of Thermal Precursors of Aspartic Acid[1]

KAORU HARADA

Anhydropolyaspartic acid has been synthesized by heating unsubstituted aspartic acid. It is found that the anhydropolyaspartic acid may be prepared by heating monoammonium malate, maleamic acid, and combinations of asparagine and malic acid, maleamic acid and malic acid. Postulated pathways to form anhydropolyaspartic acid are discussed and the resulting polymers are characterized.

A century ago, aspartic acid was prepared by heating ammonium fumarate or ammonium malate.[2] Recently it has been emphasized that thermal homopolymerization accompanies these reactions.[3] On the other hand, heating unsubstituted aspartic

acid also yielded a homopolymer which gave aspartic acid upon hydrolysis.[4,5] It is reported in this paper that the infrared absorption spectra of these two aspartic acid homopolymers prepared from

(1) Contribution No. 123 of the Oceanographic Institute, Aided by Grant C-3971 of the National Institutes of Health, U. S. Public Health Service.

(2) J. Wolff, *Ann.,* **75,** 294 (1850); Dessaignes, *Compt. rend.,* **30,** 324 (1850).

(3) S. W. Fox, J. E. Johnson, and M. Middlebrook, *J. Am. Chem. Soc.,* **77,** 1048 (1955).

(4) J. Kovacs, I. Koenyves, and A. Pusztai, *Experientia,* **9,** 459 (1953); J. Kovacs and I. Koenyves, *Naturwiss,* **41,** 333 (1954).

(5) A. Vegotsky, K. Harada, and S. W. Fox, *J. Am. Chem. Soc.,* **80,** 3361 (1958).

ammonium fumarate or ammonium malate and from unsubstituted aspartic acid indicate completely identical anhydropolyaspartic acid structure (III, IV).[6] By alkaline treatment these polymers (III, IV) are easily converted to poly-peptide structures (I, II).[4,5]

Experiments reported in this paper revealed that there were many ways to synthesize anhydro-polyaspartic acid thermally from aspartic acid, fumaric acid, malic acid, maleic acid, and their derivatives and combinations of these compounds. Typical hypothetical routes of polycondensation reactions are indicated in Fig. 1.

aspartate and malic acid or fumaric acid. Both reactions resulted in good yields. The products gave positive biuret tests and negative ninhydrin tests. It was found, in general, that higher reaction temperature and longer heating gave larger yields.

(A) *Polycondensation of monoammonium dl-malate.* Mono-ammonium malate was prepared by mixing equimolar quantities of *dl*-malic acid and aqueous ammonia which were then evaporated under reduced pressure. The resulting white crystalline substance was used for this reaction.

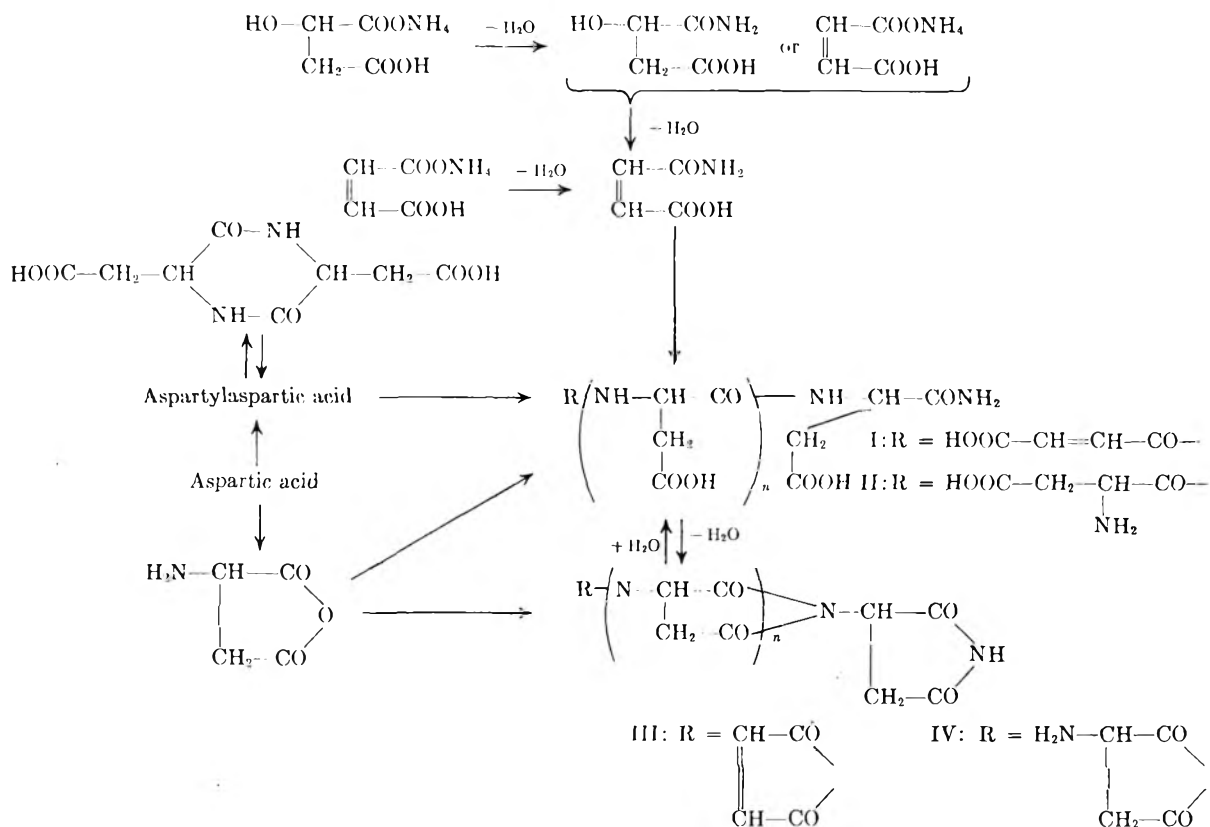Monoammonium malate, 1.50 g. (0.01 mole), was heated

Fig. 1. Flowsheet of postulated reactions

A number of variations of the reactions were attempted in order to verify the proposed pathway illustrated in Fig. 1. The main hypothesis is based on the thermal conversion of ammonium carboxylate to an amide, the addition reaction[7] of the amide to a double bond and a ring closure of the aspartyl group to the imide structure (Fig. 1).

Two kinds of reaction were carried out. In (A), anhydropolyaspartic acid was synthesized from different kinds of derivatives of malic acid, fumaric acid, maleic acid, and also combinations of these compounds. In (B)[8] anhydropolyaspartic acid was prepared from asparagine or monoammonium

in an open test tube in an oil bath under varying conditions. The substance melted easily and began to evolve gas. After cooling, the yellow-brown glassy substance was vigorously rubbed with 15 ml. of water to yield a precipitate. The precipitate was filtered and washed with 15 ml. of water and 10 ml. of ethanol and dried in air. The material was dialyzed for 3.5 days. Yields are reported in Table I.

Polycondensation of maleamic acid. Maleamic acid was prepared by acidification of the ammonium salt of male-amic acid, m.p. 151–152°, which was prepared by ammonol-ysis of maleic anhydride in dry benzene.[9] Maleamic acid, 1.15 g. (0.01 mole), was heated under nitrogen under varying conditions. The substance melted easily and evolved gas. After cooling, the resulting red-brown glassy substance was

(6) The compound is actually a polymaleimide.

(7) D. S. Breslow, G. E. Hulse, and A. S. Matlack, *J. Am. Chem. Soc.*, **79**, 3760 (1957).

(8) The same type of condensation has been reported already. Glutamic acid–aspartic acid copolymers were prepared from *l*-glutamine and *dl*-malic acid. K. Harada and S. W. Fox, *Arch. Biochem. Biophys.*, in press.

(9) R. Anschütz, *Ann.*, **259**, 138 (1890).

TABLE I

POLYCONDENSATION OF MONOAMMONIUM dl-MALATE

| Reaction Condition, °C.[a] | Yield of Polymer | | Yield of Polymer, after dialysis, %[b] |
	Before dialysis, g.	After dialysis, g.	
(a) 150	Trace	. . .	. . .
160	0.45	0.37	32
170	0.77	0.72	63
180	0.86	0.74	64
190	0.93	0.84	73
200	0.92	0.83	73
Hr.			
(b) 1/4	Trace	. . .	. . .
1/2	0.31	0.21	18
1	0.79	0.67	58
2	0.90	0.84	73
4	0.98	0.88	77

[a] In (a), monoammonium dl-malate (0.01 mole) was heated for 1.5 hr. In (b), monoammonium dl-malate (0.01 mole) was heated at 180°. [b] Yields were based on hydrated polymaleimide,[5] in the following tables.

treated with 15 ml. of water and was rubbed by glass rod to yield a precipitate. The pale red-brown precipitate was filtered, washed with 10 ml. of water and 10 ml. of ethanol, and dried. After pulverizing, the materials were dialyzed for 5 days. Yields are reported in Table II.

TABLE II

POLYCONDENSATION OF MALEAMIC ACID

| Reaction Condition, °C.[a] | Yield of Polymer | | Yield of Polymer, after Dialysis, % |
	Before dialysis, g.	After dialysis, g.	
(a) 150	0.37	0.28	24
160	0.74	0.64	56
170	0.87	0.77	67
180	0.90	0.83	73
190	0.92	0.86	75
200	0.90	0.85	74
Hr.			
(b) 1/2	0.73	0.61	53
1	0.83	0.72	63
2	0.86	0.77	67
3	0.92	0.81	70
5	0.91	0.81	70

[a] In (a) maleamic acid (0.01 mole) was heated for 1 hr. In (b) maleamic acid (0.01 mole) was heated at 170°.

Other reactions studied were: polycondensation of dl-monoammonium malate and of maleamic acid, polycondensation of dl-malic acid and ammonium maleamate, polycondensation of maleic anhydride and ammonium maleamate, polycondensation of fumaric acid and ammonium maleamate. The procedures and yields were similar in most cases to those in the previous reactions.

(B) *Polycondensation of l-asparagine and dl-malic acid.* l-Asparagine monohydrate, 1.50 g. (0.01 mole), and dl-malic acid, 1.34 g. (0.01 mole), were ground together in a mortar. The mixture was heated in an open test tube in an oil bath under varying conditions. The mixture melted and began to evolve gas. After cooling the resulting yellow-brown glassy material was rubbed with 15 ml. of water. The resulting light yellow precipitate was filtered and washed with 15 ml. of water and 10 ml. of ethanol and dried. After crushing in a

mortar the materials were dialyzed for 5 days. The yields are reported in Table III.

TABLE III

POLYCONDENSATION OF l-ASPARAGINE MONOHYDRATE AND dl-MALIC ACID

| Reaction Condition, °C.[a] | Yield of Polymer | | Yield of Polymer, after dialysis, % |
	Before dialysis, g.	After dialysis, g.	
(a) 150	0.53	0.43	19
160	1.65	1.39	60
170	1.87	1.62	70
180	1.88	1.73	75
190	1.93	1.80	78
200	1.97	1.83	79
Hr.			
(b) 1/2	Trace	. . .	. . .
1	1.80	1.49	65
2	1.86	1.56	68
4	1.89	1.62	70
6	1.95	1.69	73

[a] In (a), l-asparagine monohydrate (0.01 mole) and dl-malic acid (0.01 mole) was heated for 2 hr. In (b), the same mixture was heated at 175–180°C.

Polycondensation of monoammonium dl-aspartate and dl-malic acid. Monoammonium dl-aspartate was prepared by neutralization of dl-aspartic acid with equimolar proportion of aqueous ammonia and evaporation under reduced pressure in a desiccator. The colorless sirup which remained crystallized after 3 days. Crystallization proceeded more rapidly after seeding. The resulting white crystalline substance was used in this reaction.

Monoammonium dl-aspartate, 1.50 g. (0.01 mole), was mixed with dl-malic acid, 1.34 g. (0.01 mole), and then heated under varying conditions. The material was melted and gas evolution occurred. After cooling, 15 ml. of water was added to yield a precipitate. The slightly colored material was filtered and washed with 15 ml. of water and 10 ml. of ethanol. After crushing in a mortar, the material was dialyzed for 5 days. Yields are recorded in Table IV(a). Other reactions studied were: polycondensation of l-asparagine monohydrate and fumaric acid, polycondensation of monoammonium dl-aspartate and fumaric [Table IV(b)]. The reaction of procedures are same as above.

Reaction of dl-aspartic acid diketopiperazine diamide and dl-malic acid. dl-Aspartic acid diketopiperazine diamide,[5] 1.14 g. (0.005 mole), was ground with dl-malic acid, 1.34 g. (0.01 mole) in a mortar. The mixture was heated at 180–183° for 2 hr. Gas evolution occurred. After cooling, the yellow material was rubbed with 15 ml. of water with a glass rod. The mixture was allowed to stand overnight and the precipitate was isolated by centrifugation. This was washed with 10 ml. of water and 10 ml. of ethanol, and dried. A gray-white polymer was obtained after dialysis, 1.68 g.

Conversion of polyimide (III, IV) to polypeptide (I, II) by alkaline treatment. Polymer (IV) (prepared from dl-aspartic acid alone) 0.5 g., was dissolved in 5 ml. of 1.0N sodium hydroxide and was heated for 10 min. at 80°. After heating, the solution was cooled rapidly in ice water, acidified with 3.0N hydrochloric acid (pH 3) and then dialyzed in cellophane tubing for 3 days. No precipitation occurred. The dialyzed solution was dried in a vacuum desiccator under an infrared lamp. A yellow film remained, 0.23 g.

Two grams of polymer(IV) (prepared from dl-aspartic acid and orthophosphoric acid) was dissolved in 20 ml. of 1.0N sodium hydroxide and was heated for 10 min. at 80°, and the product was treated as described above. A pale yellow gelatin-like substance was obtained, 1.67 g. A

TABLE IV

POLYCONDENSATION OF MONOAMMONIUM dl-ASPARTATE AND dl-MALIC ACID OR FUMARIC ACID

Temp., °C.	Yield of Polymer		Yield of Polymer, after Dialysis, %
	Before dialysis, g.	After dialysis, g.	
(a)[a] 150	0.05	0.02	1.1
160	0.92	0.77	...
170	1.56	1.33	57
180	1.70	1.56	68
190	1.90	1.74	76
200	1.87	1.80	78
(b)[b] 150	0.50	0.01	...
160	0.75	0.15	6
170	0.90	0.36	16
180	0.95	0.43	19
190	1.20	0.98	43
200	1.70	1.58	69

[a] In (a), monoammonium dl-aspartate (0.01 mole) and dl-malic acid (0.01 mole) were heated for 1.5 hr. [b] In (b), monoammonium dl-aspartate (0.01 mole) and fumaric acid (0.01 mole) were heated for 1.5 hr.

2.0 g. sample of polymer (III) prepared from l-asparagine and malic acid was treated with 1.0N alkali in the same way as above. A pale yellow-brown substance was obtained, 0.64 g.

Determination of equivalent weight by electrometric titration[10]

The titrations were carried out at room temperature by dissolving in excess 0.102N sodium hydroxide and back-titrating with standard 0.476N hydrochloric acid using a Beckman model H 2 pH meter. Observed values are as follows: Imide-type polymer (IV), 123; peptide-type polyaspartic acid (II), 128; peptide-type polyaspartic acid sodium salt, 4400.

DISCUSSION

Some of the properties of the imide-type polymers (IV) have already been reported in a previous paper.[5]

Infrared absorption spectra showed that all of the thermal polycondensation products prepared from different materials had the polyimide structure.[5] Typical infrared absorption spectra show bands at 1780 cm.$^{-1}$ and 1701 cm.$^{-1}$ indicating a
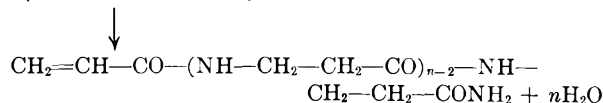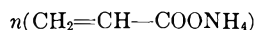
5-membered cyclic imide structure
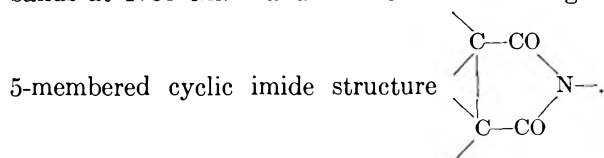
The polyimide structure can be converted to a polypeptide structure by alkaline treatment.[4,5] Characteristic absorption bands of the resulting peptide-type polyaspartic acid are: 3300 cm.$^{-1}$, 3080 cm.$^{-1}$ (NH stretching); 1710 cm.$^{-1}$ (CO of carboxyl group), 1650 cm.$^{-1}$ (amide I), 1550 cm.$^{-1}$ (amide II). With very weak alkali, e.g., sodium bicarbonate, the imide structure is hydrolyzed

(10) These samples were prepared by condensation of dl-aspartic acid. Peptide-type polyaspartic acid was prepared by alkaline treatment as described in the experimental part. Peptide-type polyaspartic acid sodium salt was prepared by dialysis after alkaline treatment without acidification.

slowly; the treatment increases the proportion of peptide structure in the polymer. By refluxing with water, the water-insoluble imide type polymer was converted partially to water-soluble material. The infrared absorption spectra show that this treatment increases the proportion of peptide structure. Completely converted peptide-type polyaspartic acid and DNP derivatives of the polymer are both water soluble and do not precipitate even in strong acid.
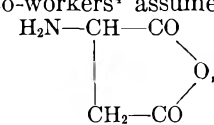
The thermal conversion of ammonium carboxylate to an amide structure is a common reaction. Recently it has been reported that the amide bond of acrylic acid amide reacts with the double bond of other acrylic acid amide molecules to form poly β-alanine in the presence of basic catalysts.[7] Application of the β-alanine formation reaction was studied in this laboratory. It was found that the ammonium acrylate also forms white water-insoluble crystalline poly β-alanine when heated at 160–200° for 1–8 hr. without a basic catalyst. The polymers produce β-alanine upon hydrolysis. Infrared absorption spectra show that the substance is completely polypeptide; 3300 cm.$^{-1}$, 3080 cm.$^{-1}$,
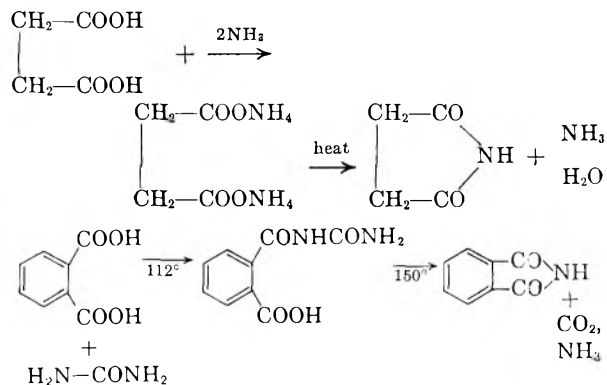
$$n(CH_2{=}CH{-}COONH_4)$$
$$\downarrow$$
$$CH_2{=}CH{-}CO{-}(NH{-}CH_2{-}CH_2{-}CO)_{n-2}{-}NH{-}$$
$$CH_2{-}CH_2{-}CONH_2 + nH_2O$$

NH stretching; 1650 cm.$^{-1}$, amide I; 1550 cm.$^{-1}$, amide II.

All reactions for preparing anhydropolyaspartic acid which are presented in this paper are very similar to the above poly β-alanine formation reaction. The amide group or the precursor ammonium carboxylate is the key moiety in forming peptide bonds in that it adds to a double bond of maleic acid or fumaric acid. In the case of malic acid, it should be converted at first to the α-β unsaturated acid upon heating, which could then react with another (unsaturated) dicarboxylic acid amide. After the addition reaction the resulting peptide-type aspartyl residues are converted to imide type structures at high temperature (Fig. 1).
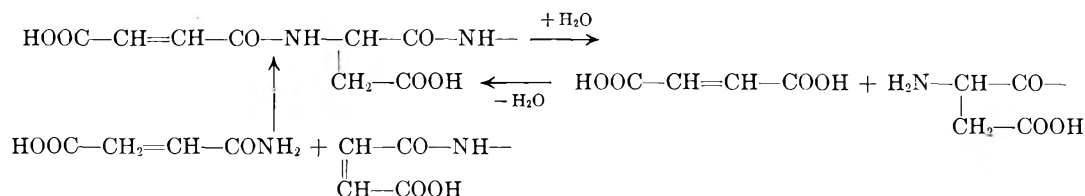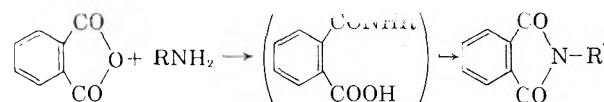
In reaction A, for example, the monoammonium dl-malate or the maleamic acid is simultaneously a nitrogen donor and a nitrogen acceptor. In the reaction of ammonium maleamate with malic acid or fumaric acid, the former substance is the nitrogen donor and the latter is the nitrogen acceptor. Although the starting substances are not amino acids, they yield anhydropolyaspartic acid in polycondensation. In reaction B, aspartic acid and monoammonium aspartate are nitrogen donors, whereas malic acid and fumaric acid are nitrogen acceptors. These nitrogen donors are amino acid derivatives and the nitrogen acceptors are not amino acid derivatives and the nitrogen acceptors are not amino acids. Anhydropolyaspartic acid results after copolycondensation in each case.

Kovacs and co-workers[4] assumed that aspartic

acid anhydride,

$$H_2N-CH-CO \diagdown$$
$$| \qquad O,$$
$$CH_2-CO \diagup$$

is the inter-

mediate in the condensation of unsubstituted aspartic acid. All of the reactions described in this paper indicate that the aspartic acid anhydride is not a necessary intermediate in the free aspartic acid condensation reaction. The literature provides examples in which an imide is formed without passing through the anhydride step.[11,12] Piutti

$$CH_2-COOH$$
$$| \qquad + \xrightarrow{2NH_3}$$
$$CH_2-COOH$$

$$CH_2-COONH_4 \qquad\qquad CH_2-CO \diagdown$$
$$| \qquad\qquad \xrightarrow{\text{heat}} \qquad | \qquad NH + \begin{array}{l} NH_3 \\ H_2O \end{array}$$
$$CH_2-COONH_4 \qquad\qquad CH_2-CO \diagup$$

(phthalic acid) $\xrightarrow{112°}$ (CONHCONH_2, COOH) $\xrightarrow{150°}$ (CO NH, CO + CO_2, NH_3)

$$+$$
$$H_2N-CONH_2$$

found that the reaction of phthalic acid and urea[12] gives N-phthalylurea at 112° but at 150° ring closure of the ureide occurs to yield a phthalimide.

(anhydride) O + RNH_2 → (CONHR, COOH) → (CO, CO) N—R

HOOC—CH=CH—CO—NH—CH—CO—NH— $\xrightarrow{+H_2O}$

$$CH_2-COOH \xleftarrow{-H_2O} HOOC-CH=CH-COOH + H_2N-CH-CO-$$
$$\uparrow \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_2-COOH$$
$$|$$
$$HOOC-CH_2=CH-CONH_2 + CH-CO-NH-$$
$$\| $$
$$CH-COOH$$

Even in the reaction of an anhydride[13] with an amine, the anhydride must pass through the amide step as an intermediate as in the reaction of γ-butyrolactone with ammonia pass the amide step.[14] The amide intermediate in these reactions

(lactone) O O + NH_3 → (HO CONH_2) → (N O, H) + H_2O
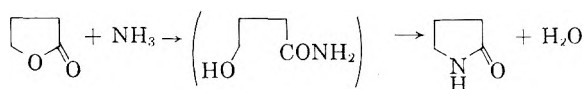
of imide formation corresponds to the peptide bond (I) in the polyimide (III) formation reaction (Fig. 1). Therefore, it is possible to assume that the

resulting peptide-type polyaspartic acid (I, II) is converted to the imide-type polymer (III, IV) under these reaction conditions. If aspartic acid anhydride is an intermediate in the formation of the imide type polymer, it must pass through a peptide step rather than function as a direct intermediate.

The reaction of aspartic acid diketopiperazine diamide with malic acid gives almost completely an imide-type polymer. This fact suggests that the diketopiperazine is not stable under these reaction conditions. It is possible to assume that aspartic acid diketopiperazine formed thermally as an intermediate is converted to dipeptide again and that the peptide reacts with another amino acid or peptide to yield polyimide as shown in Fig. 1.

The close agreement of titration values of the imide type (123) and the peptide type (128) polymers shows that the imide-type polymers are completely converted to peptide-type polyaspartic acid by excess alkali during titration. Both titration values agree closely with the calculated value of 115 for peptide-type polyaspartic acid. The titration value of the peptide-type polyaspartic acid sodium salt (4400) shows that almost all of the carboxyl groups of the polymer combine with sodium ions which are held tightly even after 4 days of dialysis.

The molecular weights of some of these polymers were studied by assay with DNFB. The molecular weight of the products prepared by methods A and B indicate values in the range of 15,000–28,000. It is conceivable that some of the polymers do not

have N-terminal amino groups (Fig. 1). Therefore, molecular weight determination by the N-terminal assay method must be expected to give inaccurate values in such products. However, it is notable that even in the polycondensation of monoammonium malate or maleamic acid fairly high N-terminal amino group content was indicated. This suggests that hydrolysis of the peptide bond accompanies the polycondensation reaction.

Since the determination of the ratio of α to β linkages of peptide-type polyaspartic acid prepared by alkaline treatment has been studied by Kovacs and co-workers,[4] it has not been considered here.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI, AND RESEARCH LABORATORIES OF CHATTEM CHEMICALS]

Synthesis and Antibacterial Activity of Some 4-Substituted Benzenesulfonylhydrazones[1]

HANS ZIMMER, BENJAMIN H. GROSS, E. HUGH GERLACH, KENNETH FRY, ANDREW C. PRONAY, AND HORST SCHMANK

A representative number of 4-amino-, 4-acetamido-, and 4-nitrobenzenesulfonylhydrazones of a great variety of aldehydes and ketones have been prepared. The *in vitro* activity of these compounds against *Streptococcus pyogenes*, *Micrococcus pyogenes*, and *Escherichia coli* is reported.

In view of the physiological activity of many hydrazine derivatives, especially the action of isonicotinic acid hydrazide toward *Mycobacterium tuberculosis*, it was considered of interest to investigate the antibacterial properties of a representative group of hydrazine analogs of the well known sulfa drugs. The compounds prepared for this study are derivatives of 4-acetamido, 4-amino, and 4-nitrobenzenesulfonylhydrazine which may be represented by formula I.

$$X-\langle\ \rangle-SO_2NHN=C\begin{smallmatrix}R\\R'\end{smallmatrix}$$

I
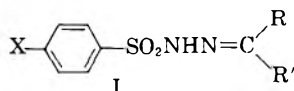
where X = CH_3CONH-, O_2N-, or H_2N-
R = H— or alkyl
R′ = alkyl or aryl

A few examples of each series of these compounds have been reported in the literature.[2-8] However, no systematic characterization of the antibacterial properties of compounds of this type has been reported. Lehmann and Grivsky[3] investigated a few 4-aminobenzenesulfonylhydrazones and found them to have some activity against *Pneumococcus* and *Escherichia coli*. However, since this observation was noted after the introduction of the sulfa drugs, the discovery of activity among these hydrazone derivatives was not followed by a more thorough investigation. Offe and Siefken[5] tested five 4-acetamidobenzenesulfonylhydrazones for their activity against *Mycobacterium tuberculosis* and found some *in vitro* inhibition but no *in vivo* activity when tested in mice. An investigation of a repre-

sentative number of these compounds, therefore, appeared desirable in view of the increasing number of strains of bacteria which are becoming resistant to the sulfa drugs.

The hydrazone derivatives reported in this paper (see tables I, II, and III) were prepared by the chemical interaction of the known hydrazides, 4-acetamido-, 4-nitro, and 4-aminobenzenesulfonylhydrazine (II) with various aldehydes and ketones. These modifications of the parent

$$X-\langle\ \rangle-SO_2NHNH_2\ +\ O=C\begin{smallmatrix}R\\R\end{smallmatrix}\ \rightarrow\ I$$

II
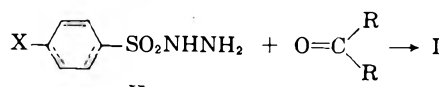
where X = CH_3CONH-, O_2N-, or H_2N-

molecules were planned with a two-fold purpose in mind. First of all, it was desired to lower the toxicity of the hydrazides toward animals. A concomitant consideration was that the hydrazone formation reaction offered a convenient means of altering the chemical structures so as to uncover a possible relation between structure and activity in these compounds.

The 4-acetamido- and 4-nitrobenzenesulfonylhydrazines were prepared by interaction of the respective acid chlorides with hydrazine under appropriate conditions. The preparation of 4-aminobenzenesulfonylhydrazine was somewhat more difficult due to the instability of the corresponding acid chloride. After investigating several approaches to the preparation of this compound, we found the method of Jensen and Hansen[9] to be useful in our laboratory. This method entails the conversion of 4-acetamidobenzenesulfonyl chloride to the corresponding acid fluoride, hydrolysis of the 4-acetamidobenzenesulfonylfluoride to the rather stable 4-aminobenzenesulfonylfluoride, and subsequent reaction with hydrazine to yield the desired hydrazide.

In most cases the chemical interaction of the hydrazide and the aldehyde or ketone occurred rapidly, leading to the desired hydrazone in good yield. However, some combinations were achieved

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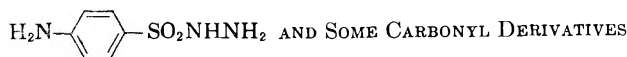(5) H. A. Offe, W. Siefken, and G. Domagk, *Z. Naturforsch*, **7b**, 446 (1952).

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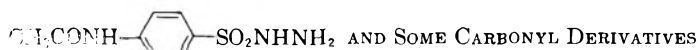(9) K. A. Jensen and O. R. Hansen, *Acta Chem. Scand.*, **6**, 195 (1952).

TABLE I

H_2N—⟨benzene⟩—SO_2NHNH_2 AND SOME CARBONYL DERIVATIVES

Carbonyl Compound	Molecular Formula	Calculated			Found			M.P., °C. (dec.)	Lit. Ref.	Biological Assay		
		C	H	N	C	H	N			sp	mp	ec
. . .	$C_6H_9N_3O_2S$	. . .	. . .	. . .	. . .	. . .	. . .	131–132	a	2	4	2
Trifluoroacetone	$C_9H_{13}F_3N_3O_2S$	38.42	3.58	14.94	38.41	3.74	15.12	150–151		4	4	2
Acetone	$C_9H_{13}N_3O_2S$	. . .	. . .	. . .	. . .	. . .	. . .	181–182	b	4	4	4
Butanone-2	$C_{10}H_{15}N_3O_2S$	49.77	6.27	17.41	49.73	6.45	17.47	163–164		4	4	4
5-Nitrofurfural	$C_{11}H_{10}N_4O_6S$	42.57	3.25	18.06	43.50	3.20	17.23	160–161		4	3	1
Furfural	$C_{11}H_{11}N_3O_3S$	49.80	4.18	15.84	49.91	4.29	15.82	142–143		4	4	1
Cyclopentanone	$C_{11}H_{15}N_3O_2S$	52.15	5.97	16.59	51.92	6.11	16.41	182–183		4	4	4
Levulinic acid	$C_{11}H_{15}N_3O_4S$	46.31	5.30	14.73	46.25	5.35	14.56	145–146		4	4	4
2-Acetylthiophene	$C_{12}H_{13}N_3O_2S_2$	48.79	4.43	14.22	48.48	4.35	14.02	206–207		4	4	4
Mesityl oxide	$C_{12}H_{17}N_3O_2S$	. . .	. . .	. . .	. . .	. . .	. . .	155–156	c	4	4	4
Cyclohexanone	$C_{12}H_{17}N_3O_2S$	. . .	. . .	. . .	. . .	. . .	. . .	170–171	d	4	4	4
Ethyl acetoacetate	$C_{12}H_{17}N_3O_4S$	48.15	5.73	14.04	48.33	5.96	13.82	146–147		3	4	4
Pinacolone	$C_{12}H_{19}N_3O_2S$	53.50	7.11	15.60	53.59	7.09	15.65	186–187		4	2	2
3,4-Dichlorobenzaldehyde	$C_{13}H_{11}Cl_2N_3O_2S$	45.36	3.22	12.21	45.21	3.23	12.28	168–169		4	4	4
2-Chlorobenzaldehyde	$C_{13}H_{12}ClN_3O_2S$	50.40	3.90	13.56	50.43	3.81	13.47	149–150		4	2	4
5-Chlorosalicylaldehyde	$C_{13}H_{12}ClN_3O_3S$	47.97	3.71	12.90	47.68	3.91	12.69	193–194		4	2	3
2-Nitrobenzaldehyde	$C_{13}H_{12}N_4O_4S$	48.74	3.78	17.49	48.60	3.78	17.90	168–169		4	4	4
3-Nitrobenzaldehyde	$C_{13}H_{12}N_4O_4S$	48.74	3.77	17.49	48.53	3.88	17.36	163–165		4	4	4
5-Nitrosalicylaldehyde	$C_{13}H_{12}N_4O_5S$	46.43	3.60	16.66	45.86	3.50	16.18	208–209		4	1	4
Benzaldehyde	$C_{13}H_{13}N_3O_2S$	. . .	. . .	. . .	. . .	. . .	. . .	172–173	e	1	4	4
Salicylaldehyde	$C_{13}H_{13}N_3O_3S$	53.60	4.50	14.42	53.71	4.60	14.36	176–177		1	4	1
4-Hydroxybenzaldehyde	$C_{13}H_{13}N_3O_3S$	53.59	4.50	14.42	53.45	4.57	14.62	154–155		4	4	4
2-Methylcyclohexanone	$C_{13}H_{19}N_3O_2S$	55.48	6.81	14.93	55.49	6.98	15.07	149–150		4	4	4
4-Methylcyclohexanone	$C_{13}H_{19}N_3O_2S$	55.48	6.81	14.93	55.60	6.90	15.02	172–173		4	4	4
2-Heptanone	$C_{13}H_{21}N_3O_2S$	55.09	7.47	14.83	54.89	7.47	14.72	168–169		4	4	4
3-Heptanone	$C_{13}H_{21}N_3O_2S$	55.09	7.47	14.83	55.05	7.67	14.96	155–156		2	4	4
Acetophenone	$C_{14}H_{15}N_3O_2S$	. . .	. . .	. . .	. . .	. . .	. . .	193–194	f	4	4	4
4-Methylbenzaldehyde	$C_{14}H_{15}N_3O_2S$	58.12	5.23	14.52	58.11	5.33	14.62	177–178		4	4	4
Anisaldehyde	$C_{14}H_{15}N_3O_3S$	. . .	. . .	. . .	. . .	. . .	. . .	166	g	4	4	4
2-Hydroxyacetophenone	$C_{14}H_{15}N_3O_3S$	55.07	4.95	13.76	54.76	4.94	13.66	184–185		1	4	3
Vanillin	$C_{14}H_{15}N_3O_4S$	52.33	4.71	13.08	52.38	4.79	13.32	174–175		2	4	4
2,4-Dihydroxyacetophenone	$C_{14}H_{15}N_3O_4S$	52.33	4.71	13.08	52.39	4.76	13.00	212–213		4	4	2
4-Aminoacetophenone	$C_{14}H_{16}N_4O_2S$	55.24	5.30	18.41	55.02	5.25	18.21	196–197		4	4	3
2-Methoxybenzaldehyde	$C_{14}H_{15}N_3O_3S$	55.06	4.95	13.76	54.76	5.13	13.51	162–163		4	4	4
2-Nitrocinnamaldehyde	$C_{15}H_{14}N_4O_4S$	52.01	4.07	16.18	52.11	4.10	16.05	161–162		3	4	4
Cinnamaldehyde	$C_{15}H_{15}N_3O_2S$	59.77	5.02	13.94	59.92	5.19	13.70	179–180		4	4	4
Piperonal	$C_{15}H_{15}N_3O_3S$	52.66	4.10	13.16	52.69	4.23	12.96	174–175		3	4	4
2-Hydroxy-3-methyl-5-nitroacetophenone	$C_{15}H_{16}N_4O_5S$	49.44	4.43	15.38	49.62	4.58	15.25	262–263		. .	. .	. .
2-Hydroxy-5-methyl-3-nitroacetophenone	$C_{15}H_{16}N_4O_5S$	49.44	4.43	15.38	49.38	4.53	15.23	224–225		. .	. .	. .
Phenylacetone	$C_{15}H_{17}N_3O_2S$	59.38	5.65	13.85	59.56	5.85	13.88	166–167		4	4	4
Propiophenone	$C_{15}H_{17}N_3O_2S$	59.38	5.65	13.85	59.42	5.71	13.99	166–167		4	4	4
4-Methylacetophenone	$C_{15}H_{17}N_3O_2S$	59.38	5.65	13.85	59.49	5.58	13.68	215–216		. .	. .	. .
2-Hydroxypropiophenone	$C_{15}H_{17}N_3O_3S$	56.41	5.37	. . .	56.66	5.32	. . .	208–209		1	3	3
4-Hydroxypropiophenone	$C_{15}H_{17}N_3O_3S$	56.41	5.37	. . .	56.24	5.46	. . .	200–201		3	4	3
2-Ethoxybenzaldehyde	$C_{15}H_{17}N_3O_3S$	56.41	5.37	13.16	56.27	5.53	12.90	170–171		2	4	4
4-Dimethylaminobenzaldehyde	$C_{15}H_{18}N_4O_2S$	56.58	5.70	17.60	56.40	5.69	17.64	186–187		4	4	4
Benzalacetone	$C_{16}H_{17}N_3O_2S$	60.93	5.43	13.32	60.92	5.48	12.77	180–181		. .	. .	. .
4-Isopropylbenzaldehyde	$C_{16}H_{19}N_3O_2S$	60.54	6.03	13.24	60.63	6.04	13.24	162–163		4	4	4
2,4-Dimethylacetophenone	$C_{16}H_{19}N_3O_2S$	60.54	6.03	13.24	60.38	6.05	13.01	176–177		4	4	4
2-Hydroxy-n-butyrophenone	$C_{16}H_{19}N_3O_3S$	57.64	5.74	. . .	57.66	5.66	. . .	215		3	4	4
4-Hydroxy-n-butyrophenone	$C_{16}H_{19}N_3O_3S$	57.64	5.74	. . .	57.50	5.74	. . .	181–182		4	4	4
3,4,5-Trimethoxybenzaldehyde	$C_{16}H_{19}N_3O_5S$	52.59	5.24	11.50	52.52	5.18	11.26	167–168		4	4	4
1-Naphthaldehyde	$C_{17}H_{15}N_3O_2S$	62.75	4.65	12.91	62.91	4.57	12.89	162–163		3	4	4
2-Hydroxy-1-naphthaldehyde	$C_{17}H_{15}N_3O_3S$	59.81	4.43	12.31	59.95	4.42	12.11	183–184		4	4	4
2-Hydroxy-n-valerophenone	$C_{17}H_{21}N_3O_3S$	58.77	6.09	. . .	58.54	6.07	. . .	205–206		3	4	4

TABLE I (Continued)

Carbonyl Compound	Molecular Formula	Calculated C	H	N	Found C	H	N	M.P., °C. (dec.)	Lit. Ref.	Biological Assay sp	mp	ec
4-Hydroxy-n-valero-phenone	$C_{17}H_{21}N_3O_3S$	58.77	6.09	...	58.96	6.15	...	176–177		3	4	4
4-Diethylaminobenz-aldehyde	$C_{17}H_{22}N_4O_2S$	58.94	6.40	16.17	58.76	6.58	16.12	192–193		4	4	4
4-Bromo-1-hydroxy-2-acetonaphthone	$C_{18}H_{15}BrN_3O_3S$	49.77	3.71	...	49.79	3.78	...	244–245		..	..	..
1-Hydroxy-4-nitro-2-acetonaphthone	$C_{18}H_{16}N_4O_5S$	53.99	4.03	13.99	55.10	4.23	12.56	219–221		..	..	..
1-Hydroxy-2-acetonaph-thone	$C_{18}H_{17}N_3O_3S$	60.83	4.82	11.82	60.99	4.79	11.68	218–219		4	4	4
1-Hydroxy-4-acetonaph-thone	$C_{18}H_{17}N_3O_3S$	60.83	4.82	11.82	60.80	4.80	11.90	217–218		4	3	4

[a] Reported[2] m.p. 131°; [b] reported[2] m.p. 136°; [c] reported[3] m.p. 164–165°; [d] reported[3] m.p. 172°; [e] reported[2] m.p. 172°; [f] reported[3] m.p. 191.5°; [g] reported[3] m.p. 164°.

TABLE II

$C_2H_5CONH-\langle\ \rangle-SO_2NHNH_2$ AND SOME CARBONYL DERIVATIVES

Carbonyl Compound	Molecular Formula	Calculated C	H	N	Found C	H	N	M.P., °C. (dec.)	Lit. Ref.	Biological Assay sp	mp	ec
...	$C_8H_{11}N_3O_3S$	...	...	...	...	...	...		a	4	4	4
Propionaldehyde	$C_{11}H_{15}N_3O_3S$	49.06	5.61	15.60	49.17	5.66	15.53	128–129		4	4	4
Acetone	$C_{11}H_{15}N_3O_3S$	...	...	...	...	...	...	185–186	b	4	3	4
Butyraldehyde	$C_{12}H_{17}N_3O_3S$	50.87	6.05	14.83	50.99	6.18	14.70	122–123		4	4	4
Methyl ethyl ketone	$C_{12}H_{17}N_3O_3S$	50.87	6.05	14.83	50.76	6.14	14.79	160–161		4	4	4
Isovaleraldehyde	$C_{13}H_9N_3O_3S$	52.50	6.44	14.13	52.66	6.57	14.31	132–133		4	4	4
5-Nitrofurfural	$C_{13}H_{12}N_4O_6S$	44.31	3.43	15.90	44.39	3.49	15.71	209–211		4	4	4
2-Furfural	$C_{13}H_{13}N_3O_4S$	50.80	4.26	...	50.95	4.24	...	186–188		4	4	4
Cyclopentanone	$C_{13}H_{17}N_3O_3S$	52.84	5.80	...	52.77	5.91	...	185–186		4	4	4
Levulinic acid	$C_{13}H_{17}N_3O_5S$	47.69	5.23	12.84	47.78	5.25	12.76	174–175		4	4	4
α-Acetylbutyrolactone	$C_{14}H_{17}N_3O_5S$	49.54	5.05	12.38	49.55	5.14	12.14	169–170		4	4	4
Mesityl oxide	$C_{14}H_{19}N_3O_3S$	54.35	6.19	13.58	54.35	6.14	13.65	157–158		4	4	4
Cyclohexanone	$C_{14}H_{19}N_3O_3S$	54.35	6.19	...	54.30	6.37	...	171–172		4	4	4
Ethyl acetoacetate	$C_{14}H_{19}N_3O_5S$	...	...	...	...	...	...	115–117	c	4	4	4
n-Hexanal	$C_{14}H_{21}N_3O_3S$	54.00	6.80	13.49	54.22	6.69	13.30	136–137		3	4	4
Pinacolone	$C_{14}H_{21}N_3O_3S$	53.99	6.80	...	54.18	6.93	...	228–229		4	4	4
5-Chlorosalicylaldehyde	$C_{15}H_{13}ClN_3O_4S$	48.98	3.84	11.42	49.13	3.36	11.18	215–216		4	4	4
2,4-Dichlorobenzaldehyde	$C_{15}H_{13}Cl_2N_2O_3S$	46.64	3.39	10.88	46.39	3.46	10.66	216–217		..	..	..
3,4-Dichlorobenzaldehyde	$C_{15}H_{13}Cl_2N_3O_3S$	46.64	3.39	10.88	46.87	3.39	10.49	198–199		2	4	4
2-Chlorobenzaldehyde	$C_{15}H_{14}ClN_3O_3S$	51.21	4.01	...	51.29	4.16	...	209–210		4	4	4
2-Hydroxy-5-nitrobenz-aldehyde	$C_{15}H_{14}N_3O_6S$	47.61	3.73	...	48.18	3.81	...	238–239		..	..	..
3-Nitrobenzaldehyde	$C_{15}H_{14}N_4O_5S$	49.71	3.89	15.46	49.70	3.67	14.87	211–212		..	..	..
Benzaldehyde	$C_{15}H_{15}N_3O_3S$	...	...	...	...	...	...	193–194	d	4	4	4
Salicylaldehyde	$C_{15}H_{15}N_3O_4S$	54.04	4.54	...	54.34	4.69	...	225–226		4	4	4
4-Hydroxybenzaldehyde	$C_{15}H_{15}N_3O_4S$	54.04	4.54	12.60	53.86	4.63	12.49	178–179		4	4	4
2,4-Dihydroxybenzalde-hyde	$C_{15}H_{15}N_3O_5S$	51.57	4.33	...	51.47	4.50	...	196–198		4	4	4
2-Methylcyclohexanone	$C_{15}H_{21}N_3O_3S$	55.71	6.55	12.99	55.63	6.51	12.78	150–151		4	4	4
4-Methylcyclohexanone	$C_{15}H_{21}N_3O_3S$	55.71	6.55	12.99	55.56	6.59	12.74	162–163		4	4	4
n-Heptanal	$C_{15}H_{23}N_3O_3S$	55.36	7.12	12.91	55.66	6.91	12.86	106–107		4	4	4
2-Heptanone	$C_{15}H_{23}N_3O_3S$	55.36	7.12	...	55.07	7.20	...	158–159		4	4	4
3-Heptanone	$C_{15}H_{23}N_3O_3S$	55.36	7.12	12.91	55.59	7.14	12.98	159–160		4	4	4
Piperonal	$C_{16}H_{15}N_3O_5S$	53.17	4.78	11.63	52.94	4.36	11.56	203–204		..	..	..
Acetophenone	$C_{16}H_{17}N_3O_3S$	57.98	5.17	12.68	58.04	5.03	12.51	206–207		..	..	..
4-Methylbenzaldehyde	$C_{16}H_{17}N_3O_3S$	57.98	5.17	12.68	58.11	5.40	12.58	190		4	4	4
2-Methoxybenzaldehyde	$C_{16}H_{17}N_3O_4S$	55.31	4.93	12.10	55.62	5.15	11.97	196–197		4	4	4
Anisaldehyde	$C_{16}H_{17}N_3O_4S$	...	...	...	...	...	...	195	e	4	4	4
2-Hydroxyacetophenone	$C_{16}H_{17}N_3O_4S$	55.32	4.93	12.10	55.13	5.09	11.91	227–228		..	..	..
Vanillin	$C_{16}H_{17}N_3O_5S$	52.88	4.72	11.56	53.04	4.84	11.74	186–187		4	2	1
4-Aminoacetophenone	$C_{16}H_{18}N_4O_3S$	55.47	5.24	16.17	55.30	5.47	16.27	206–207		4	4	4
2-Nitrocinnamaldehyde	$C_{17}H_{16}N_4O_5S$	52.55	4.15	...	52.60	4.14	...	200–203		..	..	..
Cinnamaldehyde	$C_{17}H_{17}N_3O_3S$	59.46	4.99	...	59.26	5.17	...	202–203		2	4	4

<div align="center">TABLE II (Continued)</div>

Carbonyl Compound	Molecular Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N	M.P., °C. (dec.)	Lit. Ref.	sp	mp	ec
2-Hydroxy-3-nitro-5-methylacetophenone	$C_{17}H_{18}N_4O_6S$	50.24	4.46	...	50.47	4.24	...	241–242		..	..	..
Hydrocinnamaldehyde	$C_{17}H_{19}N_3O_3S$	59.11	5.54		59.26	5.67	...	135–136		1	3	4
4-Methylacetophenone	$C_{17}H_{19}N_3O_3S$	59.11	5.54	12.17	59.13	5.77	12.55	199		..	..	..
Phenylacetone	$C_{17}H_{19}N_3O_3S$	59.11	5.54	...	58.46	5.61	...	189–190		4	3	4
Propiophenone	$C_{17}H_{19}N_3O_3S$	59.11	5.54	12.17	59.32	5.47	12.17	178–179		4	4	4
4-Methoxyacetophenone	$C_{17}H_{19}N_3O_4S$	56.49	5.30	11.64	56.52	5.41	11.39	211–212		..	..	..
2-Ethoxybenzaldehyde	$C_{17}H_{19}N_3O_4S$	56.49	5.30	...	56.42	5.48	...	209–210		..	..	..
4-Dimethylaminobenzaldehyde	$C_{17}H_{20}N_4O_3S$	56.65	5.59	...	56.60	5.66	...	219–220		4	4	4
Isophorone	$C_{17}H_{23}N_3O_3S$	58.43	6.63	...	58.28	6.83	...	176–177		4	4	4
3-Acetylthionaphthene	$C_{18}H_{17}N_3O_3S_2$	55.78	4.42	10.84	55.92	4.41	10.60	224–225		..	..	..
Benzalacetone	$C_{18}H_{19}N_3O_3S$	60.48	5.36	...	60.19	5.27	...	186–187		4	4	4
4-Isopropylbenzaldehyde	$C_{18}H_{21}N_3O_3S$	60.14	5.89	...	59.86	5.90	...	195–196		4	4	4
Citral	$C_{18}H_{23}N_3O_3S$	59.48	6.93	...	59.25	7.03	...	138–139		4	4	2
1-Naphthaldehyde	$C_{19}H_{17}N_3O_3S$	62.10	4.66	11.43	61.99	4.53	11.43	201–202		4	4	4
2-Hydroxy-1-naphthaldehyde	$C_{19}H_{17}N_3O_4S$	59.51	4.47	10.96	59.67	4.51	11.09	219–220		4	3	4
4-Diethylaminobenzaldehyde	$C_{19}H_{24}N_4O_3S$	58.74	6.23	14.42	58.79	6.36	14.54	187–188		4	4	4
1-Hydroxy-4-bromo-2-acetonaphthone	$C_{20}H_{18}BrN_3O_4S$	50.43	3.81	8.82	50.40	3.74	8.84	252–253		..	..	..
1-Hydroxy-4-nitro-2-acetonaphthone	$C_{20}H_{18}N_4O_6S$	54.29	4.10	12.66	54.46	4.24	12.64	271–272		..	..	..
1-Hydroxy-2-acetonaphthone	$C_{20}H_{19}N_3O_4S$	60.44	4.82	10.57	60.23	4.88	10.71	271–272		..	..	..
1-Hydroxy-4-acetonaphthone	$C_{20}H_{19}N_3O_4S$	60.44	4.82	10.57	60.48	4.82	10.64	242–243		4	2	4

^a Reported[2] m.p. 177–178°; ^b reported[4] m.p. 174°; ^c reported[4] m.p. 118–120°; ^d reported[5] m.p. 190–190.5°; ^e reported[5] m.p. 179–180°.

<div align="center">TABLE III</div>

<div align="center">O_2N—⟨ ⟩—SO_2NHNH_2 AND SOME CARBONYL DERIVATIVES</div>

Carbonyl Compound	Molecular Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N	M.P., °C. (dec.)	Lit. Ref.	sp	mp	ec
...	$C_6H_7N_3O_4S$	...	...	...	...	...	...		^a	4	4	4
Acetone	$C_9H_{11}N_3O_4S$	...	...	...	...	...	...	176–177	^{b–d}	4	4	4
5-Nitrofurfural	$C_{11}H_8N_4O_7S$	38.82	2.37	16.47	38.91	2.35	16.38	182–183		..	..	..
2-Furfural	$C_{11}H_9N_3O_5S$	...	...	...	...	...	...	150–151	^e	4	4	4
Levulinic acid	$C_{11}H_{13}N_3O_6S$	41.90	4.15	13.33	42.08	4.22	13.55	174–175		4	4	3
Isovaleraldehyde	$C_{11}H_{15}N_3O_4S$	...	...	...	...	...	...	118–119	^f	4	4	4
2-Acetylthiophene	$C_{12}H_{11}N_3O_4S_2$	44.29	3.41	12.91	44.37	3.19	12.66	167–168		4	4	4
Cyclohexanone	$C_{12}H_{15}N_3O_4S$	...	...	...	...	...	...	157–158	^g	4	4	4
Pinacolone	$C_{12}H_{17}N_3O_4S$	48.14	5.72	14.04	47.95	5.68	14.20	184–185		2	4	4
Glucose	$C_{12}H_{17}N_3O_9S$	37.99	4.52	11.08	37.95	4.46	10.84	156–157		4	4	4
3,4-Dichlorobenzaldehyde	$C_{13}H_9Cl_2N_3O_4S$	41.72	2.42	11.23	41.30	2.37	11.28	184–185		4	4	4
2-Chlorobenzaldehyde	$C_{13}H_{10}ClN_3O_4S$	45.95	2.97	...	46.55	2.99	...	174–175		4	4	4
5-Chlorosalicylaldehyde	$C_{13}H_{10}ClN_3O_5S$	43.89	2.83	11.81	44.18	2.76	11.54	201–202		3	2	3
2-Nitrobenzaldehyde	$C_{13}H_{10}N_4O_6S$	...	...	...	...	...	...	201–202	^h	..	..	..
3-Nitrobenzaldehyde	$C_{13}H_{10}N_4O_6S$	...	...	...	...	...	...	204–205	ⁱ	..	..	..
5-Nitrosalicylaldehyde	$C_{13}H_{10}N_4O_6S$	42.62	2.75	...	42.83	2.60	...	180–185		2	1	4
Benzaldehyde	$C_{13}H_{11}N_3O_4S$	...	...	...	...	...	...	139–141	^{j–l}	4	4	4
Salicylaldehyde	$C_{13}H_{11}N_3O_5S$	...	...	...	...	...	...	190–191	^{m, n}	2	4	4
2,4-Dihydroxybenzaldehyde	$C_{13}H_{11}N_3O_6S$	46.29	3.29	...	46.21	3.19	...	222–224		4	4	4
2-Methylcyclohexanone	$C_{13}H_{17}N_3O_4S$	50.14	5.50	13.50	50.34	5.44	13.26	124–125		4	4	4
4-Methylcyclohexanone	$C_{13}H_{17}N_3O_4S$	50.14	5.50	13.50	50.14	5.54	13.42	167–168		4	2	2
2-Heptanone	$C_{13}H_{19}N_3O_4S$	49.82	6.11	13.41	49.82	5.99	13.32	144–145		4	4	4
3-Heptanone	$C_{13}H_{19}N_3O_4S$	49.82	6.11	13.41	49.82	6.14	13.55	99–101		4	4	4
Acetophenone	$C_{14}H_{13}N_3O_4S$	52.65	4.10	13.16	52.89	4.13	13.34	188–189		..	..	..
4-Methylbenzaldehyde	$C_{14}H_{13}N_3O_4S$	52.65	4.10	13.16	52.51	3.99	12.69	162–163		4	4	4
2-Methoxybenzaldehyde	$C_{14}H_{13}N_3O_5S$	50.14	3.91	12.53	50.25	3.73	12.27	159–161		4	4	4

TABLE III (Continued)

Carbonyl Compound	Molecular Formula	Calculated			Found			M.P., °C. (dec.)	Lit. Ref.	Biological Assay		
		C	H	N	C	H	N			sp	mp	ec
Anisaldehyde	$C_{14}H_{13}N_3O_5S$	...	...	...	...	...	...	185–186	o	4	4	4
2-Hydroxyacetophenone	$C_{14}H_{13}N_3O_5S$	50.14	3.91	12.53	50.17	4.07	12.62	165–166		4	4	4
Vanillin	$C_{14}H_{13}N_3O_6S$	...	...	...	...	...	...	167–168	p	3	4	4
2,4-Dihydroxyaceto-phenone	$C_{14}H_{13}N_3O_6S$	47.86	3.73	11.96	47.59	3.85	11.72	180–182		4	4	4
4-Aminoacetophenone	$C_{14}H_{14}N_4O_4S$	50.29	4.22	16.76	50.18	4.19	16.58	166–167		4	4	4
2-Nitrocinnamaldehyde	$C_{15}H_{12}N_4O_6S$	47.87	3.21	...	47.98	3.21	...	183–184		..	..	..
Cinnamaldehyde	$C_{15}H_{13}N_3O_4S$	54.37	3.95	12.68	54.27	3.89	12.65	144–145		4	4	4
6-Nitroveratraldehyde	$C_{15}H_{14}N_4O_8S$	43.90	3.44	...	44.13	3.67	...	184–185		..	..	..
Propiophenone	$C_{15}H_{15}N_3O_4S$	54.05	4.54	12.61	54.04	4.35	12.41	160		4	4	4
4-Methylacetophenone	$C_{15}H_{15}N_3O_4S$	54.05	4.54	12.60	54.19	4.55	12.85	191–192		..	..	..
Phenylacetone	$C_{15}H_{15}N_3O_4S$	54.05	4.54	...	54.77	4.63	...	149–151		4	4	4
2-Ethoxybenzaldehyde	$C_{15}H_{15}N_3O_5S$	51.51	4.33	...	51.79	4.36	...	163–165		4	4	4
4-Dimethylaminobenz-aldehyde	$C_{15}H_{16}N_4O_4S$	51.71	4.63	...	52.07	4.70	...	166–167		4	4	4
Isophorone	$C_{15}H_{19}N_3O_4S$	53.40	5.68	...	53.18	5.64	...	149–150		3	4	4
Benzalacetone	$C_{16}H_{15}N_3O_4S$	...	...	...	...	...	...	175–176	q	4	4	4
4-Isopropylbenzaldehyde	$C_{16}H_{17}N_3O_4S$	55.32	4.93	...	55.63	4.96	...	142–143		1	3	4
2,4-Dimethylaceto-phenone	$C_{16}H_{17}N_3O_4S$	55.32	4.93	12.09	55.49	5.03	12.01	189–190		4	4	4
Citral	$C_{16}H_{21}N_3O_4S$	54.68	6.02	11.96	54.93	6.10	12.17	116–117		4	4	4
α-Naphthaldehyde	$C_{17}H_{13}N_3O_4S$	57.45	3.69	...	57.50	3.74	...	173–174		3	4	4
2-Hydroxy-1-naphthal-dehyde	$C_{17}H_{13}N_3O_5S$	54.98	3.53	11.31	55.04	3.48	11.44	200–201		4	2	1
Phenyl isobutylketone	$C_{17}H_{19}N_3O_4S$	56.49	5.30	...	56.77	5.24	...	157–158		4	4	4
4-Diethylaminobenzal-dehyde	$C_{17}H_{20}N_4O_4S$	54.24	5.36	...	54.12	5.45	...	165–167		4	4	4
4-Bromo-1-hydroxy-2-acetonaphthone	$C_{18}H_{14}BrN_3O_5S$	46.57	3.04	9.05	46.33	2.95	9.14	223–224		..	..	..
1-Hydroxy-4-nitro-2-acetonaphthone	$C_{18}H_{14}N_4O_7S$	50.23	3.28	13.02	50.33	3.30	12.85	225–226		..	..	..
1-Hydroxy-2-acetonaph-thone	$C_{18}H_{15}N_3O_5S$	...	...	10.90	...	...	10.90	195–196		..	..	..
1-Hydroxy-4-acetonaph-thone	$C_{18}H_{15}N_3O_5S$	...	...	10.90	...	...	10.47	221–222		3	4	3

[a] Reported[7] m.p. 150–152°; [b] reported[6] m.p. 169–171° (from acetone), 183–184° (from methanol); [c] reported[7] m.p. 169–171°; [d] reported[8] m.p. 172°; [e] reported[6] m.p. 152°; [f] reported[6] m.p. 132–133°; [g] reported[6] m.p. 162°; [h] reported[6] m.p. 199–200°; [i] reported[6] m.p. 195–196°; [j] reported[7] m.p. 142–144°; [k] reported[8] m.p. 142–144°; [l] reported[8] m.p. 142°; [m] reported[6] m.p. 192°; [n] reported[8] m.p. 178–179°; [o] reported[8] m.p. 160°; [p] reported[6] m.p. 166–167°; [q] reported[6] m.p. 173–174°.

with great difficulty. In the case of 1-hydroxy-2-acetylnaphthalene, it was found that the usual reaction conditions were inoperable. This difficulty was overcome by a fusion of the reactants in the presence of a catalytic quantity of sulfuric acid. Many structural features were thus included in the products obtained, by the use of a variety of aldehydes and ketones.

For the most part, these hydrazone derivatives are only slightly soluble in aqueous systems. In contrast with the sulfa drugs which usually are soluble in the form of their alkali metal salts, these compounds display no corresponding salt formation. In view of this consideration, certain aldehydes and ketones were selected on the basis of a structural feature which would enhance solubility. For example, the reaction of the hydrazides

II
+
CH₃
C=O
CH₂CH₂COOH
→ X—⟨benzene ring⟩—SO₂NHN=C(CH₃)(CH₂CH₂COOH)   III
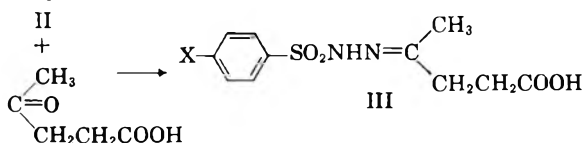
with levulinic acid yielded derivatives (III) soluble in the form of their sodium salts. On the other hand, when aromatic aldehydes and ketones substituted with chloro-, nitro-, and methoxy-groups were used in the hydrazone formation reaction, the products displayed slight solubility, not only in water and alcohols, but also in many common nonpolar solvents.

The products, for the most part, were readily purified by one or two recrystallizations. As is the case with the hydrazides, the hydrazones do not exhibit discrete melting points, but rather are thermally unstable and decompose at elevated temperatures with effervescence. These decompositions are dependent upon the rate of heating and purity of the material. Therefore, in spite of ease of preparation and low solubility of most of the carbonyl derivatives, they are not well suited for the identification of aldehydes and ketones.

All compounds of sufficient solubility were submitted to a routine screening for in vitro activity against Streptococcus pyogenes, Micrococcus

pyogenes, and *Escherichia coli*. Since these bacteria represent both Gram positive and Gram negative organisms, it was felt that this approach would uncover compounds of potential antibacterial value. The results obtained are qualitative in nature. Test compounds were compared with sulfanilamide and sulfadizine in respect to their ability to produce zones of inhibition of bacterial growth. For the results of these tests see tables I, II, and III. The code used for expressing activity is as follows: sp = *Streptococcus pyogenes*, mp = *Micrococcus pyogenes*, ec = *Escherichia coli*. The numbers 1, 2, 3, and 4 express a comparison with sulfadiazine as the standard: 1, being more active; 2, of equal activity; 3, very low activity; and 4, no apparent activity.

It was found that 4-aminobenzenesulfonylhydrazine, which is structurally related to sulfanilamide, displayed an *in vitro* inhibition to the growth of *Escherichia coli* and *Streptococcus pyogenes* which is comparable to the activity of sulfadiazine. However, as would be expected, this compound proved to be quite toxic in animal studies. Modification of this parent structure by hydrazone formation in some instances yielded derivatives with enhanced antibacterial properties along with a decrease in toxicity. This dual effect was noted also with the other hydrazides. Although this study indicates that a wide variety of structural modifications alter the activity of the parent molecules, a closer inspection of the active structures reveals a re-occurring feature. Two of the compounds which are quite active as agents for the inhibition of *Streptococcus pyogenes* are the 4-aminobenzenesulfonylhydrazones of salicylaldehyde (IV) and 2-hydroxyacetophenone (V). These struc-

tures are similar in that they contain aromatic rings substituted in the *ortho* position by a hydroxy group. Derivatives of 5-nitrosalicylaldehyde, 2-hydroxy-1-naphthaldehyde, 2,4-dihydroxyacetophenone, and 2-hydroxypropiophenone, all of which contain a similar structural feature, also display good anti-bacterial properties.
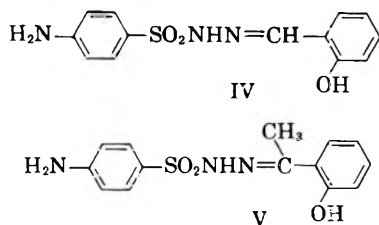
At the present, a satisfactory explanation for the activity of these compounds cannot be offered. Experiments indicate that the ability of IV and V to inhibit the *in vitro* growth of *Diplococcus pneumoniae* is not altered by the addition of *p*-aminobenzoic acid to the medium. Since *p*-aminobenzoic acid interferes with the action of the sulfa drugs in the case of this strain of bacteria, it, therefore, is evident that these hydrazones must be

acting by some other mechanism. Although the mode of action is unknown, it appears that the chelate ring formed by hydrogen bonding between the hydroxy group and the terminal nitrogen atom of the hydrazone linkage may make a significant contribution to the activity. It is of interest
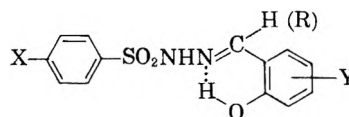
that H. Erlenmeyer and co-workers[10] found that compounds containing a similar chelate ring are effective against *Mycobacterium tuberculosis* in the form of copper chelates.

At the present, work is in progress to determine if these compounds display *in vivo* antibacterial activity. Results of this investigation will be reported in a subsequent publication.

Because of the similarity in structure to isonicotinic acid hydrazide and derivatives thereof, the following compounds of this series were also tested for activity against *Mycobacterium tuberculosis*, H37Rv, 4-aminobenzenesulfonylhydrazine, 4-nitrobenzenesulfonylhydrazine, 4-acetamidobenzenesulfonylhydrazine, 4-aminobenzenesulfonylhydrazone of salicylaldehyde, 4-aminobenzenesulfonylhydrazone of vanillin, 4-aminobenzenesulfonylhydrazone of 4-dimethylaminobenzaldehyde, 4-aminobenzenesulfonylhydrazone of furfural, 4-aminobenzenesulfonylhydrazone of 3,4,5-trimethoxybenzaldehyde, 4-nitrobenzenesulfonylhydrazone of vanillin. In the experiments conducted no inhibition of the indicated bacteria was noted.

EXPERIMENTAL

Melting points and decomposition points are uncorrected. Microanalyses by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Muelheim Ruhr, Germany. *Materials:* Generally, Eastman White Label products or comparable grades were employed without further purification.

The following are examples of typical condensations for the three series of compounds.

(1) *4-Acetamidobenzenesulfonylhydrazone of methyl ethyl ketone.* Nine and two-tenths grams (0.040 mole) of 4-acetamidobenzenesulfonylhydrazine were dissolved in 500 ml. of hot water. To the above solution, with vigorous stirring, were added 2.9 g. (0.040 mole) of methyl ethyl ketone. Stirring was continued as the warm solution cooled to room temperature. During this period colorless crystals began to separate from the reaction mixture. After 2 hr., the crystals were collected on a suction filter and dried in a 95° oven. The crude product weighed 7.9 g. (70% yield) and melted with decomposition at 158–161°.

The product was recrystallized from a mixture of three parts methanol and two parts water. The yield was 5.6 g. (50% yield) and the crystals melted with decomposition at 160–161°.

Anal. Calcd. for $C_{12}H_{17}N_3O_3S$: C, 50.87; H, 6.05; N, 14.83. Found: C, 50.76; H, 6.14; N, 14.79.

(10) E. Sorkin, W. Roth, and H. Erlenmeyer, *Helv. Chim. Acta*, **35**, 1736 (1952).

(2) *4-Aminobenzenesulfonylhydrazone of salicylaldehyde.* Seven and five-tenths grams (0.040 mole) of 4-amino-benzenesulfonylhydrazine were dissolved in a hot solution composed of 50 ml. of methanol and 50 ml. of water. To the above solution were added with stirring, 6.1 g. (0.040 mole) of salicylaldehyde. The mixture developed an orange-yellow color and became almost homogeneous. Shortly thereafter yellow-orange crystals began to precipitate from the reaction mixture. The separation of the product was facilitated by the dilution of the reaction mixture with water. The crystals were collected on a suction filter and air dried. The product weighed 11.6 g. (quantitative yield) and melted with decomposition at 167–168°.

The product was recrystallized two times from equal volumes of methanol and water. The yellow crystals weighed 5.6 g. (47% yield) and melted with decomposition at 176.5–177°.

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.42. Found: C, 53.71; H, 4.60; N, 14.36.

(3) *4-Nitrobenzenesulfonylhydrazone of propiophenone.* Seven and four-tenths grams (0.034 mole) of 4-nitrobenzene-sulfonylhydrazine were dissolved in 100 ml. of hot methanol containing a little water. Four grams (0.030 mole) of propio-phenone were then added dropwise with stirring. Yellow crystals separated from the reaction mixture as it cooled to room temperature. After 2 hr. at room temperature the crystals were collected on a suction filter and dried in a 95° oven. The yellow crystals weighed 9.8 g. (98% yield) and melted with decomposition at 147–150°.

The product was recrystallized from methanol containing a little water. The pale yellow crystals weighed 8.1 g. (81% yield) and melted with decomposition at 150–152°.

Anal. Calcd. for $C_{15}H_{15}N_3O_4S$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.04; H, 4.35; N, 12.41.

(4) *4-Acetamidobenzenesulfonylhydrazone of 2-acetyl-1-hydroxynaphthalene.* In a mortar 1.86 g. (0.01 mole) of 2-acetyl-1-hydroxynaphthalene and 2.3 g. (0.01 mole) of 4-acetamidobenzenesulfonylhydrazine were thoroughly mixed. After transferring to a large wide-diameter test tube the contents then were heated to 125° (oil bath). At this temperature the mixture liquefied somewhat and water evaporated; after 15 min., 5 ml. of glacial acetic acid and 2 drops concentrated sulfuric acid together with 15 ml. absolute ethanol were added and the mixture refluxed. After about 1 hr. everything went into solution. Shortly after this a yellow precipitate began to appear, after 1 additional hr. of refluxing, the contents were poured on ice, and washed with alcohol and ether. Yield 2.4 g.

The compound was extremely insoluble in all common solvents. Therefore, the analytical sample was extracted with boiling alcohol.

Anal. Calcd. for $C_{20}H_{19}N_3O_4S$: C, 60.44; H, 4.82; N, 10.57. Found: C, 60.23; H, 4.88; N, 10.71.

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

Derivatives of (+)-Limonene. II. 2-Amino-1-p-menthanols[1]

WILLIAM F. NEWHALL

Several new aminoalcohols including 2-amino-1-p-menthanol have been synthesized from (+)-limonene. Partial hydrogenation of (+)-limonene followed by oxidation with peracetic acid affords p-menthane-1,2-epoxide. The epoxide ring is readily opened by ammonia and amines to give derivatives of 2-amino-1-p-menthanol. The direction of ring opening in p-menthane-1,2-epoxide and the configurations of the two *trans* isomers of 2-amino-1-p-menthanol isolated have been established by an independent synthesis from *trans*-p-menthane-1,2-diol of known configuration.

A number of new 2-amino-1-p-menthanols have been synthesized from (+)-limonene in connection with a study of limonene derivatives having possible physiological activity.

Hydrogenation of (+)-limonene[2] without solvent, at low pressure, over a 5% platinum on Darco G-60 catalyst proceeds smoothly to afford Δ^1-p-menthene (I) in virtually quantitative yield. The details of this hydrogenation have been presented in a previous publication.[3] This ease of partial hydrogenation of (+)-limonene was first described by Vavon[4] and has since been utilized by a number of other authors[5,6] to prepare Δ^1-p-menthene (I).

Treatment of (I) with perbenzoic acid in anhydrous chloroform at 10° according to the method of Pigulevskii and Kozhin[6] affords p-menthane-1,2 epoxide (II) in 80% yield. Royals[7] has recently reported the preparation of (II) by hydrogenation of (+)-limonene epoxide over Adams' catalyst. Because of the difficulties inherent in the preparation of large quantities of (II) by perbenzoic acid

(1) Florida Agricultural Experiment Stations Journal Series, No. 898.

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

(3) W. F. Newhall, *J. Org. Chem.*, **23**, 1274 (1958).

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

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

(6) G. V. Pigulevskii and S. A. Kozhin, *Zhur. Obshchei Khim.*, **27**, 803 (1957).

(7) E. Earl Royals, paper no. 92, Southeastern Regional Meeting of American Chemical Society, December 1958.

oxidation, an alternate procedure was sought employing commercially available 40% peracetic acid as the epoxidizing agent. Terry and Wheeler[8] have shown that the epoxidation of natural oils can be conducted in the two-phase system which results when the oils are stirred with aqueous peracetic acid solutions. The *in situ* epoxidations discussed by Gall and Greenspan[9] were also conducted in a two-phase system maintained by using a large amount of water along with a hydrocarbon diluent. It was found that the epoxidation of (I) can be accomplished in a similar manner. The free sulfuric acid in the peracetic acid is neutralized with sodium acetate and the epoxidation performed at room temperature. Sufficient water and benzene are added to keep the reaction mixture two-phase at all times. Using this procedure, a 60% yield of (II) has been obtained after a reaction time of 1.5 hours.

By heating at 135–140° for 24 hours in a sealed tube with excess aqueous ammonia solution, (II) is converted to a mixture of two *trans* aminomenthanols (III) and (IV). It is well known that the overall result of oxide formation and cleavage is equivalent to *trans* addition.[10] Both (III) and (IV) are represented as *trans* isomers of 2-amino-1-*p*-menthanol from analogy with the work of Royals,[7] who has shown that the cleavage of (II) by ethyl alcohol under the influence of basic catalysts yields exclusively 2-ethoxy-1-*p*-menthanol. The configuration of (III) has been established by an independent synthesis and therefore it is reasonable to assign configuration (IV) to the other isomer isolated.

The formation of (III) and (IV) is possible only if the epoxide (II) is a mixture of isomers, one with the oxygen on the same side of the ring and the other with the oxygen on the opposite side of the ring as the isopropyl group. This is analogous to the known formation of two *trans-p*-menthane-1,2-diols from the hydroxylation of Δ[1]-*p*-menthene[3,11] (I). The mixed *trans* isomers of 2-methylamino-1-*p*-menthanol (IX), 2-dimethylamino-1-*p*-menthanol (X) and 2-piperidyl-1-*p*-menthanol (XI) are prepared in a similar manner by reaction of (II) with aqueous methylamine, aqueous dimethylamine, and piperidine respectively. All of these aminoalcohols are high boiling, colorless, slightly viscous liquids which are strong bases only slightly soluble in water.

In order to establish that the direction of cleavage of the oxide ring in (II) does proceed, as shown, to give derivatives of 1-*p*-menthanol, isomer (III)
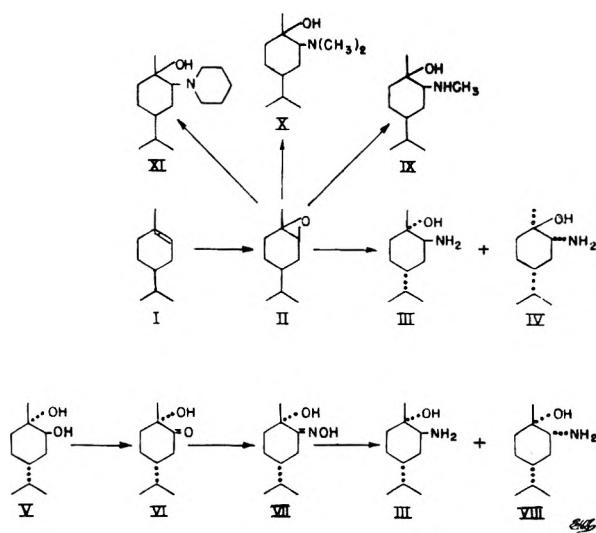
of 2-amino-1-*p*-menthanol has been synthesized from *trans-p*-menthane-1,2-diol (V). The configuration of (V) is known[3] from the reported work of Jefferies and Milligan[11] and Cole and Jefferies[12] on the racemic *trans-p*-menthane-1,2-diols. Tertiary butyl chromate[13] oxidation of (V), according to the procedure of Linder and Greenspan,[14] gives the liquid ketol (VI) which is converted by conventional means to the crystalline hydroxyoxime (VII). Hydrogenation of (VII) at low pressure over Raney nickel catalyst affords a mixture of the two isomers of 2-amino-1-*p*-menthanol (III) and (VIII) predicted from the two possible orientations of the amino group. This mixture is separated by fractional crystallization of the amine picrates into two picrates, which both form crystalline hydrates. One hydrate melts at 69–73° and is converted by vacuum drying at 85° to a crystalline, anhydrous picrate melting at 132°. The other hydrate crystallizes as yellow needles, m.p. 85–95°, and is converted by vacuum drying at 64° to an amorphous glass. The aminoalcohol regenerated from this amorphous picrate is a pure, crystalline compound melting at 79.4–80.0°.

The liquid mixture of trans-2-amino-1-*p*-menthanols (III) and (IV) on treatment with picric acid also affords two crystalline amine picrates. One crystallizes as an anhydrous picrate melting at 187°, while the other crystallizes as a hydrate (m.p. 71–74°) which, on drying, affords an anhydrous picrate melting at 132°. The latter picrate is identical in all respects, including infrared absorption, to the picrate melting at 132° synthesized from (V) above.

(8) D. E. Terry and D. H. Wheeler, U. S. Patent 2.458,484 (to General Mills, Inc.) Jan. 4, 1949.

(9) R. J. Gall and F. P. Greenspan, *Ind. Eng. Chem.*, **47**, 147 (1955).

(10) *Organic Chemistry*, Fieser and Fieser, second ed., D. C. Heath and Company, 1950, p. 287.

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

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

(13) R. V. Oppenauer and H. Oberrauch, *Anales asoc. quim argentina*, **37**, 246 (1949).

(14) S. M. Linder and F. P. Greenspan, *J. Org. Chem.*, **22**, 949 (1957).

This establishes the configuration of the parent aminoalcohol from the picrate melting at 132° as (III) since the formation of (III) is predicted from each of the two reaction schemes. The amino-alcohol corresponding to the amorphous picrate (hydrate m.p. 95°) must then have the configuration of (VIII). If cleavage of (II) is assumed to proceed exclusively in one direction,[7] (IV) must represent the configuration of the aminoalcohol from the picrate melting at 187°. In contrast to the cis aminoalcohol (VIII) which, as mentioned previously, is a crystalline solid, the two trans isomers (III) and (IV) are liquids.

EXPERIMENTAL

All melting points reported are uncorrected.

p-Menthane-1,2-epoxide (II). Six grams of sodium acetate was added with stirring to a solution of 100 ml. of 43% peracetic acid (0.566 moles) in 300 ml. of water at 25°. A solution of 70 g. (0.507 moles) of Δ^1-p-menthene (I) in 200 ml. of benzene was added rapidly and the resulting mixture was stirred and cooled to maintain a temperature of 22–24° for 1.5 hr. The benzene layer was then separated, washed 5 times with water, once with sodium bisulfite, once with sodium carbonate solution, and again with water until neutral. After drying over anhydrous sodium sulfate, the benzene was removed under vacuum at 40° and the residual liquid was distilled. At 69–70° (5.0 mm.) 46.8 g. (60%) of colorless liquid was collected. This product is sufficiently pure for use directly in the preparation of 2-amino-1-p-menthanols. Redistillation to remove traces of Δ^1-p-menthene (I) gave 42.3 g. (54%) of p-menthane-1,2-epoxide (II), which distilled at 66.0–66.3 (5.2 mm.), n_D^{23} 1.4493; $[\alpha]_D^{23}$ +57.88 (reported,[6] b.p. 66.5–66.7°/7 mm.; n_D^{23} 1.4509; $[\alpha]_D^{20}$ +57.53).

2-Amino-1-p-menthanols (III) and (IV). Two sealed glass tubes each containing 14.5 g. of p-menthane-1,2-epoxide (II) and 24 ml. of aqueous ammonium hydroxide (28%) were heated at 135–140° for 24 hr. The cooled tubes were then opened, the contents combined and extracted once with benzene. The benzene layer was separated, dried over anhydrous sodium sulfate and the benzene removed under reduced pressure (40°). Distillation of the residual oil gave 23.2 g. (75%) of colorless, viscous, mixed trans-2-amino-1-p-menthanols (III) and (IV), b.p. 95–100° (1.5 mm.). Redistillation afforded material boiling at 100–101° (1.6 mm.). n_D^{23} 1.4853, $[\alpha]_D^{23}$ +39.

Anal. Calcd. for $C_{10}H_{21}ON$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.10; H, 12.18; N, 8.33.

Twenty-four grams of the mixed trans-2-amino-1-p-menthanols (III) and (IV) (b.p. 95–100°/1.5 mm.) was fractionally distilled through an 18-inch Vigreux column at 0.95 mm. and separated into three crude fractions. Each of the three fractions was treated with excess picric acid in methanol. After removal of the methanol under vacuum, the picrates were crystallized from water. After several recrystallizations from water, pale yellow needles, m.p. 69–73°, were obtained from fraction (1). After drying under vacuum at 85°, these crystals lost water of hydration and recrystallized to afford the picrate of (III), m.p. 130–132°.

Anal. Calcd. for $C_{16}H_{24}O_8N_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.54; H, 5.84; N, 13.82.

The free aminoalcohol (III) was not regenerated from its picrate.

Yellow needles of the picrate of (IV) were obtained from fraction (3). After several recrystallizations from water, a sample melting at 184–187° was obtained.

Anal. Calcd. for $C_{16}H_{24}O_8N_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 48.31; H, 5.95; N, 13.65.

The free aminoalcohol (IV) was not regenerated from its picrate. Fraction (2) contained a mixture of the two picrates isolated from fractions (1) and (3).

2-Methylamino-1-p-menthanols (IX). Reaction of p-menthane-1,2-epoxide (II) with aqueous methyl amine (30%), using the same amounts of reactants and reaction conditions identical to those described for the preparation of the 2-amino-1-p-menthanols (III) and (IV), gave a liquid product which was vacuum distilled. At 101–107° (2.0 mm.), 25.6 g. (74%) of the mixed trans isomers of 2-methylamino-1-p-menthanol (IX) distilled as a colorless viscous oil. Redistillation afforded material boiling at 94–97° (1.5 mm.). n_D^{20} 1.4790, $[\alpha]_D^{23}$ +44.

Anal. Calcd. for $C_{11}H_{24}ON$: C, 71.29; H, 12.51; N, 7.56. Found: C, 71.04; H, 12.21; N, 7.59.

2-Dimethylamino-1-p-menthanols (X). Reaction of p-menthane-1,2-epoxide (II) with aqueous dimethyl amine (25%), using the same amounts of reactants and reaction conditions identical to those described for the preparation of the 2-amino-1-p-menthanols (III) and (IV), gave a liquid product which was vacuum distilled. At 103–108° (2.5 mm.), 25.3 g. (68%) of the mixed trans isomers of 2-dimethyl-amino-1-p-menthanol (X) distilled as a colorless, fluid oil. Redistillation afforded material boiling at 90–95° (1.4 mm.). n_D^{23} 1.4722, $[\alpha]_D^{23}$ +36.

Anal. Calcd. for $C_{12}H_{25}ON$: C, 72.30; H, 12.64; N, 7.03. Found: C, 71.81; H, 12.57; N, 6.98.

2-Piperidyl-1-p-menthanols (XI). The preparation of (XI) required more drastic conditions than that of any of the other 2-amino-1-p-menthanols. Two sealed glass tubes were prepared, each containing 14.5 g. of p-menthane-1,2-epoxide (II) and 15 ml. of piperidine. This mixture is homogeneous in contrast to the two-phase systems resulting from admixture of (II) with aqueous bases. After heating at 145–150° for 72 hr., the cooled tubes were opened, most of the piperidine was removed at reduced pressure (50°) and the residual oil was distilled under vacuum. At 69–71° (5.1 mm.) 13.4 g. of unchanged (II) was recovered (n_D^{23} 1.4489). A mixture of the trans-2-piperidyl-1-p-menthanols (XI) (14.5 g.) distilled at 126–130° (1.6 mm.) as a pale yellow oil. This represents a conversion yield to (XI) of 61%. Redistillation afforded material boiling at 126–129° (1.6 mm.). n_D^{23} 1.4872, $[\alpha]_D^{23}$ +39.

Anal. Calcd. for $C_{15}H_{29}ON$: C, 75.25; H, 12.21; N, 5.85. Found: C, 75.67; H, 11.94; N, 5.95.

2-Keto-1-p-menthanol (VI). tert-Butyl chromate was prepared by adding 29.5 g. of chromium trioxide in small portions to 84 ml. of tert-butyl alcohol with slight cooling. A solution of 49.3 g. of trans-p-menthane-1,2-diol (V) in 400 ml. of benzene was added dropwise to the oxidant while stirring and cooling the solution to maintain a temperature of 25–28°. The mixture was stirred for a total reaction time of 2 hr. at the same temperature. The complex was hydrolyzed by the addition in succession of 300 ml. of water, 60 g. of hydrated oxalic acid, and 300 ml. of 20% sulfuric acid with stirring. After 3 hr. the benzene layer was separated, washed once with sodium carbonate solution and dried over anhydrous sodium sulfate. After removal of the benzene at reduced pressure, the residual oil was distilled under vacuum. At 90–94° (1.4 mm.), 17.4 g. (36%) of colorless, slightly viscous oil was collected. Redistillation afforded material boiling at 88° (1.3 mm.). n_D^{23} 1.4647, $[\alpha]_D^{23}$ +9.8.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 69.70; H, 10.20.

2-Keto-1-p-menthanol oxime (VII). Seventeen grams of 2-keto-1-p-menthanol (VI) was warmed for a few minutes in an aqueous alcoholic solution containing 50 g. of hydroxylamine hydrochloride and 20 g. of sodium hydroxide. On cooling, colorless platelets of oxime (VII) separated from solution. These crystals weighed 12.6 g. (68%) and melted at 104–105°. Several recrystallizations from benzene–petroleum ether (30–60°) solution afforded colorless prisms, $[\alpha]_D^{23}$ +95.69 (10% acetone solution) m.p. 105–106°.

Anal. Calcd. for $C_{10}H_{19}O_2N$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.75; H, 10.50; N, 7.70.

2-Amino-1-p-menthanols (III) *and* (VIII). Two teaspoons of Raney nickel catalyst were added to a solution of 20 g. of (VII) in 150 ml. of methanol and hydrogenation was carried out at 50 p.s.i. at 65°. Ninety-three % of the theoretical volume of hydrogen calculated for 2 moles was taken up in 70 min. The catalyst was removed by filtration and about one half of the methanol was evaporated from the filtrate at reduced pressure. Excess picric acid was added together with enough water to make the solution saturated at the boiling point. A picrate crystallized from the cooled solution as yellow needles, m.p. 88–94°, 22.6 g. [47% from (VII)]. This melting point was not improved after repeated recrystallizations from water. During vacuum drying at 64°, this picrate lost water of hydration and became an amorphous glass.

Anal. Calcd. for $C_{16}H_{24}O_8N_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.47; H, 5.91; N, 13.95.

The *cis* isomer of 2-amino-1-p-menthanol (VIII) was regenerated from the hydrated picrate (m.p. 88–94°) by treatment with dilute aqueous sodium hydroxide followed by ether extraction. Evaporation of the ether afforded colorless needles which were purified by vacuum sublimation. The sublimed material melted at 79.4–80.0°, $[\alpha]_D^{23}$ −97.72 (10% acetone solution).

Anal. Calcd. for $C_{10}H_{21}ON$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.85; H, 11.86; N, 8.26.

The filtrate from the above picrate (m.p. 88–94°) was evaporated to dryness under vacuum and the residue dissolved in water. A crystalline picrate m.p. 63–72° (10.4 g.) [21.7% from (VII)] separated slowly from the cooled solution. Several recrystallizations from water afforded pale yellow needles, m.p. 71–74°. After drying under vacuum at 85°, these crystals lost water of hydration and recrystallized to give the picrate of III, m.p. 130–132°. A mixture of this picrate with the picrate (m.p. 130–132°) prepared from (II) showed no melting point depression.

LAKE ALFRED, FLA.

The Preparation and Bacteriostatic Activity of Substituted *m*-Nitrocarbanilides
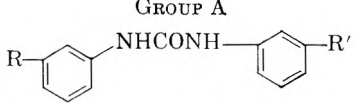
D. J. BEAVER, D. P. ROMAN, AND P. J. STOFFEL

The preparation and *in vitro* bacteriostatic activity of some substituted *m*-nitrocarbanilides against *Staphylococcus aureus* are described. A discussion of specific activity as related to chemical structure is included.

The present paper is a continuation of work described previously[1,2] interrelating chemical structure with bacteriostatic activity. The remarkable specificity encountered in the tri- and tetra-chlorocarbanilides[3] has now been duplicated in the substituted nitrocarbanilides. In both cases, antimicrobial activity was enhanced or completely lost with slight modifications in chemical structure. The more effective nitrocarbanilides completely inhibited the growth of *Staphylococcus aureus* (SA) in dilutions of one to ten million.

In the course of screening the carbanilides reported in this paper it was soon apparent that the substituted nitrocarbanilides were as specific in their structural requirements to obtain bacteriostatic activity as was found previously for the trichlorocarbanilides.[3] The 3-nitrocarbanilides were found to be inactive unless substituted with a halogen in the 3 position of the second phenyl ring when the maximum activity at a dilution of one part to ten million parts was obtained. The presence of either the nitro or the halogen in positions other than the 3 position completely inactivated the compounds. These data are shown in groups A and B. (The compounds are numbered consecutively for ready cross reference to Table I where their physical properties are listed)
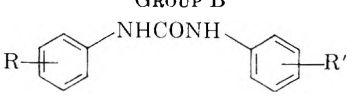
GROUP A

No.	R	R'	SA[4]
4	Chloro	Chloro	0
8	Nitro	Nitro	0
6	Nitro	Chloro	10 Million

GROUP B

No.	R	R'	SA
24	2-Nitro	2-Nitro	0
5	2-Nitro	4-Chloro	0
23	3-Nitro	2-Nitro	0
35	3-Nitro	2-Methyl-5-nitro	0
7	3-Nitro	4-Chloro	0
34	4-Nitro	4-Nitro	0
1	4-Nitro	3-4-Dichloro	0
2	2-Nitro	3,4-Dichloro	0

(1) D. J. Beaver and P. J. Stoffel, *J. Am. Chem. Soc.*, **74**, 3410 (1952).

(2) D. J. Beaver, R. S. Shumard, and P. J. Stoffel, *J. Am. Chem. Soc.*, **75**, 5579 (1953).

(3) D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1236 (1957).

(4) In groups A–F, the figures under "SA" refer to the maximum dilution which will completely inhibit the growth *in vitro* of the organism *Staphylococcus aureus*. The bacteriostatic test procedure is described in ref. (3).

TABLE I

$$R-\underset{}{\bigcirc}-NH\overset{O}{C}NH-\bigcirc-R'$$

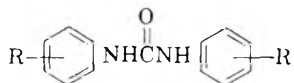| No.	R	R'	Yield %	M.P. °C	Empirical Formula	Molecular Weight	Nitrogen Analysis % Chlorine* Calcd.	Found
1	4-Nitro	3,4-Dichloro	95.3	294–295	$C_{13}H_9Cl_2N_3O_3$	326.2	12.88	13.23
2	2-Nitro	3,4-Dichloro	87.0	229.7–230.3	$C_{13}H_9Cl_2N_3O_3$	326.2	21.75*	21.73*
3	3-Nitro	3,4-Dichloro	99.5	241.8–242.7	$C_{13}H_9Cl_2N_3O_3$	326.2	21.75*	21.76*
4	3-Chloro	3-Chloro	93.0	252–253[a]	$C_{13}H_{10}Cl_2N_2O$	281.2	25.20*	25.00*
5	2-Nitro	4-Chloro	89.7	208.7–209.2[b]	$C_{13}H_{10}ClN_3O_3$	291.7	12.18*	12.20*
6	3-Nitro	3-Chloro	88.0	187.5–188.1[c]	$C_{13}H_{10}ClN_3O_3$	291.7	12.18*	12.11*
7	3-Nitro	4-Chloro	79.5	223.2–224.0[d]	$C_{13}H_{10}ClN_3O_3$	291.7	12.18*	12.37*
8	3-Nitro	3-Nitro	93.4	249.5–250.2[e]	$C_{13}H_{10}N_4O_5$	302.2		
9	3-Nitro	3-Methyl	96.4	193.1–193.7[f]	$C_{14}H_{13}N_3O_3$	271.2		
10	3-Nitro	Hydrogen	94.7	199.3–200.2[g]	$C_{13}H_{11}N_3O_3$	257.1		
11	3-Nitro	3-Carboxy	91.3	263 decomp.	$C_{14}H_{11}N_3O_5$	301.2	13.94	14.40
12	3-Nitro	3-Chloro-2-methyl	94.7	222.7–223.4	$C_{14}H_{12}ClN_3O_3$	305.7	11.62*	11.56*
13	3-Nitro	2,5-Dichloro	94.0	252.3–252.8	$C_{13}H_9Cl_2N_3O_3$	326.2	21.75*	21.69*
14	3-Nitro	3-Chloro-4-methyl	89.0	218.9–219.5	$C_{14}H_{12}ClN_3O_3$	305.7	11.62*	11.81*
15	3-Nitro	3-Aceto	88.7	214 decomp.	$C_{15}H_{13}N_3O_4$	299.2	14.08	13.85
16	3-Nitro	3-Ethoxy	84.0	154.7–155.3	$C_{15}H_{15}N_3O_4$	301.2	13.94	14.08
17	3-Nitro	3-Acetamino	72.7	181 decomp.	$C_{15}H_{14}N_4O_4$	314.2	17.83	17.99
18	3-Nitro	4-Ethoxy	77.2	194.5–195.0	$C_{15}H_{15}N_3O_4$	301.2		
19	3-Nitro	4-Methyl	95.5	211.5–212.1[h]	$C_{14}H_{13}N_3O_3$	271.2		
20	3-Nitro	4-Acetamino	99.8	325 decomp.	$C_{15}H_{14}N_4O_4$	314.2	17.83	17.69
21	3-Nitro	4-Carboxy	99.0	267 decomp.	$C_{14}H_{11}N_3O_5$	301.4	13.95	13.64
22	3-Nitro	2-Methoxy	85.5	186.4–187.3[i]	$C_{14}H_{13}N_3O_4$	288.1		
23	3-Nitro	2-Nitro	84.7	246.7–247.2[j]	$C_{13}H_{10}N_4O_5$	302.2		
24	2-Nitro	2-Nitro		224.7–225.2[k]	$C_{13}H_{10}N_4O_5$	302.2		
25	3-Nitro	5-Chloro-2-methyl	98.8	251.4–252.0	$C_{14}H_{12}ClN_3O_3$	305.7	11.62*	11.75*
26	3-Nitro	2-Methoxy-5-nitro	97.7	280–281	$C_{14}H_{12}N_4O_6$	332.1	16.88	17.02
27	3-Nitro	3-Ethyloxycarbonyl	82.5	170.9–171.5	$C_{16}H_{15}N_3O_5$	329.3	12.75	13.06
28	3-Nitro	3-Dimethylamino		187.7–188.4	$C_{15}H_{16}N_4O_3$	300.3	18.50	18.36
29	3-Nitro	5-Chloro-2-methoxy	94.3	215.4–216.1	$C_{14}H_{12}ClN_3O_4$	321.7	11.03*	11.12*
30	3-Nitro	2,5-Dichloro	97.7	246.5–247.3	$C_{13}H_9Cl_2N_3O_3$	326.2	21.75*	21.70*
31	3-Nitro	3-Bromo	96.0	211.9–212.6	$C_{13}H_{10}BrN_3O_3$	336.2	12.49	12.70
32	3-Nitro	4-Hydroxy-2-methyl	82.0	205.5–206.1	$C_{14}H_{13}N_3O_4$	288.1	14.63	14.40
33	3-Chloro	2-Methyl-5-nitro	92.0	252.8–253.6	$C_{14}H_{12}ClN_3O_3$	305.7	11.62*	11.88*
34	4-Nitro	4-Nitro	89.4	318–319[l]	$C_{13}H_{10}N_4O_5$	302.2		
35	3-Nitro	2-Methyl-5-nitro	98.5	271–272	$C_{14}H_{12}N_4O_5$	316.3	17.74	17.84
36	3-Nitro	2-Methyl-4-nitro	74.7	235.7–236.3	$C_{14}H_{12}N_4O_5$	316.3	17.74	17.59
37	3,4-Dichloro	2-Methyl-5-nitro	89.5	273–274	$C_{14}H_{11}Cl_2N_3O_3$	340.3	20.85*	21.09*
38	3-Nitro[m]	3-Chloro	93.3	79.9–80.7	$C_{15}H_{14}ClN_3O_3$	319.5	11.11*	11.17*
39	3-Nitro[n]	3-Chloro	76.1	113.7–114.2	$C_{14}H_{10}ClN_3O_4$	319.5	11.11*	11.42*
40	3-Nitro[p]	3-Chloro	92.3	147.7–148.5	$C_{13}H_{10}ClN_3O_2S$	307.7	11.60*	11.66*
41	3-Nitro[p]	3,4-Dichloro	55.0	162–163	$C_{13}H_9Cl_2N_3O_2S$	342.1	20.6*	20.0

[a] H. Vittenet, *Bull. soc. chim. France*, [3] **21**, 151 (1899), gives m.p. 245°. [b] C. H. Kao, H. Y. Fang, and P. P. T. Sah, *J. Chinese Chem. Soc.*, **3**, 137 (1935), gives m.p. 206°. [c] P. P. T. Sah, *J. Chinese Chem. Soc.*, **4**, 513 (1936), gives m.p. 248°. [d] K. C. Meng and P. P. T. Sah, *J. Chinese Chem. Soc.*, **4**, 75 (1936), gives m.p. 212°. [e] Reference [a] gives m.p. 242°. [f] Ref. [d] gives m.p. 192°. [g] A. W. Hofmann, *Ann.*, **67**, 156, (1848) gives m.p. 195°. [h] Reference [d] gives m.p. 202°. [i] K. J. Karrman, *Svensk. Kem. Tid.*, **60**, 61 (1948), gives m.p. 207.° [j] C. Naegeli, A. Tyabji, and L. Conrad, *Helv. Chem. Acta*, **21**, 1127 (1938) gives m.p. 228°. [k] Ref. [a] gives m.p. 225°. [l] Ref. [a] gives m.p. 312°. [m] N-Ethyl derivative. [n] N-Formyl derivative. [p] These compounds are *thio*carbanilides.

Group C illustrates the striking activity of the carbanilides having a nitro group in the 3 position of one phenyl ring and a halogen in the 3 position of the other phenyl ring.

These results confirm the data obtained previously in a homologous series in which the 3 chloro substituent is held constant while replacing the 3 prime nitro group.[3]

In group D are shown the results obtained by additional substitution in the 4 position of the phenyl ring containing the 3′ halogen. In general,

the additional group had no effect on the activity of the compounds. As was found previously with the polychloro carbanilides,[3] the *thio* compounds were not as active as their oxygen analogues. In group E are tabulated the results obtained by additional substitution in either the 2 or 6 position of either phenyl ring of the 3-nitro-3′ halocarbanilide. In every case the biological activity of the compounds was lost.

In Group F the data show that when 3-nitro-carbanilide is substituted in the 2 or 4 position of

GROUP C
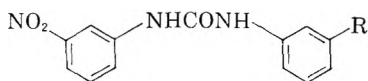
No.	R	SA
6	Chloro	10 Million
31	Bromo	10 Million
10	Hydrogen	0
8	Nitro	0
9	Methyl	0
11	Carboxy	0
27	Ethyloxycarbonyl	0
16	Ethoxy	0
15	Aceto	0
17	Acetamino	0
28	Dimethyl amino	0

GROUP D

No.	R	X	SA
6	Hydrogen	O	10 Million
40	Hydrogen	S	1 Million
3	Chloro	O	10 Million
41	Chloro	S	1 Million
14	Methyl	O	10 Million
38	Hydrogen (N-ethyl)	O	1 Million
39	Hydrogen (N-formyl)	O	1 Million

GROUP E
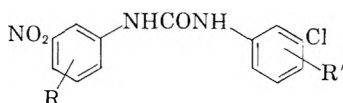
No.	R	R'	SA
6	Hydrogen	Hydrogen	10 Million
12	Hydrogen	2-Methyl	0
25	Hydrogen	6-Methyl	0
29	Hydrogen	2-Methoxy	0
30	Hydrogen	6-Chloro	0
33	6-Methyl	Hydrogen	0
37	6-Methyl	4-Chloro	0

the second phenyl ring, activity was lost completely.

The *in vivo* bacteriostatic activity of the nitro carbanilides given in Groups A–F show that the

GROUP F

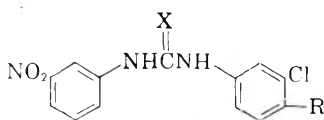| No.	R	SA
23	2-Nitro	0
22	2-Methoxy	0
10	Hydrogen	0
36	2-Methyl-4-nitro	0
35	2-Methyl 5 nitro	0
26	2-Methoxy-5-nitro	0
13	2,5-Dichloro	0
7	4-Chloro	0
19	4-Methyl	0
18	4-Ethoxy	0
20	4-Acetamino	0
21	4-Carboxy	0
32	4-Hydroxy-2-methyl	0

most active compounds have a 3-nitro group in one ring of the parent carbanilide and a 3'-halogen in the other ring. The presence of either the nitro group or the halogen in the 2 or 4 positions of either ring completely inactivated the compounds. The activity of the *thio*carbanilides parallels the structural requirements of their oxygen analogues.

EXPERIMENTAL

The compounds were prepared following Procedure A. The isocyanates and amines were commercially available or prepared in this laboratory[3] and used without further purification. The appropriate isocyanate and amine were reacted in ether or acetone under anhydrous conditions to prevent formation of the symmetrical carbanilides.

Procedure A.[3] 3-Chloro-3'-nitrocarbanilide (6). A solution of 16.4 g. (0.1 mole) of *m*-nitrophenylisocyanate in 50 ml. of acetone was added dropwise with stirring to 12.8 g. (0.1 mole) of *m*-chloroaniline in 50 ml. of acetone. The product separated during the addition period. The slurry was held for 2 hr., filtered, and washed with 20 ml. of ether. Recrystallization from ethanol gave small white granules.

Conversely the product was prepared from 15.4 g. (0.1 mole) of *m*-chlorophenylisocyanate and 13.8 g. (0.1 mole) of *m*-nitro aniline.

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

Resolution of 2,6-Diphenyl-1-methyl-4-piperidone Oxime, a Novel Example of Molecular Isomerism[1,2]
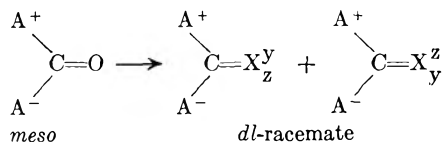
ROBERT E. LYLE AND GLORIA G. LYLE

The Michael condensation of dibenzalacetone with methylamine produced *cis*-2,6-diphenyl-1-methyl-4-piperidone (IV). The configuration was proved by failure to resolve IV and reduction of IV to two isomeric alcohols. Configurational assignments of the alcohols were based on the conformational interpretation of equilibration studies, modes of reduction, and infrared spectra of the acetyl derivatives. The oxime of the *cis*-ketone (IV) was shown to be racemic, for it could be resolved. The formation of a racemic mixture by introduction of an unsymmetrically substituted double bond, oximino group, into the *meso* isomer constitutes the first recorded illustration of geometrical enantiomorphic isomerism.

The existence of optical activity may result from the presence of an asymmetric carbon atom in a molecule or from a condition of molecular enantiomorphism in which the lack of symmetry is caused by the restricted rotation of single bonds as in biphenyls[3] and certain aryl amines[4] or by the freezing of a configuration by means of small rings as in allenes,[5,6] cyclohexylidene derivatives,[7] and spiranes.[8,9] One type of molecular asymmetry which was predicted[10] and whose experimental confirmation is the subject of this report has been designated "geometrical enantiomorphic isomerism" by the authors.[1] A compound shows such isomerism when an unsymmetrically substituted double bond

is centrally located between two similar asymmetric carbon atoms of opposite configuration.[11]

The earliest attempts to demonstrate geometrical enantiomorphic isomerism was made by Mills who successfully synthesized and resolved the pyridyl-hydrazone (II) of cyclohexene trithiocarbonate (I).[12] If the bicyclic compound (I) contained a *cis* ring junction, the hydrazone (II) would be optically active because of molecular dissymmetry, and Mills originally made this assignment on the hypothesis that a fusion involving six- and five-membered rings could be stable only in a *cis*-configuration. He therefore made no attempt to ascertain the configuration of I. The discovery that hydrindanes could exist as either *cis* or *trans* isomers caused Mills[13] to withdraw the claims he had made in his earlier paper.

An examination of the recent literature permits an assignment of configuration to I. The hydrolysis of cyclohexene trithiocarbonate (I)[14] produced the same 1,2-dimercaptocyclohexane (III) as that obtained by hydrosulfide ring opening of cyclohexene sulfide.[15] Since the hydrolytic cleavage of I would not disturb the relative configuration of the sulfur atoms of I[16] and since an epithio ring opening produces a *trans* dithiol,[17] I must have a *trans* ring

$$A^+ \diagdown C=O \longrightarrow A^+ \diagdown C=X^y_z + A^+ \diagdown C=X^z_y$$
$$\underset{A^-}{} \qquad \underset{A^-}{} \qquad \underset{A^-}{}$$

meso   *dl*-racemate

(1) For preliminary communication, see R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, **22**, 856 (1957).

(2) Abstracted from a thesis presented by G. G. Lyle to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Dissertation Abstracts, **19**, 673 (1958).

(3) G. H. Christie and J. Kenner, *J. Chem. Soc.*, 614 (1922).

(4) R. Adams and M. J. Gortakowski, *J. Am. Chem. Soc.*, **79**, 5525 (1957) and preceding papers by R. Adams and co-workers.

(5) P. Maitland and W. H. Mills, *Nature*, **135**, 994 (1935); *J. Chem. Soc.*, 987 (1936).

(6) E. P. Kohler, J. T. Walker, and M. Tishler, *J. Am. Chem. Soc.*, **57**, 1743 (1935).

(7) W. H. Perkin, W. J. Pope, and O. Wallach, *Ann.*, **371**, 180 (1909); *J. Chem. Soc.*, **95**, 1789 (1909).

(8) W. H. Mills and C. R. Nodder, *J. Chem. Soc.*, 1407 (1920).

(9) S. E. Jansen and W. J. Pope, *Chem. & Ind. (London)*, **10**, 316 (1932).

(10) R. L. Shriner, R. Adams, and C. S. Marvel in Gilman's *Organic Chemistry*, Vol. I, 2nd Ed., John Wiley and Sons, New York, 1943, p. 240.

(11) The name arises from the introduction of the elements of geometrical isomerism centrally between two enantiomorphic carbon atoms of a *meso* isomer. Since molecular enantiomorphism is a general designation for optically active compounds, geometrical enantiomorphic isomerism denotes the special case in which optical activity is partially the result of geometrical isomerism.

(12) W. H. Mills and H. Schindler, *J. Chem. Soc.*, 312 (1923).

(13) W. H. Mills and B. C. Saunders, *J. Chem. Soc.*, 537 (1931).

(14) C. C. J. Culvenor and W. Davies, *Australian J. Sci. Research*, Series A, **1**, 236 (1948).

(15) C. C. J. Culvenor, W. Davies, and N. S. Heath, J. Chem. Soc., 282 (1949).

(16) *Cf.* the alkaline hydrolysis of the isothiuronium group to the thiol. T. Taguchi and M. Kojima, *J. Am. Chem. Soc.,* **78**, 1464 (1956).

(17) *Cf.* the addition of 2,4-dinitrophenylsulfenyl halides to alkenes *via* sulfonium ion and the stereochemistry of the ring opening reactions of three-membered heterocycles. A. J. Havlik and N. Kharasch, *J. Am. Chem. Soc.*, **78**, 1207 (1956); H. L. Goering, D. I. Relyea, and K. L. Howe, *J. Am. Chem. Soc.*, **79**, 2502 (1957); O. E. Paris and P. E. Fanta, *J. Am. Chem. Soc.*, **74**, 3007 (1952); S. Winstein and R. B. Henderson in *Heterocyclic Compounds*, Vol. I, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, 1950, p. 1; D. H. R. Burton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956).

junction. As a consequence, II was resolvable because of atomic and not molecular asymmetry.
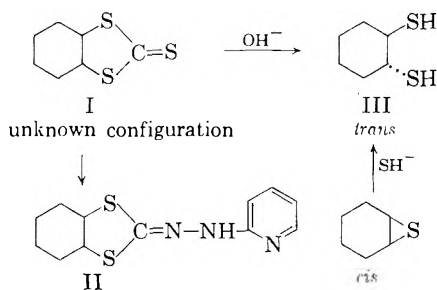
Noller and co-workers attempted the synthesis and resolution of the p-dimethylaminobenzylidene derivative of N,N'-bis(1-phenylethyl)-malonamide, but the resolution failed because of the decomposition of the salts on recrystallization.[18] Therefore, prior to our preliminary communication,[1] no demonstration of geometrical enantiomorphic isomerism had been made.

The compound selected for this study was the oxime of 2,6-diphenyl-1-methyl-4-piperidone (IV), synthesized by the condensation of dibenzalacetone with methylamine. IV can exist in three isomeric forms, a pair of enantiomorphs in which the two asymmetric carbon atoms have the same configuration, the two isomers constituting a racemic mixture, and a *meso* isomer in which the two similar asymmetric carbons are enantiomorphs. If the ketonic function in the *meso* isomer is replaced by an unsymmetrically substituted double bond, *e.g.*, an oximino group, the resulting racemate would be optically active because of molecular dissymmetry.
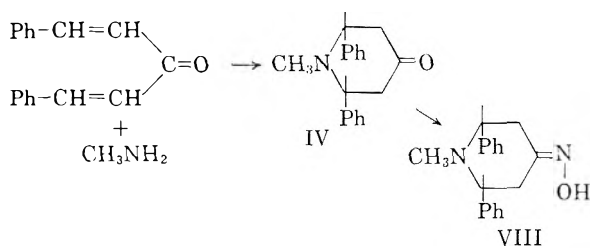
The condensation of dibenzalacetone with methylamine has been reported[19] to produce an isomer of 2,6-diphenyl-1-methyl-4-piperidone (IV), m.p. 152–153°. Repetition of the reaction produced the same compound, and no conditions were found whereby a second modification could be isolated. An alternative synthesis of IV *via* the 3,5-dicarbethoxy derivative[20] failed, for this compound did not undergo hydrolysis and decarboxylation to IV.

The configuration of IV would be expected to show the *cis* relationship of the phenyl groups if thermodynamic control of the formation obtained,

for such a configuration would permit the equatorial conformation of the large aromatic groups. At the transition from the acyclic to cyclic forms, the structure showing the least steric interference would be that in which the phenyl groups were *trans* to each other, thus leading to the formation of *trans*-IV by kinetic control. If the formation of the piperidone were irreversible, this should be the only isomer isolated. As will be demonstrated conclusively below, the *cis* isomer was the exclusive product of the Michael condensation. A similar instance has been noted in the formation of *cis*-2,6-dimethyl-4-piperidone *via* the Mannich condensation of diethyl acetonedicarboxylate with acetaldehyde and ammonia followed by hydrolysis and decarboxylation.[21] The conditions for these two reactions are quite similar, and the resultant piperidones would be presumed to undergo equilibration leading to the production of the thermodynamically more stable isomer.

The infrared and ultraviolet absorption spectra of IV were consistent with the structure of the molecule, and the crystalline ketone showed no alteration of properties on standing. Ethanolic solutions of IV, however, changed markedly in ultraviolet absorption on standing at room temperature for several weeks. The carbonyl absorption band (290 $m\mu$, ϵ_{max} 322) for IV underwent a bathochromic shift (to 325 $m\mu$) with a concomitant increase in intensity, ϵ_{max} 2300. The solution became yellow in color during this period. Assuming that the major decomposition product was dibenzalacetone, the ultraviolet absorption spectrum showed that approximately 10% of the piperidone (IV) had disappeared during the three-week period, and subtraction of the absorption of the remaining IV from the spectrum of the mixture gave a differential curve which had maxima at 229 and 325 $m\mu$; dibenzalacetone, $\lambda_{max}^{95\% \text{ EtOH}}$ 208, 230, 330 $m\mu$; ϵ_{max} 15,400; 12,000, 27,000.

The ultraviolet absorption data indicate an equilibration which could reasonably be compared with the isomeric changes observed with some of the lobelia alkaloids.[22] Salts of these alkaloids are stable, and reduction of the carbonyl groups produces stable derivatives. (−)-Lobeline, however, undergoes mutarotation on standing in alcoholic solution

(18) C. R. Noller, A. G. Yartzoff, and W. N. Jones, Jr., *J. Am. Chem. Soc.*, **78**, 5016 (1956).
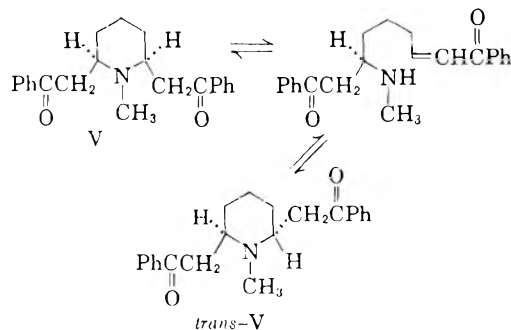
(19) J. D. Riedel, German Patent 269,429, July 18, 1913; *Chem. Zentr.*, **85**, 507 (1914).

(20) C. R. Noller and V. Baliah, *J. Am. Chem. Soc.*, **70**, 3853 (1948).

trans-V

(21) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5444 (1957).

(22) A. Ebnother, *Helv. Chim. Acta*, **41**, 386 (1958).

for several hours, and lobelanine (V), having the *meso* configuration, and *trans*-lobelanine are mutually interconverted on refluxing in ethyl acetate.

The above changes have been explained as resulting from the reversal of the Michael addition in the β-aminoketone leading to ring opening. Closure of the ring could produce the same or a different isomer. This suggests that any compound containing the R—N—CH—CH$_2$—C—R' grouping

characteristic of the lobelia alkaloids could undergo a similar reaction, and in the case of cyclic compounds such as IV, the ring could open on both sides of the nitrogen leading to the formation of dibenzalacetone. Such a mechanism would also indicate that production of the more stable *cis* isomer of IV resulted from thermodynamic control.
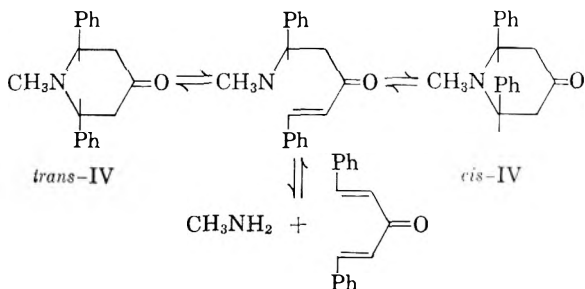

Evidence for the *meso* configuration of IV came from the failure to resolve IV with the aid of (+)-10-camphorsulfonic acid. Recrystallization of the salt gave fractions which showed essentially the same optical rotation as the salt before recrystallization.

A study of the reduction of IV supplied the proof of configuration as the *meso* isomer. If IV were a DL-racemate, reduction would produce only a DL-racemate, 2,6-diphenyl-1-methyl-4-piperidinol, regardless of the method of hydrogenation. If IV had the *meso* configuration, however, reduction would yield two optically inactive alcohols (VI), the thermodynamically more stable all *cis*-isomer having an equatorial hydroxyl group (VIb) and the epimer with an axial hydroxyl group (VIa). On the basis of reports by Barton[23] and Dauben[24] reduction of an unhindered ketone by lithium aluminum hydride should produce a mixture of alcohols predominating in the isomer having an equatorial hydroxyl. Reduction of IV under these conditions produced only one isolable isomer, m.p. 170–172.5°, designated the β-alcohol, VIb.

Catalytic hydrogenation of IV over Adams' catalyst in neutral medium gave VIb mixed with a different isomer (VIa), m.p. 156–157.5°. The presence of acid in the hydrogenation medium led to a mixture from which only VIb could be isolated in pure form. Attempts to separate the mixture by chromatography over basic alumina yielded only pure VIb.

The reaction of IV with sodium in alcohol led to decomposition of IV. The Meerwein-Ponndorf-Verley reduction of IV produced a mixture of alcohols containing approximately 80% of the axial α-alcohol (VIa), determined as the hydrochlorides of the acetyl derivatives (VII), a value consistent with results from other studies.[25] Equilibration studies of the two alcohols showed that it was possible to convert VIa to VIb but not the reverse. Treatment of VIb with sodium amyloxide produced only unchanged VIb, but a similar reaction with VIa gave a mixture of higher melting point than the starting material. No pure VIb could be isolated, however. When VIa was treated with the lithium aluminum hydride–aluminum chloride mixture described by Eliel[26] for equilibration of cyclohexanol derivatives, a mixture was obtained from which some pure VIb was separated by chromatographic absorption on basic alumina. No attempt was made to ascertain the exact percentage in the equilibrium mixture, but at least 50% of VIb was obtained.

VIa. R = H   VIb. R = H
VIIa. R = Ac   VIIb. R = Ac
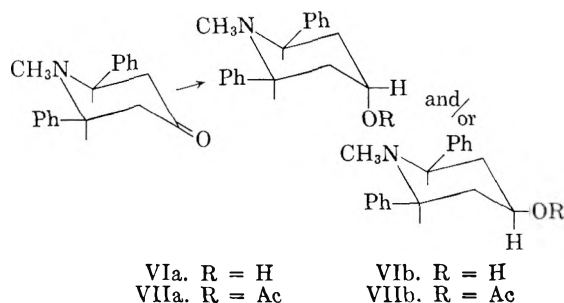
The infrared absorption spectra of VIa and VIb were quite similar, but the melting points and solubilities of the hydrochlorides were distinctly different. Conversion of VI to the acetate hydrochlorides gave compounds having marked differences in all three properties. In the steroid series, the 3-axial acetoxyl group usually gives a complex spectrum in the region from 1200 to 1250 cm.$^{-1}$ while the equatorial acetoxyl group possesses a single, sharp band.[27] The spectrum of VIIa in carbon disulfide revealed a split peak at 1230 and 1237 cm.$^{-1}$ with a shoulder at 1258 cm.$^{-1}$, but VIIb showed a single band at 1236 cm.$^{-1}$. Mulls of the hydrochlorides of VII gave similar bands, that of VIIa being the more complex having a peak at 1243 cm.$^{-1}$ and shoulders at 1235 and 1253 cm.$^{-1}$, while VIIb hydrochloride gave a single band at 1238 cm.$^{-1}$. Thus the modes of formation of the alcohols (VI), the equilibration studies of the alcohols, and the infrared absorption spectra of the acetyl derivatives

(23) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953), ref. 23.

(24) W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, 78, 3752 (1956).

(25) H. R. Nace and G. L. O'Connor, *J. Am. Chem. Soc.*, 73, 5824 (1951).

(26) M. Rerick and E. Eliel, Abstracts of Papers, 133rd Meeting, American Chemical Society, San Francisco, Calif., April, 1958, p. 4 N.

(27) A. R. H. Cole, R. N. Jones, and K. Dobriner, *J. Am. Chem. Soc.*, 74, 5571 (1952).

(VII) all led to the assignment of the axial hydroxyl to VIa and of the equatorial hydroxyl to VIb.

The conversion of the *meso* ketone (IV) to the racemic oxime (VIII) was accomplished readily. An interesting reaction was observed on heating the racemic oxime with an equimolar amount of D-10-camphorsulfonic acid in 95% ethanol. The specific rotation of the salt solution decreased during the reaction period, and addition of base produced a mixture containing, in addition to the levorotatory oxime, small amounts of 2,6-diphenyl-1-methyl-4-piperidone (IV) and dibenzalacetone. It appeared that the acidic solution effected hydrolysis of the oxime to the ketone which underwent a reversal of the original condensation to produce dibenzalacetone. It is impossible to state whether the reversal of the Michael addition occurred in the acidic solution or during the chromatographic separation on basic alumina. The latter is the more plausible. The optically active acid apparently catalyzed the stereospecific degradation kinetically favoring the decomposition of the dextrorotatory isomer.

The oxime (VIII) formed a crystalline salt on reaction with (+)-10-camphorsulfonic acid in methanol-ether solution, and three recrystallizations yielded a dextrorotatory diastereoisomer of maximum rotation. Regeneration of VIII from the salt produced the dextrorotatory enantiomer with a specific rotation of +31° in either benzene or 95% ethanol. Treatment of the mother liquors with base to obtain the levorotatory isomer failed to yield a crystalline product.

Proof that the asymmetry of the oxime (VIII) was due to molecular asymmetry was obtained by a study of the racemization and hydrolysis of VIII. The rate of acid catalyzed racemization of (+)-VIII could not be measured because of the lack of solubility of the oxime in acidified solutions of water, alcohols, dioxane, nitromethane, acetonitrile, chloroform, carbon tetrachloride, and benzene. When the oxime was allowed to react with thionyl chloride in benzene in a heterogeneous mixture, the oxime was recovered unchanged but racemic, conditions which would alter only the oxime group. Hydrolysis of (+)-oxime by the pyruvic acid method of Hershberg[28] gave 2,6-diphenyl-1-methyl-4-piperidone (IV) which produced no rotation of plane polarized light. The above reactions affected stereochemically only the oximino function and not the asymmetric carbon atoms, thus adding confirmatory proof that this was the first example of geometrical enantiomorphic isomerism.

EXPERIMENTAL[29]

2,6-Diphenyl-1-methyl-4-piperidone (IV). Methylamine was bubbled into a suspension of 20 g. (0.086 mole) of dibenzalacetone[30] in 200 ml. of methanol until solution was effected. The quantity of methylamine dissolved was 8 to 10 g. The solution was allowed to stand for 48 hr. at room tem-

perature. Most of the solvent was removed by distillation at steam bath temperature under reduced pressure, and the residual oil was dissolved in 100 ml. of ether. An equal amount of water was added to the ethereal solution, and on standing crystals were deposited at the interface. The crude product, 32.0 g., from two combined runs was recrystallized from 95% ethanol yielding 24.0 g. (52.6%) of 2,6-diphenyl-1-methyl-4-piperidone (IV), m.p. 151–153°; ν_{max}^{Nujol} 1720 (carbonyl); $\lambda_{max}^{95\% \text{ EtOH}}$ (ϵ_{max}) 210 (19,400); 252 (680); 258 (735); 264 (630); 290 (400); lit.[19] m.p. 152–153°.

Oximation under standard conditions gave a product, m.p. 191–193°, after recrystallization from 95% ethanol; lit.[31] m.p. 190°; $\lambda_{max}^{95\% \text{ EtOH}}$ (ϵ_{max}) 210 (23,800); 252 (565); 258 (608); 264 (506); 289 (246).

Reduction of 2,6-Diphenyl-1-methyl-4-piperidone (IV). (a) *With lithium aluminum hydride.* A suspension of 1.6 g. (0.04 mole) of lithium aluminum hydride in dry ether was prepared in a 500 ml. Grignard apparatus and was stirred vigorously for 15 min. A solution of 5.3 g. (0.02 mole) of 2,6-diphenyl-1-methyl-4-piperidone (IV) in dry ether was added over a period of 45 min. The mixture was heated under reflux with stirring for 1.75 hr. and decomposed cautiously with water. The ethereal layer was separated and dried over potassium carbonate. Removal of the solvent left a white solid, 2,6-diphenyl-1-methyl-4β-piperidinol (VIb), 5.12 g. (95.9%), m.p. 164.5–167°. An analytical sample, m.p. 170–172.5°, was obtained on recrystallization of VIb from 95% ethanol; ν_{max}^{Nujol} 3240, 3150 (bonded OH), 1020 (OH); $\nu_{max}^{CS_2}$ 3618 (unbonded OH), 1022 (OH); $\nu_{max}^{CCl_4}$ 3618 (unbonded OH); lit.[19] m.p. 167°.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 81.03; H, 8.02.

The hydrochloride of VIb was prepared by conventional methods and melted in a sealed tube at 306–309° with decomposition and sublimation.

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30. Found: C, 71.02; H, 7.02.

The preparation of the acetyl derivative of the β-alcohol was accomplished by heating 1.0 g. of VIb with 0.5 g. of fused, powdered sodium acetate and 5 ml. of acetic anhydride on a steam bath for 2 hr. The mixture was poured into ice and water causing the precipitation of 4β-acetoxy-2,6-diphenyl-1-methylpiperidine (VIIb). Recrystallization of the ester from ethanol-water gave an analytical sample, m.p. 101–104°; lit.[19] m.p. 105–106°; $\nu_{max}^{CS_2}$ 1742, 1236 (acetate).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 77.71; H, 7.39.

The acetic acid solution, after removal of VIIb, was neutralized with potassium hydroxide solution, and the amine was extracted with ether. After the ethereal extract was dried over sodium sulfate and the solvent removed by distillation, the residual oil was dissolved in anhydrous ether

(28) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(29) Infrared absorption spectra were determined on a Perkin-Elmer spectrophotometer, Model 21. Spectra of solids were determined as mulls in series 11–14 Halocarbon oil from 4000–1300 cm.⁻¹ and in Nujol from 1300–650 cm.⁻¹ unless otherwise designated. For use of these agents see R. E. Lyle, R. E. Adel, and G. G. Lyle, *J. Org. Chem.*, **24**, 342 (1959); D. S. Crocket and H. M. Haendler, *Anal. Chem.*, **13**, 626 (1959). Optical rotations were determined on a Franz Schmidt and Haensch polarimeter using a sodium vapor lamp as a light source, and all measurements were made in a 2 dcm. tube. Microanalyses were determined by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ultraviolet absorption spectra were obtained using a Perkin-Elmer Model 4000 recording spectrophotometer partially financed by funds from a grant, NSF G 3901, from the National Science Foundation.

(30) C. R. Conard and M. A. Dolliver, *Org. Syntheses*, **Coll. Vol. II**, 167 (1943).

(31) P. W. Neber, A. Burgard, and W. Thier, *Ann.*, **526**, 277 (1936).

and treated with dry hydrogen chloride. Recrystallization of the hydrochloride of VIIb from absolute methanol gave an analytical sample, m.p. 279–281° with sublimation; ν_{max}^{mull} 1737, 1238 (acetate); $\bar{\nu}_{max}^{CHCl_3}$ 1735 (acetate).

Anal. Calcd. for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99. Found: C, 68.94; H, 7.06.

(b) *With hydrogen over platinum oxide.* Solution of 2.65 g. (0.01 mole) of 2,6-diphenyl-1-methyl-4-piperidone (IV) in 65 ml. of anhydrous methanol was effected by heating the reagents. On cooling, the piperidone remained in solution, and 0.1 g. of platinum oxide was added. The mixture was shaken under 2.5 atm. of hydrogen at room temperature for 2.5 hr., and the catalyst was removed by filtration. After the solvent was removed by distillation under reduced pressure, the solid residue was triturated with methanol and separated by filtration yielding 0.86 g. of 2,6-diphenyl-1-methyl-4α-piperidinol (VIa), m.p. 155–156°. Four additional crops, m.p. 149–153°, were obtained from the methanol washings. The combined solids represented a 63% yield. A small amount of material, m.p. 166–167°, was obtained from the mother liquors and was shown to be identical with the β-alcohol (VIb). A mixture of the α-alcohol and the starting ketone (IV) melted at 131–141°, while a mixture of the two isomeric alcohols, m.p. 156–157° and 165–168°, melted at 151–154°. Recrystallization of VIa from benzene gave an analytical sample, m.p. 156–157.5°; $\bar{\nu}_{max}^{mull}$ 3500 (w) (unbonded OH), 3270 (bonded OH), 1025 (OH); $\nu_{max}^{CS_2}$ 3620 (unbonded OH), 1025 (OH); $\nu_{max}^{CCl_4}$ 3630 (unbonded OH).

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.86; H, 7.71.

The hydrochloride of the α-alcohol melted in a sealed tube at 287–288° (dec.) after recrystallization from 70% aqueous isopropyl alcohol.

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30. Found: C, 71.11; H, 7.45.

(c) *With aluminum isopropoxide.* Reduction of 5.3 g. (0.02 mole) of IV with 4 g. of aluminum isopropoxide in 50 ml. of isopropyl alcohol was accomplished by standard procedure.[32] The distillate gave a negative acetone test after 1.5 hr. Decomposition of the mixture with dilute hydrochloric acid yielded 4.51 g. (74.3%) of the hydrochloride of 2,6-diphenyl-1-methyl-4α-piperidinol (VIa), m.p. 283–285° (dec.), contaminated with a small amount of the β-alcohol hydrochloride. Neutralization of an aqueous isopropyl alcohol solution of the hydrochloride gave the α-alcohol (VIa), m.p. 155–156° after recrystallization from benzene, which did not depress the melting point of the α-alcohol prepared in (b).

The acetyl derivatives (VII) of the α- and β-alcohols were prepared by heating 1.0 g. of the hydrochlorides of VI, obtained from the Meerwein-Ponndorf-Verley reduction of IV, with 4 ml. of acetic anhydride in 10 ml. of dry pyridine for 20 min. The solution was cooled, diluted with water, and acidified with concentrated hydrochloric acid. The solution was extracted twice with ether, and the extracts were discarded. Strong potassium hydroxide solution was added, and the basic solution was extracted with ether. After drying over potassium carbonate, the ether solution was concentrated, and the residual yellow oil was dissolved in anhydrous ether and treated with hydrogen chloride yielding 0.42 g. of the hydrochlorides of the acetoxy derivatives (VII). Recrystallization from anhydrous ethanol gave 0.07 g. of the hydrochloride of VIIb. Dilution of the ethanolic solution with dry ether gave 0.17 g. of VIIa hydrochloride, m.p. 264–265° (dec.); ν_{max}^{mull} 1737, 1253 (sh.), 1243, 1235 (sh.) (acetate); $\bar{\nu}_{max}^{CHCl_3}$ 1740 (acetate); free amine: $\nu_{max}^{CS_2}$ 1748, 1258 (sh.), 1237, 1230 (acetate). From the amounts of the two acetoxy hydrochlorides, it was calculated that the Meerwein-Ponndorf-Verley reduction of IV produced approximately 80% of the α-alcohol (VIa) and 20% of the β-alcohol (VIb).

Anal. Calcd. for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99. Found: C, 69.40; H, 7.03.

(d) *With hydrogen in weakly acidic solution over platinum oxide.* A solution of 5 g. of the piperidone (IV) in 100 ml. of absolute methanol and 5 ml. of acetic acid was reduced over 0.2 g. of platinum oxide at a pressure of 3 atm. of hydrogen at room temperature for 40 min. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure, and the residue was dissolved in aqueous hydrochloric acid. The acidic solution was extracted once with ether, and the extract was discarded. The aqueous solution was made basic with potassium hydroxide solution and extracted with ether. Concentration of the ethereal extracts yielded crystalline material which, on recrystallization from 95% ethanol, gave 2.32 g. of β-alcohol, m.p. 160–165°. Evaporation of the mother liquor gave 0.72 g. of impure solid, 300 mg. of which was chromatographed on basic alumina using a solution of four parts benzene and one part low-boiling petroleum ether. A dry ether eluent produced 170 mg. of β-alcohol, m.p. 161–166°, and some impure material which was rechromatographed to give 30 mg. of β-alcohol, m.p. 160–165°, and 50 mg. of crude material melting below 130°. It is possible that the basic alumina caused isomerization of the alcohols converting any α-alcohol produced in the reaction to the β-isomer.

(e) *With hydrogen over Raney nickel.* A solution of 4.5 g. of IV in 100 ml. of absolute methanol was hydrogenated at low pressure at room temperature over Raney nickel catalyst. The product was isolated as in (d) yielding 2.37 g. of a mixture consisting chiefly of unreduced IV. Treatment of 0.5 g. of the reduction product, m.p. 135–138°, with hydroxylamine produced 0.52 g. of an oxime, m.p. 186–190°, which did not depress the melting point of an authentic sample of the oxime of 2,6-diphenyl-1-methyl-4-piperidone (IV).

(f) *With hydrogen over platinum oxide in strongly acidic solution.* A solution of 5 g. of the piperidone (IV), 100 ml. of methanol, and 1.6 ml. of concentrated hydrochloric acid was treated with 3 atm. of hydrogen over 0.2 g. of platinum oxide at room temperature for 4.5 hr. The precipitated hydrochloride of VI and catalyst were removed by filtration. The mixture of solids was neutralized, triturated with methanol, and the catalyst separated by filtration. Concentration of the methanolic solution yielded 2.21 g. of VIb, m.p. 167–169°.

The acidic filtrate from the separation of the hydrochloride of VIb was concentrated and neutralized with potassium hydroxide solution yielding 1.28 g. of a mixture of the alcohols, m.p. 154–170°. Recrystallization of the mixture from benzene gave a small amount of the β-alcohol as the only pure component.

Equilibration of the isomeric alcohols (VI). (a) *With sodium methoxide.* A solution of 0.35 of the α-alcohol (VIa), 10 ml. of anhydrous methanol, and 0.2 g. of commercial sodium methoxide was heated under reflux for 2.5 hr. On addition of water, the piperidinol precipitated and was separated by filtration giving a quantitative recovery of the α-alcohol (VIa), m.p. 153–154°.

(b) *With sodium amyloxide and VIa.* Sodium amyloxide was prepared by dissolving 0.5 g. of sodium in 10 g. of amyl alcohol, and the solution was added to 5 ml. of amyl alcohol containing 0.35 g. of VIa recovered from (a) above. The solution was heated under reflux for 3.5 hr., cooled, and poured into 20 ml. of water. The mixture was acidified with hydrochloric acid and was extracted with ether to remove the amyl alcohol. The aqueous solution was made basic with potassium carbonate and extracted with ether. The extracts were dried over potassium carbonate, and the solvent was removed by distillation yielding, as a residue, 0.2 g. of a mixture of the alcohols, m.p. 156–159°. Recrystallization failed to resolve the mixture of alcohols.

(c) *With sodium amyloxide and VIb.* A solution of sodium amyloxide prepared from 1.0 g. of sodium and 15 g. of amyl alcohol was added to 1.0 g. of VIb, m.p. 166–167°,

(32) A. L. Wilds, *Org. Reactions*, II, 203 (1944).

and the solution was heated under reflux for 3 hr. The product was isolated as in (b) yielding 0.91 g. of material which melted at 166–168°. None of the α-alcohol was isolated from the reaction mixture.

(d) *With lithium aluminum hydride–aluminum chloride.* An ethereal solution of 0.6 g. of the α-alcohol (VIa) was added to a mixture of 0.1 g. of lithium aluminum hydride and 1.38 g. of aluminum chloride in 30 ml. of dry ether. The mixture was heated under reflux for 2.5 hr. and 5 ml. of acetone was added to decompose the reagent. Water was added, and the ether layer was decanted. The basic mixture was acidified with hydrochloric acid and extracted with ether, and the ethereal extracts were discarded. The aqueous solution was made strongly basic with sodium hydroxide solution and extracted with two 30-ml. portions of ether. After the ethereal extracts were dried over sodium sulfate, distillation of the solvent yielded 0.5 g. of crude material, m.p. 148–154°. Chromatographic separation of 300 mg. of the mixture on basic alumina as described in (d), under reduction of IV, yielded 130 mg. of β-alcohol, m.p. 170–173°, 100 mg. of α-alcohol, m.p. 153–156°, and 60 mg. of a mixture of the alcohols.

Attempted resolution of 2,6-diphenyl-1-methyl-4-piperidone (IV). A solution of 4.7 g. of (+)-10-camphorsulfonic acid in methanol-ether solution was added to a solution of 5.0 g. of 2,6-diphenyl-1-methyl-4-piperidone (IV) in methanol-ether. The precipitated salt was removed by filtration and failed to show any change in optical rotation, $[\alpha]_D^{25}$ +10.6° (ethyl alcohol, $c = 2.1$), on three recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{28}H_{35}NO_5S$: C, 67.58; H, 7.09. Calcd. for $C_{28}H_{35}NO_5S \cdot H_2O$: C, 65.22; H, 7.23. Found: C, 65.67; H, 7.42.

(+)-2,6-Diphenyl-1-methyl-4-piperidoneoxime (VIII). A solution of 6 g. of (+)-10-camphorsulfonic acid, prepared by suspending the acid in 60 ml. of dry ether and adding methanol until solution was effected, was added to an ether solution containing 6 g. of the oxime (VIII) of 2,6-diphenyl-1-methyl-4-piperidone. The salt crystallized as needles, 10.9 g., m.p. 155–160°. Fractional crystallization of 22.7 g. of the salt from methanol and ether gave 4.15 g., m.p. 167.5–172° (dec.), $[\alpha]_D^{25}$ +30.08° (95% ethanol, c = 2.0). A portion of the salt was recrystallized from acetone yielding 2.5 g., m.p. 172–175° (dec.), $[\alpha]_D^{25}$ +31.61°. When the methanolic ether solution of the salt was seeded with a small crystal of the dextrorotatory isomer and allowed to stand in a refrigerator overnight, 10 g. of the oxime produced 7.8

g. of the salt, m.p. 164–170° (dec.), $[\alpha]_D^{26}$ +26.35°, after one recrystallization from methanol-ether.

Anal. Calcd. for $C_{28}H_{36}N_2O_5S$: C, 65.60; H, 7.08. Found: C, 65.67; H, 7.43.

A solution of 3.0 g. of the (+)-10-camphorsulfonic acid salt of the oxime (VIII), $[\alpha]_D^{25}$ +30.06°, was neutralized with aqueous potassium carbonate. The precipitated oxime, 1.6 g., was removed by filtration and washed with water. Recrystallization of the crude solid from ethanol gave 1.05 g. of oxime, m.p. 188–192°, $[\alpha]_D^{25}$ +32.63° (95% ethanol, $c = 2.2$); $[\alpha]_D^{25}$ +31.16° (benzene, c = 1.8).

Attempts to obtain the levorotatory isomer of the oxime by adding base to the filtrates from which the dextrorotatory salt had been isolated failed to yield crystalline material in most cases. A few experiments gave crystalline oxime which had no significant rotation.

Reaction of oxime (VIII) *with* (+)-10-camphorsulfonic acid. An equimolar mixture of the oxime (VIII) and (+)-10-camphorsulfonic acid was added to 95% ethanol, and the solution was heated under reflux for 8 hr. The specific rotation of the solution showed a decrease of 4.76°.[33] When the oxime was freed of the acid, the oxime, m.p. 187–189.5°, had a specific rotation of −0.40° ± 0.19°. After removal of the oxime, the oily residue was chromatographed on basic alumina, and small amounts of 2,6-diphenyl-1-methyl-4-piperidone (IV) and dibenzalacetone were obtained.

Hydrolysis of (+)-2,6-diphenyl-1-methyl-4-piperidone-oxime (VIII). A mixture of 10 ml. of concentrated hydrochloric acid, 20 ml. of water, 1.0 g. of the oxime, $[\alpha]_D^{25}$ +15°, and 1.0 g. of a 50% aqueous solution of pyruvic acid was heated under reflux on a steam bath for 1 hr., cooled, and diluted with water. On basification of the solution with aqueous potassium carbonate, a precipitate formed and was separated by filtration. Trituration of the solid with ether gave 0.22 g. of 2,6-diphenyl-1-methyl-4-piperidone, m.p. 148–151°, which did not depress the melting point of authentic IV. From 1.5 g. of the oxime, $[\alpha]_D^{25}$ +21°, 0.3 g. of recrystallized ketone (IV) was obtained from a similar reaction. A solution of the two samples of the ketone (IV) in an alcohol-acetone solution gave no significant rotation of plane polarized light.

Durham, N. H.

(33) When (+)-10-camphorsulfonic acid was heated with 95% ethanol, no change in the specific rotation was observed.

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

The Conductivity, Dielectric Constants, and E.m.f.'s of Some Ethylmagnesium Compounds

RAYMOND E. DESSY AND RICHARD M. JONES

The conductivity of ethereal solutions of "ethylmagnesium bromide,"[1] diethylmagnesium, magnesium bromide, and mixtures of diethylmagnesium and magnesium bromide have been measured. Some discrepancies existing in the literature have been rectified. Some data on the dielectric constants of these solutions are presented. An observed linear relationship between the ln (molar conductance) of "ethylmagnesium bromide" solutions and the e.m.f.'s of such solutions is discussed.

The first report of the electrical conductivity of ethereal solutions of "ethylmagnesium bromide" was by Jolibois,[2] and this report was confirmed in a preliminary paper by Nelson and Evans.[3] A study by Kondyrew[4] indicated that the equivalent conductance decreased with increasing concentration while a study of "ethylmagnesium iodide"[5] showed a maximum. The results of a study of "ethylmagnesium bromide" by Evans and Lee[6] indicated that the molar conductance increased with decreasing concentration. This apparent discrepancy was explained by Evans in analogy with the "ethylmagnesium iodide" work as being due to a difference in the concentration ranges used for the two studies. Evans felt that the "ethylmagnesium bromide" should also show a maximum. A critical evaluation of Kondyrew's work shows, however, that both investigations were carried out in the same range of concentration. The original misinterpretation by Evans arose because of the frequency with which Kondyrew changed his definition of formula and equivalent weight.

Since the electrical properties of such solutions may in time lead to a better understanding of the structure of the Grignard reagent, it was evident that a careful reinvestigation of the conductivity of "ethylmagnesium bromide" was necessary.

It has recently been found[7] that the presence of tertiary amines markedly increases the rate of reaction of Grignard reagents with certain substrates. While this effect has been studied in other ways[8,9] no conductance data has been reported.

The purpose of this paper is therefore fourfold: (1) to resolve the difference in the values of conductance reported for "ethylmagnesium bromide," (2) to provide some data on the conductance of a Grignard reagent in the presence of a tertiary amine, (3) to shed some light on the constitution of "ethylmagnesium bromide" solutions by a study of the conductances of some diethylmagnesium–magnesium bromide systems, and (4) to present some data concerning the dielectric constants of some of these solutions.

In addition some correlations with observed e.m.f. values will be presented, and some tentative explanations for these correlations offered.

EXPERIMENTAL

Ether. Merck Anhydrous Analytical Reagent freshly distilled from "ethylmagnesium bromide."

Ethylmagnesium bromide. The "ethylmagnesium bromide" was prepared in the usual manner from ethyl bromide and magnesium turnings in ethyl ether.[10]

The magnesium used was Mallinckrodt magnesium metal turnings. The ethyl bromide was freshly distilled. The bromine/basic Mg ratio was 1.09.

Diethylmagnesium. Prepared as previously described.[11]

Magnesium bromide in ether. Prepared as previously described.[12]

Since it was felt that the vigorous reaction conditions indicated by this method (direct bromination of magnesium in ether) might lead to erroneous results the magnesium bromide was prepared from the hexahydrate by fusion with ammonium bromide followed by dissolution in ether. The two solutions showed no difference with respect to conductivity. Magnesium bromide in ether forms a two phase system—the heavy lower layer showing a concentration of $MgBr_2$ of $2.63M$, the light upper layer a concentration of $0.138M$. Depending upon the final concentration desired both layers were used.

(1) Since evidence seems to indicate that no such species as $C_2H_5\text{-Mg-Br}$ exists in ethereal solution, quotation marks will be used around the name ethylmagnesium bromide to indicate a reagent prepared from ethyl bromide and magnesium. No actual structure is meant to be implied. *Cf.* R. E. Dessy and G. S. Handler, *J. Am. Chem. Soc.,* **80,** 5824 (1958).

(2) P. Jolibois, *Compt. rend.,* **155,** 353 (1912).

(3) J. M. Nelson and W. V. Evans, *J. Am. Chem. Soc.,* **39,** 82 (1917).

(4) N. W. Kondyrew and D. P. Manogew, *Ber.,* **58B,** 464 (1925).

(5) N. W. Kondyrew and A. K. Ssusi, *Ber.,* **62B,** 1856 (1929).

(6) W. V. Evans and F. H. Lee, *J. Am. Chem. Soc.,* **55,** 1974 (1933).

(7) J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Org. Chem.,* **20,** 1949.

(8) J. H. Wotiz, C. A. Hollingsworth, R. E. Dessy, and Lang Ching Lin, *J. Org. Chem.,* **23,** 228 (1958).

(9) J. H. Wotiz and A. W. Simon, 133rd Meeting, ACS, San Francisco, Calif., April 13-18, 1958, Division of Organic Chemistry, p. 7N.

(10) *Cf.* J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Org. Chem.,* **20,** 1545 (1955).

(11) R. E. Dessy and G. F. Handler, *J. Am. Chem. Soc.,* **80,** 5824 (1958).

(12) J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Org. Chem.,* **21,** 1063 (1956).

Triethylamine. The triethylamine was purified by distillation from "ethylmagnesium bromide" followed by storage in sealed ampoules.

Handling of reagents. All reagents were handled with hypodermic syringes in dry boxes, polyethylene bags filled with an inert atmosphere, etc. All glass ware was suitably dried at 110°. The reagents were stored in serum-capped bottles in desiccators. Care was taken to prevent oxygen contamination at all steps.

Conductivity measurements. The conductivity measurements were made using the following bridge: The source unit was an audio frequency generator giving variable frequencies from 10–100,000 c.p.s. at a level of from 0–10 v. The bridge itself was a Heath Model 1B-2A Impedance Bridge modified to accept compensating capacitors. The detector was a VTVM feeding an amplified signal to an oscilloscope which was used as a final balance indicator in the manner described by Fuoss.[13]

The cell was a spherical glass container possessing 2 bright platinum electrodes 3 cm. in diameter placed 5 mm. apart. The cell constant was 0.04. The reagents were added through a capillary side arm protected by a stopcock.

Dielectric measurements. The dielectric measurements were made in a Sargent Model V Chemical Oscillometer at 5 megacycles using a cell with external electrodes.

DISCUSSION AND RESULTS[14]

Fig. 1 shows plots of molar conductance *vs.* concentration for "ethylmagnesium bromide" and diethylmagnesium. The data for "ethylmagnesium bromide" agree well with those of Evans[6] and indicate that the work of Kondyrew[4] is in error. On the chance that the two workers may have
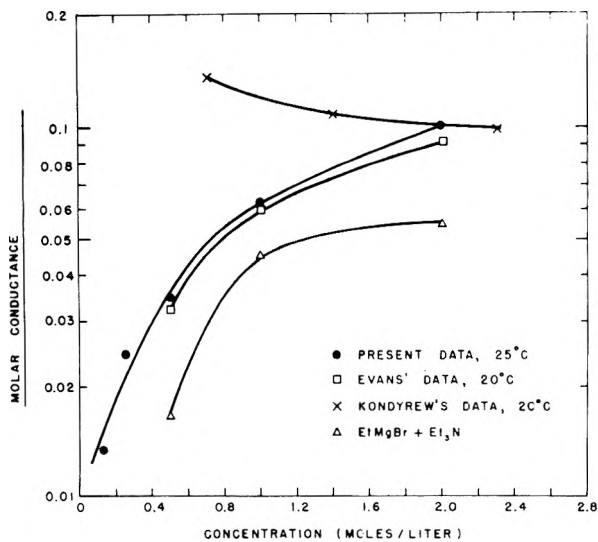

Fig. 1. Plots of molar conductance *versus* concentration for "ethylmagnesium bromide" as reported by various workers

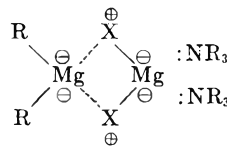(13) R. M. Fuoss and D. Edelson, *J. Chem. Ed.*, **27**, 610 (1950).

(14) Because of the difficulty in assigning a definite structure to "ethylmagnesium bromide" it is necessary to define clearly what a mole is in presenting conductivity data. In all of the data which follows a mole of "ethylmagnesium bromide" will be taken as the formula weight of the unit C_2H_5MgBr, and there will be, by definition, one equivalent weight per mole. For diethylmagnesium one mole will be, as usual, taken as the formula weight of the unit $(C_2H_5)_2Mg$, with *two* equivalents per mole.

been working at different frequencies, an experimental condition not reported, the effect of frequency on conductance was examined.

From 300–100,000 c.p.s. no appreciable change in conductance values was noted. There appears to be no logical explanation for the erroneous data reported by Kondyrew. In any event, all of the data for other Grignard reagents reported by him are open to question.

Fig. 1 also shows the results of the addition of equimolar amounts of triethylamine to solutions of "ethylmagnesium bromide." By varying the amount of amine at a fixed concentration of "ethylmagnesium bromide" it was found that the conductance varied approximately inversely with the amount of amine present.

Examination of reaction rate data of "ethylmagnesium bromide" with hexyne-1 would lead to the tentative conclusion that the ionization is enhanced by the addition of amine.[8] The mechanism of such an effect would be through the coordination of the amine with the magnesium-bearing Lewis acid species in solution. This coordination would be a replacement of the previously coordinated ether by the more basic amine. The greater electron donor ability of the amine would then facilitate the release of a carbanion from such a structure as

$$
\begin{array}{c}
\text{R} \quad \overset{\oplus}{\text{X}} \\
\diagdown \ominus \diagdown \ominus \\
\quad \text{Mg} \quad \text{Mg} \quad :\text{NR}_3 \\
\diagup \ominus \diagup \ominus \\
\text{R} \quad \text{X} \quad :\text{NR}_3 \\
\quad \underset{\oplus}{\ }
\end{array}
$$

Since it has been found[8] that the relative reactivity of diethylmagnesium with hexyne-1 is unaffected by the presence of triethylamine there appears to be good justification for associating the amine with the magnesium bromide.

Unfortunately the conductance data belies the foregoing proposals and any others which would give enhanced ionization or dissociation as the reason for greater reactivity. Further investigation seems to be indicated in order to resolve the effect of amines on the reactivity of Grignard reagents.

Table I shows the results of conductance measurements on various mixtures of diethylmagnesium and magnesium bromide.

It is interesting to note that over the concentration ranges employed that the log (specific conductivity) *versus* molar concentration for diethylmagnesium is linear. It is hoped that this will prove valuable in future kinetic investigations. It is also apparent from the data that diethylmagnesium and magnesium bromide interact when mixed to form a system which is more conducting than would be predicted from the conductivity of the two components.

This appears to be quite logical since diethylmagnesium may act as a Lewis acid and magnesium

TABLE I
THE CONDUCTANCE OF VARIOUS MIXTURES OF DIETHYL-
MAGNESIUM AND MAGNESIUM BROMIDE AT 25° IN ETHER

Molar Et$_2$Mg	Concentration MgBr$_2$	Specific Conductance ohm^{-1} cm.$^{-1}$ ($\times 10^4$)
0.139	. . .	0.013
0.250	. . .	0.032
0.500	. . .	0.092
1.000	. . .	0.328
. . .	0.069	0.079
. . .	0.139	0.056
0.139	. . .	0.013
0.139	0.139	0.460
0.125	0.500	Two Phase System
0.250	0.500	1.15
0.500	0.500	2.26
0.750	0.500	2.57
0.500	0.125	0.370
0.500	0.250	6.89
0.500	0.500	2.26
0.500	0.750	2.30

bromide as a Lewis base. Together they would then form a complex which would have a greater ability to ionize than either one as an individual. The data thus support a structure for "ethylmagnesium bromide" of the type Et$_2$Mg·MgBr$_2$.

It is somewhat disconcerting to compare the values for solution 0.5M in magnesium bromide and 0.5M in diethylmagnesium with solutions 1.0M in "ethylmagnesium bromide." Work indicates that the same species is (are) present in both solutions.[15] In spite of this the values of specific conductance of the two systems are at variance with each other (2.26·10^{-4} ohm^{-1} cm.$^{-1}$ for Et$_2$Mg, MgBr$_2$; 0.61·10^{-4} ohm^{-1} cm.$^{-1}$ for "EtMgBr"). Two different lots of ethylmagnesium bromide were made and run to check this discrepancy and it was found in both cases. The method of preparing the magnesium bromide was also varied but no change in conductivity was noted. Considering the crude synthetic methods involved in the preparation of the reagents and the inability to purify it is not difficult to foresee side reactions which could create this difference. However, it is still a most unfortunate circumstance.

Two other points should be noted (1) that as the diethylmagnesium concentration is increased in a solution containing a fixed amount of magnesium bromide, the specific conductivity increases, as would be expected, but that (2) as the magnesium bromide concentration is increased in a solution containing a fixed amount of diethylmagnesium the specific conductivity goes through a distinct maximum, and then falls to a constant level.

Table II presents the dielectric constants *versus* concentration for various ethylmagnesium systems.

(15) R. E. Dessy and G. S. Handler, *J. Am. Chem. Soc.*, 79, 3476 (1957).

The measurements were made on a Sargent Model V Oscillometer at 5 megacycles. Above specific conductances of 10^{-4} the conductivity of the solutions will effect the apparent capacity of the cell by introducing a conductive path having a resistance. Therefore above 1 molar concentrations values could not be measured.

TABLE II
THE DIELECTRIC CONSTANTS (K) OF VARIOUS ETHYLMAGNESIUM SYSTEMS AT 25° IN ETHER

System	Molar Concentrations	K
"EtMgBr"	0.125	5.1
	0.250	6.5
	0.500	11
	0.750	20
	1.000	35
Et$_2$Mg	0.125	4.6
	0.250	5.3
	0.500	6.6
	0.750	9.0
	1.000	11
"EtMgBr" + Et$_3$N	1.00	30
Et$_2$Mg + Et$_3$N	0.500	6.2

The dielectric constant of ethereal solutions of diethylmagnesium is a linear function of the concentration, indicating that no serious association is occurring; the data for "ethylmagnesium bromide" indicate increasing association.

In both cases the addition of triethylamine reduces the dielectric constant, thus confirming the results of the conductivity measurements.

One very interesting detail should be pointed out. It is often assumed in many discussions of reactions of organometallic compounds in nonpolar solvents that the medium cannot support ionic mechanisms in the ordinary sense of the word because of its low dielectric. The present data indicates that a one molar solution of Grignard reagent in ether does indeed present a highly polar environment.

It is interesting to speculate, rather freely it is admitted, on the relationship between the present data and that reported by Gay[16] on the e.m.f.'s of various concentrations of ethylmagnesium bromide in ether using a Pt-calomel electrode system (Table III). Gay showed that the observed potential, E$_c$, could be expressed as follows

$$E_c = E_c^0 + \frac{RT}{F} \ln (c)^2 \qquad (1)$$

where E_c° is the potential of a solution of unit activity, taken as 1 molar, n is the number of

(16) Unpublished results by F. R. Gay, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Del. Abstracts of Papers, 131st Meeting, American Chemical Society, Miami, Fla., 1957, p. 50-O.

TABLE III

RELATIVE POTENTIALS[a] OF "ETHYLMAGNESIUM BROMIDE" SOLUTIONS

M	E.m.f.
1.28	1.255
0.65	1.227
0.59	1.221
0.29	1.195
0.185	1.181
0.099	1.150

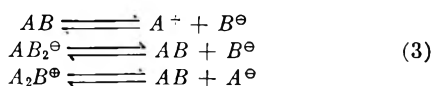[a] Uncorrected for Pt-saturated calomel electrode potentials.

Faraday's per mole involved, R is the gas constant, T the absolute temperature, F the Faraday, and (c) the concentration of Grignard.

The present conductivity data for ethylmagnesium bromide can be represented in the form

$$\ln (\Lambda) = k \ln (c) + k' \qquad (2)$$

where Λ is the molar conductance and k and k' are constants having the values 0.7 and 1.22 respectively.

If one assumed that in solvents of sufficiently low dielectric constant triple ions of the type $(+ - +)$ or $(- + -)$ are stable, and that they arise from equilibria of the following nature

$$\begin{aligned} AB &\rightleftharpoons A^+ + B^{\ominus} \\ AB_2^{\ominus} &\rightleftharpoons AB + B^{\ominus} \\ A_2B^{\oplus} &\rightleftharpoons AB + A^{\ominus} \end{aligned} \qquad (3)$$

it is easy to show[17] that

$$\Lambda = K_1 c^{-1/2} + K_2 c^{1/2} \qquad (4)$$

if one assumes that c_{AB}, the concentration of AB, is equal to the stoichiometrical concentration c— in other words, that little ionization and/or dissociation occurs. As c increases the molar conductance will pass through a minimum, and eventually yield a curve in which the molar conductance is direction proportional to $c^{1/2}$, or $\ln \Lambda = 0.5 \ln (c) + k'$. The observed slope 0.7, therefore seems to indicate that the conductivity measurements support triple ion formation in Grignard reagents in ether, and that these are the current carriers. Previous rough measurements of transport numbers[15] have also indicated that the ions are large aggregates, probably involving 2 or 3 molecules, since the amount of material transported during an electrolysis of ethylmagnesium bromide is approximately 4 times that discharging at the electrodes.

It is obvious that we may relate E_c and V as follows

$$E_c = K \ln \Lambda + K' \qquad (5)$$

where K and K' are again constants. The physical significance of this relationship is not difficult to

conceive if one assumes that the species responsible for the conductivity of the solution are those responsible for the e.m.f. It has recently been shown[18] by tracer techniques that the Grignard reagent is best written as a complex $Et_2Mg \cdot MgBr_2$, and that in the electrolysis of ethyl Grignard the ionization appears to involve

$$Et_2Mg \cdot MgBr_2 \rightleftharpoons EtMg^{\oplus} + EtMgBr_2^{\ominus} \qquad (6)$$

These species, involved in discharge, might reasonably also be involved in the conductivity and e.m.f. processes, although, one realizes that the species that discharges is not necessarily the main current carrier.

This speculation receives support from the fact that the relative e.m.f.'s of various Grignard reagents, such as ethyl, i-propyl, t-butyl, n-propyl, and i-butyl, at 1 molar concentrations, as determined by Gay, are approximately inversely related to the decomposition potentials, E_d, of these same Grignard reagents as determined by Evans.[19] Although the electrode processes are not necessarily the same, the relationship seems reasonable. If these three processes (1) conductivity (2) e.m.f. and (3) decomposition potential do have a species concentration in common it is perhaps worth while to carry the extrapolation a little bit farther. It has been pointed out[20] that there is a linear relationship between E_d, and the ln (relative rate) as determined by the reaction

$$\begin{aligned} R-C \equiv C-H + R'MgX &\longrightarrow \\ R'H + R-C \equiv C-MgX \end{aligned} \qquad (7)$$
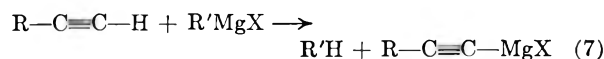
for the Grignards mentioned above. The decomposition potential can be expressed as

$$E_d = E^{\circ} - \frac{RT}{aF} \ln q \qquad (8)$$

where a is a constant and q is the activity quotient given by

$$q = \frac{a \,(\text{product})}{a \,(\text{Grignard reagent})} \qquad (9)$$

If E° is assumed constant throughout the series together with the activity of the products, then E_d will be a function of a(Grignard reagent). The linear relationship suggests that the rate of equation (7) could be given by

$$d\frac{(RH)}{dt} = c(1/q)^n a(R-C \equiv C-H)^m \qquad (10)$$

where c, m, and n are constants. This would imply that the activation energy is constant throughout the series and that variations in E_d and relative reactivity are reflections of changes in the activity

(17) M. Dole, *Principles of Experimental and Theoretical Electrochemistry*, p. 78, McGraw-Hill Book Co., Inc., New York, 1935.

(18) R. E. Dessy, G. S. Handler, *J. Am. Chem. Soc.*, 80, 5824 (1958).

(19) W. V. Evans, F. H. Lee, and C. H. Lee, *J. Am. Chem. Soc.* 57, 489 (1935).

(20) R. E. Dessy, C. A. Hollingsworth, and J. H. Wotiz, *J. Am. Chem. Soc.*, 77, 4410 (1955).

of the reactive species in both reactions, regardless of its form.

The resonance stabilization of carbanions (free or incipient) that has been proposed by Polanyi[21] could explain the order of the reaction rates and decomposition voltages if the results obtained by assuming $E°$ a constant are used.
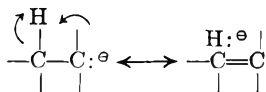
It thus appears that all four sets of data can be tied together in a common ground—the concentration, or availability of, a common ion.

Work is presently being carried out using both conductivity measurements and dielectric constant measurements as a method of following the rates

(21) E. C. Bangham, M. G. Evans, and M. Polanyi, *Trans. Faraday Society*, 37, 377 (1947).

of reaction of Grignard reagents with various substrates.

Synthesis of (−)-6-exo,7-endo-Dihydroxy-3-tropanone; An Optically Active Product from a Robinson-Mannich Condensation[1]

ROBERT STERN[2] AND HARRY H. WASSERMAN

Oxidation of 3,4-monoacetone-D-mannitol (I) by means of lead tetraacetate, followed by acid hydrolysis and treatment of the resulting L-tartardialdehyde solution with acetone dicarboxylic acid and methylamine hydrochloride, resulted in the formation of (−)-6-exo, 7-endo-dihydroxy-3-tropanone (IVa).

We wish to report the synthesis of (−)-6-exo, 7-endo-dihydroxy-3-tropanone[3,4] ("levorotatory teloidinone"), using D-mannitol as starting material, and involving L-tartardialdehyde[6] as an intermediary product. Our results, along with other recent work in this field,[7] show that a Mannich-type reaction involving an enolizable optically active alde-

hyde, R′—CH—CHO, can lead to an optically ac-
$\diagup$
R

tive condensation product.

Partial hydrolysis of triacetone-D-mannitol,[8] obtained from D-mannitol and acetone, yielded 3,4-monoacetone-D-mannitol,[9] I, m.p. 86–88°, $[\alpha]_D^{20.0}$ +23.0. The oxidation of I with pure lead tetraacetate according to the procedure of Fischer and Appel afforded acetone-L-tartardialdehyde[10] (acetone-D-α,α'-dihydroxysuccindialdehyde), II, an intermediate which was not isolated. Hydrolysis of the crude reaction product with 0.1N sulfuric acid, to

(1) Presented at the 131st Meeting of the American Chemical Society in Miami, Fla., April 8, 1957.

(2) Present address: Dept. of Chemistry, Connecticut College, New London, Conn.

(3) We are using the *exo-endo* designations in describing derivatives of tropane (*N*-methyl-8-aza-[1, 2, 3]-bicyclo-octane) in accordance with the usage of K. Alder and H. A. Dortmann, *Ber.* 86, 1545 (1953). An alternate nomenclature used for tropane derivatives has been adapted from steroids by G. Fodor and K. Nador, *J. Chem. Soc.*, 722 (1953).

(4) The absolute configuration of this optically active compound is identical to that of L(−)-tartaric acid.[5] It can be called R(−)-6,7-dihydroxy-3-tropanone, according to a general stereochemical nomenclature recently proposed by R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956).

(5) (a) K. Freudenberg, "Stereochemie", Franz Deuticke, Leipzig and Wien, 1933, p. 668; (b) C. D. Nenitzescu, *J. Chem. Educ.*, 34, 147 (1957).

(6) An alternative designation of this compound is D-α,α'-dihydroxysuccindialdehyde.

(7) Since we first reported our results [see footnote (1)] E. Hardegger and H. Furter, *Helv. Chim. Acta,* 40, 872 (1957), have published the account of an independent synthesis of s(+)-6,7-dihydroxy-3-tropanone from D(+)-tartaric dialdehyde. Their condensation product is the dextrorotatory enantiomer of the one we have prepared. Furthermore, K. Zeile and A. Heusner, *Ber.*, 90, 1869 (1957), have recently published an independent synthesis of (−)-alloteloidinone, a product which appears to be identical with our material.

(8) E. Fischer, *Ber.*, 28, 1167 (1895).

(9) L. F. Wiggins, *J. Chem. Soc.*, 13 (1946).

(10) H. O. L. Fischer and H. Appel, *Helv. Chim. Acta*, 17, 1574 (1934).
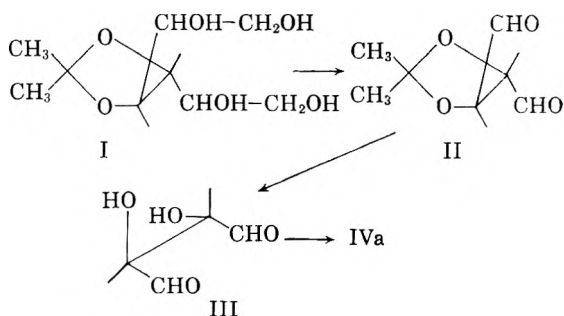
remove the isopropylidene protecting group (cf. III), was followed by treatment with excess methylamine hydrochloride and excess acetonedicarboxylic acid, under slightly modified conditions of the usual Robinson synthesis.[11] Extraction with ether and crystallization from isopropanol afforded the condensation product IVa in the form of large white prisms, m.p. 183.5–185.0°, $[\alpha]_D^{25.0}$ -37.64 ± 0.90 (in water).

The melting point and the optical activity of this material show clearly that it does not possess the stereochemical structure of the known teloidinone,[11] V, a *meso* compound. The infrared absorption spectrum of the levorotatory adduct in the solid state (potassium bromide) is very similar to that of an authentic sample of $(\pm)$-6,7-dihydroxy-3-tropanone, IVb, recently prepared by Sheehan.[12] In pyridine solution, on the other hand, our optically active material and Sheehan's compound[12] exhibit completely superimposable infrared absorption spectra. The structure of adduct IVa is thus $(-)$-6-*exo*,7-*endo*-dihydroxy-3-tropanone.

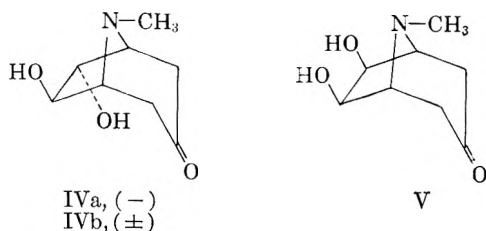

IVa, $(-)$
IVb, $(\pm)$

V

The following observations are significant in connection with these experiments:

(a) No optically inactive tropane derivative, whether it be *racemic* or *meso* could be isolated from the reaction mixture in repeated condensations utilizing the above components. The fact that optical integrity was thus preserved shows that the Robinson synthesis and related Mannich-type condensations can take place without racemization of an optically active center adjacent to the aldehyde function.

(b) The successful synthesis of adduct IVa shows clearly that tropanone derivatives with substituents in the *endo*-configuration at C-6 or C-7 (both of which have their origin in the aldehyde component of the condensation, cf. IVa) can be formed[13] in the Robinson synthesis.[14]

EXPERIMENTAL[17]

1,2,3,4,5,6-Triacetone-D-mannitol. This compound, m.p. 67–68°, was prepared from commercial D-mannitol and acetone in the presence of sulfuric acid according to the procedure of Wiggins[9] and that of Fischer.[8] Our yield was 53% as compared to 75% reported by Wiggins.

3,4-Monoacetone-D-mannitol (I). The following modification of Wiggins' procedure[9] gave best results when adapted to a larger scale: 1,2,3,4,5,6-Triacetone-D-mannitol (60.4 g.; 0.2 mole) was dissolved in 1200 ml. of 70% acetic acid and the solution heated to 40° for 30 min. The solvent was then removed *in vacuo* at 40–50°, an operation that took 2 hr. The residue was taken up in 750 ml. of boiling acetone, the solution filtered from insoluble mannitol, concentrated to 250 ml. and poured into 1300 ml. of boiling benzene. Concentrating the solution to 700 ml. and cooling yielded 33.5 g. (75.4% yield) of white crystals, m.p. 75–84°. Three consecutive crystallizations from ethyl acetate and benzene raised the melting point to 86–88°. Wiggins[9] reported a melting point of 86–87° for this compound; Fischer and Appel,[10] and Irvine and Patterson[18] recorded 85° as the m.p.

Oxidation of 3,4-monoacetone-D-mannitol (I) *to L-tartardialdehyde*[6] (III). 3,4-Monoacetone-D-mannitol (22.22 g., 0.1 mole) was added to a solution of 88.6 g. (0.2 mole) of lead tetraacetate in 400 ml. of hot benzene, and the mixture was heated on the steam bath for about 5 min. with constant agitation. After a positive starch–iodide reaction was obtained, the benzene solution was cooled to 5°, filtered, and the precipitate washed with benzene. The solvent was removed from the combined benzene phase *as fast as possible* by distillation under reduced pressure (oil-pump vacuum) at a temperature (5°) just above the melting point of the mixture.

The dialdehyde residue, a viscous oil, was taken up in 150 ml. of 0.18N sulfuric acid, and the solution heated on the steam bath for a few minutes until all of the oil had dissolved. The solution was allowed to stand for about 3 hr. and was then filtered from the precipitated lead salts. Finally, the dialdehyde solution was concentrated to about 65 ml. under reduced pressure (oil-pump) and *without heating*, in order to remove the acetone formed during hydrolysis, and was brought to a pH of 5 by careful addition of solid sodium bicarbonate. The dialdehyde III was not isolated; it was used in the form of its aqueous solution for the subsequent Robinson condensation.

(11) (a) C. Schöpf and W. Arnold, *Ann.*, **558**, 109 (1947); (b) J. C. Sheehan and B. M. Bloom, *J. Am. Chem. Soc.*, **74**, 3825 (1952).

(12) An authentic sample of this compound was kindly made available to us by Professor J. C. Sheehan of the Massachusetts Institute of Technology. *Cf.* G. Fodor, *Tetrahedron*, **1**, 95 (1957).

(13) See in this connection: (a) K. Alder and H. A. Dortmann, *Ber.*, **86**, 1545 (1953); (b) J. Keberle and P. Karrer, *Helv. Chim. Acta*, **37**, 484 (1954).

(14) The possibility [G. Fodor, *Experientia*, **11**, 138 (1955)] that a 6-*endo*-substituted product may have been obtained previously, as a component of Stoll's synthetic valerinone,[15] is excluded, since on reduction, the latter affords an optically inactive material identical with the 3,6-dihydroxytropane, independently obtained by hydrogenolysis of scopolamine,[16] in which the exclusive *exo*-orientation of the 6-hydroxyl group has been firmly established.[16]

(15) (a) A. Stoll, B. Becker and E. Jucker, *Helv. Chim. Acta*, **35**, 1263 (1952); (b) A. Stoll, A. Lindenmann, and E. Jucker, *Helv. Chim. Acta*, **36**, 1506 (1953).

(16) G. Fodor and O. Kovacs, *J. Chem. Soc.*, 2341 (1953).

(17) All melting points are uncorrected and were taken on a Kofler block.

(18) J. C. Irvine and B. M. Patterson, *J. Chem. Soc.*, 898 (1914).

(−)-6-exo,7-endo-Dihydroxy-3-tropanone[3] (IVa). To an aqueous L-tartardialdehyde solution prepared, as described above, from 22.22 g. (0.1 mole) of 3,4-monoacetone-D-mannitol, there was added 29.2 g. (0.2 mole) of pure acetonedicarboxylic acid dissolved in a buffer prepared from 150 g. of sodium acetate and 425 ml. of distilled water. This was followed by the addition of 13.5 g. (0.2 mole) of pure methylamine hydrochloride dissolved in 30 ml. of distilled water. The very slightly yellow solution had a total volume of about 550–600 ml. and a pH of 5.2. It was allowed to stand for 7 days in a thermostat at 25.0°. A very slow evolution of carbon dioxide started after about 15 min. and the color of the solution darkened gradually.

After 7 days the *cooled* reaction mixture was saturated with solid potassium carbonate. The resulting deep-brown solution was extracted continuously with ether for 7 days. Large crystals separated from the ether extract, and a further small crop of crystals could be isolated by evaporating the solvent. The total weight of the crystalline residue was 3.2 g. (19% yield), m.p. 178–183.5°. Six consecutive crystallizations from isopropyl alcohol afforded pure IVa in the form of white prisms, constant melting point 183.5–185°, constant rotation (measured in a micropolarimeter) in water solution $[\alpha]_D^{25.0}$ −37.64 ± 0.90.

Anal. Calcd. for $C_8H_{13}O_3N$: C, 56.12; H, 7.65; N, 8.18. Found: C, 56.26; H, 7.39; N, 7.98.

The crystals were quite insoluble in ether, chloroform, carbon tetrachloride, carbon disulfide, acetonitrile, and in aliphatic and aromatic hydrocarbons. They were slightly soluble in, and could be recrystallized from, isopropyl alcohol, acetone, and dioxane (solubility approximately 30 g./l.) and dissolved readily in ethyl alcohol and pyridine. The compound was infinitely soluble in water.

The aqueous solution from which the major part of IVa had been removed by ether extraction was evaporated to dryness, and the carefully dried residue, largely inorganic in nature, repeatedly refluxed with several portions of absolute ethyl alcohol. Although both *racemic* IVa and *meso*-teloidinone are very soluble in hot ethyl alcohol, no appreciable quantities of any organic material could be isolated from the alcoholic extracts.

Studies with Quinolines. I. Synthesis of Quinaldic Acid and Some of Its Amide Derivatives[1]

JEFFERSON W. DAVIS, JR.

Quinaldic acid has been prepared and isolated in quantitative yield by the acid catalyzed hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile, using hydrobromic acid in acetic acid as the reaction medium. The use of the quinaldyl radical as a means of identification of primary and secondary amino groups has been demonstrated, and a number of quinaldoamides have been prepared and characterized.

Recent developments in the fields of nutrition and chemotherapy have resulted in a resurgence of interest in amino acids, peptides and proteins, and the need for more reagents for identification and isolation of these important substances has become of prime importance. 1-Fluoro-2,4-dinitrobenzene (FDNB), studied by Sanger[2–4] in his work on insulin, has been used extensively for the identification of amino acids, and particularly for the determination of the N-terminal residues of proteins and peptides. Subsequent workers[5] have prepared DNP-amino acids and studied some of their properties. Yields in many instances were low, and often no crystalline derivatives were obtained. The phthaloyl group[6] has also been used for the identification of amino compounds, but this reagent is limited and its use has not been extended to peptides.

The quinaldyl radical may be used effectively for the identification of primary and secondary amino groups. Amide derivatives are prepared very easily in semiquantitative yields, and have sharp characteristic melting points. These melting points are generally high—a fact which probably accounts for the highly crystalline form of these compounds.

Because of the difficulties involved in the preparation, isolation and purification of the quinaldic acids by existing methods, a thorough investigation of the synthesis of this important class of compounds was undertaken. The original synthesis of the quinaldic acids goes back to the year 1905 when Arnold Reissert[7] found that quinoline, in the presence of alkali cyanide and benzoyl chloride,

(1) The work in this paper was initiated in the Laboratories of Pharmacology of the Pasteur Institute, under the direction of Prof. J. Trefouel, and was supported in part by a grant from the Centre National de la Recherche Scientifique, Paris, France.

(2) F. Sanger, *Biochem. J.*, **39**, 507 (1945).

(3) F. Sanger, *Biochem. J.*, **40**, 261 (1946).

(4) R. R. Porter and F. Sanger, *Biochem. J.*, **42**, 287 (1948).

(5) K. R. Rao and Herbert A. Sober, *J. Am. Chem. Soc.*, **76**, 1328–31 (1954).

(6) John H. Bellman and William F. Harting, *J. Am. Chem. Soc.*, **70**, 1473 (1948).

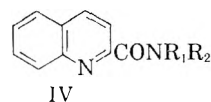(7) A. Reissert, *Ber.*, **38**, 1610 (1905).

formed an addition compound which, on treatment with mineral acid, gave quinoline carboxylic acid and benzaldehyde. These addition compounds have subsequently been termed "Reissert compounds" and are generally formed by the addition of an acyl and cyano group to the azomethine linkage of certain N-heterocycles.
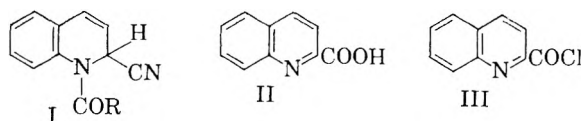
Compounds of the type (I) have been the subject of extensive investigations in recent years,[8] and particular attention has been centered about the formation of aldehydes from the acid catalyzed hydrolysis of these intermediates. In many instances the yields of aldehydes were greater than 90% of theory, but yields of acids were often low and not much superior to those obtained by Reissert. Other investigators[9-11] have prepared quinaldic acid by modifications of Reissert's method and other procedures.

We have found that compounds of the type (I) undergo complete hydrolysis with the evolution of heat in mixtures of aqueous hydrobromic acid and acetic acid. The formation of aldehydes and the corresponding acids is complete within 20 minutes and, with the exception of a trace of pigmented material, these are the only products detected. The acid hydrobromide formed is insoluble in the reaction medium, and is obtained in a very pure state by simple filtration. Yields of from 95 to 100% of pure acid based on (I) were obtained when the acid hydrobromide was treated with excess of ammonium hydroxide and then with excess of acetic acid. High yields of aldehydes were also obtained.

Although quinaldic acid (II) is an amino acid, it may be converted to the acid chloride (III) on treatment with thionyl chloride without formation of the hydrochloride. This acid chloride is stable under ordinary conditions and is only slightly soluble in water, which decomposes it on long standing. It reacts quantitatively with primary and secondary amino compounds, in aqueous or non-aqueous media, with evolution of heat and formation of amide adducts (IV).[12]

(8) W. E. McEwen and R. Lynn Cobb, *Chemical Reviews*, 55, 511 (1955).

(9) Thomas W. J. Taylor, *J. Chem. Soc.*, 1110–11 (1929).

(10) Campbell et al., *J. Am. Chem. Soc.*, 68, 1841 (1946).

(11) Hammick, *J. Chem. Soc.*, 123, 2883 (1923).

(12) These amide derivatives of quinoline carboxylic acid are being studied to determine their action against certain types of tumors and bacteria. Since chelation is possible in many instances, it is felt that they may have some effect on the metabolism of inorganics in the cell. The results of this study will be reported elsewhere.

EXPERIMENTAL

1-Benzoyl-1,2-dihydroquinaldonitrile(I)R=C₆H₅. 1-$Benzoyl$-$1,2$-$dihydroquinaldonitrile(I)R=C_6H_5$. This compound was prepared by the procedure of Reissert[7] in yields of from 90 to 95% of theory. It may be advantageously purified by recrystallization from 60% aqueous acetone. The colorless prismatic needles melted at 155°.

Quinaldic acid hydrobromide. Twenty-five grams of the above purified 1-benzoyl-1,2-dihydroquinaldonitrile was suspended in 25 ml. of glacial acetic acid. To this suspension was added 25 ml. of aqueous hydrobromic acid (d = 1.7). There was an immediate evolution of heat and after several minutes the red-brown reaction mixture was warmed under reflux for 15 minutes. On cooling, the monohydrate of quinaldic acid hydrobromide crystallized. The light brown crystals were collected by filtration with suction and were thoroughly washed with glacial acetic acid and then with ether. After drying under vacuum over sodium hydroxide, the product weighed 28.0 grams and melted with decomposition at 220–224°. When the residue obtained from evaporation of a decolorized aqueous solution of the hydrobromide was recrystallized from 90% acetic acid, the pale yellow crystals melted at 220–221° (dec.):

Analysis:	C%	H%	N%	Br%
Cal. for $C_{10}H_8O_2BrN$,				
H₂O	44.10	3.68	5.15	29.40
Found	44.22	3.78	5.22	29.16
After drying at 110° in vacuum over P₂O₅ for 24 hours:				
Found	46.76	3.17		31.42
Cal. for $C_{10}H_8O_2BrN$...	47.10	3.14		31.40

Quinaldic acid (II). The quinaldic acid hydrobromide monohydrate obtained above was converted to the free acid as follows: 28 gm. of the crude material were dissolved in 50 ml. of hot water and treated with 0.5 gm. of norite. To the almost colorless solution obtained upon filtration was added 20 ml. of concentrated ammonium hydroxide. The ammonium salt, which is only sparingly soluble under these conditions and which may be isolated by filtration was made to dissolve by heating the mixture to boiling. The hot solution, which contained a small amount of insoluble pigmented material, was treated with a small quantity of norite. After filtration, 20 ml. of glacial acetic acid was added to the colorless solution, and on cooling the quinaldic acid dihydrate separated as long colorless needles. The acid was washed several times with ice water, and after drying at 60° for 24 hr. the product weighed 20.1 gm., 96% of theory, and melted at 155–156°. Other runs on a smaller scale gave almost quantitative yields of acid based on Reissert's compound. On recrystallization from 75% acetic acid, the melting point was raised to 156.5–157°. A sample for analysis was dried at 100° over P₂O₅ for 24 hr.

Analysis:	N%
Cal. for $C_{10}H_7O_2N$	8.00
Found	8.22

The melting point was not depressed when the above prepared acid was mixed with an authentic sample of quinaldic acid.

Benzaldehyde. In order to demonstrate that benzaldehyde, and not benzoic acid, was formed in the hydrolysis medium used for the conversion of Reissert's compound to the corresponding acid, the aldehyde was isolated and distilled. An excess of water was added to the mother liquors obtained after removal of the quinaldic acid hydrobromide from the

TABLE I

Yields, Physical Properties, and Elemental Analysis[a] of Some Amide Derivatives of Quinaldic Acid

Amine[b]	M.P. °C.[c]	Crystallization solvent	Crystalline Form	Molecular Formula	% Carbon		% Hydrogen		% Nitrogen		Number[d]
					Cal.	Found	Cal.	Found	Cal.	Found	
2-Aminoethanol	107–108	Ether	Colorless elongated prisms	$C_{12}H_{12}O_2N_2$	66.67	66.98	5.54	5.46	12.93	12.60	3522
Alanine ethyl ester	80–81	Petroleum ether	Colorless prisms	$C_{15}H_{18}O_3N_2$	66.30	66.72	5.88	5.86	10.30	10.28	3521
Alanine	123.5–124	Chloroform petroleum ether	Colorless plates	$C_{13}H_{12}O_3N_2$	63.63	66.71	4.92	5.30	11.47	11.72	3520
Glycine ethyl ester	79.5–80	Ligroin	Colorless plates	$C_{14}H_{14}O_4N_2$	65.10	64.95	5.43	5.22	10.85	10.88	PF 200
Glycine	188–190	Methanol-water	Colorless plates	$C_{12}H_{10}O_3N_2$	62.60	62.53	4.35	4.38	12.20	12.49	3515
Aniline	139.5–140	Isopropyl-ether	Colorless needles	$C_{16}H_{16}ON_2$	77.50	77.87	4.83	4.88	11.30	11.24	3519
Phenylalanine ethyl ester	72–72.5	Ether-petroleum ether	Colorless needles	$C_{21}H_{30}O_3N_2$	72.41	72.76	5.74	4.67	8.04	7.80	PF 60
Phenylalanine	172.5–173	Methanol	Prismatic needles	$C_{19}H_{16}O_4N_2$	71.25	71.02	5.00	4.91	8.75	8.70	3514
N-Methylaniline	144–146	Ligroin	Prismatic needles	$C_{17}H_{14}ON_2$	77.90	78.23	5.35	5.54	10.70	10.65	3511
p-Toluidine	109.5–110	Ligroin	Long needles	$C_{17}H_{14}ON_2$	78.00	77.95	5.34	5.23	10.70	10.79	3510
p-Chloroaniline	135–135.5	Isopropyl-ether	Rectangular prisms	$C_{16}H_{11}ON_2Cl$	67.90	68.09	3.90	3.87	9.90	9.93	3509
o-Nitroaniline	179.5–180	Isopropyl ether	Yellow needles	$C_{16}H_{11}O_3N_3$	65.50	65.56	3.76	3.82	14.33	14.32	3512
Norleucine	143–144	Chloroform-petroleum ether	Small plates	$C_{16}H_{18}O_3N_2$	67.20	67.18	6.30	6.31	9.80	9.67	3513
Glycylglycine	229–230	Methanol	Short needles	$C_{14}H_{13}O_4N_3$	58.63	58.90	4.53	4.70	14.62	14.43	3516
Dicyclohexylamine	140–141	Isopropyl-ether	Colorless needles	$C_{22}H_{28}ON_2$	78.57	78.80	8.33	8.00	8.33	8.50	PF 110
Hydrazine	250–251	Chloroform-petroleum ether	Short needle clusters	$C_{20}H_9ON_3$	64.17	64.32	4.81	5.00	22.46	22.70	PF 113
Glycyl-L-valine	170–1701.5	Chloroform petroleum ether	Prismatic needles	$C_{17}H_{19}O_4N_3$	62.00	62.40	5.77	5.81	2.75	13.10	PF 114

[a] The microanalyses were carried out in the Laboratories of Pharmacology at the Pasteur Institute, Paris, France, under the direction of J. Trefouel. [b] Only racemic amino acids were used except in the case of #PF 114, glycyl-L-valine. [c] All melting points were taken by the capillary method and are uncorrected. [d] Compounds with numbers greater than three thousands are Pasteur Institute catalogue numbers; others are catalogue numbers of the Pasadena Foundation for Medical Research.

original reaction mixture, and the oil was taken into ether. The ethereal solution was washed with water until the washings were free of acid. On drying and removal of solvent, the dark red oil was distilled under reduced pressure. The fraction, distilling at 42–44° and 1 mm., was collected and weighed 9.5 gm. or 87% of theory. It was shown to be 98–100% pure benzaldehyde by its reaction with 2,4-dinitrophenylhydrazine. The hydrazone melted at 236–237°. The melting point did not change when the material was mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of benzaldehyde.

Quinaldyl chloride. Anhydrous quinaldic acid[13] was converted to the acid chloride by treatment with an excess of thionyl chloride (Eastman White Label) after the procedure of Besthorn and Ibele.[14] Seventeen and three-tenths grams of the anhydrous acid were suspended in 140 ml. of thionyl chloride and the mixture was heated on a water bath until evolution of HCl ceased. The excess thionyl chloride was removed under reduced pressure and the bright red crystalline mass of quinaldyl chloride recrystallized from ether. Eighteen grams of long yellow needles which melted at 96–97° were obtained.

The compounds listed in Table I which follows were prepared by two different procedures, depending upon the use of aqueous or non-aqueous reaction media. These are designated as *Procedure A* and *Procedure B*, and are described below.

Procedure A: Ten millimoles of the amino acid, peptide, etc., were dissolved in 20 ml. of normal sodium hydroxide and cooled to 0–10°. The solution was stirred, and 10 milli-

moles of quinaldic acid were added over a period of about 10 minutes. The cooling bath was removed and the mixture was allowed to come to room temperature. The clear orange solution was treated with a small amount of norite and filtered. On acidification with 10 ml. of normal hydrochloric acid an oil precipitated, which usually crystallized on standing. The crystals were collected by filtration and dried in air. When the oil formed on acidification did not crystallize, it was extracted with methylene chloride and dried. On removal of solvent and scratching with a glass rod, crystals were formed. Yields were from 95–100% of theory. The material was recrystallized from the appropriate solvent. In general, the quinaldyl amino acids will crystallize from chloroform–petroleum ether, but some of them may be crystallized from alcohol water.

Procedure B: Ten millimoles of amine, amino acid ester, etc., were dissolved in 10 ml. of methylene chloride to which had been added 10 millimoles of triethylamine or other tertiary base.[15] The solution was cooled to 0–10° and 10 millimoles of quinaldyl chloride was added over a period of 10 minutes. After the reaction mixture was allowed to come to room temperature it was washed well with water, dried, and treated with norite. The solvent was removed under reduced pressure and the residual oil crystallized on being scratched with a glass rod. The yields were similar to those obtained in *Procedure A* above. The quinaldyl amides usually crystallize from petroleum ether (B.P. 60–100°) or isopropyl ether. Water sometimes interferes with the crystallization.

It is of interest to note that the presence of a hydroxyl group in the amino compound does not interfere with the reaction under the conditions described above. This is exemplified in the preparation of the ethanolamine adduct.

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(13) Obtained by heating several hundred grams of the hydrated material under high vacuum at 100° for 24 hr. This material, as well as quinaldyl chloride, is available commercially from Radio-Carbon Laboratories, Pasadena, California.

(14) E. Besthorn and J. Ibele, *Ber.*, **38**, 2127 (1905).

(15) When possible, it is preferable to use a 1 mole excess of the amine being acylated instead of the tertiary base.

The Preparation of Alicyclic Trioximes

DONALD C. BATESKY and NEIL S. MOON

The reaction of cyclohexanone and its 4-methyl derivative with isoamyl nitrite results in the formation of the symmetrical dioximino ketones: 1,2,3-cyclohexanetrione-1,3-dioxime and 5-methyl-1,2,3-cyclohexanetrione-1,3-dioxime, instead of the expected keto monoximes. Oximation of the keto dioximes gives the corresponding trioximes. These trioximes give color reactions with various cations.

Alicyclic *vic*-dioximes, commonly prepared by the oxidation of alicyclic ketones with selenium dioxide to α-diketones followed by oximation,[1] and more recently by oximation of α-bromoalicyclic ketones,[2] have found widespread use as analytical reagents for nickel and palladium.[3] 1,2-Cyclohexanedione dioxime and its 4-methyl derivative, owing to their greater solubility than dimethylglyoxime in water, are excellent substitutes for this latter reagent in analysis.

To avoid the use of the toxic and expensive selenium dioxide, another route was taken to attempt the preparation of these reagents. Murakami and Yukawa[4] have reported the preparation of 1,2-cyclohexanedione dioxime by passing ethyl nitrite gas into a mixture of cyclohexanone and hydrochloric acid to obtain 1,2-cyclohexanedione monoxime, a solid decomposing at 227° which was then treated with hydroxylamine to yield the *vic*-dioxime melting at 186–187°. This method, because of the availability and low cost of starting materials, was selected in these Laboratories to pre-

(1) D. T. Hooker and C. V. Banks, *U. S. Atomic Energy Comm., ISC-597*, 113 pp. (1955).

(2) R. Belcher, W. Hoyle, and T. S. West, *J. Chem. Soc.*, 2743 (1958).

(3) C. V. Banks and D. T. Hooker, *Anal. Chem.*, **28**, 79 (1956).

(4) M. Murakami and Y. Yukawa, *Mem. Inst. Sci. Ind. Research Osaka Univ.*, **5**, 150 (1947); *Chem. Abstr.*, **47**, 2714 (1953).

pare 1,2-cyclohexanedione dioxime and its 4-methyl derivative.

On reacting equimolecular portions of cyclohexanone or 4-methylcyclohexanone with isoamyl nitrite (used in place of ethyl nitrite because of the greater ease of handling) in the presence of hydrochloric acid, well defined crystalline compounds were obtained. This is in agreement with Murakami and Yukawa but contrary to the results reported by other authors[1,5-7] who obtained the "monoxime" as a noncrystallizable oil. Elemental and infrared analysis of these compounds showed however, that two rather than one isonitroso groups had added to the cyclohexane ring, one on each side of the carbonyl group. This reaction took place even with an insufficient amount of isoamyl nitrite for the addition of two groups and at temperatures from $-15°$ to $+20°$. Thus, keto dioximes (I, II), rather than the expected keto monoximes, were formed.

I. R = H
II. R = CH$_3$

III. R' = H
IV. R' = CH$_3$
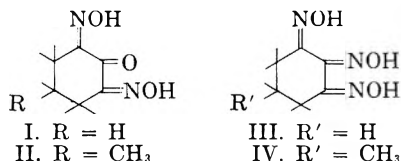
This may account for the stability of product formed as opposed to the low stability of the product obtained by other investigators who used different methods to obtain the keto monoxime. On treating each of the keto dioximes with hydroxylamine, the predicted trioximes (III, IV) were obtained. The trioximes exhibit good water solubility and gave, as well as did the keto dioxime intermediates, color reactions with various cations. 5-Methyl-1,2,3-cyclohexanetrione-1,3-dioxime gave color reactions with Fe^{+2}, Fe^{+3}, Co^{+2}, Hg^{+2}, and Cu^{+2} ions. 1,2,3-Cyclohexanetrione trioxime

and its 5-methyl derivative gave color reactions with Fe^{+2}, Fe^{+3}, Co^{+2}, Cu^{+2}, Cr^{+3}, Pb^{+2}, Hg^{+2}, and Sn^{+2} ions, and a deep red precipitate with Ni^{+2} ion. The analytical applications of these new compounds have not been exploited and are open for development.

EXPERIMENTAL

5-Methyl-1,2,3-cyclohexanetrione-1,3-dioxime (II). To a well stirred mixture of 112 g. (1 mole) of 4-methylcyclohexanone and 4 ml. (0.05 mole) of concentrated hydrochloric acid, cooled in a Dry-Ice–isopropyl alcohol bath, 117 g. (1 mole) of isoamyl nitrite was slowly added in four hr. at $-5°$. The product separated during the addition of a fine tan solid. Upon completion of the addition the product was filtered, washed with light petroleum ether, and recrystallized from ethanol, yielding pale yellow platelets decomposing at 202°. The yield was 59.5 g. or 70% (based on the isoamyl nitrite used).

Anal. Calcd. for C$_7$H$_{10}$N$_2$O$_3$: C, 49.5; H, 5.9; N, 16.5. Found: C, 49.4; H, 6.1; N, 16.3.

5-Methyl-1,2,3-cyclohexanetrione trioxime (IV). To a cooled, stirred solution of 23 g. (1 mole) of freshly cut sodium dissolved in 300 ml. of methanol was added a slurry of 69.5 g. (1 mole) of hydroxylamine hydrochloride in 200 ml. of methanol, followed by 170 g. (1 mole) of 5-methyl-1,2,3-cyclohexanetrione-1,3-dioxime. The mixture was stirred overnight at room temperature, filtered to remove the insoluble salt, and slowly concentrated to near dryness at reduced pressure and low heat. The resulting solid was recrystallized once from distilled water and finally from ethyl acetate, giving white crystals decomposing at 170°. The yield was 82 g. or 45%.

Anal. Calcd. for C$_7$H$_{11}$N$_3$O$_3$: C, 45.4; H, 6.0; N, 22.7. Found: C, 45.4; H, 6.0; N, 23.0.

1,2,3-Cyclohexanetrione-1,3-dioxime (I). This was prepared using the procedure just described for preparing the 5-methyl derivative. The keto dioxime is a yellow-brown solid decomposing at 197°. This material was not purified since it appeared to break down when heated in solvents. The yield was 46%.

Anal. Calcd. for C$_6$H$_8$N$_2$O$_3$: C, 46.2; H, 5.2; N, 17.9. Found: C, 46.0; H, 5.1; N, 18.0.

1,2,3-Cyclohexanetrione trioxime (III). This was prepared by the oximation of 1,2,3-cyclohexanetrione-1,3-dioxime with hydroxylamine. The trioxime is a white crystalline solid (from dioxane) melting at 170°, with decomposition. The yield was 25%.

Anal. Calcd. for C$_6$H$_9$N$_3$O$_3$: C, 42.1; H, 5.3; N, 24.6. Found: C, 42.2; H, 5.4; N, 24.7.

ROCHESTER, N. Y.

(5) F. M. Jaeger and J. A. van Dijk, *Proc. Koninkl. Ned. Akad. Wetenschap.*, 39, 384 (1936).

(6) T. A. Geissman and M. J. Schlatter, *J. Org. Chem.*, 11, 771 (1946).

(7) E. G. Rauh, G. F. Smith, C. V. Banks, and H. Diehl. *J. Org. Chem.*, 10, 199 (1945).

Heterogeneous Bimolecular Reduction. III. The Coreduction of Pyridine with Imines and the Preparation of Pyridylmethylamines[1]

G. BRYANT BACHMAN AND MICHAEL KARICKHOFF[2]

The coreduction of mixtures of pyridine and imines with magnesium or aluminum amalgams has been shown to lead to substituted α-pyridylmethylamines in accord with the mechanism previously proposed for closely related reactions involving pyridine and carbonyl compounds or esters. Aromatic imines give considerably better yields than aliphatic imines. The electronic effects of substituent groups have been studied and the variations in yields of products discussed.

Previous reports on heterogeneous bimolecular reduction have served to define the scope of the reaction and to determine conditions necessary for the coreduction of pyridine with carbonyl compounds and acid derivatives.[3,4] We wish now to describe the extension of these reactions to the coreduction of pyridine with imines and the development of a one-step synthesis of substituted α-pyridylmethylamines. During the course of this investigation we have also attempted to study the electronic effects of substituent groups and to relate the yields of products obtained with the mechanisms previously proposed for these reactions.

It has been found that imines, obtained by condensation of primary amines with aldehydes and ketones, react with pyridine in the presence of aluminum or magnesium amalgams to form the expected coupled products in yields ranging up to 75% based on the imine or the metal. The results
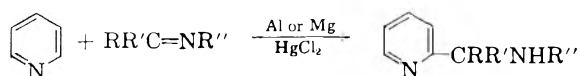
of these experiments are summarized in Table I. It will be noted that far better yields are generally obtained with aromatic imines than with aliphatic imines. The replacement of aromatic groups by aliphatic groups in R or R' is especially detrimental to the yields. The influences of substituent groups in the ortho- or para- positions of the aromatic nuclei seem to depend upon the inductive effects of these groups, being favorable for those groups which show a +I effect (electron supply) and detrimental for those groups which show a −I effect (electron withdrawal). In accord with previously observed inductive effects, the influence of substituent groups is generally greater in the ortho-

position than the para- position.[5] In addition to their electronic effects, ortho substituents probably exhibit steric effects[4,5] although not enough data is available from our experiments to determine the relative importance of this effect.

The relative results obtained with aluminum and magnesium amalgam are confusingly erratic. All that can be said about them is that in some cases aluminum amalgam gives better yields while in other cases magnesium amalgam gives better yields. There is no apparent basis for predicting in advance which amalgam will be preferable, although the more aromatic imines appear to work better with magnesium while the more aliphatic amines work better with aluminum. No γ-substituted pyridylmethylamines were isolated from our experiments using either aluminum amalgam or magnesium. This is in contradistinction to the results obtained in the coreduction of pyridine with carbonyl compounds and acid derivatives where aluminum amalgam (but not magnesium amalgam) gives small yields of the γ-isomer.[3,4] The reason for this difference may lie in the very high boiling points of the pyridylmethylamines obtained. The γ-isomers normally boil higher than the α-isomers in these series and may decompose before they reach their boiling points. It is also possible of course that they are not formed in the reaction.

The poor yields obtained with aliphatic imines are probably the results of self-condensations of these substances before they can condense with the pyridine nucleus. Thus Emerson and co-workers[6] have observed that N-butylidenebutylamine rapidly forms 2-ethyl-2-hexylidenebutylamine under the catalytic influence of bases. This hypothesis is also in accord with the fact that aluminum amalgam gives better yields with aliphatic amines than does magnesium amalgam. The latter of these metals forms the more basic intermediates in the reaction. It is also in accord with the fact that it is difficult to obtain aliphatic imines in good yields since, in the process of their formation from carbonyl com-

(1) Taken from a thesis submitted by M. Karickhoff to the faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the Ph.D. degree, January 1959.

(2) Continental Oil Co. Fellow, 1956–58.

(3) G. B. Bachman, M. Hamer, E. Dunning, and R. M. Schisla, J. Org. Chem., 22, 1296 (1957).

(4) G. B. Bachman and R. M. Schisla, J. Org. Chem, 22, 1302 (1957).

(5) These observations are also in accord with the results obtained by C. H. Tilford, R. S. Shelton, and M. G. Van Campen, Jr., J. Am. Chem. Soc., 70, 4001 (1948).

(6) W. S. Emerson, S. M. Hess, and F. C. Uhle, J. Am Chem. Soc., 63, 782 (1941).

TABLE I
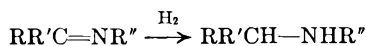
SUBSTITUTED 2-PYRIDYLMETHYLAMINES AND THEIR DERIVATIVES

CRR'NHR''

No.	R	R'	R''	Yield, %		B.P.		M.P.	
				Al	Mg	°C.	(Mm.)	Product	Picrate
1	Phenyl	Phenyl	Phenyl	10.6	75.0	156	(0.08)	53	...
2	Phenyl	Hydrogen	Phenyl	18.8	48.5	158	(0.01)	78	175
3	Phenyl	Hydrogen	p-Chloro-phenyl	Trace	12.7	171	(0.08)	113	158
4	Phenyl	Hydrogen	o-Chloro-phenyl	0	18.1	168	(0.05)	100	154
5	Phenyl	Hydrogen	p-Tolyl	34.5	34.5	166	(0.03)	81	128
6	Phenyl	Hydrogen	o-Tolyl	19.2	70.0	161	(0.01)	Oil	156
7	Phenyl	Hydrogen	p-Anisyl	...	34.2	185	(0.03)	91	131
8	Phenyl	Hydrogen	o-Anisyl	...	27.2	176	(0.02)	Oil	146
9	p-Chloro-phenyl	Hydrogen	Phenyl	20.0	27.0	163	(0.03)	80	169
10	o-Chloro-phenyl	Hydrogen	Phenyl	17.8	0	183	(0.09)	96	163
11	p-Tolyl	Hydrogen	Phenyl	20.0	47.5	167	(0.02)	Oil	163
12	Phenyl	Hydrogen	Benzyl	38.4	0	184	(0.03)	Oil	131
13	Phenyl	Hydrogen	Ethyl	36.8	14.9	106	(0.50)	Oil	150
14	Phenyl	Hydrogen	Methyl	30.0	...	122	(0.50)	Oil	195 (d)
15	Methyl	Isobutyl	Phenyl	10.3	0	145	(0.08)	Oil	Oil
16	Methyl	Hexyl	Phenyl	0	13.8	141	(0.03)	Oil	Oil
17	Butyl	Hydrogen	Butyl	0	0				

pounds and primary amines, they tend to condense with themselves and form high molecular weight tars.

We have also observed that aliphatic acid derivatives give much poorer yields of acylated pyridines than do aromatic acid derivatives. In this case, however, the self-condensation undoubtedly occurs after the formation of the pyridyl ketone since oxidation of the large amounts of high-boiling nitrogeneous byproducts leads to considerable amounts (40% yields) of picolinic acid. Similar oxidations on the tarry byproducts obtained in the coreduction of pyridine and N-butylidenebutylamine did not yield picolinic acid, suggesting that in this case self condensation occurs before condensation with the pyridine nucleus can occur.

The structure of the N-methyl-1-phenyl-1-(2'-pyridyl)methylamine obtained by the heterogeneous bimolecular reduction of pyridine with N-benzylidenemethylamine was established by comparison with the known physical constants for this pyridylmethylamine.[5]

A by-product of these reactions is the homogeneous monomolecular reduction product of the imine. These secondary amines were usually obtained in 10 to 20% yields. Their compositions were confirmed by analyses or by comparison with previously published physical constants.

$$RR'C{=}NR'' \xrightarrow{H_2} RR'CH{-}NHR''$$

The heterogeneous bimolecular reduction of pyridine with imines makes available a series of compounds of potential interest as intermediates

in the preparation of pharmaceutically active compounds. As a preliminary step in a proposed study of such preparations we have accomplished the following condensation:

$$\underset{N}{\bigcirc}\!\!-CRR'NHR''$$
$+$
$ClC_2H_4N(CH_3)_2$
$\xrightarrow{NaNH_2}$
$\underset{N}{\bigcirc}\!\!-CRR'NR''C_2H_4N(CH_3)_2$
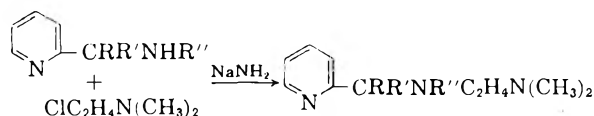
where R = R'' = phenyl and R' = hydrogen.

The product is closely related in structure to compounds known to possess antihistaminic activity.[5]

EXPERIMENTAL

The following experiments illustrate the procedures used in this investigation:

Preparation of 1-methylhexylideneaniline. Methyl hexyl ketone, 256.0 g. (2.0 mol.), aniline, 186.0 g. (2.0 mol.), and benzene, 50 ml., were refluxed together for 24 hr., the water produced (35 ml.) being separated by azeotropic distillation. Distillation of the crude anil through a 30-cm. glass-helix packed column gave the previously undescribed 1-methylhexylideneaniline, 266.0 g. (60% theory), b.p. 96° (1.0 mm.).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.90; H, 10.40; N, 7.20.

The other imines were prepared similarly. They are adequately described in the literature.

Preparation of N-phenyl-1-phenyl-1-(2'-pyridyl)methylamine using magnesium amalgam.[7] Magnesium turnings,

(7) When aluminum was used as the reducing agent, smaller amounts of mercuric chloride, 5.0 g. (0.018 mol.), were used in preparing the amalgam, but the same molar amount of aluminum was used, 13.5 g. (0.5 mol.).

TABLE II

CRR'NHR''
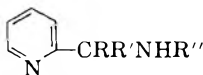
SUBSTITUTED 2-PYRIDYLMETHYLAMINES AND THEIR DERIVATIVES

No.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
1	$C_{24}H_{20}N_2$	85.68	85.63	5.99	6.01	8.33	7.98
2	$C_{18}H_{16}N_2$	83.04	83.10	6.20	6.47	10.76	10.65
3	$C_{18}H_{15}N_2Cl$	73.34	73.41	5.14	5.30	9.51	9.35
4	$C_{18}H_{15}N_2Cl$	73.34	73.63	5.14	5.40	9.51	9.48
5	$C_{19}H_{18}N_2$	83.17	82.90	6.61	6.76	10.21	10.25
6	$C_{19}H_{18}N_2$	83.17	83.00	6.61	6.38	10.21	10.36
7	$C_{19}H_{18}N_2O$	78.59	78.76	6.25	6.48	9.65	9.79
8	$C_{19}H_{18}N_2O$	78.59	78.73	6.25	6.25	9.65	9.57
9	$C_{18}H_{15}N_2Cl$	73.34	73.60	5.14	5.40	9.51	9.61
10	$C_{18}H_{15}N_2Cl$	73.34	73.44	5.14	4.99	9.51	9.54
11	$C_{19}H_{18}N_2$	83.17	83.00	6.61	6.40	10.21	10.36
12	$C_{19}H_{18}N_2$	83.17	82.90	6.61	6.45	10.21	10.04
13	$C_{14}H_{16}N_2$	79.21	79.51	7.60	7.44	13.20	13.12
14	$C_{13}H_{14}N_2$	78.75	78.59	7.12	7.26	14.13	13.99
15	$C_{17}H_{22}N_2$	80.27	80.42	8.72	8.95	11.01	11.09
16	$C_{19}H_{26}N_2$	80.80	81.08	9.28	9.11	9.92	10.02

12.0 g. (0.5 mol.), mercuric chloride, 50.0 g. (0.18 mol.), and 10 drops of mercury were heated together for 2 hr. at 100°. A mixture of pyridine, 25.0 g., and N-benzylideneaniline, 25.0 g., was added to initiate the reaction. A deep violet color developed almost immediately and gradually turned to red-brown over a period of time. Pyridine, 91.0 g. (1.15 mol.), was added and the reaction mixture stirred for 20 min. The remainder of the N-benzylideneaniline, 90.5 g. (0.5 mol. total), was added dropwise over a 4-hr. period. During this period it was necessary to add more pyridine, 276.0 g. (3.5 mol.) in order to prevent caking in the reaction flask. During the anil addition and for 6 hr. thereafter heat was supplied so that the pyridine refluxed gently. The partially cooled reaction mixture was poured into a mixture of 500 ml. of 3N sodium hydroxide and ice, stirred for 5 hr. at room temperature, and then filtered through Celite. The dark organic layer was separated, and the aqueous layer extracted several times with benzene. The combined extracts and organic layer were dried and the excess pyridine and other volatile materials were removed by distillation at aspirator pressure. The resulting red viscous material was distilled rapidly and gave the following fractions:

Fraction	B.P. (Mm.)	Amount, G.
1	70–118 (1.5)	2.0
2	118–140 (0.5)	30.0
3	168–210 (0.5)	52.0
4	Residue	4.0

Redistillation of Fraction 2 through a 30-cm. glass-helix packed column yielded N-benzylaniline, 15.0 g., b.p. 169–171° (11.0 mm.), n_D^{25} 1.6115, m.p. of hydrochloride 210–212°. Reported values, b.p. 171.5° (10.0 mm.),[8] $n_D^{24.8}$ 1.6118,[9] m.p. of hydrochloride 214–216°.[10] Fraction 3 was redistilled and identified as N-phenyl-1-phenyl-1-(2'-pyridyl) methylamine, b.p. 155–162° (0.1 mm.), m.p. of picrate 175°. The yield of yellow viscous material was 40.0 g. or 48.1%. On trituration with petroleum ether this oil slowly solidified.

(8) C. Courtot and P. Petitcolas, Bull. Soc. Chem., [4], 39, 452 (1926).

(9) P. Groth, Chem. Krystallographie, 5th part, Leipzig (1906–19).

(10) K. Brand, Ber., 42, 3462 (1909).

It then recrystallized readily from petroleum ether, m.p. 78–79°.

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.10; H, 6.47; N, 10.65.

The coreduction of pyridine with 1-methylhexylideneaniline gave the previously undescribed N-(1-methylhexyl)-aniline, b.p. 116–117° (3.0 mm.).

Anal. Calcd. for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 82.13; H, 11.01; N, 6.84.

Similarly 1,3-dimethylbutylideneaniline gave N-(1,3-dimethylbutyl)aniline, b.p. 110° (12.0 mm.).

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.58; H, 10.51; N, 8.20.

Preparation of 2-{α-[N-(2-dimethylaminoethyl)-N-phenylamino]benzyl}pyridine or 1-(α-pyridyl)-1,2-diphenyl-5-methyl-2,5-diazahexane. A solution of N-phenyl-1-phenyl-1-(2'-pyridyl)methylamine, 26.0 g. (0.1 mole), in dry toluene, 50 ml., was added to a stirred solution of sodamide, 7.8 g. (0.2 mole) in toluene, 50 ml., at 100°. The mixture was heated on a steam bath for 3 hr. and then treated with a toluene solution of β-dimethylaminoethyl chloride, 27.4 g. (0.19 mole). The reaction mixture was heated and stirred for an additional 24 hr. The cooled reaction mixture was washed with water and the toluene layer separated. The aqueous layer was saturated with potassium carbonate and then extracted with toluene. The combined toluene fractions were dried and distilled. After an initial rapid distillation the crude product was twice distilled using a 12-in. unpacked column. The desired pyridyl derivative boiled at 160–163° (0.03 mm.); yield 10 g. (33.3% theory).

Anal. Calcd. for $C_{22}H_{25}N_3$: C, 79.77; H, 7.55; N, 12.69. Found: C, 79.83; H, 7.60; N, 12.48.

Reaction of pyridine and phenyl hexanoate using aluminum amalgam (nitrogen atmosphere). The general procedure of Bachman and Schisla[4] was followed in this experiment. Reactants employed were:

	Grams	Moles
Aluminum metal	13.5	0.5
Mercuric chloride	10.0	0.032
Phenyl hexanoate	96.0	0.5
Pyridine	120.0	1.5

A total reflux period of 43 hr. and additional amounts of mercuric chloride, 5.0 g., were required before most of the

metal had reacted. Work-up and distillation of the nitrogeneous material gave the following fractions:

Fraction	B.P. (Mm.)	n_D^{20}	Amount, G.
1	75–84 (2.5)	1.4624	1.6
2	94–104 (2.5)	1.4832	1.9
3	108–110 (2.5)	1.5010	10.5
4	Residue		5.0

Fraction 3 did not give classification tests for a carbonyl compound or a tertiary nitrogen atom. Permanganate oxidation[11] of a 5.0-g. sample of fraction 3 yielded picolinic acid, 1.2 g. (40% based on sample alone, 28.1% based on phenyl hexanoate), m.p. 135°. Reported m.p. 133–134°.[11] Work-up of the neutral fraction gave phenol, 80.0 g.

LAFAYETTE, IND.

(11) G. R. Clemo and G. R. Ramage, J. Chem. Soc., 440 (1931).

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

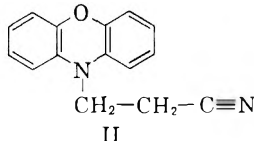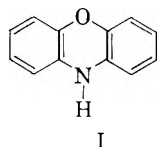# β-Cyanoethylation of Phenoxazine and 7H-Benzo[c]phenothiazine

PAULETTE MÜLLER, N. P. BUU-HOÏ, and R. RIPS

Phenoxazine and 7H-benzo[c]phenothiazine have been found to condense smoothly with acrylonitrile in the presence of organic alkaline catalysts; α-methylacrylonitrile failed to react. Friedel-Crafts cyclization of β-(10-phenoxazinyl)propionic acid has been performed, and its reaction products are investigated.

From the triad formed by phenoxazine, phenothiazine, and phenoselenazine, the behavior of the last two in β-cyanoethylation reactions has already been investigated, and both phenothiazine[1] and phenoselenazine[2] were found to give the corresponding N-propionic acid in good yields.

It is now shown that phenoxazine (I) likewise undergoes smooth β-cyanoethylation with acrylonitrile in the presence of benzyltrimethylammonium methoxide, to give β-(10-phenoxazinyl)propionitrile (II), the reaction being even more energetic than in the case of phenothiazine and phenoselen-

azine, probably because of its higher solubility in acrylonitrile. In similar and even more drastic experimental conditions, α-methylacrylonitrile failed to undergo condensation. Alkaline hydrolysis afforded β-(10-phenoxazinyl)propionic acid (III); cyclization of this acid could be effected, as in the case of the corresponding propionic acids derived from phenothiazine[1] and phenoselenazine,[2] with phosphorus pentoxide, but afforded two products, both of them yellow, the lower-melting one being 2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]-phenoxazine (IV), as it possessed a reactive keto
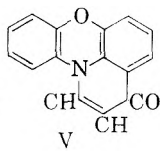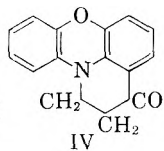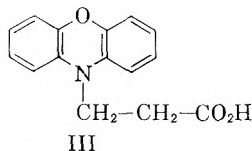
group and readily gave a phenylhydrazone. The higher-melting product, which did not form a phenylhydrazone in the same conditions, and which contained two atoms less of hydrogen, could be tentatively formulated as the dehydro derivative (V) of the former ketone. The differences in the degree of saturation of the two compounds are reflected in their infrared spectra (see Figure 1); in the case of ketone IV, the absorption band characterizing the ketone function is located at 1655 cm.$^{-1}$, while for compound V there are two ketone bands, one at 1630 cm.$^{-1}$ and the other at 1640 cm.$^{-1}$, a splitting resembling that observed with quinones. The infrared spectrum of ketone IV is similar to those of 2,3-dihydro-3-keto-1H-pyrido-[3,2,1-kl]phenoselenazine and its 10-chloro- derivative (see Figure 2).

In the framework of our investigations on potential carcinogenic nitrogen-containing heterocycles, the phenylhydrazones of ketone IV and of its analogs 2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]-phenothiazine (VI; X = S) and 2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]phenoselenazine (VI; X = Se) were converted by Fischer cyclizations into indolo[3',2'-2,3]-1H-pyrido[3,2,1-kl]phenoxazine (VII) and its phenothiazine and phenoselenazine analogs (VIII) and (IX). The Pfitzinger reaction of ketone (VI; X = S) with isatin afforded 4'-
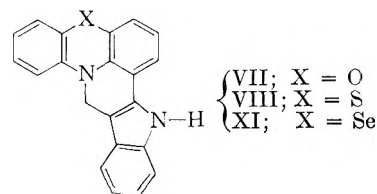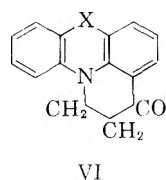
(1) N. L. Smith, J. Org. Chem., 15, 1125 (1950).
(2) P. Müller, N. P. Buu-Hoï, and R. Rips, J. Org. Chem., 24, 37 (1959).

carboxyquinoleino[3',2'-2,3]-1H-pyrido[3,2,1-kl]-phenothiazine (X; X = S), which underwent

Fig. 1
- - - - compound IV
———— compound V

decarboxylation to the base (XI). A similar reaction with the phenoselenazine ketone afforded 4'-

X   XI
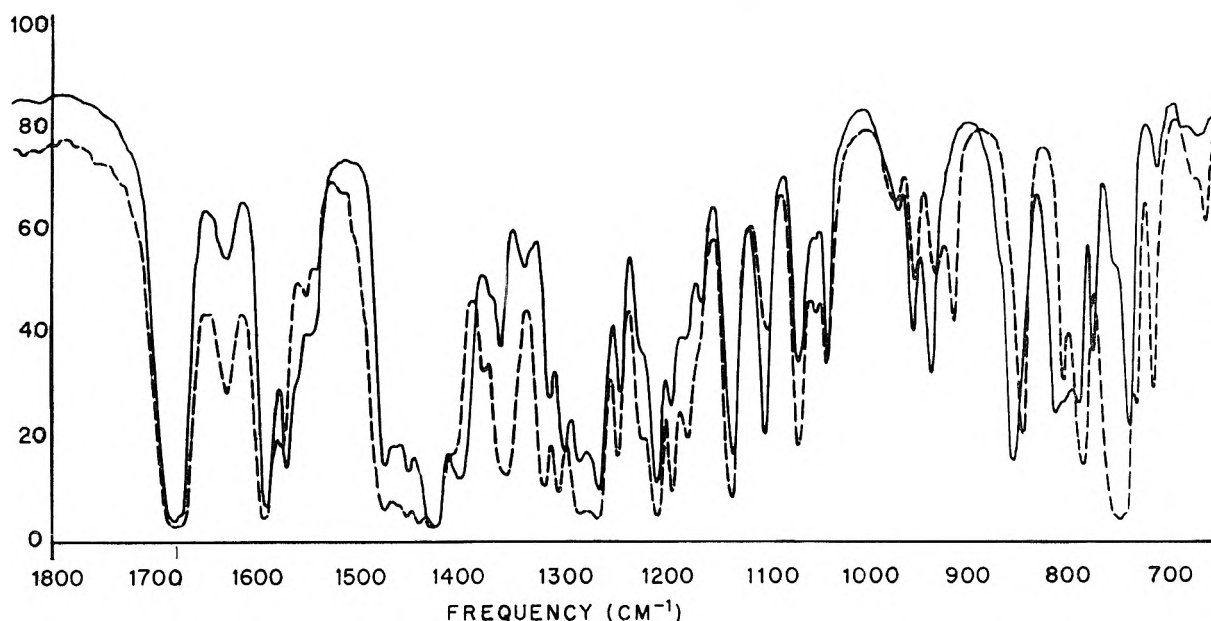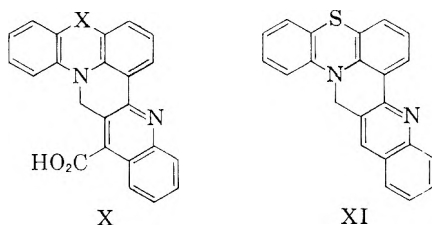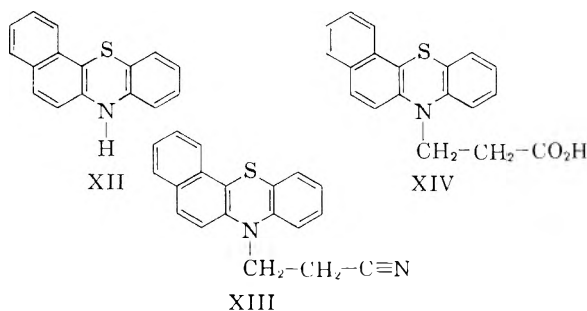
carboxyquinoleino[3',2' - 2,3] - 1H - pyrido[3,2,1-kl]phenoselenazine (X; X = Se).

In the course of this work, 7H-benzo[c]phenothiazine (XII) was also found to undergo ready β-cyanoethylation, to give β-7-[7H-benzo[c]pheno-

XII

XIV

XIII

thiazinyl]propionitrile (XIII); this compound underwent hydrolysis to the corresponding acid (XIV), whose cyclization will be discussed in a later paper.

EXPERIMENTAL

β-(10-Phenoxazinyl)propionitrile (II). To a mixture of 11 g. of phenoxazine and 15 ml. of acrylonitrile 0.5 ml. of benzyltrimethylammonium methoxide was added dropwise with stirring, whereupon an exothermic reaction set up accom-

panied by a deep red coloration. The mixture was then heated on a water bath for 30 minutes, the acrylonitrile in excess was distilled off *in vacuo*, and the solid residue taken up in benzene. The benzene solution was filtered, the solvent removed *in vacuo*, and the residue recrystallized from ether or ethanol, to form 33.5 g. of fine colorless needles, m.p. 123°, giving a red coloration in sulfuric acid.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.3; H, 5.1; N, 11.9. Found: C, 76.2; H, 5.4; N, 12.1.

β-(10-Phenoxazinyl)propionic acid (III). A solution of 6.8 g. of the foregoing nitrile and 7.5 g. of sodium hydroxide in 100 ml. of ethanol was gently refluxed for 10 hr.; after cooling, water was added, and the solid precipitate of phenoxazine (m.p. 156°) was filtered off by suction. The filtrate yielded on acidification with dilute hydrochloric acid, 5 g. of an *acid*, crystallizing from cyclohexane in shiny colorless needles, m.p. 138°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.5; H, 5.1; N, 5.5. Found: C, 70.8; H, 5.2; N, 5.6.

Cyclization of β-(10-Phenoxazinyl)propionic acid (III). A solution of 3.5 g. of the above acid in 75 ml. of anhydrous benzene was refluxed for 1 hr. on a water bath with 19 g. of phosphorus pentoxide, and left overnight at room temperature. The reaction mixture, which consisted by then of a brownish solid and a supernatant benzene phase, was carefully poured onto ice, the benzene solution was washed with aqueous sodium carbonate, then with water, and dried over sodium sulfate, and the solvent distilled off *in vacuo*. The yield was 2.7 g. of a solid which was dissolved in a mixture of benzene and cyclohexane; the less soluble portion consisted of 0.5 g. of *3-keto-1H-pyrido[3,2,1-kl]phenoxazine* (V), bright yellow prisms which melted at 228° after recrystallization from ethanol. This compound gave in sulfuric acid a tawny coloration which rapidly turned yellow.

Anal. Calcd. for $C_{15}H_9NO_2$: C, 76.6; H, 3.8; O, 13.6. Found: C, 76.5; H, 3.7; O, 13.6.

The mother liquors were concentrated, and furnished on cooling, 2 g. of *2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]-phenoxazine* (IV), which was recrystallized from ethanol to yield orange yellow prisms, m.p. 144°, giving in sulfuric acid a deep blue coloration which turned yellow on heating.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.9; H, 4.6; O, 13.5. Found: C, 75.8; H, 4.5; O, 13.5.

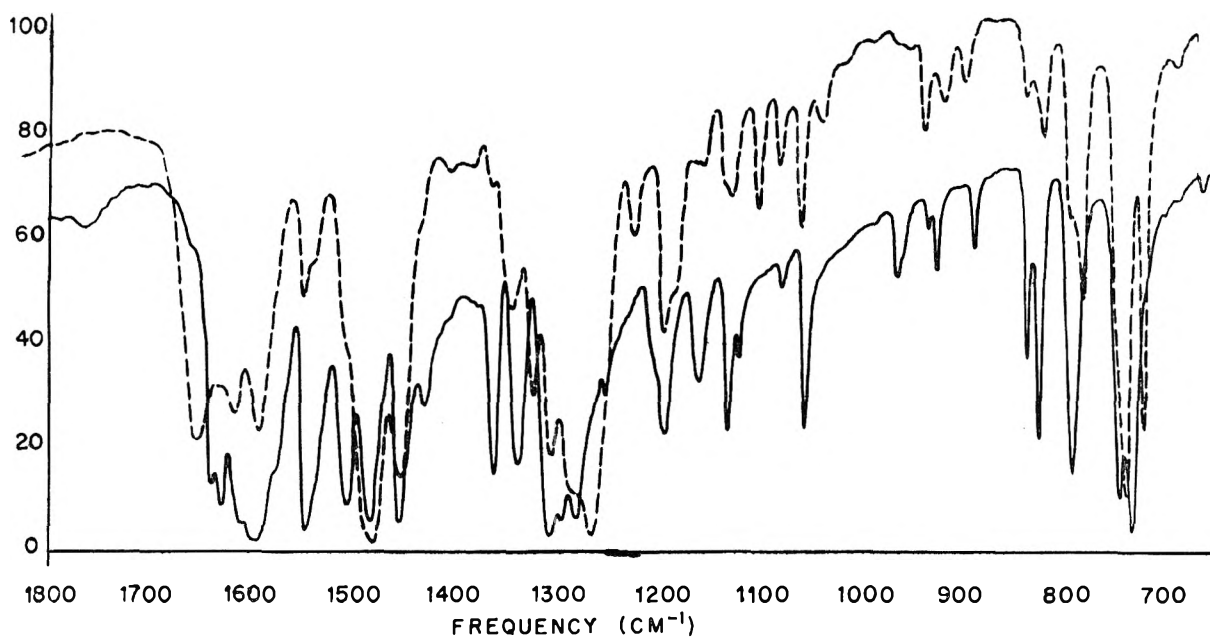The corresponding *phenylhydrazone*, prepared in ethanol,

Fig. 2
- - - - compound (VI; X = Se)
———— 10-chloro derivative of compound (VI; X = Se)

crystallized from that solvent in pale yellow needles, m.p. 187°, giving a red coloration in sulfuric acid.

Anal. Calcd. for $C_{21}H_{17}N_3O$: N, 12.8. Found: N, 12.8.

Indolo[*3',2'-2,3*]*-1H-pyrido*[*3,2,1-kl*]*phenoxazine* (VII). The Fischer cyclization of the foregoing phenylhydrazone (0.25 g.) was effected by boiling for a few minutes its solution in 5 ml. of acetic acid saturated with hydrogen chloride. After cooling, water was added, and the deep yellow precipitate (0.18 g.) was recrystallized from ethanol, giving yellow prisms melting above 300° and containing 1.5 moles of ethanol (the analytical sample was dried for 30 minutes at 160°). This compound gave in sulfuric acid a yellow halochromy with a green fluorescence.

Anal. Calcd. for $C_{21}H_{14}N_2O$: C, 81.3; H, 4.6; N, 9.0. Found: C, 81.0; H, 4.3; N, 9.0.

Indolo[*3',2'-2,3*]*-1H-pyrido*[*3,2,1-kl*]*phenothiazine* (VIII). Similarly prepared from 2 g. of the phenylhydrazone of ketone (VI; X = S), this *compound* (1.5 g.) crystallized from ethanol in microscopic yellow needles, melting with decomposition at 275° and containing crystallization solvent (the analytical sample was dried at 160° as in the previous case). The halochromy in sulfuric acid was yellow.

Anal. Calcd. for $C_{21}H_{14}N_2S$: C, 77.3; H, 4.3; N, 8.5. Found: C, 77.0; H, 4.6; N, 8.4.

Indolo[*3',2'-2,3*]*-1H-pyrido*[*3,2,1-kl*]*phenoselenazine* (IX). Prepared as for the above from 0.3 g. of the phenylhydrazone of ketone (VI; X = Se), this *indole* (0.2 g.) crystallized from ethanol in yellow needles, m.p. 258°, giving a yellow halochromy in sulfuric acid.

Anal. Calcd. for $C_{21}H_{14}N_2Se$: N, 7.8. Found: N, 7.7.

4'-Carboxyquinoleino[*3',2'-2,3*]*-1H-pyrido*[*3,2,1-kl*]*phenothiazine* (X; X = S). A mixture of 2.5 g. of ketone (VI; X = S), 1.5 g. of isatin, and 1.7 g. of potassium hydroxide in 10 ml. of ethanol was refluxed for 40 hr.; after cooling, water was added, and the yellow potassium salt of the cinchoninic acid obtained was filtered off, suspended in water, and the free acid liberated by addition of acetic acid. Yield: 2.7 g. of reddish-brown microcrystals, m.p. 325°, giving a green coloration in sulfuric acid.

Anal. Calcd. for $C_{23}H_{14}N_2O_2S$: N, 7.4; S, 8.4. Found: N, 7.1; S, 8.1.

Quinoleino[*3',2'-2,3*]*-1H-pyrido*[*3,2,1-kl*]*phenothiazine* (XI), prepared by thermal decarboxylation of the foregoing acid, crystallized from ethanol in yellow prisms, m.p. 202°.

Anal. Calcd. for $C_{22}H_{14}N_2S$: N, 8.3; S, 9.5. Found: N, 8.3; S, 9.2.

4'-Carboxyquinoleino[*3',2'-2,3*]*-1H-pyrido*[*3,2,1-kl*]*phenoselenazine* (X; X = Se). Prepared and purified as for the sulfur analog, this *acid* crystallized from ethanol in brownish needles, melting with decomposition above 300°, and giving a dark green halochromy in sulfuric acid.

Anal. Calcd. for $C_{23}H_{14}N_2O_2Se$: C, 64.3; H, 3.3. Found: C, 64.0; H, 3.3.

β-7-[*7H-Benzo*[*c*]*phenothiazinyl*]*propionitrile* (XIII). To a suspension of 15.5 g. of 7H-benzo[c]phenothiazine (XII; prepared from N-phenyl-β-naphthylamine and sulfur in the presence of iodine[3]; the product was purified by distillation *in vacuo:* b.p. 235–240°/0.1 mm., m.p. 178°) in 25 ml. of acrylonitrile, 1 ml. of benzyltrimethylammonium methoxide was added dropwise, and the mixture heated for 30 minutes on a water bath. The paste obtained was left overnight at room temperature; the reaction product was then taken up in 250 ml. of hot benzene, the solvent was removed, and the residue recrystallized from acetone, to furnish 12 g. of colorless needles, m.p. 224°, giving a deep blue halochromy in sulfuric acid.

Anal. Calcd. for $C_{19}H_{14}N_2S$: C, 75.5; H, 4.7; N, 9.3. Found: C, 75.5; H, 5.0; N, 9.4.

β-7-[*7H-benzo*[*c*]*phenothiazinyl*]*propionic acid* (XIV). A suspension of 5.5 g. of the foregoing nitrile in 100 ml. of a 5% solution of sodium hydroxide in ethanol was refluxed for 10 hr.; after cooling, 200 ml. of water was added, and the precipitate of 7H-benzo[c]phenothiazine (2 g.) was filtered off. The filtrate yielded on acidification with dilute hydrochloric acid, 3.3 g. of a solid *acid*, crystallizing from ethanol in fine colorless needles, m.p. 190°. The halochromy in sulfuric acid was deep blue.

Anal. Calcd. for $C_{19}H_{15}NO_2S$: C, 71.0; H, 4.7; N, 4.4. Found: C, 71.0; H, 5.0; N, 4.1.

(3) E. Knoevenagel, *J. prakt. Chem.*, [2] 89, 17 (1914).

2,2,6-Trisubstituted-3,5-thiomorpholinediones. The Isolation of Racemic Intermediates

GLENN S. SKINNER AND JAMES S. ELMSLIE

A series of 2,2,6-trisubstituted-3,5-thiomorpholinediones has been prepared. The intermediate thio ethers containing two asymmetric centers could be separated each into two racemates. Cyclization of the paired intermediates gave the identical thiomorpholinedione.

In a previous report[1] from this laboratory there has been described a series of 2,2-disubstituted-3,5-thiomorpholinediones. We now wish to report our studies involving 2,2,6-trisubstituted-3,5-thimorpholinediones (I), one of which, 2-n-butyl-2-ethyl-6-methyl-3,5-thiomorpholinedione (Ik, Table II), had been made in collaboration with Lovett.[2]

In our experience these compounds were best prepared (Fig. 1) by pyrolysis of either of the

Fig. 1. Synthesis of 2,2,6-trialkyl-3,5-thiomorpholinediones

corresponding thiodiacetamic acids (II or III) or by the condensation of the thiodiacetamide (IV) in boiling hydrochloric acid. The second procedure gave better yields and cleaner products. These intermediates were prepared by condensing a disubstituted mercaptoacetic acid or amide with a monosubstituted bromoacetic acid or amide.

The mercapto acids and mercapto amides were separated[3] by before use.

Previously the condensation of α-bromoacetamides with the mercaptoacetic acids had been conducted in aqueous sodium hydroxide. In this work it was necessary to employ sodium ethoxide in ethanol since α-bromocaproamide and α-bromobutyramide were not soluble in aqueous sodium hydroxide and the amide group was partially hydrolyzed during the time required for completion of the reaction. The product could be precipitated from the ethanol solution by acidification and dilution with water. The partial hydrolysis in aqueous solution increased the difficulty of separation of the racemates.

Several of these intermediate amic acids and diamides possess two unequivalent centers of asymmetry which leads one to expect two racemates. In most cases the two racemates were separated and purified; in others there were strong indications that the two racemates were present, but only one was isolated. However, in the preparation of α-methylcarbamylmethyl-α'-mercapto-α'-ethylisocaproic acid (IId) only one product was isolated and there was no evidence that the other racemate had formed in this case. Both amic acids IIg, IIIc, and the diamide IVf related to α-ethyl-α-phenyl-α'-n-butylthiodiacetic acid have all been separated into their racemates. The pairs of racemates that have been separated are indicated by A and B (Table I). The thiomorpholinediones are listed in Table II.

All of the 2,2,6-trisubstituted-3,5-thiomorpholinediones (I) were stable to heat below 220° and to refluxing concentrated hydrochloric acid. They were cleaved to amic acids of type III when allowed to stand in dilute base at room temperature.

There was no evidence for the existence of two racemates of the thiomorpholinediones which have two unlike asymmetric centers. In fact, each of the racemates of α-ethyl-α-phenyl-α'-n-butylthiodiacetamide, namely IVf-A and IVf-B, gave the same thiomorpholinedione (Ij) by acid condensation, and this product is identical with the

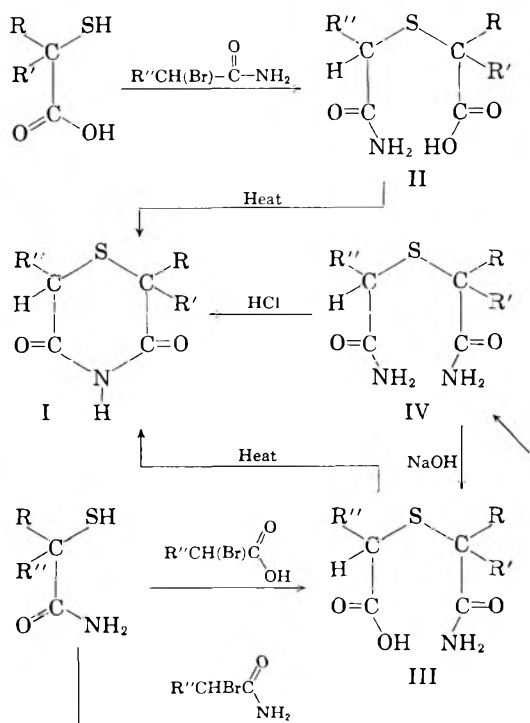(1) G. S. Skinner and J. B. Bicking, J. Am. Chem. Soc., 76, 2776 (1954).

(2) John R. Lovett, Ph.D. Thesis, University of Delaware, 1957.

(3) G. S. Skinner, J. S. Elmslie, and J. D. Gabbert, J. Am. Chem. Soc., 81, 3756 (1959).

TABLE I

AMIDES OF TRISUBSTITUTEDTHIODIACETIC ACIDS

$$X-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle R''}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-S-\overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle R'}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-Y$$

	X	Y	R	R'	R"	M.P.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
IIa	NH₂	OH	CH₃	CH₃	n-C₄H₉	130–131	70	6.00	6.16	51.47	51.62	8.21	8.19
IIb	NH₂	OH	C₂H₅	C₂H₅	CH₃	170.5–171	95	6.39	6.36	49.29	49.26	7.82	7.83
IIc	NH₂	OH	C₂H₅	C₂H₅	C₂H₅	162.5–163	61	6.00	5.99	51.47	51.61	8.21	8.15
IId	NH₂	OH	C₂H₅	iso-C₄H₉	CH₃	177.5–178	82	5.66	5.64	53.41	53.33	8.56	8.35
IIe-A	NH₂	OH	C₆H₅	C₂H₅	CH₃	174.5–175	69[a]	5.24	5.23	58.40	58.78	6.41	6.46
IIe-B	NH₂	OH	C₆H₅	C₂H₅	C₂H₅	161–161.5	52	5.24	5.21	58.40	58.58	6.41	6.32
IIf	NH₂	OH	C₆H₅	C₂H₅	C₂H₅	166.5–167				59.76	59.87	6.81	6.86
IIg-A	NH₂	OH	C₆H₅	C₂H₅	n-C₄H₉	175–176	68[a]	4.53	4.68	62.11	62.12	7.49	7.56
IIg-B	NH₂	OH	C₆H₅	C₂H₅	n-C₄H₉	173–174		4.53	4.78	62.11	61.95	7.49	7.47
IIh	NH₂	OH	C₂H₅	n-C₄H₉	CH₃	126.5–127.5	42.5	5.66	5.61	58.40	58.56	6.41	6.41
IIIa	OH	NH₂	C₆H₅	C₂H₅	C₂H₅	149	82	5.24	5.20	59.76	59.95	6.81	6.91
IIIb	OH	NH₂	C₆H₅	C₂H₅	C₂H₅	152.5–153	88						
IIIc-A	OH	NH₂	C₆H₅	C₂H₅	n-C₄H₉	159–159.5	90	4.53	4.56	62.11	62.36	7.49	7.28
IIIc-B	OH	NH₂	C₆H₅	C₂H₅	n-C₄H₉	140–141	10	4.53	4.73	62.11	62.21	7.49	7.58
IVa	NH₂	NH₂	C₂H₅	C₂H₅	C₂H₅	177–177.5	100	12.06	12.00	51.69	52.20	8.68	8.54
IVb	NH₂	NH₂	C₂H₅	C₂H₅	n-C₄H₉	146.5–147	83	10.76	10.77				
IVc-A	NH₂	NH₂	C₂H₅	n-C₄H₉	CH₃	156–157	94[a]	10.76	10.73	55.35	55.77	9.29	9.30
IVc-B	NH₂	NH₂	C₂H₅	n-C₄H₉	C₂H₅	140–141		10.76	10.77	55.35	55.44	9.29	9.22
IVd-A	NH₂	NH₂	C₂H₅	iso-C₄H₉	C₂H₅	156–156.5	87[a]	10.76	10.74	55.35	55.53	9.29	9.27
IVd-B	NH₂	NH₂	C₂H₅	iso-C₄H₉	C₂H₅	152.5–153		10.52	10.52	55.35	55.85	9.29	9.38
IVe-A	NH₂	NH₂	C₆H₅	C₂H₅	CH₃	194–195	66[a]	10.52	10.51	58.62	59.00	6.81	7.09
IVe-B	NH₂	NH₂	C₆H₅	C₂H₅	CH₃	166–167		10.52					
IVf-A	NH₂	NH₂	C₆H₅	n-C₄H₉	n-C₄H₉	153–153.5	79[a]	9.08	8.94	62.30	62.58	7.84	7.75
IVf-B	NH₂	NH₂	C₆H₅	C₂H₅	n-C₄H₉	160–160.5		9.08	9.04	62.30	61.70	7.84	7.78
IVg	NH₂	NH₂	C₂H₅	n-C₄H₉	CH₃	139–140	32.5	11.37	11.18				

[a] Total yield of A and B.

TABLE II
2,2,6-TRISUBSTITUTED-3,5-THIOMORPHOLINEDIONES
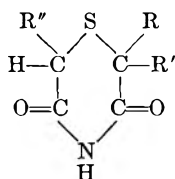
	R	R'	R''	M.P. or B.P. (Mm.)	Yield from	%	Nitrogen, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Ia	CH_3	CH_3	n-C_4H_9	51–52[m]		72	6.51	6.49	55.78	56.10	7.96	7.86
Ib	C_2H_5	C_2H_5	CH_3	74.5–75[m]		95	6.96	6.93	53.70	53.78	7.51	7.49
Ic	C_2H_5	C_2H_5	C_2H_5	64.5–65[n]	IVa IIc	85 85	6.51	6.50	55.78	55.86	7.96	7.78
Id	C_2H_5	C_2H_5	n-C_4H_9	66.5–67[m]		97	5.76	5.74	59.22	59.37	8.70	8.75
Ie	C_2H_5	n-C_4H_9	C_2H_5	136.5–137[n] (0.35)		92	5.76	5.63	59.22	59.27	8.70	8.39
If	C_2H_5	iso C_4H_9	CH_3	127–128[n] (0.19)		69	6.11	6.01	57.61	57.47	8.35	8.29
Ig	C_2H_5	iso C_4H_9	C_2H_5	137[n] (0.23)		98	5.76	5.64	59.22	59.42	8.70	8.54
Ih	C_2H_5	C_2H_5	CH_3	108–109[m]	IIe IVe IIIa	84 72 92	5.62	5.59	62.62	62.99	6.06	6.03
Ii	C_6H_5	C_2H_5	C_2H_5	78–78.5[m]	IIIb IIf	86 63			63.85	63.92	6.51	6.60
Ij	C_6H_5	C_2H_5	n-C_4H_9	69–69.5[m]	IVf-A IVf-B IIg	72 85 68	4.81	4.76	65.94	65.87	7.26	7.13
Ik	C_2H_5	n-C_4H_9	CH_3	137–139[n] (0.80)	IIh	79	6.11	5.86				

m. Melting point; n. Boiling point.

product from the pyrolysis of a mixture of the two racemic amic acids IIg-A and IIg-B.

Base hydrolysis of the same thiomorpholinedione (Ij) gave the racemic amic acids IIIc-B and IIIc-B in yields of 90% and 10%, respectively. In the separate hydrolysis of the racemic diamides IVf-A and IVf-B more of the racemic amic acid IIIc-A was produced than the racemic amic acid IIIc-B; however, the racemic diamide IVf-A gave a higher percentage of the racemic amic acid IIIc-A than did the racemic diamide IVf-B. Thus, it would appear that the formation of the higher melting racemate is favored.

Several derivatives of thiodiacetic acid previously have been separated into their racemates or into meso and DL forms.[4–6] However, no one has reported the formation of the same thiomorpholinedione from either racemate of the thiodiacetic acid derivatives. In fact, Rasenan and Jenkins[7] reported two different thiomorpholinediones upon pyrolysis of the ammonium salt of a symmetrical dialkyl derivative, α,α'-thiodipropionic acid. They believed that these were the meso and DL forms.

This phenomenon has been observed in the succinimide series by Linstead and co-workers.[8–10] Dry distillation of the ammonium salt of either racemate of a substituted succinic acid which has two asymmetric centers produced only one succinimide. In the case of unsymmetrical disubstituted succinic acids, the imide which formed has been shown to be the one in which the two substituent groups are trans to each other.

Pharmacological screening tests indicate that the 2,2,6 - trisubstituted - 3,5 - thiomorpholinediones possess anticonvulsant activity.[11]

EXPERIMENTAL

Ethylisobutylmercaptoacetic acid and amide. 5-Ethyl-5-isobutyl-2-imino-4-thiazolidone (50 g., 0.25 mole) was dissolved in a 5% solution of sodium hydroxide (1.00 mole) and the mixture was refluxed for 30 hr. The products were separated by method A[3] (Ref. 3):

Ethylisobutylmercaptoacetic acid, yield 11 g. (25%), b.p. 111.5–112° (0.53 mm.), n_D^{26} 1.4730.

Anal. Calcd. for $C_8H_{16}O_2S$: C, 54.51; H, 9.15; S, 18.19. Found: C, 54.64; H, 8.93; S 18.10.

Ethylisobutylmercaptoacetamide, yield 22 g. (51%), b.p. 108° (0.50 mm.), n_D^{28} 1.4946.

(4) J. M. Loven and R. Ahlberg, *Ber.*, **54**, 228 (1921).
(5) R. Ahlberg, *Ber.*, 61B, 811, 827 (1928).
(6) R. Ahlberg, *Svensk Kem. Tidskr.*, **44**, 48 (1932).
(7) P. R. Rasenan and G. L. Jenkins, *J. Am. Pharm. Assoc.*, **38**, 559 (1949).

(8) R. P. Linstead and M. Whalley, *J. Chem. Soc.*, 3722 (1954).
(9) G. F. Ficken, R. B. Johns and R. P. Linstead, *J. Chem. Soc.*, 2280 (1956).
(10) J. H. Golden and R. P. Linstead, *J. Chem. Soc.*, 1732 (1958).
(11) Tests by Merck, Sharp and Dohme, West Point, Pa.

Anal. Calcd. for $C_8H_{17}NOS$: C, 54.81; H, 9.79; N, 7.99. Found: C, 54.20; H, 9.62; N, 7.88.

Dimethylmercaptoacetic acid. 5,5-Dimethyl-2-imino-4-thiazolidone (28.8 g., 0.20 mole) was dissolved in a 3.5% solution of sodium hydroxide (0.63 mole) and the mixture was refluxed for 17 hr. The hydrolysate was cooled and acidified with sulfuric acid. No oil separated. The mixture was distilled under diminished pressure. The water was removed from the aqueous distillate by passing air over the liquid at room temperature. The residue was dimethylmercaptoacetic acid, yield 6.8 g. (34%), m.p. 56–57°. Biilmann[12] reported that the melting point of this compound was "not sharp" at 47°. Our product was converted to the amic acid IIa and the thiomorpholinedione Ia.

Monosubstituted-α-bromoacetamides. In a typical experiment α-bromopropionyl bromide (21.6 g., 0.100 mole) was added rapidly dropwise to a stirred cold saturated solution of dry ammonia in petroleum ether, instead of benzene[13] in which the amides are more soluble. Ammonia was passed into the mixture through an adapter with a wide outlet during the addition and for 1 hr. longer. The solid mixture of α-bromopropionamide and ammonium bromide was filtered and washed first with petroleum ether and then carefully with water to remove the ammonium bromide. Recrystallization from benzene gave the pure amide, yield 92%, m.p. 128–129°. α-Bromobutyramide and α-bromocaproamide were prepared in similar yields.

Condensation of a disubstituted mercaptoacetic acid with a monosubstituted-α-bromoacetamide. In a typical example in which only one racemate would be expected, 7.3 g. (0.049 mole) of diethylmercaptoacetic acid was dissolved in a solution of sodium ethoxide prepared from 2.5 g. (0.108 mole) of sodium and 100 cc. of ethanol. To the stirred mixture was added 8.0 g. (0.053 mole) of α-bromopropionamide all at once. The solution became cloudy and solidified after 15 min. After standing 30 min. more the mixture was cooled in ice, diluted with water and acidified with concentrated hydrochloric acid. The solid which precipitated was collected and recrystallized from ethanol to yield the pure amic acid IIb.

α-Methylcarbamylmethyl-α'-mercapto-α'-ethylisocaproic acid (IId). Ethylisobutylmercaptoacetic acid (4.4 g., 0.025 mole) was dissolved in a solution of sodium ethoxide prepared from 1.3 g. (0.057 mole) of sodium and 35 cc. of ethanol. To this stirred solution was added 3.8 g. (0.025 mole) of α-bromopropionamide. The solution became cloudy and liberated heat. The mixture was cooled to room temperature and stirred for 30 min., at which time the entire solution appeared to solidify. This was cooled in ice, diluted with water until the solid dissolved, and then acidified. A finely divided white solid formed which was filtered, washed with water, and dried, m.p. 177–178°. One recrystallization from ethanol gave the pure product.

α-Methylcarbamylmethyl-α'-mercapto-α'-phenylbutyric acid (IIe-A and IIe-B). To a stirred solution of sodium ethoxide prepared from 0.5 g. (0.022 mole) of sodium and 25 cc. of ethanol were added in succession 2.0 g. (0.01 mole) of ethylphenylmercaptoacetic acid and 1.6 g. (0.01 mole) of α-bromopropionamide. In 3 min. the solution became cloudy. After stirring for 2 hr. at room temperature the mixture was cooled and acidified. An oily solid formed which was separated by decantation. Trituration of the solid with ethanol afforded 0.25 g. of solid, m.p. 170–171°. Recrystallization from isopropyl alcohol produced pure IIe-A. Dilution of the supernatant liquid with water produced 1.6 g. of another solid, m.p. 135–141°. Recrystallization of this from ethanol gave pure IIe-B.

α-Ethylcarbamylmethyl-α'-mercapto-α'-phenylbutyric acid (IIf). Ethylphenylmercaptoacetic acid (1.4 g., 0.0072 mole) was dissolved in a solution of sodium ethoxide prepared from 0.40 g. (0.017 mole) of sodium and 30 cc. of ethanol.

To the stirred solution was added 1.25 g. (0.0075 mole) of α-bromobutyramide all at once. After stirring for 3 hr. the solution was cooled in ice, acidified and diluted with water until a solid precipitated, m.p. 135–145°. Recrystallization from ethanol afforded pure IIf.

α-n-Butylcarbamylmethyl-α'-mercapto-α'-phenylbutyric acids (IIg-A and IIg-B). To a stirred solution of sodium ethoxide prepared from 4.6 g. (0.20 mole) of sodium and 100 cc. of ethanol were added in succession 19.6 g. (0.10 mole) of ethylphenylmercaptoacetic acid and 19.4 g. (0.10 mole) of α-bromocaproamide. The mixture became cloudy immediately and a solid slowly precipitated. After stirring for 2 hr. the mixture was cooled, acidified, and diluted with water. The solid dissolved and a second solid formed which was treated with boiling isopropyl alcohol. About half of this solid did not dissolve. It had m.p. 160–161.5°. Thorough washing with hot ethanol and recrystallization from dimethylformamide-water (1:1) produced pure IIg-A. As the filtrate cooled another solid precipitated, m.p. 163–165°. Recrystallization of this from ethanol produced pure IIg-B. A melting point of a mixture of the two pure racemates was 162–167°. Each racemate was dissolved in dimethylformamide and tested for optical activity. Both were optically inactive as expected.

Condensation of a disubstituted mercaptoacetamide with a monosubstituted-α-bromoacetamide. In a typical example in which only one racemate was expected, diethylmercaptoacetamide (6.0 g., 0.041 mole) was dissolved in a solution of sodium ethoxide prepared from 1.2 g. (0.052 mole) of sodium and 50 cc. of ethanol. α-Bromobutyramide (7.0 g., 0.042 mole) was added all at once to the stirred solution. The mixture became cloudy and liberated heat. A water bath was used to keep the temperature near 25°. In 5 min. the product solidified. After standing for 1 hr. the mixture was cooled in ice, diluted with water until the solid dissolved, and then acidified. Upon further dilution a solid formed which was filtered. Recrystallization from ethanol produced only the pure diamide IVa.

In a typical example in which two racemates were separated ethylphenylmercaptoacetamide (9.8 g., 0.050 mole) and α-bromocaproamide (9.7 g., 0.050 mole) were added in succession to a solution of sodium ethoxide prepared from 1.3 g. (0.056 mole) of sodium and 75 cc. of ethanol and the solution was stirred for 2 hr. After 5 min. the solution became cloudy and a finely divided solid precipitated. The mixture was cooled in ice, acidified, and diluted with water. As the water was added the solid dissolved and another solid precipitated. This solid was filtered and washed with methanol, m.p. 143–144°. Upon addition of more water to the filtrate a second crop of solid formed, m.p. 152–155°. A mixture of the two crops melted at 134–144°. Recrystallization of the first crop from isopropyl alcohol produced the pure diamide IVf-A. Recrystallization of the second crop from dimethylformamide-water (1:1) afforded the pure diamide IVf-B.

In a similar manner ethylphenylmercaptoacetamide was condensed with α-bromopropionamide. Upon acidification and solution with water an oil formed which was separated by decantation. Upon standing in 5% sodium hydroxide solution the oil solidified. When this solid was treated with hot ethanol about half of it dissolved. The ethanol insoluble portion, m.p. 191–193°, was recrystallized from dimethylformamide-water (1:1) producing the pure diamide IVe-A. The ethanol solution, upon concentration, yielded another solid, m.p. 162–167°. Recrystallization of this from dimethylformamide-water (1:1) produced the pure diamide IVe-B. A mixture of the two pure racemates melted at 158–170°.

α-Ethyl-α-phenylcarbamylmethyl-α'-mercaptopropionic acid (IIIa). A mixture of the diamides IVe-A and IVe-B (4.3 g., 0.016 mole) was added to 14 cc. of 5% sodium hydroxide and heated for 2 hr. The solid slowly dissolved and ammonia was liberated. Upon acidification of the cooled solution an oil formed which was dissolved in sodium bicarbonate solution and extracted with ether. The sodium bicarbonate layer

(12) E. Biilman, *Ann.,* 348, 129 (1906).
(13) C. A. Bischoff, *Ber.,* 30, 2310 (1897).

was then cooled, acidified and extracted with ether. Concentration of the ether solution produced a solid product, m.p. 133–140°. Recrystallization from dimethylformamide-water (1:1) and then from ethanol-water (1:1) yielded the pure amic acid IIIa.

α-Ethyl-α-phenylcarbamylmethyl-α'-mercaptobutyric acid (IIIb). Ethylphenylmercaptoacetamide (3.0 g., 0.015 mole) was dissolved in 32 cc. (0.08 mole) of 10% sodium hydroxide solution. α-Bromobutyric acid (2.7 g., 0.016 mole) was added dropwise to the stirred solution. After stirring for 1 hr. the mixture was cooled and acidified. The oil which formed was taken up in ether and the ether solution was extracted with sodium bicarbonate. The bicarbonate layer was cooled, acidified and extracted with ether. Concentration of the ether layer produced a solid, m.p. 142–144°. Repeated recrystallization from dimethylformamide-water (1:1) and then from ethanol-water (1:1) produced the pure amic acid IIIb.

α-Ethyl-α-phenylcarbamylmethyl-α'-mercaptocaproic acids (IIIc-A and IIIc-B). *From* IVf-A. This diamide (1.0 g., 0.0027 mol.) was dissolved in 3 cc. of 5% sodium hydroxide solution (0.0037 mol.) and heated to 70° for 1 hr. Upon cooling and acidifying a gunky white precipitate formed which hardened on standing, m.p. 140–150°. Recrystallization from isopropyl alcohol produced 0.8 g. of pure IIIc-A. By working up the filtrates and recrystallizing from ethanol a small amount of impure IIIc-B was obtained.

From IVf-B. This diamide was treated similarly. The solid which precipitated was filtered and washed with water. It was then recrystallized from isopropyl alcohol; first crop, m.p. 157–158° (IIIc-A); second crop, m.p. 135–142° (mostly IIIc-B).

From the thiomorpholinedione Ij (Table II). This compound (1.0 g., 0.0034 mole) was dissolved in 10 cc. of 1.5% sodium hydroxide solution (0.0037 mol.). The mixture was allowed to stand at room temperature for 24 hr. All of the solid had dissolved after standing for 16 hr. The solution was cooled in ice and acidified. The precipitate was collected, m.p. 145–148°. Recrystallization from isopropyl alcohol-water (5:1) gave pure IIIc-A. A second crop from the filtrate of the first recrystallization was obtained, m.p. 137–140°. Repeated recrystallization of this from ethanol-water (5:1) gave pure IIIc-B. The melting point of a mixture of the two isomers was lower (*ca.* 135°).

2,2,6-Trisubstituted-3,5-thiomorpholinediones. From an

amic acid type III. The amic acid IIIb (5.6 g., 0.020 mol.) was heated at 150–155° for 1 hr. while being evacuated. Water was evolved vigorously at first. Upon cooling an oily solid residue remained which was triturated with sodium bicarbonate solution leaving a solid, m.p. 67–70°. Recrystallization from an isopropyl alcohol-water mixture produced pure 2,6-diethyl-2-phenyl-3,5-thiomorpholinedione.

From an amic acid type II. In a typical example a mixture of IIg-A and IIg-B (8.1 g., 0.026 mol.) was placed in a distilling flask and heated at 180–190° for 90 min. under a vacuum. The oil which remained on cooling was taken up in isopropyl alcohol and cooled. Water was added until the solution became cloudy. The crystalline product was collected and recrystallized from isopropyl alcohol producing pure 6-*n*-butyl-2-ethyl-2-phenyl-3,5-thiomorpholinedione.

From the diamide. In a typical example IVa (7.6 g., 0.033 mol.) was dissolved in 20 cc. of concentrated hydrochloric acid and refluxed for 1 hr. Upon cooling, white needles formed. Recrystallization from ethanol gave pure 2,2,6-triethyl-3,5-thiomorpholinedione.

From the racemic diamide IVf-A. This diamide (7.6 g., 0.025 mol.) was dissolved in 20 cc. of hydrochloric acid (S.G. 1.18) and the solution was refluxed for 1 hr. When cooled an oil separated which would not crystallize. Distillation of the oil under diminished pressure gave a viscous colorless oil which solidified on standing. Recrystallization from isopropyl alcohol produced pure 6-*n*-butyl-2-ethyl-2-phenyl-3,5-thiomorpholinedione.

From the racemic diamide IVf-B. This diamide (1.5 g., 0.0049 mol.) was dissolved in 5 cc. of hydrochloric acid (S.G. 1.18) and the solution was refluxed for 75 min. Upon gradual cooling, finally in ice, a solid formed. One crystallization of this from isopropyl alcohol gave the identical 6-*n*-butyl-2-ethyl-2-phenyl-3,5-thiomorpholinedione.

Reactions of Perfluoroalkyl Isocyanates with Amines

RALPH L. DANNLEY, DONALD YAMASHIRO,[1] AND ROBERT G. TABORSKY[2]

Perfluoroalkyl isocyanates react with stoichiometric quantities of primary amines at low temperatures to form perfluoroalkyl ureas. These ureas readily undergo replacement of the alpha fluorine atoms to yield perfluoroacyl ureas. Solvolysis of the ureides to remove the perfluoroacyl group can be accomplished by refluxing with excess amine. The reaction of the perfluoroalkyl isocyanates with secondary amines could not be controlled and produced perfluoroacyl amidines.

It has been reported[3] that perfluoroalkyl isocyanates react abnormally with amines to yield compounds of undetermined structure instead of the expected ureas. These isocyanates also react abnormally with alcohols but by observing proper

(1) From the thesis to be submitted by Donald Yamashiro to the Graduate School of Western Reserve University in partial fulfillment of the requirements for the doctor's degree. Presented at the Chicago meeting of the American Chemical Society, September 1958.

(2) Present address, Roswell Park Memorial Institute, Buffalo, N.Y.

(3) A. Ahlbrecht, D. Husted, T. Reid, and O. Smith, Contribution No. 34 of Central Research Department, Minnesota Mining and Manufacturing Co., St. Paul, Minn., "Chemistry of Perfluoro Acids and Their Derivatives. IV. Fluoroalkyl Isocyanates."

precautions[4] the expected urethans can be obtained in excellent yield. The present investigation was initiated in expectation that by observing similar precautions, the addition of amines to these isocyanates could be controlled to yield ureas.

It has been shown[4] that perfluoroalkyl isocyanates react normally with stoichiometric quantities of alcohol at low temperatures. With excess alcohol the alpha fluorine atoms of the urethan are replaced to form perfluoroacyl urethans. By refluxing the perfluoroacyl urethans with alcohol, further alcoholysis occurs to give a simple carbamate and an ester. This sequence is represented below:

$$C_3H_7NCO \xrightarrow{C_2H_5OH} C_3F_7N-\underset{O}{\overset{H}{\underset{\|}{C}}}-OC_2H_5 \xrightarrow{C_2H_5OH}$$

$$C_2F_5C-\underset{O}{\overset{H}{\underset{\|}{N}}}-\underset{O}{\underset{\|}{C}}-OC_2H_5$$

$$\downarrow C_2H_5OH \quad (1)$$

$$C_2F_5-\underset{O}{\underset{\|}{C}}-OC_2H_5 + H_2N-\underset{O}{\underset{\|}{C}}-OC_2H_5$$
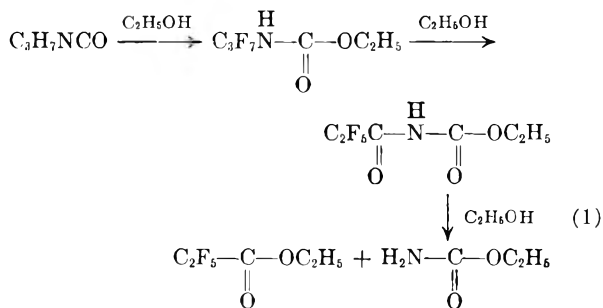
In the present work it has been found that treatment of the perfluoroalkyl isocyanates with stoichiometric quantities of primary amines at low temperatures gives the corresponding ureas in yields of 27 to 86%. These ureas not only hydrolyze with great ease but in addition undergo appreciable decomposition at room temperature in a period of a few days. Although careful recrystallization from chloroform gives samples of sharp melting point, sufficient decomposition occurs during shipping to a commercial analytical laboratory to result in C, H, and F analyses of limited accuracy. Kjeldahl nitrogen determinations performed on freshly prepared samples provided analytical figures which checked properly with theoretical values.

The ureas obtained from aromatic amines are the most stable. This is to be expected, for the ureas on standing give an odor of hydrogen fluoride and etch the glass containers. This loss of hydrogen fluoride would certainly be accelerated by the presence of residues of the amines of greater basicity.

The decomposition of the ureas on standing leads partially to the formation of perfluoroacyl ureas. In the initial investigation[3] of the reaction of perfluoroalkyl isocyanates with primary amines, the products of undetermined structure were probably mixtures of the expected ureas and the corresponding perfluoroacyl derivatives. The pure perfluoroacyl compounds are very stable and can be obtained in essentially quantitative yield by heating the ureas with aqueous acetone.

The perfluoroacyl ureas undergo solvolysis if refluxed with excess amine. This reaction and those already discussed are represented below.

(4) R. L. Dannley and M. Lukin, J. Org. Chem., 21, 1036 (1956).

$$C_3F_7NCO \xrightarrow{\phi NH_2} C_3F_7N-\underset{O}{\overset{H}{\underset{\|}{C}}}-N_\phi^H \longrightarrow$$

$$C_2F_5C-\underset{O}{\overset{H}{\underset{\|}{N}}}-\underset{O}{\underset{\|}{C}}-N\phi$$

$$\downarrow \phi NH_2 \quad (2)$$

$$C_2F_5CN_H^\phi + \underset{O}{\overset{H}{\underset{\|}{H}}}N-\underset{O}{\underset{\|}{C}}-N_H^\phi + \underset{O}{\overset{\phi}{\underset{\|}{H}}}N-\underset{O}{\underset{\|}{C}}-N_H^\phi$$
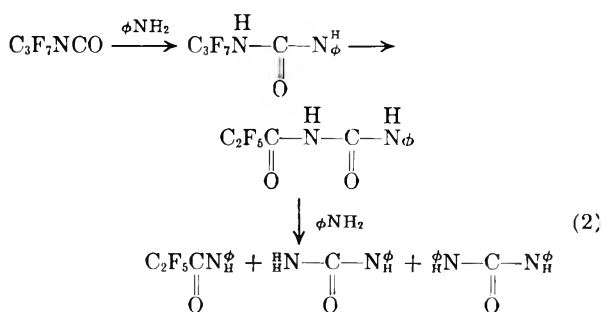
This series essentially parallels the reactions given in Equation 1. The initial reactions of the perfluoroalkyl isocyanates with both alcohols and primary amines are normal but are complicated by con-
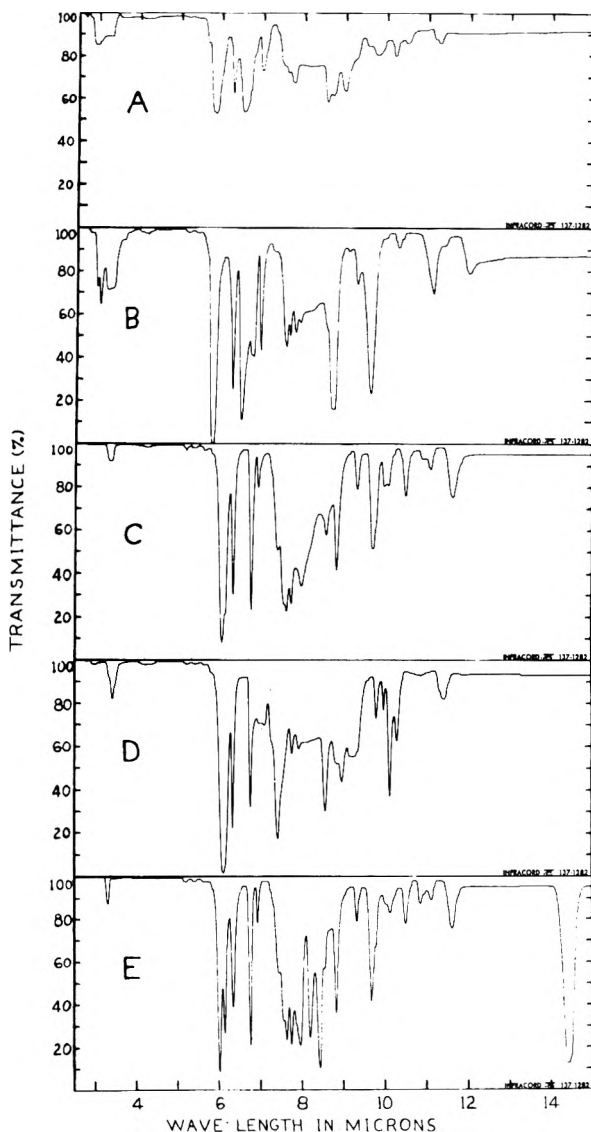
Fig. 1. Infrared spectra: A, N-n-perfluoropropyl-N'-phenylurea, 0.5% in chloroform; B, N-perfluoropropionyl-N'-phenylurea, 0.91% in chloroform; C, N,N-diphenyl-N',N'-diphenylcarbamylperfluoropropionamidine, 0.94% in chloroform; D, N,N-methylphenyl-N',N'-methylphenyl-carbamylperfluoropropionamidine, 0.94% in chloroform; E, N,N-diphenyl-N',N'-diphenylcarbamylperfluoropropion-amidine, 0.82% in carbon tetrachloride

<div style="text-align:center">

TABLE I

DESCRIPTIONS OF PRODUCTS

</div>

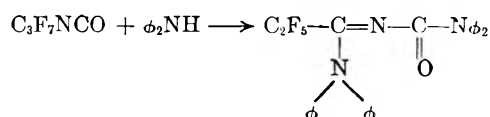| Product	Yield, %	M.P.[f]	Analysis							
			C		H		F		N	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
N-n-perfluoropropyl-N'-benzylurea[a]	51[d]	111–112[g]	41.52	42.16	2.85	2.60	41.8	38.5	8.81	8.87[h]
N-n-perfluoropropyl-N'-p-chlorophenylurea[b]	86[d]	122–123[g]	35.47	35.58	1.79	1.63	39.3	35.5	8.27	8.30[h]
N-n-perfluoropropyl-N'-n-butylurea	27[a]	84–84.5[g]	33.81	34.75	3.90	4.09	46.8	46.0	9.86	9.85[h]
N-n-perfluoroheptyl-N'-p-chlorophenylurea	52	120–123[g]							5.21	5.18[h]
N-perfluoropropionyl-N'-benzylurea	. . .	157.5–158	44.60	44.80	3.06	3.08			9.46	9.47[h]
N-perfluoropropionyl-N'-p-chlorophenylurea	92	157–158	37.93	37.98	1.91	1.74			8.85	8.87
N-perfluoropropionyl-N'-n-butylurea	93	97.5–98	36.64	36.79	4.19	4.21				
N-n-perfluoroheptanoyl-N'-p-chlorophenylurea	88	142–143							5.42	5.41
N,N-diphenyl-N'-N'-diphenylcarbamylperfluoropropionamidine[c]	54[e]	167.7–168.3	66.01	66.13	3.96	4.04			8.25	8.40

[a] Run at $-80°$. [b] Run in toluene instead of ether. [c] Reaction mixture heated 5 hr. at $130°$ in a sealed tube after initial period at room temperature. Mol. wt. calcd. for $C_{28}H_{20}F_5N_3O$, 509. Found, 477. [d] Reaction mixture evaporated to $^1/_5$ its volume and then diluted with 10 volumes of petroleum ether (Skelly B) to precipitate the product. [e] This yield calculated on the basis of two moles of amine needed for each mole of isocyanate consumed. The diphenylamine is therefore the reagent used in limited quantity. [f] All m.p.s are uncorrected. [g] All of these compounds melt with decomposition and evolution of a gas. Recrystallized from ether–petroleum ether. [h] Kjeldahl nitrogen determinations on freshly prepared samples.

secutive reactions involving the labile alpha fluorine atoms.

The last step in the sequence of reactions with aniline is unexpected in that both phenylurea and *sym*-diphenylurea are found. The diphenylurea is probably not a primary product but results from the reaction of excess aniline with phenylurea. This conclusion is substantiated by the absence of perfluoropropionamide which should be present if the diphenylurea is a primary product of solvolysis. This is not a rigid proof of the mechanism, however, for perfluoropropionamide could have been originally present but later converted to the anilide by reaction with excess amine.

The reaction of secondary amines with the isocyanates could not be controlled to form ureas. The only products isolated were amidines produced from the initial urea by a replacement of one alpha fluorine atom by an amino group and the loss of a molecule of hydrogen fluoride.

$$\text{C}_3\text{F}_7\text{NCO} + \phi_2\text{NH} \longrightarrow \text{C}_2\text{F}_5-\text{C}=\text{N}-\overset{\overset{\displaystyle\text{O}}{\|}}{\text{C}}-\text{N}\phi_2$$
$$\overset{\displaystyle\text{N}}{\underset{\phi\quad\phi}{\diagdown}}$$

A similar solvolysis has been reported[5] to occur when these perfluoroalkyl isocyanates are treated with ammonia. Amidines of similar structure have been obtained from polyfluoro olefins and amines.[6]

(5) A. Ahlbrecht and D. Husted, U. S. Patent 2,617,817.
(6) R. L. Pruett, J. T. Barr, K. E. Rapp, C. T. Bahner, J. D. Gibson, and R. H. Lafferty, *J. Am. Chem. Soc.*, **72**, 3646 (1950).

The structures of the amidines were substantiated by infrared spectra in addition to analyses and molecular weights. A strong amide peak (N–H stretch) found in every spectrum of a perfluoroalkyl or a perfluoroacyl urea is absent in the amidines. Also, a strong sharp peak at 5.9μ for the urea derivatives is shifted and broadened to 6.05–6.2μ for the amidines. The shift is due partially to the presence of the dialkyl nitrogen structure in place of the monoalkyl type. The broadening and extension to 6.2μ are due to a strong C=N stretch peak at 6.15μ. This 6.15μ absorption can be obtained as a completely independent and sharp peak in dilute solutions of N,N-diphenyl-N',N'-diphenylcarbamylperfluoropropionamidine in carbon tetrachloride. The infrared spectra of these compounds together with those of a representative urea and acyl urea are given in Fig. 1.

EXPERIMENTAL

N-n-Perfluoropropyl-N'-phenylurea. A well stirred solution of 10 g. (0.047 mol.) of *n*-perfluoropropyl isocyanate in 20 ml. of anhydrous ether was cooled to $0°$ during the slow addition of 4.4 g. (0.047 mol.) of aniline (distilled from zinc). Stirring was continued for 2 hr. at $0°$ and the solution evaporated under reduced pressure to give 11.0 g. (80% yield) of crude product, m.p. $109°$ with decomposition. Recrystallization from chloroform gave an analytical sample of *N-n*-perfluoropropyl-*N'*-phenylurea, m.p. $111°$ with decomposition.

Anal. Calcd. for $C_{10}H_7F_7N_2O$: C, 39.48; H, 2.32. Found: C, 39.42; H, 2.61.

This material slowly decomposed at room temperature, and recrystallization from chloroform after 4 weeks gave

only N-perfluoropropionyl-N'-phenylurea, m.p. 143–145° (see below for proof of structure).

Hydrolysis of N-n-perfluoropropyl-N'-phenylurea to the acyl ureide. Refluxing an acetone solution of a small sample of N-n-perfluoropropyl-N'-phenylurea for a few minutes and addition of water produced a white precipitate. Recrystallization from acetone-water gave N-perfluoropropionyl-N'-phenylurea, m.p. 145.5–146°.

Anal. Calcd. for $C_{10}H_7F_5N_2O_2$: C, 42.56; H, 2.50; N, 9.93. Found: C, 42.67; H, 2.39; N, 9.81.

N-Perfluoropropionyl-N'-phenylurea. The structure of this compound was proved by an independent synthesis.[7] A solution of 2.01 g. (0.0123 mol.) of perfluoropropionamide and 1.45 g. (0.0122 mol.) of phenyl isocyanate in 10 ml. of dry toluene was refluxed for 48 hr. After storing at 0° for 3 days, the precipitate which formed was isolated and recrystallized from acetone-water to give 1.50 g. (43% yield) of N-perfluoropropionyl-N'-phenylurea, m.p. 144.5–146.5. A mixed m.p. with the hydrolysis product of N-n-perfluoropropyl-N'-phenylurea showed no depression.

Reaction of N-perfluoropropionyl-N'-phenylurea with excess aniline. A mixture of 1.00 g. (.00354 mol.) of the N-perfluoropropionyl-N'-phenylurea and 3.25 ml. (0.0357 mol.) of aniline was heated to 90° for 20 hr., cooled, and then acidified with 30 ml. of 10% hydrochloric acid. The aqueous acid solution was extracted with four 50-ml. portions of ether. The combined ether extracts, dried over magnesium sulfate, were evaporated to dryness and the solids treated with 30 ml. of boiling ligroin. Filtration of the hot solution gave an insoluble residue from which by fractional crystallization from ethanol-water was isolated 0.30 g. of *sym*-diphenylurea (m.p. 234–235°) and 0.08 g. of phenylurea (m.p. 137–141°). The identities were established through further purification and mixed m.p. with authentic samples.

(7) P. F. Wiley, *J. Am. Chem. Soc.*, **71**, 1310 (1949).

Evaporation of the ligroin solution to 15 ml., chilling to −60°, and filtering gave 0.56 g. of white crystals, m.p. 95–97°. Recrystallization from ethanol-water gave pure perfluoropropionanilide, m.p. 97.5–98.5°.

Anal. Calcd. for $C_9H_6F_5NO$: C, 45.20; H, 2.53; N, 5.86; mol. wt. 239.16. Found: C, 45.25; H, 2.53; N, 6.10; mol. wt. 247.

The identity was confirmed by a mixed m.p. with an authentic sample of perfluoropropionanilide prepared by passing perfluoropropionyl chloride into a solution of aniline in ether.

Reactions of benzylamine with perfluoropropyl isocyanate. To prove the generality of the above sequence of reactions, the entire series through the ultimate solvolysis to benzyl urea was successfully repeated using benzyl amine.

N,N-Methylphenyl-N',N'-methylphenylcarbamylperfluoropropionamidine. Over a period of 40 min., 3.44 ml. (0.0318 mol.) of methylaniline in 30 ml. of dry ether was slowly added at −60° to 6.7 g. (0.0317 mol.) of perfluoropropyl isocyanate in 30 ml. of dry ether. After an additional 1.5 hr. at −60° and 6 hr. at room temperature, the mixture was stored at −30° for 2 weeks. Vacuum evaporation of the ether left an oily residue which was dissolved in 10 ml. of ligroin and 10 ml. of benzene. Vacuum evaporation of the mixture gave three successive crops of crystals, 4.27 g. (70%), m.p. 68.5–70°. Recrystallization from acetone-water and decolorizing with Norit gave white, crystalline N,N-methylphenyl-N',N'-methylphenylcarbamylperfluoropropionamidine, m.p. 71–72°.

Anal. Calcd. for $C_{19}H_{18}F_5N_3O$: C, 56.10; H, 4.19; N, 10.90; mol. wt., 385. Found: C, 56.27; H, 4.29; N, 11.09; mol. wt., 378; (m.p. depression of benzene).

CLEVELAND, OHIO

Fluorinated Paraffins

R. H. GROTH[1]

Paraffins with fluorinated clusters at one end, both ends, or in the middle of the chain have been synthesized from perfluorinated acids and their derivatives.

Many propanes and butanes are known[2] which have clustered fluorine atoms as in $CF_3C_3H_7$, $CF_3CH_2CH_2CF_3$, or $CF_3CF_2CF_2CH_3$. One pentane, $CF_3C_4H_9$, has been reported,[3] but no longer paraffin. The present paper shows the synthesis of hexanes and heptanes with their fluorinated groups diversely spaced, namely $C_3F_7C_3H_7$, $C_2H_5C_2F_4C_2H_5$, C_3F_7-$CH_2CH(CH_3)_2$, and $CF_3(CH_2)_4CF_3$. They were prepared for an examination of their physical

properties and the character of their carbon-hydrogen bond to be reported separately.[4]

The syntheses of these hexanes and heptanes involved basically a reduction starting with readily available perfluorinated acids. Particularly advantageous would be a reduction to a carbonyl function from an acid or derivative by use of Grignard or similar reagent. The carbonyl could be further reduced to the desired paraffin.

Esters of perfluorinated acids were unsuitable as they were known to give alcohols exclusively on treatment with $LiAlH_4$ or Grignards.[5] Anhydrides of unfluorinated acids yielded some carbonyl compounds at low temperatures[6] which was explained

(1) Present address: Department of Chemistry, University of Hartford, Hartford, Conn.

(2) A. L. Henne, J. W. Shepard, and E. J. Young, *J. Am. Chem. Soc.*, **72**, 3577 (1950).

(3) R. N. Haszeldine, *J. Chem. Soc.*, 2856 (1949).

(4) This phase of the work will be published by A. L. Henne. It has been orally presented by A. L. H. at the International Symposium on Fluorine Chemistry, at Birmingham, England in July 1959.

(5) E. Gryskiewicz-Trochimowski, *Rec. trav. chim.*, **66**, 427 (1947).

(6) M. S. Newman and Fr. O'Leary, *J. Am. Chem. Soc.*, **68**, 258 (1946).

in terms of the possible stability of the intermediate organometallic complexes,[7] and hence it seemed worth-while to extend this reaction to perfluorinated acid anhydrides in the hope of achieving carbonyl products.

The anhydride of trifluoroacetic acid, $(CF_3CO)_2O$, on reduction with $LiAlH_4$ gave a mixture of alcohol, acid, ester, and aldehyde in which the latter amounted to 21.5%. With CH_3MgBr, there was only a trace of CF_3COCH_3 in the products, while with $(CH_3)_2CHMgBr$, the main products were the acid, CF_3COOH, and a secondary alcohol, $CF_3CHOHCH(CH_3)_2$, made by reduction of the intermediate. From the anhydride of perfluorobutyric acid, $(C_3F_7CO)_2O$, and CH_3MgBr, no ketone was isolated. The main products were the acid and the ester of the acid, $C_3F_7CO_2C(CH_3)_2$-C_3F_7.

Recent work[8] has indicated that some perfluorinated monobasic acids could be converted to ketones with Grignard reagents. In this investigation, this work was extended to include perfluorinated dibasic acids. The reaction of perfluorosuccinic acid, $(CF_2)_2(COOH)_2$, with CH_3-MgBr gave 45% of the diketone, $CH_3COCF_2CF_2$-$COCH_3$. The next perfluorinated homolog, perfluorinated glutaric acid, $(CF_2)_3(COOH)_2$, with CH_3MgBr gave, however, a mixture, in which two products boiling respectively at $147°$ and $177°$ predominated; the lower boiling one was probably a mixture of $CH_3CO(CF_2)_3COCH_3$ and CH_3CO-$(CF_2)_3C(CH_3)=CH_2$, while the higher boiling one was the cyclic hemiketal, $CH_3C(OH)(CF_2)_3C$-$\overline{\qquad\qquad O\qquad}$-
$(CH_3)_2$. Infrared spectra of the lower boiling fragment indicated a carbonyl and olefin function and tests with Br_2, MnO_4^- and 2,4-DNPH were all positive. On this basis, it could be (a) CH_3CO-$(CF_2)_3C(CH_3)=CH_2$ or (b) $CH_3CO(CF_2)_3CH=CH_2$. The first (a) could involve addition of CH_3MgBr to the diketone $CH_3CO(CF_2)_3COCH_3$ followed by loss of water; the second, (b) would require reduction of the carbonyl without addition of an alkyl group which has not been observed with CH_3-MgBr. A 2,4-DNPH formed from the $147°$ material gave an analysis [$\%$ N found 13.86, calculated for mono derivative of (a) 13.52, calculated for mono derivative of (b) 14.47] which favored (a) but analysis of the $147°$ mixture [$\%C$, $\%$ H found 38.79, 2.47; calculated for (a) 41.03, 3.42; calculated for (b) 38.18, 2.73] favored structure (b)]. This contradiction can be resolved by assuming a mixture of $CH_3CO(CF_2)_3COCH_3$ ($\%$ C, $\%$ H calculated 35.59, 2.54) and (a). The 2,4-DNPH formed would be the derivative of (a); any formed

from the diketone was presumably lost in purification by recrystallization.

Guided by these considerations and the fact that fluorinated ketones could not be reduced directly to paraffins in a Clemmensen or Wolff-Kishner procedure, the following synthesis were settled as follows:

$C_3F_7C_3H_7$. $C_3F_7CH=CHCH_3$, prepared by addition of C_2H_5MgBr to $C_3F_7CO_2CH_3$ followed by dehydration with P_2O_5 in accord with reported procedures[9,10] was hydrogenated in presence of Raney nickel to give a 41% yield of $C_3F_7C_3H_7$.

$C_3F_7CH_2CH(CH_3)_2$. $C_3F_7CH=C(CH_3)_2$, prepared by reduction of $C_3F_7CO_2CH(CH_3)_2$ with $LiAlH_4$ followed by dehydration with P_2O_5 in accord with reported procedures[9,10] was hydrogenated in presence of PtO_2 to give a 89% yield of $C_3F_7CH_2CH$-$(CH_3)_2$.

$C_2H_5C_2F_4C_2H_5$. $CH_3COCF_2CF_2COCH_3$, prepared by the reaction of CH_3MgBr on the perfluorinated succinic acid, was reduced in 64% yield to give $CH_3CHOHCF_2CF_2CHOHCH_3$. This diol, on treatment with P_2O_5, gave only a cyclic ether, CH_3-$\underset{\underline{\qquad\quad O\quad\qquad}}{CHCF_2CF_2CHCH_3}$ in 72% yield. Therefore reduction to the paraffin was achieved by acetylation of the diol with $(CH_3CO)_2O$ in 92% yield to the diacetate, $CH_3CH(OCOCH_3)CF_2CF_2CH(OCOCH_3)$-$CH_3$, pyrolysis of this diacetate to the diene $CH_2=$=CHCF_2CF_2CH=CH_2$ in 67% yield and finally hydrogenation of the diene in 85% yield to the paraffin $C_2H_5C_2F_4C_2H_5$.

$CF_3(CH_2)_4CF_3$. $CF_3CO_2C_2H_5$ was reacted with diethyl succinate and $NaOC_2H_5$ in the usual Claisen condensation followed by decarboxylation to give a 65% yield of the unsaturated lactone,
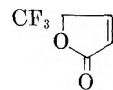
which was then hydrogenated in 80% yield to give
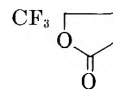
This saturated lactone was reacted with CF_3CO_2-C_2H_5 and $NaOC_2H_5$ in a second Claisen condensation which gave on decarboxylation a 67% yield of the hemiketal, $CF_3C(OH)CH_2CH_2CHCF_3$. Reduction of
$\underline{\qquad\qquad O\qquad\qquad}$
the hemiketal with $LiAlH_4$ gave a 75% yield of diol, $CF_3CHOHCH_2CH_2CHOHCF_3$. Dehydration of the diol with P_2O_5 gave only tar and acrid fumes. Therefore, dehydration was achieved by acetylation of the diol in essentially quantitative yield to the diacetate, $CF_3CH(OCOCH_3)CH_2CH_2CH$-$(OCOCH_3)CF_3$, followed by pyrolysis in 83% yield to

(7) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Non-metallic Substances*, Prentice-Hall, Inc., New York, 1954, p. 549.

(8) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2269 (1956).

(9) E. T. McBee, O. R. Pierce, and M. C. Chen, *J. Am. Chem. Soc.*, **75**, 2325 (1953).

(10) F. Swarts, *Bull. sci. roy. acad. Belg.*, **8**, 343 (1922).

the diene, CF_3CH=$CHCH$=$CHCF_3$. Finally the diene was hydrogenated in 94% yield to the paraffin $CF_3(CH_2)_4CF_3$.

In this last synthesis, the first Claisen presumably gave a gamma keto acid which in acid media formed the unsaturated lactone. This is in accord with expectations based on unfluorinated analogs. The second Claisen presumably gave a keto alcohol which as expected formed the stable hemiketal by reaction of the two functional groups.

The identity of the new compounds was established from analysis, method of preparation, subsequent reactions and optical refractivity computations as detailed below. Infrared red spectra was used to confirm the structure.

EXPERIMENTAL

Reaction of $(CF_3CO)_2O$ with $LiAlH_4$. $(CF_3CO)_2O$ was prepared from the corresponding acid by the method of Swarts[11] and modified by Paridon.[12] A slurry of $LiAlH_4$ (10 g., 0.263 mole in 300 ml. of dry ether) was refluxed for 3 days under an atmosphere of nitrogen with continuous stirring under the refluxing of a water condenser leading to a dry ice trap and $CaCl_2$ drying tube. This $LiAlH_4$ solution, determined by titration to contain 0.12 mole, was added dropwise in 2 hr. to $(CF_3CO)_2O$ (48.5 g., 0.23 mole) in 100 ml. of dry ether at $-55°$ to $-45°$. The mixture was protected from moisture as before and stirred overnight at $-45°$. Decomposition was achieved by addition of 10 ml. of water followed by 25 ml. of concentrated H_2SO_4 in 55 ml. of water and allowing the mixture to reach room temperature. The ether layer and ether extracts of the aqueous layer were dried over Na_2SO_4 and then fractionated to give:

i. 16.2 g. boiling between 45–70°, mostly 60–65°.
ii. 4.2 g. boiling between 70–85°.
iii. 20.0 g. pot residue, which on fractionation gave:
iv. 1.4 g. boiling between 78–103°.
v. 22.4 g. boiling between 103–106°.

v with P_2O_5 gave a material, boiling at $-19°$, which formed a 2,4-DNPH, melting at 148°; mixed m.p. with 2,4-DNPH of CF_3CHO was 148°.

Refractionation of i, ii, and iii combined gave:

vi. 3.4 g. boiling between 47–52°.
vii. 1.4 g. boiling between 52–60°.
viii. 12.0 g. boiling between 68–74°.

vi on the basis of infrared spectra (max. at 5.56 μ) and boiling point (compared to known 52–55°[11]) and preparation of amide, CF_3CONH_2 (m.p. 75°, mixed m.p. 75°) was identified as the ester $CF_3CO_2CH_2CF_3$. viii, by infrared spectra (max. at 3.00 μ) and boiling point comparison (known b.p. 74°[11]) was identified as CF_3CH_2OH. v was strongly acidic and gave a positive 2,4-DNPH test. Titration of an aliquot with base indicated 10.1 g. of CF_3COOH (0.089 mole, 19.3%). Reaction of another aliquot with 2,4-DNPH indicated 9.7 g. of CF_3CHO (0.099 mole, 21.5%).

Reaction of $(CF_3CO)_2O$ with excess CH_3MgBr. CH_3MgBr (about 0.7 mole) in 300 ml. of dry ether was added dropwise in 1.25 hours to $(CF_3CO)_2O$ (50 g., 0.238 mole) in 100 ml. of dry ether at 0°. The solution was continuously stirred and protected from moisture as previously described. After addition, the temperature was allowed to rise to room temperature and the solution stand overnight. The complex was then decomposed at 0° by dropwise addition of 120 ml. of saturated NH_4Cl solution with continuous stirring.

A small aliquot was treated with 2,4-DNPH and gave only traces of the 2,4-DNPH derivative of CF_3COCH_3 (m.p. 138°, mixed m.p. 138°). The main portion of the mixture was treated with dilute HCl and the ether layer and ether extracts of the aqueous layer treated as before after a washing with dilute Na_2CO_3 solution. Fractionation gave $CF_3C(CH_3)_2OH$ (25.3 g., 0.198 mole, 42%), boiling between 76–80° (known b.p. 81°[13,14]) and having an index of refraction of 1.3350 at 20° (known 1.3350[13,14]). Continuous ether extraction of the acidified aqueous layer resulted in isolation of CF_3COOH (15.7 g., 0.138 mole, 29%).

The reaction of $(CF_3CO)_2O$ with equimolar amounts of CH_3MgBr gave comparable results.

Reaction of $(CF_3CO)_2O$ with $(CH_3)_2CHMgBr$. $(CH_3)_2CH$-$MgBr$ (prepared from 0.7 mole of $(CH_3)_2CHBr$) in 500 ml. of dry ether was added dropwise in 2 hr. to $(CF_3CO)_2O$ (59 g., 0.28 mole) in 100 ml. of dry ether at 0°. After reaction with protection from moisture, the mixture stood overnight at room temperature and was then decomposed by addition of 100 ml. of saturated NH_4Cl solution at 0°. Fractionation after washing the ether layer and extracts with dilute Na_2CO_3 solution and drying over Na_2SO_4 gave:

i.	8.2 g.	b.p. 35–62°	n_D^{20} 1.3520
ii.	13.0 g.	62–87°	1.3440
iii.	11.8 g.	87–	1.3515
iv.	4.0 g.	residue	

Infrared spectra indicated i to be essentially ether, ii alcohol, $CF_3CHOHCH(CH_3)_2$ (max. at 2.92 μ), and iii an alcohol and ester mixture (max. at 2.92 μ and 5.56 μ). Continuous ether extraction of the acidified aqueous layer gave CF_3-COOH (20 g., 0.175 mole, 31%). The alcohol could not be purified for analysis and was prepared by reaction of $CF_3CO_2C_2H_5$ and $(CH_3)_2CHMgBr$ at 0° with a yield of 55%.[15] Comparison of the infrared spectra of the alcohol present in ii and that of the synthesized sample indicated them to be the same.

Reaction of $(C_3F_7CO)_2O$ with CH_3MgBr. $(C_3F_7CO)_2O$ was prepared from C_3F_7COOH and P_2O_5 by the method of Minnesota Mining and Mfg. Co.[16] modified by the use of some concentrated H_2SO_4 (10 ml. per 129 g., 0.603 mole of C_3F_7-COOH and 85 g., 0.589 mole of P_2O_5) in 85% yield. CH_3-$MgBr$ (containing about 0.24 mole) in 200 ml. of dry ether was added dropwise in 1.5 to 2 hr. to $(C_3F_7CO)_2O$ (46 g., 0.112 mole) in 150 ml. of dry ether at 0°. After reaction and subsequent standing overnight at room temperature, the mixture at 0° was decomposed by dropwise addition of 40 ml. of saturated NH_4Cl solution. Treatment of the ether layer and extracts was as before and fractionation gave:

i.	2.2 g.	b.p. 37–97°	n_D^{24} 1.3225
ii.	2.8 g.	97–110°	1.3226
iii.	5.2 g.	110–125°	1.3270
iv.	3.5 g.	residue	

Infrared spectra indicated i, ii, and iii to be mainly ester in character (max. at 5.56 μ). A small aliquot gave a $(-)$ test for ketone with 2,4-DNPH. Continuous ether extraction of the acidified aqueous layer gave C_3F_7COOH (24.8 g., 0.116 mole, 50.2%). Inasmuch as attempts to purify the ester were unsatisfactory, a synthesis of the ester was effected by repeating the reaction with excess CH_3MgBr to form the tertiary alcohol, $C_3F_7C(OH)(CH_3)_2$ converting it to the sodium alcoholate and reacting this alcoholate with C_3H_7-COCl. Using CH_3MgBr (prepared from 0.3 mole of CH_3Br) in 175 ml. of dry ether and $(C_3F_7CO)_2O$ (32 g., 0.078 mole) in 150 ml. of dry ether, the tertiary alcohol (11.3 g., 0.0496 mole, 31.8%), boiling between 105–107°, n_D^{20} 1.3279 was

(11) F. Swarts, *Compt. rend.*, **197**, 1261–4 (1933).
(12) L. Paridon, private communication, March 1955.
(13) F. Swartz, *Bull. soc. chim. Belg.*, **36**, 191 (1927).
(14) F. Swarts, *Bull. soc. chim. Belg.*, **38**, 99 (1929).
(15) E. T. McBee, O. R. Pierce, and W. F Marzluff, *J. Am. Chem. Soc.*, **75**, 1609 (1953).
(16) Minnesota Mining & Mfg. Co., Literature, Sept. 1, 1949.
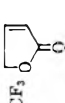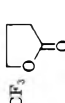
TABLE I

New Compound

Compound	M.P.[a]	B.P.[a]	n_D^{20}	d_4^{20}	M.R.	ARF	% C[b] Calcd.	% C[b] Found	% H[b] Calcd.	% H[b] Found	% N[b] Calcd.	% N[b] Found
$C_3F_7CO_2C(CH_3)_2C_3F_7$		146°	1.3082	1.572	51.7	1.22	28.30	28.15	1.41	1.68		
$CH_3CO(CF_2)_2COCH_3$		129°	1.3520 (25°)	1.311 (25°)	30.70	1.29	38.71	39.03	3.23	3.40		
di-2,4-DNPH	283–284° dec.										20.51	20.17
$C_3H_7C_3F_7$		64–65°	1.30000	1.260 (25°)			33.97	33.58	3.30	3.58		
lactone, CF_3		83/12–13 mm.	1.3853	1.444	24.68	1.02	39.49	39.42	1.97	2.72		
lactone, CF_3		78–79/25 mm.	1.3748	1.413	24.97	1.18	38.96	38.90	3.24	3.30		
$CF_3C(OH)CH_2CH_2CHCF_3$ —O—		140	1.3468 (25°)	1.525 (25°)	31.11	1.14	32.14	32.13	2.68	2.84		
$(CF_3CHOCOCH_3CH_2)_2$	65°	133/75 mm.	1.3630 (26°)	1.310 (26°)	52.25	1.20	31.86	31.63	3.54	3.68		
$CF_3CH=CHCH=CHCF_3$		85.5–86.5	1.3403 (25°)	1.286 (25°)	30.995	1.22	37.89	38.09	2.11	2.38		
$CH_3CHOHCF_2CF_2CHOHCH_3$		201	1.3865 (25°)	1.359 (25°)	32.875	1.08	37.90	38.08	5.26	5.45		
$(CH_3CHOCOCH(CF_2-)_2)$		205	1.3870 (25°)	1.246 (25°)	51.78	1.12	43.80	43.97	5.11	5.19		
$CH_3CHCF_2CF_2CHCH_3$ —O—		91	1.3425 (24°)	1.229 (24°)	29.53	1.14	41.86	40.05	4.66	4.66		
$CH_2=CHCF_2CF_2CH=CH_2$		75.5–76.5	1.3415	1.135	28.55	1.00	46.75	46.45	3.90	4.14		
$C_2H_5C_2F_4C_2H_5$		78.5–79.5	1.3292 (25°)	1.089 (25°)	29.54	1.01	45.57	45.70	6.33	6.49		
$C_3F_7CH_2CH(CH_3)_2$		81.5	1.3130	1.220	36.02	1.33	37.17	37.40	3.98	4.25		
$CH_3C(OH)CF_2CF_2CF_2C(CH_3)_2$ —O—		177	1.3781	1.433	40.375	1.14	38.09	37.75	3.97	4.35		
$CH_2=C(CF_2)_3C(CH_3)_2$ —O—		136	1.3650	1.350	38.74	1.20	41.04	41.04	3.19	3.42		
$CH_3CH(CF_2)_3C(CH_3)_2$ —O—		139	1.3571	1.332	38.791	1.13	40.67	40.81	4.23	4.43		
$CH_3CHOH(CF_2)_3CH(CH_3)_2$ or $CH_3CH_2(CF_2)_3C(OH)(CH_3)_2$	107°	165	1.3670	1.339	39.91	0.98	40.43	40.41	5.04	5.19		
$C_3F_7COCH_3$ as semicarbazone	75–120°						26.76	26.44	2.24	2.64	15.61	15.67
$CF_3CHOHCH_2CH_2CHOHCF_3$	46°						31.86	31.63	3.54	3.68		
$CF_3CHOHCH_2CH_2CONH_2$											8.19	8.22

[a] All temperatures uncorrected. [b] Analysis by Galbraith Laboratories.

formed. Its identity was established by comparison with known constants (b.p. 105–107°, n_D^{20} 1.3279[15]) and confirmed by infrared spectra (max. at 2.92 μ). This alcohol (45.6 g., 0.2 mole) was added dropwise to Na sand (4.6 g., 0.2 mole) prepared in hot toluene and suspended in 250 ml. of dry ether, as rapidly as refluxing under a water condenser permitted. The mixture was protected from moisture. C_3F_7COCl (48.5 g., 0.208 mole) prepared from C_3F_7COOH and PCl_5 in accord with the procedure of Minnesota Mining and Mfg. Co.,[16] was added dropwise to the suspension of the sodium alcoholate as rapidly as refluxing of the water condenser permitted with continuous stirring. Fractionation gave the ester (63.5 g., 0.15 mole, 75%) boiling 140–146°. Infrared spectra indicated it to be alcohol free and identical to the ester formed by reaction of CH_3MgBr with $(C_3F_7-CO)_2O$.

Reaction of $(CF_2)_2(COOH)_2$ *with* CH_3MgBr. Two identical runs were made in which $(CF_2)_2(COOH)_2$ (220 g., 1.157 moles) in 300 ml. of dry ether was reacted in 4.5 hr. with CH_3MgBr (prepared from 545 g., 5.85 moles CH_3Br and 146 g., 6 g.a.a. Mg) in 2000 ml. of dry ether using the procedure outlined earlier. The residue from the ether layers and extracts of both runs were combined and treated as before, and then fractionated to give the diketone, $CH_3CO-CF_2CF_2COCH_3$, (198 g., 1.06 moles, 45%) boiling 128–130°. In addition, a forecut (85 g.) boiling 65–125° and a tarry residue (45 g.) were isolated. The aqueous phase contained F^- and continuous ether extraction of it gave only traces of $(CF_2)_2(COOH)_2$. The diketone was identified on the basis of its mode of preparation, subsequent reactions, atomic refractivity computations, and analysis. A solid 2,4-DNPH melted at 283–284° with decomposition. Infrared spectra (max. at 5.62 μ) confirmed this structure.

Reaction of $(CF_2)_3(COOH)_2$ *with excess* CH_3MgBr. Two identical runs were made simultaneously by reacting $(CF_2)_3(COOH)_2$ (1.5 equivalents on the basis of titration of a small aliquot with base) in 500 ml. of dry ether in 2.5 hr. with CH_3MgBr (prepared from 6 moles CH_3Br and 6.05 g.a.a. Mg) in 750 ml. of dry ether at 0°. (The Grignard reagent was used in large excess because the very hygroscopic acid was thought to contain some water.) Fractionation of the residue from the combined ether layers and extracts, treated as before, gave a mixture containing an olefin and ketone function (174 g., 0.814 mole, 54.3% including estimates in the fore and tail cuts) boiling mostly at 147°, and a hemiketal (82.4 g., 0.327 mole, 21.8% including estimates in fore and tail cuts) boiling mostly at 177°. The 147° material gave a 2,4-DNPH melting at 120°, positive tests for olefin with MnO_4^- and Br_2, and an infrared spectra (max. at 5.62 μ and 6.02 μ) which confirmed presence of double bond and carbonyl. Infrared spectra of the hemiketal, $CH_3C(OH)(CF_2)_3C(CH_3)_2$, showed characteristic alcohol band (max. 2.85 μ) and absence of olefin and carbonyl bands.

Hydrogenation of $C_3H_7CH=CHCH_3$. $C_3F_7CH=CHCH_3$ (70 g., 0.333 mole) in 250 ml. of dry ether was placed in a glass lined high pressure steel autoclave (capacity 1 l.) with 4 g. Raney nickel and enough hydrogen to produce a pressure of 106.7 atmospheres. The autoclave was mechanically rocked and heated to 100°. Fractionation of the product gave the hydrocarbon, $C_3F_7C_3H_7$ (29 g., 0.137 mole, 41%) as the main product boiling 64–65°. Infrared spectra confirmed that the product was olefin free.

Hydrogenation of $C_3F_7CH=C(CH_3)_2$. $C_3F_7CH=C(CH_3)_2$ (30.8 g., 0.138 mole) in 50 ml. of dry ether was placed in a 220 ml. glass bottle in a Parr hydrogenation apparatus with 50 mg. of PtO_2 and enough hydrogen to produce a pressure of 3.3 atmospheres at room temperature. In 36 hr., a total of 2.54 atmospheres was absorbed. Fractionation of the product gave $C_3F_7CH_2CH(CH_3)_2$ (19 g., 0.083 mole, 60% practical yield, 89% including estimates on fore and tail cuts) boiling mostly 80–82°. Infrared spectra confirmed the

absence of the olefin band. (The constant for the apparatus is 1.87 to 2 atmospheres per 0.1 mole of hydrogen absorbed.)

Reduction of $CH_3COCF_2CF_2COCH_3$ *with* $LiAlH_4$. $LiAlH_4$ (25 g., 0.658 mole) in 500 ml. of dry ether was refluxed for 3 hr. with suitable precautions to exclude moisture. $CH_3CO-CF_2CF_2COCH_3$ (173.5 g., 0.933 mole) was added with continuous stirring to this solution in 2.5 hr. at 0°. After standing overnight at room temperature, the mixture was decomposed at 0° by dropwise addition with continuous stirring of 50 ml. of ice water followed by 50 ml. of concentrated H_2SO_4 in 150 ml. of ice water. The dried ether layer and extract gave on fractionation the diol, $CH_3CHOHCF_2CF_2-CHOHCH_3$ (112.5 g., 0.592 mole, 64% including estimates on fore and tail cuts) boiling at 201°. A forecut (17 g., 0.093 mole, 10%) of starting material was also recovered. Continuous ether extraction of the aqueous layer gave 22 g. of material, consisting of diol and diketone. The identity of the diol was confirmed by infrared spectra (max. 3.06 μ).

Direct reduction of the ketones to paraffins was tried without success by Clemmensen and Wolff-Kishner procedures. Using CF_3COCH_3 and also $CF_3COC_4H_9$ and the usual Clemmensen procedure, no reaction occurred. The Wolff-Kishner reaction was tried using $C_3F_7COCH_3$ (prepared by a Claisen condensation between $C_3F_7CO_2C_2H_5$ and $CH_3CO_2C_2H_5$ in the presence of $NaOC_2H_5$ with a yield of 46% in addition to 37% recovered ethyl acetate and 19% diethyl carbonate) and CF_3COCH_3 as semicarbazones. In both cases decomposition occurred giving CF_3H, CO, CO_2 and NH_3 in the case of CF_3COCH_3 and C_3F_7H, CO, CO_2 and NH_3 in the case of $C_3F_7COCH_3$.

Acetylation of $CH_3CHOHCF_2CF_2CHOHCH_3$. The diacetate was prepared in the usual manner by adding $(CH_3-CO)_2O$ (118 g., 1.15 moles) dropwise with continuous stirring in 1.5 hr. to $CH_3CHOHCF_2CF_2CHOHCH_3$ (100 g., 0.526 mole) containing 2 drops of concentrated H_2SO_4. The mixture was maintained at 100° for 3 hr. and then fractionated to give the diacetate, $CH_3CH(OCOCH_3)CF_2CF_2CH(OCO-CH_3)CH_3$ (126.6 g., 0.462 mole, 87% yield, 92% including estimates in fore and tail cuts). Infrared spectra (max. at 5.72 μ) confirmed the presence of acetate esters and absence of alcohol.

Dehydration of the diol with P_2O_5 gave a 72% yield of $CH_3CHCF_2CF_2CHCH_3$, boiling between 90–92° and having
$\underset{\textstyle\longmapsto \ \ O \ \ \longmapsto}{}$
an olefin, alcohol, and carbonyl-free infrared spectra.

Pyrolysis of $CH_3CH(OCOCH_3)CF_2CF_2CH(OCOCH_3)CH_3$. This pyrolysis was carried out using the method of Hinkamp.[17] In all 5 passes were made and the product (47 g., 0.306 mole, 67% practical yield) obtained on fractionation, boiling 75.5–76.5° was confirmed by infrared spectra (max. at 5.75 μ and 6.05 μ) as the diene, $CH_2=CHCF_2CF_2CH=CH_2$. The usual positive tests with MnO_4^- and Br_2 were noted. The rate of addition of diacetate was 1 drop/6 to 8 seconds; nitrogen inlet rate 2 bubbles/second, and temperature 460–480°.

Hydrogenation of $CH_2=CHCF_2CF_2CH=CH_3$. Hydrogenation of the diene was effected in the same manner as that used with $C_3F_7CH=C(CH_3)_2$. The hydrocarbon, $C_2H_5-C_2F_4C_2H_5$ (16.3 g., 0.103 mole, 72% practical yield, 85% including estimates in fore and tail cuts) isolated showed negative tests with Br_2 and MnO_4^- and absence of olefin bands in its infrared spectra.

Dehydration of $CH_3C(OH)(CF_2)_3C(CH_3)_2$. The hemiketal
$\underset{\textstyle\longmapsto \ \ O \ \ \longmapsto}{}$
(14.4 g., 0.057 mole) and P_2O_5 (15 g., 0.104 mole) were heated together and the product distilled out. The main product (9.8 g., 0.042 mole, 73.7%) boiled at 136°. This olefin, $CH_2=C(CF_2)_3C(CH_3)_2$, showed the usual tests with
$\underset{\textstyle\longmapsto \ \ O \ \ \longmapsto}{}$
Br_2 and MnO_4^- and had an infrared spectra (max. at 5.92 μ) which confirmed the olefin and showed absence of alcohol and carbonyl bands.

(17) A. L. Henne and P. Hinkamp, *J. Am. Chem. Soc.*, 76, 5147 (1954).

Hydrogenation of $CH_2=C(CF_2)_3C(CH_3)_2$. The olefin (32.6

g., 0.139 mole) in 50 ml. of dry ether with 50 mg. of PtO$_2$ absorbed 3.41 atmospheres of hydrogen in 37 hr. in the Parr Hydrogenation apparatus. Fractionation gave: CH$_3$CH-

$(CF_2)_3C(CH_3)_2$ (22.1 g., 0.094 mole, 67.3% including esti-

mates in fore and tail cuts) boiling mostly at 138–140°. Infrared spectra of the oxide showed no olefin or carbonyl group. An alcohol (8.8 g., 0.037 mole, 26.6% including estimates in fore and tail cuts) boiling mostly at 165° was also isolated. The infrared spectra of this material showed an alcohol band (max. at 2.92 μ).

Condensation of $(CH_2)_2(CO_2C_2H_5)_2$ *with* $CF_3CO_2C_2H_5$ *in presence of* $NaOC_2H_5$. NaOC$_2$H$_5$ (4 moles) was prepared from Na sand (92 g., 4 g.a.a.) and C$_2$H$_5$OH (184 g., 4 moles) and suspended in 1 liter of dry ether. CF$_3$CO$_2$C$_2$H$_5$ (586 g., 4 moles) was added with some external cooling to the NaOC$_2$H$_5$ slurry. Half of the $(CH_2)_2(CO_2C_2H_5)_2$ (174 g. of 348 g., 2 moles) was added dropwise at room temperature in 1.25 hr. to the continuously stirred solution. The mixture was refluxed under a water condenser which led to a dry ice trap for 12 hr. The remainder of the $(CH_2)_2(CO_2C_2H_5)_2$ was added in 2.75 hr. and the mixture refluxed for 24 hr. The solvent was then removed and on fractionation of it, small amounts of recovered ester, CF$_3$CO$_2$C$_2$H$_5$, and CF$_3$COCH$_3$, characterized as CF$_3$CONH$_2$ (m.p. 75°, mixed m.p. 75°) and 2,4-DNPH of CF$_3$COCH$_3$ (m.p. 138°, mixed m.p. 138°) respectively; ethyl alcohol (170 g., 3.7 moles), and a small amount of unfluorinated carbonyl containing compound in the tails. The remaining solid mass was neutralized with 1200 ml. of 25% H$_2$SO$_4$ solution and the resulting organic layer (885 g.) was added to 200 ml. of 25% H$_2$SO$_4$ solution. The two layer system, continuously stirred, was refluxed under a reflux head whose outlet led to a dry ice receiver and trap for 2.5 days, at which time no further evidence of CO$_2$ evolution was noted. In the dry ice trap, 45 g. of material was isolated and identified as before as mostly CF$_3$CO$_2$C$_2$H$_5$ and lesser amounts of CF$_3$COCH$_3$. The ether extract of the main organic layer was dried and fractionated to give small amounts of CF$_3$CO$_2$C$_2$H$_5$, an intermediate cut consisting largely of ethyl alcohol, and a main fraction of a high boiling material and tar. Fractionation of this main cut gave a yellowish product (236 g.) boiling between 170–172° and tar (50 g.). Refractionation of the yellowish product gave a slightly yellow liquid (200 g.) boiling at 76°/16 mm. Infrared spectra (max. at 5.62 μ and 6.24 μ) confirmed other evidence that it was an unsaturated lactone. The structure of this entity was ascertained by a study of comparative reactions of it and alpha and beta angelicalactones as follows:

Reaction with:	α angelicalactone gave:	β angelicalactone gave:	This lactone gave:
H$_2^{18}$	Acid	Saturated lactone	Saturated lactone
Aniline[19]	Anilide	No reaction	No reaction
Alcoholic HCl	Ester of keto acid	No reaction	No reaction
Br$_2$	Decolorized	No reaction	No reaction
MnO$_4^-$	MnO$_2$	MnO$_2$	MnO$_2$

Hydrogenation of CF$_3$. The unsaturated lactone

(7.5 g., 0.05 mole) in 40 ml. of dry ether with 100 mg. of PtO$_2$ was hydrogenated in the Parr hydrogenation apparatus to give a product (6.0 g., 0.039 mole, 80%) boiling 78–79°/25 mm. Infrared spectra showed loss of double bond and presence of lactone group (max. at 5.60 μ). Larger runs gave nearly quantitative results. The product on treatment with liquid NH$_3$ gave a crystalline product melting at 46° and confirmed by infrared spectra (max. at 3.10 μ, 6.05 μ and 6.22 μ) to be the amide.

Condensation of CF$_3$ *with* CF$_3$CO$_2$C$_2$H$_5$ *in presence*

of $NaOC_2H_5$. CF$_3$CO$_2$C$_2$H$_5$ (284 g., 2 moles) was added with some external cooling to a slurry of NaOC$_2$H$_5$ in 700 ml. of dry ether. Using a similar procedure as that in previous condensation, the saturated lactone (308 g., 2 moles) was added in 3 hr. and refluxed for 40 hr. Fractionation of the removed solvent gave 3 moles of ethyl alcohol and small amounts of CF$_3$CO$_2$C$_2$H$_5$. The residue was treated with 500 ml. of 25% H$_2$SO$_4$ solution for neutralization and then 70 ml. of concentrated H$_2$SO$_4$ was added. Decarboxylation was effected in 84 hr. Fractionation of the dried ether extract of the organic layer gave a hemiketal, CF$_3$C(OH)CH$_2$CH$_2$-

CHCF$_3$ (294 g., 1.31 moles, 67% including estimates on

fore and tail cuts) boiling between 139–141°. The hemiketal gave a (−) test with 2,4-DNPH and its infrared spectra (max. at 3.00 μ) showed an alcohol but no carbonyl band.

Reduction of CF$_3$C(OH)CH$_2$CH$_2$CHCF$_3$ *with* $LiAlH_4$. The

hemiketal (264.7 g., 1.18 moles) was added dropwise in 2.6 hr. to LiAlH$_4$ (30 g., 0.80 mole) in 750 ml. of dry ether at 0°. The excess LiAlH$_4$ was decomposed by dropwise addition of CH$_3$CO$_2$C$_2$H$_5$ (35 g., 0.4 mole) at 0° and the complex decomposed by addition of 60 ml. of ice water followed by 60 ml. of concentrated H$_2$SO$_4$ in 180 ml. of ice water. The ether layer and extracts were washed with dilute Na$_2$CO$_3$ and dried over Na$_2$SO$_4$. On fractionation after removal of a forecut of starting material (47 g.), the remainder of the material solidified on cooling. This solid (198.5 g., 0.78 mole, 75%) was confirmed by infrared spectra (max. at 3.08 μ) as the diol. Sublimation of the solid gave a crystalline material melting between 75–120°, presumably a mixture of D, L, and *meso* forms.

Acetylation of CF$_3$CHOHCH$_2$CH$_2$CHOHCF$_3$. The diol (190 g., 0.84 mole) in 200 ml. of glacial acetic acid was acetylated by addition of (CH$_3$CO)$_2$O (225 g., 2.20 moles, 30% in excess) in the usual manner to give a quantitative yield of crude diacetate boiling at 133°/75 mm., which solidified on standing and melted at 65° on recrystallization from ethyl alcohol. Infrared spectra (max. at 5.67 μ) confirmed presence of acetate esters.

Pyrolysis of CF$_3$CH(OCOCH$_3$)CH$_2$CH$_2$CH(OCOCH$_3$)CF$_3$. This pyrolysis was carried out in the manner already described. The diacetate (99 g., 0.319 mole) on two passes gave the diene (40 g., 0.21 mole, 66% yield, 83% including estimates in fore and tail cuts) boiling 85.5–86.5°. The rate of diacetate addition, nitrogen flow, and temperature were the same as in the previous case. Infrared spectra (max. at 5.82 μ and 6.06 μ) confirmed the diene structure. Attempts to prepare the adduct with maleic anhydride were unsuccessful indicating the material to be probably *cis*. Carr[20] in this laboratory simultaneously prepared a diene having nearly the same constants (differences probably due to isomers in Carr's material) which gave on hydrogenation the same paraffin.

Hydrogenation of CF$_3$CH=CHCH=CHCF$_3$. The diene

(18) F. A. Kuehl, R. P. Winstead, and B. A. Orkin, *J. Chem. Soc.*, 2213 (1950).

(19) W. A. Jacobs and A. B. Scott, *J. Biol. Chem.*, **87**, 601 (1930).

(20) R. L. K. Carr, Ph.D. dissertation to Ohio State University, 1955.

(26.5 g., 0.14 mole) in 40 ml. of dry ether with 50 mg. of PtO$_2$ was hydrogenated to give the paraffin (25.5 g., 0.132 mole, 94% including estimates in fore and tail cuts) boiling 97.5–99.5°. The olefin free spectra was superimposable with that obtained by Carr on a sample prepared by another method and having the constants: b.p. 99°, n_D^{20} 1.3103, and d_4^{20} 1.231. (My data for a purified sample: b.p. 99°, n_D^{20} 1.3105, and d_4^{20} 1.232.)

Preparation of Esters of Pentaerythritol Arsenite and of Other Pentaerythritol Esters

TRAVIS E. STEVENS

Several esters of pentaerythritol arsenite (I) have been prepared. The arsenite ester portion of these compounds was found to be selectively hydrolyzed, acetolyzed, or nitrolyzed to produce the corresponding pentaerythritol monoester, the pentaerythritol ester triacetate, or the ester of pentaerythritol trinitrate.

Esters of pentaerythritol can be prepared in several ways,[1] but selective partial esterification is not easily carried out. One obvious method of preparation of pentaerythritol monoesters would be that of blocking three of the hydroxyl groups with some functional group that could be removed readily. Such a monofunctional pentaerythritol, the product obtained by merely heating a mixture of arsenic trioxide and pentaerythritol and removing the water formed, is pentaerythritol arsenite, I.[2] This compound, m.p. 106–107°, also has been

I   II
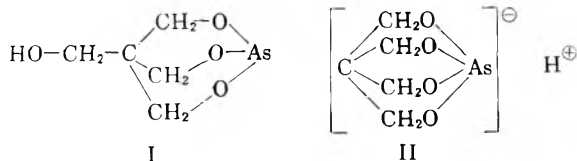
formulated as II and designated pentaerythritol arsenious acid.[3] However, the infrared spectrum of pentaerythritol arsenite which possessed the characteristic hydroxyl absorption at 3420 cm.$^{-1}$ (Nujol mull), and the facile esterification of the arsenite support the structure (I) originally formulated by Englund.

Esterification of I by the conventional methods outlined in the experimental section to produce the carboxylic or sulfonic acid esters III proceeded readily. The esters prepared are listed in Table I.
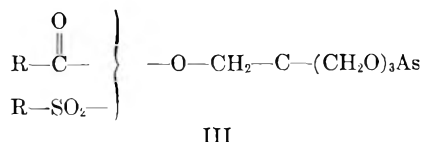
III

These esters and the arsenite I were not hygroscopic, but were hydrolyzed on contact with water. Because these esters were susceptible to hydrolysis, isolation was accomplished by evaporating the reaction mixture to dryness and then either extracting the ester into petroleum ether (Method B, Table I) or by adding cold methanol to remove the pyridine hydrochloride and leave the ester as a residue (Method C, Table I). Pentaerythritol acetate arsenite, however, was prepared from isopropenyl acetate and pentaerythritol arsenite (Method A, Table I), and the acetate was distilled directly from the reaction mixture.

As expected, the pentaerythritol arsenite esters hydrolyzed to produce the corresponding pentaerythritol monoesters. This hydrolysis was carried out efficiently by placing a methylene chloride solution of the arsenite ester on a short silica gel column and eluting the hydrolyzed product with methanol in methylene chloride. The pentaerythritol monoesters prepared in this way are listed in Table II.

Acetolysis of some of the arsenite esters III was carried out to produce the corresponding ester triacetate. This reaction proceeded readily on mixing the ester III, acetic anhydride, and a catalytic amount of sulfuric acid. In addition to pentaerythritol tetracetate, pentaerythritol tosylate triacetate, m.p. 70° and pentaerythritol benzoate triacetate, m.p. 95°, were prepared in this manner.

The nitrolysis of the arsenite esters to produce an organic acid ester of pentaerythritol trinitrate[4] also appeared to be a general reaction. Both pentaerythritol arsenite *p*-toluenesulfonate and pentaerythritol arsenite acetate were converted to the trinitrate esters on treatment with 90% nitric acid at 0°. The same nitration procedure

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(1) E. Berlow, R. H. Barth, and J. F. Snow, *The Pentaerythritols*, Reinhold Publishing Corporation, New York, N.Y., 1958, pp. 212–58.

(2) B. Englund, *J. prakt. Chem.*, **124**, 191 (1930).

(3) Ref. (1) p. 50.

(4) N. S. Marans, D. E. Elrick, and R. F. Preckel, *J. Am. Chem. Soc.*, **76**, 1304 (1954).

TABLE I
PREPARATION OF PENTAERYTHRITOL ARSENITE ESTERS

Arsenite Ester	M.P., °C.	Yield, %	Method of Preparation[a]	Anal. Calcd.			Anal. Found		
				C	H	As	C	H	As
Acetate	90–91.5	88	A	33.62	4.43	29.96	33.71	4.54	30.13
Propionate	55–57	48	B	36.68	4.96	28.36	36.05	5.07	28.95
Caproate	40–42	49	B	43.15	6.26	24.47	43.12	6.38	24.63
Benzoate	133–134	60	C	46.17	4.20	24.00	45.82	4.29	24.54
Benzenesulfonate	138–139	37	C	37.94	3.76	21.51	38.22	4.22	22.15
p-Toluenesulfonate	177–178	73	C	39.71	4.26	20.77	39.79	4.17	20.68
m-Nitrobenzoate	159–161	64	C	40.55	3.39	...	40.14	3.47	...

[a] Methods outlined in experimental section.

TABLE II
PENTAERYTHRITOL MONOESTERS

Ester	M.P., °C.	Analysis			
		Calcd.		Found	
		C	H	C	H
Acetate	69–70[4]	...	...	...	...
Propionate	15–17	49.99	8.39	49.22	8.64
Caproate	20–22	56.39	9.47	56.27	9.98
Benzoate	86–87	59.44	6.71	59.27	6.84
p-Toluenesulfonate	73–74	49.64	6.25	49.15	6.15
Benzenesulfonate	60–62	47.81	5.84	48.11	6.06
m-Nitrobenzoate	120–121	50.52	5.30	50.10	5.59
p-Nitrobenzoate[a]	141–142	50.52	5.30	50.61	5.16

[a] Arsenite ester was not purified.

has been used to convert pentaerythrito_ monoacetate to the trinitrate.[4]

EXPERIMENTAL[5]

Reaction of pentaerythritol and arsenic trioxide. The procedure outlined by Englund[2] was followed using 54.4 g. (0.40 mole) of pentaerythritol and 39.6 g. (0.20 mole) of arsenic trioxide. The mixture began to melt at 80° and water began to distill from the flask when the reaction temperature reached 120°. The mixture was quickly heated to 230° and then allowed to cool. Distillation of the residue gave pentaerythritol arsenite (I), 77 g. (93%), b.p. 140° (1 mm.), m.p. 106–107°, reported 102–103°.[2]

Preparation of pentaerythritol arsenite esters. Method A. Preparation of pentaerythritol arsenite acetate. A mixture of pentaerythritol (27.2 g., 0.20 mole) and arsenic trioxide (19.8 g., 0.10 mole) was heated to 230° as described above. The mixture was allowed to cool to 60°, and isopropenyl acetate (24 ml., 0.22 mole) then was added with stirring. Addition of 0.5 g. of p-toluenesulfonic acid monohydrate resulted in an exothermic reaction which was controlled by external cooling. When the exotherm had subsided the reaction mixture was heated at 100° for 1 hr. and acetone was allowed to distill from the reaction mixture. The mixture was warmed to 130°, 0.10 g. of magnesium carbonate was added, and the contents of the flask were distilled. There was thus obtained pentaerythritol arsenite acetate, 44 g. (88%), b.p. 125–127° (1 mm.). The acetate slowly solidified and melted at 90–91.5° after recrystallization from ligroin.

Method B. Preparation of pentaerythritol arsenite propionate. A solution of 10.4 g. (0.05 mole) of pentaerythritol arsenite in 20 ml. of pyridine was cooled to keep the temperature of the reaction mixture below 30° while 4.5 ml. (0.51 mole) of propionyl chloride was added over a 5-min.

period. The reaction mixture was stirred at 45–50° for 2 hr., then excess pyridine and propionyl chloride were removed at reduced pressure. To the solid residue was added 150 ml. of ligroin and the mixture was refluxed for 15 min. The ligroin was decanted and chilled in dry ice, and was then filtered to remove a semisolid. Flash distillation of the semisolid at 130° (0.5 mm.) gave pentaerythritol arsenite propionate, 6.3 g., (48%), m.p. 55–57°.

Method C. Preparation of pentaerythritol arsenite p-toluenesulfonate. To a stirred solution of 10.4 g. of pentaerythritol arsenite in 20 ml. of pyridine 9.5 g. of p-toluenesulfonyl chloride was added portionwise. The reaction mixture slowly exothermed to 42°; when the exotherm subsided the mixture was maintained at 45–50° for 2 hr. The excess pyridine was then removed at reduced pressure. The residue was triturated with 50 ml. of absolute methanol at 0°, and was then filtered to give pentaerythritol arsenite p-toluenesulfonate, 13.2 g., m.p. 170–173°. Recrystallization from methanol raised the m.p. to 177–178°.

Hydrolysis of pentaerythritol arsenite esters. The method used to convert the arsenite esters of Table I to the pentaerythritol monoesters listed in Table II is illustrated by the procedure given below for the hydrolysis of pentaerythritol arsenite p-toluenesulfonate.

A 1.0 g. sample of pentaerythritol arsenite p-toluenesulfonate dissolved in methylene chloride was placed on a 1-in. by 6-in. column of silica gel packed in methylene chloride. The column was eluted with 200 ml. methylene chloride, 300 ml. of methylene chloride–ethyl acetate (9:1) and 500 ml. of methylene chloride–methanol (6:1). The solid eluted by the last eluent was recrystallized from ethyl acetate–ligroin to give of pentaerythritol monotoluenesulfonate, 0.63 g., (75%), m.p. 73–74°.

Preparation of pentaerythritol p-toluenesulfonate triacetate. To a suspension of 2.0 g. of pentaerythritol arsenite p-toluenesulfonate in 15 ml. of acetic anhydride was added 2 drops of concentrated sulfuric acid. A slightly exothermic reaction occurred and within 1 hr. all material had dissolved. The mixture was allowed to stand at ambient temperature for 24 hr., and then was poured into 150 ml. of water. After 1 hr. the water was decanted from an oily residue. This residue was dried and then recrystallized from ligroin to give pentaerythritol triacetate tosylate, m.p. 70–71°.

Anal. Calcd. for $C_{18}H_{24}SO_9$: C, 51.91; H, 5.81. Found: C, 51.92; H, 5.93.

Preparation of pentaerythritol benzoate triacetate. The procedure outlined above was used for the preparation of pentaerythritol benzoate triacetate, m.p. 95–96°.

Anal. Calcd. for $C_{18}H_{22}O_8$: C, 59.00; H, 6.05. Found: C, 59.30; H, 6.29.

Preparation of pentaerythritol acetate trinitrate. An air-sparged solution of 0.4 g. of urea dissolved in 40 ml. of 90% nitric acid was stirred at 0° while 4.7 g. of pentaerythritol arsenite acetate was added over 5 min. There was a slight exotherm during the addition process. The mixture was stirred at 0° for an hour and at 5–10° for an additional hour. Methylene chloride (75 ml.) was added and the reaction

(5) All melting points and boiling points are uncorrected.

mixture poured on ice. The mixture was filtered to remove arsenic trioxide and the organic layer was separated and washed with water and dilute sodium bicarbonate solution. Evaporation of the methylene chloride left pentaerythritol acetate trinitrate, 5.7 g. (97%), m.p. 86–87°. One recrystallization from ethanol gave 5.0 g. of product, m.p. 87–88°, reported 87–88°.[4]

Preparation of pentaerythritol p-toluenesulfonate trinitrate. The procedure outlined for the nitration of pentaerythritol arsenite acetate was followed using 0.3 g. of urea, 30 ml. of nitric acid, and 3.0 g. of pentaerythritol p-toluenesulfonate arsenite. Two recrystallizations of the product from methanol gave pentaerythritol p-toluenesulfonate trinitrate, 2.97 g., m.p. 96–98°, reported 97–100°.[4]

HUNTSVILLE, ALA.

Preparation, Properties, and Infrared Spectra of 2,6-Disubstituted Phenoxysilanes

GLENN R. WILSON, ARTHUR G. SMITH, AND FRED C. FERRIS

Two series of 2,6-disubstituted-phenoxy di- and trimethylsilanes in which the 2,6-substituents are H—, CH₃—, and (CH₃)₂-CH— groups are reported. Attention is called to the intense absorption band in the 10–11 μ region of the infrared absorption spectra of these compounds that appears to be characteristic of the Si-O-phenyl linkage.

In conjunction with studies on improving the thermal and hydrolytic stability of some organosilicon compounds, two series (I and II) of 2,6-disubstituted-phenoxy silanes were prepared. An additional chloro-derivative, IIIc, was also prepared as an intermediate for conversion to a

a. R = H—
b. R = CH₃—
c. R = (CH₃)₂CH—

disiloxane derivative. Only two of the compounds reported here, Ia[1] and IIa[2,3] have been reported in the literature.

The phenoxy silanes were prepared by first converting the respective phenol to its bromomagnesium salt (reacting the phenol with methylmagnesium bromide in tetrahydrofuran) followed by treating this intermediate with dimethyldichlorosilane or trimethylchlorosilane. For laboratory-scale preparations this procedure was found more expedient than the conventional methods of preparing the alkali metal phenoxides, especially in the case of the more hindered phenols.

Di-*tert*-butylphenol, when subjected to this sequence of reactions, failed to yield a silicon derivative and the starting materials were recovered. Due to steric factors it was initially anticipated that the product would have structure IV rather than II in accord with the work of Coffield, Filbey, Ecke, and Kolka[4] on 2,6-disubstituted phenoxides. Very recently, however, Kornblum and Lurie[5] have shown that a new factor, homogeneity vs. heterogeneity, is of paramount importance in this type reaction. Oxygen alkylation is obtained in homogeneous solutions and the truly heterogeneous reaction gives exclusively carbon alkylation. This factor correlates well with Coffield's[4] work and also the findings reported here. Our reaction mixtures were homogeneous and we obtained only oxygen alkylation.

Several attempts were made to hydrolyze IIIc to the corresponding silanol for subsequent conversion to the disiloxane; however, hydrolytic cleavage of the 2,6-diisopropylphenoxy group occurred simultaneously.

The physical properties of the various derivatives reported here are summarized in Table I.

Infrared absorption spectra. The infrared spectra of the derivatives reported here were recorded on a Perkin-Elmer Infracord, Model 137 in the 2.5–15.0 μ region. All spectra were taken from capillary films between sodium chloride windows with the exception of bis(2,6-diisopropylphenoxy)dimethylsilane (IIc), which was prepared as a Nujol mull. The spectra are reproduced in Figs. 1 and 2.

(1) S. H. Langer, S. Connell, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958).

(2) P. D. George and A. E. Newkirk, U. S. Patent 2,837,552 (1958).

(3) E. Larsson, *Chem. Ber.*, **86**, 1382 (1953).

(4) T. H. Coffield, A. H. Filbey, G. G. Ecke, and A. J. Kolka, *J. Am. Chem. Soc.*, **79**, 5019 (1957).

(5) K. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959).

PHYSICAL PROPERTIES OF 2,6-DISUBSTITUTED-PHENOXYSILANES

Silane	M.P. (°C.)	B.P. (°C.)/mm.	d_4^{25}	n_D^{20}	Yield, %
Ia	-55^a	113/94	0.9209	1.4782	58
Ib	-44^a	127/50	0.9228	1.4862	74
Ic	-12.4^a	154/50	0.9015	1.4838	74
IIa	-23^a	104–106/0.8	$1.0599^{27.5}$	1.5330	79.9
IIb	37.0–38.0	130–131/0.2–0.3	. . .	1.5320^b	80.1
IIc	89.0–89.5	142–146/0.15	. . .	. . .	74.4
IIIc	. . .	66–67/0.4–0.45	. . .	1.4925	20.3

^{a} Freezing point from cooling curves. ^{b} Supercooled liquid.

Fig. 1. Absorption spectra of phenoxy silanes
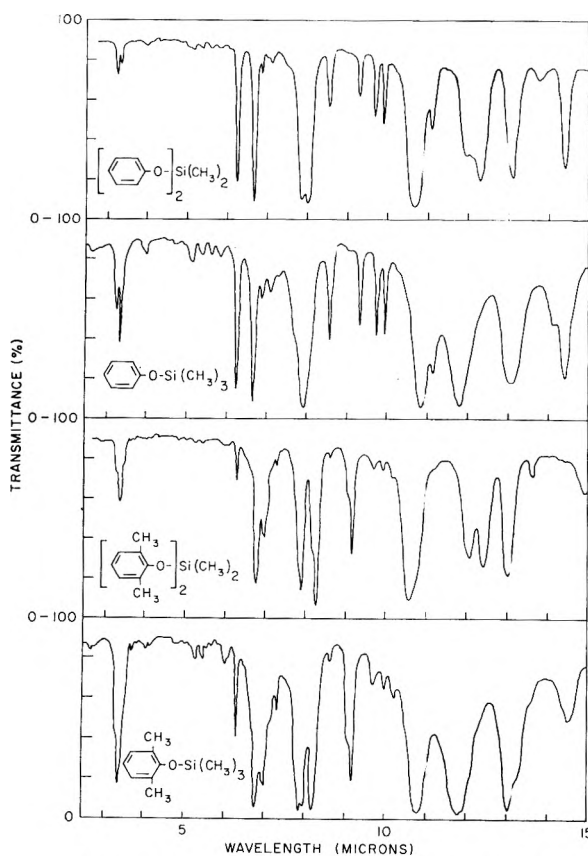
Fig. 2. Absorption spectra of phenoxy silanes

The spectra are somewhat complicated by the fact that absorptions characteristic of organosilicon bonds occur in the same regions as those characteristic of the parent phenols. One exception, however, is noted in the 10.0–11.0 μ region where a very intense and slightly broadened band appears in all the spectra reported here. The intensity of this band is the same in all these derivatives but varies in wave length, depending upon the substitution—the dimethylsilyl derivatives absorb at somewhat shorter wave lengths than the respective trimethylsilyl derivatives. This same intense band also occurs in the spectrum of phenyl silicate at 10.3 μ. In view of the paucity of spectra of phenoxy silanes in the literature, we are wondering if this strong absorption band is characteristic of the Si—O—phenyl linkage. The absorption band often associated with the Si—O—C linkage has been
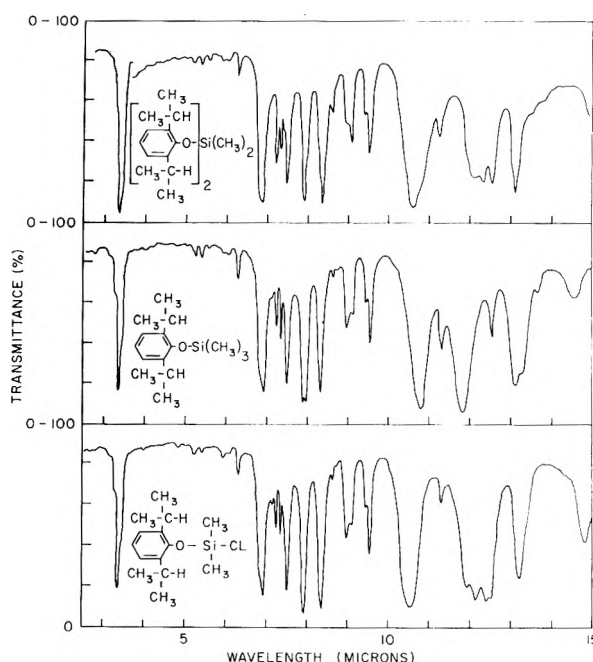
assigned to the 9.2 μ region by Stuart, laLau, and Breederveld[6] from their investigations of alkoxytrichlorosilanes and to the 9.5–9.65 region by Kreshkov, Mikhailenko, and Yakimovich[7] from their investigations of alkyl silicates and phenyl silicate—unfortunately the latter investigators studied only the 2–10 μ region. Certain alkoxy silanes, such as ethyl silicate, diethoxydimethylsilane, ethoxytrichlorosilane, and the ethoxy- and methylethoxysilicones also exhibit strong absorptions in the 10.0–11.0 μ region, however; Okawara[8] has assigned these absorptions to the ethyl group.

The 8.0 μ region of the spectra (characteristic of the Si—CH$_3$ linkage) of these derivatives is complicated by the equally intense and sharp absorption of the phenyl—O linkage. In several derivatives this band appears as equally intense doublets depending upon the degree of substitution. A similar phenomenon was also noted by Dahlgard

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(7) A. P. Kreshkov, Yu. Ya. Mikhailenko, and G. F. Yakimovich, Zhur. Fiz. Khim., 28, 537 (1954).

(8) R. Okawara, Bull. Chem. Soc., Japan, 31, 154 (1958).

and Brewster[9] in their studies on *ortho*-substituted diphenyl ethers.

The 11.6–14.3 μ region of the spectra (characteristic of the Si—C linkage) is equally complicated by aromatic absorption bands.

The absence of hydroxy absorptions in the 2.7–3.0 μ region of these spectra supports the fact that these derivatives are phenoxy-substituted silanes and not hydroxyphenyl-substituted silanes.

EXPERIMENTAL

General procedure. All reactions were carried out under a dry nitrogen atmosphere and the sequence of reactions was the following:

A molar solution of the phenol in tetrahydrofuran was prepared in a flask equipped with a stirring assembly, condenser, dropping funnel, and a nitrogen inlet. To the solution was added an equivalent molar quantity or slight excess of ethereal three molar methylmagnesium bromide. After a short reflux period, the appropriate chlorosilane, dimethyldichloro- or trimethylchlorosilane, was added.

The reaction mixture was then refluxed for a short time, cooled, diluted with benzene, toluene, or a hydrocarbon, concentrated to remove any unreacted chlorosilane and ethereal solvent, then filtered to remove the magnesium halides formed. The filtrate was then fractionated at reduced pressures.

Due to the almost identical boiling points of the phenols and their trimethylsilyl derivatives, these filtrates were treated with metallic sodium or methylmagnesium bromide in order to retain the phenol present during the distillation.

Phenoxytrimethylsilane (Ia). The yield of Ia from 94.1 g. (1 mole) of phenol, 1.29 moles of methylmagnesium bromide, and 1.43 moles of trimethylchlorosilane was 96.6 g. (58% yield): b.p. 110° (90 mm.); f.p. −55°, d_4^{25} 0.9209, n_D^{20} 1.4782. (Langer[1] lists b.p. 181.9–182.4; d_4^{25} 0.9209; n_D^{20} 1.4782.)

Anal. Calcd. for $C_9H_{14}SiO$: C, 65.01; H, 8.49; Si, 16.88. Found: C, 64.95; H, 8.44; Si, 16.92.

2,6-Dimethylphenoxytrimethylsilane (Ib). The yield of Ib from 122.2 g. (1 mole) of 2,6-dimethylphenol, 1.33 moles of methylmagnesium bromide, and 200 ml. (1.58 moles) of trimethylchlorosilane was 144.2 g. (74% yield): b.p. 120° (43 mm.); f.p. −44°; d_4^{25} 0.9228; n_D^{20} 1.4862.

Anal. Calcd. for $C_{11}H_{18}SiO$: C, 67.99; H, 9.34; Si, 14.44. Found: C, 68.25; H, 9.22; Si, 14.74.

2,6-Diisopropylphenoxytrimethylsilane (Ic). The yield of Ic from one mole quantities of 2,6-diisopropylphenol, methylmagnesium bromide, and trimethylchlorosilane was 184 g. (74% yield): b.p. 154° (50 mm.); f.p. −12.4°; d_4^{25} 0.9015; n_D^{20} 1.4838.

Anal. Calcd. for $C_{15}H_{26}SiO$: C, 71.94; H, 10.47; Si, 11.20. Found: C, 72.14; H, 10.46; Si, 11.30.

Diphenoxydimethylsilane (IIa). The yield of IIa from 226 g. (2.4 moles) of phenol, 800 ml. of $3M$ methylmagnesium bromide, and 154.9 g. (1.2 moles) of dimethyldichlorosilane was 234.3 g. (79.9% yield): b.p. 104–106° (0.8 mm.) and 93–94° (0.15 mm.); f.p. −23°; d_4^{25} 1.0599; n_D^{20} 1.5330. (George and Newkirk[2] list b.p. 206° (100 mm.); d_{20} 1.063; n_D^{20} 1.5335.)

Anal. Calcd. for $C_{14}H_{16}O_2Si$: C, 68.82; H, 6.60; Si, 11.48. Found: C, 68.92; H, 6.20; Si, 11.60.

Bis(2,6-dimethylphenoxy)dimethylsilane (IIb). The yield of IIb from 293.3 g. (2.4 moles) of 2,6-dimethylphenol, 2.4 moles of methylmagnesium bromide, and 159.9 g. (1.2 moles) of dimethyldichlorosilane was 288.7 g. (80.1% yield): b.p. 130–131° (0.2–0.3 mm.); m.p. 37–38°; n_D^{20} 1.5320 (supercooled).

Anal. Calcd. for $C_{18}H_{24}O_2Si$: C, 71.96; H, 8.05; Si, 9.34. Found: C, 71.91, 72.14; H, 7.99, 8.19; Si, 9.24, 9.11.

Bis(2,6-diisopropylphenoxy)dimethylsilane (IIc). The yield of IIc from 178.3 g. (1.0 mole) of 2,6-diisopropylphenol, 1.05 moles of methylmagnesium bromide, and 64.5 g. (0.50 mole) of dimethyldichlorosilane was 154.0 g. (74.7% yield) after recrystallizing from denatured ethanol: b.p. 142–146° (0.15 mm.); m.p. 89.0–89.5°.

Anal. Calcd. for $C_{22}H_{40}O_2Si$: C, 75.76; H, 9.77; Si, 6.80. Found: C, 76.10, 75.95; H, 9.71, 9.89; Si, 6.60, 6.52.

2,6-Diisopropylphenoxydimethylchlorosilane (IIIc). A solution of bromomagnesium-2,6-diisopropylphenoxide, prepared from 178.3 g. (1.0 mole) of 2,6-diisopropylphenol and 1.05 moles of methylmagnesium bromide in tetrahydrofuran, was added to a second solution of 258 g. (2.0 moles) of dimethyldichlorosilane in tetrahydrofuran. The yield of IIIc was 55.0 g. (20.3% yield): b.p. 66–67° (0.4–0.45 mm.); n_D^{20} 1.4925.

Anal. Calcd. for $C_{14}H_{23}OSiCl$: C, 62.08; H, 8.56; Si, 10.36; Cl, 13.09. Found: C, 61.76; H, 8.48; Si, 10.59; Cl, 13.58.

DEARBORN, MICH.

(9) M. Dahlgard and R. Brewster, *J. Am. Chem. Soc.*, **80,** 5861 (1958).

Reaction of Epoxides with 2-Aminobenzenethiol

JAMES F. KERWIN,[1] JOHN E. McCARTY,[1a] AND CALVIN A. VANDERWERF[1a]

Reaction of ethylene oxide, cyclopentene oxide, and styrene oxide with 2-aminobenzenethiol anion has been found to give the corresponding 2-aminophenyl-2-hydroxyethyl sulfides. With styrene oxide, the product is a mixture of 2-aminophenyl-2-hydroxy-1-phenylethyl sulfide and 2-aminophenyl-2-hydroxy-2-phenylethyl sulfide. 2-Aminobenzene thiol in basic solution effects debromination of *trans*-1,2-dibromocyclohexane to give an almost quantitative yield of cyclohexene.

In 1949, Culvenor and co-workers[2] reported that the reaction of 2-aminobenzenethiol anion with ethylene oxide, cyclohexene oxide, styrene oxide, and benzoylphenylethylene oxide, respectively, afforded in every case the corresponding dihydrobenzo-1,4-thiazine [2,3-dihydrobenzo-1,4-thiazine

(1) Smith Kline and French Laboratories.
(1a) University of Kansas.

(2) C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 278 (1949).

(I), hexahydropheno-1,4-thiazine (II), 2-phenyl-2,3-dihydrobenzo-1,4-thiazine (III), or one of the two possible benzoylphenyl-2,3-dihydrobenzo-1,4-thiazines (IV and V)].
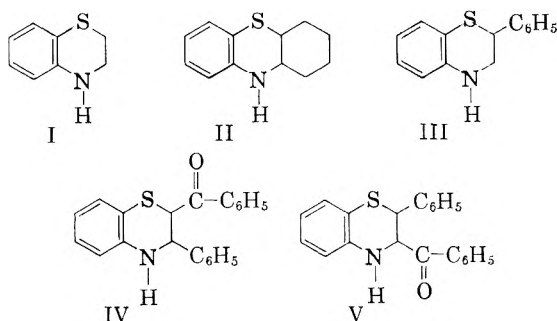
Ring closure presumably resulted from elimination of a molecule of water between the amino group of 2-aminobenzenethiol and the hydroxy group formed upon nucleophilic opening of the epoxide ring by the negatively charged sulfur.

Fusco and Palazzo[3] in 1951 extended this work. They likewise reported that the reaction of the anion of 2-aminobenzenethiol with ethylene oxide afforded I, which, they noted, however, underwent hydrolysis with ring opening to form a dibenzoyl derivative under Schotten-Baumann conditions and to form a coupled product with β-naphthol under typical coupling conditions. These authors reported further that with propylene oxide the product was 3-methyl-2,3-dihydrobenzo-1,4-thiazine but that with styrene oxide a mixture of III and 2-aminophenyl-2-hydroxy-2-phenylethyl sulfide (VI) was obtained.
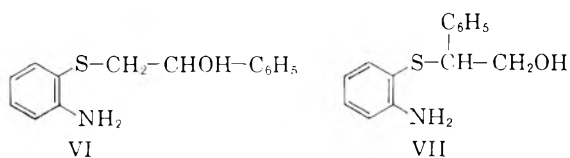
Since then, other workers[4,5] have based dihydrobenzothiazine structure assignments on the work of Culvenor et al.[2]

As part of a continuing study on the opening of epoxide rings, we undertook to re-examine these reactions. It soon became apparent that reaction of 2-aminobenzenethiol anion with epoxides does not normally proceed with ring closure to the dihydrobenzothiazine. While our work was in progress, Fujii[6] demonstrated conclusively that the product of reaction of 2-aminobenzenethiol with ethylene oxide was the uncyclized 2-aminophenyl-2-hydroxyethyl sulfide, and not I, an au-

thentic sample of which had been prepared by reaction of 2-aminobenzenethiol with ethylene bromide,[7] and more recently by the lithium aluminum hydride reduction of 2,3-dihydrobenzo-1,4-thiazin-3-one.[8] The confusion concerning the separate identity of I and of 2-aminophenyl-2-hydroxyethyl sulfide apparently arose from the chance circumstance that both compounds melt at exactly the same temperature (40°), as do also their phenylthiourea derivatives (129°).

More recently Hromatka and co-workers[9] have shown that the reaction of the anion of 2-aminobenzenethiol with cyclohexene oxide leads not to II, but to the uncyclized amino alcohol 2-aminophenyl-2-hydroxycyclohexyl sulfide. This group has since reported the synthesis of hexahydrophenothiazine-9-dioxide[10] and of hexahydrophenothiazine[11] itself.

Our work has confirmed the results of Fujii[6] and of Hromatka.[9] We have found, further, that 2-aminobenzenethiol anion reacts with cyclopentene oxide to form 2-aminophenyl-2-hydroxycyclopentyl sulfide and with styrene oxide to form a mixture of the uncyclized isomers 2-aminophenyl-2-hydroxy-2-phenylethyl sulfide (VI) and 2-aminophenyl - 2 - hydroxy - 1 - phenylethyl sulfide (VII), formed by opening of the epoxide ring at the primary and secondary carbon atoms, respectively. The ring-closed 2-phenyl-2,3-dihydrobenzo-1,4-thiazine (III), reported by Fusco,[3] was absent. VII is a solid, m.p. 105.0–106.5°, whereas VI is a liquid, m.p. of hydrochloride 175.5–177.0°.

The structures of VI and VII were established by means of analytical and infrared data and by desulfurization of VI to 2-phenylethanol or, through the use of freshly prepared W-6 Raney nickel catalyst, to a mixture of toluene and ethylbenzene.[12]

Authentic 2 - phenyl - 2,3 - dihydrobenzo-1,4-thiazine was prepared by the lithium aluminum hydride reduction of 2-phenyl-2,3-dihydrobenzo-1,4-thiazin-3-one, and its properties differed markedly from those of either VI or VII.

An attempt to prepare hexahydrophenothiazine by reaction of the anion of 2-aminobenzenethiol with trans-1,2-dibromocyclohexane gave only cyclohexene and 2,2'-diaminodiphenyldisulfide in

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(8) J. C. Craig, W. P. Rogers, and G. P. Warwick, Australian J. Chem., 8, 252 (1955).

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(11) O. Hromatka, J. Augl, M. Vaculny, and H. Petrousek, Monatsh., 89, 517 (1958).

(12) J. A. Zderic, W. A. Bonner, and T. W. Greenlee, J. Am. Chem. Soc., 79, 1696 (1957), have shown that by treatment with very active Raney nickel 2-phenylethanol is converted into a mixture of toluene and ethylbenzene and 1-phenylethanol into ethylbenzene.

high yields. Preliminary experiments indicate that this reaction is fairly general for thiols and 1,2-dihaloalkanes. Further studies on this reaction are in progress.

EXPERIMENTAL

2-Aminophenyl-2-hydroxyethyl sulfide. Ethylene oxide (35 g., 0.79 mole) was added from a Dry Ice-jacketed dropping funnel to a stirred and cooled solution of 94 g. (0.75 mole) of 2-aminobenzenethiol and 42 g. (0.75 mole) of potassium hydroxide in 750 ml. of alcohol. After the addition was complete, the reaction mixture was warmed slowly, refluxed for 1 hr. and then concentrated under reduced pressure. The residue was distilled under reduced pressure to give 75 g. (66%) of colorless 2-aminophenyl-2-hydroxyethyl sulfide, b.p. 200–203° (20 mm.), m.p. after one recrystallization from ether–petroleum ether, 39.5–41.0°. Comparable results were obtained when ethylene chlorohydrin was used in place of ethylene oxide. The product was readily diazotized, and its infrared spectrum showed the bands for a primary amine and a hydroxyl group.

Anal. Calcd. for $C_8H_{11}NOS$: C, 56.8; H, 6.55; N, 8.28. Found: C, 57.1; H, 6.50; N, 8.23.

Admixture of the product with authentic 2,3-dihydrobenzo-1,4-thiazine, m.p. 39.0–40.8°, obtained by lithium aluminum hydride reduction of 2,3-dihydrobenzo-1,4-thiazin-3-one, synthesized according to Unger,[13] formed an oil.

The phenylthiourea derivative melted at 128.0–129.5° (reported[8] 127–128°) after recrystallization from alcohol. It depressed the melting point (128.3–129.1°) of the phenylthiourea derivative of authentic 3,4-dihydrobenzo-1,4-thiazine.

Anal. Calcd. for $C_{15}H_{16}N_2OS_2$: C, 59.2; H, 5.30. Found: C, 59.5; H, 5.42.

A dibenzoyl derivative, m.p. 82.5–84.0° after recrystallization from alcohol, was formed by the Schotten-Baumann procedure.

Anal. Calcd. for $C_{22}H_{19}NO_3S$: C, 70.0; H, 5.07. Found: C, 70.1; H, 5.16.

The acid tartrate salt melted at 127.0–128.3° after recrystallization from alcohol.

Anal. Calcd. for $C_{12}H_{17}NO_7S$: C, 45.1; H, 5.37. Found: C, 45.2; H, 5.34.

Reaction of 2-aminobenzenethiol with cyclopentene oxide. Cyclopentene oxide (8.4 g., 0.10 mole) was added dropwise to a stirred solution of 12.5 g. (0.10 mole) of 2-aminobenzenethiol and 5.6 g. (0.10 mole) of potassium hydroxide in 100 ml. of ethanol. The mixture was refluxed for 30 min., then cooled, and several volumes of water were added. The oil layer was separated, the water layer was extracted with two 150-ml. portions of ether, and the organic layers were combined and dried over magnesium sulfate. After removal of the ether, the residue was distilled to give 16.7 g. (80%) of a colorless solid, m.p. 74.5–75.2°, which on the basis of its analysis, the fact that its infrared spectrum showed two strong absorption maxima in the N—H and one in the O—H stretching region, and its ready formation of a diazonium salt, was assigned the structure 2-aminophenyl-2-hydroxycyclopentyl sulfide.

Anal. Calcd. for $C_{11}H_{15}NOS$: C, 63.1; H, 7.23; N, 6.69. Found: C, 63.4; H, 7.40; N, 6.64.

Treatment of the amino alcohol with *p*-nitrobenzoyl chloride in refluxing pyridine gave a mixture of the mono- and di-*p*-nitrobenzoates, m.p. 149.2–150.1° and 107.0–108.2°, respectively, which were separated chromatographically on an alumina column.

Anal. Calcd. for $C_{18}H_{18}N_2O_4S$: C, 60.3; H, 5.06; N, 7.82; S, 8.93. Found: C, 60.1; H, 5.04; N, 7.91; S, 9.06.

Anal. Calcd. for $C_{25}H_{21}N_3O_7S$: C, 59.2; H, 4.17; N, 8.28. Found: C, 59.4; H, 4.13; N, 8.40.

(13) O. Unger, *Ber.*, **30**, 607 (1897).

Reaction of 2-aminobenzenethiol with styrene oxide. Styrene oxide (30 g., 0.25 mole) was added dropwise with stirring over a 30-min. period to a solution of 31 g. (0.25 mole) of 2-aminobenzenethiol and 14.0 g. (0.25 mole) of potassium hydroxide in 250 ml. of ethanol. The solution was refluxed for 1 hr. and then concentrated to half its original volume. Several volumes of water were added, the oil layer separated, and the water layer extracted with two 125-ml. portions of ether. The combined organic layers were extracted with 250 ml. of 3N hydrochloric acid. The acid layer was cooled in an ice bath, and a hydrochloride salt gradually separated. This was removed by filtration and treated with 100 ml. of 10% sodium hydroxide solution and 150 ml. of ether. The ether solution was separated, dried over magnesium sulfate and the ether removed. Vacuum distillation of the residue afforded 23 g. (38%) of a heavy yellow oil, b.p. 192–197° (0.3 mm.), which was converted to the hydrochloride, m.p. 175.5–177.1° after recrystallization from alcohol.

Anal. Calcd. for $C_{14}H_{16}ClNOS$: C, 59.7; H, 5.7. Found: C, 59.7, 59.7; H, 6.0, 5.9.

The acid filtrate remaining after removal of the crystalline hydrochloride was made basic with sodium hydroxide and extracted with ether. The ether solution was dried over magnesium sulfate and the ether removed. The solid remaining was recrystallized from alcohol and afforded 18 g. (30%) of colorless needles, m.p. 104.6–105.5°.

Anal. Calcd. for $C_{14}H_{15}NOS$: C, 68.6; H, 6.16. Found: C, 68.6; H, 6.36.

Both products showed two strong infrared absorption peaks in the N—H and one in the O—H stretching region and both were readily diazotized. On the basis of its subsequent desulfurization to 2-phenylethanol and to a mixture of toluene and ethylbenzene, the solid isomer was assigned the structure 2-aminophenyl-2-hydroxyethyl-1-phenylethyl sulfide (VII). The liquid isomer is, accordingly, 2-aminophenyl-2-hydroxyethyl-2-phenylethyl sulfide (VI).

Treatment of VII with *p*-nitrobenzoyl chloride in refluxing pyridine afforded a mixture of the mono-*p*-nitrobenzoyl derivative, m.p. 109.5–110.6° after recrystallization from benzene-hexane, and the di-*p*-nitrobenzoate, m.p. 177.0–178.4° after recrystallization from benzene-hexane. The two *p*-nitrobenzoates were separated by chromatographic adsorption on alumina from a solution of 50% (by volume) of hexane and chloroform.

Anal. Calcd. for $C_{21}H_{18}N_2O_4S$: C, 64.0; H, 4.60; N, 7.10. Found: C, 64.2; H, 4.75; N, 6.92.

Anal. Calcd. for $C_{28}H_{21}N_3O_7S$: C, 61.9; H, 3.89; N, 7.73. Found: C, 62.0; H, 4.07; N, 7.53.

Desulfurization of 2-aminophenyl-2-hydroxy-1-phenylethyl sulfide. Seven grams of the solid isomer (m.p. 104.6–105.5°) formed in the reaction of 2-aminobenzenethiol with styrene oxide was refluxed for 4 hr. with 120 g. of Raney nickel and 200 ml. of 95% alcohol. The mixture was filtered, the solvent removed, and the residue taken up in ether and washed several times with dilute hydrochloric acid. The ether was removed and the remaining oil, b.p. 215–221° (748 mm.), distilled. The phenylurethane prepared directly from the distillate melted at 79.0–80.2° and did not depress the melting point (80.0–80.5°) of the phenylurethane of authentic 2-phenylethanol.

With freshly prepared W-6 Raney nickel the product was a mixture of toluene and ethylbenzene, analyzed by means of vapor phase chromatography.

2-Phenyl-2,3-dihydrobenzo-1,4-thiazine. To a slurry of 3 g. of lithium aluminum hydride in 200 ml. of ether was added a suspension in 250 ml. of ether of 13.2 g. of 2-phenyl-2,3-dihydrobenzo-1,4-thiazin-3-one, m.p. 205.0–206.5°, prepared by reaction of 2-aminobenzenethiol with D,L-2-chlorophenylacetic acid in ethanol according to the general method of Unger.[13] The mixture was heated under reflux for 24 hr. The complex was then decomposed with methanol, the resulting mixture was filtered, and the filtrate evaporated to dryness. The residue was leached with benzene and hexane added to the benzene solution. The solid product which

crystallized was recrystallized from benzene-hexane to yield 9.2 g. (74%) of 2-phenyl-2,3-dihydrobenzo-1,4-thiazine, m.p. 131.2–132.4°, depressed upon admixture with either VI or VII. The infrared spectrum of the product showed only one band in the N—H and none in the O—H stretching region.

Anal. Calcd. for $C_{14}H_{13}NS$: C, 74.0; H, 5.77. Found: C, 73.7; H, 5.98.

Reaction of 2-aminothiophenol with trans-1,2-dibromocyclohexane. To a cooled solution of 12.5 g. (0.10 mole) of 2-aminobenzenethiol and 5.60 g. (0.10 mole) of potassium hydroxide in 50 ml. of ethanol, 12.1 g. (0.050 mole) of *trans*-1,2-dibromocyclohexane in 50 ml. of ethanol was added dropwise with stirring. The mixture was heated under reflux for 1 hr. and the ethanol then removed by distillation.

The residue was washed with water and crystallized from ethanol to give 12.0 g. (96%) of 2,2′-diaminodiphenyl disulfide, m.p. 90.8–91.5° (reported[14] 89–91°). The aqueous washes upon evaporation afforded 10.8 g. (91%) of potassium bromide.

The ethanol distillate was added to 750 ml. of water and twice extracted with 200-ml. portions of ether. The ether extracts were combined, washed with water, and dried over magnesium sulfate, and the ether was removed. Distillation of the residue yielded 4.0 g. (95%) of cyclohexene, b.p. 81–83°, identified as the 2,4-dinitrobenzenesulfenyl chloride adduct, m.p. 117.2–118.4° (reported[15] 117–118°).

(14) J. A. Gardner, British Patent **558,887**, Jan. 26, 1944; *Chem. Abstr.*, **40**, 7237 (1946).

(15) N. Kharasch and C. M. Buess, *J. Am. Chem. Soc.*, **71**, 2724 (1949).

Synthesis of Some Heterocyclic Derivatives of α-Keto Acids

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Hippuric acid was condensed with several alicyclic, aliphatic, and aromatic aldehydes to yield the corresponding 4-(substituted)-2-phenyl-2-oxazoline-5-ones. Using acid hydrolysis, several of these compounds were converted to the corresponding α-keto acid derivative. Cyclohexane- and cyclopentane-glyoxylic acids were condensed with o-phenylenediamine to form the corresponding 2-(cycloalkyl)-3-hydroxyquinoxalines, and the latter two keto acids were also allowed to react with 4,5,6-triaminopyrimidine to form the corresponding cycloalkyl-hydroxy-4-amino pteridine derivatives.

For the purpose of study of the biological properties of keto acids which are structurally related to certain naturally occurring keto acids, several derivatives have been prepared in this and a previous investigation.[2] The chemistry of certain of these keto acids was further examined to the extent of preparing the corresponding quinoxaline and pteridine derivatives.

2-Oxo-3-(3-cyclohexene)propionic acid, the keto acid analog corresponding to the leucine antagonist, 3-cyclohexenealanine,[3] was prepared by the interaction of 3-cyclohexene-1-carboxaldehyde with hippuric acid to form the corresponding 2-oxazoline-5-one derivative. Acid hydrolysis of the latter compound yielded the desired keto acid analogue.[4] In the preparation of 4-(3-cyclohexene-1-methylidene)-2-phenyl-2-oxazoline-5-one, the use of sodium acetate as the condensing agent gave a low yield of the intermediate; however, a much superior yield was obtained later by carrying out the reaction in tetrahydrofuran using lead acetate as the condensing agent.[5] Alkaline hydrolysis of the 2-oxazoline-5-one condensation product described above gave 2-benzamido-3-(3-cyclohexene)-acrylic acid. The sequence of these reactions is indicated in the accompanying equations.

The yield of the corresponding 2-oxazoline-5-one derivative through the above reaction is found to be much better in the case of aromatic aldehydes than in the case of aliphatic aldehydes and ketones[4]; however, using the appropriate conditions, cyclopentanone, which has been reported to fail to condense with hippuric acid,[5,6] has recently been converted to the desired derivative, 4-cyclopentylidene-2-phenyl-2-oxazoline-5-one,[2] although in poor yield. Using the above described preparative procedure, tiglic aldehyde was condensed with both hippuric acid and *N*-acetylglycine to yield

(1) Rosalie B. Hite pre-doctoral fellow 1957–1959.

(2) J. D. Fissekis, C. G. Skinner, and W. Shive, *J. Am. Chem. Soc.*, **81**, 2715 (1959).

(3) J. Edelson, C. G. Skinner, J. M. Ravel, and W. Shive, *Arch. Biochem. Biophys.*, **80**, 416 (1959).

(4) Patterned after the procedure of G. R. Ramage and J. L. Simonsen, *J. Chem. Soc.*, 532 (1935); and R. Neher, M. Spillman, L. H. Werner, A. Wettstein, and K. Miescher, *Helv. chim. Acta*, **29**, 1874 (1946).

(5) E. Baltazzi and R. Robinson, *Chem. & Ind. (London)*, **1954**, 191.

(6) V. Boekelheide and L. M. Schramm, *J. Org. Chem.*, **14**, 298 (1948).

$$R{=}O + H_2C{-}COOH \quad R{=}C{-}C{=}O \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}OH$$

with the intermediate structures bearing NH / C=O / C_6H_5 and $R{=}C{-}COOH$ / NH / C=O / C_6H_5 groupings.
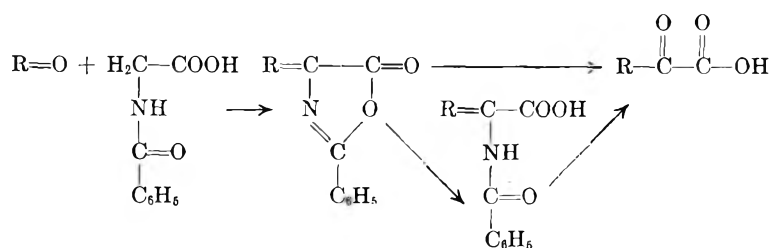
4-(2-methyl-2-butenylidene)-2-phenyl-2-oxazoline-5-one and the 2-methyl-2-oxazoline-5-one, respectively. Hydrolysis of either of these derivatives gave a reaction mixture from which the desired keto acid analog could not be easily recovered.

In addition to the above described oxazolone derivatives, salicylaldehyde and 2,4-dihydroxybenzaldehyde were both converted to the corresponding heterocyclic analogs; however, in the latter instance the product isolated contained one acetylated hydroxyl group. In view of the fact that both of these latter aldehydes contain an o-hydroxy grouping, and that only the second one was acetylated by the acetic anhydride present in the reaction mixture, it appears that the product isolated from the 2,4-dihydroxy compound was 4-(4-acetoxy-2-hydroxybenzylidene)-2-phenyl-2-oxazoline-5-one.

The alicyclic keto acid derivatives undergo the typical reactions of α-keto acids; for example, both the cyclopentane- and cyclohexane-glyoxylic acids readily condense with o-phenylenediamine to form the corresponding 2-cycloalkyl-3-hydroxy-quinoxalines in good yield. In contrast to the unambiguous structure of the latter two condensation products, the material isolated from the interaction of 4,5,6-triaminopyrimidine with each of the above glyoxylic acids may yield two isomeric pteridines, as indicated in the accompanying equations. Accordingly, utilizing cyclohexanegly-

(reaction scheme of 4,5,6-triaminopyrimidine condensing with $R{-}\overset{O}{\underset{}{C}}{-}\overset{O}{\underset{}{C}}{-}OH$ to give 4-amino-7-R-6-hydroxypteridine and/or 4-amino-6-hydroxy-7-R-pteridine)
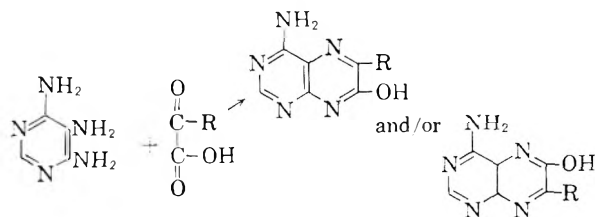
oxylic acid, the two anticipated isomeric products would be the 6-cyclohexane-7-hydroxy- and 7-cyclohexane-6-hydroxy- derivatives of 4-aminopteridine. Since the mode of condensation may be directed by carrying out the reaction under the proper conditions of pH,[7] both isomers were prepared and characterized. The two isomeric products were purified by recrystallization until a constant ultraviolet absorption spectrum was obtained at the most intense λ_{max}.[8]

The ultraviolet spectrum of the product isolated from the condensation of cyclohexaneglyoxylic acid and 4,5,6-triaminopyrimidine in the presence of strong acid (compound A) was qualitatively similar to the spectra of xanthopterin and 7-methylxanthopterin[9]; and the isomeric product isolated from the "pH 5" reaction mixture (compound B) was comparable to the reported spectra of isoxanthopterin and 6-methylisoxanthopterin.[9] Compound A is appreciably more soluble in water than compound B which is comparable to the reported greater solubility of 6-hydroxypteridine over that of the 7-hydroxy-isomer.[9] Finally, compound A possesses a strong fluorescence under a 365 mμ lamp; whereas, compound B has a very weak bluish fluorescence under this ultraviolet light source. After compound B is exposed to the 365 mμ light for several minutes, it then fluoresces very strongly as does compound A. This latter property is comparable to the fluorescent characteristics observed with 7-hydroxypteridine.[10] All of the above data supports the view that compound A (which was prepared by condensing in the presence of strong acid) is 4-amino-7-cyclohexyl-6-hydroxypteridine and that compound B (which was prepared by condensation at pH 5) is 4-amino-6-cyclohexyl-7-hydroxypteridine.

The interaction of cyclopentaneglyoxylic acid with 4,5,6-triaminopyrimidine under strongly acidic conditions yielded a reaction product which had an ultraviolet absorption spectrum similar to that of the 4-amino-7-cyclohexyl-6-hydroxypteridine described above. Its solubility properties and appearance under a 365 mμ ultraviolet light source was also comparable, and, since it was prepared by the "strong acid" technique which normally produces a 6-hydroxypteridine derivative, it was concluded that the isolated material from the above reaction mixture is 4-amino-7-cyclopentyl-6-hydroxypteridine.

A preliminary microbiological study of these compounds suggests that they do not have a wide spectrum of inhibitory properties; however, the two 4-amino-7-(cycloalkyl)-6-hydroxypteridines do inhibit the growth of Streptococcus faccalis 8043 and Leuconostoc citrovorum 8081 in a previously

(7) R. R. Purrmann, Ann., 548, 284 (1941); G. B. Elion, G. H. Hitchings, and P. B. Russell, J. Am. Chem. Soc., 72, 78 (1950).

(8) A. Albert, Quart. Rev. Chem. Soc., VI, No. 3, p. 198.

(9) G. B. Elion and G. H. Hitchings, J. Am. Chem. Soc., 69, 2554 (1947).

(10) A. Albert, D. J. Brown and G. Cheeseman, J. Chem. Soc., 1620 (1952).

described medium[11] using a paper disk assay technique. Since the corresponding 6-cyclohexyl-7-hydroxy- derivative was not inhibitory to growth under these conditions, these results offer further evidence for the identical substitution of the hydroxy group in the 6-position of the two active pteridines.

EXPERIMENTAL[12]

4-(3-Cyclohexene-1-methylidene)-2-phenyl-2-oxazoline-5-one. Method A: A mixture of 40 g. of dry hippuric acid, 18.5 g. of freshly fused sodium acetate, 100 ml. of acetic anhydride, and 27 g. of 3-cyclohexene-1-carboxaldehyde was heated on a steam cone for about 1 hr. to yield a dark pink solution. After cooling, the reaction mixture was added slowly, with vigorous stirring, to 3 l. of ice cold water; and then, stirred an additional 8 hr. while the temperature was kept between 0 and 5°. The resulting semisolid precipitate was recovered, washed thoroughly with ice cold water, and taken up in hot ethyl alcohol. The alcohol solution was then reduced in volume, and cooled overnight in an isopropyl alcohol–dry ice bath to yield 9.0 g. of orange-yellow needles, m.p. 104–105°. A sample was recrystallized twice from ethyl alcohol for elemental analysis, m.p. 109–110°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.97; N, 5.53. Found: C, 76.12; H, 6.23; N, 5.60.

Method B: A much improved procedure consisted of mixing 35 g. of 3-cyclohexene-1-carboxaldehyde, 53 g. of hippuric acid, 100 ml. of acetic anhydride, 19 g. of lead acetate,[13] and 500 g. of freshly distilled tetrahydrofurane, and heating to reflux for about 5 hr. to yield a pink solution. The tetrahydrofurane was removed by distillation *in vacuo,* and the residue was cooled and added to about 3.5 l. of ice cold water with efficient stirring. After stirring an additional 5 hr. in the cold, the precipitated material was recovered, washed with ice water, and dried *in vacuo* over phosphorus pentoxide to yield 71 g. of crude product, *m.p.* 92–97°; which, after recrystallization from ethyl alcohol, had a melting range of 106–108°, and was identical with the analyzed material described above.

2-Benzamido-3-(3-cyclohexene)acrylic acid. A 10-g. sample of 4-(3-cyclohexene-1-methylidene)-2-phenyl-2-oxazoline-5-one was heated on a steam cone in the presence of 100 ml. of 10% potassium hydroxide for about 15 min. to yield a clear yellow solution. After cooling, the reaction mixture was washed twice with ether, the aqueous phase was diluted two-fold, and then acidified to pH 2 with 2N hydrochloric acid. The semisolid material which ultimately separated was taken up in ethyl alcohol, and the solution was treated with Norit. The resulting yellow solution was reduced *in vacuo* to yield an oil residue which was then taken up in benzene. Reduction in volume of the benzene phase followed by cooling overnight in the refrigerator yielded 3.6 g. of product,

m.p. 163–165°. An analytical sample was recrystallized from chloroform–Skellysolve B, m.p. 164–166°.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.03; H, 6.46; N, 5.14.

2-Oxo-3-(3-cyclohexene)propionic acid. A mixture of 15 g. of 4-(3-cyclohexene-1-methylidene)-2-phenyl-2-oxazoline-5-one and 300 ml. of 8N hydrochloric acid was heated on a steam bath for 20 hr. The precipitated benzoic acid which separated upon cooling was removed, and the filtrate was continuously extracted with ether for about 15 hr. The ether extract was dried over sodium sulfate, and the solvent was removed to yield an oily residue, which was purified by heating to 60° under 0.04 to 0.01 mm. pressure and there was collected 2.0 g. of a waxy-like distillate on a cold finger. After crystallization from ether–Skellysolve B the product melted 225–227°.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.24.

Using the procedure of Metzler and Snell,[14] a sample of the keto acid was treated with pyridoxamine, and the reaction mixture was examined by paper chromatographic techniques. There was observed only a single ninhydrin active spot which was identical with 2-amino-3-(3-cyclohexene)propionic acid in several solvent systems.

The 2,4-dinitrophenylhydrazone derivative of this keto acid was prepared by the usual method, m.p. 190°.

Anal. Calcd. for $C_{15}H_{16}N_4O_6$: N, 16.13. Found: N, 15.91.

4-(2-Methyl-2-butenylidene)-2-phenyl-2-oxazoline-5-one. Using the general procedure A described above for the corresponding 4-(3-cyclohexene-1-methylidene)- derivative, 40 g. of hippuric acid, 18.5 g. of sodium acetate, 100 ml. of acetic anhydride, and 37 g. of tiglic aldehyde were allowed to react; and, after precipitating with cold water, the reaction mixture yielded 18.3 g. of light yellow needles, m.p. 143°. Recrystallization from ethyl alcohol, followed by Skellysolve B, gave a product which melted 147–148°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.86; H, 5.63; N, 6.17.

2-Benzamido-4-methylhexa-2,4-dieneoic acid. A mixture of 8 g. of 4-(2-methyl-2-butenylidene)-2-phenyl-2-oxazoline-5-one and 80 ml. of 10% potassium hydroxide was heated over a steam cone for about 15 min. to yield a clear yellow solution. The reaction mixture was cooled, diluted with 160 ml. of water, and the resulting aqueous phase was washed with ether, and finally, acidified to pH 2 with 2N hydrochloric acid. Upon cooling, a precipitate formed which was filtered, washed with cold water, and then taken up in hot ethyl alcohol and decolorized with Norit. After standing in the refrigerator there was recovered 5.0 g. of yellow needles, m.p. 181–183°. An analytical sample was obtained by recrystallizing from ethyl alcohol–water to yield colorless needles, m.p. 184–186°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.54; H, 6.09; N, 5.53.

4-(o-Hydroxybenzylidene)-2-phenyl-2-oxazoline-5-one. A mixture of 60 g. of hippuric acid, 41.5 g. of salicylaldehyde, 120 ml. of acetic anhydride, and 27.2 g. of freshly fused sodium acetate was heated to reflux for 45 min., cooled, and poured with vigorous stirring into 2 l. of ice cold water. The precipitate which formed was collected, washed with cold water, and dried *in vacuo* over potassium hydroxide to yield 29 g. of product. Crystallization from acetone–water followed by acetone gave light pink needles, m.p. 181–182°.[15]

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.94; H, 4.52; N, 5.48.

4-(4-Acetoxy-2-hydroxybenzylidene)-2-phenyl-2-oxazoline-5-one. A mixture of 14 g. of hippuric acid, 11 g. of 2,4-dihydroxybenzaldehyde, 30 ml. of acetic anhydride and 6.4 g.

(11) Same as in J. M. Ravel, B. Felsing, E. M. Lansford, Jr., R. H. Trubey, and W. Shive, *J. Biol. Chem.,* 214, 498 (1955) except that the Tween 80 was omitted.

(12) All melting points are uncorrected. The paper chromatographs were made by the ascending technique and the papers were examined in a darkroom using an ultraviolet lamp of the appropriate wave length. The ultraviolet absorption spectra were determined on a Beckman model DK-2 recording spectrophotometer at a concentration of 10 γ/ml. in water with the pH adjusted to 1 or 11 using hydrochloric acid or sodium hydroxide, respectively. The authors are indebted to W. H. Orme-Johnson, J. Morehead, and A. G. Lane for the chemical analyses and to Drs. J. M. Ravel and E. M. Lansford, Jr., for a preliminary study of the microbiological properties of some of these compounds.

(13) Pb(OAc)₂·3H₂O proved to be as satisfactory as anhydrous lead acetate.

(14) D. E. Metzler and E. E. Snell, *J. Am. Chem. Soc.,* 74, 979 (1952).

(15) E. Erlenmeyer, Jr., and W. Stadlin, *Ann.,* 337, 283 (1904) reported a m.p. 137–138°.

of sodium acetate was reacted and worked up as described above to yield 7 g. of product. Crystallization from ethyl alcohol–water gave yellow needles, m.p. 192–193°.

Anal. Calcd. for $C_{18}H_{13}NO_5$: C, 66.86; H, 4.05; N, 4.33. Found: C, 67.00; H, 3.91; N, 4.50.

2-Methyl-4-(2-methyl-2-butenylidene)-2-oxazoline-5-one. To a mixture of 29 g. of N-acetylglycine, 20 g. of freshly fused sodium acetate, and 100 ml. of acetic anhydride was added 40 g. of tiglic aldehyde. After standing for 4 hr. at room temperature, the reaction mixture was heated to 100° for about 8 hr., and then allowed to cool. The solid mass which separated upon cooling was washed thoroughly with a large volume of ice water and the residual semisolid material was taken up in ethyl alcohol. After cooling overnight in a dry ice–isopropyl alcohol mixture, a solid precipitated which was filtered and quickly taken up in fresh ethyl alcohol, treated with Norit, and reduced in volume to induce crystallization. Upon cooling, there was recovered 4 g. of light yellow crystals, 86–88°. An analytical sample was obtained by recrystallization from ethyl alcohol, m.p. 87–89°.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.03; H, 6.61; N, 8.44.

2-Cyclopentyl-3-hydroxyquinoxaline. A solution of 108 mg. of o-phenylenediamine in 40 ml. of 2N hydrochloric acid was added to a solution of 142 mg. of cyclopentaneglyoxylic acid dissolved in 5 ml. of ethyl alcohol. The reaction mixture was stirred at room temperature for about 15 min., warmed on a steam cone for a few minutes, and finally cooled in an ice bath to yield a precipitate. The product was filtered, washed with small portions of cold water, and recrystallized once from ethyl alcohol–water, and twice from ethyl alcohol. There was recovered 110 mg. of colorless needles, m.p. 237–238° dec. The ultraviolet absorption is recorded elsewhere.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.82; H, 6.61; N, 13.07.

2-Cyclohexyl-3-hydroxyquinoxaline. Using the same procedure as described above for the cyclopentane- derivative, 108 mg. of o-phenylenediamine was allowed to react with 156 mg. of cyclohexaneglyoxylic acid. The reaction product was recrystallized several times from ethyl alcohol to yield 140 mg. of colorless crystals, m.p. 257–258° dec.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.92; H, 7.07; N, 12.50.

ULTRAVIOLET ABSORPTION SPECTRA OF
2-R-3-HYDROXYQUINOXALINES

R	λmax, mμ (pH 1)	λmax, mμ (pH 11)	λmin, mμ (pH 1)	λmin, mμ (pH 11)
Cyclopentyl-	334, 286 249–255 228	346 238	300 267 244	280–300 226
Cyclohexyl-	330, 282 250, 227	346 238	306 264 242	280–298 228

4-Amino-7-cyclohexyl-6-hydroxypteridine. A 125-mg. sample of 4,5,6-triaminopyrimidine was dissolved in 40 ml. of 2N sulfuric acid with gently warming, and, after cooling to room temperature, 156 mg. of cyclohexaneglyoxylic acid dissolved in 5 ml. of ethyl alcohol was added. The reaction mixture was stirred at room temperature for about 2 hr., heated an additional hour over a steam cone, and then cooled and taken to pH 5 with 10% potassium hydroxide solution. Upon cooling in an ice bath a precipitate formed which was filtered, washed with several small volumes of cold water,

and dried to yield 100 mg. of crude product. The material was crystallized by taking it up in hot ethyl alcohol and slowly reducing the volume of the solvent using an air jet. The resulting crystals start decomposing at about 260°, and melted with decomposition at 298°.

Anal. Calcd. for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.56. Found: C, 58.70; H, 5.88; N, 27.82.[16]

R_f value in pyridine:2,6-lutidine:water (3:3:4) was 0.85. The spot was observed using a 365 mμ ultraviolet light source, and was strongly fluorescent. The other solvent systems tried carried the compound to the solvent front, and were discarded. This derivative was chromatographically different from its isomer prepared below, as evidenced by overlay techniques in the solvent system indicated above. The ultraviolet absorption spectrum is presented elsewhere.

4-Amino-6-cyclohexyl-7-hydroxypteridine. A sample of 156 mg. of cyclohexaneglyoxylic acid in 5 ml. of ethyl alcohol was added to a solution of 125 mg. of 4,5,6-triaminopyrimidine dissolved in 40 ml. of acetate buffer at pH 5. The reaction mixture was stirred at room temperature for about 2 hr., and then heated an additional 2 hr. on a steam cone; after which, the volume was reduced to about one half the original, and a precipitate formed. The product was filtered, washed with a small volume of cold water, and recrystallized from ethyl alcohol–water to yield 7.0 mg. of material, m.p. 330–332° dec.

Anal. Calcd. for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.56. Found: C, 58.05; H, 6.38; N, 28.36.

R_f value in pyridine:2,6-lutidine:water (3:3:4) was 0.93. Using a 365 mμ ultraviolet lamp, the spot was observed as a weak bluish fluorescent spot. After being irradiated with a 254 mμ light source for several minutes, the intensity of fluorescence at 365 mμ increased until it was comparable to the isomeric 6-hydroxy derivative described above. The ultraviolet absorption spectrum of this compound is presented elsewhere.

4-Amino-7-cyclopentyl-6-hydroxypteridine. To a solution of 4,5,6-triaminopyrimidine dissolved in 40 ml. of 2N sulfuric acid was added 142 g. of cyclopentaneglyoxylic acid dissolved in 5 ml. of ethyl alcohol. The reaction mixture was stirred at room temperature for about 2 hr., and then heated for 1 hr. over a steam cone. After cooling, it was taken to pH 5 with 10% potassium hydroxide, cooled in an ice bath, and the resulting light yellow precipitate which formed was collected, washed with cold water, and dried *in vacuo.* There was recovered 176 mg. of product, which was recrystallized from ethyl alcohol–water until a constant ultraviolet spectrum was obtained, m.p. 260°.

Anal. Calcd. for $C_{11}H_{13}N_5O$: N, 30.29. Found: N, 30.62.

ULTRAVIOLET ABSORPTION SPECTRA OF SOME
SUBSTITUTED-4-AMINOPTERIDINES

Substituent Groups	λmax, mμ pH 1	λmax, mμ pH 11	λmin, mμ pH 1	λmin, mμ pH 11
7-Cyclohexyl-6-hydroxy-	355, 339 243	362 253	348 292, 225	304 235
6-Cyclohexyl-7-hydroxy-	324 293	328 231	259	273
7-Cyclopentyl-6-hydroxy-	352, 338	360 252	349 295	303 236

AUSTIN, TEX.

(16) Nitrogen analyses of hydroxy- and amino-pteridines frequently give low values due to a difficulty in burning, A. Albert, *Quart. Rev. Chem. Soc.,* VI, No. 3, 1952, p. 198.

α-Oximino Ketones. III. A New Synthesis of α-Amino Acids[1]

ARTHUR F. FERRIS

The reaction of α-alkoximino methyl ketones with aqueous sodium hypochlorite has been found to give α-alkoximino acids in good yield. This reaction is the key step in a new synthesis of α-amino acids from methyl ketones, which involves nitrosation of the ketone, alkylation of the resulting α-oximino ketone, cleavage of the resulting α-alkoximino ketone with hypochlorite, and reduction of the resulting α-alkoximino acid to an α-amino acid. Overall yields of α-amino acids from methyl ketones ranged from 14 to 63%.

In the course of a study of the reactions of α-alkoximino ketones it was found that α-alkoximino methyl ketones readily undergo the haloform reaction with aqueous sodium hypochlorite to give chloroform and the corresponding α-alkoximino carboxylic acids in good yield. This discovery has been developed into a new and quite general synthesis of α-amino acids from methyl ketones, comprising the steps of (1) nitrosation of the methyl ketone, (2) alkylation of the resulting α-oximino ketone, (3) cleavage of the resulting α-alkoximino ketone with alkaline hypohalite, and (4) reduction of the resulting α-alkoximino acid to an α-amino acid. The synthesis is presented in generalized equation form below:

$$RCH_2CCH_3 \xrightarrow[HCl]{R''ONO} RC-CCH_3 \xrightarrow[NaOH]{R'X}$$
$$(1) \qquad\qquad (2)$$

$$RC-CCH_3 \xrightarrow[\text{Then } H^+]{NaOCl} RC-CO_2H \quad (4)$$
$$(3) \qquad\qquad \downarrow H_2 \mid Pd/C$$
$$RCHCO_2H \;\; NH_2$$
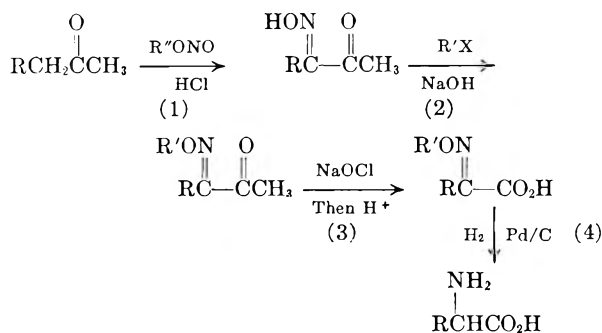
Overall yields of α-amino acids from methyl ketones were: norleucine, 63% from 2-heptanone; phenylalanine, 50% from 1-phenyl-3-butanone; valine, 34% from 4-methyl-2-pentanone; and alanine, 14% from 2-butanone. The last yield is not regarded as representative because the volatility of the intermediates made mechanical losses high.

The nitrosation reaction (step 1) is a well known one and can be carried out in several ways, amply documented in a recent review.[2] Treating a solution of the methyl ketone in ether with methyl nitrite in the presence of a small amount of hydrochloric acid was found to be a satisfactory technique for the ketones used in this study. The α-oximino ketones prepared are described in Table I.

TABLE I
α-OXIMINO KETONES

$$CH_3-\overset{O}{\overset{\|}{C}}-\overset{NOH}{\overset{\|}{C}}-R$$

R	Yield, %	Melting Point, °C.[a] Found	Lit.
—(CH$_2$)$_3$CH$_3$	78	59–60	. . .[b]
—CH(CH$_3$)$_2$	68	78–79	75[c]
—CH$_3$	48	75.5–76.5	76.5[d]
—CH$_2$C$_6$H$_5$	75	80–81	80–81[e]
—C$_6$H$_5$	91	162–163	164–165[f]

[a] All melting points are uncorrected. [b] *Anal.* Calcd. for C$_7$H$_{13}$O$_2$N: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.85; H, 9.25; N, 9.77. [c] B. Westenberger, *Ber.*, 16, 2991 (1883). [d] W. L. Semon and V. R. Damerell, *Org. Syntheses*, Coll. Vol. II, 204 (1943). [e] G. Ponzio, *Gazz. chim. ital.*, 35, 394 (1905). [f] H. Rheinboldt and O. Schmitz-Dumont, *Ann.*, 444, 130 (1925).

Although the alkylation of α-oximino ketones (step 2) has been described,[3] it was necessary to work out methods for carrying out the reaction in good yield. Since the nature of the alkyl group is unimportant because it is removed later in reduction, the method developed by Waters and Hartung[4] for the ethylation of α-oximino acids is very convenient. In applying this technique, the α-oximino ketone was dissolved in aqueous base and treated simultaneously with ethyl sulfate and equivalent base, usually at elevated temperature. A particular virtue of this method was that it permitted synthesis of α-ethoximino ketones from ketones without the necessity of isolating the intermediate α-oximino ketones. Thus, the ether solutions from the nitrosation reaction could be extracted with aqueous base, and the resulting solutions treated with ethyl sulfate as described to give the α-ethoximino ketones in yields of 50–75% from the corresponding ketones. Another procedure, capable of giving α-alkoximino ketones with a wide variety of alkyl groups, involved treating the sodium salt of the α-oximino ketone in aqueous methanol with an alkyl

(1) Paper I of this series: *J. Org. Chem.*, 24, 580 (1959); Paper II: *Chem. & Ind. (London)*, 996 (1959).

(2) O. Touster, *Org. Reactions*, VII, 327 (1953).

(3) M. Ceresole, *Ber.*, 16, 833 (1883). O. Diels and G. Plaut, *Ber.*, 38, 1917 (1905).

(4) K. L. Waters and W. H. Hartung, *J. Org. Chem.*, 12, 469 (1947).

TABLE II

α-ALKOXIMINO KETONES

$$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-\overset{\displaystyle NOR'}{\overset{\|}{C}}-R$$

R	R'	Prep. Method[a]	Yield	B.P.[b] °C	B.P.[b] Mm.	n_D^{35}	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
—(CH₂)₃CH₃	—CH₂CH₃	A	91	48.5–50	1.35	1.4325	63.12	10.01	8.18	63.38	9.86	8.46
		B	77									
		C	83									
—(CH₂)₃CH₃	—CH₂C₆H₅	D	81	104–106	0.6	1.5000	72.07	8.21	6.00	72.10	8.09	5.75
—(CH₂)₃CH₃	—CH₃	C	58	133–135	0.55	1.4630	61.51	9.03	8.97	61.40	9.14	9.03
—(CH₂)₃CH₃	—CH₂CH₂OH	C	68	81–82	0.45	1.4590	57.73	9.15	7.48	57.85	8.93	7.30
—CH(CH₃)₂	—CH₂CH₃	B	51	60–61.5	15	1.4263	61.12	9.62	8.91	61.30	9.48	8.91
—CH(CH₃)₂	—CH₂C₆H₅	D	25	84–87	0.5	1.5017	71.20	7.82	6.39	71.56	7.80	6.37
—CH₃	—CH₂CH₃	C	68	42–42.5	13	1.4280	55.92	8.61	10.87	55.45	8.36	10.63
—CH₃	—CH₂C₆H₅	D	75	78–81	0.45[c]	1.5160	69.09	6.85	7.33	69.00	7.40	6.96
—CH₂C₆H₅	—CH₂CH₃	B	77	73–75	0.18	1.5069	70.22	7.37	6.83	70.42	7.48	6.95

[a] A = α-Oximino ketone + ethyl sulfate; B = nitrosation + alkylation with ethyl sulfate, overall yield; C = α-oximino ketone + alkyl bromide; D = α-oximino ketone + alkyl chloride. [b] All boiling points are uncorrected. [c] O. Diels and F. terMeer, *Ber.*, **42**, 1940 (1909) report b.p. 130° (12 mm.).

TABLE III

α-ALKOXIMINO ACIDS

$$R-\overset{\displaystyle R'ON}{\overset{\|}{C}}-CO_2H$$

R	R'	Yield	M.P., °C[a]	B.P.[a] °C	B.P.[a] Mm.	n_D^{35}	Calcd. C	Calcd. H	Calcd. N	Calcd. Neut. Equiv.	Found C	Found H	Found N	Found Neut. Equiv.
—(CH₂)₃CH₃	—CH₂CH₃	96	...	65–67	0.4[b]	1.4510	55.47	8.73	8.09	173.2	55.31	8.60	8.04	173.4
—(CH₂)₃CH₃	—CH₃	74[c]	105.5–107[d]	...	...	...	53.15	7.65	8.86	158.2	53.22	7.78	8.89	159.3
—CH(CH₃)₂	—CH₂CH₃	74	...	55–53.5	0.5	1.4432	52.80	8.23	8.80	159.2	52.84	8.12	8.97	161.1
—CH₃	—CH₂CH₃	46	68–70[e]	73–76	2.1	...	45.79	6.92	10.68	131.1	45.95	6.71	10.71	132.8
—CH₃	—CH₂C₆H₅	36	84–85[f]	...	...	...	62.16	5.74	7.25	193.2	62.35	5.66	7.09	194.8
—CH₂C₆H₅	—CH₂CH₃	70	61–62[g]	...	...	...	63.75	6.32	6.76	207.2	64.00	6.18	6.88	206.8

[a] All melting points and boiling points are uncorrected. [b] Waters and Hartung[4] report b.p. 83–88° (1–3 mm.). [c] Conversion 19%. [d] Recrystallized from a mixture of water and ethanol. [e] Recrystallized from carbon tetrachloride. [f] Recrystallized from petroleum solvent (b.p. 65–67°). [g] Recrystallized from a mixture of carbon tetrachloride and petroleum solvent. Waters and Hartung[4] report m.p. 58.5–59°.

halide. The α-alkoximino ketones prepared are described in Table II.

The haloform reaction (step 3) was carried out using either a commercial 5.25% sodium hypochlorite solution or a solution of about 10% concentration made by adding chlorine to aqueous sodium hydroxide. The use of a cosolvent such as dioxane to improve the miscibility of the organic and aqueous phases was helpful in giving better yields. Experiments with reaction conditions indicated that best results were obtained by adding the cosolvent and the α-alkoximino ketone to the aqueous hypochlorite at room temperature or below, and allowing the mixture to warm spontaneously while stirring vigorously to insure good mixing. Cooling was applied if the temperature of the mixture exceeded 75°. The acids prepared are described in Table III.

In addition to the α-alkoximino acids listed in Table III, α-benzyloximinocaproic and α-benzyloximinoisovaleric acids were prepared in 73 and 79% yields, respectively, from 3-benzyloximino-2-heptanone and 2-benzyloximino-1-methyl-3-pentanone. These acids were reduced to the corresponding α-amino acids without purification. In working up the α-benzyloximinoisovaleric acid in the usual manner, it was found that much of the sodium salt of this acid was extracted into the chloroform and ether used to remove unreacted starting material. Since it has been noted[4] that the sodium salt of α-benzyloximino-β-phenylpropionic acid is similarly soluble in organic solvents, it appears that this complication is one which should be anticipated whenever salts of α-alkoximino acids containing bulky organic groups are being processed.

The action of alkaline hypochlorite solutions on α-oximino ketones wherein the oxime group was not protected by alkylation led to an entirely different result from that found with the α-alkoximino ketones. Although a chloronitroso derivative similar to that obtained from simple oximes by the action of hypochlorite[5] was not the final product, it may have been an intermediate, since in a preliminary experiment a transient green color was noted when 3-oximino-2-heptanone was treated with sodium hypochlorite solution. In larger scale experiments using a 10% sodium hypochlorite solution containing excess base, 3-oximino-2-heptanone was converted to a mixture of about equal amounts of n-valeronitrile and n-valeric acid, and 1-oximino-1-phenyl-2-propanone gave benzoic acid in 86% yield. In the latter experiment, a strong odor of benzonitrile was noted at an intermediate stage. It thus appears that the action of hypohalite on α-oximino ketones leads in essence to a "second order" Beckmann rearrangement, followed by at least partial hydrolysis of the nitrile initially formed. This interesting reaction deserves further study,

which was not possible when this investigation was carried out.

Although the reduction of α-alkoximino acids (step 4) was reported by previous workers to be difficult to carry out in good yield,[4] it was found in this study that the combination of ethanol solvent and palladium-on-charcoal catalyst gives essentially quantitative yields of amino acids from α-ethoximino acids when hydrogenation is carried out at moderate pressure (50 p.s.i.). Chemical reduction with metal and acid was also effective but far less convenient than hydrogenation. All reduction studies are summarized in Table IV.

TABLE IV

REDUCTION OF α-ALKOXIMINO ACIDS TO α-AMINO ACIDS

$$\begin{array}{c} R'ON \\ \| \\ R—C—CO_2H \end{array} \longrightarrow \begin{array}{c} NH_2 \\ | \\ R—CH—CO_2H \end{array}$$

R	R'	Method[a]	Yield
—(CH₂)₃CH₃	—CH₂CH₃	A	85
		B	69
—(CH₂)₃CH₃	—CH₂C₆H₅[b]	A	21
		B	26
—(CH₂)₃CH₃	—CH₂CH₂—	A	93
—CH(CH₃)₂	—CH₂CH₃	A	91
—CH(CH₃)₂	—CH₂C₆H₅[b]	A	33
—CH₃	—CH₂CH₃	A	93
—CH₃	—CH₂C₆H₅	A	88
—CH₂C₆H₅	—CH₂CH₃	A	93

[a] A = Catalytic hydrogenation in ethanol over 5% palladium-on-charcoal. B = Chemical reduction with zinc and acetic acid. [b] Not purified before reduction.

As a method of preparing α-amino acids, the synthesis described herein is obviously of fairly general utility, since almost any ketone having a methyl group on one side of the carbonyl function and a methylene group on the other can be converted to an α-amino acid with loss of the methyl group. The new sequence deserves consideration as a substitute for the classical Erlenmeyer synthesis of amino acids, since the same aldehyde which is condensed with hippuric acid, hydantoin, thiohydantoin, diketopiperazine, or rhodanine in variants of the Erlenmeyer synthesis[6-8] may be condensed with acetone and converted to the desired α-amino acid by the sequence shown below:

$$RCHO \xrightarrow{CH_3COCH_3} RCH{=}CHCCH_3 \xrightarrow[\text{Catalyst}]{H_2}$$

$$RCH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \xrightarrow{\text{Steps 1-4}} RCH_2\overset{\overset{\displaystyle NH_2}{|}}{C}HCO_2H$$

(5) O. Piloty, Ber., 31, 452 (1898).
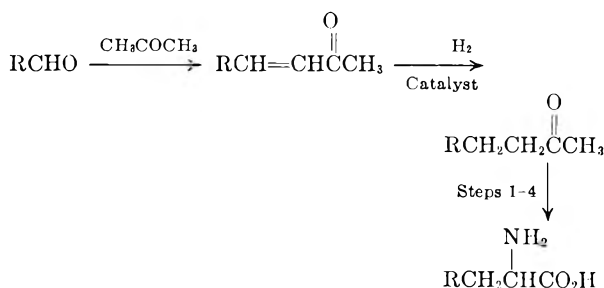
(6) L. F. Fieser and M. Fieser, Organic Chemistry, 3rd Ed., Reinhold Publishing Corp., New York, 1956, p. 434.

(7) H. E. Carter, Org. Reactions, III, 218 (1946).

(8) H. Gilman, Organic Chemistry, Vol. 2, 2nd Ed., John Wiley and Sons, Inc., New York, 1943, p. 1107.

In the only case where a direct comparison is possible, the conversion of benzaldehyde to phenylalanine, combination of the data presented here with that of others[9,10] gives a calculated overall yield of 37% for the new sequence, not greatly different from the 39–43% reported[11] for the Erlenmeyer azlactone synthesis. Since the new sequence involves more steps than the Erlenmeyer procedure, it probably will be preferred only when it is desired to take advantage of the virtues of the intermediate α-alkoximino acid. As pointed out by Waters and Hartung,[4] the potential amino group in this intermediate is present in a chemically rather inert structure, so that chemical modification of the carboxyl function, as in the preparation of intermediates for peptide formation and in peptide formation itself, can be carried out. When the desired modification has been achieved, conversion of the alkoximino group to the amino group can be carried out under very mild reduction conditions.

EXPERIMENTAL[12]

Not all experiments reported in the tables are described below, but examples of all techniques used are given.

3-Oximino-2-heptanone. Into 800 ml. of ether containing 207.4 g. (1.814 moles) of 2-heptanone and 23 ml. of concentrated hydrochloric acid was passed methyl nitrite, generated from 82.6 g. (2.58 moles) of methanol, 165.9 g. (2.28 moles) of 95% sodium nitrite in 100 ml. of water, and 160 ml. (2.86 moles) of concentrated sulfuric acid diluted with 145 ml. of water. The reaction temperature rose spontaneously to 39° and was held there by refluxing ether. Addition of the methyl nitrite required about 2 hr. When all had been added, the reaction mixture was stirred for 20 min., and then a solution of 33.6 g. of sodium bicarbonate in 400 ml. of water was added cautiously. When gas evolution had ceased, the aqueous layer was separated and washed with 100 ml. of ether. The combined ether solution was dried over anhydrous magnesium sulfate. Evaporation of the ether left 244.0 g. (94%) of crude 3-oximino-2-heptanone. Recrystallization from carbon tetrachloride gave 176.3 g. (68%) of pure white crystals, m.p. 59–60°.

Anal. Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.85; H, 9.25; N, 9.77.

2-Ethoximino-1-phenyl-3-butanone. Into a solution of 148.2 g. (1.00 mole) of 1-phenyl-3-butanone and 12 ml. of concentrated hydrochloric acid in 400 ml. of ether was passed the methyl nitrite generated by adding a solution of 33.4 ml. (0.60 mole) of concentrated sulfuric acid in 60 ml. of water to a mixture of 35.2 g. (1.10 moles) of methanol, 76.4 g. (1.05 moles) of sodium nitrite, and 50 ml. of water. About 4.5 hr. were required for the addition, the temperature being maintained at 33–38° by refluxing ether. When addition was complete, the mixture was stirred for 30 min., then cooled to 17°. A solution of 60 g. (1.50 moles) of sodium hydroxide in 250 ml. of water was added over 10 min., the temperature being kept below 20° by external cooling. This mixture was stirred for 30 min., and then the basic oxime solution was separated from the ether layer. The basic solution was heated to 70°, and 185.0 g. (1.20 moles) of ethyl

(9) N. L. Drake and P. Allen, Jr., *Org. Syntheses,* Coll. Vol. I, 2nd Ed., 77 (1941).

(10) L. W. Covert, R. Connor, and H. Adkins, *J. Am. Chem. Soc.,* 54, 1658 (1932).

(11) Ref. 6, p. 437.

(12) All boiling points and melting points are uncorrected.

sulfate and a solution of 48.0 g. (1.20 moles) of sodium hydroxide in 160 ml. of water were added simultaneously over 30 min. Heat of reaction maintained the temperature at 70–75°. At the end of this time heat was applied, and the mixture was held at 70–75° for an hour. Then the mixture, which had separated into two layers, was cooled to room temperature, and the organic layer was separated. The aqueous layer was extracted with three 200-ml. portions of ether, and the ether extracts combined with the organic layer were dried over anhydrous magnesium sulfate. Evaporation of the ether left 166.2 g. (81%) of crude 2-ethoximino-1-phenyl-3-butanone. Distillation at reduced pressure gave 157.2 g. (77%) of pure material, b.p. 73–75° (0.18 mm.), n_D^{25} 1.5069.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.42; H, 7.48; N, 6.95.

O,O'-Ethylenebis(3-oximino-2-heptanone). To a solution of 12.0 g. (0.30 mole) of sodium hydroxide in 15 ml. of water and 150 ml. of methanol was added 42.9 g. (0.30 mole) of 3-oximino-2-heptanone. The oxime dissolved to give an orange-brown solution. Then 18.8 g. (0.10 mole) of ethylene dibromide was added, and the solution was allowed to stand for several days in a tightly stoppered bottle. At the end of this time the methanol was evaporated under reduced pressure, and 100 ml. of water was added to the pasty residue. A liquid organic layer separated, and was extracted into three 100-ml. portions of ether. The combined ether layer was washed with three 50-ml. portions of 10% sodium hydroxide solution, and then was dried over anhydrous magnesium sulfate. Acidification of the combined original water layer and basic washes led to the recovery of 18.2 g. (0.127 mole) of 3-oximino-2-heptanone. Evaporation of the ether from the liquid organic product left 23.3 g. of orange oil. Distillation under reduced pressure gave 18.2 g. (58%) of O,O'-ethylenebis(3-oximino-2-heptanone), b.p. 133–135° (0.55 mm.), n_D^{25} 1.4630.

Anal. Calcd. for $C_{16}H_{29}O_4N_2$: C, 61.51; H, 9.03; N, 8.97. Found: C, 61.40; H, 9.14; N, 9.03.

2-Ethoximinocaproic acid. To 639 g. of a 5.25% sodium hypochlorite solution (containing 0.45 mole of sodium hypochlorite) was added 17.1 g. (0.10 mole) of 3-ethoximino-2-heptanone and 50 ml. of dioxane. The solution was heated to 90° with stirring, and was held at 90–96° for 20 min. while chloroform, water, and dioxane distilled out slowly. The resulting clear solution was cooled to room temperature and tested for excess hypochlorite with acidified potassium iodide solution. A positive test (brown color) was obtained, and the solution was treated with solid sodium bisulfite until the test was negative. The solution was then acidified with 5N sulfuric acid. An oil separated, and was extracted into three 100-ml. portions of ether. The ether solution was dried over anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, the residue was distilled under reduced pressure to give 13.1 g. (76%) of 2-ethoximinocaproic acid, b.p. 67–69° (0.4 mm.), n_D^{25} 1.4487. Redistillation of part of the product gave b.p. 65–67° (0.4 mm.), n_D^{25} 1.4510.

Anal. Calcd. for $C_8H_{15}O_3N$: C, 55.47; H, 8.73; N, 8.09; Neut. equiv., 173.2. Found: C, 55.31; H, 8.60; N, 8.04; Neut. equiv., 173.4.

2-Ethoximino-3-methylbutyric acid. A solution of 80.0 g. (2.0 moles) of sodium hydroxide in 600 ml. of water was cooled to −4°, and 56.7 g. (0.80 mole) of liquid chlorine was added dropwise with stirring, keeping the temperature below 0°. To the resulting solution was added 100 ml. of dioxane, and (rapidly) 31.4 g. (0.20 mole) of 3-ethoximino-4-methyl-2-pentanone. Over about 40 min., the temperature rose spontaneously to 52° and then dropped off slowly. When the mixture had cooled to room temperature, it was tested for unreacted hypochlorite (negative) and then was acidified with 120 ml. of 5N sulfuric acid. The oil which separated was extracted into three 150-ml. portions of ether, and the ether solution was dried over anhydrous magnesium sulfate. The ether was evaporated, and the residue was

distilled under reduced pressure to give 23.5 g. (74%) of 2-ethoximino-3-methylbutyric acid, b.p. 62–64° (0.9 mm.), n_D^{35} 1.4436. Part of the material on redistillation gave b.p. 53–53.5° (0.5 mm.), n_D^{35} 1.4432.

Anal. Calcd. for $C_7H_{13}O_3N$: C, 52.80; H, 8.23; N, 8.80; Neut. equiv., 159.2. Found: C, 52.84; H, 8.12; N, 8.97; Neut. equiv., 161.1.

DL-*Phenylalanine.* A solution of 10.4 g. (0.05 mole) of 2-ethoximino-3-phenylpropionic acid in 50 ml. of absolute ethanol was placed in the reaction bottle of a Parr Pressure Reaction Apparatus, Type 3911. The bottle was flushed with nitrogen, and 3.0 g. of a commercial 5% palladium-on-charcoal catalyst was added. The bottle was placed in the apparatus, evacuated, pressurized with hydrogen to 50 p.s.i., heated to 50°, and agitated until the theoretical amount of hydrogen had been taken up. This required 3 hr. The reduction mixture was cooled to 0° and filtered by suction. The recovered solid (catalyst and most of the product) was boiled for 10 min. with 250 ml. of water, and the mixture was filtered hot. The undissolved solid (catalyst) was washed on the filter with three 30-ml. portions of boiling water. The combined aqueous filtrate was concentrated to 175 ml. and cooled in ice. The first crop of DL-phenylalanine crystallized and was recovered by filtration and dried. It amounted to 5.0 g. Further concentration of the filtrate, followed by crystallization and recovery, gave an additional 2.7 g. of product. The total recovery was thus 7.7 g. (93%). The infrared spectrum of this product was identical with that of an authentic specimen of DL-phenylalanine.

DL-*Norleucine.* A solution of 7.3 g. (0.10 mole) of 2-ethoximinocaproic acid in 300 ml. of glacial acetic acid was heated to 100°, the heat was removed, and 65.4 g. (1.0 mole) of zinc powder was added over 30 min. at such a rate that the temperature was held at 95–101°. External heating was then applied, and the temperature was held at 95–101° for 1 hr. At the end of this time, 150 ml. of acetic acid was distilled off under reduced pressure, and the residue was taken up in a liter of water. The suspended solid was removed by filtration, and hydrogen sulfide gas was passed into the filtrate until no further zinc sulfide precipitated. The zinc sulfide was removed by filtration, and the filtrate was concentrated to 250 ml. A precipitate began to form, and more appeared when the mixture was cooled to 2° and brought to pH 3.5 with about 5 ml. of 10% aqueous sodium hydroxide. The white crystals of DL-norleucine, after recovery by filtration and drying, amounted to 7.1 g. More product, amounting to 1.9 g., was recovered by extracting the solids originally recovered from the reduction mixture with 150 ml. of boiling water, treating with hydrogen sulfide to precipitate zinc sulfide, removing the precipitate by filtration, and concentrating. The total yield of DL-norleucine was thus 9.0 g. (69%). The infrared spectrum of this product was identical to that of authentic DL-norleucine.

Action of sodium hypochlorite on 3-oximino-2-heptanone. A solution of 80.0 g. (2.0 moles) of sodium hydroxide in 600 ml. of water was cooled to −5°, and 56.7 g. (0.80 mole) of liquid chlorine was added dropwise with stirring, the temperature being held between −5 and 0°. The solution was then warmed to 26°, and the addition of 28.6 g. (0.20 mole)

of 3-oximino-2-heptanone was begun. The temperature rose rapidly and after 10 min. and addition of about a third of the oxime it has reached 75°. Cooling was applied, and the rest of the oxime was added over 20 min. with the temperature held at 72–76°. The mixture was allowed to cool slowly to 29° over 4 hr., at which point a test for unreacted hypochlorite was negative. A small amount of organic liquid had separated, and this was extracted into three 100-ml. portions of ether. The aqueous solution was then cooled in ice and acidified with concentrated hydrochloric acid. The organic layer which separated was extracted into three 100-ml. portions of ether. Both ether solutions were dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue from the extraction of the basic solution amounted to 7.1 g. On the basis of its infrared spectrum, it appeared to be largely *n*-valeronitrile. The residue from the extraction of the acidic solution amounted to 15.3 g., and appeared on the basis of infrared spectrum to be largely *n*-valeric acid. Distillation of this material under reduced pressure gave 8.4 g. of fairly pure *n*-valeric acid, b.p. 80–84° (10 mm.), n_D^{35} 1.4038. Authentic *n*-valeric acid gave n_D^{35} 1.4024.

Action of sodium hypochlorite on 1-oximino-1-phenyl 2-propanone. To a solution of sodium hypochlorite prepared as described above was added 32.6 g. (0.20 mole) of 1-oximino-1-phenyl-2-propanone over 45 min. The temperature was held at 22–29° by external cooling. A strong odor of benzonitrile was noted as the reaction progressed. When the oxime had all been added, the mixture was stirred for 30 min. at 22–26°, at the end of which time some solid remained undissolved. A test for hypochlorite was positive, and the remaining hypochlorite was destroyed by adding solid sodium bisulfite. The mixture was then extracted with four 100-ml. portions of ether, the solid passing into solution. The ether solution was dried over anhydrous magnesium sulfate, and the ether was evaporated under reduced pressure. There was obtained 9.7 g. of white solid, shown by infrared spectrum to be unchanged starting material. The aqueous solution remaining after the extraction was cooled in ice and acidified with concentrated hydrochloric acid. A heavy white precipitate came down. It was recovered by suction filtration, washed with two 50-ml. portions of cold water, sucked as dry as possible, and finally dried under vacuum. There was obtained 14.7 g. (86%, based on starting material not recovered) of benzoic acid, m.p. 121–122°. A mixture with authentic benzoic acid gave m.p. 122.5–124°.

PRINCETON, N. J.

Preparation of Ketone Acetals from Linear Ketones and Alcohols

N. B. LORETTE, W. L. HOWARD, AND J. H. BROWN, JR.

Simple ketone acetals were prepared by reaction of alcohols with ketones. The composition of several ketone-alcohol reaction systems at equilibrium was determined at 24° and −28° and in each case the formation of the acetal was favored at the low temperature.

In the past most ketone acetals were prepared by one of two general methods. One of these methods was the reaction of an ortho ester with a ketone to give the desired ketone acetal.[1-4] The alkyl orthosilicates were also reacted in a similar manner.[5] The second general method was the reaction of a substituted acetylene with two moles of alcohol to give a ketone acetal.[6,7] A related preparation utilized the reaction of isopropenyl acetate with an alcohol.[8,9] While both of these general methods give satisfactory to good yields of ketone acetals, they are limited by the availability of the *ortho* esters and substituted acetylenes.

A large number of aldehyde acetals have been prepared by the reaction of an alcohol with an aldehyde, but until recently the status of the analogous reaction between an alcohol and a ketone was characterized by the following statement of Carswell and Adkins:[10] "The reaction of ketones with alcohols to form acetals analogous to the reaction of aldehydes with alcohols proceeds to so slight an extent, if at all, that the reaction is of no importance." The first successful published experiment that was found on this reaction was in a paper presented at the Southwide Chemical Conference in 1956 by Suter and Guedin.[11] They reported that when acidic solutions of simple aliphatic ketones and methanol were introduced into the mass spectrometer, the resulting mass peaks indicated that some ketals had been formed. It was also reported that "no new ketals were prepared by this new method."

Independently and at about the same time as our work,[12] McCoy, Baker, and Gohlke[13] reported the preparation of cyclohexanone dimethyl acetal from cyclohexanone and methanol. Their work was limited to cyclohexanone, which is much more reactive than the linear ketones with methanol. Although our interest was primarily in the linear ketones, some work with cyclohexanone is included for comparative purposes.

We have found that linear ketones react directly with simple alcohols to give ketone acetals and that the ketone acetals can be readily recovered. The success of the reaction depends on shifting the equilibrium in favor of the ketone acetal by conducting the reaction at low temperature. Strong acids, including the sulfonic acid ion exchange resins, are good catalysts for the reaction. The isolation of the lower ketone acetals was based largely on washing with strong aqueous sodium hydroxide, as described by Bond and Klar,[14] to separate the alcohols from the ketals and thus avoid the troublesome alcohol-acetal azeotropes.

The use of Dowex 50 (a sulfonic acid cation exchange resin) in conjunction with Dowex 2 (a quaternary ammonium anion exchange resin) made possible a reaction system that resulted in good temperature control and a crude reaction product that was neutral. The use of the acid ion exchange resin also provides the means of conveniently achieving a very high concentration of acid catalyst which is necessary for producing reasonably large reaction rates at the low temperatures employed. In experiments with soluble acids at practicable concentrations, the reactions were impracticably slow. The catalyst is exceedingly long lived; after three months of continuous use no detectable decrease in activity was observed.

Stock solutions of alcohols and ketones were slowly passed successively through a bed of the cation exchange resin in the acid form and a bed of the anion exchange resin in the hydroxyl form, both maintained at the desired temperature. The rate of flow was low enough that equilibrium was approached at the low temperature in the acid resin bed. Passage through the basic resin then removed any dissolved acid and effectively prevented any reversal of the reaction due to the effect of any sub-

(1) L. Claisen, *Ber.*, **29**, 1005 (1896).

(2) L. Claisen, *Ber.*, **31**, 1010 (1898).

(3) L. Claisen, *Ber.*, **40**, 3903 (1907).

(4) A. E. Arbusow, *Ber.*, **40**, 3301 (1907).

(5) B. Helferich and J. Hausen, *Ber.*, **59B**, 795 (1924).

(6) D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **56**, 1384 (1934).

(7) G. F. Hennion, D. B. Killian, T. H. Vaughn, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **56**, 1130 (1934).

(8) W. J. Croxall, F. J. Glavis, and H. T. Neher, *J. Am. Chem. Soc.*, **70**, 2805 (1948).

(9) W. J. Croxall and H. T. Neher, U. S. Patent **2,490,337** (1949).

(10) H. E. Carswell and H. Adkins, *J. Am. Chem. Soc.*, **50**, 235 (1928).

(11) H. A. Suter and R. M. Guedin, *Southern Chemist*, **16**, 102 (1956).

(12) J. H. Brown, Jr., and N. B. Lorette, U. S. Patent **2,827,494** (1958).

(13) R. E. McCoy, A. W. Baker, and R. S. Gohlke, *J. Org. Chem.*, **22**, 1175 (1957).

(14) G. C. Bond and L. A. Klar, U. S. Patent **2,827,495** (1958).

sequent temperature changes on the position of the equilibrium. The acid-free reaction solution which passed from the reactor could be stored at room temperature and even distilled without further treament; however, a small amount of sodium hydroxide or sodium methylate was usually added prior to distillation to insure the maintenance of alkalinity. The presence of any acid would not only cause a change in the composition of the products but would also cause pyrolytic cracking of the ketone acetal to an unsaturated ether during the distillation. It was advantageous to wash the reaction solution with the strong sodium hydroxide solution to remove the water-soluble reactants from the ketone acetal. This was necessary in three cases where it was found that the alcohol and the ketone acetal formed an azeotrope. No binary azeotropes composed of the ketone and the ketone acetal were noted. Good conversion of acetone was obtained with methanol, but conversions were lower with ethanol, propanol, and butanol.

In the reaction of several alcohols with acetone, methanol gave the largest conversions to acetal. For this reason it was selected for reaction with three other linear ketones. For the three ketones chosen, conversions were smaller and decreased with increase in molecular weight.

All of the ketone acetals described in the experimental section were prepared directly from ketone and alcohol; however, except for the dimethyl acetals of acetone and butanone, the conversions were low. Thus, although they can be made directly, ketone acetals other than these two are more easily prepared by ketone and/or alkoxyl moiety interchange reactions, and since acetone dimethyl acetal is now commercially available these interchanges provide an excellent method of obtaining a large number of ketone acetals. A paper now in preparation will describe these interchange reactions in detail.

EXPERIMENTAL

Preparation of the catalyst and reactor. Dowex 50 was converted to the hydrogen form with $3N$ hydrochloric acid and thoroughly washed successively with distilled water and methanol. Dowex 2 was converted to the hydroxyl form with 5% sodium hydroxide solution and then washed similarly. A straight tube Pyrex condenser 90 cm. long, 19 mm. ID was mounted vertically and an 18-cm. layer of the Dowex 2 was put at the bottom followed by a 55-cm. layer of the Dowex 50. The acid resin catalyst occupied a total volume of 155 ml. of which 120 ml. was resin and 35 ml. was void volume. The temperature of the catalyst bed was controlled by passing a coolant with the desired temperature through the jacket of the condenser.

Preparation of acetone dimethyl acetal. A stock solution of methanol and acetone in a 4 to 1 mole ratio was passed over the resin bed at $-27°$ at a rate of 10 to 15 ml./min. The refractive index of the reaction solution changed from n_D^{24} 1.3380 to n_D^{24} 1.3455. After a steady state had been obtained, a 1500-ml. sample of the effluent solution was combined with 200 ml. of a 160-170° fraction of Stoddard solvent. The combined solution was washed 3 times with a 15% sodium hydroxide water solution, first with a volume

1.5 times and then twice with volumes equal to that of the reaction solution. The insoluble organic layer was dried with potassium carbonate and distilled. At 56°, 10 ml. of a ternary azeotrope consisting of 75% (vol.) acetone, 20% methanol, and 5% acetone dimethyl acetal was collected. A second 10-ml. fraction at 61–62° was a binary azeotrope consisting of 55% acetone dimethyl acetal and 45% methanol. Finally 175 ml. of acetone dimethyl acetal was collected, b.p. 80° (760 mm.) and 43° (205 mm.), d_{24} 0.835 g./ml., n_D^{25} 1.3748 (lit.[6] b.p. 78–80° (747 mm.), d_{20} 0.8448, n_D^{20} 1.3746).

Preparation of butanone dimethyl acetal. A stock solution of methanol and butanone (4 to 1 mole ratio) was passed through the reactor at $-26°$ at a rate of 5 to 10 ml./min. The refractive index of the reaction solution changed from n_D^{24} 1.3470 to n_D^{24} 1.3520. Two liters of the steady-state effluent solution was added to 200 ml. of Stoddard solvent (b.p. 160-170°) and the combined solution was washed 3 times with 15% aqueous sodium hydroxide, each time with a volume of wash solution equal to that of the organic phase. The organic portion was dried with potassium carbonate and distilled at 200 mm., giving 260 ml. of butanone and 180 ml. of butanone dimethyl acetal, b.p. 66° (200 mm.), 50° (100 mm.), n_D^{24} 1.3915, d_{24} 0.8505 (lit.[6] b.p. 48–50° (100 mm.), d_4^{28} 0.8535, n_D^{28} 1.3899).

Mixtures of methanol and butanone dimethyl acetal distill as an azeotrope which boils at 64.5°, n_D^{25} 1.3385, and is 18.5% acetal by weight.

Preparation of cyclohexanone dimethyl acetal. A solution of methanol and cyclohexanone (4 to 1 mole ratio) was passed over the resin catalyst at $-26°$ at 5 to 10 ml./min. An 800-ml. portion of the effluent was washed 3 times with 15% aqueous sodium hydroxide. The organic layer was dried with potassium carbonate and distilled, giving 168 ml. of cyclohexanone, b.p. 74° (50 mm.), and 179 ml. of cyclohexanone dimethyl acetal, b.p. 83° (50 mm.), n_D^{24} 1.4373, d_{24} 0.9484 (lit.[13] n_D^{25} 1.4372).

Other ketone acetals. The following ketone acetals were prepared in a similar manner and used as infrared standards to obtain the data in Table I.

TABLE I

EQUILIBRIUM CONVERSION OF KETONES

Ketone[a]	Alcohol[a]	Conversion, % 24°	Conversion, % −28°
Acetone	Methanol	11	32
Acetone	Ethanol	2	17
Acetone	Propanol	2	19
Acetone	Butanol	<1	17
2-Butanone	Methanol	7	24
3-Pentanone	Methanol	3	13
4-Methyl-2-pentanone	Methanol	4	9
Cyclohexanone	Methanol	46	86

[a] Mole ratio of alcohol to ketone was 4 to 1.

Acetone diethyl acetal. b.p. 45° (60 mm.), n_D^{25} 1.3851, d_{25} 0.824, (lit.[15] n_D^{25} 1.3861). This acetal forms an azeotrope (b.p. 76°, n_D^{25} 1.3660, 20% by vol. acetone diethyl acetal) with ethanol.

Acetone dipropyl acetal. b.p. 86° (83 mm.), n_D^{25} 1.3995, d_{24} 0.827, (lit.[16] b.p. 91° (95 mm.), n_D^{20} 1.4026).

Acetone dibutyl acetal. b.p. 66° (5 mm.), n_D^{26} 1.4103, d_{26} 0.831, (lit.[16] n_D^{22} 1.4084).

3-Pentanone dimethyl acetal. b.p. 59° (63 mm.), n_D^{26} 1.4013, d_{25} 0.863.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.65; H, 12.18.

(15) H. P. Crocker and R. H. Hall, *J. Chem. Soc.*, 2052 (1955).

(16) H. W. Post, *J. Am. Chem. Soc.*, 55, 4176 (1953).

4-Methyl-2-pentanone dimethyl acetal. b.p. 58° (35 mm.), n_D^{25} 1.4042, d_{26} 0.850.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 66.07; H, 12.35.

Yields. The acetone-methanol reaction system was the only case where attempts were made to account for all of the starting materials. It was possible to distill the unreacted acetone and methanol from the alkaline wash solution with recovery of more than 90% of the unreacted acetone and methanol. Therefore, for this system the conversion of acetone was 25–30% and the yield based on unrecovered acetone and methanol was consistently over 90%. No effort was made to account for all of the materials used in the other reaction systems, but it is believed that most of the unreacted materials could be recovered because no appreciable discoloration of the solutions was observed and no high boiling distillation residues or other by-products were obtained.

Effect of temperature on the reaction of ketones with alcohols. Stock solutions of 4 moles of alcohol per mole of ketone were passed slowly through the reactor at the desired temperature to ensure thorough displacement of all foreign fluids by the reaction solution. The flow was then stopped and the stock solution was kept in contact with the catalyst for a period of time. When the flow was again started, the effluent was collected in increments of 10 ml. each and the refractive index of each increment was measured. This procedure was repeated with successively longer contact times until there was no further increase in the maximum index observed in each set of effluent increments. Since the refractive index increases with conversion, the sample with the highest refractive index was taken as the one most nearly approaching equilibrium. The amount of ketone acetal present was then determined from its absorbance in the infrared. Methanol and ethanol were at equilibrium after 1 hr. in their reactions with every ketone except cyclohexanone. In the methanol-cyclohexanone system, the conversion of the cyclohexanone increased from 79% after 5 hr. to 86% after an 8-hr. contact period. Both propanol and butanol were at equilibrium in the reaction with acetone after a 5-hr. contact period. The values in Table I give the conversion of the ketones at equilibrium as determined in this manner.

An Improved Synthesis of Dichlorocarbene from Ethyl Trichloroacetate[1]

WILLIAM E. PARHAM AND EDWARD E. SCHWEIZER

The reaction of ethyl trichloroacetate(IV) with sodium methoxide (commercial), sodium ethoxide, or potassium *t*-butylate in the presence of the olefins cyclohexene and isobutylene were studied both in the presence and absence of solvent (pentane). Similar results were obtained with all bases used, and yields of 72–88% of the derived cyclopropanes resulted. This reaction affords significantly higher yields of cyclopropanes than analogous reactions in which chloroform is used as the carbene precursor.

The reaction of chloroform, potassium *t*-butylate, and olefin constitutes an excellent synthesis of certain cyclopropane derivatives.[2] The yield of cyclo-

$$HCCl_3 + RO^- \longrightarrow ROH + \overline{C}Cl_3 \longrightarrow$$
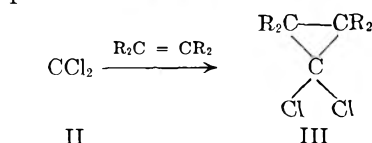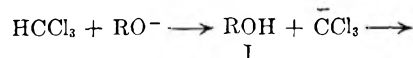
propane(III), obtained from such reactions, is generally 55–65%[2] and is unquestionably lowered by a side reaction occurring between dichlorocarbene and the alcohol (I) formed in the reaction.[2a,3] The superiority of *t*-butylate[2b] over other alkoxides in this reaction may be related, at least in part, to decreased reactivity of the more highly hindered *t*-alcohol with the derived carbene.

The formation of dichlorocarbene,[4] in the absence of alcohol, from *t*-butyl trichloroacetate (IV. R = *t*-butyl) and potassium *t*-butylate (V. R = *t*-butyl), and its further reaction with isobutylene to
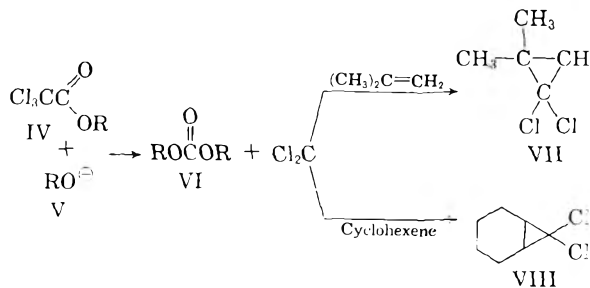
give 1,1-dichloro-2,2-dimethylcyclopropane (VII, 55% yield) suggested that the reaction of esters of

(1) This work was supported by a grant (G-7382) from the National Science Foundation.

(2) (a) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954); (b) W. von E. Doering and W. A. Henderson, Jr., *J. Am. Chem. Soc.*, **80**, 5274 (1958); (c) W. E. Parham, H. E. Reiff, and P. Swartzentruber, *J. Am. Chem. Soc.*, **78**, 1437 (1956); (d) A. P. Ter. Borg and A. F. Bickel, *Proc. Chem. Soc.*, 283 (1958); (e) S. M. McElvain and P. L. Weyna, Abstracts of Papers, 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958, p. 1P.

(3) J. Hine, E. L. Pollitzer, and H. Wagner, *J. Am. Chem. Soc.*, **75**, 5607 (1953).

(4) W. E. Parham and F. C. Loew, *J. Org. Chem.*, **23**, 1705 (1958).

TABLE I

$$RO^{\ominus} + Cl_3CCO_2R \xrightarrow{\text{olefin}}$$ VIII or VII $+ ROCOR$ (VI)
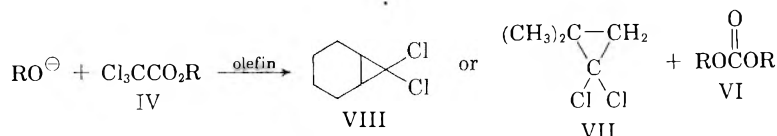
Run	Base	Moles Base	Addition Time IV in Min.	Solvent ml. Pentane	ml. Olefin	% Yield VIII[a]	% Yield VII[b]	% Yield VI[b]
1	Potassium t-butylate	0.32	96	0	250	43		
2	Potassium t-butylate	0.32	90	150	75	72		76
3	Potassium t-butylate	0.25	0.25	0	250	53[d]		
4	Potassium t-butylate	0.25	0.25	150	100	56[d]		
5	Sodium methoxide	0.25	0.25	0	250	78		
6	Sodium methoxide	0.32	0.25	0	250	79		
7	Sodium methoxide	0.32	0.25	150	75	79		
8	Sodium methoxide	0.32	0.25	150	25.4[c]	88		
9	Potassium t-butylate	0.25	72	100	75		86	89
10	Potassium t-butylate	0.32	30	125	150		74	72
11	Sodium ethoxide	0.32	120	150	150		73	69
12	Sodium ethoxide	0.32	0.25	150	150		78	86
13	Sodium ethoxide	0.25	0.25	150	150		74	93
14	Sodium ethoxide	0.25	0.25	0	250		82	94
15	Sodium methoxide	0.25	0.25	0	250		76	73

[a] Yield compound VIII by isolation. [b] Yield compound VII and VI by gas chromatography. [c] Measured as 20.54 g. (0.25 mole) of cyclohexene, 0.3 mole of ethyl trichloroacetate used. [d] Uncontrollable large exotherm experienced.

trichloroacetic acid with alkoxides may represent an improved and more convenient synthesis of dichlorocarbene and the corresponding cyclopropanes derived by further reaction of the carbene with an olefin. This has been shown to be the case. This report describes the reactions of ethyl trichloroacetate (IV) with sodium ethoxide, potassium t-butylate and with commercially available sodium methoxide. The reactions were carried out both in the presence and absence of solvent (pentane), and with the olefins isobutylene and cyclohexene. The conditions and yields of the experiments resulting in the formation of 1,1-dichloro-2,2-dimethylcyclopropane(VII), from isobutylene, and 7,7-dichlorobicyclo[4,1,0]-heptane(dichloronorcarane, VIII), from cyclohexene, are summarized in Table I.

From the table one may see that the yields of the derived cyclopropanes were quite high (generally 72–88%). It is interesting to note that the yields of 1,1-dichloro-2,2-dimethylcyclopropane(VII) were quite similar regardless of the base used (potassium t-butylate, 86%; sodium ethoxide, 82%; commercial sodium methoxide, 76%). Similar results were obtained in the preparation of 7,7-dichlorobicyclo-[4,1,0]heptane(VIII) (potassium t-butylate, 72%; commercial sodium methoxide, 79%). The maximum yield of compound VIII (88%) was obtained (run No. 8) when an excess of sodium methoxide and ethyl trichloroacetate(IV) in pentane was used. The yield was based on the olefin used.

In reactions employing sodium methoxide or sodium ethoxide, the presence of solvent or the speed of addition of the ester had little effect on the yield of the derived cyclopropanes (runs 6, 7, and 11–14). However, when potassium t-butylate was employed, yields were greatly enhanced by the presence of solvent (runs 1 and 2) and by a slower addition of the ethyl trichloroacetate (runs 2 and 4). The use of commercial sodium methoxide has a number of advantages over the use of potassium t-butylate: (1) ready availability; (2) little exotherm is evidenced due to the lessened nucleophilicity of the methoxide ion over the t-butylate ion, and/or due to the lower solubility of of the methoxide over the t-butylate in the solution.

Initial experiments[5] with t-butyl α,α-dichloropropionate(IX) have failed to yield di-t-butyl carbonate and the corresponding addition product (XI) of the carbene(X) and isobutylene.

$$CH_3-CCl_2CO_2R \ (IX) + RO^- \longrightarrow$$

$$CH_3-\overset{O}{\overset{\|}{C}}-Cl \ (X) + ROCOR \xrightarrow{(CH_3)_2C=CH_2} XI$$
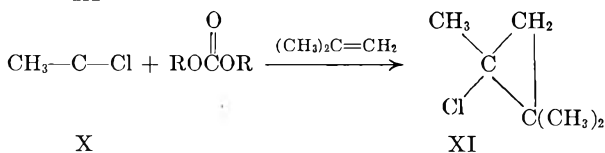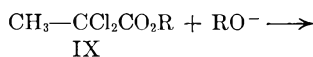
The investigation is being extended to other halo-esters and carbene acceptors.

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(5) W. E. Parham and F. C. Loew, unpublished results.
(6) Boiling points are uncorrected.
(7) Matheson Coleman and Bell Division, The Matheson Co., Inc., East Rutherford, N. J.

Analyses of products. The 1,1-dichloro-2,2-dimethyl-cyclopropane (VII) and carbonates produced were analyzed by vapor-phase chromatography using a column[8] of polyethylene glycol on diatomaceous earth with helium as the eluent. The weight per cent composition of each component was obtained by determining the ratio of the individual peak areas which were calculated from the product of the peak height and the half-band width. These areas were weighted according to the areas found for standard predetermined amounts of standard samples. The yield of 2,2-dichlorobicyclo[4,1,0]heptane(VIII) was obtained by isolation. All samples of compound VIII had boiling points ranging over a one-degree range between b.p. 78–82.5° (15–16 mm.) and refractive indices ranging between n_D^{25} 1.5001–1.5005 (reported[2a] b.p. 78–79° (15 mm.), n_D^{23} 1.5014).

Ethyl trichloroacetate(IV) was prepared from trichloroacetic acid by the Fischer method using A.R. trichloroacetic acid[9] and absolute ethanol, with concentrated sulfuric acid as catalyst. The ethyl trichloroacetate(IV) used had b.p.

50.5–51.5° (8 mm.), n_D^{25} 1.4477. (Reported[10] b.p. 58–59° (13 mm.), n_D^{20} 1.4505.)

2,2-Dichlorobicyclo[4,1,0]heptane(VIII). Ethyl trichloroacetate(IV), 47.86 g. (0.25 mole), was added (under dry N_2) all at once to a cold (2.5°) mixture of commercial sodium methoxide (17.3 g., 0.32 mole) and dry cyclohexene (250 ml.). The mixture was cooled in an ice water bath and stirred (under N_2) for a period of 8 hr. After allowing the mixture to stand overnight, water (200 ml.) was added. The layers were separated and the aqueous phase was extracted twice with two 100-ml. portions of pentane. The organic layers were combined and dried ($MgSO_4$). The dried solution was filtered and concentrated. Distillation of the residue yielded 32.6 g. (79%, based on ethyl trichloroacetate) of 2,2-dichlorobicyclo[4,1,0]heptane(VIII), b.p. 81.5–82.5° (16 mm.), n_D^{25} 1.5004 (reported[2a] b.p. 78–79° (15 mm.), n_D^{23} 1.5014).

All the reactions were run in essentially the same manner as this experiment. Reactions with isobutylene were started in a dry ice bath and once the ester IV had been introduced, the mixture was allowed to reflux (at −6°).

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(8) Perkin-Elmer Co., Norwalk, Conn. Vapor Fractometer, Model 154-C, column K.

(9) Mallinckrodt Chemical Works, St. Louis 7, Mo.

(10) M. H. Palomaa, E. J. Salmi, and R. Korte, *Ber.*, 72, 790 (1939).

Pyrolysis of Allylic Acetates

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2-Acetoxy-*trans*-3-heptene and 4-acetoxy-*trans*-2-heptene have been pyrolyzed; the former pyrolyzed satisfactorily at 350°, whereas the latter required 363° for comparable pyrolysis. Both esters produced a mixture of 1,3- and 2,4-heptadiene. The evidence showed that the esters underwent thermal isomerization, and that in this isomerization the *trans*-configuration of the carbon-carbon double bond was essentially retained. The facts can be interpreted as supporting an intramolecular mechanism for the thermal rearrangement of allylic esters.

The pyrolysis of allylic acetates has been rarely used as a method for the preparation of conjugated dienes. In one of the early examples of this reaction van Pelt and Wibaut[1] found that the pyrolysis of 4-acetoxy-2-hexene gave a 66% yield of a diene which was designated as 2,4-hexadiene. Marvel and Williams[2] successfully employed the pyrolysis of 3-acetoxy-2-alkyl-1-butenes for the preparation of 2-alkyl-1,3-butadienes. And in the same laboratory 3-cyano-1,3-butadiene was obtained[3] by the pyrolysis of 3-acetoxy-3-cyano-1-butene. More recent work has indicated that where possible the pyrolysis of allylic acetates may give rise to a mixture of conjugated dienes as products. Grummitt and co-workers[4] have shown that the pyrolysis of either 1-cyclohexyl-3-acetoxy-

butene or 1-cyclohexyl-1-acetoxy-2-butene produced as product a mixture of 1-cyclohexyl-1, 3-butadiene and 1-cyclohexylidene-2-butene. The mixture of dienes was explained by isomerization of either of the acetates to the other prior to pyrolysis.

Isomerization of the allylic ester during pyrolysis had been observed by Marvel and Brace.[3] Bailey and Barclay[5] reported isomerization of 1,4-diacetoxy-2-butene during pyrolysis, and Bailey and Goossens[6] have explained the obtention of 3-methylenecyclohexene from the pyrolysis of 1-cyclohexenylmethyl acetate by isomerization of the ester to 2-methylenecyclohexyl acetate before pyrolysis. Grummitt and Mandel[4] have shown that either of a pair of allylic acetates will undergo thermal rearrangement to the other. This type of isomerization also occurs with propargylic acetates, for the Landors[7] have reported the rearrangement

(1) A. J. van Pelt, Jr., and J. P. Wibaut, *Rec. trav. chim.*, 60, 55 (1941).

(2) C. S. Marvel and J. L. R. Williams, *J. Am. Chem. Soc.*, 70, 3842 (1948).

(3) C. S. Marvel and N. O. Brace, *J. Am. Chem. Soc.*, 70, 1775 (1948).

(4) O. Grummitt and J. Splitter, *J. Am. Chem. Soc.*, 74, 3924 (1952); O. Grummitt and Z. Mandel, *J. Am. Chem. Soc.*, 78, 1054 (1956).

(5) W. J. Bailey and R. Barclay, Jr., *J. Org. Chem.*, 21, 328 (1956).

(6) W. J. Bailey and J. C. Goossens, *J. Am. Chem. Soc.*, 78, 2804 (1956).

(7) P. D. Landor and S. R. Landor, *J. Chem. Soc.*, 1015 (1956).

of propargylic acetates on pyrolysis to an allenic system. The ease with which this isomerization occurs does not appear to have been always properly appreciated, and proper precaution should be observed in the esterification of allylic alcohols. Heilbron et al.[8] found that 3-acetoxy-1,4-hexadiene when warmed to 100° in acetic anhydride isomerized to 5-acetoxy-1,3-hexadiene. Burton[9] reported another allylic ester which isomerized when heated with acetic anhydride.

In the present work 2-acetoxy-trans-3-heptene and 4-acetoxy-trans-2-heptene were pyrolyzed. The 2-acetoxy compound pyrolyzed satisfactorily (about 50% pyrolysis) at 350°, but to achieve comparable pyrolysis with the 4-acetoxy compound a temperature of 363° was required. Under the experimental conditions employed the ester had a contact time of 3.8 sec. In each case diene was obtained in about an 80% yield, and this diene proved to be a mixture of 1,3- and 2,4-heptadiene. The 2-acetoxy compound gave a 36% yield of the 1,3-diene and a 32% yield of the 2,4-diene, whereas from the 4-acetoxy compound a 44% yield of the 2,4-diene and a 30% yield of the 1,3-diene were obtained. The two dienes could not have been formed by isomerization of one to the other, for when the 2,4-diene was subjected to the pyrolysis conditions used for the esters the diene underwent almost no isomerization to the 1,3-diene. The 1,3-diene when pyrolyzed did isomerize to the 2,4-diene, but the isomerization was not extensive enough to account for the yield of 2,4-diene obtained from the 2-acetoxy compound. Moreover, the 1,3-diene on pyrolysis gave no trans, trans-2,4-heptadiene, and this geometric isomer constituted about half of the 2,4-diene obtained by ester pyrolysis. The obtention of the mixture of dienes can only be explained by some of the ester's isomerizing before pyrolysis.

That these allylic esters did isomerize under the pyrolysis conditions was shown by examination of the unpyrolyzed ester recovered from the pyrolysis condensate. The 2-acetoxy and 4-acetoxy compounds had the same boiling point, the same refractive index, and the same retention time in gas chromatography. The infrared absorption of the two esters were somewhat different, and this enabled one to determine the approximate composition of a mixture of the esters. In this way the ester recovered from the pyrolyzate of each ester was found to contain 60±5% of the 2-acetoxy compound and 40±5% of the 4-acetoxy compound.

From the yields of crystalline maleic anhydride adducts the 1,3-diene obtained from either ester was found to be predominantly the trans-isomer, and the 2,4-diene in each case was about 50% of the

trans, trans-configuration. One might expect that the loss of acetic acid from the 4-acetoxy-trans-2-heptene would give rise to approximately equal amounts of the trans, trans- and trans, cis-isomers. The above-mentioned facts indicated that in the rearrangement of the trans-allylic esters the trans-configuration of the double bond was essentially retained. This conclusion is strengthened by the gas chromatographic analysis of the ester recovered from the pyrolysis of the 4-acetoxy compound. The esters when initially prepared were found to contain on gas chromatography 96–97% of a component of retention time 7.83 minutes and 1.42–2.3% of a component of retention time 6.54 minutes. Because of the proximity of the 6.54-component to the main component and the marked differences between these retention times and those of the other minor constituents, the 6.54-component was believed to be the cis-ester. Careful distillation of the recovered ester gave fractions that were essentially constant boiling and essentially of constant refractive index. Gas chromatography of the combined fractions showed the recovered ester to be 83% of the 7.83-component and 15% of the 6.54-component. If the 6.54-component were a compound not closely related to the trans-esters, one would expect that the component in a mixture containing 15% of it could have been detected during the distillation. The above facts would support the essential retention of configuration of a trans-double bond during thermal isomerization of an allylic acetate.

The retention of optical activity during the thermal rearrangement of allylic systems[10] has been the prime evidence for the proponents of an intramolecular, essentially non ionic mechanism for this rearrangement. More recent evidence[11] has given support to this viewpoint. When this intramolecular conception is applied to the thermal isomerization of allylic esters, the intermediate complex is one where the carbonyl oxygen atom approaches within bond forming distance of the α-carbon atom of the allylic system. In an allylic acetate system the molecule may assume a conformation where the carbonyl oxygen atom approaches the α-carbon atom from one side, or it may assume a conformation where the approach is to the opposite side of the α-carbon atom. In the one case the hydrogen atoms on the α-and β-carbon atoms of the allylic system are cis (cis-conformation), whereas in the other these hydrogen atoms are trans (trans-conformation). In the cis-conformation there is considerable interaction of the alkyl group on the α-carbon atom and the hydrogen atom on the α-carbon atom. This is not the case in the trans-conformation. This interaction

(8) I. M. Heilbron, E. R. H. Jones, J. T. McCombie, and B. C. L. Weedon, J. Chem. Soc., 147, 88 (1945).
(9) II. Burton, J. Chem. Soc., 130, 1650 (1928).

(10) M. P. Balfe and J. Kenyon, Trans. Faraday Soc., 37, 721 (1941).
(11) E. A. Braude, D. W. Turner, and E. S. Waight, J. Chem. Soc., 2396 (1958); E. A. Braude and D. W. Turner, J. Chem. Soc., 2404 (1958).

in the *cis*-conformation is true with both esters. The models would indicate that the *trans*-conformation is the preferred one when the ester undergoes isomerization. This explains the fact that the *trans*-configuration of the double bond was essentially retained when the allylic acetates underwent thermal isomerization, and this fact can be interpreted as supporting the concept of an intramolecular mechanism for this rearrangement.

EXPERIMENTAL

Chemicals. Methyl iodide (Matheson, Coleman and Bell) was distilled through an 18-plate, Fenske column, and the material of b.p. 43°/758 mm. collected.

n-Propyl chloride (Matheson, Coleman and Bell)was distilled as was the methyl iodide, and the material of b.p. 47°/761 mm. collected.

Crotonaldehyde (Matheson, Coleman and Bell) was distilled under nitrogen through the Fenske column, and the material of b.p. 103–104°/756 mm. collected. The aldehyde was used immediately after distilling. Crotonaldehyde has the *trans*-configuration at its double bond.[12]

trans-2-Hexenal was prepared from 1,1,3-triethoxyhexane[13] by the method of Hoaglin and Hirsh.[14] The aldehyde was distilled from a Claisen flask having a distilling arm (25 mm. O.D. × 245 mm.) packed with $1/8$ inch glass helices. The material collected (235 g., 73% yield) had b.p. 29–30°/7 mm., n_D^{25} 1.4433. This should be the *trans*-isomer.[15] The infrared absorption (very strong absorption at 10.3 μ and little absorption in the 12–14 μ range) of the material was in keeping with the assignment of the *trans*-configuration to the double bond.[16] In the ultraviolet the material had $\lambda_{\text{isooctane}}^{\text{max.}}$ 215 mμ, ϵ 17,300.

trans-Hept-2-en-4-ol was prepared by the interaction of crotonaldehyde and *n*-propyl Grignard reagent, hydrolysis of the reaction mixture with aqueous ammonium chloride and distillation of the crude material from the modified Claisen flask. The product (265 g., 78% yield) had b.p. 58–59°/11 mm., n_D^{25} 1.4348.

trans-Hept-3-en-2-ol was prepared from *trans*-2-hexenal and methyl Grignard reagent by the procedure outlined for the preceding alcohol. The material (259 g., 95% yield) had b.p. 63–64°/14 mm., n_D^{25} 1.4346. The infrared absorption of the compound (very strong band at 10.35 μ and little absorption in the 12–14 μ region) was consistent with the assignment of the trans-configuration.[16]

4-Acetoxy-trans-2-heptene was obtained from the alcohol by the esterification procedure of Heilbron *et al.*,[8] which does not effect rearrangement of the molecule. The ester was distilled from the modified Claisen flask, and the ten fractions (190 g., 91% yield) collected as product distilled at 63.5–64.0°/11 mm.; all fractions had n_D^{25} 1.4226. The infrared curve (strong absorption at 10.35 μ and little

(12) W. G. Young, *J. Am. Chem. Soc.*, **54**, 2498 (1932).

(13) We are indebted to the Carbide and Carbon Chemicals Company for this chemical.

(14) R. I. Hoaglin and D. H. Hirsh, *J. Am. Chem. Soc.*, **71**, 3468 (1949).

(15) M. Jacobson, *J. Am. Chem. Soc.*, **78**, 5084 (1956). A private communication from Dr. Jacobson stated that the 2-hexenal supplied by Carbide and Carbon Chemicals Company was identical with the aldehyde obtained by converting the carboxyl group of *trans*-2-hexenoic acid (prepared from *n*-butyraldehyde and malonic acid by a Doebner reaction which gives rise to a *trans*-configuration at the double bond) to an aldehyde group.

(16) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, J. Wiley and Sons, Inc., New York, 1958, pp. 45–48.

absorption in the 12–14 μ region) again indicated the material to be of the *trans*-configuration and the essential absence of the *cis*-isomer. Gas chromatography (polyethylene glycol 400 column) of the ester showed it to be 96.7% of a component of retention time 7.83 minutes (minutes from air peak), 1.4% of a component of retention time 6.54 minutes and four other components each present to the extent of less than 1%. The 7.83-component must be the *trans*-ester. Because of the nearness of its retention time to that of the main component and the wide difference between the retention times of the four minor components and the other two components, the 6.54-component was believed to be a small amount of the *cis*-ester.

2-Acetoxy-trans-3-heptene was prepared from the corresponding alcohol by the procedure[8] indicated above. Nine fractions of ester (318 g., 90% yield) were obtained at b.p. 68.0–68.5°/14 mm.; each fraction had n_D^{25} 1.4226. The infrared curve of this ester was quite similar to that of the 4-acetoxy-*trans*-2-heptene, but there were definite differences. Strong absorption at 10.35 μ and little absorption in the 12–14 μ region substantiated the *trans* assignment. Gas chromatography of the ester indicated it to be 96.4% of a component of retention time 7.83 minutes, 2.3% of a component of retention time 6.54 minutes, and two other components of very short retention times each present to the extent of less than 1%. The 7.83- and 6.54-component were believed to be the *trans*- and *cis*-ester, respectively.

1,3-Heptadiene. The diene from various preparations[17] was combined and distilled through a Nester spinning band column (7 mm. I.D. × 600 mm.). The fractions of b.p. 66.0–66.2°/235 mm., n_D^{25} 1.4428–1.4433 were accepted as the diene. The infrared curve of this material had very strong absorption at 10.0 and 11.17 μ, strong absorption at 10.53 μ and little absorption in the 12–14 μ region. Gas chromatography (Apiezon L and tricresyl phosphate columns) showed the material to be 99.0% of a component of relative retention time 0.52 (relative to *n*-octane). Preparation (one hour reflux of reactants in benzene) of a maleic anhydride adduct of the diene gave a 62% yield (one crystallization, 81% crude yield) of derivative, m.p. 71.8–72.3°. The infrared data and the yield of adduct indicated[16,18] that the diene was primarily the *trans*-isomer.

2,4-Heptadiene. Various samples of the diene[17] were combined and distilled through the spinning-band column. The fraction of b.p. 60.0–60.2°/140 mm., n_D^{25} 1.4543–1.4549 were accepted as the diene. Gas chromatography (Apiezon L) showed the material to be 100% of a component of relative retention time 0.70. The tricresyl phosphate column indicated two components (91.3% of one and 8.7% of another). The diene gave a 26% yield (one crystallization, 46% crude yield) of maleic anhydride adduct, m.p. 72.2–73.0°. The infrared curve of the material was a good check with that reported earlier,[17] and there was a peak at 13.1 μ which was indicative of a *cis*-configuration.[16] The isomer of *trans-trans* configuration of a conjugated diene is the one which should give[19] the maleic anhydride adduct readily, and the data would indicate that this diene was not particularly rich in this isomer.

Preliminary pyrolysis experiments. The apparatus was essentially that described by Bailey *et al.*,[20] except that a wet test meter was attached to the Dry Ice-cooled condenser. Dry, oxygen-free nitrogen was passed through the apparatus at different rates in different experiments and a rate of 18.5 l./hr. selected as the desirable one. This rate of nitrogen flow was used in all pyrolyses reported and gave a

(17) F. L. Greenwood and J. A. Sedlak, *J. Org. Chem.*, **22**, 776 (1957).

(18) D. Craig, *J. Am. Chem. Soc.*, **72**, 1678 (1950).

(19) *Cf.* ref. 15 and refs. cited therein.

(20) W. J. Bailey, J. Rosenberg, and L. J. Young, *J. Am. Chem. Soc.*, **76**, 2251 (1954).

contact time[21] of 3.8 sec. for the ester in the pyrolysis tube. The top of the helices had to be sufficiently far inside the furnace so that they were hot enough to vaporize the ester (b.p. 173°/762 mm.) immediately. Otherwise, polymeric material formed at the top of the helices. In these experiments 10.0 g. of ester was pyrolyzed, and the percent of pyrolysis calculated from the acetic acid formed. Table I gives the results of these experiments.

TABLE I

Ester Pyrolyzed	Temp., °C.	Addition Rate of Ester, g./min.	Percent Pyrolysis
2-Acetoxy-3-heptene	350	0.34	56
	350	0.64	44
	375	0.80	72
4-Acetoxy-2-heptene	350	0.35	28
	363	0.34	52
	363	0.67	46
	375	0.34	73

The interesting finding in these experiments was the rather small increase in temperature necessary to obtain pyrolysis of the 4-acetoxy compound comparable to that obtained with the 2-acetoxy compound at 350°.

From these experiments it was decided to use an addition rate of 0.34 g./min. for the ester. When larger quantities of ester were pyrolyzed, it was found that the degree of pyrolysis was somewhat less than indicated in Table I.

Pyrolysis of 2-acetoxy-trans-3-heptene. A trap containing 130 ml. of 1N sodium hydroxide was placed between the Dry Ice-cooled trap and the wet test meter. The furnace was maintained at 350° during the pyrolysis of 93.7 g. (0.600 mole) of ester which was added at the rate of 0.34 g./min. As the helices were just slightly discolored after the pyrolysis, very little carbonization had occurred.

At the conclusion of the pyrolysis carbonate was determined in the sodium hydroxide solution by precipitating and weighing as barium carbonate. After correcting for a blank (0.13 mmole), barium carbonate equivalent to 2.22 mmoles of carbon dioxide was found. This small amount of carbon dioxide was evidence against the formation of any appreciable amount of acetate radical during the pyrolysis.

The condensate from the pyrolysis was diluted with pentane, and this solution (260 ml.) was extracted with six 75 ml. portions of water. The combined aqueous extracts were made to volume in a 500 ml. volumetric flask, and titration of aliquots with standard base indicated the formation of 276 ml. of acetic acid during the pyrolysis. From this value, the ester was pyrolyzed to the extent of 46%.

The organic materials were always kept under a nitrogen atmosphere and some hydroquinone was present in the liquid. After drying over freshly heated sodium sulfate, the pentane was removed from the pentane solution through the Fenske column. The distillation was discontinued when the pot temperature reached 80°. The residue was distilled through the spinning-band column. The diene and unpyrolyzed ester were rather rapidly separated by gradually lowering the pressure in the system and slowly increasing the temperature of the distilling flask. This process was discontinued when the pressure had been lowered to 11 mm. and the bath temperature of the distilling flask raised to 76°. The more volatile material was collected in Dry Ice-cooled traps. This material was then stored in the refrigerator.

The unpyrolyzed ester was distilled through the spinning-band column and eighteen fractions (total wt. 46.88 g.)

(21) C. D. Hurd and H. T. Bollman, *J. Am. Chem. Soc.*, 55, 699 (1933).

were collected over the boiling range 61.2–62.0°/12 mm. Each fraction had n_D^{25} 1.4225 or 1.4226. This ester represents 93% of the possible recoverable ester.

Infrared analysis proved this recovered ester to contain both the 4-acetoxy and 2-acetoxy compounds. The infrared curves of the two esters were quite similar. However, the 2-acetoxy compound had peaks at 9.6 and 11.9 μ which were not present in the absorption curve of the 4-acetoxy compound, and the latter had peaks at 9.8 and 12.1 μ which were not present in the curve of the 2-acetoxy compound. The 9.6 and 9.8 μ peaks overlapped too much to be useful for quantitative analysis; the overlap of the 11.9 and 12.1 μ peaks was such that these could be used for an approximate analysis. Determination of the infrared absorption in the 11–13 μ region of a series of known mixtures of the two esters indicated that one could determine the composition of a mixture of the esters with an error of about ±5%. The above-mentioned ester fractions were combined, and infrared analysis of this mixture indicated it to be 60 ± 5% of the 2-acetoxy compound and 40 ± 5% of the 4-acetoxy compound. Clearly, both esters were present in the recovered ester, and this indicated that the ester which did not pyrolyze did undergo rearrangement.

The pentane was removed from the pentane-diene solution through the spinning-band column, and the diene then carefully fractioned. The total distillate collected (19.82 g.) represented a 75% yield of diene (based on the ester actually pyrolyzed). Of the diene 9.66 g. (36% yield, ten fractions, b.p. 53.0–54.5°/152 mm., n_D^{25} 1.4410–1.4425) was accepted as 1,3-heptadiene, and 8.39 g. (32% yield, five fractions, b.p. 61.4–62.4°/152 mm., n_D^{25} 1.4531–1.4540) was accepted as 2,4-heptadiene.

The material accepted as the 1,3-diene gave a 78% yield (after one crystallization, 94% crude yield) of maleic anhydride adduct, m.p. 72.2–72.8° (no m.p. depression when mixed with an authentic sample). The infrared absorption of this diene was an excellent match with that of the 1,3-heptadiene reported under *Chemicals.* Gas chromatography proved the material to be 98.4% of a component of relative retention time 0.53. The data indicated that this diene was principally *trans*-1,3-heptadiene.

The material accepted as the 2,4-diene gave a 48% yield (after one crystallization, 61% crude yield) of maleic anhydride adduct, m.p. 72.8–73.3° (no depression with authentic sample). The infrared absorption of this diene checked well with that of the 2,4-diene reported under *Chemicals.* Gas chromatography showed the material to be 99.7% of a component of relative retention time 0.72. These data indicated that this 2,4-diene was approximately 50% *trans,trans*-isomer.

Pyrolysis of 4-acetoxy-trans-2-heptene. The pyrolysis and work-up procedure were the same as those described for the preceding ester, except that the furnace was kept at 370°. At the conclusion of the pyrolysis the helices in the pyrolysis tube were only slightly discolored. The ester (132.5 g., 0.848 mole) on pyrolysis liberated 468 me. of acetic acid, which indicated pyrolysis to the extent of 55%. The barium carbonate obtained from the trap containing the alkali solution showed the formation of 0.21 mmole of carbon dioxide.

Distillation of the unpyrolyzed ester gave 54.57 g. of ester, b.p. 64.0–65.7°/13 mm., n_D^{25} 1.4223–1.4226 (21 fractions). This ester corresponded to 92% of the possible recoverable ester. In the infrared curves of various fractions the 10.37 μ band (*trans* double bond) was not as strong in the first few fractions as it was in later fractions, and the 13.7 μ band (*cis* double bond) was fairly strong (42% transmission; 2% transmission at strongest band of the curve) in the early fractions and diminished in later fractions. These infrared spectra indicated that the *cis*-ester tended to concentrate in the early ester fractions. Infrared analysis of the combined ester fractions showed it to be 60 ± 5% of the 2-acetoxy compound and 40 ± 5% of the 4-acetoxy compound. Gas chromatography of the combined ester fractions showed it to be 83.1% of a component of retention

time 7.83 minutes and 15.4% of a component of retention time 6.54 minutes. These data indicated that the unpyrolyzed ester was a mixture of the two structural isomers, and that the *trans*-esters predominated.

The total diene distillate (36.01 g.) calculated to an 80% yield. The material (13.67 g., 30% yield) accepted as 1,3-heptadiene had b.p. 54.2–54.7°/152 mm., n_D^{25} 1.4422–1.4426 (12 fractions), and the fractions (19.94 g., 44% yield) accepted as 2,4-diene had b.p. 61.9–62.5°/153 mm., n_D^{25} 1.4534–1.4542 (11 fractions).

The 1,3-diene gave a 73% yield (after one crystallization, 87% crude yield) of maleic anhydride adduct, m.p. 72.2–73.0° (no depression with an authentic sample). The infrared curve matched well with that of the 1,3-diene reported under *Chemicals*, and gas chromatography showed the material to be 98.9% of a component of relative retention time 0.53. These data proved the diene to be primarily the *trans*-1,3-heptadiene.

The 2,4-diene on gas chromatography was shown to be 100% of a component of relative retention time 0.69. The infrared absorption agreed well with that of the 2,4-diene reported under *Chemicals*. The material gave a 54% yield (after one crystallization, 65% crude yield) of maleic anhydride adduct, m.p. 72.8–73.2° (no depression with an authentic sample). These data indicated that the diene must be approximately 50% *trans,trans*-2,4-heptadiene.

Pyrolysis of 1,3-heptadiene. The apparatus and conditions for this experiment were the same as those used for the ester pyrolyses. The furnace was kept at 363°. There was no discoloration of the helices at the conclusion of the pyrolysis. After pyrolysis of the diene (20.97 g., *cf. Chemicals*) the condensate was rinsed with pentane into a flask and distilled through a spinning-band column. After removal of the pentane, fractions totalling 18.19 g. (87% recovery of the diene pyrolyzed) were collected. Of this material 13.55 g. (nine fractions, b.p. 65.4–66.5°/233 mm., n_D^{25} 1.4413–1.4429) was accepted as 1,3-heptadiene, and 2.69 g. (five fractions, b.p. 68.5–69.1°/194 mm., n_D^{25} 1.4563–1.4567) was accepted as 2,4-heptadiene. The absence of residue in the distilling flask indicated the absence of polymerization of the diene during the pyrolysis.

The material accepted as the 1,3-diene had an infrared curve which checked well with that of the starting diene. Gas chromatography showed the material to be 97.4% of a component of relative retention time 0.51 and 2.3% of a component of relative retention time 0.72. The material gave a 77% yield (after one crystallization, 97% crude yield) of maleic anhydride adduct, m.p. 71.8–72.4° (no depression with an authentic sample). These data proved this recovered diene to be predominately *trans*-1,3-heptadiene.

The material accepted as the 2,4-diene on gas chromatography was found to be 99.7% of a component of relative retention time 0.71 and 0.3% of a component of relative retention time 0.52. The material gave no Diels-Alder adduct with maleic anhydride. In the ultraviolet it had λ_{max}^{EtOH} 230.5 mμ, ϵ 22,200. The infrared absorption agreed well with that of the 2,4-diene (*cf. Chemicals*). These data indicated the material to be 2,4-heptadiene and the absence of the *trans-trans* isomer.

The above data showed that under the conditions of pyrolysis of the ester the 1,3-diene (mostly *trans*) did isomerize to the 2,4-diene, but it did not isomerize to any significant extent and it did not isomerize to form any *trans,trans*-2,4-diene.

Pyrolysis of 2,4-heptadiene. The diene (16.07 g., *cf. Chemicals*) was pyrolyzed as described above for the 1,3-diene. The helices were not discolored after the pyrolysis. Distillation of the condensate gave 11.86 g. of material (74% recovery of the material pyrolyzed). The absence of residue in the distilling flask indicated the absence of polymerization of the diene during the pyrolysis. The first fraction (0.45 g.) had n_D^{25} 1.4403, and the remainder of the distillate (11 fractions) had b.p. 57.6–59.3°/134 mm., n_D^{25} 1.4531–1.4556. Gas chromatography of the first fraction showed it to be 40.1% of a component of relative retention time 0.52, 48.5% of a component of relative retention time 0.68 and 11.4% of various components of relative retention time 0.03–0.43. The infrared curve of this material had strong bands at 10.15 and 11.10 μ, which were indicative of a terminal methylene group. The remainder of the distillate proved to be the 2,4-diene. Gas chromatography showed it to be 99% of a component of relative retention time 0.69. It gave a 31% yield (first crystallization, 49% crude yield) of maleic anhydride adduct, m.p. 71.6–72.4° (no depression with an authentic sample), and the infrared spectrum was identical with that of the starting material.

These data showed that the 2,4-diene on pyrolysis isomerized to the 1,3-diene to a very slight extent.

Reactions with Diazoalkanes. VII. Action of Diazomethane on o-Hydroxychalkones

AHMED MUSTAFA AND ABDALLAH M. FLEIFEL

Phenolic hydroxyl groups ortho to a carbonyl group frequently exhibit abnormal behavior which is ascribed to intramolecular hydrogen bonding. Failure to react with diazomethane under normal conditions is a well known example. This is of diagnostic value in establishing the structure of hydroxy-anthraquinones, -flavones, -xanthones, and o-hydroxyanils.[1-7]

The generally accepted reason[8,9] for the stability of ortho phenolic hydroxyl groups and related substances toward diazomethane is the formation of a chelate ring system, *e.g.*, I in the case of o-hydroxyacetophenone.[3]

I
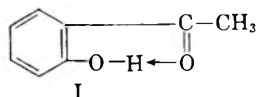
We now have examined the behavior of a number of o-hydroxy-substituted chalkones having the phenolic hydroxyl group ortho to the carbonyl group (IIa–i) toward the action of ethereal diazomethane solution.
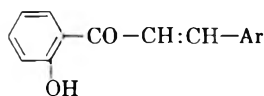
IIa. Ar = C_6H_5
b. Ar = C_6H_4—$CH_3(p)$
c. Ar = C_6H_4—$OCH_3(o)$
d. Ar = C_6H_4—$OCH_3(p)$
e. Ar = C_6H_4—$N(CH_3)_2(p)$
f. Ar = C_6H_3:O_2:CH_2 (3:4)
g. Ar = $C_6H_3(OCH_3)_2$ (3:4)
h. Ar = C_6H_4—Cl (o)
i. Ar = $C_6H_3(OH)(Cl)$ (2:5)

The reactivity of the α, β-unsaturated bond in α, β-unsaturated esters and ketones (*cf.* benzalacetophenone) toward the action of diazomethane to give pyrazoline derivatives (*cf.* Scheme A) has been thoroughly investigated.[10-15]

$$C_6H_5CH = CH - COC_6H_5 + CH_2N_2 \longrightarrow$$

Scheme A

The phenolic hydroxyl groups of (IIa–i) have failed to react with diazomethane under normal conditions, even after prolonged contact. At low temperature no methylation occurred, thus showing the abnormal behavior of such groups ortho to a carbonyl group which is ascribed to chelation.

III
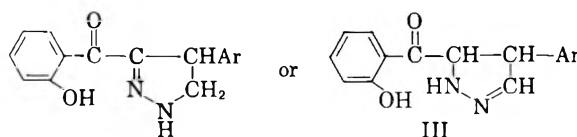
The analytical results are concordant with the values corresponding to addition of one molecule of diazomethane. Treatment of (IIa–i) with ethereal diazomethane in presence of methanol does not effect methylation of the hydroxyl group ortho to the carbonyl group.[16]

On the other hand, treatment of (IIi) with ethereal diazomethane under normal conditions effects the methylation of the hydroxyl group not in an ortho position to the carbonyl group, as well as addition to the α, β-unsaturated bond to form the pyrazoline derivative [IIIi, Ar = C_6H_3-$(OCH_3)Cl(2:5)$]. The latter gives color reaction with ferric chloride, showing the presence of a free phenolic hydroxyl group, most probably that ortho to the carbonyl group.

The pyrazoline derivatives are assigned the structure (III), in favor of which is the fact that

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(16) *Cf.* the finding that methylation of a number of o-hydroxyketones could be rendered possible with ethereal diazomethane in presence of methanol.[2,3,5]

TABLE I

Δ²-Pyrazoline Derivatives

Starting Material	Product	Solvent[a]	M.p., °C	Yield, %	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found
IIa	IIIa	A	188–189	68	$C_{16}H_{14}N_2O_2$	71.09	71.90	5.46	5.37	10.94	10.72		
IIb	IIIb	B	162–163	85	$C_{17}H_{16}N_2O_2$	72.85	72.72	5.71	5.95	10.0	9.85		
IIc	IIIc[b]		130	65	$C_{17}H_{16}N_2O_3$	68.91	68.85	5.40	5.33	9.45	9.51		
IId	IIId	C	176–177	71	$C_{17}H_{16}N_2O_3$	68.91	68.69	5.40	5.41	9.45	9.50		
IIe	IIIe	D	157–158	69	$C_{16}H_{13}N_2O_2Cl$							11.81	11.65
IIf	IIIf	D	172–173	78	$C_{18}H_{19}N_3O_2$	69.90	69.13	6.14	6.40	13.59	13.32		
IIg	IIIg	E	146–147	70	$C_{17}H_{14}N_2O_4$	65.80	66.04	4.51	4.65	9.03	8.89		
IIh	IIIh	D	65–66	70	$C_{18}H_{18}N_2O_4$	66.25	66.24	5.52	5.60	8.58	8.30		
IIi	IIIi[b]	D	80	70	$C_{17}H_{15}N_2O_3Cl$	61.71	61.21	4.53	4.60	8.47	8.68	10.74	10.45

IIa, W. Feuerstein and St. V. Kostanecki, *Ber.*, **31**, 715 (1898); IIc, J. Tambor and Hans Gulber, *Chem. Zentr.*, I, 737 (1919); IId, F. Herstein and St. V. Kostanecki, *Ber.*, **32**, 318 (1899); IIe, H. Nageli and J. Tambor, *Chem. Zentr.*, I, 2366 (1924); IIf and IIg, H. Ozawa, T. Okuda, M. Kawanishi, and K. Fujji, *J. Pharm. Soc. Japan*, **71**, 1178 (1951); *cf. Chem. Abstr.*, 6124 (1952); IIh, A. Rothlishberger, C, I, 2226 (1925).

IIb and IIi were prepared as follows: A solution of one mole of o-hydroxyacetophenone and one mole of the aldehyde (p-tolualdehyde or 2-hydroxy-5-chlorobenzaldehyde) in ethanol was treated with 50% sodium hydroxide solution. The reaction mixture was heated 1 hr. (50° bath temperature). It was left for 48 hr. and the sodium salt that separated was acidified with dilute hydrochloric acid, and crystallized.

IIb (90%) crystallized from ethanol as yellow crystals, m.p. 71°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.67; H, 5.88. Found: C, 80.09; H, 5.74.

IIi (85%) was crystallized from benzene in shining plates, m.p. 198–199°.

Anal. Calcd. for $C_{15}H_{11}O_3Cl$: C, 65.57; H, 4.00; Cl, 12.93. Found: C, 65.61; H, 3.98; Cl, 12.91.

[a] A = ethanol; B = dilute ethanol; C = methanol; D = benzene–light petroleum (b.p. 50–70°); E = benzene.

Active hydrogen of IIIa: Calcd. for one active hydrogen, 25%; for two active hydrogens, 50%. Found: 33%. This value may correspond to a free active hydrogen atom and a bonding hydrogen atom.

[b] Recrystallization of the crystalline reaction product gave yellow oil from which no crystalline material could be separated.

Δ¹-pyrazolines rearrange very readily to give Δ²-pyrazolines (*cf.* the ready rearrangement Δ¹-3,4-dibenzoylpyrazoline and Δ-¹3-aceto-4 phenylpyrazoline). Such rearrangements have been occasionally reported and are even effected by repeated crystallization or even by effect of glassware.[13–15] When pyrolyzed, the Δ²-pyrazolines (IIIa and IIId) give largely dark tars from which we have not succeeded to isolate crystalline products. The Δ²-pyrazolines were stable in air, and could be stored for several months without decomposition. When (IIIb) was allowed to react with phenyl isocyanate, no reaction could be reported under the given experimental conditions, and the starting material was recovered almost completely. The decomposition of the pyrazolines is under further investigation.

EXPERIMENTAL

Action of diazomethane on the chalkones (IIa–i). A solution of 1 g. of each of (IIa–i) in ether (*ca.* 50 ml.) or benzene-ether mixture was treated with ethereal diazomethane solution (from 5 g. of nitrosomethylurea). The reaction mixture was kept at 0° for 48 hr., during which fresh amounts of diazomethane were added. The reaction products were washed with cold light petroleum (b.p. 40–60°) several times and crystallized. The pyrazoline derivatives (IIIa–i) are yellow crystals which dissolve in aqueous sodium hydroxide solution; their alcoholic solutions give violet color with alcoholic ferric chloride and red color with cold concentrated sulfuric acid. The products are listed in the following table:

Action of diazomethane in presence of methanol on chalkones. The previous experiments were repeated on (IIa–i) and in each case 5 ml. of methanol were added. Similar are obtained as mentioned above.

Action of phenyl isocyanate on IIIb. One gram of the pyrazoline was heated with 0.85 g. of phenyl isocyanate on the steam bath for 3 hr. Methanol (30 ml.) was added to destroy excess phenyl isocyanate, the yellow solution was diluted with water, and the precipitate obtained proved to be unchanged pyrazoline (m.p. and mixed m.p.).

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A Study of the Physical and Chemical Properties of the Esters of Indophenols
I. Preparation

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A series of indophenol esters has been prepared. Methods are given for the acylation of unsymmetrically substituted indophenols. Acyl anhydride alone yields 2,6 dihalo indophenyl esters whereas acyl anhydride and pyridine yields predominately the 3',5' dihalo esters. Ultraviolet, visible, and infrared spectra of the esters are reported along with the pKa values of the free indophenols.

Indophenols have been extensively employed for many years as redox indicators[1] as in the determination of ascorbic acid,[2] and the detection of bacteriological contamination in foodstuffs.[3] Early attempts to use the indophenols as dyestuffs in color photography[4] were unsuccessful because of the instability and high water solubility of the colored indophenolate ion. The conversion of phenols to indophenols is the basis for an extremely sensitive method for the quantitative determination of phenolic compounds.[5,6]

The authors[7] have recently introduced the use of esters of this series of compounds as chromogenic substrates for the estimation of acetylcholinesterase activity. Moreover, Nachlas *et al.*[8] have attempted to employ these substances in the histochemical localization of esteratic enzymes.

Indophenols have been prepared by a variety of procedures. However, as reported by Gibbs, Hall, and Clark,[1] the method of Hirsch[9] or some modification thereof yields the best results. This method is essentially the coupling of the appropriate N-chloro quinoneimine with a phenol under alkaline conditions. While previous workers[1,10] encountered difficulties in obtaining pure indophenol salts, we found that esters could be readily made following a modification of the method of Heller[11] and purified from suitable solvents yielding yellow to red crystalline solids with characteristic physical properties.

A series of esters of the indophenols was prepared in an endeavor to study the effect of structure on the enzymatic activity of various esterases with particular attention to acetylcholinesterase and serum cholinesterase. The results of these studies will be published elsewhere. Tables I–III list the indophenol esters that have been prepared. The physical constants of these compounds are presented in Table IV.

Other than the N(4'-acetoxy phenyl)-p-quinoneimine (IPA) reported by Heller,[11] no other esters of the indophenols have been recorded in the literature. However, Meyer and Elbers[12] did prepare the benzoate of the indophenol-N-oxide.
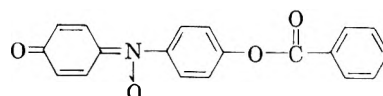
We are likewise preparing a variety of esters in the indophenol-N-oxide series and the results of these investigations will be published at a later date.

As there is a possibility for acylation to occur on either oxygen of the unsymmetrically substituted mesomeric ionic salt, two possible isomeric esters can be prepared. In the case of dichloroindophenol acetate, these are I and II. These compounds were actually prepared and identified, one being red and
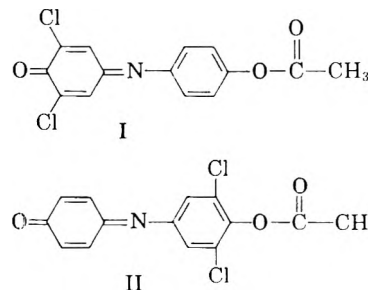
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TABLE I. ANALYTICAL DATA, INDOPHENYL ESTERS

Structure: indophenyl ester (positions 2,3,5,6 and 2',3',5',6') with O–O–C(=O)–R group.

| Compound | Substituent | | | | | | | R | Molecular Formula | Calculated | | | | Found | | | |
	2	3	5	6	2'	3'	5'	R		C	H	N	Halogen	C	H	N	Halogen
1								CH₃	C₁₄H₁₁NO₃	69.7	4.6	5.8	…	69.6	5.2	5.7	…
2	CH₃							CH₃	C₁₅H₁₃NO₃	70.6	5.1	5.5	…	69.4	5.1	…	…
3	OCH₃							CH₃	C₁₅H₁₃NO₄	66.4	4.8	5.2	…	66.1	4.8	…	…
4						CH₃	CH₃	CH₃	C₁₆H₁₅NO₂	71.4	5.6	5.2	…	71.3	5.5	5.1	…
5						OCH₃	OCH₃	C₂H₅	C₁₅H₁₃NO₃	63.8	5.0	4.7	…	62.9	4.9	4.6	…
6								CH₃	C₁₅H₁₃NO₂	70.6	5.1	5.5	…	70.0	5.1	…	…
7A[a] / 7B[b]	Br			Br			Br	CH₃	C₁₄H₉Br₂NO₃	42.1	2.3	3.5	40.1	42.3	2.6	4.1	…
8A[a] / 8B[b]	Br			Br	CH₃		Br	CH₃	C₁₅H₁₁Br₂NO₃	43.6	2.7	3.4	38.7	43.2	2.3	…	38.5
9	CH₃			Br		Br	Br	CH₃	C₁₅H₁₁Br₂NO₃	43.6	2.7	3.4	38.7	43.7	2.8	…	…
10	Br			Br	CH₃		Br	CH₃	C₁₆H₁₃Br₂NO₃	45.0	3.0	3.3	37.5	43.9	3.0	3.3	…
11	C₂H₅			Br	C₂H₅		Br	CH₃	C₁₆H₁₃Br₂NO₃	45.0	3.0	3.3	37.5	45.4	3.2	…	…
12	OCH₄			Br			Br	CH₃	C₁₅H₁₁Br₂NO₄	42.0	2.6	3.3	37.3	45.0	3.1	…	37.2
13	CH₃			CH₃		Br	Br	CH₃	C₁₆H₁₃Br₂NO₃	45.0	3.0	3.3	37.5	42.6	3.0	3.3	37.9
14	Br	CHCHCOOH		Br				CH₃	C₁₇H₁₁Br₂NO₅	43.5	2.4	3.0	34.1	46.6	3.2	3.7	…
15	Br	C₆H₅		Br				CH₃	C₂₀H₁₃Br₂NO₃	50.5	2.7	3.0	33.7	43.5	3.0	3.1	…
16	Br			Br		Br	Br	CH₃	C₁₄H₈Br₄NO₃	35.2	1.7	2.9	50.2	51.9	3.1	2.9	…
17	Br	NHCOCH₃					Br	CH₃	C₁₄H₇Br₄NO₃	30.2	1.3	2.5	57.5	36.5	2.1	3.0	…
18		NHCOC₆H₄NO₂					Br	CH₃	C₁₆H₁₂Br₂N₂O₄	42.1	2.6	6.1	35.1	30.8	1.4	…	…
19		NHCOC₂H₄COOH					Br	CH₃	C₁₆H₁₂Br₂N₂O₄	42.1	2.6	6.1	35.1	42.0	2.5	6.3	…
20							Br	CH₃	C₂₁H₁₃Br₂N₂O₆	44.8	2.3	7.5	28.4	42.8	2.7	6.3	28.4
21							Br	CH₃	C₁₈H₁₄Br₂N₂O₆	42.0	2.7	5.5	31.1	44.8	2.7	7.6	…
22A[a] / 22B[b]	Br			Br			Br	C₃H₇	C₁₆H₁₃Br₂NO₃	45.0	3.0	3.3	37.5	42.1	2.7	…	…
23A[a] / 23B[b]	Cl			Cl			Cl	C₃H₇	C₁₄H₉Cl₂NO₃	54.2	2.9	4.5	22.9	45.2	3.1	…	…
24	Cl			Cl	CH₃		Cl	CH₃	C₁₅H₁₁Cl₂NO₃	55.6	3.4	4.3	21.9	45.2	3.3	…	…
25	CH₃			Cl			Cl	CH₃	C₁₅H₁₁Cl₂NO₃	55.6	3.4	4.3	21.9	54.2	2.9	…	…
26	Cl			Cl	OCH₃		Cl	CH₃	C₁₆H₁₁Cl₂NO₄	52.9	3.2	4.1	20.9	54.5	3.0	…	…
27	OCH₃			Cl			Cl	CH₃	C₁₆H₁₃Cl₂NO₄	52.9	3.2	4.1	20.9	54.9	3.8	5.2	…
28	CH₃			CH₃			Cl	CH₃	C₁₆H₁₃Cl₂NO₃	56.8	3.9	4.1	21.0	55.3	3.5	4.4	…
29	CH₃		CH₃	CH₃			Cl	OC₂H₅	C₁₇H₁₅Cl₂NO₄	55.4	4.1	3.8	19.3	53.1	3.6	4.3	19.6
30	CH₃						Cl	CH₃	C₁₆H₁₃Cl₂NO₃	56.8	3.9	4.1	21.0	53.1	3.5	…	…
31	Cl		Cl	Cl			Cl	CH₃	C₁₄H₈Cl₃NO₃	48.8	2.3	4.1	30.9	56.8	4.1	4.4	…
32	CH₂CH=CH₂			CH₃			Cl	CH₃	C₁₆H₁₀Cl₂NO₃	50.2	2.8	3.9	29.7	55.4	4.0	…	…
33	Cl	CHCHCOOH				CHCHCOOH	Cl	CH₃	C₁₇H₁₃Cl₂NO₅	58.3	3.7	4.0	20.3	56.5	3.9	3.8	…
34	C₆H₅						Cl	CH₃	C₁₇H₁₃Cl₂NO₃	53.7	2.9	3.7	18.7	49.1	2.9	4.0	…
35				Cl			Cl	CH₃	C₂₀H₁₃Cl₂NO₅	62.2	3.4	3.6	18.4	50.9	3.1	3.9	…
36	NHCOCH₃	NHCOCH₃					Cl	CH₃	C₁₆H₁₂Cl₂N₂O₄	52.3	3.3	7.6	19.4	58.5	4.4	3.4	…
37	NHCOCH₃						Cl	CH₃	C₁₇H₁₄Cl₂N₂O₄	52.3	3.3	7.6	19.4	61.9	3.7	7.6	…
38	NHCOC₂H₅	NHCOC₂H₅					Cl	CH₃	C₁₇H₁₄Cl₂N₂O₄	53.5	3.7	7.4	18.6	52.4	3.9	…	…
39	Cl			Cl			Cl	C₃H₇	C₁₆H₁₃Cl₂NO₃	56.8	3.9	4.1	21.0	52.0	4.3	7.5	…
40							Cl	C₆H₅	C₁₉H₁₁Cl₂NO₃	61.3	3.0	3.8	19.1	53.8 / 56.8 / 61.4	3.8 / 3.9 / 3.2	… / … / 4.1	…

[a] Prepared by Procedure B. [b] Prepared by Procedure A.

TABLE II
ANALYTICAL DATA, INDONAPHTHYL ACETATES

$O=$⟨ ⟩$=N-$ ... $O-C(=O)-CH_3$

(positions 2 3 6 5 on left ring; 6' 7' 4' 3' 2' on naphthyl)
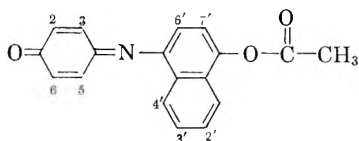
Compound	Substituent[a] 2	6	Molecular Formula	Calculated % C	H	N	Observed % C	H	N
41			$C_{18}H_{13}NO_3$	74.2	4.6	4.8	74.1	4.6	
42	Cl	Cl	$C_{18}H_{11}Cl_2NO_3$	60.0	3.1	3.9	60.7	3.2	4.2
43	Br	Br	$C_{19}H_{11}Br_2NO_3$	48.1	2.5	3.1	48.1	2.5	3.5

[a] Position of acyl group (1 or 8') was not determined.

TABLE III
ANALYTICAL DATA INDOQUINOLINYL ACETATES

$O=$⟨ ⟩$=N-$ ... $O-C(=O)-CH_3$

(positions 2 3 6 5 on left ring; 6' 7' 4' 3' 2' N on quinolinyl)

Compound	Substituent[a] 2	6	2'	Molecular Formula	Calculated % C	H	N	Found % C	H	N
44				$C_{17}H_{12}N_2O_3$	69.9	4.1	9.6	70.1	4.4	9.6
45	Cl	Cl		$C_{17}H_{10}Cl_2N_2O_3$	56.5	2.8	7.8	56.8	3.1	
46	Cl	Cl	CH_3	$C_{18}H_{12}Cl_2N_2O_3$	57.6	3.2	7.5	58.0	3.3	
47	Br	Br		$C_{17}H_{10}Br_2N_2O_3$	45.3	2.2	6.2	44.2	2.5	6.8
48	Br	Br	CH_3	$C_{18}H_{11}Br_2N_2O_3$	46.6	2.6	6.0	46.5	2.7	6.0

[a] Position of acyl group (1 or 8') was not determined.
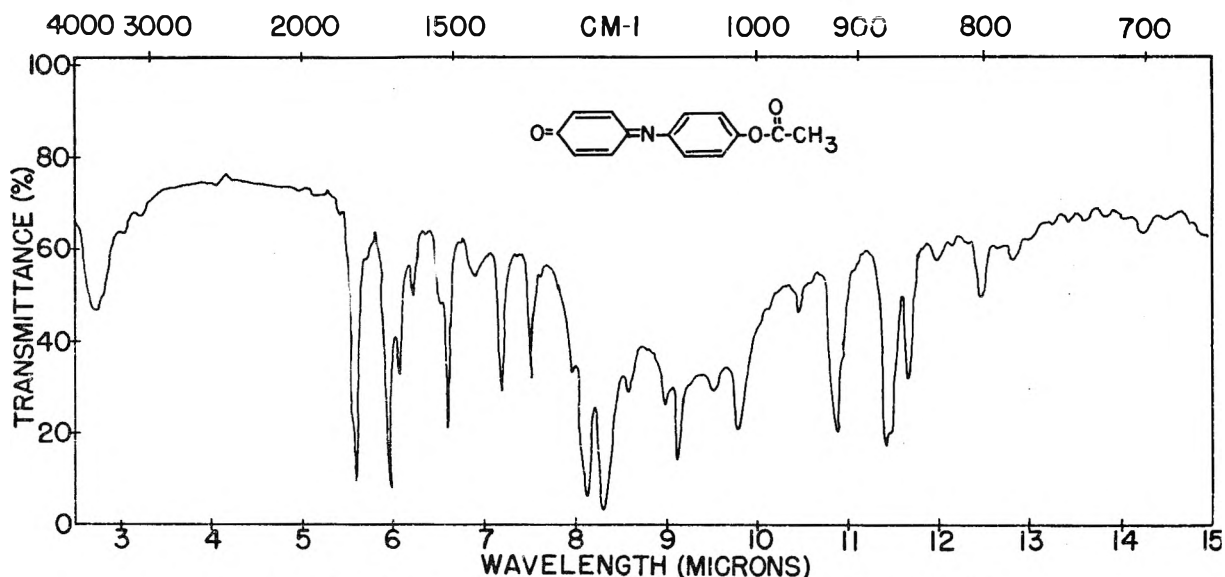
Fig. 1. Infrared spectrum of indophenyl acetate in a potassium bromide pellet

one orange. The red form is predominantly obtained by procedure A and the orange form by procedure B. The isolation of the two isomers and assignment of structures will be discussed in another publication.[13]

The infrared spectrum of indophenyl acetate is given in Figure 1.

EXPERIMENTAL

Preparation of Indophenol Sodium Salts. Some of these compounds are available from the Eastman Kodak Co. and National Aniline and Dye Co. The other salts were prepared by the following procedure: A mixture of 0.1 mole of appropriate phenol and 0.21 mole of sodium carbonate was dis-

(13) R. M. Gamson, D. N. Kramer and F. M. Miller, *J. Org. Chem.*, in press (paper II).

TABLE IV

PHYSICAL CONSTANTS OF INDOPHENYL ESTERS

Compound	Appearance	M.P.[a] °C	Ester λmax (log ε)[b,c]	Indophenylate Ion λmax (log ε)	pKa Observed	pKa Lit.[a]
1	Red needles, red plates	115–118	233(3.94), 262(4.23), 290(4.13), 460(3.52)	625(4.50)	8.1	8.10
2	Red needles	110–112	263(4.13), 290(4.00), 460(3.38)	650(4.32)	8.8	8.55
3	Red-orange needles	109	285(3.83), 455(3.45)	605(4.00)	...	...
4	Red platelets	82–84	233(3.81), 285(4.14), 443(3.49)	595(4.23)	8.7	8.9
5	Orange-red microcrystals	175	222(4.12), 313(4.26), 444(3.55)	600(4.18)	9.0	...
6	Red needles	48–49	225(3.74), 256(3.89), 455(3.05)	...	...	...
7A	Orange needles	119–121	213(4.44), 266(4.43), 433(3.47)	620(4.30)	5.8	5.70
B	Red-black, lustrous needles	145	226(4.19), 266(4.21), 274s(4.17), 470(3.76)	...	...	...
8A	Red-orange microcrystals	110–112	227(4.19), 268(4.27), 445(3.34)	600(4.11)	5.6	5.9
B	Deep red	171	233(4.01), 233s(3.88), 316(3.94), 495(3.64)	...	...	...
9	Orange microcrystals	130	226(4.12), 272(4.29), 440(3.40)	595(4.24)	5.4	5.4
10	Deep-red microcrystals	132–136	225(4.27), 450(3.11)	595(3.33)	6.4	...
11	Red-orange microcrystals	108	225(4.24), 270(4.23), 440(3.45)	595(4.20)	5.2	...
12	Orange microcrystals	98–100	227(4.18), 298(4.16), 420(3.35)	575(3.99)	6.0	5.6
13	Orange needles	129	226(4.23), 282(4.46), 432(3.47)	580(3.18)	5.4	...
14	Brick-red microcrystals	142–146	225(4.32), 274(4.26), 302s(4.19), 475(3.49)	625(4.01)	5.7	...
15	Red microcrystals	64–68	226(4.36), 302(4.00), 460(3.64)	610(4.18)	6.1	...
16	Red microcrystals	64	228(4.18), 313(4.14), 465(3.57)	650(4.05)	5.4	5.1
17	Deep-red microcrystals	190	227(4.28), 311(4.21), 470(3.45)	630(4.09)	6.1	...
18	Yellow microcrystals	108–111	226(3.50), 398(3.55)	...	...	...
19	Yellow-orange microcrystals	163	215(4.41), 282(4.19), 443(3.48)	...	...	...
20	Orange microcrystals	100–102	229(4.37), 268(4.34), 452(3.32)	...	...	...
21	Red-orange microcrystals	104–105	229(4.09), 275(3.95), 305s(3.89), 436(3.36)	...	...	...
22A	Orange microcrystals	77	267(4.39), 435(3.48)	...	...	...
B	Red microcrystals	79–81	313(4.23), 470(3.77)	...	...	...
23A	Orange needles	88	229(4.23), 264(4.20), 274s(4.00), 305(4.07), 470(3.76)	615(4.30)	5.8	5.70
B	Red needles	101–103	229(4.07), 274s(4.00), 305(4.07), 470(3.76)	...	...	...
24	Deep-red microcrystals	70–74	223(4.26), 280(4.12), 492(3.46)	595(3.56)	5.9	...
25	Orange microcrystals	102–103	227(3.96), 269(4.20), 435(3.42)	590(4.28)	5.7	5.50
26	Red microcrystals	113	228(4.09), 262s(3.86), 275(3.91), 460(3.29)	595(3.88)	6.2	...
27	Red-orange microcrystals	135	223(4.23), 283(3.95), 433(3.32)	596(3.85)	5.6	...
28	Red-orange needles	118–119	226(3.83), 284(4.27), 435(3.39)	575(4.18)	5.9	...
29	Orange needles	107	221(4.25), 282(4.41), 434(3.35)	...	...	...
30	Red-orange microcrystals	75	228(3.76), 283(4.28), 435(3.29)	590(4.10)	6.1	...
31	Orange-red microcrystals	125	227(4.18), 278(4.17), 457(3.45)	650(4.11)	5.7	5.80
32	Red-brown microcrystals	119	227(4.13), 283(4.18), 447(3.33)	620(4.15)	5.5	...
33	Orange platelets	95–96	217(4.29), 274(4.26), 445(3.46)	600(4.26)	...	...
34	Red microcrystals	74–76	225(4.35), 288(4.31), 475(2.81)	632(4.34)	5.6	...
35	Red-orange needles	116	229(4.37), 262(4.29), 434(3.56)	620(4.27)	5.8	...
36	Yellow microcrystals	205–208	232(4.29), 276(4.05), 404(3.56)	...	...	...
37	Yellow-orange microcrystals	154–156	232(4.06), 293(4.06), 443(2.26)	...	...	...
38	Orange needles	138	229(4.31), 273(4.03), 400(3.56)	...	...	...
39	Red-black lustrous plates	75	305(4.18), 475(3.66)	...	...	...

TABLE IV (Continued)

Compound	Appearance	M.P.[a] °C.	Ester λ_{max} (log ϵ)[b,c]	Indophenylate Ion λ_{max} (log ϵ)[b]	pKa Observed	pKa Lit.[d]
40	Deep-orange needles	136–137	233(4.32), 266(4.35), 440(3.45)	...	...	...
41	Red-orange microcrystals	149–152	230(4.20), 260(4.30), 455(3.50)	508(4.13)	9.1	...
42	Orange-red platelets	150–153	227(4.18), 262(4.25), 428(3.41)	580(3.97)	6.8	...
43	Orange red platelets	146–148	227(4.38), 263(4.35), 436(3.40)	585(4.06)	6.9	...
44	Red needles	151	242(4.26), 445(3.51)	620(4.23)	9.5	...
45	Orange microcrystals	183	231(4.21), 268(4.29), 425(3.42)	590(4.03)	5.9	...
46	Red-orange plates	192–194	223(4.27), 268(4.37), 425(3.43)	585(4.06)	5.9	...
47	Orange plates	212–214	228(4.42), 265(4.39), 428(3.42)	590(4.10)	6.0	...
48	Yellow orange needles	197–200	225(4.36), 268(4.40), 420(3.49)	595(3.98)	6.0	...

[a] All melting points are uncorrected. Determined using Fisher-Johns melting point apparatus. [b] Dioxane solutions. [c] Anal. Chem., 31, 42A (1959). [d] W. L. Hall, P. W. Preisler, and B. Cohen, Supplement No. 71, Public Health Reports (1928).

solved in 100 ml. of water. This solution was placed in a round bottom flask, immersed in an ice bath and was stirred magnetically until solution was complete, small amounts of dioxane being added if necessary. The appropriate N-chloroquinoneimine (0.1 mole) was dissolved in 100 ml. of dioxane and added dropwise to the cooled phenolic solution over a period of about 30 minutes. Mixing was continued for another 15 minutes. The solid sodium salt was filtered and air dried. If no solid formed, the solution was evaporated to dryness. No attempts were made to further purify the sodium salts.

Preparation of Esters. Procedure A. The following procedure is typical for the compounds described in Table I. The dry sodium salt (0.1 mole) was placed in an Erlenmeyer flask and 0.3 mole of acid anhydride added. The flask was then shaken on a mechanical wrist-action shaker for 2 hr. and allowed to stand at room temperature for 1 hr. It was poured onto crushed ice (600 g.) and after 1.5 hr. was filtered and the solid precipitate was washed with water. Glasses were sometimes obtained and washed with water, taken up in ether, and dried over sodium sulfate. The dried ether was concentrated on a steam bath to about 10 ml., diluted with four volumes of petroleum ether until a cloudiness appeared, and filtered. The filtrate was cooled in a freezer and the crystalline ester filtered. It was recrystallized from ether–petroleum ether.

Procedure B. The dry sodium salt (0.1 mole) was placed in a flask and 0.3 mole of acid anhydride and 0.1 mole of pyridine were added. The mixture was stirred for about 30 minutes, poured onto crushed ice and stirred for 1 hr. at room temperature until the excess acetic anhydride had hydrolyzed. The product was extracted with ether and the extracted portion washed free of acetic acid and pyridine and dried over anhydrous magnesium sulfate. The ether was removed under vacuum and a glassy product obtained. It was triturated with methanol and a yellow-orange solid thus formed was collected by filtration. Recrystallization from hot methanol gave the desired substance.

Spectra. Ultraviolet and visible spectra were determined in C.P. dioxane with a Perkin-Elmer Model 13U Spectrophotometer. Concentrations were $2 \times 10^{-5}M$ and $2 \times 10^{-4}M$ respectively. Spectra of the hydrolyzed product were determined immediately after hydrolysis of the dioxane solutions with 0.1N NaOH and dilution to volume so as to obtain $2 \times 10^{-5}M$ solutions. Infrared absorption spectra were obtained with a Perkin-Elmer Infracord using a sodium chloride prism and potassium bromide pellets.

pKa Values.[14] The pKa values were obtained spectrophotometrically by the addition of 0.2 ml. of $2 \times 10^{-3}M$ dioxane solutions of the substrate to 4 ml. of 0.1N sodium hydroxide. After a predetermined time to obtain maximum hydrolysis, a solution of 0.1M potassium dihydrogen phosphate was added until the solution turned from blue to purple. It was sometimes necessary to add hydrochloric acid to effect the color change. The solutions were diluted to 10 ml. with deionized water and the pH determined. The absorption of the solution was simultaneously obtained at the

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(14) Some difficulties were noted in obtaining the pKa values. As the rate of hydrolysis varied between compounds, a determination was made of the time required for complete hydrolysis of each compound. After hydrolysis for the required period using a second sample, the solution was immediately neutralized to its intermediate color. This color was usually purple, but in some cases a grey range was obtained and these compounds were adjusted to the grey end of the blue range. During neutralization, the solution was not rendered strongly acid as the indophenols are unstable in their acidic forms.[1] However, best results were obtained by making the solution just pink and then adding dilute alkali to obtain a purple solution.

λ max of the hydrolyzed product. The pKa were then calculated in the usual manner.[16]

(15) E. Salm, *Z. physik. Chem.*, **57**, 471 (1907); L. Flexser, L. P. Hammet, A. Dingwall, *J. Am. Chem. Soc.*, **57**, 2103 (1935).

A Study of the Physical and Chemical Properties of the Esters of Indophenols. II. Structural Studies of the Isomeric Esters

ROBERT M. GAMSON, DAVID N. KRAMER, and F. M. MILLER

A study is reported on isomeric dihalo substituted indophenyl esters leading to the identification of a red form as the 2,6 dihalo derivative and an orange form as the 3',5' dihalo ester. Structural assignments were made on the basis of comparative preparative methods and hydrolytic and spectral characteristics.

The authors have reported[1] the synthesis and chemical properties of esters of various indophenols for use as synthetic chromogenic substrates for hydrolytic enzymes. As previously indicated, the existence of the isomeric esters I and II was anticipated.

This has been verified by the isolation of two distinct compounds, obtained in red (I) and orange (II) forms. Structural assignments of the two stereoisomeric esters were made on the basis of comparative preparative, hydrolytic, and spectral

X = Cl, Br   R = CH₃—, CH₃CH₂CH₂—
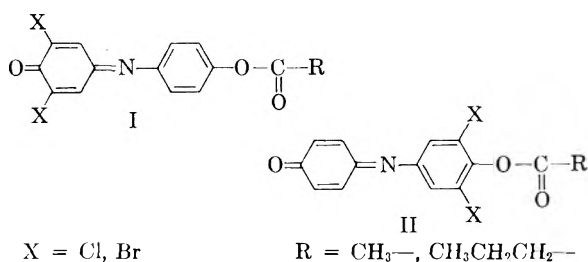
(u.v., visible, and I.R.) data which are the subject of this report.

Comparative preparative studies. Of the two isomeric forms, the orange product was obtained by the procedure involving the use of the halogenated sodium indophenol, acyl anhydride, and pyridine catalyst.[1] On the other hand, the red isomer was produced following the procedure employing the acyl anhydride without a catalyst.[2]

Experiments are now in progress to elucidate the mechanism of the acylation reaction with or without pyridine as a catalyst. Preliminary results

(1) D. N. Kramer, R. M. Gamson, and F. M. Miller, *J. Org. Chem.*, **24**, 1742 (1959). (Paper I.)

(2) The complete separation of the isomers was confirmed by gas chromatography of the individual compounds and of a mixture of the two. Only one peak was obtained with either form; a mixture produced two well defined peaks.

indicate that the following rationalization may account for the two courses of the reaction.

Pyridine reacts with acetic anhydride to yield an acetylpyridinium complex III.[3] The acetyl
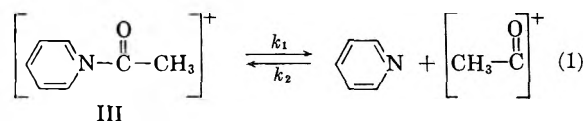
pyridinium complex may dissociate as shown in equation 1, where $k_2 > k_1$. Since the esterification employs the sodium salt of the indophenol as the starting material, the acetyl pyridinium ion will associate with the oxygen bearing the highest electron density to form an ion pair as follows:
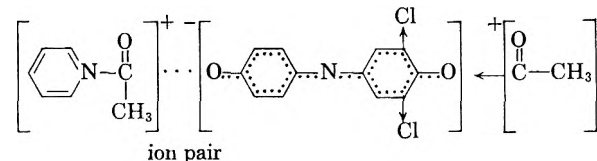
ion pair

The formation of the ion pair results in an orientation of the dihalo indophenolate ion which, for steric and energetic reasons, prevents attack on the more nucleophilic oxygen and promotes the acylation of the less nucleophilic oxygen. As the acylation step is completed, the ion pair is destroyed. The above is essentially an SN_2 reaction, yielding II.

On the other hand, in the absence of pyridine, the course of the reaction proceeds as expected with the attack of the nucleophilic oxygen of the indophenolate ion directly on the acetic anhydride, as shown:

(3) V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1409 (1953).
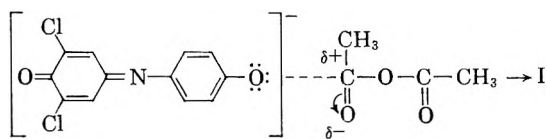
Table I summarizes the physical properties of a number of representative unsymmetrically substituted indophenyl esters. In general, the orange forms have lower melting points than the isomeric red compounds. The mixed melting point of the dibromo butyrate is depressed (58–63° against 79–81° for red and 77° for orange forms) indicating that the two forms are different entities.

TABLE I

PHYSICAL CHARACTERISTICS OF UNSYMMETRICALLY SUBSTITUTED INDOPHENYL ESTERS

Substituent						Melting[a] Point, °C.
2	6	3'	5'	R	Color	
Cl	Cl			CH₃	Red	101
		Cl	Cl	CH₃	Orange	88
Br	Br			CH₃	Red	145
		Br	Br	CH₃	Orange	119–121
Br	Br			nC₃H₇	Red	79–81
		Br	Br	nC₃H₇	Orange	77

[a] Melting points are uncorrected and were determined using a Fisher-Johns melting point apparatus.

Comparative hydrolytic studies. In further studies to elucidate the structure, the esters were spontaneously hydrolyzed. The spontaneous hydrolysis was performed at various temperatures and constant pH. The buffer provides a constant hydroxyl ion concentration and the normally second-order hydrolysis becomes pseudo-first order. As one of the hydrolytic products is the intensely colored indophenolate ion, the reaction rate can be readily determined spectrophotometrically. Under these conditions, the percent of hydrolysis was measured as indicated in Table II. Comparing the orange forms of the esters, it can be seen that the hydrolytic rates are slower than the parent indophenyl acetate. This is taken as further evidence that structure II represents the orange form, as steric effects of the halogens ortho to the esteratic bonds would hinder hydrolysis. The dichloro derivatives were hydrolyzed faster than the corresponding dibromo compounds as expected. On the other hand, the red forms of the ester are all hydrolyzed

TABLE II

HYDROLYSIS OF SUBSTITUTED INDOPHENYL ACETATES IN pH 8.5 BUFFER AT VARIOUS TEMPERATURES

	% Hydrolysis			
Substituent	10 minutes		20 minutes	
	24°	45°	24°	45°
II	2.87	11.75	6.05	21.00
DiBr (orange)	1.25	4.25	1.75	8.75
(red)	5.00	15.00	9.50	21.50
DiCl (orange)	2.25	8.25	4.75	17.50
(red)	4.50	15.00	8.75	22.75
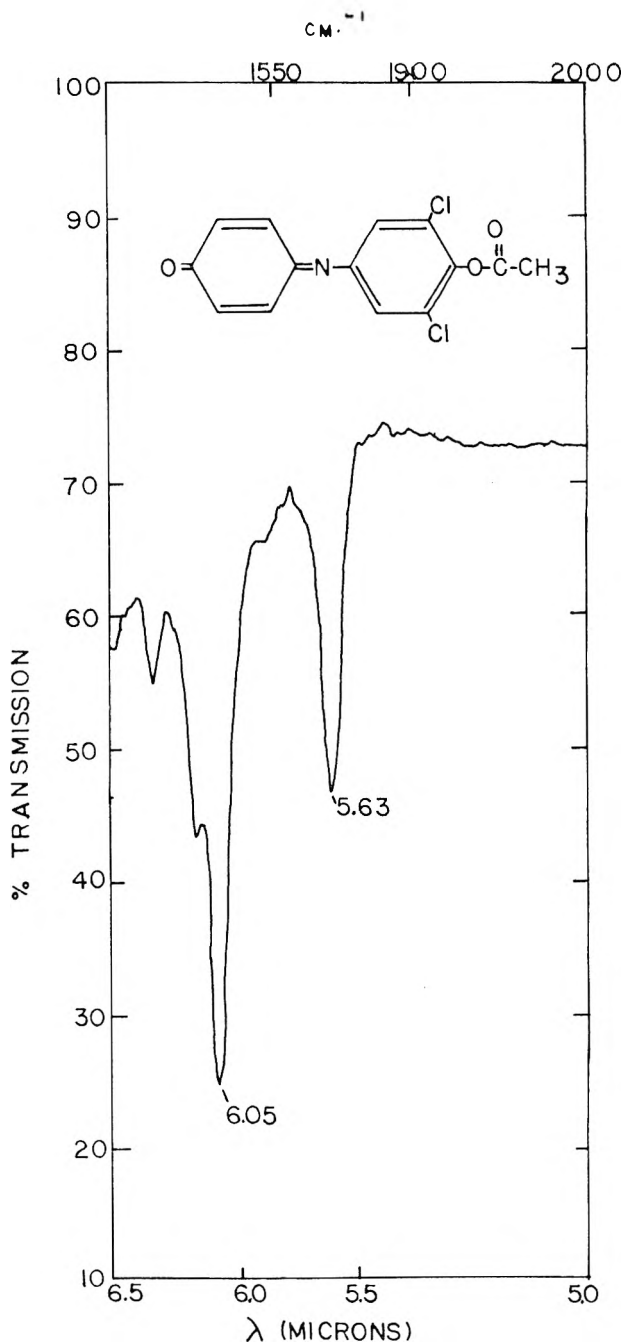
Fig. 1. Infrared spectrum of orange form of 2,6-dichloro-indophenyl acetate in the 6 micron region

at a greater rate than the parent substance. Thus it is believed that the halogens in the quinoid ring are increasing the hydrolytic susceptibility of the esteratic bond by decreasing the electron density at the carbonyl carbon. Just as there was no appreciable difference in pK values of dichloro and dibromo indophenylates,[1] there was no marked difference in the hydrolytic rates of the dihalo red forms.

Comparative spectral studies. The λmax of the red forms (both the dibromo and dichloro, 7B and 23B, respectively[1]) in the visible portion of the spectrum is at 470 mμ and that of the orange forms (7A
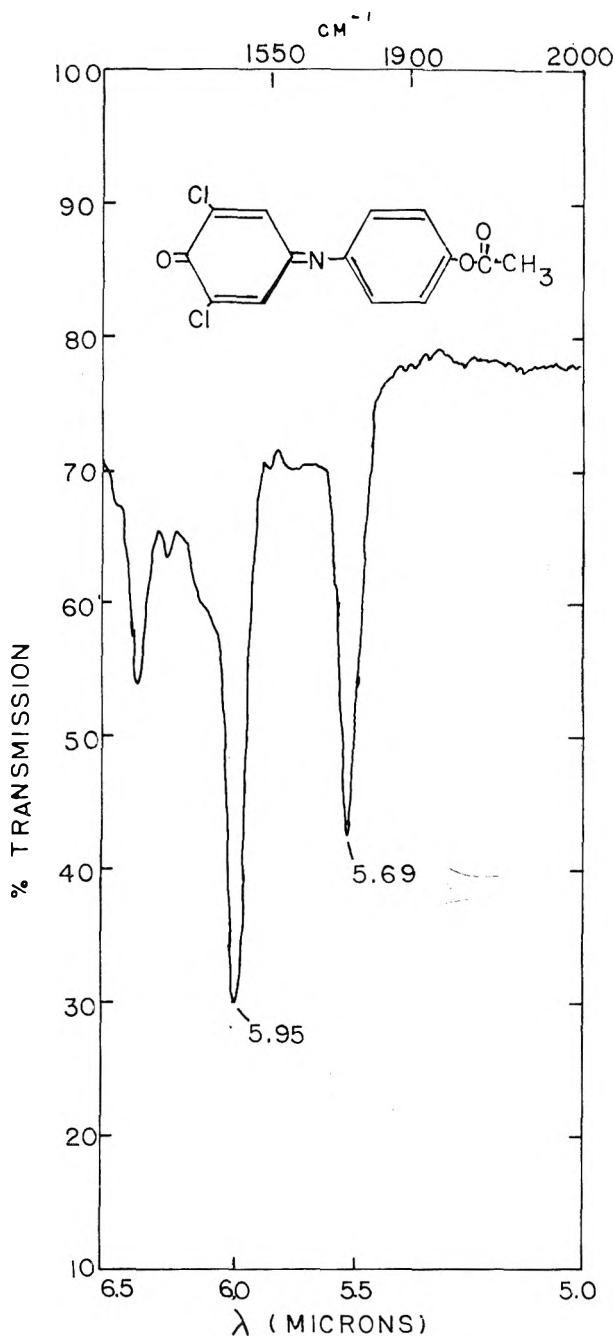
Fig. 2. Infrared spectrum of red form of 2,6-dichloroindophenyl acetate in the 6 micron region
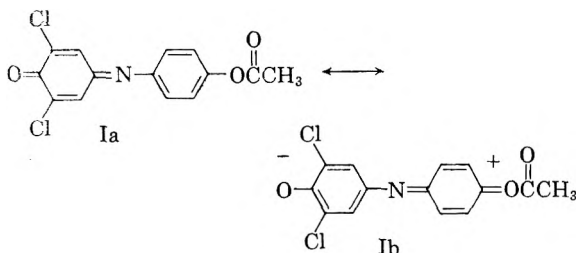
from halogen substituents in the quinoid ring. This is attributed to the stabilization of an excited state such as Ib by the inductive withdrawal of the halogens. Such stabilization would not be anticipated for IIb. Indeed, IIb should be destabilized by the inductive effect of the halogens and therefore absorb at shorter wavelengths. A comparable
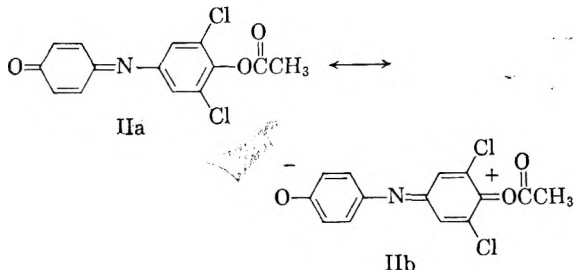
absorption at longer wavelengths by the red form of dichloro indophenyl acetate is also observed in the ultraviolet spectra of the two isomers. The λ_{max} of the red form are at 229, 274s and 305 (compound No. 23B[1]) while those of the orange form are at 226, 264 and 274s (compound No. 23A[1]). Support for this concept is found in the spectra of quinones having halogen substitution[5] and in the spectra of N-chloroquinoneimines,[6] where in both cases the effect of dihalogen substitution is a bathochromic shift of 30 mμ.[7]

It is of interest to compare the infrared spectra of the two isomeric dichloroindophenyl acetates as shown in Figs. 1 and 2. The red form has a carbonyl absorption at 5.95 μ, whereas the corresponding absorption of the orange form is at 6.05 μ. Weissberger[8] states that halogenation in the α position to a ketone raises the carbonyl frequency. This is additional evidence that structure I is consistent with the red form of the ester. Moreover, a similar effect is noted in the carbonyl ester absorbance, which is reported to be about 5.69 μ.[9] It would be expected that the ester corresponding to structure II would absorb at a lower wave length because of the proximity of the halogens. Figure 1 shows that the orange form has an absorbance peak at 5.62–5.64 μ and Fig. 2 indicates that the red form has a peak at 5.68–5.70 μ. These results are confirmed by de Borst *et al.*,[10] who also report that a

(4) P. W. Vittum and G. H. Brown, *J. Am. Chem. Soc.*, 68, 2237 (1946).

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

(6) Unpublished results of this laboratory.

(7) The λ_{max} of the quinoneimines are: N-chloroquinone imine, 286 mμ; 2,6-dibromo-N-chloroquinoneimine, 319 mμ; and 2,6-dichloro-N-chloroquinoneimine, 308 mμ.

(8) A. Weissberger, *Technique of Organic Chemistry, Chemical Applications of Spectroscopy*, Interscience, New York, 1956, Volume IX, p. 472.

(9) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Wiley and Sons, New York, 1954, p. 153, 156.

(10) C. de Borst, F. N. Hooge, G. J. Arkenbout, *Nature*, 182, 1017 (1958). This work was done independently following a visit by one of the authors (DNK) to the Chemical Laboratory, National Defense Research Council, TNO, Rijswijk, Netherlands.

and 23A respectively[1]) is at 445 mμ compared to 460 mμ for the unsubstituted indophenyl acetate. In an analogous study in the indaniline series, Vittum and Brown[4] found a similar shift resulted

similar shift due to C—O—C vibration was observed in the 8.3 μ region.[9]

EXPERIMENTAL

The esters were prepared by the procedure of Kramer *et al.*[1] Procedure A was used to obtain the red isomer while procedure B, using pyridine yielded the orange product. The analyses, melting points, and spectral characteristics of the esters have been previously reported.[1]

Spontaneous hydrolysis. A $2 \times 10^{-3}M$ solution of the ester in dioxane was aliquoted and diluted with tris buffer pH 8.5 so as to obtain a $2 \times 10^{-5}M$ solution. This solution was placed in a DU spectrophotometer cell at room temperature and its absorbance obtained at the λ_{max} of the hydrolysis product at 10 minute intervals for 1 hr. *vs.* a blank containing no ester. This was repeated at 5° intervals, from 25° to 45°. The buffer was thermostated at the working temperature and adjusted to pH 8.5 against standard buffer which was maintained at room temperature. This thermostated buffer was then used in the hydrolysis study. The Beckman DU spectrophotometer's cell compartment was maintained at the investigative temperature by the use of thermospacers and a circulating bath. The extinction coefficient and the absorbance values were used to calculate the concentration of hydrolysis product.

Spectral studies. Ultraviolet, visible and infrared spectra were obtained using a Perkin-Elmer Model 13U Spectro-photometer. The ultraviolet and visible spectra were determined in peroxide-free dioxane[11] at concentrations of $2 \times 10^{-5}M$ and $2 \times 10^{-4}M$ respectively. The infrared spectra were determined in potassium bromide pellets (1 mg. of ester per 200 mg. of bromide) using a sodium chloride prism.

Gas chromatography. The samples were chromatographed on a one foot column with a packing of 30% silicone grease on 40–100 mesh Celite 545. The block temperature was 240° and the column temperature was 200°. A helium flow of 45 ml. per min. was used with 400 ma. on the bridge circuit and a chart speed of 10″/hr. The orange form emerged in 2.5 minutes and the red form in 3.75 minutes. No other peaks appeared. A mixture of the red and yellow samples gave two peaks.

(11) W. Dasler and C. D. Bauer, *Ind. and Eng. Chem. Anal. Ed.*, **18**, 52 (1946).

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some Applications of the Nenitzescu Reaction

EDGAR A. STECK[1] WITH R. PAULINE BRUNDAGE AND LYNN T. FLETCHER

A group of 1-substituted 3-carbethoxy-5-hydroxy-2-methylindoles was prepared from ethyl *N*-substituted β-amino-crotonates and a mechanism proposed for the Nenitzescu reaction.

Several recent publications,[2-7] especially those of Grinev and co-workers,[2-5] have rendered it desirable that we record certain findings in our applications of the Nenitzescu[8,9] reaction for the synthesis of 5-hydroxyindole types. Our interest lay in the use of the indole derivatives as intermediates for other syntheses, and attempts were

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(2) A. N. Grinev, N. K. Kul'bovskaya, and A. P. Terent'ev, *Zhur. Obshcei Khim.*, **25**, 1355 (1955); *Chem. Abstr.*, **50**, 4903g (1956).

(3) A. N. Grinev, N. E. Rozdevich, and A. P. Terent'ev, *Zhur. Obschei Khim.*, **27**, 1690 (1957); *Chem. Abstr.*, **52**, 3762b (1958).

(4) A. N. Grinev, I. A. Zaĭtsev, N. K. Venevtseva, and A. P. Terent'ev, *Zhur. Obschei Khim.*, **28**, 1853 (1958); *Chem. Abstr.*, **53**, 1299b (1959).

(5) A. N. Grinev, V. N. Ermakova, and A. P. Terent'ev, *Doklady, Akad. Nauk S.S.R.*, **121**, 862 (1958); *Chem. Abstr.*, **53**, 1167e (1959).

(6) H. J. Teuber and G. Thaler, *Chem. Ber.*, **91**, 2264 (1958).

(7) J. H. Koehneke and M. E. Speeter, U. S. Patent **2,707,187**; *Chem. Abstr.*, **50**, 5035e (1956).

(8) C. D. Nenitzescu, *Bull. Soc. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110⁸ (1930).

(9) R. Beer, K. Clarke, H. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951).

III
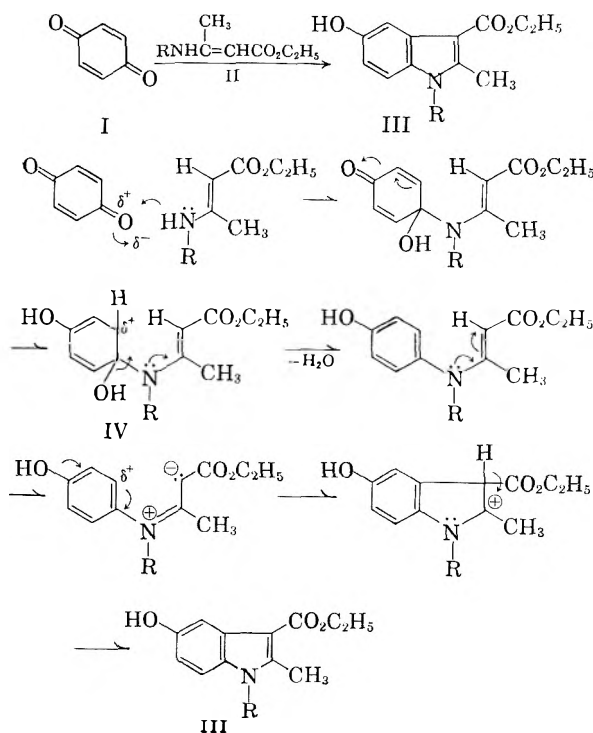
made to improve the yields. The method involved reaction of a 1,4-benzoquinone (I) with a β-aminocrotonic ester (II) in ethanol or acetone to produce a 3-carbethoxy-5-hydroxy-2-methylindole-(III). An ionic mechanism for this transformation is proposed below.

In the present work, which was terminated as a result of several intervening circumstances, a small group of the indole derivatives of structure III was made. The ethyl β-aminocrotonates required for this were made by the method of Michaelis[10] or that of Cope,[11] and included the parent compound, and the N-methyl, N-hexyl-, N-(3-dimethylaminopropyl)-, and N-benzyl derivatives. Excellent yields of these were obtained. These esters were subjected to the Nenitzescu reaction, to form the desired compounds, albeit in poor to very poor yields, ranging from 10–35%. Attempts were made to isolate coproducts from the garnet mother-liquors in several instances. It was considered (cf. ref. 12) that compounds of structure V or VI might have been formed, however no discrete substances were obtained.
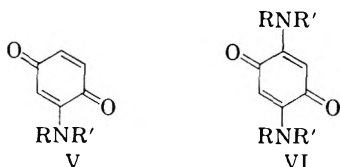
This is an aspect of an over-all program designed for the sythesis of compounds having effects on the central nervous system. For several reasons it was desirable to prepare at least one indole type from 2-benzylmercapto-1,4-benzoquinone, VII. Previous workers[4,6,9] have shown preference for the 6-sustituted indole types (IX) as products derived from 2-substituted 1,4-benzoquinones, but without indicating reason for this choice over the alternative types X and XI. Grinev[2] viewed the structure of the product in a noncommital way. From a consideration of structural features in the 2-substituted 1,4-benzoquinones having an o-, p- directing substituent, we concur with the previous view that 6-substituted indole derivatives do result. In our particular instance, examination of the features present in VII (indicated in detail as VIII) leads us to find the 6-benzylmercapto structure XII to be much preferred, expecially in light of the inductive effects in the intermediates (e.g., IV). It was intended that this feature of the Nenitzescu reaction be demonstrated conclusively through use of the benzylmercapto group, which could be removed readily by hydrogenolysis. Unfortunately for this aspect, conditions now preclude continuation of this work, and the structure XII must be based on mechanistic features.

It may be noted that the presence of the 2-substituent (or of 2, 3-disubstitution) on the benzoquinone leads to better yields of product than when 1,4-benzoquinone itself was used. This would be consistent with the intermediate forms in the proposed mechanism and also with probable steric effects, including those in V and VI. The very low yield of the 1-(3-dimethylaminopropyl) type may be ascribable to the presence of the basic group.
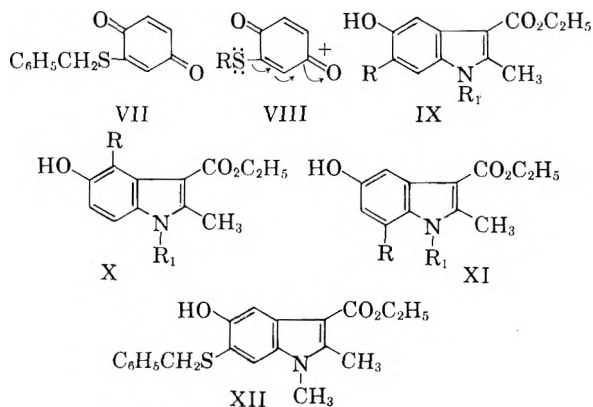
EXPERIMENTAL[13]

A. *Ethyl β-aminocrotonates.* The conversion of ethyl acetoacetate to β-aminocrotonate followed the scheme of Michaelis,[10] and the closely related one of Glickman and Cope[11] was used for the β-methylamino compound. In the preparation of the β-aminocrotonic ester derivatives here required, very slight modification of the earlier methods was employed. A 10% excess of amine was added to ethyl acetoacetate, with stirring during 2 to 3 hr., meanwhile maintaining the temperature at 45–50° by adjusting the rate of addition or by cooling in a water bath. After standing at 25° for one day, the mixture was heated at 90–95° for 2 hr., the layers separated, and the crude ester was dried over sodium sulfate. Excellent yields of the ethyl β-aminocrotonates were obtained by fractionation of the crude materials; all were colorless oils.

Ethyl β-hexylaminocrotonate: 92.3% yield; b.p. 108–109° (0.3 mm.); n_D^{25} 1.4852.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.48; H, 10.70; N, 6.60.

Ethyl β-(3-dimethylaminopropylamino) crotonate: 97% yield; b.p. 93–93.5° (0.2 mm.); n_D^{25} 1.4954.

Anal. Calcd. for $C_{11}H_{22}N_2O_2$: N, 13.08; O, 14.93. Found: N,[14] 12.72; O, 14.50.

Ethyl β-benzylaminocrotonate: 88.5% yield; b.p. 129–130° (0.4 mm.); n_D^{25} 1.5554.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.82; N, 6.39. Found: C, 71.05; H, 7.70; N, 6.41.

B. *2-Benzylthio-1,4-benzoquinone* was prepared by application of the method[15,16] used for 2-phenylthiobenzoquinone rather than that which Alcalay[17] had used. A solution of 64.8 g. (0.6 mole) of benzoquinone in 2.2 l. of ethanol was

(10) A. Michaelis, *Ann.,* **366,** 337 (1909).

(11) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.,* **67,** 1019 (1945).

(12) C. J. Cavallito, A. E. Soria, and J. O. Hoppe, *J. Am. Chem. Soc.,* **72,** 2661 (1950).

(13) Melting points are corrected values; boiling points are not. Analyses were carried out under the direction of Mr. M. E. Auerbach and Mr. K. D. Fleischer in the Analytical Section of this Institute.

(14) Determined by acetous–perchloric acid titration, after the method of G. Toennies and T. P. Callan, *J. Biol. Chem.,* **125,** 259 (1938).

(15) J. M. Snell and A. Weissberger, *J. Am. Chem. Soc.,* **61,** 452 (1939).

(16) O. Dimroth, L. Kraft, and K. Achinger, *Ann.,* **545,** 130 (1940).

stirred at 20° and 37.3 g. (0.3 mole) of benzyl mercaptan in 300 ml. of ethanol was added during 10 min. The mixture became maroon, and then changed to garnet as the temperature rose to 31°. Solid began to separate after about 20 min. After stirring for 1.5 hr., the temperature had fallen to 25°. The red-orange solid was then collected and washed with about 75 ml. of cold ethanol (to remove hydroquinone) and dried, giving 34.0 g. of crude 2-benzylthiobenzoquinone, m.p. 119–121.5°. Evaporation of the filtrates under reduced pressures left a nearly black residue, which was boiled in about 300 ml. of ethanol and the solution chilled. The reddish crystals were collected, washed with about 50 ml. of cold ethanol and dried; 22.2 g. of product melting at 122–123° resulted. Crystallization of the two fractions (81.5% yield) from hexane gave 43.1 g. (62.4% yield, based on benzyl mercaptan) of pure compound as fan-shaped aggregates of orange-red needles, m.p. 124–124.5° (lit.,[17] m.p. 119°).

Anal. Calcd. for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; O, 13.90; S, 13.92. Found: C, 68.20; H, 4.36; O, 13.80; S, 14.18.

A ten-fold run gave a 60% yield of 2-benzylthiobenzoquinone (m.p. 123–124°, from carbon tetrachloride) and an alcohol-insoluble fraction (50 g.) which melted over 200°. The latter was crystallized twice from diethylene glycol methyl ether (Methylcarbitol) to give 37.0 grams of lustrous scarlet plates which melted at 230 5–231.5°. This proved to be the 3,6-*bis*(benzylthio) compound, for which Posner and Lipski[18] recorded the m.p. 223–224°.

Anal. Calcd. for $C_{20}H_{16}O_2S_2$: C, 68.15; H, 4.58; S, 18.19. Found: C, 67.90; H, 4.70; S, 18.37.

C. *Nenitzescu reactions.* The limited accessibility of the original work of Nenitzescu[8] renders desirable a recounting of the procedure. It is to be noted that, while the yields were generally very low, the ease of manipulation was considerable. All of the new 1-substituted 3-carbethoxy-5-hydroxy-2-methylindoles were made as described for the parent type.

Ethyl 5-hydroxy-2-methylindole-3-carboxylate. Ethyl β-aminocrotonate (1104 g., 8.55 moles) was dissolved in acetone (6 l.) and an atmosphere of nitrogen was maintained over the stirred solution and the addition of *p*-benzoquinone (970 g., 8.95 moles) made in 20 min. There was little exothermic effect until the red solution was warmed to about 40°, whereupon ensuing reaction caused sufficient liberation of heat to start vigorous boiling. Gentle cooling was applied for some 20 min., after which time, there was refluxing for 0.5 hr. without need for warming. It was further refluxed for 1 hr., and then nearly 5 l. of solvent were removed, with the still under nitrogen. After chilling, the sticky garnet magma was filtered, washed at the pump with 2 l. of cold 1:10 mixture of acetone and pentane, then it was slurried in a minimal amount of acetone and stored in the cold for

(17) W. Alcalay, *Helv. Chim. Acta*, **30**, 578 (1947).
(18) T. Posner and J. Lipski, *Ann.*, **336**, 150 (1904).

a day. The crude ester was collected, washed with some cold acetone, and dried. Six hundred forty-three grams (34.3% yield) of light tan solid resulted, m.p. 200–202°. The crude product could be crystallized well from methanol containing traces of sodium dithionite, or from aqueous acetone, however the large batch was more readily purified by a somewhat different method. It was dissolved in hot acetic acid to produce a solution of some 3 liters volume, then hot ethyl acetate was added, after charcoaling, to a total volume of 4 l. The purified ester was collected after chilling, then it was washed with cold ethyl acetate and dried. Ethyl 5-hydroxy-2-methylindole-3-carboxylate was obtained as fine white needles, m.p. 211–212° (lit.[2,3] reports m.p. 205°); the yield was 483 g., or 25.8%. Other preparations of the "Nenitzescu product" gave purified yields of 22–28%, and only intractable gums were obtained from the liquors.

Ethyl 1,2-dimethyl-5-hydroxyindole-2-carboxylate was obtained in 32% yield in the form of cryptocrystals from Methylcellosolve; m.p. 211–212° (lit.[2] m.p. 207–208°).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.91; H, 6.44; N, 6.19.

Ethyl 1-hexyl-5-hydroxy-2-methylindole-2-carboxylate: 22% yield of chalky, cryptocrystalline solid, m.p. 134.5–135° (from cyclohexane).

Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.28; H, 8.30; N, 15.83. Found: C, 71.66; H, 8.19; N, 15.70.

Ethyl 1-(3-dimethylaminopropyl)-5-hydroxy-1-methylindole-2-carboxylate hydrochloride was a light tan cryptocrystalline solid, m.p. 267.5–269.5°. It was prepared directly from the crude Nenitzescu product and crystallized repeatedly from aqueous ethanol; the yield of pure product was only 10%.

Anal. Calcd. for $C_{16}H_{22}N_2O_3 \cdot HCl$: N, 8.22; Cl, 10.40. Found: N, 8.25; Cl, 10.43.

Ethyl 1-benzyl-5-hydroxy-1-methylindole-2-carboxylate was a pinkish cryptocrystalline solid as obtained from ethyl acetate, m.p. 196.5–197.5°. The yield was 22%.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; O, 15.52. Found: C, 73.92; H, 6.17; O, 15.85.

Ethyl 6-benzylthio-1,2-dimethyl-5-hydroxyindole-2-carboxylate. 2-Benzylmercapto-1,4-benzoquinone (228 g., 0.99 mole) was caused to react with ethyl β-methylaminocrotonate (144 g., 1 mole) in acetone (1 l.) in the usual manner. The yield of crude product (162 g., m.p. 176–180°) was 46%. It was crystallized from glacial acetic acid to obtain a 38% yield of pure compound in the form of off-white needles, m.p. 182.5–184°.

Anal. Calcd. for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.96; S, 9.02. Found: C, 67.53; H, 5.68; S, 8.93.

Vinylation Rates of Primary, Secondary, and Tertiary Alcohols

EARL D. HOLLY

Because of the low acidity of tertiary alcohols and since alkoxide ion is the catalyst, it is necessary to use an alkali metal alkoxide rather than a hydroxide in the vinylation of tertiary alcohols. Relative vinylation rates of *n*-, *sec*- and *tert*-butyl alcohols are reported. It is suggested that F-strain in the transition state accounts for the order of vinylation rates.

The base-catalyzed vinylation of alcohols was reported in 1931 by W. Reppe.[1] At the time of the

(1) W. Reppe, U. S. Patent 1,959,927 (1934); Ger. Patent 584,840 (1932); Brit. Patent 369,297 (1932); French Patent 724,955 (1931).

tertiary alcohol had appeared despite considerable present work no description of the vinylation of a interest in the vinylation reaction.[2–8] Since the

(2) P. B. Reports 40,816; 1112; 13,366; 11,394; 67,694. and 18,842-s.

completion of this work such a description has been published.[9] The present work gives relative rates of vinylation of n-, sec- and tert-butyl alcohols. The catalyst was the respective potassium alkoxide and the reaction was studied both without solvent and in a glycol ether.

Reppe[1,2] considered the vinylation reaction to involve an equilibration of the basic catalyst with the alcohol to form alkoxide. This would be followed by addition of the alkoxide to acetylene forming the salt of the vinyl ether. Reaction of this salt with alcohol would form the vinyl ether and regenerate alkoxide. This is very similar to the mechanism proposed by Hanford and Fuller.[4] Such a mechanism is consistent with the kinetics found by Miller and Shkapenko[8] for the methoxide-catalyzed addition of methanol to phenylacetylene. They found the reaction to be first order in methoxide and in phenylacetylene but zero order in methanol.

$$ROH + K \text{ Base} \underset{k_2}{\overset{\text{fast}}{\rightleftharpoons}} ROK + H \text{ Base}$$

$$\Big| + HC{\equiv}CH$$

$$ROCH{=}CH_2 + ROK \xleftarrow[+ ROH]{\text{fast}} ROCH{=}CHK$$

$$\text{Rate} = k_2[ROK][HC{\equiv}CH]$$

The bases used by Reppe included the hydroxides and alkoxides of sodium and potassium. The potassium salts were generally superior to the sodium salts. In the vinylation of ethanol, the 95% azeotrope reacted as well as absolute alcohol. Potassium hydroxide was as good a catalyst as the ethoxide. These observations must have contributed to the attitude that potassium hydroxide was the best and most convenient catalyst.[10] The general use of potassium hydroxide as catalyst must, in turn, account for previous difficulties in the vinylation of tertiary alcohols.

The reason for such difficulties is apparent from consideration of the equilibrium between hydroxide and alkoxide. For ethanol, a primary alcohol, Cal-

din and Long[11] have found an equilibrium constant of 0.7. In 2% aqueous ethanol, which is about the composition of a reaction mixture made up by dissolving 5% of potassium hydroxide pellets in absolute alcohol, 94% of the base is present as ethoxide. Thus, in the vinylation of a primary alcohol, the use of potassium hydroxide is satisfactory, as nearly all the base is present as alkoxide.

Secondary alcohols are weaker acids than are primary and hence the equilibrium will be less favorable. Indeed, Nummy[12] found, in competitive vinylation of equal parts of 1-octanol and 2-octanol at 190° using 4 mole % potassium hydroxide, that the primary alcohol was initially vinylated about 7 times as fast as the secondary alcohol (see Fig. 1).

Fig. 1. Competitive vinylation of 1-octanol and 2-octanol

The reactivities found in the present work suggest that the major portion of this difference (about a factor of three) is due to the greater acidity of the primary alcohol. The acidity of tertiary alcohols must, then, be too low for a significant amount of alkoxide to be present in equilibrium with hydroxide.

With these considerations in mind, potassium tert-butoxide was used to catalyze the vinylation of tert-butyl alcohol. The vinylation proceeded to high conversion and, under the conditions initially chosen, nearly as fast as with n-butyl alcohol or sec-butyl alcohol (Figure 2). Suspecting from this that the rate at which acetylene dissolved in the reaction solution was determining the rate of vinylation, two series of experiments were run leaving acetylene pressure constant but lowering the rate of vinylation by changing the temperature or the butoxide concentration.

In one series, the temperature and the catalyst concentration were lowered and the alcohol was diluted with a better solvent for acetylene. The relative rates, corrected for catalyst concentration, were n-butyl alcohol 5.4, sec-butyl alcohol 2.4 and

(3) J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publishing Corp., New York, 1949, Chapter 2.

(4) W. E. Hanford and D. L. Fuller, *Ind. and Eng. Chem.*, **40**, 1171 (1948).

(5) C. E. Schildknecht, A. O. Zoss, and C. McKinley, *Ind. and Eng. Chem.*, **39**, 180 (1947).

(6) G. M. Kline, *Modern Plastics*, **23**, 152A (Oct. 1945); **23**, 169 (February 1946); **24**, 159 (January 1947).

(7) J. Furukawa, T. Ando, and M. Yokoyama, *Bull. Inst. for Chem. Res. of Kyoto Univ.*, **31**, #3, 220 (1953).

(8) S. I. Miller and G. Shkapenko, *J. Am. Chem. Soc.*, **77**, 5038 (1955).

(9) S. Otsuka, Y. Matsui and S. Murahashi, *Nippon Kagaku Zasshi*, **77**, 766 (1956); *Chem. Abstr.*, **52**, 8935 (1958).

(10) Hanford and Fuller,[4] for instance, recommend the use of potassium hydroxide with anhydrous alcohols while stating that potassium hydroxide and alkoxide give better results than other bases tried.

(11) E. F. Caldin and G. Long, *Nature*, **172**, 583 (1953).

(12) W. R. Nummy, previously unpublished results in this laboratory.

Fig. 2. Diffusion-controlled vinylation of butyl alcohols

Fig. 3. Vinylation of butyl alcohols in dimethyl ether of diethylene glycol
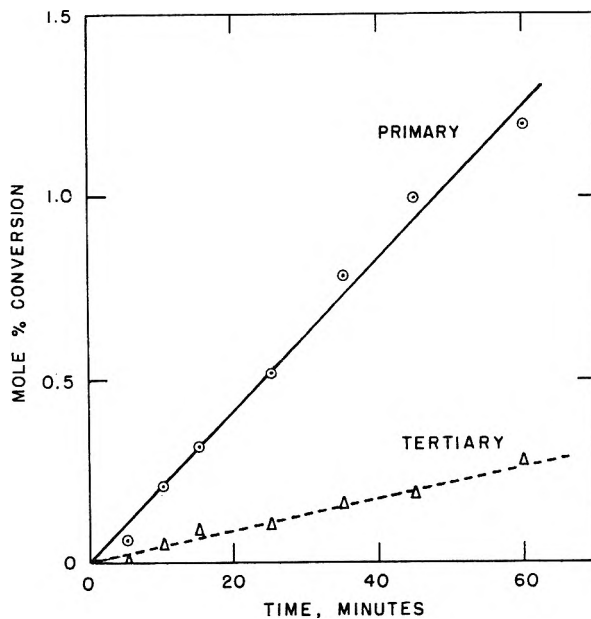
Fig. 4. Vinylation of butyl alcohols at low catalyst concentrations

tert-butyl alcohol 1.0 (see Figure 3 and Table I). In straight alcohol at low catalyst concentrations, the primary alcohol reacted 3.7 times as fast as the tertiary (see Figure 4).

The reaction rates given here cannot be compared directly with those given by Otsuka, Matsui and Murahashi.[9] Moreover, the method they used to calculate the vinylation rates of primary alcohols by difference is open to objection. They vinylated solutions of primary alcohols in *tert*-butyl alcohol containing potassium *tert*-butoxide. From the rate at which *tert*-butyl alcohol alone was vinylated, they tried to correct the observed rate to obtain the rate for the primary alcohol. However, with no information regarding the distribution of the catalyst between primary alkoxide and *tert*-butoxide, it is not possible either to correct for the vinylation of *tert*-butyl alcohol in the mixture or to tell the primary alkoxide concentration responsible for the vinylation of the primary alcohol. However, the rate curves in their paper show that the rates were leveling off with increasing concentration of primary alcohol. One may, therefore, estimate that in the pure primary alcohols the rates relative to *tert*-butyl alcohol would be 2-ethoxyethanol 9, 1-octanol 5 and *iso*-butyl alcohol 4. The latter two values are in general agreement with the values reported here for *n*-butyl alcohol.

The observed order of reactivity cf the butoxide ions toward acetylene is the reverse of their base

strengths and the reverse of the expected electron densities on the oxygen atoms. An explanation for this observation is to be sought, then, not in the differences in activation energy but rather in increasing entropy of activation as the alkyl group is branched. Such an interpretation seems reasonable when one examines molecular models of alkoxide

TABLE I

VINYLATION OF BUTYL ALCOHOLS

Medium Mole % cat. Temp.	n-BuOH 3.9 147	sec-BuOH 4.5 147	tert-BuOH 4.6 147	10% n-BuOH 90% E-141 1.6 122	10% sec-BuOH 90% E-141 1.7 122	10% tert-BuOH 90% E-141 1.3 122	n-BuOH 1.3 147	tert-BuOH 1.0 147
Time, Min.				Mole % vinyl ether				
5	0.52	0.61	0.27	0.11	0.09	(>0.05)	0.07	0.03
10	0.76	0.97	0.61	0.30	0.27	0.06	0.22	0.08
15	1.9	1.6	0.97	0.30	0.40	0.08	0.33	0.12
25	2.7	2.9	1.5	0.66	0.62	0.10	0.53	0.14
35	4.2	4.3	2.6	0.88	0.86	0.15	0.80	0.19
45	5.0	5.2	4.9	1.2	1.0	0.20	1.0	0.22
60	8.0	7.3	6.2	2.1	1.3	0.33	1.2	0.29
90	11	12	9.4	3.2	1.7	0.46		
120		18	14	4.4	2.2	0.68		
m	0.127	0.148	0.120	0.0380	0.0178	0.0057	0.0210	0.0043
b	−0.27	−0.79	−0.89	−0.25	0.14	−0.03	0.01	0.03
r	0.0326	0.0329	0 0261	0 0237	0.0104	0.0044	0.0161	0.0043
Rel. rate				5.4	2.4	1.0	3.7	1.0

ions and acetylene. The presence of any carbon atoms attached to the alkoxide carbon atom restricts effective approach of the oxygen atom to acetylene. In effect, then, it is suggested that F-strain determines the reactivity of the butoxide ions toward acetylene.[13]

A similar effect has been noted by Brown and Moritani[14] in the reaction of potassium alkoxides in the respective alcohols with tert-amyl bromide. The relative rates were ethoxide 4.46, isopropoxide 2.28 and tert-butoxide 1.00. The similarity of these results with those for the vinylation reaction is consistent with a like cause, steric strain in the transition state, despite the fact that one is an elimination reaction whereas the other is an addition reaction.

A parallel case to alkoxide reactivity is the base strength of corresponding primary amines toward various reference acids. Toward the proton, branching slightly decreases relative base strength[15] in the series n-butyl 1.5, sec-butyl 1.3 and tert-butyl 1.0 and somewhat more so in the series ethyl 2.0, isopropyl 1.5 and tert-butyl 1.0. Brown and Pearsall[16]

showed a much greater effect of branching upon the relative base strength in the latter series of amines toward trimethyl boron, a larger reference acid: Ethyl 14.5, isopropyl 6.9 and tert-butyl 1.0. Here, too, the magnitude of the effect of branching the alkyl group depends upon the steric requirements of the reaction in question.

EXPERIMENTAL

The vinylation was done in an American Instrument Company 316 stainless steel bomb of 1.5 l. capacity. The bomb was packed in 0.5 in. lengths of 0.5 in. stainless steel pipe and fitted with a gas inlet line and a dip tube for sampling the liquid phase. It was heated electrically, to maintain the internal temperature within a range of 5°. The heater was clamped in a horizontal reciprocating shaker which has been found to give less efficient mixing than the more common rockers.

The alcohols used were dried by the method of Lund and Bjerrum[17] using magnesium turnings to form hydroxide and alkoxide, then distilled with precautions to exclude water. The approximate amount of potassium desired was allowed to react with 500 g. of the alcohol. The concentration of potassium alkoxide was determined by titration with standard hydrochloric acid. The dimethylether of diethylene glycol used in the solvent runs was Ansul Chemical Company E-141 which had been dried by reaction with sodium wire and redistilled.

The bomb was charged but butoxide solution, sealed, purged with nitrogen, and heated to temperature. Acetylene was then admitted to maintain the total pressure constant at 50 (± 2) p.s.i.g. in excess of the vapor pressure observed. Samples of the reaction solution were withdrawn at intervals and analyzed by vapor phase chromatography at the Dow Spectroscopy Research Laboratory. The data are given in Table I. For each experiment a straight line described by the slope m and intercept b was obtained by the method of least squares. Taking the rate to be first order in butoxide concentration, a rate r was calculated by dividing the slope by this concentration. The data, shifted to pass through the origin, is presented in Figs. 2, 3 and 4.

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(13) Even if the transition state were termolecular involving concerted transfer of a proton from the alcohol to the β-carbon atom of the vinyl group, one would expect that formation of the oxygen-carbon bond would be the more important process in determining the rate of reaction. Moreover, the greater ease of breaking the hydrogen-oxygen bond of the primary alcohol should be reflected in the lesser reactivity of the alkoxide thus formed toward acetylene unless a further effect such as F-strain is also operative.

(14) H. C. Brown and I. Moritani, J. Am. Chem. Soc., 76, 455 (1954); cf. also H. C. Brown, I. Moritani, and Y. Okamoto, J. Am. Chem. Soc., 78, 2193 (1956) for a discussion of the effect of steric requirements of alkoxide bases on the direction of bimolecular elimination.

(15) "Handbook of Chemistry," N. A. Lange, Editor, Handbook Publishers, Inc., Sandusky, Ohio, 9th Edition (1956), pages 1202–1204.

(16) H. C. Brown and H. Pearsall, J. Am. Chem. Soc., 67, 1765 (1945).

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Structure and Properties of Dinaphthofurandiones

MARIO F. SARTORI

Mixtures of about equal amounts of 9-nitro- and 12-nitrodinaphtho[2,1-2',3']furan-8,13-dione (III and IV) are formed in the condensation of 2,3-dichloro-5-nitro-1,4-naphthoquinone with 2-naphthol in pyridine. Under the same conditions 1-naphthol gives 8-nitro- and 11-nitrodinaphtho[1,2-2',3']furan-7,12-dione (X and IX), with the latter in slightly larger amount.

Methods for the separation of these nitro isomers and for the determination of their structures are given. The physical properties of several derivatives of these nitrodinaphthofurandiones are discussed. The amino and benzamido dinaphthofurandiones are interesting dyes for natural and synthetic fibers.

As established by Buu-Hoï[1] and by Suryanarayana[2] the condensation of 2,3-dichloro-1,4-naphthoquinone with 1- and 2-naphthol gives the dinaphthofurandiones of structures I and II, respectively. No work has been reported, however, concerning the structures of the dinaphthofurandiones obtained in these condensations when substituents are present in the benzenoid ring of 2,3-dichloro-1,4-naphthoquinone.

This paper demonstrates that the condensation of 2,3-dichloro-5-nitro-1,4-naphthoquinone with 2-naphthol in pyridine gives a mixture of 9-nitro (III) and 12-nitrodinaphtho [2,1-2', 3']furan-8,13-dione (IV), in approximately equal amounts.
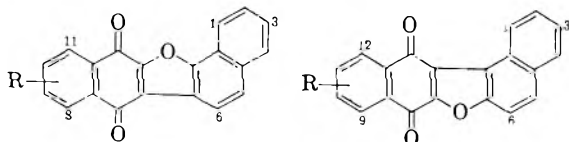

Dinaphtho[1,2-2',3']furan-7,12-dione

I. R = H
IX. R = 11-NO$_2$
X. R = 8-NO$_2$
XI. R = 11-NH$_2$
XII. R = 8-NH$_2$

Dinaphtho[2,1-2',3']furan-8,13-dione

II. R = H
III. R = 9-NO$_2$
IV. R = 12-NO$_2$
V. R = 9-NH$_2$
VI. R = 12-NH$_2$
VIII. R = 9-Br

The two nitro isomers were separated by means of their different solubilities in concentrated sulfuric acid. Orientation of the 9-nitroisomer (III) was established by reducing the nitro group to the amino and replacing the latter by a bromine atom. Comparison of this bromo derivative with an authentic specimen of 9-bromodinaphtho [2, 1-2',3']-furan-8,13-dione (VIII) confirmed its identity. This structure proof of III is obviously also an indirect proof for the structure of IV, since the latter can have only the alternative structure.

Authentic 9-bromodinaphtho [2,1-2',3']furan-8,13-dione (VIII) was synthesized from o-bromo-

phenacyl bromide and naphtho[2,1-b]furan-1,2-dione, according to the following route:
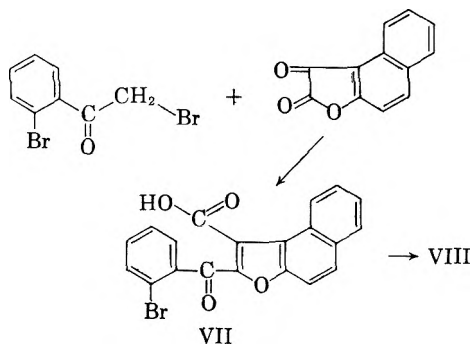
This route is similar to that developed by Chatterjea[3] for the preparation of 7-methylbenzo [b]naphtho[2,3-d]furan-6,11-dione. The last step of this route, the ring closure, was carried out by treating the carbonyl chloride derived from VII with aluminum chloride in nitrobenzene at room temperature. Under these conditions a 35% yield of the cyclized product (VIII) was obtained and 63% of the acid (VII) was recovered unchanged.

The physical properties of the two nitro isomers and their derivatives are summarized in Table I. The 9-nitro isomer (III) has a higher melting point than the 12-nitro (IV) and the 9-amino isomer (V) has a lower melting point than the 12-amino (VI). These results are in line with those observed in the 5- and 8-substituted thiophanthraquinones[4] and in the 2- and 3-substituted dibenzofurans.[5,6] The visible spectra of the 9- and 12-nitro isomers are identical. In comparison with these nitro isomers, the visible absorption maximum of the 9-amino isomer shows a bathochromic shift ($\Delta \lambda$ of 32 mμ), whereas the absorption maximum of the 12-amino isomer shows a hypsochromic shift ($\Delta \lambda$ of 22 mμ). The infrared spectra of the

(1) Ng. Ph. Buu-Hoï and P. Demerseman, *J. Chem. Soc.*, 4699 (1952).

(2) B. Suryanarayana and B. D. Tilak, *Proc. Indian Acad. Sci.*, 37-A, 81 (1953).

(3) J. N. Chatterjea, *J. Indian Chem. Soc.*, 32, 265 (1955).

(4) H. E. Schroeder and V. Weinmayr, *J. Am. Chem. Soc.*, 74, 4357 (1952).

(5) W. Borsche and W. Bothe, *Ber.*, 41, 1940 (1908).

(6) H. Gilman, G. E. Brown, W. G. Bywater, and W. H. Kirkpatrick, *J. Am. Chem. Soc*, 56, 2473 (1934).
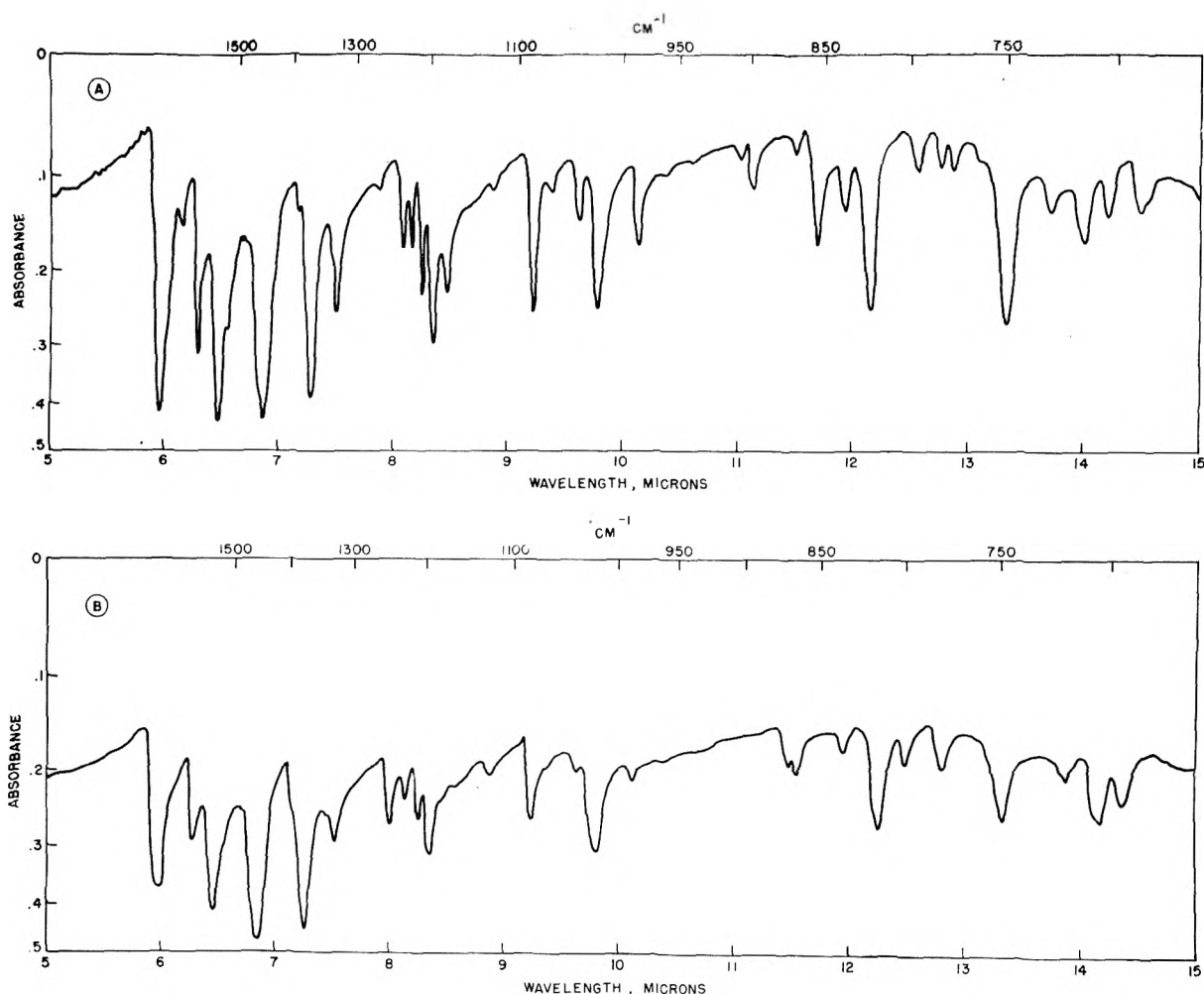
Fig. 1. Infrared spectra of the nitrodinaphtho[2,1-1',2']furan-8,13-diones
A: 9-Nitro isomer (III)
B: 12-Nitro isomer (IV)

nitro isomers are similar up to about 8 μ, both isomers exhibiting the characteristic bands of carbon-carbon double bonds, of the carbonyl and of the nitro groups (Fig. 1). A good region for differentiation is 8–15 μ, where the individual isomers present the following bands: isomer III at 11.15, 11.65, 12.15, 13.70 and 14.50 μ and isomer IV at 8.0, 12.25 and 14.35 μ.

The condensation of 2,3-dichloro-5-nitro-1,4-naphthoquinone with 1-naphthol gives a mixture of 11-nitro- (IX) and 8-nitrodinaphtho[1,2-2',3'] furan-7,12-dione (X), with the former in slightly larger amount. In this case also the two isomers were separated by means of their different solubilities in concentrated sulfuric acid.

Attempts to prepare these isomers by an unambiguous route failed. However, the comparison of the properties of the 9-nitro (III) and 12-nitro-dinaphtho[2,1-2',3']furan-8,13-dione (IV) and their derivatives with the properties of IX and X and their derivatives, respectively, indicate that IX should be the 11-nitro- and X the 8-nitrodinaphtho-[1,2-2',3']furan-7,12-dione (see Table I).

The dinaphthofurandiones described here are highly colored compounds. The amino and the benzamido derivatives were found useful as dyes for natural and synthetic fibers. These derivatives show, in comparison with the anthraquinone analogs, higher molar extinction coefficients and, in the case of the 9- and 11-amino isomers, a strong bathochromic shift of the absorption maxima (see Table I).

(7) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. The visible spectra were obtained in *o*-dichlorobenzene and recorded on a Cary Model 14 Spectrophotometer. The infrared spectra were taken in Nujol mulls on a Perkin-Elmer Model 21 Recording Spectrophotometer equipped with sodium chloride optics.

(8) K. Fries, W. Pense, and O. Peeters, *Ber.*, 61, 1395 (1928).

TABLE I

PHYSICAL PROPERTIES OF ANTHRAQUINONE AND
DINAPHTHOFURANDIONE DERIVATIVES

Derivatives	M.P., °C.	Absorption Maxima[a] λ, mμ	$\epsilon^b \times 10^{-3}$
Anthraquinone			
1-Amino	245	462	6.0
1-Benzamido	246	418	6.2
Dinaphthofuran-8,13-dione			
9-Nitro (III)	342	468	5.8
12-Nitro (IV)	314	468	5.8
9-Amino (V)	298	500	9.8
12-Amino (VI)	338	446	9.2
9-Benzamido	342	480	15.0
12-Benzamido	300	450	10.0
Dinaphthofuran-7,12-dione			
11-Nitro (IX)	344	452	5.3
8-Nitro (X)	322	452	5.3
11-Amino (XI)	302	496	8.2
8-Amino (XII)	362	440	7.5
11-Benzamido	292	470	13.0
8-Benzamido	310	450	9.6

[a] Solvent: o-dichlorobenzene. [b] Molar Extinction Coefficient, ϵ, defined as $\dfrac{\text{Optical Density}}{C \, 1}$, where C is concentration g. mol./liter and 1 is cell length in cm.

pyridine (150 ml.). A dark brown suspension was formed and the temperature rose to 50°C. The mixture was then heated to 100–110°C. in about 1 hr. and kept at this temperature for an additional three hr. After stirring for twelve hr. at room temperature, the orange precipitate was collected, washed with ethanol, and dried. The crude product (13.5 g.) was repeatedly extracted with boiling water to remove the nitropyridinium compound.[2,9] The residue (11.0 g.), m.p. 284–286°, was a mixture of III and IV. Microscopic examination showed the presence of yellow and orange crystals.

Anal. Calcd. for $C_{20}H_9NO_5$: C, 70.0; H, 2.6; N, 4.1. Found: C, 70.1; H, 2.7; N, 4.0.

The aqueous extract by concentration gave the nitropyridinium compound as yellow crystals (2.5 g.) of m.p. 302–304°.

Anal. Calcd. for $C_{15}H_7N_2O_5$: C, 61.0; H, 2.7; N, 9.5. Found: C, 60.6; H, 2.7; N, 9.4.

The above mixture of nitro isomers III and IV (5 g.) was stirred at 15–18° for 1 hr. with concentrated sulfuric acid (200 ml.). A deep blue slurry was obtained. The insoluble material was collected, washed first with concentrated sulfuric acid and then with ice water, dried and crystallized from o-dichlorobenzene to yield 2.3 g. of III as long, yellow needles; m.p. 342–344°.

Anal. Calcd. for $C_{20}H_9NO_5$: C, 70.0; H, 2.6; N, 4.1. Found: C, 70.0; H, 2.7; N, 4.0.

The sulfuric acid filtrate was drowned slowly on ice to give 2.5 g. of IV as orange precipitate of m.p. 310°, which after crystallization from o-dichlorobenzene yielded short orange-red needles; m.p. 314–316°.

Anal. Calcd. for $C_{20}H_9NO_5$: C, 70.0; H, 2.6; N, 4.1. Found: C, 70.0; H, 2.6; N, 4.0.

9-Aminodinaphtho[2,1-2',3']furan-8,13-dione (V). 9-Nitrodinaphtho[2,1-2',3']furan-8,13-dione (III) (2.0 g.) was added to a stirred solution of sodium hydrosulfite (10 g.) and sodium hydroxide (10 g.) in water (400 ml.). After 15 minutes at 35° the slurry changed to a clear orange solution. The agitation was continued at 35–40° for 1 hr., then the solution was filtered and the filtrate oxidized with air for

(9) B. Eistert, *Ber.*, **80**, 47 (1947).

2 hr. The dark violet precipitate (1.7 g.), m.p. 296–298°, crystallized from nitrobenzene, yielded V as violet feathery needles; m.p. 298–300°.

Anal. Calcd. for $C_{20}H_{11}NO_3$: C, 76.6; H, 3.5; N, 4.4. Found: C, 76.6; H, 3.5; N, 4.4.

The benzamide of V was obtained by heating V (0.07 g.) at 100° for 1 hr. with an excess of benzoyl chloride (0.07 ml.) in dry pyridine (2 ml.). Bright orange needles (0.07 g.) of m.p. 342° (o-dichlorobenzene) were obtained.

Anal. Calcd. for $C_{27}H_{15}NO_4$: C, 77.7; H, 3.6; N, 3.35. Found: C, 77.8; H, 3.7; N, 3.4.

The p-toluenesulfonamide of V was obtained by boiling V (0.1 g.) for 1 hr. with an excess of p-toluenesulfonyl chloride (0.2 g.) in dry pyridine (5 ml.). Orange crystals (0.12 g.) of m.p. 284–286° (acetic acid) were obtained.

Anal. Calcd. for $C_{27}H_{17}NO_5S$: C, 69.0; H, 3.6; S, 6.8. Found: C, 69.3; H, 3.8; S, 6.5.

9-Bromodinaphtho[2,1-2',3']furan-8,13-dione from V. A fine slurry of V (0.12 g.) in 85% phosphoric acid (25 ml.) was diazotized at 10°C. with sodium nitrite (0.03 g.). The resulting violet diazonium solution was poured slowly into a solution of cuprous bromide (0.7 g.) in 48% hydrobromic acid (12 ml.) and stirred for 1 hr. at room temperature, while diluting with water (50 ml.). After stirring an additional 0.5 hr. at 80–100°, the orange precipitate was filtered off, washed with water and dried (0.13 g.; m.p. 320–324°). Crystallization from acetic acid gave 0.1 g. of 9-bromodinaphtho[2,1-2',3']-furan-8,13-dione as orange crystals; m.p. 330–332°.

Anal. Calcd. for $C_{20}H_9BrO_3$: C, 63.6; H, 2.4; Br, 21.2. Found: C, 63.3; H, 2.5; Br, 20.8.

12-Aminodinaphtho[2,1-2',3']furan-8,13-dione (VI). The amine VI was prepared from the nitro isomer IV (2.0 g.) by the procedure described for the isomeric amine V. A 95% yield of VI was obtained as dark brown crystals; m.p. 338–340° (nitrobenzene).

Anal. Calcd. for $C_{20}H_{11}NO_3$: C, 76.6; H, 3.5; N, 4.4. Found: C, 76.5; H, 3.5; N, 4.4.

The benzamide of VI crystallized from chlorobenzene as red-orange crystals, m.p. 300°.

Anal. Calcd. for $C_{27}H_{15}NO_4$: C, 77.7; H, 3.6; N, 3.35. Found: C, 77.3; H, 3.7; N, 3.4.

The p-toluenesulfonamide of VI crystallized from acetic acid as orange crystals of m.p. 282–284°. The mixed m.p. with the p-toluenesulfonamide of V was 253–260°.

Anal. Calcd. for $C_{27}H_{17}NO_5S$: C, 69.0; H, 3.6; S, 6.8. Found: C, 69.0; H, 3.7; S, 6.7.

Chromatographic separation of the 9- and 12-amino isomers (V and VI). The mixture of the nitro isomers III and IV was reduced with alkaline sodium hydrosulfite as described for V and the resulting mixture of aminodinaphthofurandiones (m.p. 272–284°) dissolved in benzene was chromatographed on alumina. Elution with benzene yielded two bands: a brownish-orange band, which after evaporation of the solvent and crystallization from toluene, gave VI (40–50%) as dark brown crystals (m.p. 338°) and a violet band which gave V (50–60%) as violet crystals (m.p. 298–300°).

Proof of structure of 9-bromodinaphtho[2,1-2',3']furan-8,13-dione from V. *2-(o-Bromobenzoyl)naphtho[2,1-b]furan-1-carboxylic acid* (VII). This acid was prepared from naphtho[2,1-b] furan-1,2-dione[10] and o-bromophenacyl bromide[11] by a method similar to that described by Chatterjea[3] for the synthesis of 7-methylbenzo[b]naphtho[2,3-d]furan-6,11-dione. A 70% yield of pale yellow crystals of m.p. 174–176° was obtained.

Anal. Calcd. for $C_{20}H_{11}BrO_4$: C, 60.7; H, 3.0; Br, 20.2. Found: C, 60.5; H, 2.8; Br, 20.1.

9-Bromodinaphtho[2,1-2',3']furan-8,13-dione (VIII). Acid VII (3 g.) was converted into the acid chloride by stirring it with thionyl chloride (30 ml.) at room temperature for 16

(10) M. Giua, *Gazz. Chim. Ital.*, **54**, 509 (1924).

(11) R. L. Lutz and 15 Co-workers, *J. Org. Chem.*, **12**, 664 (1947).

hr. After removal of the thionyl chloride, the residue was dissolved in nitrobenzene (30 ml.) and aluminum chloride (12 g.) was added gradually at 20–25°. The mass turned dark then violet. After overnight stirring at room temperature, the reaction product was drowned in ice and hydrochloric acid and the nitrobenzene was steam distilled. The residue was removed by filtration and slurried with an excess of dilute sodium hydroxide solution to separate unreacted starting material. The alkali insoluble product was purified by vatting to yield 1.1 g. of crude material, m.p. 325–328°, which on crystallization from toluene (Darco) gave 1.0 g. of VIII as orange crystals; m.p. 330–332°.

Anal. Calcd. for $C_{20}H_9BrO_3$: C, 63.6; H, 2.4. Found: C, 63.4; H, 2.4.

The alkaline filtrate upon acidification with concentrated hydrochloric acid gave 1.9 g. of unreacted 2-(o-bromobenzoyl)naphtho[2,1-b]furan-1-carboxylic acid (VII); m.p. 174–176°.

A mixture of VIII with the bromo compound obtained from V (m.p. 330–332°) melted at 330–332°. The identity of the two bromo derivatives was further substantiated by comparison of the infrared spectra.

9-(p-Tolylsulfonamido)dinaphtho[2,1-2',3']furan-8,13-dione. A mixture of VIII (0.2 g.), p-toluenesulfonamide (0.14 g.), sodium carbonate (0.08 g.), cuprous chloride (0.01 g.) and nitrobenzene (15 ml.) was heated at 200° for 6 hr. The crude product was removed by filtration, washed and crystallized from acetic acid to yield bright yellow crystals (90% yield) of m.p. 286–288°.

Anal. Calcd. for $C_{27}H_{17}NO_5S$: C, 69.0; H, 3.6. Found: C, 69.3; H, 3.8.

The identity of this derivative of VIII with the p-toluenesulfonamide obtained from V was established by mixed m.p. determinations and infrared spectra. On the other hand, the mixed m.p. of the p-toluenesulfonamides of VIII and VI (m.p. 282–284°) showed a significant depression (mixed m.p. 253–260°).

Condensation of 1-naphthol with 2,3-dichloro-5-nitro-1,4-naphthoquinone. 8- and 11-Nitrodinaphtho[1,2-2',3']furan-7,12-diones (X and IX). 2,3-Dichloro-5-nitro-1,4-naphthoquinone of m.p. 175° (13.5 g.), prepared by the method of Fries,[8] was reacted with 1-naphthol (8.0 g.) in the manner described for the nitro isomers III and IV. The precipitate, after filtration and repeated extraction with boiling water, gave 11.5 g. of an orange product of m.p. 306–308°, which was a mixture of X and IX. Microscopic examination

showed the presence of orange-yellow and pale yellow crystals.

Anal. Calcd. for $C_{20}H_9NO_5$: C, 70.0; H, 2.6; N, 4.1. Found: C, 70.1; H, 2.7; N, 4.0.

The above mixture of nitro isomers X and IX (5 g.) was stirred with concentrated sulfuric acid in the manner described for the mixture of nitro isomers III and IV. The insoluble material crystallized from o-dichlorobenzene yielded 2.6 g. of IX as bright orange crystals; m.p. 344–346°.

Anal. Calcd. for $C_{20}H_9NO_5$: C, 70.0; H, 2.6; N, 4.1. Found: C, 70.0; H, 2.7; N, 4.0.

The sulfuric acid filtrate, drowned slowly on ice, gave 2.1 g. of X as a red-brown precipitate; m.p. 314–322°. Crystallization from o-dichlorobenzene yielded yellow crystals (m.p. 320–324°) with little loss.

Anal. Calcd. for $C_{20}H_9NO_5$: C, 70.0; H, 2.6; N, 4.1. Found: C, 70.2; H, 2.7; N, 4.0.

8-Aminodinaphtho[1,2-2',3']furan-7,12-dione (XII). The amine XII, obtained from the nitro isomer X as described for the amine V, crystallized from nitrobenzene as red-brown crystals of m.p. 362–364°.

Anal. Calcd. for $C_{20}H_{11}NO_3$: C, 76.6; H, 3.5; N, 4.4. Found: C, 76.8; H, 3.3; N, 4.6.

The benzamide of XII crystallized from chlorobenzene as orange needles, m.p. 310–312°.

Anal. Calcd. for $C_{27}H_{15}NO_4$: C, 77.7; H, 3.6; N, 3.35. Found: C, 77.5; H, 3.3; N, 3.4.

11-Aminodinaphtho[1,2-2',3']furan-7,12-dione (XI). The amine XI, obtained from the nitro isomer IX, crystallized from nitrobenzene as violet-red crystals, m.p. 302–304°.

Anal. Calcd. for $C_{20}H_{11}NO_3$: C, 76.6; H, 3.5; N, 4.4. Found: C, 76.6; H, 3.3; N, 4.5.

The benzamide of XI crystallized from chlorobenzene as orange needles, m.p. 292–294°.

Anal. Calcd. for $C_{27}H_{15}NO_4$: N, 3.35. Found: N, 3.4.

Chromatographic separation of the 8- and 11-amino isomers (XII and XI). The mixture of the isomeric amines XII and XI (m.p. 294–298°), obtained from the mixture of the nitro isomers X and IX by reduction with alkaline sodium hydrosulfite, was chromatographed as described for the isomeric amines V and VI. The brownish-orange band gave XII (40% of the mixture) as dark red crystals, m.p. 362–364°, and the bright violet band gave XI (60%) as red crystals, m.p. 302–304°.

<div style="text-align:right">WILMINGTON, DEL.</div>

A New Synthetic Route to Methoxytetralones

J. W. HUFFMAN

5-Methoxy-1-tetralone has been prepared from 8-chloro-5-methoxy-1-tetralone by preferential hydrogenolysis of the halogen atom. The chlorotetralone has also been converted to 5-chloro-8-methoxy-1-tetralone in low yield. The infrared and ultraviolet spectra of these compounds are discussed.

Although 5-methoxy-1-tetralone has been previously prepared, it, 8-methoxy-1-tetralone and their derivatives are relatively inaccessible, compared with the well known 6- and 7-methoxytetralones. 5-Methoxytetralone has been prepared from coumarin[1] in low yield by a six-step synthesis,

and also by hydrogenation of substituted naphthalene derivatives,[2] followed by appropriate conversions. The preparation of 7-methoxytetralone from anisole via β-(4-methoxybenzoyl)propionic

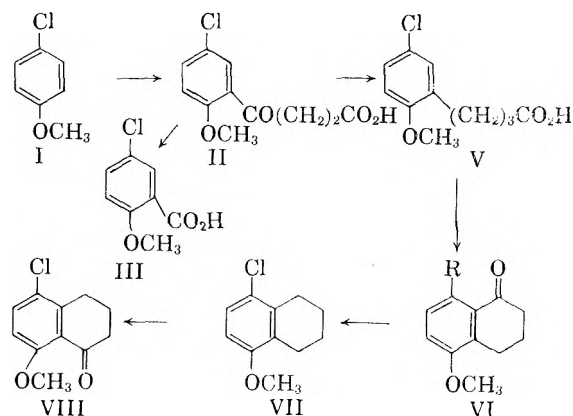(1) J. Lockett and W. F. Short, *J. Chem. Soc.*, 787 (1939).

(2) (a) E. Hardegger, D. Redlich, and A. Gal, *Helv. Chim. Acta*, 27, 628 (1944). (b) D. Papa and E. Schwenk, *J. Org. Chem.*, 14, 366 (1949).

acid is well know,[3] and the preparation of 6-methoxy-1-tetralone in moderate yield has been reported.[4] Unfortunately all attempts at preparing 5- and 8-methoxytetralone by the direct succinoylation of an unsubstituted anisole ring afford as the final product, only 7-methoxy-1-tetralone. 5-Methoxy-8-methyl-1-tetralone has, however, been prepared from p-cresyl methyl ether,[5] and 5-methoxy-4,8-dimethyl-1-tetralone has been synthesized from the same starting material.[6]

The parent 5-methoxytetralone would appear to be readily available from some appropriately *para* substituted anisole derivative, containing an easily removable blocking group. Although the facile hydrogenolysis of halogen bound to an aromatic ring is well known,[7] and has been used in the preparation of tetracycline from aureomycin, without disturbing the sensitive ring system of these antibiotics,[8] this potentially useful blocking group has found little use in organic synthesis until this time. Haworth and Perkin attempted to use a bromine atom as a blocking group in order to accomplish the synthesis of a berberine alkaloid of the natural series rather than the *pseudo* alkaloid; however, this attempt led only to the extrusion of the bromine and cyclization to the *pseudo* berberine derivative.[9] An aromatic bromine has been reported to have been successfully employed in the Pschorr synthesis of a phenanthrene derivative,[10] while one failure of this blocking group in a similar synthesis has been observed.[11]

The present investigation is concerned with the use of chlorine as a blocking group in the synthesis of 5-methoxy-1-tetralone. Succinoylation of p-chloroanisole (I) with aluminum chloride in tetrachloroethane-nitrobenzene afforded β-(2-methoxy-5-chlorobenzoyl)propionic acid (II) in 51% yield.[12] In an effort to characterize this compound it was

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(9) R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, 127, 1448 (1925).

(10) A. Girardet, *Helv. Chim. Acta*, 14, 573 (1931).

(11) E. E. Lewis and R. C. Elderfield, *J. Org. Chem.*, 5, 290 (1940).

(12) J. D. Reinheimer and J. C. Smith, *J. Org. Chem.*, 17, 1505 (1952) reported the preparation of this material; however, they failed to report analytical figures or to characterize the compound in any way. We were able to accomplish the acylation reaction using only nitrobenzene as a solvent; however, the yield and quality of the product were decidedly inferior.

oxidized with alkaline permanganate to yield the known 2-methoxy-5-chlorobenzoic acid[13] (III); however, unexpected difficulties were encountered in identifying this material. Earlier workers had found the compound to melt at 79°; our substance had m.p. 97–98°, and the infrared spectrum in chloroform solution showed carbonyl absorption at 5.75 μ, and a sharp O—H stretching band at 3.00 μ. The expected spectrum for 2-methoxy-5-chlorobenzoic acid in chloroform solution would have a broad —OH band at 3.5 to 4.0 μ and a carbonyl band at 5.88 to 5.95 μ.[14] In spite of the anomalous spectrum, the compound was a strong acid, as evidenced by its solubility in aqueous bicarbonate solution, and analysis showed the correct empirical formula, $C_8H_7ClO_3$, for a chloromethoxybenzoic acid. Since 2-chloro-5-methoxybenzoic acid has m.p. 170°;[13] our oxidation product must be 2-methoxy-5-chlorobenzoic acid. It seems probable that the acid obtained by the Italian workers was a hydrate or polymorph, because recrystallization of the acid, m.p. 98°, from water gave material, m.p. 74–75°, which could in turn be recrystallized from cyclohexane to give the original melting point. Final confirmation of the structure of the

material came in the preparation of an authentic sample by the methylation of 2-hydroxy-5-chlorobenzoic acid.[15]

The anomalous infrared spectrum appears to be a general phenomenon of 2-methoxybenzoic acids. 2-Methoxybenzoic acid itself shows sharp O—H absorption at 2.96 μ, and carbonyl absorption at 5.76 μ, while p-anisic acid shows the usual broad band at 3.4–3.6 μ, and a strong carbonyl band at 5.93 μ. Yates has observed the same peculiarities in the infrared spectrum of a number of compounds of this type related to mangostin.[16] The sharp

(13) A. Peratoner and G. B. Condorelli, *Gazz. chim. ital.*, 28 [I], 211 (1898).

(14) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Metheun, London (1954), pp. 140–150.

(15) The reaction of chlorosalicylic acid with dimethyl sulfate and base proceeded in low yield, and with some difficulty, as has been previously observed in the methylation of phenols bearing a carbonyl group *ortho* to the hydroxyl [ref. (5)].

(16) P. Yates, Private communication.

O—H band may be attributed to a tendency for the acid to internally hydrogen-bond (IV), rather than to exist as a dimer in dilute solution. The spectrum of o-methoxybenzoic acid in the solid state (nujol) indicates that under these conditions internal hydrogen bonding does not occur, for the infrared spectrum shows normal acid absorption peaks.

IV
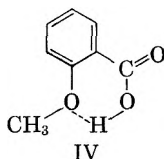
Reduction of β-(2-methoxy-5-chlorobenzoyl)propionic acid under normal Clemmensen conditions gave a good yield of γ-(2-methoxy-5-chlorophenyl)-butyric acid (V). Cyclization of this acid to 5-methoxy-8-chloro-1-tetralone (VI. R = Cl) proceeded with some difficulty. Using polyphosphoric acid as the catalyst the tetralone could be obtained; however, 29% of the phenylbutryic acid was recovered, and the yield of cyclized product based on recovered acid never exceeded 42%. Classical aluminum chloride catalyzed cyclization of the acid chloride gave 21% recovery of (V), and 13% of tetralone of decidedly inferior quality to that obtained by the use of polyphosphoric acid.

The hydrogenolysis of the chlorotetralone proceeded extraordinarily smoothly, at atmospheric pressure, using 10% palladium-on-charcoal catalyst, with one equivalent of triethylamine added to neutralize the hydrogen chloride evolved. The dehalogenated tetralone (VI. R = H) was obtained in 56% yield after purification, and agreed well in its properties with those reported by earlier workers.[1]

An interesting comparison may be found in the ultraviolet spectra (Table I) of the chlorinated (VI. R = Cl), and dehalogenated tetralone (VI. R = H).

TABLE I

Compound	$\lambda_{max,}$ mμ	log ϵ
5-Methoxy-8-chloro-1-tetralone	247	3.97
5-Methoxy-1-tetralone	257	4.10
1-Tetralone[a]	250	4.12
Benzophenone[b]	253	4.27
4-Chlorobenzophenone[c]	260	4.32
4,4'-Dichlorobenzophenone[c]	265	4.39

[a] G. D. Hedden and W. G. Brown, J. Am. Chem. Soc., 75, 3744 (1953). [b] R. N. Jones, J. Am. Chem. Soc., 67, 2141 (1945). [c] H. H. Szamant and C. McGinnis, J. Am. Chem. Soc., 74, 241 (1952).

Although the dehalogenated tetralone (VI. R = H) showed an ultraviolet spectrum very similar to that of 1-tetralone, there is a marked hypsochromic shift obtained by the addition of a halogen in the 8-position (−10 mμ). A study of the ultraviolet spectrum of benzophenone and sub-

stituted benzophenones (Table I) indicates that halogenation para to the carbonyl group results in a bathochromic shift of about 6 mμ for each halogen. On this basis one would predict from electronic considerations that the chlorotetralone (VI. R = Cl) would show ultraviolet absorption at about 263 mμ. Although a steric argument might be devised to explain these spectral anomalies, this does not seem too promising in the light of earlier work on the ultraviolet spectra of substituted benzaldehydes. It has been found that the only significant difference in the spectra of 2-methyl and 4-methyl benzaldehyde is in the intensity of the absorption.[17] This decrease in intensity may be attributed to a slight steric interaction between the carbonyl oxygen and the adjacent methyl group in 2-methylbenzaldehyde.[18] Since the chlorine atom in (VI) has a smaller Van der Waals' radius than a methyl group[19] (1.85 A as against 2.00 A); any steric effect must be smaller than that operative in the methyl benzaldehydes; however, the hypsochromic shift in the chlorotetralone is indicative of an effect of much greater magnitude. We would like to suggest that this hypsochromic shift of 10 mμ is caused by a dipole-dipole interaction between the halogen atom and the carbonyl group, resulting in either a slight out of plane twisting of the carbonyl group, or more probably, a simple electrical effect, which provides a greater ground to excited state energy barrier.[20]

It was felt that the smooth hydrogenolysis of the chlorine atom might provide an entry into the 8-methoxytetralone series via a three-step reaction sequence from VI (R = Cl). Reduction of VI under Clemmensen conditions afforded VII in mediocre yield as a yellow oil which decomposed slowly on standing. The oxidation of (VII) to (VIII) with chromic acid–acetic acid[21] gave erratic results, and generally low yields of impure product. The reaction product showed a maximum in the ultraviolet at 256 mμ and gave a 2,4-dinitrophenylhydrazone which had analytical data consistent

(17) E. A. Braude, F. Sondheimer, and W. F. Forbes, Nature, 173, 117 (1954).

(18) The analogous methyl acetophenones have also been studied [ref. (17)] and although they give evidence of considerable steric hindrance between ortho methyl groups and the acetyl groups, this is explained by a methyl-methyl interaction. The only interaction possible on the chlorotetralone (VI, R = Cl) is, of course, a chlorine oxygen steric effect.

(19) W. Klyne, Progress in Stereochemistry, Butterworths, London, 1954, p. 365.

(20) J. H. Boothe, S. Kushner, J. Petisi, and J. H. Williams, J. Am. Chem. Soc., 75, 3261 (1953), have observed a similar, but previously unexplained effect in 2-carbomethoxy-6-chloro-3-methoxyacetophenone and the corresponding unhalogenated compound. This hypsochromic shift of 15 mμ is probably due to a dipole-dipole interaction, as is the 5 mμ hypsochromic shift in the ultraviolet spectra of equatorially substituted 2-bromocyclohexanones, R. C. Cookson, J. Chem. Soc., 282 (1954).

(21) J. C. Bardhan and D. N. Mukherjee, J. Chem. Soc., 4629 (1956).

with the derivative of (VIII). It seems likely that the product is contaminated with unoxidized tetralin, (VII). In view of these difficulties this route to 8-methoxytetralone was abandoned; however, the use of aromatically bound chlorine atoms remains a potentially useful means of blocking a reactive position on the aromatic nucleus, in electrophilic aromatic substitution reactions.

EXPERIMENTAL[22]

β-(2-Methoxy-5-chlorobenzoyl)propionic acid. To a chilled mixture of 20 g. of *p*-chloroanisole and 16 g. of succinic anhydride in 200 ml. of a one-to-one mixture of *sym*-tetrachloroethane and nitrobenzene was added in portions 42.4 g. of aluminum chloride. The reaction mixture was allowed to stand in the cold for 7 days, then poured onto a mixture of ice and concentrated hydrochloric acid. The solvents were removed by steam distillation, and the resulting aqueous suspension of the product was made alkaline with 10% sodium bicarbonate, treated with decolorizing carbon, and filtered through celite. Acidification and cooling gave cream-colored crystals, which on recrystallization from cyclohexane–ethyl acetate afforded 16.2 g. (51%) of pale cream crystals, m.p. 114–116°. Further recrystallization from the same solvent pair gave crystals m.p. 118–119°.[12]

Anal. Calcd. for $C_{11}H_{11}ClO_4$: C, 54.44; H, 4.57; Cl, 14.61. Found: C, 54.63; H, 4.50; Cl, 14.59.

2-Methoxy-5-chlorobenzoic acid. (a) To a solution of 1.0 g. of *β*-(2-methoxy-5-chlorobenzoyl)propionic acid in 80 ml. of 1% potassium hydroxide was added 4 g. of potassium permanganate. The solution was heated under reflux 2 hr., acidified with dilute sulfuric acid and heated on the steam bath 30 min. On cooling the product crystallized out. Recrystallization from ethyl acetate–cyclohexane gave 0.22 g. (29%) of white needles, m.p. 92–95°. Recrystallization of this material from water gave fluffy white needles m.p. 74–75°.[13] Recrystallization of the lower melting form of this compound from cyclohexane ethyl acetate afforded material m.p. 97–98°.

Anal. Calcd. for $C_8H_7ClO_3$: C, 51.42; H, 3.79; Cl, 19.00. Found: C, 51.08; H, 4.11; C, 18.88.

(b) 2-Hydroxy-5-chlorobenzoic acid[23] was treated with dimethyl sulfate in base to give a 31% yield of crystals, m.p. and mixed m.p. 97–98°.

γ-(2-Methoxy-5-chlorophenyl)-butyric acid. The chloromethoxybenzoyl propionic acid was reduced under the usual conditions of the Clemmensen reduction.[24] From 18.0 g. of starting material 14.6 g. (86%) of white crystals, m.p. 78–80° were obtained. This material was sufficiently pure for cyclization to the tetralone. A sample was purified for analysis by distillation at 155–165° (air bath) and 1 mm., and recrystallization from hexane to give material m.p. 80–81°.

Anal. Calcd. for $C_{11}H_{13}ClO_3$: C, 57.77; H, 5.73. Found: C, 57.62; H, 5.51.

5-Methoxy-8-chloro-1-tetralone   (8-chloro-5-methoxy-3,4-dihydronaphthalene-1(2)-one). (a) A mixture of 10 g. of γ-(2-methoxy-5-chloro)butyric acid and 125 g. of polyphosphoric

acid[25] were heated on the steam bath 1.5 hr. with occasional stirring. The reaction mixture was cooled, poured into ice water, and extracted twice with ether. The ethereal extracts were combined, washed with water, and extracted with 10% sodium carbonate solution. Acidification of the basic extract afforded 2.89 g. (29%) of a brown powder with an infrared spectrum identical to the chloromethoxyphenylbutyric acid. The ethereal phase of the extract was washed again with water, dried, and the solvent removed *in vacuo* to give 3.40 g. of brown oil which partially solidified. Recrystallization from hexane afforded 2.73 g. (42% based on recovered acid) of pale yellow solid, m.p. 42–45°. Distillation of 150–160° (air bath) and 1 mm., followed by recrystallization from hexane gave small white needles, m.p. 47–48°.

Anal. Calcd. for $C_{11}H_{11}ClO_2$: C, 62.71; H, 5.26. Found: C, 62.38; H, 5.44.

The 2,4-dinitrophenylhydrazone formed orange crystals from ethyl acetate m.p. 226–228°.

Anal. Calcd. for $C_{17}H_{15}ClN_4O_5$: C, 52.25; H, 3.87; N, 14.34. Found: C, 52.23; H, 3.80; N, 14.61.

(b) To a solution of 1.0 g. of the γ-phenylbutyric acid in 30 ml. of dry benzene was added 1.44 g. of phosphorus pentachloride. The mixture was heated under reflux 3 hr., cooled to 0°, and 1.0 g. of aluminum chloride added. The cyclization mixture was allowed to warm to room temperature, heated under reflux 45 min., cooled, and poured into iced concentrated hydrochloric acid. The acid layer was drawn off, and extracted with ether. The organic phases were combined and washed with 5% sodium hydroxide. Acidification of the basic washings gave 0.21 g. (21%) of the starting acid. After drying and removal of the ether, 0.13 g. of neutral brown oil with an infrared spectrum virtually identical to the material obtained with polyphosphoric acid was obtained. The 2,4-dinitrophenylhydrazone formed crystals from ethyl acetate, m.p. 222–225°, undepressed on mixing with a sample prepared by the alternate route.

5-Methoxy-1-tetralone   (5-methoxy-3,4-dihydronaphthalene-1(2)-one). To a solution of 0.41 g. of chloromethoxytetralone in 15 ml. of 95% ethanol was added 0.05 g. of 10% palladized charcoal, and 0.28 ml. of triethylamine. The reaction mixture absorbed 1.06 moles of hydrogen at room temperature and atmospheric pressure in 15 min., whereupon the rate of hydrogen uptake virtually ceased. The reaction mixture was filtered through celite, concentrated to a small volume, taken up in ether, and washed with successive portions of water and 5% hydrochloric acid. After drying and removal of the solvent a colorless oil which readily crystallized was obtained. Recrystallization from hexane afforded 0.18 g. (53%) of white needles m.p. 81–84°. A second recrystallization gave material m.p. 85–87°. Lockett and Short[1] gave a m.p. of 89° for this compound. The 2,4-dinitrophenylhydrazone formed beautiful deep red crystals from ethyl acetate, m.p. 227–228°.

Anal. Calcd. for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.72. Found: C, 57.08; H, 4.76; N, 15.95.

4-Chloro-1-methoxy-5,6,7,8-tetrahydronaphthalene. To a suspension of 5 g. of zinc amalgam in a mixture of 24 ml. of concentrated hydrochloric acid and 12 ml. of water was added a solution of 2.0 g. of chloromethoxytetralone in 12 ml. of ethanol. The reaction was heated under reflux 13 hr. With 5-ml. portions of concentrated acid being added at three-hour intervals. The yellow solution was decanted from the undissolved metals, extracted with 2 portions of ether, and washed with water. After drying and removal of the solvent a yellow oil remained which was covered with 20 ml. and 10% sodium hydroxide and 2.0 ml. of dimethyl sulfate and heated 30 min. on the steam bath. The basic solution was cooled, extracted twice with ether, washed with 5% hydrochloric acid, 5% sodium carbonate, and water. After drying and removal of the solvent a yellow-brown

(22) Melting points were determined on a Fisher–Johns block, and are uncorrected. Infrared spectra were carried out in chloroform solution, or as liquid films on a Perkin–Elmer model 137 spectrophotometer, and ultraviolet spectra were determined in 95% ethanol on a Beckman model DK-1 recording spectrophotometer. Analyses performed by Galbraith Laboratories, Knoxville, Tenn.

(23) A. Leulier and L. Pinet, *Bull. soc. chim.*, [4], **41**, 1363 (1927).

(24) E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

(25) We would like to thank the Victor Chemical Works, Chicago, Ill., for a generous sample of this material.

oil was obtained, which distilled to give 0.66 g. (35%) of unstable pale yellow liquid, b.p. 125–135° (air bath) at 1 mm.

Anal.[21] Calcd. for $C_{11}H_{13}ClO$: C, 67.17; H, 6.66. Found: C, 65.93; H, 6.72.

8-*Methoxy-5-chloro-1-tetralone* (5-*chloro-8-methoxy-3,4-dihydronaphthalene-1(2)-one.* To a cold solution of 0.20 g. of chloromethoxytetralin in 3.0 ml. of acetic acid was added slowly 0.15 g. of chromic acid in 1 ml. of water and 2 ml. of acetic acid. The mixture was allowed to warm to room temperature, and stand overnight. The green solution was poured into water, extracted twice with ether, washed well with water, and then 10% sodium carbonate. The ethereal solution was dried, and the solvent removed at reduced pressure to give 0.1 g. of yellow oil which showed infrared absorption at 5.94 μ gave on treatment with 2,4-dinitrophenylhydrazine a small amount of derivative, m.p. 245–250° (dec.). The dinitrophenylhydrazone was purified by recrystallization from a relatively large volume of ethyl acetate to give small, very dark red crystals, m.p. 250–252° (dec.).

Anal. Calcd. for $C_{17}H_{15}ClN_4O_5$: C, 52.25; H, 3.87; N, 14.34. Found: C, 52.06; H, 4.01; N, 14.54.

ATLANTA, GA.

Substituted 1,4-Dioxanes

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A number of substituted 1,4-dioxanes were prepared as part of a search for central nervous system depressants. Hydroxylation of 2-allyl-1,4-dioxane gave 2-(2-hydroxypropyl)- and 2-(2,3-dihydroxypropyl)-1,4-dioxane. 2,2-Dialkyl-1,4-dioxanes were prepared by cyclization of 2-(2-chloroethoxy)-1,1-dialkylethanols. Cyclization of methallyloxyethanol gave 2,2-dimethyl-1,4-dioxane. Three bis(hydroxyalkyl) ethers were also prepared.

Central nervous system depressants have been found among the dioxolanes and among glyceryl ethers.[1] Both these groups of compounds have in common α,β-dioxygen functions. In unreported work which was carried out in these laboratories some years ago, it was found that 2-hydroxymethyl-1,4-benzodioxane also exerts a depressing effect on the central nervous system. We thought it would be in order to explore the pharmacological effect of some 1,4-dioxane compounds as possible central nervous system depressants.

2-Allyl-1,4-dioxane[2] was monohydroxylated to give 2-(2-hydroxypropyl)-1,4-dioxane. The hydroxylation was accomplished using 75% sulfuric acid after finding that 50% sulfuric acid had negligible effect and 100% sulfuric acid gave tars.

The 2-allyl-1,4-dioxane was dihydroxylated according to the hydroxylation procedure of Swern *et al.*,[3] using performic acid to give 2-(2,3-dihydroxypropyl)-1,4-dioxane.

The 2-allyl-1,4-dioxane has greater central nervous system depression activity than either of its hydroxylated derivatives or than dioxane itself.

We next turned to the preparation of some 2,2-disubstituted dioxanes. A survey of the literature showed that no compounds of this type had been reported, and we thought that a quaternary carbon in such structures might enhance central nervous system depression. To this end, methyl β-chloroethoxyacetate[4] was prepared from β-chloroethoxyacetonitrile which was obtained by the action of cuprous cyanide on β-chloroethyl chloromethyl ether. Reaction of this material with ethylmagnesium bromide gave 2-(2-chloroethoxy)-1,1-diethylethanol which was cyclized to 2,2-diethyl-1,4-dioxane (I). The cyclizing agent was sodium ethylate. In a similar manner 2-(2-chloroethoxy)-1,1-dibutylethanol was prepared and cyclized to 2,2-dibutyl-1,4-dioxane (II) using sodium amide. When phenylmagnesium bromide in large excess was allowed to react with methyl chloroethoxyacetate there was obtained 1,1-diphenylethylene glycol. This compound probably resulted from the action of the excess phenylmagnesium bromide as a base, on the expected 2-(2-chloroethoxy)-1,1-diphenylethanol to give the glycol directly or *via* the intermediate 2-(vinyloxy)-1,1-diphenylethanol. Hydrolysis of this vinyl ether would furnish the 1,1-diphenylethylene glycol. When a more nearly theoretical amount of phenylmagnesium bromide was used in the reaction, the desired product, 2-(2-chloroethoxy)-1,1-diphenylethanol, was obtained. There was also ob-

(1) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **93**, 470 (1948); *Arch. intern. pharmacodynamie*, **85**, 474 (1951); F. M. Berger, V. Boekelheide, and D. S. Tarbell, *Science*, **108**, 561 (1948); W. Bradley, J. Forrest, and O. Stephenson, Brit. Patent **613,735**; W. Bradley and J. Forrest, Brit. Patent **628,497**; C. H. Hine, H. E. Christensen, F. J. Murphy, and H. Davis, *J. Pharmacol. Exptl. Therap.*, **97**, 414 (1949); W. A. Lott, *Trans. N. Y. Acad. Sci.*, **11**, 2 (1948); G. L. Sauvage and V. Boekelheide, *J. Am. Chem. Soc.*, **71**, 2588 (1949); Boehringer and Sohne, Ger. Patent **226,454**; V. Boekelheide, L. Liberman, J. Figueras, C. Krespan, F. C. Pennington, and D. S. Tarbell, *J. Am. Chem. Soc.*, **71**, 3303 (1949); J. R. Geigy, Brit. Patent **555,191**; A. Grun, U. S. Patent **2,343,053**; C. H. Hine, H. Davis, and F. J. Murphy, *Arch. intern. pharmacodynamie*, **81**, 507 (1950).

(2) R. K. Summerbell and R. R. Umhoefer, *J. Am. Chem. Soc.*, **61**, 3016 (1939).

(3) D. Swern, G. N. Billin, and J. T. Scanlan, *J. Am. Chem. Soc.*, **68**, 1504 (1946).

(4) E. J. Salmi, R. Leimu, and H. Kallio, *Sumoen Kemistilehti*, **178**, 17 (1944); *Chem. Abstr.*, **40**, 6491 (1946).

tained some material which was probably 1,1-diphenylethylene glycol. Treatment of 2-(2-chloroethoxy)-1,1-diphenylethanol with sodium gave a small amount of the desired 2,2-diphenyl-1,4-dioxane (III). This compound has since been reported by Summerbell et al.[5] The trend of biological activity shown by these 2,2-disubstituted-1,4-dioxanes indicated that an improvement might be

$$ClCH_2CH_2OCH_2Cl \xrightarrow{CuCN} ClCH_2CH_2OCH_2CN \longrightarrow$$
$$ClCH_2CH_2OCH_2CO_2CH_3$$

$$\xrightarrow{RMgX} ClCH_2CH_2OCH_2\underset{R}{\overset{R}{C}}OH \xrightarrow[\text{or NaNH}_2]{NaOC_2H_5}$$

I. R = Ethyl
II. R = Butyl
III. R = Phenyl
IV. R = Methyl

$$CH_2{\equiv}CCH_2Cl + CH_2OHCH_2OH \xrightarrow{Na}$$
$$\underset{CH_3}{|}$$

$$CH_2{=}CCH_2OCH_2CH_2OH \xrightarrow{H_2SO_4} IV$$
$$\underset{CH_3}{|}$$
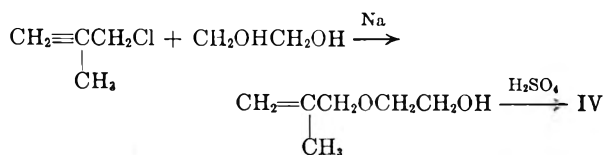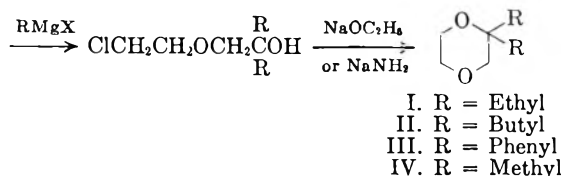
found in 2,2-dimethyl-1,4-dioxane. This compound was prepared by condensing methallyl chloride with ethylene glycol and cyclizing the resulting methallyloxyethanol using sulfuric acid. None of the compounds, however, had sufficient activity to warrant clinical investigation.

In the course of the preparation of these dioxanes, screening indicated that the intermediate chloroalkoxyethanols caused central nervous system depression. This suggested the preparation of some compounds which had two tertiary alcohol groups β to an ether group. To this end diethyl diglycolate was prepared and allowed to react with methyl, ethyl, and butyl Grignard reagents to yield respectively bis(2-hydroxy-2-methylpropyl) ether, bis-(2-hydroxy-2-ethylbutyl) ether, and bis(2-hydroxy-2-butylhexyl) ether. None of these compounds showed sufficient central nervous system depression to warrant further interest.

EXPERIMENTAL[6]

2,3-Dichloro-1,4-dioxane[7] was prepared according to the literature,[8] which reported a 61% yield. A 48% yield was obtained. The presence of unreacted dioxane reported by Summerbell and Bauer was not confirmed. A 28% excess of chlorine was used. The amount of chlorine required was not indicated in the literature.

1,4-Dioxene was prepared in 52% yield (reported 68%) from 2,3-dichloro-1,4-dioxane using ethylmagnesium bromide.[8] When 890 g. (5.7 moles) of 2,3-dichlorodioxane in 3.4

l. of ether was added to a mixture of 234 g. (9.65 moles) of magnesium and 288 g. (1.1 mole) of iodine[2] an 81% yield (395 g.) of product, b.p. 93.8–94.1°, n_D^{26} 1.4347 was obtained. (Reported 49%).

2-Chloro-1,4-dioxane was prepared from 1,4-dioxene in 54–68% yield using the procedure described in the literature.[8]

2-Allyl-1,4-dioxane was prepared from allylmagnesium bromide and 2-chloro-1,4-dioxane in 72–81% yield. The reported[2] yield was 73%.

2-(2-Hydroxypropyl)-1,4-dioxane. To 145 ml. of 75% (w/w) sulfuric acid at −15° was added 15 g. (0.117 mole) of 2-allyl-1,4-dioxane. The reaction mixture was allowed to warm to room temperature (29–30°) and then required cooling. The reaction mixture was kept at 25–30° for 6 hr. and poured into 200 g. of ice. A total of 550 g. of barium carbonate (theory 400 g.) was required to neutralize the acid. The filtered solution, on evaporation using a water pump, gave 15 g. of residue which was distilled through a Vigreux column at 85° (2.8 mm.) and twice redistilled through a 3-foot jacketed wire screen column at 123.5° (23 mm.), n_D^{24} 1.4539. The yield was 3.5 g. (21%).

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.38; H, 9.51.

2-(2,3-Dihydroxypropyl)-1,4-dioxane. To 20.0 g. (0.156 mole) of 2-allyl-1,4-dioxane was added 222 g. of 98–100% formic acid and then 17.0 ml. (0.164 mole) of 33.2% (as determined by permanganate titration) hydrogen peroxide. The reaction was heated to 40° and kept at that temperature by alternate cooling and heating for 5 hr. Titration[9] with thiosulfate at that time showed that the reaction was still incomplete. The reaction mixture was allowed to stand overnight at about 30° (total of 22 hr.). Titration showed the reaction to be complete because essentially all the performic acid had reacted. The reaction mixture was concentrated on a steam bath under water pump pressure and the water soluble residue (allyldioxane is not water soluble) was refluxed with 21.6 g. of potassium hydroxide in 312 ml. of ethanol for 1 hr. and allowed to stand overnight. The precipitate, potassium formate, was removed by filtration as was the potassium chloride which was formed on subsequent acidification with alcoholic hydrogen chloride. The filtrate was distilled through a one-foot Vigreux column b.p. 136–138° (2–2.2 mm.). The distillate was acidic and was therefore refluxed for an hour with 1 g. of sodium hydroxide in 100 ml. of ethanol. The solution was filtered and twice distilled. The yield was 7.5 g. (33%) of product, b.p., 136–137° (1.2 mm.), n_D^{26} 1.4788. The product is water soluble and ether insoluble.

Anal. Calcd. for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.63; H, 8.78.

Methyl (β-Chloroethoxy)acetate was prepared according to Salmi, et al.[4]

2-(2-Chloroethoxy)-1,1-diethylethanol. To ethylmagnesium bromide prepared from 229 g. (2.09 moles) of ethyl bromide in 300 ml. of anhydrous ether, was added with cooling 140 g. (0.925 mole) of methyl (β-chloroethoxy)acetate in 200 ml. of anhydrous ether over a period of 1 hr. Stirring of the suspension was continued for another hour and then 225 ml. of a solution of 150 g. of ammonium chloride in 350 ml. of water was added dropwise with cooling. Stirring was continued until a readily settling precipitate formed. Filtration through a sintered glass funnel was followed by distillation thru a 2.5-foot helices-packed column. The fraction distilling at 114° (17 mm.) was collected, n_D^{28} 1.4478. The yield was 108 g. This material decolorized permanganate solution and was redistilled twice more and substituted for analysis after the last distillation at 115.5° (16.5 mm.), n_D^{28} 1.4472. The pure product did not, of course, decolorize permanganate.

(5) R. K. Summerbell, J. P. Settle, and M. Kland-English, J. Org. Chem., 23, 932 (1958); R. K. Summerbell and H. E. Lunk, J. Am. Chem. Soc., 79, 4802 (1957).

(6) Analyses were carried out by Miss Linda Einstein. Temperatures are uncorrected.

(7) Some of this material was kindly supplied to us by Kay-Fries Chemicals, Inc., W. Haverstraw, N. Y.

(8) R. K. Summerbell and L. N. Bauer, J. Am. Chem. Soc., 57, 2364 (1935).

(9) R. I. Meltzer and J. Doczi, J. Am. Chem. Soc., 72, 4986 (1950).

Anal. Calcd. for $C_8H_{17}O_2Cl$: C, 53.18; H, 9.49; Cl, 19.62. Found: C, 53.19; H, 9.80; Cl, 19.65.

2-(2-Chloroethoxy)-1,1-dibutylethanol was prepared in the same manner as 2-(2-chloroethoxy)-1,1-diethylethanol. The product distilled at 128–138° (6–8 mm.) and was redistilled through a 2.5-foot Fenske column at 101–103° (0.5 mm.), n_D^{28} 1.4497. The yield was 45% of theoretical.

Anal. Calcd. for $C_{12}H_{25}O_2Cl$: Cl, 14.97; C, 60.87; H, 10.64. Found: Cl, 14.97; C, 61.18; H, 10.80.

1,1-Diphenylethylene glycol. To an ether solution of phenylmagnesium bromide prepared from 314 g. (2.2 moles) of bromobenzene was added 84.7 g. (0.55 mole) of methyl (β-chloroethoxy)acetate at a rate to maintain reflux of the reaction mixture. Refluxing was continued for an additional hour after the spontaneous reaction had subsided. The reaction mixture was decomposed with sufficient 20% aqueous ammonium chloride to dissolve all solid. The aqueous layer was extracted with ether and the combined ether solutions were dried over magnesium sulfate, filtered, and concentrated to remove the ether and leave a solid residue. This solid after 2 recrystallizations from benzene melted at 122° and weighed 65 g. (55%). A 2-g. sample, recrystallized repeatedly from isopropanol and from isopropanol-Skellysolve B, melted at 123.5–124°. Analysis corresponded to the empirical formula for 1,1-diphenylethyleneglycol reported to melt at 121°.[10]

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.19; H, 6.82.

The acetate of this glycol, prepared by reaction with acetic anhydride, melted at 148–148.5 after recrystallization from absolute alcohol. The reported melting point is 145.5°.[11]

2-(2-Chloroethoxy)-1,1-diphenylethanol. To a solution of phenylmagnesium bromide prepared from 141 g. (0.9 mole) of bromobenzene in 200 ml. of ether, was added 62 g. (0.4 mole) of methyl (β-chloroethoxy)acetate in 80 ml. of ether. The reaction mixture was heated at reflux for 1 hr. after spontaneous reaction had ceased and then was decomposed with aqueous ammonium chloride. The aqueous layer was extracted with ether and the ether solutions were combined, dried over magnesium sulfate, filtered, and concentrated to remove solvent. The oily residue crystallized on cooling and scratching. The crystalline mass, 112 g., was triturated with cold Skellysolve B and filtered to give a residue of 80 g., m.p. 40–43°. By careful, repeated recrystallizations from large volumes of Skellysolve A, 30 g. (27%) of product m.p. 59–59.5° was obtained. Some material melting at 112–115°, probably impure 1,1-diphenylethylene glycol, was obtained from the less soluble residue.

Anal. Calcd. for $C_{16}H_{17}O_2Cl$: C, 69.43; H, 6.19; Cl, 12.81. Found: C, 69.44; H, 6.47; Cl, 12.73.

2,2-Diethyl-1,4-dioxane. To dry sodium ethylate, prepared from 5.7 g. (0.25 mole) of sodium, in 150 ml. of dry benzene, was added 36 g. (0.2 mole) of 2-(2-chloroethoxy)-1,1-diethylethanol in 100 ml. of dry benzene, over a period of 25 min. Distillation of the benzene was carried out at the same rate as addition during the addition and more slowly thereafter for a total of about 2.5 hr. The benzene was replenished as necessary to keep the volume of the reaction mixture about constant. A total of 400 ml. of distillate was collected. Filtration of the reaction mixture gave 12.5 g. of water-soluble chloride-containing alkaline solid (theory, 10.7 g. sodium chloride plus 3.4 g. sodium ethylate). Alcoholic hydrogen chloride (25 ml. of 5*N*) was added to the filtrate and the reaction mixture was distilled after a filtration. The distillate contained chlorine and was therefore heated with solid sodium hydroxide for about 5 min. and redistilled. The distillate boiling at 168–176° was redistilled through a 1-foot metal helices-packed column and 10 g. (34%) of product distilling at 168°, n_D^{25} 1.4377, was collected.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.78; H, 11.31.

2,2-Dibutyl-1,4-dioxane. To a suspension of about 8 g. of sodamide (slightly over 0.2 mole) in 100 ml. of dry benzene, was added at reflux with stirring over a period of 0.5 hr., 46.5 g. (0.2 mole) of 2-(2-chloroethoxy)-1,1-dibutylethanol in 100 ml. of dry benzene. Ammonia was evolved from the slightly exothermic reaction. After 5 hr. at reflux, 10 ml. of methanol was added and solid material was removed by centrifugation. The solid was washed by centrifugation using methanol and then ether. The precipitate weighed 9.2 g. (theory, 11.7 g.). The supernatant liquid and washings were combined and treated with alcoholic hydrogen chloride and again centrifuged. Evaporation of the solvent from the supernatant solution left 51.6 g. of residue from which was distilled 28 g. (71.5%) of product 97.5–100° (5–6 mm.). This was redistilled after slurrying with magnesium sulfate and filtering. This material all distilled at 97–99° (6.5 mm.), n_D^{27} 1.4450.

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.68; H, 11.92.

2,2-Diphenyl-1,4-dioxane. To 7.39 g. of sodamide slurry (containing about 0.18 mole of sodamide) suspended in 100 ml. of dry refluxing benzene was added 32.1 g. (0.125 mole) of 1,1-diphenyl-2-(2-chloroethoxy)ethanol in 100 ml. of benzene. The reaction mixture was allowed to reflux for 4.5 hr., cooled, treated with 6 ml. of methanol, and filtered. Evaporation of the filtrate gave an oil which solidified. This material was quite basic and was taken up in 300 ml. of ether and 300 ml. of water, acidified, and extracted with ether. Evaporation of the ether left a very viscous oil. An attempt to distill a sample of this material at 1 mm. pressure gave a small amount of solid m.p. 120–122°. This material depressed the melting point of 1,1-diphenylethylene glycol. Distillation of the bulk of the material was carried out and 3 fractions collected, up to 156° (1 mm.), 156–165° (1 mm.), and 165–167° (1 mm.). These solidified and melted respectively at about 120°, 45°, and 55°. These were recrystallized from ethanol. The first two were combined when they both melted at over 115° and purification gave a product m.p. 123.5–124°. The yield was poor. The product did not decolorize permanganate.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.93; H, 6.64.

The third distillate fraction melted at 55–57° after recrystallization.

2,2-Dimethyl-1,4-dioxane. To a solution of 46 g. (2 moles) of sodium in 500 ml. of ethylene glycol, was added 182 g. (2 moles) of methallyl chloride. The reaction mixture was refluxed for 2 hr., filtered, and distilled. The fraction distilling at 82–83° (25 mm.) (175 g.)[12] was collected and redistilled at 172°, n_D^{25} 1.4372. This methallyloxyethanol weighed 162 g. (70%) and decolorized permanganate.

To 50 g. (0.43 mole) of ice cooled methallyloxyethanol was added with swirling 2 ml. of concentrated sulfuric acid. The reaction mixture was then placed under a helices-packed column in a bath at 86° at 5 mm. pressure. Practically everything distilled out of the reaction flask and was collected in the dry ice trap of the pump. Distillation of this material gave 20.5 g. (41%) of product b.p. 120–121°, n_D^{25} 1.4106, which did not decolorize permanganate.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.42; Found: C, 62.10; H, 10.58.

Bis(2-hydroxy-2-ethylbutyl) ether. To a Grignard reagent prepared from 142 g. (1.3 mole) of ethyl bromide in 350 ml. of dry ether, was added 49.2 g. (0.26 mole) of ethyl diglycolate in 450 ml. of ether at such a rate as to maintain refluxing. The reaction mixture was kept at reflux for an additional hr. and then allowed to stand overnight before decomposition with saturated ammonium chloride (125 ml.) and 20 g. of solid ammonium chloride. The resulting granu-

(10) C. Paal and E. Weidenkaff, *Ber.*, **39**, 2062 (1906).

(11) R. Stoermer, *Ber.*, **39**, 2288 (1906).

(12) U. S. Patent **2,148,437** reports b.p. 94–95° (48 mm.) for product obtained *via* another route.

lar precipitate was removed by filtration after stirring for 2 hr. Distillation of the filtrate gave 24 g. of product distilling at 92–97° (0.4 mm.) which solidified. The product was further purified by redistillation at 100° (1 mm.) to give 19 g. (25%) of product which melted at 38–40°.

Anal. Calcd. for $C_{12}H_6O_3$: C, 66.01; H, 12.00. Found: C, 66.18; H, 12.07.

Bis(2-hydroxy-2-methylpropyl) ether. This was prepared similarly to the bis(2-hydroxy-2-ethylbutyl) ether and distilled at 78° (0.2 mm.). The product was purified by recrys-

(13) M. Godchot, *Compt. rend.*, **184**, 820 (1927).

tallization from Skellysolve B and melted at 65–66°[13] (22% yield).

Anal. Calcd. for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.19; H, 11.31.

Bis(2-hydroxy-2-butylhexyl) ether. This was prepared similarly to the bis(2-hydroxy-2-ethylbutyl)ether but on distillation of the reaction solvent the product was purified by recrystallization from Skellysolve B instead of by distillation. The product melted at 85–85.5° (23% yield).

Anal. Calcd. for $C_{20}H_{12}O_3$: C, 72.67; H, 12.81. Found: C, 72.77; H, 13.08.

Morris Plains, N. J.

Preparation of Substituted 1,4-Dioxanes
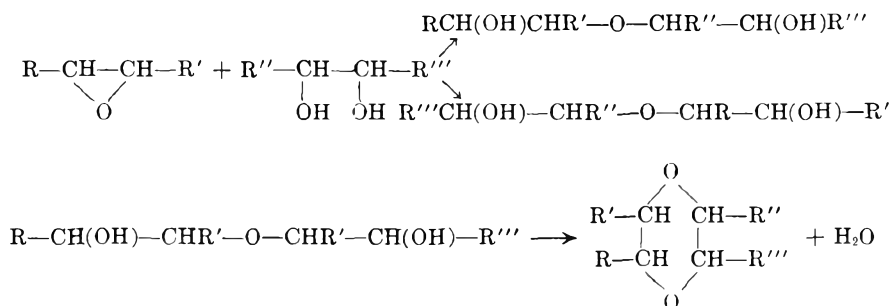
MELVIN J. ASTLE and BIRGIT EKMAN JACOBSON[1]

Olefin oxides and glycols react at low temperatures to give dihydroxyethers which on heating lose water to form substituted dioxanes. This seems to be a general method for making substituted dioxanes and a wide variety of such compounds can be made by proper selection of the olefin oxide and the glycol. The method is particularly useful in preparing unsymmetrical dioxanes.

It has been reported in the literature[2,3] that olefin oxides react with glycols to form dihydroxyethers. The reaction may be represented as follows:

tions, concentrated sulfuric acid was used as a catalyst and in all but two reactions an excess of glycol was used.

$$RCH(OH)CHR'—O—CHR''—CH(OH)R'''$$

$$R—CH—CH—R' + R''—CH—CH—R''' \nearrow$$
$$\diagdown O \diagup \quad | \quad | \quad \searrow$$
$$OH \quad OH \quad R'''CH(OH)—CHR''—O—CHR—CH(OH)—R'$$

$$R—CH(OH)—CHR'—O—CHR'—CH(OH)—R''' \longrightarrow$$

$$\begin{array}{c} O \\ R'—CH \quad CH—R'' \\ | \quad \quad | \\ R—CH \quad CH—R''' \\ O \end{array} + H_2O$$

It may be expected also that ring closure might occur to form 1,4-dioxanes, but this reaction has not been reported.

The present work describes the preparation of a number of 1,4-dioxanes from certain olefin oxides and glycols by addition and ring closure.

Reactions were carried out with three olefin oxides and five 1,2-glycols. The olefin oxides used were propylene oxide, 2,3-butylene oxide, and styrene oxide; the glycols were ethylene glycol, 1,2-propanediol, 2,3-butanediol, phenyl-1,2-ethanediol, and catechol. Eight substituted *p*-dioxanes were obtained, including methyldioxanes, phenyldioxanes, and phenylmethyldioxanes. In most of the reac-

EXPERIMENTAL

The reaction of propylene oxide and ethylene glycol is illustrative of the experimental procedures used.

Ethylene glycol (186 g., 3 mol.) was placed in a 3-neck flask in an ice bath and 10 g. of concentrated sulfuric acid was added gradually. Propylene oxide (116 g., 2 mol.) was then added dropwise during a 30-min. period with constant stirring of the mixture at temperatures below 30°. After addition of the oxide was complete, the mixture was gradually heated to reflux temperature and was then stirred under reflux at 120° for 2 hr. and allowed to cool to room temperature. The first distillation gave a distillate boiling at 75–97° at atmospheric pressure leaving a black tarry residue. The distillate separated into two layers on cooling. Each layer was separately extracted with ether and the combined ether extracts were dried over anhydrous sodium sulfate. The ether was evaporated and the residue redistilled.

Two low boiling fractions were obtained: the fraction boiling from 39–78° consisted largely of propionaldehyde and the one boiling from 80–100° was principally dioxane and water. Monomethyl-1,4-dioxane (b.p. 106–109° at 741 mm. n_D^{20} 1.4187) was then obtained. The yield was 54 g. or 27%. The infrared absorption spectra, which indicated clearly

(1) From the M.S. thesis of Birgit Ekman Jacobson.

(2) P. A. Levene and A. Walti, *J. Biol. Chem.*, **75**, 325 (1927).

(3) M. S. Kharasch and W. Nudenberg, *J. Org. Chem.*, **8**, 189 (1943).

TABLE I

REACTIONS BETWEEN OLEFIN OXIDES AND 1,2-GLYCOLS IN THE PRESENCE OF SULFURIC ACID

Oxide	Glycol	Reaction Time, Hr.	Reaction Temp.	Product	B.P.	Yield,
Propylene oxide	Ethylene glycol	2	120	Methyl-1,4-dioxane	102–108	27.0
	1,2-Propanediol	5	120	2,5-Dimethyl-1,4-dioxane	115–117	44.5
	2,3-Butanediol	7.5	120	2,3,6-Trimethyl-1,4-dioxane	128–135	44.3
	2,3-Butanediol	4.0	118	2,3,6-Trimethyl-1,4-dioxane	128–135	17.3
2,3-Butylene oxide	Ethylene glycol	6.0	119	2,3-Dimethyl-1,4-dioxane	124–128	11.0
	1,2-Propanediol	5.0	115	2,3,6-Trimethyl-1,4-dioxane	128–135	12.1
	2,3-Butanediol	5.0	126	2,3,5,6-Tetramethyl-1,4-dioxane	135–149	28.4
Styrene oxide	Ethylene glycol	3.0	25	Phenyl-1,4-dioxane	80–81/5 mm.	27.6
	Ethylene glycol	1.0	132	Phenyl-1,4-dioxane	80–81/5 mm.	41.0
	Ethylene glycol	1.0	132[1]	Phenyl-1,4-dioxane	80–81/5 mm.	36.3
	Ethylene glycol	1.0	132[2]	Phenyl-1,4-dioxane	80–81/5 mm.	29.3
	1,2-Propanediol	5.0	130	Methylphenyl-1,4-dioxane	103–106/8 mm.	47.8
	2,3-Butanediol	10.0	140	Phenyl-2,3-dimethyl-1,4-dioxane	93–95/3 mm.	25.0

(1) BF$_3$/ether catalyst
(2) Toluene sulfonic acid catalyst

the presence of a methyl substituent, were otherwise identical with the spectra of pure 1,4-dioxane.

DISCUSSION OF RESULTS

The results obtained for the reactions of olefin oxides with glycols are summarized in Table I.

More work was done with styrene oxide than with any of the other olefin oxides. The reaction with any of the glycols was exothermic and the addition of styrene oxide was carried out below room temperature. The reaction of styrene oxide with glycols gave homogeneous solutions which separated into two phases on heating to about 120°. In all cases where styrene oxide (1 mol.) and ethylene glycol (3 mol.) were reacted in the presence of concentrated sulfuric acid without external heating, the reaction mixture remained homogeneous, even after vigorous stirring at room temperature for 5 days. When the homogeneous mixture was distilled, the distillate separated into layers. One layer was ether soluble and the second ether insoluble, but water soluble. These layers were separately extracted with ether, the combined ether solutions dried over anhydrous sodium sulfate, and redistilled under reduced pressure. The yields of phenyl-1,4-dioxane thus obtained were 20–27%. A considerably better yield (41%) of this product was obtained when a similar reaction mixture was stirred under reflux (about 130°) for 1 hr. The mixture separated into a brown, oily, ether insoluble material consisting of water, dioxane, unreacted ethylene glycol and some unidentified material and an ether soluble material consisting of phenyldioxane and some phenylacetaldehyde. p-Toluenesulfonic acid and boron trifluoride were found to be effective catalysts for the preparation of substituted dioxanes.

Infrared absorption spectra indicated that the products were phenyl substituted cyclic ethers. Boiling points and indices of refraction agreed with known compounds.

These facts are consistent with the idea that the reaction proceeds in two steps in which C$_6$H$_5$CH(OH)CH$_2$OCH$_2$CH$_2$OH or C$_6$H$_5$CH(CH$_2$OH)—O—CH$_2$CH$_2$OH is first formed. Either of these compounds would be expected to be soluble in the excess glycol and water used. Cyclization gives the phenyldioxane which is much less soluble in the glycol and water and so separation into two phases occurs.

In every case 2,5-diphenyl-1,4-dioxane was obtained as a by-product. This product probably was obtained by the cyclic dehydration of 1-phenyl-1,2-ethanediol from the reaction of water with styrene oxide.

A number of reactions between styrene oxide and catechol were attempted and all failed to give an Indication of hydroxy ether or dioxane formation. Only black tars were obtained.

The formation of methyl substituted dioxanes appears to be a much slower reaction and again hydroxy ethers are first formed which lose water at higher temperatures with the formation of dioxanes. The reaction mixtures remain homogeneous even after several hours at reflux temperatures because of the greater solubilities of the alkyl substituted dioxanes in the reaction mixture. Separation into two phases does not occur until after distillation.

That the expected reaction and ring closure in fact had taken place was most evident in the three cases where the reaction product was identified as methyl-1,4-dioxane, 2,3-dimethyl-1,4-dioxane, and phenyl-1,4-dioxane. Each of these compounds could not have been formed except by a reaction of the olefin oxide with the appropriate glycol. In the reactions of propylene oxide with propylene glycol, of 2,3-butylene oxide with 2,3-butylene glycol, and of styrene oxide with phenyl-1,2-ethanediol, the substitued dioxanes could be expected to be formed either by dimerization of the glycol or by reaction between the olefin oxide and the glycol. However,

when the oxide was added to the glycol, an exothermic reaction occurred at temperatures much lower than those required for condensation of the glycol directly to the dioxane. Some of the glycol was undoubtedly converted to the corresponding dioxane by self-condensation at higher temperatures.

Neutralization of the acidic reaction mixture with sodium bicarbonate before distillation decreased the yields of the substituted dioxanes by preventing the acid catalyzed cyclization which would have occurred during distillation. For example, only a 4% yield of trimethyl dioxane and a 9% yield of phenyl dioxane was obtained compared with 12% and 20–27% yields from identical reaction mixtures distilled without neutralization. This indicates that part of the ring closure which would have taken place in acidic media during the distillation did not occur after neutralization. Instead over 60% of the weight of the reaction mixture consisted of high boiling distillation residues and unreacted glycol.

CLEVELAND, OHIO
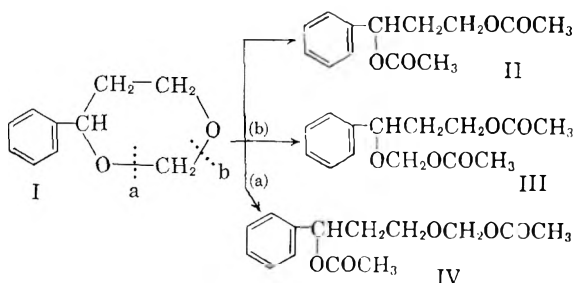

[CONTRIBUTION FROM MELLON INSTITUTE]

Reaction of 4-Phenyl-1,3-dioxane with Acetic Anhydride

H. MOE AND B. B. CORSON

The acetylation of 4-phenyl-1,3-dioxane yields 1,5-diacetoxy-3-phenyl-2-oxapentane—not 1,3-diacetoxy-1-phenylpropane as has been elsewhere reported.

Shorygina[1] reports, without evidence, that the reaction between 4-phenyl-1,3-dioxane (I) and acetic anhydride results in the formation of 1,3-diacetoxy-1-phenylpropane (II). On the contrary, we find under the experimental conditions described by Shorygina, that the product is 1,5-diacetoxy-3-phenyl-2-oxapentane (III) obtained by cleavage at position b. No evidence was found for the presence of isomeric 1,5-diacetoxy-5-phenyl-2-oxapentane (IV) which would result from ring opening at position a.

The reaction of 4-phenyl-1,3-dioxane (I) with acetic anhydride yielded a diacetate product from which was obtained, after crystallization followed by distillation, an 80% yield (based on I consumed) of 99.0–99.5 mole % pure diacetate (III). Preferential hydrolysis of the purified diacetate yielded formaldehyde plus 3-acetoxy-1-phenyl-1-propanol (V). The latter was oxidized to β-acetoxypropiophenone (VI).
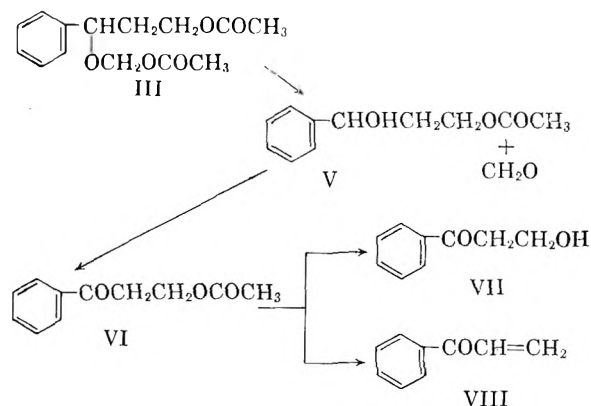

Our results are in agreement with those of Senkus[2] who reports that the acetylation of several 4- and 5-substituted 1,3-dioxanes gives diacetylated products which retain the methylene group, and of Ness, Hann, and Hudson[3] who describe the acetylation of cyclic formals to yield products in which the acetoxy group is attached to the primary carbon atom and the acetoxymethoxy to the secondary carbon atom.

Acidic hydrolysis of VI yielded β-hydroxypropiophenone (VII) whose identity was established by conversion to its known semicarbazone, α-naphthylurethane and pyrazoline derivatives.

Alkaline hydrolysis of VI with sodium hydroxide resulted in a hydrolytic product containing benzoylethylene (VIII), identified by the preparation of its dibromo derivative. The formation of benzoylethylene from VI is an example of a base-catalyzed olefin-forming elimination reaction.[4]

(1) N. V. Shorygina, J. Gen. Chem. (U.S.S.R.), 26, 1643 (1956).

(2) M. Senkus, J. Am. Chem. Soc., 68, 734 (1946).

(3) A. T. Ness, R. M. Hann, and C. S. Hudson, J. Am. Chem. Soc., 65, 2215 (1943).

(4) C. K. Ingold, Structure and Mechanism in Organic Chemistry, Cornell University Press, Ithaca, N. Y., 1953, Chap. VIII.

EXPERIMENTAL

All boiling points and melting points are uncorrected. The freezing temperature of 1,5-diacetoxy-3-phenyl-2-oxapentane (III) was determined by extrapolation of its freezing curve, temperature being measured by a certified platinum resistance thermometer and G-2 Mueller bridge, purity being estimated from the shape of the curve.

1,5-Diacetoxy-3-phenyl-2-oxapentane (III). A solution of 164 g. (1.0 mole) of 4-phenyl-1,3-dioxane[6] (I), 224 g. (2.2 moles) of acetic anhydride and 10 ml. of concentrated hydrochloric acid was stirred at 80° for 5 hr., then cooled, neutralized with aqueous sodium hydroxide and extracted with ether. The dried extract was concentrated and the residue distilled to yield 29 g. (18%) of recovered 4-phenyl-1,3-dioxane and 200 g. (93% based on dioxane consumed) of diacetate product. The latter was crystallized once out from 2150 ml. of petroleum ether (b.p. 40–45°) to yield 170 g. of solid which was distilled to yield 160 g. (80% based on dioxane consumed) of 99.0–99.5 ± 0.5 mole % pure 1,5-diacetoxy-3-phenyl-2-oxapentane; b.p. 137°/0.8 mm., n_D^{25} 1.4850; f.t. 34.41°.

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81; mol. wt. 266. Found: C, 63.47; H, 6.64; mol. wt., 264.

3-Acetoxy-1-phenyl-1-propanol (V). To a solution of 133 g. (0.50 mole) of diacetate (III) in 1 l. of absolute ethanol was added a solution of 26.5 g. (0.25 mole) of sodium carbonate in 750 ml. of water. The mixture was stirred for 1.5 hr. at 25°, filtered, and the filtrate evaporated at 25°/1 mm. to a 500-ml. aqueous concentrate which was saturated with sodium chloride and extracted with ether. The dried extract was concentrated and the residue distilled to yield 70 g. (72%) of 3-acetoxy-1-phenyl-1-propanol (V); b.p. 115–122°/0.4 mm., n_D^{25} 1.5100–1.5125. Redistillation through a 60-cm. spinning band column at 30/1 reflux ratio gave a 40-g. heart cut; b.p. 123–124°/0.45 mm., n_D^{25} 1.5125.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.26; H, 7.48.

A second hydrolytic experiment, similar to the one above, but on 1/10 the scale, was made and the product reacted with Brady's reagent[6] (a solution of 2,4-dinitrophenylhydrazinium sulfate in aqueous ethanol containing excess sulfuric acid) to yield 9.3 g. (88%) of formaldehyde 2,4-dinitrophenylhydrazone, melting point and mixture melting point with an authentic specimen 164–166°.

β-Acetoxypropiophenone (VI). *Method A.* To 21 g. (0.11 mole) of 3-acetoxy-1-phenyl-1-propanol (V) was added, in one portion, a mixture of 42 g. (0.14 mole) of sodium dichromate dihydrate, 35 ml. (0.66 mole) of concentrated sulfuric acid and 400 ml. of water. The temperature was held at 55–60° by swirling in an ice bath. When the temperature no longer tended to rise, the mixture was extracted with benzene. The extract was dried and concentrated to give a solid residue which was crystallized twice from petroleum ether (b.p. 40–45°) to yield 5.7 g. (27%) of β-acetoxypropiophenone, m.p. 53.5–54.0°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.68; H, 6.00.

β-Acetoxypropiophenone (VI). *Method B.* Ten grams (0.10 mole) of chromium trioxide was added during 1.5 hr. to a stirred solution of 19.4 g. (0.10 mole) of 3-acetoxy-1-phenyl-1-propanol (V) in 250 ml. of acetic acid. The temperature rose from 25 to 45°. The solution was stirred for an additional 3 hr., then poured into excess aqueous sodium carbonate and extracted with ether. The extract was dried and concentrated to give a solid residue which was crystallized once from petroleum ether (b.p. 40–45°) to yield 5.5 g. (27%) of β-acetoxypropiophenone, m.p. 51–54°.

2,4-Dinitrophenylhydrazone of β-acetoxypropiophenone. Orange needles from ethanol, m.p. 174–175°.

Anal. Calcd. for $C_{17}H_{16}N_4O_6$: C, 54.83; H, 4.33; N, 15.05. Found: C, 55.65; H, 4.28; N, 14.66.

β-Hydroxypropiophenone (VII). A solution of 19.2 g. (0.10 mole) of β-acetoxypropiophenone (VI), 200 ml. of water, 200 ml. of methanol and 100 ml. of concentrated hydrochloric acid was stirred for 2 hr. at 35°, then neutralized by the addition of solid sodium carbonate. Methanol was evaporated at 10 mm. and the residual solution saturated with sodium chloride and extracted with ether. The dried extract was concentrated to yield 11.5 g. (77%) of β-hydroxypropiophenone, n_D^{25} 1.5408. Distillation gave a heart cut boiling at 90°/0.15 mm.; n_D^{25} 1.5444 (lit.[7] b.p. 98°/0.2 mm., n_D^{20} 1.5450).

α-Naphthyl carbamate of β-hydroxypropiophenone. White crystals from carbon tetrachloride, m.p. 116–117° (lit.[7] m.p. 115–116°).

Semicarbazone of β-hydroxypropiophenone. White needles from aqueous methanol, m.p. 160–161° (lit.[7] m.p. 160–161°). Shorygina[1] reports 194–195° as the melting point.

1,3-Diphenyl-2-pyrazoline. Prepared by condensing β-hydroxypropiophenone with phenylhydrazine, yellow plates from aqueous methanol, melting point and mixture melting point with an authentic specimen 151–153° (lit.[8] m.p. 151–152°). Authentic 1,3-diphenyl-2-pyrazoline was prepared by reacting β-dimethylaminopropiophenone hydrochloride with phenylhydrazine.

Benzoylethylene (VIII). A mixture of 9.6 g. (0.05 mole) of β-acetoxypropiophenone (VI), 2.0 g. (0.05 mole) of sodium hydroxide and 200 ml. of water was stirred at 30° for 0.5 hr., then saturated with sodium chloride and extracted with carbon tetrachloride. The presence of benzoylethylene was demonstrated as follows: to the cold, dry extract was slowly added a cold solution of bromine in carbon tetrachloride until the appearance of a faint yellow color. The solvent was evaporated and the residue crystallized from petroleum ether (b.p. 40–45°) to yield 4.5 g. (31%) of α,β-dibromopropiophenone, melting point and mixture melting point with an authentic specimen 52–54° (lit. m.p. 53°,[9] 58°[10]). Authentic α,β-dibromopropiophenone was prepared from benzoylethylene obtained from β-dimethylaminopropiophenone hydrochloride.[11]

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(5) M. G. J. Betts, *Rec. trav. chim.*, **70**, 20 (1951); R. L. Shriner and P. R. Ruby, *Org. Syntheses*, **33**, 72 (1953).

(6) O. L. Brady, *J. Chem. Soc.*, 757 (1931).

(7) M. G. J. Beets and L. G. Heeringa, *Rec. trav. chim.*, **74**, 1096 (1955).

(8) H. O. House and R. L. Wasson, *J. Org. Chem.*, **22**, 1157 (1957).

(9) H. Jager and M. Arenz, *Ber.*, **83**, 182–5 (1950).

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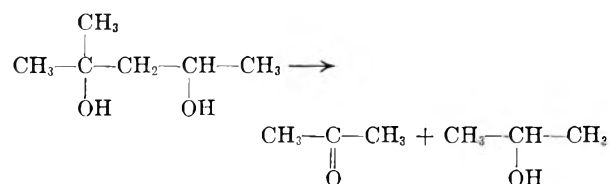
(11) C. Mannich and G. Heilner, *Ber.*, **55**, 356 (1922).

Base-Catalyzed Cleavage of 1,3-Diols[1,2]

SCOTT SEARLES, JR., EDWIN K. IVES, AND SHOGO NUKINA

A study of the action of hot alkali with 21 1,3-diols of widely varying structure is reported. The general reaction is carbon-carbon cleavage, forming an alcohol and a carbonyl compound. Generalizations regarding the direction of cleavage of unsymmetrical diols are formulated, and a mechanism is proposed, involving a dehydrogenation to ketol or aldol, retrograde aldol condensation, and hydrogenation of one of the carbonyl products. Investigation of the stereochemistry of the reaction showed preferential cleavage of cis isomers of cyclic diols, indicating the importance of an internally hydrogen bonded monoalkoxide ion as an intermediate. The reaction can be used for preparing pure trans-1,3-cyclohexanediol from a mixture of the cis and trans isomers.

In connection with a study of the base-catalyzed cleavage of 1,3-bromoalcohols,[3,4] it was observed that 1,3-diols also are cleaved by treatment with hot alkali. The products from the diols are alcohols and carbonyl compounds, whereas the bromoalcohols break down into olefins and carbonyl compounds. An example of base-catalyzed cleavage of a 1,3-diol is the conversion of 2-methyl-2,4-pentanediol to acetone and isopropyl alcohol in about 90% yields when heated with sodium hydroxide at 150°:

$$CH_3-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-\underset{\underset{OH}{|}}{CH}-CH_3 \longrightarrow$$

$$CH_3-\underset{\underset{O}{\|}}{C}-CH_3 + CH_3-\underset{\underset{OH}{|}}{CH}-CH_2$$

This is clearly a different reaction from the acid-catalyzed cleavage of 1,3-diols, which has recently received detailed study.[5] Besides a difference in products, the structural requirements are quite different, as will be shown.

Alkaline pyrolysis of 1,3-diols appears to have been first observed by Nef,[6] who reported that ethyl alcohol was obtained when a mixture of 1,3-propanediol and sodium hydroxide was heated at 150-160° for 100 min. The yield was only 20%, and propyl alcohol, acetic acid, and hydrogen were also reported to be formed.

In contrast to Nef's account, Cross and Jacobs[7] found that the best method of preparing monosodium salts of diols and triols, including 1,3-propanediol, was by heating with one mole of sodium hydroxide at 135°. They stated that the yield is quantitative, and that the same results are obtained at temperatures up to 175°.

A study of the reaction of 17 acyclic 1,3-diols with caustic alkali at 150-200° showed that cleavage to give an alcohol and a carbonyl compound is quite general. The results are presented in Table I. When the carbonyl product was an aldehyde, however, it was not isolated, although sometimes Cannizzaro[8] or Tishenko products were; e.g., ethanol, in place of acetaldehyde, from X, and butyl butyrate in place of butyraldehyde from VI.

The reaction goes about equally well with sodium or potassium hydroxide, with or without added water. The amount of base used was varied from catalytic to large amounts without much effect on the cleavage process; the minimum practical temperature for the cleavage, however, increases as the amount of base is decreased. In an interesting paper published after our initial report,[2] Brannock and Lappin[9] reported cleaving three 2,2-dialkyl-1,3-propanediols and 2,2,4-trimethyl-1,3-pentanediol by heating with the corresponding sodium alkoxides at 145-175° or with calcium oxide at a slightly higher temperature.[10]

One of the diols studied in this work, 3-methyl-1,1-diphenyl-1,3-propanediol, cleaved to form an olefin, 1,1-diphenylethylene, rather than alcohol. The expected alcohol, 1,1-diphenylethanol, could have been formed first, however, as it is known[11] to

(1) Abstracted largely from the thesis submitted by E. K. Ives in partial fullfilment of the Ph.D. degree, Kansas State College, 1959.

(2) Most of this material was presented at the 127th meeting of the American Chemical Society, Cincinnati, Ohio, April 1955 (Abstracts, p. 24N).

(3) S. Searles and M. J. Gortatowski, J. Am. Chem. Soc., 75, 3030 (1953).

(4) S. Searles, R. G. Nickerson, and W. K. Witsiepe, J. Org. Chem., submitted.

(5) H. E. Zimmerman and James English, Jr., J. Am. Chem. Soc., 76, 2294 (1954), and preceding papers.

(6) J. U. Nef, Ann., 335, 306 (1904).

(7) C. F. Cross and J. M. Jacobs, J. Soc. Chem. Ind., 45, 320T (1926).

(8) Even aldehydes with α-hydrogen are known to undergo the Cannizzaro reaction at 150-200° (A. Lederer, Monatsh., 22, 536 (1901); M. Hauserrmann, Helv. Chim. Acta, 34, 1211 (1951).

(9) K. C. Brannock and G. R. Lappin, J. Am. Chem. Soc., 77, 6052 (1955).

(10) It has been reported that 2,2-dimethyl-1,3-propanediol is cleaved by heating with activated alumina [R. W. Brown and G. Dougherty, J. Org. Chem., 13, 173 (1948)]. The products, however, are different (isobutryaldehyde and methanol), rather than isobutyl alcohol and (initially) form-aldehyde.[9] We have confirmed this observation, but find that alumina will not cleave some of the diols most easily cleaved by hot caustic, for example, 2-methyl-2,4-pentanediol. This apparently is a different reaction, which requires a quaternary carbon between the carbinol groups, suggesting cleavage to a carbonium ion intermediate.

(11) M. Tiffeneau, Ann. Chim. (8), 10, 359 (1907).

dehydrate at 200°, which was the reaction temperature.

Four compounds were not cleaved by caustic at 200°. One of them, 1,3-propanediol, was cleaved at somewhat higher temperature, and it is possible that the others would be too.

With unsymmetrically substituted 1,3-diols generally only one of the two possible modes of cleavage was observed.[12] The direction of cleavage observed can be generalized as follows: (1) The ease of cleavage of carbinol groups in 1,3-diols from an unsubstituted central methylene group, is in the order: $Me_2COH > CH_2OH > MeCHOH$ (or $RCHOH$) $> \phi CHOH$ or ϕ_2COH. (2) When the central methylene is substituted, as well as one of the carbinols, cleavage of the most substituted carbinol occurs. This may result in reversing the point of cleavage predicted from the first generalization, as in compounds VI and VIII.[13]

For a mechanism one might logically postulate the following chain process: (1) base-catalyzed dehydrogenation of the diol (I) to a β-hydroxyketone or β-hydroxyaldehyde (III), by way of an intermediate monoalkoxide ion (II); (2) cleavage of III by the retrograde aldol condensation; and (3) Meerwein-Ponndorf reduction of one of the carbonyl products formed in step 2, by the diol I.

$$RCH-C(R_2)-CR_2 \xrightarrow[-H_2O]{OH^-} RCH-CR_2CR_2 \xrightarrow{-H^-}$$
$$\underset{OH}{|} \qquad \underset{OH}{|} \qquad \qquad \underset{O^-}{|} \qquad \underset{OH}{|}$$
$$\text{I} \qquad\qquad\qquad\qquad \text{II}$$

$$RC-CR_2CR_2$$
$$\underset{O}{\|} \quad \underset{OH}{|}$$
$$\text{III}$$

$$\text{III} \xrightarrow{OH^-} RC-CHR_2 + R_2C{=}O$$
$$\underset{O}{\|}$$
$$\text{IV} \qquad\qquad \text{V}$$

$$\text{I + IV or V} \longrightarrow \text{III} + RCHCHR_2 \text{ or } R_2CHOH$$
$$\text{(via II)} \qquad\qquad\qquad\qquad \underset{OH}{|}$$

The first and last steps are analogous to those that are considered to occur in the Guerbet reaction[14] and in the base-catalyzed alkylation of fluorene with alcohols,[15] both of which occur in alkaline medium at 200–230°.

This mechanism fits all the cases studied except one, the observed cleavage of 3-methyl-1,1-diphenyl-1,3-butanediol. This di-*tert*-glycol, of course, cannot undrgo dehydrogenation to a ketol, but the benzhydrol-type structure may permit operation of ionization process in the polar medium at these high temperatures, as shown:

$$Ph_2C-CH_2-CMe_2 \longrightarrow Ph_2C^{\pm}\,CH_2\,CMe_2 \longrightarrow$$
$$\underset{OH}{|} \qquad \underset{OH}{|} \qquad\qquad \underset{OH^-}{|} \qquad \underset{O^-H}{|}$$
$$Ph_2C{=}CH_2 + Me_2C{=}O$$

An analogy that may be cited is the cleavage of 3-dialkylamino-1,1-diphenylpropanols to 1,1-diphenylethylene and other products when heated in refluxing acetic anhydride.[16] The other di-*tert*-glycol, 2,4-dimethyl-2,4-pentanediol, does not have the benzhydrol structure and is not cleaved by hot alkali.

The direction of cleavage of unsymmetrical diols is in agreement with this mechanism. This is a particularly good test in the cases of 3-methyl-1,3-butanediol and 2-methyl-2,4-pentanediol, each of which has one tertiary carbinol and thus can cleave by this mechanism in only one direction. Furthermore, examination of the products by gas chromatography gave no evidence for cleavage in the other direction. Had cleavage proceeded merely by thermal dissociation of the diol monoalkoxide (II),[17] which would be a mixture, cleavage in each direction should occur to some extent.

In the case of di-*secondary* or *primary-secondary* diols, cleavage might occur in either direction, depending on the relative ease of dehydrogenation of the carbinol group, e.g.:

$$RCH-CH_2-CH_2OH \longrightarrow RCOCH_2CH_2OH \longrightarrow$$
$$\underset{OH}{|}$$
$$RCOCH_3 + CH_2O$$
$$\text{or}$$
$$RCHOH-CH_2CHO \longrightarrow RCHO + CH_3CHO$$

As the carbinol group cleaved off is the one *not* dehydrogenated, one may surmise that the ease of dehydrogenation of carbinol groups in 1,3-diols (with a CH_2 group between the carbinol groups) under the conditions used is:

$RCORAr_2$ or
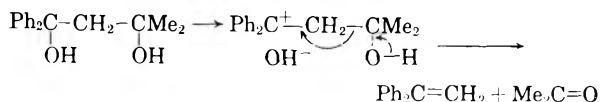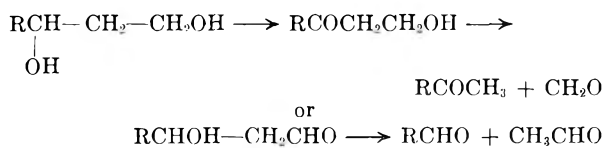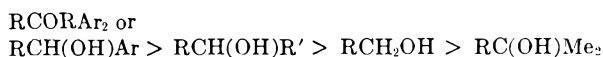$RCH(OH)Ar > RCH(OH)R' > RCH_2OH > RC(OH)Me_2$

(12) Where low yields of cleavage products were observed, fairly good recovery of starting diol was made so that it seems unlikely that any considerable amounts of products from the opposite modes of cleavage were formed. Furthermore, gas phase chromatography of the unfractionated reaction products gave no indication of any additional cleavage products in the several cases where this technique was used (Nos. II, VI, IX, X, and XIV in Table I). Due to the difficulty of recovering the starting diols efficiently, it was not possible to calculate conversion yields with any accuracy.

(13) There are two other examples of alkali cleavage of such diols in the literature and both agree with this generalization. Brannock and Lappin (Ref. 11) found that 2,2,4-trimethyl-1,3-pentanediol was cleaved almost entirely into isobutyl alcohol and isobutyraldehyde when heated with dissolved sodium. E. G. E. Hawkins, D. J. G. Long, and F. W. Major, *J. Chem. Soc.*, 1462 (1955), reported that a diol assigned the structure, 1-methylol-1-(3¹-cyclohexenylmethylol)-3-cyclohexene, was converted by heating with alkali at 200° into 1,2,3,6-tetrahydrobenzyl alcohol and 1,2,3,6-tetrahydrobenzoic acid, along with some material of higher molecular weight.

(14) H. Machemer, *Angew. chem.*, **64**, 213 (1952).

(15) K. L. Schoen and E. I. Becker, *J. Am. Chem. Soc.*, **77**, 6030 (1955).

(16) D. W. Adamson, *Nature*, **164**, 500 (1949).

(17) This direct cleavage of the monoalkoxide ion (II) was favored previously (Ref. 2), because the isopropyl alcohol formed from 3-methyl-1,3-propanediol was incorrectly identified as *tert*-butyl alcohol.

TABLE I

CLEAVAGE OF ACYCLIC 1,3-DIOLS

No.	Diol Structure	Max. Temp.	Conditions, Time	M. Base/ M. Diol	Products Identified	Yield, %[m]
I	$CH_2OHCH_2CH_2OH$[a]	225°	5	2	C_2H_5OH	7
II	$CH_2OHCMe_2CH_2OH$[a]	170	1	1	Me_2CHCH_2OH	50
III	$CH_2OHCEt_2CH_2OH$[b]	200	1.5	3	Et_2CHCH_2OH	60
IV	$CH_2OHCHPhCH_2OH$[b]	200	2	6	$PhCH_2CH_2OH$	68
V	$CH_2OHCMePhCH_2OH$[c]	210	1.5	5	no reaction	
VI	$PrCHOHCHEtCH_2OH$[a]	180	2	1	BuOH	60
					PrCOOBu	15
VII	$PhCHOHCH_2CH_2OH$[d]	210	2	6	$PhCH_2CH_2OH$	18
VIII	$PhCHOHCMe_2CH_2OH$[e]	175	2	1.2	Me_2CHCH_2OH	48
					$PhCH_2OH$	100
					PhCOOH	54
IX	$MeCHOHCH_2CH_2OH$[a]	200	2	2	Me_2CHOH	67
					Me_2CO	15[n]
X	$Me_2COHCH_2CH_2OH$[c]	200	2	2.7	Me_2CHOH	43
					Me_2CO	10[n]
XI	$MeCHOHCH_2CHOHMe$[f]	150	1	2	Me_2CHOH	74
					EtOH	8
XII	$MeCHOHCH_2CHOHPh$[g]	200	2	10	PhCHOHMe	40
XIII	$PhCHOHCH_2CHOH\phi$	200	1.5	10	no reaction[k]	
XIV	$Me_2COHOH_2CHOHMe$[a]	150	1	1	Me_2CHOH	93
					Me_2CO	93
XV	$Me_2COHCH_2COHMe_2$[h]	200	2	9	no reaction[k]	
XVI	Me_2COHCH_2COHPh[i]	200	1.5	5	MeCHOHPh[l]	28
XVII	$Me_2COHCH_2COHPh_2$[j]	200	1.5	9	$Ph_2C{=}CH_2$[l]	60

[a] Commercial source. [b] Ref. 4. [c] Procedure of W. H. Mills and L. Bain, *J. Chem. Soc.*, 2502 (1925). [d] Preparation described in experimental section. [e] Method of Reik, *Monatsh.*, 18, 599 (1877) as cited in Beilstein's "Handbuch der Organischen Chemie," Vol. VI, Springer, Berlin, 1923, p. 949. [f] Ref. 25. [g] A. Franke and M. Kohn, *Monatsh.*, 27, 1115 (1906). [h] A. Franke and M. Kohn, *Ber.*, 37, 4731 (1904). [i] A. McKenzie and G. Martin, *J. Chem. Soc.*, 103, 112 (1913). [j] M. I. Berberian, *Chem. Zentr.*, 1913 II, 766. [k] No cleavage products isolated and starting material recovered the extent of 75% or more. [l] The other product, acetone, eluded isolation probably because of the small scale and conversion for these experiments; only about 1 g. of acetone would have been expected. [m] Based on amount of starting diol, and based on the assumption that cleavage of unsymmetrical diols occurs in only one direction. [n] Estimated from gas chromatographic analysis.

This order is in agreement with that for ease of dehydrogenation of simple alcohols in aqueous solution, as determined polarographically.[18]

The cleavage of the various diols thus can be explained quite reasonably on the basis of this mechanism. For example, 1,3-butanediol is dehydrogenated to 4-hydroxy-2-butanone, which cleaves to acetone and formaldehyde, and the acetone is reduced mainly to isopropyl alcohol, the diol being oxidized to more ketol. The fate of the formaldehyde is not known; one might expect it to undergo the Cannizzaro reaction, forming methanol and formate ion, but since no methanol was detected, even by gas chromatography, perhaps it just goes to formate ion with evolution of hydrogen gas. The considerable tar formed may be polymer of the unsaturated ketone derived from the ketol.

As would be predicted from this mechanism, methylation of either hydroxyl group in a 1,3-diol prevents the cleavage reaction from occurring. The two monomethyl ethers of the easily cleavable 2-methyl-2,4-pentanediol were prepared by unambiguous methods.[19] 2-Methyl-4-methoxy-2-pent-

(18) H. Adkins and F. W. Cox, *J. Am. Chem. Soc.*, 60, 1151 (1938).

(19) Methylation of the diol with methyl sulfate and alkali was not a suitable method to prepare either monomethyl ether in pure form.

tanol was prepared by the reaction of methyl 3-methoxybutyrate with methylmagnesium bromide. 4-Methyl-4-methoxy-2-pentanol was prepared by lithium aluminum hydride reduction of 4-methyl-4-methoxy-2-pentanone. Neither of these compounds could be cleaved by alkali at temperatures up to 280°, about 90% of the starting compounding being recovered in each case.

Also in accord with this mechanism was the failure of diols other than 1,3-diols to cleave in alkali. Attempts to cleave the following in hot caustic were unsuccessful: 1,2-propanediol, glycerol, 1,4-butanediol and 1,5-pentanediol.

The stereochemistry of the reaction was investigated by a study of *cis* and *trans* cyclic 1,3-diols. Although the same ketol would be formed from each isomer, one might expect some differences in ease of dehydrogenation of the isomers.

The pure *cis* and *trans* isomers of both 1,3-cyclohexanediol and 1,3-cyclopentanediol were treated with alkali at 200°. As shown in Table II, the *cis* isomer in each series was more easily cleaved than the *trans* isomer. The difference in rate can be made use of in preparing *trans*-1,3-cyclohexanediol from the mixture of *cis* and *trans* isomers obtained by hydrogenation of resorcinol. The hot alkali treatment of this mixture

TABLE II

ALKALINE CLEAVAGE OF CYCLIC 1,3-DIOLS

Compound	Temp.	Time, Hr.	Recovered Diol	
			%	Isomer
cis-1,3-Cyclopentanediol	200	0.5	0	
trans-1,3-Cyclopentanediol	200	0.5	50	trans
cis-1,3-Cyclohexanediol	150	0.1	33	cis
trans-1,3-Cyclohexanediol	150	0.1	67	trans
cis- and trans-1,3-Cyclohexanediol[a]	170	0.25	33[b]	trans only

[a] From catalytic hydrogenation of resorcinol. [b] Corresponds to 0% recovery of cis isomer and 66% recovery of trans isomer, if the starting product were a mixture of 50% of each isomer.

preferentially cleaved the cis isomer, so that the pure trans isomer could be recovered.

At temperatures above 150°, the trans isomer reacted also, although apparently more slowly than the cis isomer. It is possible that these conditions were sufficiently rigorous to allow interconversions of the cis and trans isomers, so that the trans-diol was actually reacting by way of the cis isomer.

The faster rate of cleavage of the cis isomer in each series may be attributed to the stabilization of the monoalkoxide by internal hydrogen bond formation. It seems reasonable that the base-catalyzed dehydrogenation of a carbinol group would involve the alkoxide as an intermediate, and thus factors favoring formation of alkoxide would also favor dehydrogenation. Similar chelation of monoalkoxides of 1,2-diols has been proposed by Hine
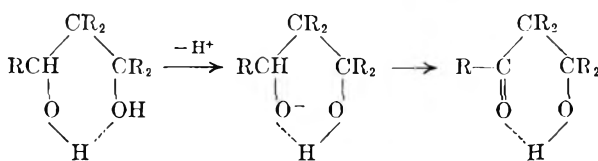
and Hine[20] to account for their acidities being considerably greater than for their monoalkyl ethers. Strong intramolecular hydrogen bonding has been demonstrated spectrally for open-chain 1,3-diols and for cis-1,3-cyclohexanediol, whereas practically no chelation was found for trans-1,3-cyclohexanediol.[21] One might expect similar and probably greater differences between the cis and the trans isomers of 1,3-cyclopentanediol, where the ring is more rigid.

EXPERIMENTAL

All of the 1,3-diols used were known compounds. They were either commercial samples or samples prepared by previously described methods, except the three described below. In each case, purification was carried out by fractional distillation until the physical constants (b.p. and n_D, or m.p.) agreed with the literature values.

Methyl 3-methyl-3-hydroxybutyrate. A solution of 226 g. of methyl bromoacetate, 103 g. of acetone, and 50 g. of dry ether was added with good stirring to 118 g. of activated zinc in 100 ml. of ether at a rate that gave gentle refluxing.

The reaction mixture was stirred several hours more at room temperature; if the temperature were allowed to rise and the ether distilled out, only methyl 3-methylacrylate was obtained as product. Following the customary method of processing a Reformatsky reaction mixture,[22] vacuum distillation (spinning band column) gave 28.5 g. (15%) of a clear, colorless liquid, b.p. 70° (12 mm.), n_D^{20} 1.4220.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.54, H, 8.96.

The same compounds, synthesized by another method, has been reported to have b.p. 70–71° (10 mm.), n_D^{20} 1.4126.[23]

3-Methyl-1,3-butanediol. A solution of 28 g. of methyl 3-methyl-3-hydroxybutyrate in 50 ml. of ether was added to a solution of 8.2 g. of lithium aluminum hydride in 150 ml. of ether. After refluxing 3 hr., the mixture was cooled and hydrolyzed with 20% sodium carbonate solution. The product was extracted with ether and dried over magnesium sulfate; distillation gave 15 g. (67%) of a colorless, viscous sirup, b.p. 104° (14 mm.), 118–119° (30 mm.), 198–200° (740 mm.), n_D^{20} 1.4415. The phenylurethan derivative melted at 88–89°. Previously reported for this compound, synthesized by other methods, are b.p. 202–204°,[24] 80° (5 mm.),[25] phenylurethan derivative m.p. 87–88°.[24,25]

1-Phenyl-1,3-propanediol. Methyl 3-hydroxy-3-phenylpropionate[26] (113 g.) was reduced with 60 g. of lithium aluminum hydride in the manner described above, to give 54.5 g (56%) of the diol, b.p. 180–185° (17 mm.), n_D^{22} 1.5425. The literature gives b.p. 175° (11 mm.).[27]

1,3-Diphenyl-1,3-propanediol. Dibenzoylmethane,[28] was reduced with lithium aluminum hydride by the above general procedure to give a 12% yield of 1,3-diphenyl-1,3-propanediol, b.p. 190–195° (5 mm.), m.p. 24–25°. The literature values[29] are somewhat higher: b.p. 214–218° (4 mm.), m.p. 94–98°. The infrared spectrum of our compound, however, was entirely in accord with expectations, showing strong absorption characteristic of chelated hydroxyl and no carbonyl absorption bands; and it analyzed satisfactorily.

Anal.[30] Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.04; H, 7.32.

(20) J. Hine and M. Hine, J. Am. Chem. Soc., 74, 5266 (1952).
(21) L. P. Kuhn, J. Am. Chem. Soc., 74, 2492 (1952).
(22) R. L. Shriner, Organic Reactions, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 17.
(23) A. M. Gakhokidze, Soobshcheniya Akad. Nauk. Gruzin. S.S.R., 10, No. 4, 193 (1949); Chem. Abstr., 47, 3236 (1953).
(24) F. V. Favorsky and A. I. Lebedeva, Bull. soc. chim. France, 6, 1347 (1939).
(25) A. T. Blomquist and J. A. Verdol, J. Am. Chem. Soc., 77, 78 (1955).
(26) W. H. Mills and L. Bains, J. Chem. Soc., 2503 (1924).
(27) H. Rupe and H. Muller, Helv. 4, 841 (1921).
(28) Org. Syntheses, Coll. Vol. I, 205 (1941).
(29) J. M. Sprague and H. Adkins, J. Am. Chem. Soc., 56, 2669 (1934).
(30) Microanalyses performed by Geller Laboratories, Hackensack, N. J.

<div align="center">

TABLE III

IDENTIFICATION OF CLEAVAGE PRODUCTS

</div>

Compound	Parent Diol	B.P. (Mm.)		n_D^{20}		Derivative	M.P.	
		Obs.[a]	Lit.[b]	Obs.	Lit.[b]		Obs.	Lit.[b]
Acetone	XIV	55–57	56	1.3595	1.3590	2,4-DNP	127–128	127–128
2-Propanol	IX, XI, XIV	78–81	82.5	1.3768	1.3793	α-Naphthylurethane	105–106	106
2-Propanol	X	80–81	82.5	1.3776	1.3793	Phenylurethane	83–85	88
						3,5-Dinitrobenzoate	119–120	122
2-Methyl-1-propanol	II, XI, VIII	104–105	107–108	1.3972	1.3968	Phenylurethane	87–88	88
						p-Nitrobenzoate	67–68	68.5–69
1-Butanol	VI	115–117	116	1.3995	1.3991	α-Naphthylurethane	70–71	71
2-Ethyl-1-butanol	III	145–147	148	1.4212	1.4208	3,5-Dinitrobenzoate	49–51	51
n-Butyl n-butyrate	VI	165–168	165	1.4298	1.4305	[c]		
1-Phenylethanol	XVI	203–205	203–204	1.5220	1.5212	p-Nitrobenzoate	42–43	43
						3,5-Dinitrobenzoate	92–93	93
2-Phenylethanol	IV	110–112 (17)	104 (14)	1.5322	1.533	Phenylurethane	78–79	79
1,1-Diphenylethylene	XVII	145–150 (14)	156 (20)	1.6075	1.6085	[d]		
Benzyl alcohol	VIII	103–105 (25)	107 (25)	1.5157	1.5275	p-Nitrobenzoate	83–84	85
Benzoic acid	VIII	. . .	. . .	. . .	. . .	. . .	121	121

[a] Observed boiling points are for 730–740 mm., unless otherwise stated. [b] As cited by E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds, *Order I*," John Wiley & Sons, Inc., New York, N. Y., 1941, or in Beilstein's "Handbuch der Organischen Chemie." [c] Saponification equivalents are: observed, 144; calcd., 142.5. [d] As in the other cases, the structure was confirmed also by infrared analysis; the infrared spectrum of this compound showed the presence of a phenyl group and of a terminal double bond, as well as the absence of hydroxyl and carbonyl functions.

A 3,5-dinitrobenzoate, m.p. 137–138° and (later) 149–150° was prepared.

2-Methyl-4-methoxy-2-pentanol. Methyl 3-methoxybutyrate[31] (150 g.) was added dropwise to a cold, stirred Grignard reagent prepared from 535 g. of methyl bromide and 123 g. of magnesium turnings in 1 l. of ether. The conditions and method of work-up were the same as for the last described compound. The yield was 104 g. (79%) of 2-methyl-4-methoxy-2-pentanol, b.p. 154–155° (735 mm.), n_D^{22} 1.4143. The infrared spectrum was in agreement with the structure assigned.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.63; H, 12.12. Found: C, 63.62; H, 12.02. The 3,5-dinitrobenzoate was prepared, m.p. 68–69°.

4-Methyl-4-methoxy-2-pentanol. 4-Methoxy-4-methyl-2-pentanone[32] (43 g.) was reduced with 16 g. of lithium aluminum hydride in ether. The excess hydride was decomposed with 50 ml. ethyl acetate, and dilute hydrochloric acid was used for hydrolysis of the reaction mixture. After the usual washing and drying, distillation gave 25 g. (58%) of 4-methoxy-4-methyl-2-pentanol, b.p. 165–170° (730 mm.), n_D^{20} 1.4388.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.63; H, 12.12. Found: C, 63.43; H, 11.84.

The 3,5-dinitrobenzoate melted at 69–70°.

2-Methyl-2,4-dimethoxypentane. In an attempt to prepare one of the above monomethyl ethers, 360 g. of dimethyl sulfate was added slowly with stirring to a solution of 160 g. of 2-methyl-2,4-pentanediol, 150 g. of sodium hydroxide in 1.5 l. of water maintained at 60–70°. The temperature was then increased to 95° for 1 hr. The mixture was cooled, while 200 ml. of 3N potassium hydroxide was added and extracted with ether. Distillation of the dried extracts gave 25 g. (16%) of the pure dimethoxy compound, b.p. 148–152° (735 mm.), n_D^{20} 1.4150. The infrared spectrum showed absence of hydroxyl groups and of double bonds, and presence of the ether linkage. The method was not suitable for either of the monomethyl ethers.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.98; H, 12.30. Found: C, 66.39; H, 11.84.

Alkaline pyrolysis. The general procedure used is illus-

trated by the following: 2-methyl-2,4-pentanediol (118 g.) was added dropwise to a stirred solution of 150 g. of potassium hydroxide in 20 ml. of water, maintained at 145–150°. The products distilling were passed through a 6-in. Vigreux column and a water-cooled condenser to a receiver, which in turn was connected to a Dry Ice–acetone trap and a bubbler containing bromine in carbon tetrachloride. (The latter was for detection of any low boiling olefins, but in no case was anything collected in the Dry Ice trap, or the bromine decolorized.)

The contents of the receiver were saturated with sodium chloride, and the organic layer dried and distilled through a 1-ft. Fenske column: 32 g. of acetone (60%) and 53 g. of isopropyl alcohol (88%) was obtained. In addition 10–20 g. of a sticky, dark brown, aromatic-smelling tar was formed; operation at higher temperatures gave more tar and less acetone and isopropyl alcohol.

A number of variations of this procedure were tested, but without any striking differences in the results. The water used was not necessary. Sodium hydroxide could be substituted for potassium hydroxide. The amount of base used could be decreased to 0.5 molar quantities without noticeable effect, but below that, higher reaction temperatures were required. A temperature of 180° was required for a reasonable rate of cleavage when 4 g. of sodium hydroxide (no water) was used with 118 g. of the above diol. There was practically no tar formation, however, with this small amount of base, and the yields of isopropyl alcohol and acetone was 92% and 56%, respectively. The best results were obtained when 40 g. of sodium hydroxide and 118 g. of the diol were heated with stirring at 150°, yielding 56 g. of isopropyl alcohol and 54 g. of acetone (93% of each).

The composition of the ethanol-isopropanol mixture, formed by the cleavage of 2,4-pentanediol, was determined by infrared spectral analysis because of the difficulty of fractional distillation. The presence of isopropyl alcohol was demonstrated by oxidation with potassium dichromate and sulfuric acid. The oxidation products were distilled from the reaction, dried and fractionally distilled to give a 25% yield (based on starting diol) of acetone, b.p. 54–55° (735 mm.), n_D^{22} 1.3595, 2,4-DNP m.p. 125–126° (lit. 127–128°[33]). The acetaldehyde formed was collected in a water solution and characterized as the DNP, m.p. 147–148° (lit., 148°[33]).

(31) T. Purdie and W. Marshall, *J. Chem. Soc.*, 476 (1891).

(32) A. Hoffman, *J. Am. Chem. Soc.*, **49**, 530 (1927).

(33) Ref. b, Table III.

In cases where the products were high boiling and did not distill, the reaction mixture was neutralized with dilute hydrochloric acid and extracted with ether, benzene, or chloroform. After removal of the solvent, the product was either crystallized or distilled. With the cyclic diols, however, no cleavage products were isolated (probably on account of high water solubility, since these products would be expected to be diols and hydroxy acids).

The products obtained from the diols numbered II, VI, IX, X, and IV (Table I) were passed through a gas-phase chromatographic column employing tricresyl phosphate on celite. All the peaks observed were consistent with the materials already known to be present, as given in Table I.

The methods of identifying the cleavage products are listed in Table III.

Alkaline pyrolysis by the above general procedure appeared to give practically no cleavage in the following cases: (1) 2-methyl-4-methoxy-2-pentanol, 44 g. of an initial 50 g. being recovered after treatment with 100 g. of potassium hydroxide at temperatures up to 280°. (2) 4-Methyl-4-methoxy-2-pentanol, with similar recovery after similar treatment. (3) 1,2-Propanediol. (4) Glycerol. (5) 2-Ethyl-1-hexanol. (6) 2,2-Dimethyl-1-propanol. (7) 2-Methyl-2-butanol, although 1% of 2-butanone, b.p. about 90°, m.p.

of DNP 116–117°, was obtained, reminiscent of the cleavage of 2-butyl-2-hexanol to 2-hexanone at 600°.[34]

trans-1,3-Dihydroxycyclohexane. Resorcinol was catalytically reduced over Raney nickel catalyst, forming a mixture of *cis*- and *trans*-1,3-dihydroxycyclohexane, b.p. 145–147° (15 mm. in 90% yield).[35] This product contains approximately equal amounts of both isomers.[35,36]

An intimate mixture of 20 g. of this material and 50 g. of powdered, 85% potassium hydroxide was heated at 170° for 15 min., followed by cooling, addition of water, and extraction with hot benzene. After drying and removal of solvent, 6.5 g. of *trans*-1,3-dihydroxycyclohexane, b.p. 137–144° (15 mm.) m.p. 110–115° (from acetone), m.p. trityl ether, 197–198° (lit.[35,36] values, b.p. 135° (13 mm.), m.p. 118°, trityl ether m.p. 199°).

The same procedure was used for pyrolysis of the other cyclic diols.

Manhattan, Kan.

(34) V. Grignard and F. Chambret, *Compt. rend.*, **182**, 299 (1926).

(35) H. Lindemann and H. Baumann, *Ann.*, **477**, 78 (1930).

(36) W. Rigby, *J. Chem. Soc.*, 1586 (1949).

[Contribution from the Department of Chemistry of DePaul University]

Synthesis of Dinaphthylamines and Tetranaphthyl Hydrazines[1]

Eugene Lieber[2] and S. Somasekhara

An improved procedure for the synthesis of the three isomeric 1,1'-, 2,2'- and 1,2'-dinaphthylamines has been devised and their oxidation, by neutral permanganate in acetone, to the corresponding symmetrical tetranaphthyl hydrazines achieved. The treatment of *N*-acetyldinaphthylamines under the same conditions results in recovery of starting material. New properties for the *N*-acetyldinaphthylamines are described. The syntheses of 1,2-dimethyl-1,2-di(1-naphthyl)- and 1,2-diphenyl-1,2-di(1-naphthyl)-hydrazines are also described.

The synthesis of heavily tetra-substituted hydrazines was undertaken with the objective of studying their dissociation in solution to disubstituted nitrogen radicals. The procedure adopted for obtaining the desired hydrazines from the corresponding secondary amines was the method described by Wieland[3] for converting diphenylamine to tetraphenyl hydrazine by oxidation with neutral potassium permanganate. As a prelude to the synthesis of tetranaphthyl hydrazines, the synthesis of three isomeric dinaphthylamines, namely, the 1,1' (I); the 2,2' (II); and, the 1,2' (III), was investigated. A survey of the literature[4–8] revealed that

I II III
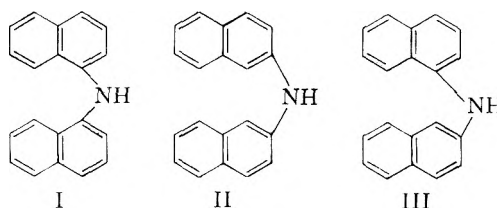
I, II, and III have been synthesized by a variety of procedures. These, in general, comprised heating naphthols or naphthylamine, either singly on in admixture, at temperatures ranging from 150–300° for extended periods of time, in the presence of substances such as ammonia chloride, zinc chloride, calcium chloride, and sodium acetate. In our hands these methods led only to tarry solids from which only the starting materials could be recovered on a very depleted scale. The method finally adopted was a variation of the procedure described by Merz and Weith[4,5] and represents a distinct improvement over that previously described. The procedure consists in gently heating a mixture of equal parts of a naphthylamine, a naphthol, freshly fused zinc chloride and ammonium chloride to the molten state. A spontaneous, exothermic reaction sets in

(1) This investigation was sponsored by the Basic Research Group, Corps of Engineers, U. S. Army, Fort Belvoir, Virginia. The authors gratefully acknowledge this assistance.

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(3) C. Weygand, *Organic Preparations*, Interscience Publishers, Inc., New York, N. Y., 1945, p. 244.

(4) V. Merz and W. Weith, *Ber.*, **13**, 1300 (1880).

(5) V. Merz and W. Weith, *Ber.*, **14**, 2344 (1881).

(6) G. Benz, *Ber.*, **16**, 8 (1883).

(7) A. Calm, *Ber.*, **15**, 613 (1882).

(8) L. Landshoff, *Ber.*, **11**, 639 (1978).

almost immediately and lasts for ten to fifteen minutes. The reaction mixture is worked up after thirty minutes. In this manner a 70% yield of II was obtained, while I and III were obtained in 25% yields.

Neutral permanganate in acetone proved a convenient reagent for obtaining the tetranaphthyl hydrazines from I, II, and III. In order to demonstrate that only the hydrogens on the secondary amine nitrogen were involved in the permanganate oxidation, N-acetyl derivatives of I and II were prepared by adopting the procedure described by Hurd and Dull[9] for the N-acetylation of carbazole. Benz[6] reported a melting point of 217° for the N-acetyl derivative of I and 114–115° for that of II. The purified products obtained in this investigation melted at 101–103° for the N-acetyl derivative of I, while that of II melted at 80–82°. When these acetyl derivatives were subjected to neutral permanganate oxidation, under the same conditions used for the secondary amines, they were recovered almost quantitatively, demonstrating that the hydrogen atoms on the naphthalene ring were not involved in the oxidation.

Two additional secondary amines, namely, N-phenyl-1-naphthylamine and N-methyl-1-naphthylamine have also been oxidized to their respective hydrazines with neutral permanganate. However, similar attempts with N-ethyl-1-naphthylamine and N-phenyl-2-naphthylamine led only to either recovery of starting material or resinous solids which could not be crystallized.

EXPERIMENTAL[10,11]

2,2′-Dinaphthylamine (II). Ten g. (0.07 mole) 2-naphthol, 2-naphthylamine (10 g.; 0.07 mole), ammonium chloride (10 g.) and freshly fused zinc chloride (10 g.) were thoroughly mixed and melted to a brown liquid by gentle heating. A vigorous reaction set in almost immediately and lasted for 15 min. The reaction mixture was maintained in the molten condition for an additional 30 min., cooled to room temperature, and thoroughly crushed under boiling water (200 ml.) to remove all the ammonium chloride and most of the zinc chloride. The solid residue obtained on filtering was treated with hot 10% KOH solution to remove any unreacted 2-naphthol and basic zinc chloride that might have been formed during the reaction. The product was then treated with hot dilute hydrochloric acid in order to remove any 2-naphthylamine present. The solid residue was finally washed with 10% KOH solution and water. It was then taken up in pyridine, charcoal treated, and precipitated with water to obtain the dinaphthylamine as a fine powder. Recrystallization from benzene yielded 12.5 g. (70%) of silvery-yellow platelets, m.p. 172.5°, literature[4] 170.5°.

Anal. Calcd. for $C_{20}H_{15}N$: N, 5.20. Found: N, 5.26.

In the ultraviolet, absorption maxima are exhibited at 265 and 316 mμ with log ϵ of 4.71 and 4.53, respectively.

1,1′-Dinaphthylamine (I). The procedure and quantities described above were carried out with 10 g. (0.07 mole) of

1-naphthylamine. The brown solid finally obtained was given a charcoal treatment in ethanol and crystallized from ethanol as pale-yellow platelets, m.p. 113.5–114.5°, literature,[8] 111°. The yield was 7 g. (35%).

Anal. Calcd. for $C_{20}H_{15}N$: N, 5.20. Found: N, 5.16.

In the ultraviolet, absorption maxima are exhibited at 248 and 338 mμ with log ϵ at 4.53 and 4.21, respectively.

1,2′-Dinaphthylamine (III). The procedure described above was carried out with a mixture of 7.2 g. (0.05 mole) each of 1-naphthylamine and 2-naphthol. The pale-brown solid obtained was given 2 charcoal treatments in ethanol and crystallized from aqueous ethanol. A yield of 3.6 g. (27%) of crystalline material, m.p. 98–100°, literature,[6] 111°. Attempts to raise the m.p. by recrystallization were unsuccessful.

Anal. Calcd. for $C_{20}H_{15}N$: N, 5.20. Found: N, 5.40.

In the ultraviolet, absorption maxima are exhibited at 254 and 344 mμ with log ϵ of 4.73 and 4.30, respectively.

1,1,2,2-Tetra(2-naphthyl)hydrazine. One-hundredth mole (2.7 g.) of II was dissolved in acetone (distilled from permanganate) and the solution cooled in an ice bath. Potassium permanganate (1.2 g.) was added in 6 portions over a period of 2 hours, care being taken to see that the pink color of the solution disappeared before making the next addition of potassium permanganate. At the end of 2 hr., 1 additional g. of potassium permanganate was added in 1 lot, and the reaction allowed to stand at room temperature for 1 hr. Ordinary acetone (20 ml.) was added to remove the remaining pink color and the resulting mixture filtered free of manganese dioxide. The filtrate on concentration and dilution with 95% ethanol, yielded 1.7 g. (65%) of a brownish-yellow solid, m.p. 210–215°. This could not be crystallized from either acetone, alcohol, chloroform, or benzene. It was, therefore, purified by repeated dissolution in acetone and precipitation with ethanol. After 3 such treatments, a yellow powder having a constant m.p. of 256–259° was obtained. It was very sparingly soluble in ethanol but very soluble in acetone, chloroform, and benzene.

Anal. Calcd. for $C_{40}H_{28}N_2$: C, 89.54; H, 5.22; N, 5.22. Found: C, 89.37; H, 5.16; N, 4.96.

In the ultraviolet, absorption maxima are exhibited at 256 and 316 mμ with log ϵ of 4.71 and 4.53, respectively.

1,1,2,2-Tetra(1-naphthyl)-hydrazine. This was obtained in 60% yield from I by the procedure described above. The analytical sample melts at 235–238°.

Anal. Calcd. for $C_{40}H_{28}N_2$: N, 5.22. Found: N, 5.13.

In the ultraviolet, absorption maxima are exhibited at 248 and 358 mμ with log ϵ of 4.31 and 4.09, respectively.

1,2-Di(1-naphthyl)-1,2-di(2-naphthyl)hydrazine. This was obtained in 45% yield from III by the procedure described above. The analytical sample melted at 240–242°.

Anal. Calcd. for $C_{40}H_{28}N_2$: C, 89.54; H, 5.22; N, 5.22. Found: C, 89.08; H, 5.62; N, 5.36.

In the ultraviolet, absorption maxima are exhibited at 250 and 330 mμ with log ϵ of 4.58 and 4.00, respectively.

1,2-Dimethyl-1,2-di(1-naphthyl)hydrazine. From N-methyl-1-naphthylamine in 10% yield, m.p. 187–190°.

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.61; H, 6.40; N, 8.97. Found: C, 84.20; H, 6.13; N, 9.13.

1,2-Diphenyl-1,2-di(1-naphthyl)hydrazine. From N-phenyl-1-naphthylamine by the above procedure; m.p. 177–180°.

Anal. Calcd. for $C_{32}H_{24}N_2$: N, 6.42. Found: N, 6.24.

N-Acetyl-2,2′-dinaphthylamine. One and a half g. of II was refluxed with acetic anhydride (8 ml.) for 3 hr. The reaction was then poured into warm water (50 ml. at 50°). The mixture was neutralized with K_2CO_3, producing an oily substance. This was taken up in acetone-alcohol mixture, charcoal treated, the filtrate concentrated, cooled, and diluted with water. On standing, fragile needles precipitated, very soluble in acetone, benzene, and hot ethanol. Recrystallization, was effected from ethanol, m.p. 80–82°.

Anal. Calcd. for $C_{22}H_{17}NO$: N, 4.50. Found: N, 4.24.

N-Acetyl-1,1′-dinaphthylamine. From I in 50% yield, m.p. 101–103°.

(9) C. D. Hurd and M. F. Dull, *J. Am. Chem. Soc.*, **54**, 2432 (1932).

(10) Melting points are uncorrected.

(11) Micro analyses by Dr. C. Weiler and Dr. F. B. Strauss, Oxford, England.

Anal. Calcd. for $C_{22}H_{17}NO$: C, 4.50. Found: N, 4.32.

Oxidation of N-acetyldinaphthylamines. The procedure with *N*-acetyl-2,2'-dinaphthylamine was typical. One-half gram of the amide was dissolved in acetone (50 ml. distilled from permanganate). After cooling in an ice bath, 0.08 g. $KMnO_4$ was added. The oxidizing agent was not decolorized on standing at 0° for 1 hr. or overnight at room temperature. Since no decolorization had taken place, additional permanganate

was not added. The pink color of the solution was then discharged by the addition of ethanol (5 ml.) and gentle warming. It was filtered and concentrated. Dilution of the concentrate with ice water regenerated the starting material in nearly quantitative yield. A similar result was obtained on oxidation of *N*-acetyl-1,1'-dinaphthylamine.

CHICAGO 14, ILL.

Studies of Quinoid Structures. III.[1] Action of Grignard Reagents on Phenanthrenequinone Monosemicarbazone, Chrysenequinone Monosemicarbazone, and Benzil Monosemicarbazone

WILLIAM IBRAHIM AWAD, ABDEL REHIM ABDEL RAOUF, AND AIDA MOUSTAFA KAMEL

The preferential addition of alkyl and arylmagnesium halides to the carbonyl group of phenanthrenequinone monosemicarbazone, chrysenequinone monosemicarbazone, and benzil monosemicarbazone is described. The constitution of the products is discussed. Infrared data are given for these monosemicarbazones and some of their Grignard products.

Awad and Raouf[1,2] found that Grignard reagents add preferentially to the carbonyl group of phenanthrenequinonimine, chrysenequinonimine, phenanthrenequinone monoxime, and chrysenequinone monoxime. This investigation is now extended to phenanthrenequinone monosemicarbazone, chrysenequinone monosemicarbazone, and benzil monosemicarbazone. The reaction seems to proceed according to scheme A.
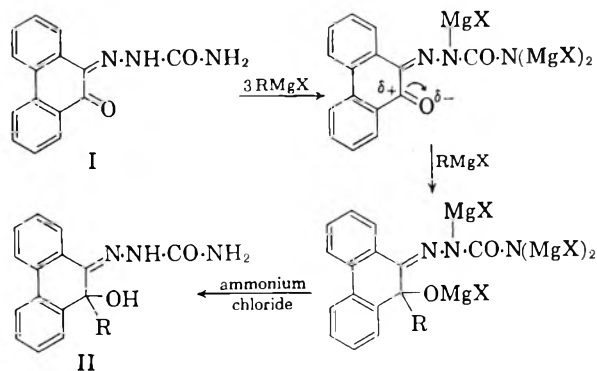

IIa. R = CH_3; IIb. R = C_2H_5; IIc. R = C_6H_5; IId. R = $C_{10}H_7(\alpha)$

Scheme A

The constitution of the Grignard products is based upon the following: (1) the preferential addition of the Grignard reagent to the carbonyl group,[1–4] (2) the action of acetic acid on (IIc) to yield the ketone (III),[1,2] (3) the infrared spectral study (inter-alia), (4) elemental analysis, (5) the

inactivity of acetophenone semicarbazone towards Grignard reagent under the conditions of the experiment.


III
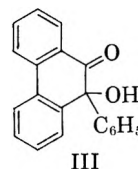
When (IIc) was heated with alcoholic hydrochloric acid, water is lost to give (IV). The constitution of (IV) is based upon: (1) elemental analysis, and (2) a comparative study of its infrared spectra with that of (V).[5]

IV

V
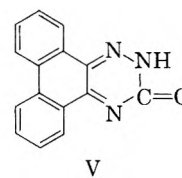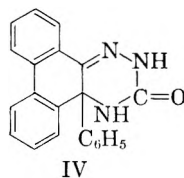
(or its enol form).

Similarly, chrysenequinone monosemicarbazone for which structure (VI) was assigned on steric grounds[1,6] reacted with Grignard reagents to give compounds for which structure (VII) was given.

VI

VII
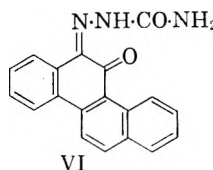
VIIa. R = CH_3; VIIb. R = $C_{10}H_7(\alpha)$

(1) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **23**, 282 (1958).

(2) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **22**, 881 (1957).

(3) O. Diels and F. ter Meer, *Ber.*, **42**, 1940 (1909).

(4) O. Diels and J. M. Johlin, *Ber.*, **44**, 403 (1911).

(5) Schmidt, Schairer, and Glatz, *Ber.*, **44**, 276 (1911).

(6) W. I. Awad and A. R. A. Raouf, *J. Am. Chem. Soc.*, **77**, 3913 (1955).

TABLE I

	ν(NH) Un- bonded	Amide I	ν(C=O)	Amide II	δ(NH) Un- bonded (Rock- ing Modes)
Acetophenone semicarbazone	3485^a 3571^b	1750 ^{a} 1754^b		1590^a 1587^b	772^a 763^b
Benzil mono- semicarbazone	3636	1724	1695	1587	776
Phenanthrene- quinone mono- semicarbazone	3571	1724	1695	1639 (1600)	763
Chrysenequi- none mono- semicarbazone	3636	1754	1709	1600	758 w.^{c}
IIc	3571	1681		1587	769
IV	3571	1695		1612	NA^d
V		1754	1681	1612	758
VIIa	3508	1696		1612	745
VIII	3571	1695		1587	769

^{a} These values are quoted from ref. (7). ^{b} Obtained in the present investigation. ^{c} w, weak band. ^{d} NA, not assigned.

I showed similar shifts to those observed by David-son and Christie[8] in the case of the semicarbazones of aromatic carbonyl compounds. The stretching frequency of the carbonyl group does not exist in the spectra of the products of interaction of Grignard reagents with the monosemicarbazones.

EXPERIMENTAL[9]

Reaction of phenanthrenequinone monosemicarbazone with methylmagnesium iodide. A solution of methylmagnesium iodide (from methyl iodide, 7 g. and magnesium, 1 g.) was prepared in the usual way. A suspension of phenanthrene-quinone monosemicarbazone[6] (1 g.) in dry benzene (40 ml.) was added to the above solution. The reaction mixture was refluxed for 2 hr. on a boiling water bath and left overnight at room temperature. The Grignard product was hydrolyzed with 100 ml. of a saturated solution of ammonium chloride. The ether-benzene layer was separated, washed with water, and dried (Na$_2$SO$_4$). The product was precipitated by the addition of petroleum ether (40–60°) and was recrystallized from a large bulk of benzene to give IIa as colorless crystals, m.p. 205°, yield 47%. The product gave a dichromate color with concentrated sulfuric acid.

TABLE II

Com- pound	Sol- vent of Crystal- lization	M.P., °C.	Yield,^{a} %	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Color with Concd. Sulfuric Acid
IIb	A	194	45	$C_{17}H_{17}O_2N_3$	69.1	69.2	5.8	5.99	14.2	14.3	Dichromate
IIc	A	218	46	$C_{21}H_{17}O_2N_3$	73.5	73.4	5.0	5.0	12.2	12.3	Green
IId	A	225	40	$C_{25}H_{19}O_2N_3$	76.32	76.65	4.9	4.8	10.7	10.7	Brownish-green^b
VIIa	A	216–217	47	$C_{20}H_{17}O_2N_3$	72.5	72.5	5.2	5.2	12.7	12.7	Violet^b
VIIb	A	198–200	50	$C_{29}H_{21}O_2N_3$	78.6	78.8	4.8	5.1	9.48	8.93	Dark green
VIIIa	A	198–200	57	$C_{16}H_{17}O_2N_3$	67.8	67.7	6.4	6.3	14.84	15.39	
VIIIb	A	200–202	54	$C_{17}H_{19}O_2N_3$	68.7	68.9	6.1	6.3	14.1	14.0	Pale yellow
VIIIc	A	215–216	46	$C_{21}H_{19}O_2N_3$	73.0	72.7	5.6	5.6	12.2	12.0	Greenish-brown
VIIId	A	215–216	47	$C_{25}H_{21}O_2N_3$	75.9	76.2	5.4	5.3	10.6	10.4	Reddish-brown

A, benzene. ^{a} Yield is calculated for pure material. ^{b} Turned to brown.

When benzil monosemicarbazone was similarly treated with Grignard reagents, compounds of the structure (VIII) were analogously obtained.
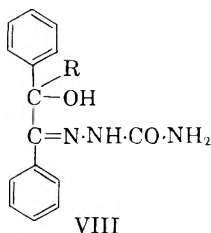
VIII

VIIIa. R = CH$_3$; VIIIb. R = C$_2$H$_5$; VIIIc. R = C$_6$H$_5$;
VIIId. R = C$_{10}$H$_7(\alpha)$

The infrared spectra[7] of the different semicar-bazones used in this work (see Table I) were similar to those of the semicarbazones of the different aldehydes and ketones investigated by Davidson and Christie.[8] The stretching frequencies for amide

Anal. Calcd. for C$_{16}$H$_{15}$O$_2$N$_3$: C, 68.3; H, 5.4; N, 14.94. Found: C, 68.5; H, 5.4; N, 15.09.

Reaction of phenanthrenequinone monosemicarbazone with alkyl and arylmagnesium halides. The reaction was carried out as in the case of methylmagnesium iodide. The products are listed in Table II.

Action of glacial acetic acid on IIc. IIc (1 g.) in glacial acetic acid (30 ml.) was refluxed for 2 hr. The colorless solution became orange-brown. The cold solution was poured on ice. The precipitated product, which was found to be a mixture containing mostly the starting material, was fractionally crystallized from methyl alcohol to give 9-hydroxy-9-phenyl-9(10H)-phenanthrone, III, as colorless crystals, m.p. 117°, not depressed on admixture with an authentic sample,[2] yield 12%. It gave a brown color with concentrated sulfuric acid, which turned to violet.

Action of alcoholic hydrochloric acid on IIc. A mixture of IIc (0.2 g.), ethyl alcohol (30 ml.), and concentrated hydro-chloric acid (4 ml.) was refluxed for 2 hr. on the water bath. The product which was precipitated on concentration and cooling, was crystallized from ethyl alcohol to give IV as colorless crystals, m.p. 304°, yield 95%.

Anal. Calcd. for C$_{21}$H$_{15}$ON$_3$: C, 77.5; H, 4.7; N, 12.9. Found: C, 77.7; H, 5.2; N, 12.9.

(7) The infrared measurements were carried out on a Perkin-Elmer Infracord Model 137, in Nujol medium.

(8) W. H. T. Davidson and P. E. Christie, *J. Chem. Soc.*, 3389 (1955).

(9) Microanalyses were carried out by Alfred Bernhardt, in Max-Planck-Institut, Mülheim (Ruhr), Germany. Melting points are not corrected.

Reaction of acetophenone semicarbazone with phenylmagnesium bromide. The substance was recovered unchanged when allowed to react with phenylmagnesium bromide under the same previous conditions. This was proved by melting point and mixture melting point determinations.

Preparation of chrysenequinone monosemicarbazone. A solution of chrysenequinone (2 g.) in ethyl alcohol (800 ml.) was treated with a solution of semicarbazide hydrochloride (1 g.) in the least amount of water and refluxed for 15 min. on the water bath. The product began to separate after 5 min. reflux as yellow crystals, and completely precipitated on cooling, dried by heating at 150° under reduced pressure, m.p. 256–258°, yield almost quantitative. It gave a brownish-violet color with concentrated sulfuric acid.

Anal. Calcd. for $C_{19}H_{13}O_2N_3$: N, 13.3. Found: N, 13.6.

Reaction of chrysenequinone monosemicarbazone with Grignard reagents. The reaction was carried out as in the case of phenanthrenequinone monosemicarbazone. The products are listed in Table II.

Reaction of benzil monosemicarbazone with Grignard reagents. The reaction was carried out as in the case of phenanthrenequinone monosemicarbazone. The products are listed in Table II.

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# *Notes*   A department for short papers of immediate interest.

Chemistry of Lactones. IV. Conversion of α-Benzylidene-γ-phenyl-Δ$^{\beta,\gamma}$-butenolide into 4-Phenyl-2-naphthoic Acid by Intramolecular Alkylation

Robert Filler, Lourdes H. Mark,[1]
and Edmund J. Piasek

As part of our research on highly conjugated lactone systems, we have previously reported[2] the reaction of the azlactone, 2-phenyl-4-benzylidene-5(4H)-oxazolone (I) with benzene in the presence of anhydrous aluminum chloride. Although azlactones often resemble cyclic anhydrides in their chemical behavior, I did not act as an acylating agent under these conditions. The reaction followed a different course, the 1,4 addition of benzene to the α,β-unsaturated carbonyl system.

In a continuation of our comparative studies of I and the structurally analogous α-benzylidene-γ-phenyl-Δ$^{\beta,\gamma}$-butenolide (II),[3] with which it is iso-electronic, we have also examined the behavior of II under Friedel-Crafts conditions.
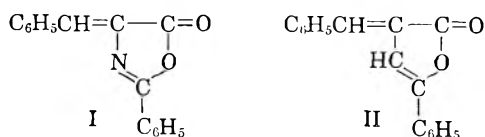
II reacted in the presence of excess benzene and anhydrous AlCl$_3$ to give a 71% yield of a substance (III), whose elemental analysis and molecular weight (determined by neutralization equivalent) indicated that it was a carboxylic acid isomeric with II. The infrared and ultraviolet spectra of III offered additional evidence that this compound was a substituted aromatic acid. III exhibited a strong band at 1695 cm.$^{-1}$, which may be attributed to the carbonyl stretching mode of aromatic carboxylic acids.[4] The weak band at 2600 cm.$^{-1}$ is characteristic of the hydrogen-bonded —OH moiety of the carbonyl group.[5] 2-Naphthoic acid also possessed bands at these frequencies.

In the ultraviolet, the intense K band at 245 mμ (ε 31,000) and the less intense B-band at 290 mμ (ε 7990) are also in general agreement with the spectra of compounds of this type.[6]

On the basis of possible ring opening reactions of the butenolide under these conditions and of the data previously cited, it appeared plausible that III was 4-phenyl-2-naphthoic acid, formed *via* an *intramolecular alkylation* reaction. Thus, the butenolide could readily be converted to a resonance-stabilized carbonium ion (IV), which, by electrophilic attack at the ortho position, would form III:
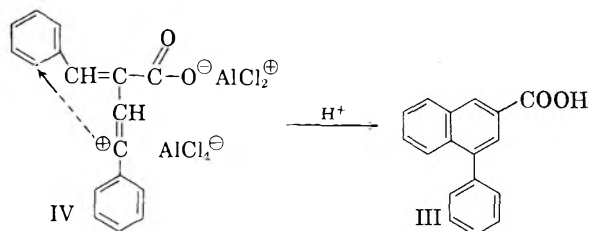
Decisive evidence for the structure of III was obtained by its decarboxylation to 1-phenylnaphthalene, which was identified by its physical properties and by its conversion to 4-nitro-1-phenylnaphthalene. There was no evidence of any product which could be obtained *via* an incipient acylium ion V (*i.e.*, by inter- or intramolecular acylation). Such an intermediate would be formed by the alternate mode of ring opening of II.

The butenolide failed to react when AlCl$_3$ was replaced by polyphosphoric acid, but when the original procedure was carried out using anisole in place of benzene, III was again the sole product isolated, though only in 50% yield. This result further emphasizes the intramolecular nature of this reaction.

Whereas the isomeric 1-phenyl-2-naphthoic and 4-phenyl-1-naphthoic acids[7] are known, 4-phenyl-2-naphthoic acid (having a considerably higher melting point) has, to our knowledge, not been de-

(1) From the M. S. thesis of L. H. M., April, 1959.

(2) R. Filler and L. M. Hebron, *J. Org. Chem.*, **23**, 1815 (1958).

(3) R. Filler and L. M. Hebron, *J. Am. Chem. Soc.*, **81**, 391 (1959).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 168.
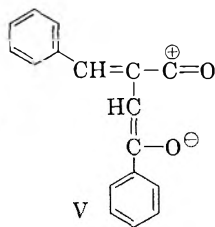
(5) Ref. 4, p. 163.

(6) Benzoic acid, for example, exhibits comparable maxima at 230 mμ and 270 mμ. A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," 2nd ed., Edward Arnold, Ltd., London, 1957, p. 141.

(7) *Chemical Abstracts* nomenclature.

scribed previously and would appear to be quite difficult to obtain by any other means. It seems clear that we have available an excellent method for preparing certain substituted naphthalene compounds from selected β,γ-unsaturated lactones. The scope and limitations of the method are being explored further.

Other striking differences in chemical behavior between I and II have been observed and these will be discussed in a forthcoming paper.

EXPERIMENTAL[8]

Reaction of α-benzylidene-γ-phenyl-Δ^β,γ-butenolide (II) with benzene. In a 2-l., round bottomed flask, fitted with a mechanical stirrer, dropping funnel, and reflux condenser, were placed 19.8 g. (0.15 mol.) of anhydrous aluminum chloride in 250 ml. of dry, thiophene-free benzene. The mixture was cooled to 10–20° and stirred for 1 hr. To this mixture was added dropwise with stirring a solution containing 12.4 g. (0.05 mol.) of II in 250 ml. of dry benzene, the temperature being maintained at 10–20° during the addition. The mixture turned brick-red. When all of the butenolide had been added, the mixture was stirred for an additional 3 hr. at room temperature. The complex was decomposed with dilute hydrochloric acid and the resulting mixture extracted with ether. The ether layer was washed with dilute sodium bicarbonate solution and water and then dried over anhydrous magnesium sulfate. Upon evaporation of the solvent on steam bath, a yellowish white solid was obtained. Crystallization from 95% ethanol gave 8.5 g. (70.8%) of white needles of 4-phenyl-2-naphthoic acid (III), m.p. 262.5–263.5°.

Anal. Calcd. for $C_{17}H_{12}O_2$: C, 82.24; H, 4.83. Found: C, 82.52; H, 4.81. Mol. wt. calcd.: 248. Found: 248 (neut. equiv.).

λ_{max}^{EtOH} 245 mμ (ε 31,000), 290 mμ (ε 7990). Infrared absorption at 1695 cm.$^{-1}$ (s) and 2600 cm.$^{-1}$ (w).

Reaction of II with anisole. In a 500-ml. round bottomed flask, fitted with a mechanical stirrer, dropping funnel, and reflux condenser, were placed 4.7 g. (0.036 mol.) of anhydrous aluminum chloride and 3.8 g. (0.036 mol.) of anisole in 65 ml. of methylene chloride. The mixture was stirred for 1 hr. at 10°. To this mixture was added dropwise with stirring a solution containing 3 g. (0.012 mol.) of II in 100 ml. methylene chloride, the temperature being maintained at 10–20° during the addition. When all of the butenolide had been added, the mixture was stirred for an additional 3 hr. at room temperature. The complex was decomposed with 250 ml. of dilute (1:15) hydrochloric acid and the two layers which formed were separated, the water layer was washed with methylene chloride and the combined extracts were washed with dilute acid and water until neutral to litmus. Excess methylene chloride was removed by evaporation on a steam bath. The product was crystallized from 95% ethanol to give 1.5 g. (50%) of white needles, m.p. 258–260°.

Anal. Calcd. for $C_{17}H_{12}O_2$: C, 82.24; H, 4.83. Found: C, 82.57; H, 5.17.

Mixed melting point with the product obtained with benzene showed no depression. The ultraviolet and infrared spectra were also identical.

Decarboxylation of 4-phenyl-2-naphthoic acid (III). III [8.13 g. (0.033 mol.)] and 0.648 g. (0.0028 mol.) of copper chromite in 10 ml. of quinoline were heated under slow reflux for 7 hr. The mixture was treated with 100 ml. of ether and washed with several portions of dilute hydrochloric acid followed by sodium bicarbonate solution and water. The ether layer was dried over anhydrous magnesium sulfate.

The ether was removed by evaporation and 1-phenylnaphthalene was obtained as a viscous oil, b.p. 333–335° at

(8) M.p.'s are corrected.

748 mm., $n_D^{23.4}$ 1.6654 (reported b.p. 334–336°,[9] n_D^{18} 1.6692[10]).

Nitration of 1-phenylnaphthalene. To 3 ml. of a 50-50 mixture of fuming nitric acid and glacial acetic acid, cooled in an ice bath, was added dropwise 0.25 ml. of 1-phenylnaphthalene. The solution was mixed and poured over ice. The 4-nitro-1-phenylnaphthalene thus obtained was crystallized from petroleum ether to give yellow crystals melting at 129–130° (reported[11] m.p. 129–130°).

Spectral measurements and analyses. Infrared spectra were obtained on a Perkin-Elmer 21 spectrophotometer, using chloroform as solvent. Ultraviolet spectra were measured in 95% ethanol using a Beckman DK-2 spectrophotometer. Microanalyses were conducted by Micro-Tech Laboratories, Skokie, Ill.

(9) R. Weiss and K. Woidich, *Monatsh.*, 46, 455 (1925).
(10) W. Davies, N. W. Gamble, and W. E. Savage, *J. Chem. Soc.*, 4678 (1952).
(11) R. T. Arnold, C. Collins, and W. Zenk, *J. Am. Chem. Soc.*, 62, 983 (1940).

Aluminum Iodide as a Friedel-Crafts Catalyst[1]

ERNEST R. KLINE, BRUCE N. CAMPBELL, JR.,[2]
AND EARL C. SPAETH[3]

A comparison of aluminum iodide with aluminum chloride and aluminum bromide as catalysts in typical Friedel-Crafts alkylations and acylations seems not to have been reported. The absence of such an investigation may be due, in part, to the well known sensitivity of aluminum iodide to air and moisture.[4]

Aluminum iodide was prepared by two methods which minimize contact with air and moisture. Comparisons have been made with aluminum chloride and aluminum bromide as catalysts in the isopropylation, succinoylation, and benzoylation of benzene. The results of these experiments are summarized in Table I. The reactions using aluminum chloride reported in this table are each the best of several made to determine conditions which give moderately good yields. The alkylations with aluminum bromide and aluminum iodide (Method B) represent the average of two runs. Although aluminum iodide acts as a catalyst in all these reactions,

(1) Based on part of the Ph.D. thesis of B.N.C., University of Connecticut, 1958.
(2) To whom inquiries should be sent. Present address: Department of Chemistry, MacMurray College, Jacksonville, Ill.
(3) Present address: Apt. 203, 1600 N. Quinn St., Arlington, Va.
(4) G. W. Watt and J. L. Hall, *Inorganic Syntheses*, McGraw-Hill Book Company, Inc., New York, N. Y., 1953, Vol. IV, p. 119.

only in the case of isopropylation does it appear to have a possible advantage over the other two catalysts. Since in this case aluminum iodide causes a greater total isopropylation it may well prove to be a useful catalyst for compounds which are diffiult to alkylate. The products obtained with aluminum iodide in the other two reactions were distinctly more difficult to purify than those obtained with the other two catalysts due to difficulties in freeing from iodine.

TABLE I

RESULTS OF COMPARISON REACTIONS WITH BENZENE AS THE SUBSTRATE

Substituting Reagent	Catalyst	Products Yields, %	
		Isopropyl-benzene	Diisopropyl-benzene
Isopropyl chloride	AlCl$_3$	49.0	10.4
Isopropyl chloride	AlBr$_3$	59.0	8.4
Isopropyl chloride	AlI$_3$[a]	48.5	25.7
Isopropyl chloride	AlI$_3$[b]	62.5	13.7
		β-Benzoylpropionic acid	
Succinic anhydride	AlCl$_3$	55.0	
Succinic anhydride	AlBr$_3$	78.5	
Succinic anhydride	AlI$_3$[b]	43.2	
		Benzophenone	
Benzoyl chloride	AlCl$_3$	69.5	
Benzoyl chloride	AlBr$_3$	71.5	
Benzoyl chloride	AlI$_3$[b]	19.5	

[a] Method A. [b] Method B.

EXPERIMENTAL

The two methods used to prepare aluminum iodide are like many previously reported in that they are based on elemental combination. They differ in the apparatus and manipulations needed for the preparation and use of this catalyst.

Method A. Several small, sealed, glass tubes, closed at one end with a fragile glass membrane and containing 5 g. of iodine and 1 g. of aluminum, were heated gradually in a small, improvised, electric furnace to 300°, and this temperature was maintained overnight. Cooling was completed by rolling the tubes just as the product was solidifying. An attempt to prepare larger amounts of aluminum iodide by this method resulted in an explosion. A special reaction flask with a test tube-like appendage was used to allow the catalyst tube to be opened beneath the surface of the reaction solvent.

Method B. This method used a two compartment apparatus for the preparation of aluminum iodide. Compartment A was about 100 mm. long and 40 mm. in diameter and was joined to a standard-taper joint through a thin septum C. Compartment B, initially about 200 mm. long and 25 mm. in diameter, was joined at its midpoint to A by a 7-cm. length of 16-mm. tubing. The middle third of this connecting tube was thickened to facilitate sealing later. The open end D was stoppered and a vacuum applied through E before introducing the reactants. This operation tested the strength of the septum.

The weighed quantity of iodine was introduced into A through D and F. The aluminum was introduced into B through D. It is important that no iodine remain in B when the aluminum is introduced. The open end of B was sealed off below D, and a vacuum was applied at E. During this operation, the mechanical pump should be protected with a NaOH trap. Tube E was sealed off under vacuum. Both chambers were heated gently until some iodine distilled, and a visible amount of aluminum iodide had formed.
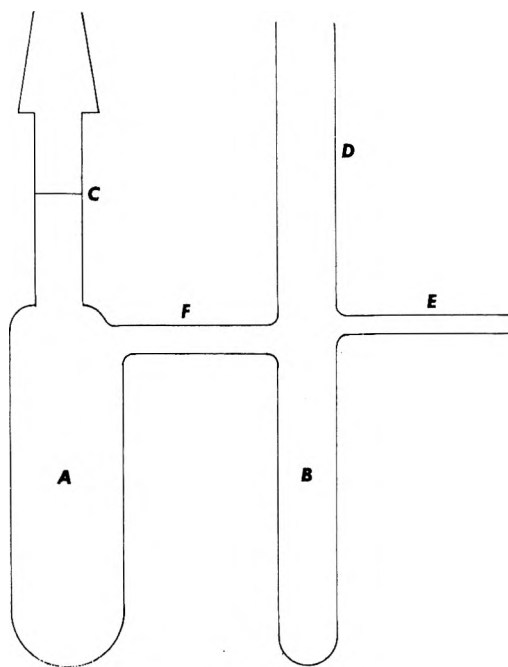

Figure 1

Heating was then continued and intensified until all the iodine had reacted. When the reaction was complete, the aluminum iodide was distilled away from the excess aluminum and sealed in the larger chamber by collapsing the connecting tube at F and removing the smaller chamber. About 0.1 mol. of aluminum iodide was usually made in each apparatus. There would seem to be no limitation on the amount of catalyst which could be made by this method if sufficient care is taken during the initial stages of this preparation. Before the solid aluminum iodide was used it was pulverized by loosening large pieces from the walls with gentle heating and shaking when again cool. This enabled the catalyst to pass more easily and completely through the neck of the large chamber into a reaction flask when the glass septum was opened.

Isopropylation. This method was developed along the lines suggested by Spaeth and Germain.[5] In the present work the benzene (1.6 mol.), which also served as the solvent, and the catalyst (0.01 mol.) were combined, and isopropyl chloride (0.4 mol.) was added at room temperature. Ice and hydrochloric acid were used for hydrolysis. The product layer was extracted once with 10% sodium hydroxide and twice with water before it was dried and an aliquot was fractionally distilled.

Succinoylation. The method used was an adaptation of that described by Sommerville and Allen and modified by Martin and Fieser.[6] In the present investigation the relative amounts of catalyst, succinic anhydride, and benzene were 0.1 mol., 0.05 mol., and 50 ml. (0.565 mol.) respectively, and the reflux time was about 0.5 hr. The solid product was collected in a manner similar to that suggested by these authors.

Benzoylation. These reactions were carried out by a modification of the method of Minnis.[7] The mole ratio of benzoyl chloride to catalyst was 1/1.5. An excess of benzene was used, and carbon disulfide was the solvent. The reaction mixture was stirred at room temperature for about 18 hr. and

(5) E. C. Spaeth and C. B. Germain, *J. Am. Chem. Soc.* **77**, 4066 (1955).

(6) L. F. Sommerville and C. F. H. Allen, *Org. Syntheses,* **Coll. Vol. II**, 81 (1943). E. L. Martin and L. F. Fieser, *Org. Syntheses,* **Coll. Vol. II**, 82 (1943).

(7) W. Minnis, *Org. Syntheses,* **Coll. Vol. II**, 520 (1943).

refluxed for 4 hr. The products were isolated by distillation at reduced pressure and allowed to crystallize.

DEPARTMENT OF CHEMISTRY
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Studies in the Hydroxyanthracene Series, II.[1] Synthesis of Some Heterocyclic Compounds from 2-Anthrol
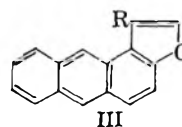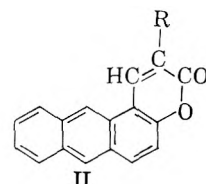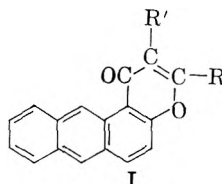
N. H. SHAH AND SURESH SETHNA

The present work deals with the synthesis of pyrone and furan derivatives from 2-anthrol.

In the Pechmann condensation of 2-anthrol with ethyl acetoacetate in presence of either concentrated or 80% sulfuric acid, a pure condensation product could not be obtained. However, in the presence of phosphorus pentoxide (Simonis reaction) 2'-methyl-2,1-anthra-γ-pyrone (Ia) was obtained. This gave a styryl derivative with benzaldehyde and on hydrolysis gave 1-acetyl-2-anthrol. A similar reaction with ethyl benzoylacetate gave 2'-phenyl-2,1-anthra-γ-pyrone(Ib). On condensation with malic acid in presence of concentrated sulfuric acid, 2-anthrol gave an unworkable mass, but the desired 2,1-anthra-α-pyrone(IIa) was synthesised by the Perkin acetylation of 1-formyl-2-anthrol, as well as by the Knoevanagel condensation of malonic ester with 1-formyl-2-anthrol and subsequent hydrolysis and decarboxylation of ethyl-2,1-anthra-α-pyrone-3'-carboxylate (IIb) formed.

1-Acetyl-2-anthrol on Kostanecki-Robinson acetylation gave 2'-methyl-3'-acetyl-2,1-anthra-γ-pyrone (Ic), which on heating with dilute alcoholic sodium carbonate solution gave 2'-methyl-2,1-anthra-γ-pyrone (Ia) described above. The same ketone on Kostanecki-Robinson benzoylation gave 2' - phenyl - 3' - benzoyl - 2, 1 - anthra - γ - pyrone (Id) which on heating with dilute alcoholic sodium hydroxide on a steam bath gave 2'-phenyl-2,1-anthra-γ-pyrone (Ib) described before. 1-Acetyl-2-anthrol required for this work was prepared by the Friedel-Crafts acetylation of 2-anthrol, and also by the Fries rearrangement of 2-anthrolacetate at room temperature in nitrobenzene solution. Its structure was proved by oxidation of its methyl ether with sodium hypochlorite solution to 2-methoxyanthraquinone - 1 - carboxylic acid, pre-

viously prepared by Ch. Marschalk[2] by the nuclear methylation of 2-hydroxyanthraquinone to 1-methyl-2-hydroxyanthraquinone and subsequent oxidation of its methyl ether.

1-Formyl-2-anthrol condensed with ethyl bromoacetate to give ethyl-1-formyl-2-anthroxyacetate which on hydrolysis and ring closure gave anthra [2,1-b] furan (IIIa). Through the same series of reactions, 1-acetyl-2-anthrol furnished 1-methyl anthra [2,1-b] furan (IIIb).

a. R = CH₃, R' = H
b. R = C₆H₅, R' = H
c. R = CH₃, R' = COCH₃
d. R = C₆H₅, R' = COC₆H₅

a. R = H
b. R = COOC₂H₅
c. R = COOH

a. R = H
b. R = CH₃

EXPERIMENTAL

All melting points are uncorrected.

2'-Methyl-2,1-anthra-γ-pyrone (Ia). To a mixture of 2-anthrol (1.94 g.) (prepared according to Perkin and Hall[3]) and ethyl acetoacetate (1.3 g.), phosphorus pentoxide (2.5 g.) was gradually added with stirring. The reaction mixture was heated on a steam bath for 1 hr. Crushed ice was then added and the residue taken up in ether. The ethereal layer was repeatedly washed with alkali (2%, 200 ml. in all) and then with water. The residue obtained on evaporating the ether, crystallized from dilute acetic acid (charcoal) in light brown needles, m.p. 173°. It gave a bluish green fluorescence with concentrated sulfuric acid.

Anal. Calcd. for $C_{18}H_{12}O_2$: C, 83.1; H, 4.6. Found: C, 82.9; H, 4.5.

This compound (0.5 g.) on heating with alcoholic potassium hydroxide (30%, 20 ml.) on a steam bath for 10 hr. gave 1-acetyl-2-anthrol described below.

2'-Styryl-2,1-anthra-γ-pyrone, prepared from the above pyrone, crystallized from absolute alcohol in long yellow needles, m.p. 237–238°.

Anal. Calcd. for $C_{25}H_{16}O_2$: C, 86.2; H, 4.6. Found: C, 86.1; H, 4.6.

2'-Phenyl-2,1-anthra-γ-pyrone (Ib). Obtained from 2-anthrol (1 g.), and ethyl benzoylacetate (0.65 g.) in dry ether (10 ml.) and phosphorus pentoxide (2 g.), crystallized from dilute acetic acid in pale yellow needles, m.p. 219°.

Anal. Calcd. for $C_{23}H_{14}O_2$: C, 85.7; H, 4.3. Found: C, 85.7; H, 4.8.

2,1-Anthra-α-pyrone (IIa). A mixture of 1-formyl-2-anthrol (prepared according to Jain and Seshadri[4]) (2.22 g.), acetic anhydride (2 g.) and fused sodium acetate (0.82 g.) to which a crystal of iodine was added, was refluxed in an

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(1) Part I, S. S. Lele, N. H. Shah, and Suresh Sethna, *J. Org. Chem.*, **21**, 1293 (1956).

(2) Ch. Marschalk, *Bull. soc. chim.*, **6**, 655 (1939); [*Chem. Abstr.*, **33**, 5388 (1939)].

(3) J. Hall and A. G. Perkin, *J. Chem. Soc.*, 2031 (1923).

(4) A. C. Jain and T. R. Seshadri, *J. Sci. Industr. Res.*, **15B**, 61 (1956).

oil bath at 180° for 8 hr. The product obtained crystallized from dilute alcohol (charcoal) in needles, m.p. 192°.

Anal. Calcd. for $C_{17}H_{10}O_2$: C, 82.9; H, 4.1. Found: C, 83.1; H, 4.6.

Ethyl-2,1-anthra-α-pyrone-3'-carboxylate (IIb). A mixture of 1-formyl-2-anthrol (2.22 g.), diethyl malonate (1.92 g.) and a few drops of piperidine was kept at room temperature for 4 days. The product, which separated on treating the reaction mixture with dilute hydrochloric acid, crystallized from alcohol (charcoal) in yellow needles, m.p. 194°.

Anal. Calcd. for $C_{20}H_{14}O_4$: C, 75.5; H, 4.4. Found: C, 75.3; H, 4.6.

2,1-Anthra-α-pyrone-3'-carboxylic acid (IIc). Obtained on alkaline hydrolysis of the above ester was first crystallized from dilute alcohol and then from benzene in fine red needles, m.p. 305–306° (dec.).

Anal. Calcd. for $C_{18}H_{10}O_4$: C, 74.5; H, 3.5. Found: C, 74.7; H, 3.7.

The acid on decarboxylation in quinoline solution with copper powder gave 2,1-anthra-α-pyrone described above.

1-Acetyl-2-anthrol. 2-Anthrol (1.9 g.) and acetic anhydride (1.3 g.) in nitrobenzene (30 ml.) was mixed with a solution of anhydrous aluminium chloride (2.7 g.) in nitrobenzene (20 ml.), and the reaction mixture, protected from moisture, was kept for 72 hr. at room temperature. It was then treated with ice and hydrochloric acid, and the nitrobenzene steam-distilled. The product obtained was extracted with alkali, and the alkaline extract acidified with hydrochloric acid. The precipitated solid crystallized from dilute alcohol (charcoal) in yellow needles, m.p. 112–113°. (Jain and Seshadri[4] who prepared it by the Fries migration of 2-anthrolacetate at higher temperature give m.p. 219°). It gave a bluish coloration with alcoholic ferric chloride, which turned green on keeping.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.4; H, 5.1. Found: C, 81.3; H, 5.2.

The same product was obtained in inferior yield (i) on heating the above reaction mixture on a steam bath for 2 hr. and (ii) in the Fries rearrangement of 2-anthrolacetate in nitrobenzene by keeping for 24 hr. at room temperature.

The *2,4-dinitrophenylhydrazone* prepared as usual crystallized from acetic acid, m.p. 235°.

Anal. Calcd. for $C_{22}H_{16}O_5N_4$: N, 13.5. Found: N, 14.1.

The *methyl ether* crystallized from dilute alcohol in small yellowish plates, m.p. 99°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.6; H, 5.6. Found: C, 82.0; H, 5.7.

On sodium hypochlorite oxidation at 85° it gave a product which crystallized from acetic acid in small yellow needles, m.p. and mixed m.p. with 2-methoxyanthraquinone-1-carboxylic acid, prepared according to Ch. Marschalk[2] was 276–277°.

2'-Methyl-3'-acetyl-2,1-anthra-γ-pyrone (Ic). 1-Acetyl-2-anthrol (1 g.) was heated with freshly fused sodium acetate (3 g.) and acetic anhydride (6 ml.) in an oil bath at 180° for 8 hr. The product obtained on working up the reaction mixture crystallized from acetic acid (charcoal) in yellow needles m.p. 252–253°.

Anal. Calcd. for $C_{20}H_{14}O_3$: C, 79.5; H, 4.6. Found: C, 79.6; H, 4.9.

The above γ-pyrone (0.5 g.) in alcohol (50%, 50 ml.) when refluxed with sodium carbonate (2 g.) for 2 hr. gave the deacetylated product, which crystallized from dilute acetic acid in needles, m.p. and mixed m.p. with 2'-methyl-2,1-anthra-γ-pyrone, described above.

2'-Phenyl-3'-benzoyl-2,1-anthra-γ-pyrone (Id). 1-Acetyl-2-anthrol (1 g.) was heated with freshly fused sodium benzoate (1.5 g.) and benzoic anhydride (5 g.) in an oil bath at 180° for 8 hr. The reaction mixture was then treated repeatedly with hot water and sodium bicarbonate solution. The residue crystallized from acetic acid in small yellow needles, m.p. 270°.

Anal. Calcd. for $C_{30}H_{18}O_3$: C, 84.5; H, 4.2. Found: C, 84.1; H, 4.2.

The above γ-pyrone (0.2 g.) was refluxed with alcoholic sodium hydroxide (5%, 20 ml.) on a steam bath for 1 hr. and the product obtained crystallized from dilute acetic acid in pale yellow needles. M.p. and mixed m.p. with 2'-phenyl-2,1-anthra-γ-pyrone described above was 219°.

Ethyl-1-formyl-2-anthroxyacetate. 1-Formyl-2-anthrol (0.5 g.) was dissolved in dry acetone (50 ml.) and refluxed on a steam bath with ethyl bromoacetate (0.5 ml.) and anhydrous potassium carbonate (3 g.) for 3 hr. The product obtained on working up the reaction mixture crystallized from alcohol (charcoal) in yellow needles, m.p. 140°.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.0; H, 5.2. Found: C, 73.9; H, 5.1.

1-Formyl-2-anthroxyacetic acid obtained on alkaline hydrolysis of the above ester, crystallized from dilute acetone (charcoal) in reddish yellow needles, m.p. 222–223°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.8; H, 4.3. Found: C, 72.4; H, 4.2.

Anthra[2,1-b]furan (IIIa). The above acid (0.1 g.), acetic anhydride (2 ml.) and freshly fused sodium acetate (0.3 g.) was boiled for 30 min. The product, which separated on addition of water, crystallized from dilute acetic acid (charcoal) in greenish yellow plates, m.p. 177–178°.

Anal. Calcd. for $C_{16}H_{10}O$: C, 88.1; H, 4.6. Found: C, 88.1; H, 4.7.

Ethyl-1-acetyl-2-anthroxyacetate was obtained from 1-acetyl-2-anthrol and ethyl bromoacetate. It crystallized from alcohol (charcoal) in greenish yellow needles, m.p. 127–128°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.7; H, 5.7.

1-Acetyl-2-anthroxyacetic acid was obtained on alkaline hydrolysis of the above ester. It crystallized from dilute acetic acid in greenish yellow needles, m.p. 190°.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.5; H, 4.8. Found: C, 73.5; H, 4.4.

1-Methylanthra[2,1-b]furan (IIIb) was obtained on cyclization of the above acid with acetic anhydride and fused sodium acetate. It crystallized first from dilute acetic acid (charcoal) and then from alcohol in needles, m.p. 139–140°.

Anal. Calcd. for $C_{17}H_{12}O$: C, 87.9; H, 5.2. Found: C, 87.5; H, 5.4.

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Alkylidene- and Arylideneaminomorpholines

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A study of the dimethylhydrazones described recently[1] as of interest as isosteres of 3,3-dimethyl-1-phenyltriazene in tumor growth retardation studies disclosed a border line activity in some derivatives and prompted the study of additional related hydrazones. This report describes the preparation, infrared absorption characteristics, and preliminary evaluation of the 4-aminomorpholine derivatives (III) of some of the alkyl and aromatic aldehydes which, as dimethylhydrazones, showed such activity. The only previously known compounds of this

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(1) Richard H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, 204 (1957).

type are the benzaldehyde derivative[2] and the o-, m-, and p-hydroxy-; o- and m-nitro-; 3-methoxy-4-hydroxy-; and 3,4-methylenedioxy-substituted benzaldehyde[3] derivatives.

The 4-aminomorpholine (II) used in our studies was prepared by the chloramine amination of morpholine (I)[4,5,6,7] and used without isolation in the preparation of the derivatives. Our preferred procedure, which is significantly different from the previously defined optimum conditions for chloramine and hydrazine formation, involves the use of a 2:1 mole ratio of ammonia to hypochlorite in the formation of chloramine and reaction of the unisolated chloramine within 5 min. with an equimolar quantity of morpholine. This solution was concentrated to about one half its volume, diluted with methanol to precipitate sodium chloride, and then reacted with .5 mol. of the aldehyde. Yields based on the aldehyde used are given in Table I. The previously defined optimum conditions for hydrazine formation[4,5,6,7] specify a 3:1 mole ratio of ammonia to hypochlorite, a much longer time (1.5 hr.) for completion of the chloramine formation, and a 6:1 mol. ratio of amine to chloramine. We prefer the lower ratio of ammonia to hypochlorite to avoid the presence of increased quantities of ammonia to be neutralized prior to addition of the aliphatic aldehydes. The use of a short (5 min.) hypochlorite ammonia reaction time is based on the observation[7] that for 2:1 ammonia to hypochlorite ratio the slope of the chloramine decomposition curve shows a very high initial decomposition rate and extrapolates to an initial yield of over 90%. We prefer the lower (1:1) ratio of amine to chloramine in the hydrazine formation to avoid the separation problems arising from use of a larger excess of amine. In order to overcome the decrease in yield resulting from use of this lower ratio we have used more concentrated reagents and lengthened the reaction time from 2 to 6 hr. In favorable examples, such as with 2-methoxybenzaldehyde, using a 2:1 mol. ratio of the unisolated hydrazine thus prepared to the aldehyde we have obtained essentially quantitative yields of the aldehyde hydrazone. This establishes that in these favorable examples, at least, a minimum yield of 50% of the hydrazine was obtained from the chloramine. It is to be noted that these conditions have been defined in terms of a convenient method for preparing carbonyl derivatives and not in terms of absolute maximum yields of hydrazine in the chloramine reaction.

(2) L. Knorr and H. W. Brownsdon, Ber., **35**, 4474 (1902).

(3) L. Dugan and H. M. Haendler, J. Am. Chem. Soc., **64**, 2502 (1942).

(4) L. F. Audrieth and L. H. Diamond, J. Am. Chem. Soc., **76**, 4869 (1954).

(5) L. H. Diamond and L. F. Audrieth, J. Am. Chem. Soc., **77**, 3131 (1955).

(6) R. A. Rowe and L. F. Audrieth, J. Am. Chem. Soc., **78**, 563 (1956).

(7) L. F. Audrieth and R. A. Rowe, J. Am. Chem. Soc., **77**, 4726 (1955).

TABLE I
ALKYLIDENE- AND ARYLIDENEAMINOMORPHOLINES

Carbonyl Compound	Yield (%)	b.p. or m.p.[a]	Nitrogen Analysis	
			Calcd.	Found
3-Methylbutanal	37	b100/9[b]	16.46	16.39
2-Ethylbutanal	42	b69/1[c]	15.20	15.33
1-Heptanal	24	b126/6[d]	14.13	14.31
Benzaldehyde	..	m89EW	14.73	14.69
4-acetamido	77	m206MW	16.99	16.79
4-chloro-	..	m99E	12.47	12.62
3,4-diethoxy-	90	m99MW	10.07	9.80
2-methoxy-	96	m76EW	12.72	12.56
4-dimethylamino-	58	m166EW	18.01	17.82
3-nitro-	90	m153EW	...	...
Naphthaldehyde	67	m63EW	11.66	11.24
2-hydroxy-	73	m121MW	10.93	10.72
9-Anthraldehyde	58	m193EW	9.65	9.50
Pyridine:				
2-carboxaldehyde-	44	m47-56[e]	19.41	19.46[g]
6-methyl-2-carbox-				
aldehyde	35	m53-7[f]	19.00	18.83[g]
2,6-dicarboxaldehyde	32	m136MW	23.09	23.03

[a] b, boiling point in °C./mm; m, melting point. Solids recrystallized from M, methanol; E, ethanol; W, water. [b] n_D^{25} 1.4739. [c] n_D^{25} 1.4746. [d] n_D^{26} 1.4746. [e] b 118/0.15. [f] b 168/1. [g] analysis on dipicrate.
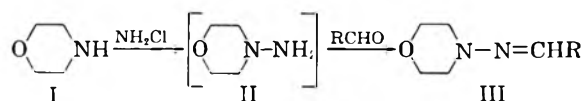
The infrared absorption data provide additional confirmation for the assignments previously reported for the dimethylhydrazones.[1] The absorption in the 1610 cm.$^{-1}$ region attributable to the C=N stretching vibration is identifiable in the aliphatic types but obscured in the aromatic types. For the three aliphatic aldehyde derivatives where the absorption is clearly attributable to the stretching vibration of the carbon-nitrogen double bond the absorption is at 1614 cm.$^{-1}$ and is relatively weak (in chloroform). For the aromatic aldehydes, in which both carbon-carbon and carbon-nitrogen double bond vibrations occur, there are usually two or three well-defined strong bands in this region. Often the absorption band at 1615 cm.$^{-1}$ is the weaker or weakest and because it is nearly always present and the others, although also usually present, occur at variable positions in differently substituted types, it is probable that this band can be attributed with some confidence to the carbon nitrogen double bond or a contribution therefrom. The pyridine aldehyde derivatives show, as the most intense band in this region, a broad absorption at 1570-1582 cm.$^{-1}$ accompanied by a shoulder or weak band at 1600 cm.$^{-1}$ This probably represents overlap of the ring and side chain carbon-nitrogen double bond vibrations.

The stretching vibrations attributable to the methylene groups appear clearly defined at 2950, 2850, and 1450 cm.$^{-1}$ in spectra determined in chloroform and carbon tetrachloride solutions. The last

appear as medium or strong bands within the 1445–1460 cm.[-1] range. In the aliphatic types this is the sole band in this region. Also the benzaldehyde and naphthaldehyde derivatives show but one band (at 1458 cm.[-1]) in this region. The pyridine derivative shows three clearly resolved bands at 1471, 1452, 2435 cm.[-1] in carbon tetrachloride. The carbon-oxygen stretching vibration associated with the morpholine ring occurs at 1120 ± 10 cm.[-1].

The absorption band in the 865 cm.[-1] region previously[1] correlated with the carbon-hydrogen out of plane deformation of the H—C=N grouping is also regularly present in this series of compounds. It appears in all of the morpholine derivatives within a narrow (± 2 cm.[-1]) range regardless of solvent or medium used. The previously noted and unassigned strong band in the 990–1010 cm.[-1] region is also present in the morpholine derivatives. This is one of the strongest bands in the entire spectrum and only the carbon-nitrogen (1610 cm.[-1]) and the carbon-oxygen (1120 cm.[-1]) stretching vibration are of comparable or greater intensity. Only in the heptylidene derivative is this band of decreased intensity.

Initial data[8] on the evaluation of these materials in tumor growth retardation studies have shown that 4-(2'-methoxybenzylideneamino)-morpholine has a ±, − rating at a dose level of 500 mg./kg. and a − rating at a dose level of 125 mg./kg. in tests on experimental mouse sarcoma 180. These results do not establish either a strong or consistent activity. Other compounds in the series, including the pyridinecarboxaldehyde derivatives, which gave dimethylhydrazones of some interest, showed no evidence of tumor growth retardation. Further testing and study of related structures is in progress.

EXPERIMENTAL[9]

Details of typical preparations are given. Data for other compounds are given in the Table. The aldehydes and morpholine were obtained from commercial sources. Products from 2,4-dimethoxybenzaldehyde (m.p. 105°) and from thiophene-2-carboxaldehyde (m.p. 93°) were unstable solids which analyzed low for nitrogen as did also the p-nitrobenzaldehyde derivative (m.p. 153°).

4-Aminomorpholine. One hundred and sixty one grams (0.113 mole) of a 5.25% commercial solution of sodium hypochlorite was cooled to 0–2° and this temperature maintained as 13.4 ml. (0.226 mole) of concentrated ammonium hydroxide was poured in slowly with gentle swirling. After standing in an ice bath for 5 min., 11.5 grams, (0.113 mole) of morpholine was added at once. This solution was then allowed to warm slowly to room temperature over a period of 6 hr. with occasional swirling. The solution was filtered to separate a small amount (ca. 0.25 g.) of 4,4'-azomorpholine, m.p. 151°.

4-(2'-Methoxybenzylideneamino)morpholine. The aqueous solution of 4-aminomorpholine, prepared as described in the preceding paragraph, was concentrated to 100 ml. on a steam

bath under reduced pressure. One hundred ml. of methanol were then added and after standing 15 min. the solution was filtered to remove precipitated sodium chloride. To this filtrate was then added 7.68 g. (0.0565 mole) of o-methoxybenzaldehyde and the mixture was refluxed for 2 hr. After standing overnight, the white, crystalline product was collected. Recrystallization from ethanol gave 11.9 g., 95.7% of the theoretical yield, of the product as colorless plates, m.p. 76–77°.

4-(2'-Ethylbutylideneamino)morpholine. Twice the quantity (0.226 mol.) of a solution of 4-aminomorpholine prepared as described above was acidified with concentrated hydrochloric acid to the point at which the solution turns from colorless to bright yellow. Ten grams (0.1 mol.) of the 2-ethylbutanal was then added and the mixture refluxed vigorously for 2 hr. After standing overnight and extraction with 100 ml. of ether, the solution was made strongly basic with concentrated ammonium hydroxide and extracted twice again with 100 ml. of ether. The ether extracts of the alkaline solution were combined, dried over anhydrous magnesium sulfate, and evaporated to remove the ether. The residue was distilled to give 7.65 g., 41.6% of the theoretical amount, of product b.p. 69°/1 mm. $n_D = 1.4746/25°$.

Infrared spectra were determined using a Baird double beam recording spectrophotometer with sodium chloride optics. All measurements were calibrated against the 3.419 μ band for polystyrene and were run at approximately 5% concentrations in spectral grade chloroform.

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Plant Polyphenols. X. 7- and 4'-O-Methylcoumestrol

LEONARD JURD[1]

Coumestrol (I R − R$_1$ = H), recently isolated from a large number of legume forages by Bickoff, Booth, and their associates, has been shown to be a potent and potentially valuable estrogen.[2-5] Since 4',7-di-O-methylcoumestrol possesses only about $\frac{1}{4}$ the estrogenic activity of coumestrol[6] it was of some importance to prepare and quantitatively bio-assay the 7- (I R = Me; R$_1$ = H) and 4'- (I R = H; R$_1$ = Me) mono-O-methyl derivatives in order to determine the contribution of each of the hydroxyl

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(8) The authors are indebted to Drs. C. C. Stock, D. A. Clarke, and R. K. Barclay, Sloan-Kettering Institute, for conducting these tests. The procedure and rating scales are given in Cancer Research, Suppl. No. 1, p. 91 (1953) and Suppl. No. 2, p. 179 (1955).

(9) Analyses by Micro-Tech Laboratories, Skokie, Illinois.

(1) Financial support for this work was provided by the Diamond Walnut Growers, Inc., Stockton, Calif.

(2) E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson, and G. O. Kohler, *J. Agr. Food Chem.*, 6 (7), 536 (1958).

(3) E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson, and F. DeEds, *Science*, 126, 969 (1957).

(4) E. M. Bickoff, R. L. Lyman, A. L. Livington, and A. N. Booth, *J. Am. Chem. Soc.*, 80, 3969 (1958).

(5) O. H. Emerson and E. M. Bickoff, *J. Am. Chem. Soc.*, 80, 4381 (1958).

(6) E. M. Bickoff, private communication.

groups to the estrogenic activity of the 3-phenyl-4-hydroxycoumarin nucleus. Attempts to prepare these monomethyl compounds by the direct methylation of coumestrol, however, were not satisfactory.[6] At the kind invitation of E. M. Bickoff, therefore, these new monomethyl derivatives have now been prepared by the selective alkylation of coumestrol diacetate, a technique which was recently employed in the preparation of partial ethers of polyhydroxyflavones.[7,8]

I
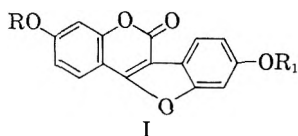
In coumestrol the 7-hydroxyl, being conjugated with the lactone carbonyl group, is strongly acidic. In confirmation of this the long wave length band of coumestrol (λmax 343 mμ) is shifted to 387 mμ in sodium ethylate but only to 362 mμ in sodium acetate (Table I), indicating that of the two hydroxyl groups of coumestrol only one is sufficiently acidic to be ionized by the weakly basic sodium acetate and this is probably the 7-hydroxyl. On this basis it would be anticipated that alkylation of coumestrol diacetate would result in the selective replacement of the 7-acetoxyl group only. In agreement with this it has been found that coumestrol diacetate reacts with excess of methyl iodide, potassium carbonate in acetone to give 7-O-methylcoumestrol monoacetate. On acid hydrolysis this gives 7-O-methylcoumestrol, m.p. 274°, the ultraviolet spectrum of which is unaffected on the addition of sodium acetate (Table I). Benzylation of coumestrol diacetate under similar conditions gives 7-O-benzylcoumestrol monoacetate. Hydrolysis of this gives 7-O-benzylcoumestrol, m.p. 211°, which is methylated to form (I R = C$_6$H$_5$CH$_2$—; R$_1$ = Me). Debenzylation of the latter compound then gives 4'-O-methylcoumestrol, m.p. 337°. The ultraviolet spectrum of this ether in sodium acetate has a peak at 362 mμ due to ionization of the 7-hydroxyl and a peak at 377 mμ indicating partial opening of the lactone ring.

Preliminary data on the bio-assay of these monoalkyl ethers has indicated that they are estrogenic although less than $^{1}/_{3}$ as active as the parent compound. The 4'-O-methyl derivative is more active than either the 7-O-methyl- or 7-O-benzyl compounds.[6]

EXPERIMENTAL

7-O-Methylcoumestrol. A mixture of coumestrol diacetate (2.0 g.), methyl iodide (30.0 ml.), anhydrous potassium carbonate (12.0 g.) and acetone (140 ml.) was heated under reflux for 32 hr. The filtered acetone solution was concentrated to small volume and diluted with ethanol. A colorless crystalline solid (1.75 g.) separated. It was collected and recrystallized from acetone-methanol. The 7-O-methylcoumestrol acetate thus obtained separated in colorless needles, m.p. 204-206°.

Anal. Calcd. for C$_{18}$H$_{12}$O$_6$: C, 66.7; H, 3.73; 1 MeO—, 9.63. Found: C, 66.5; H, 3.87; MeO—, 9.26.

15% Aqueous hydrochloric acid (30 ml.) was added to a solution of the above product (1.7 g.) in acetone (100 ml.) and ethanol (80 ml.). The volume of the solution was reduced to about 50 ml. by heating on a steam bath during 1.5 hr. Water (50 ml.) was added and the solid was collected and recrystallized from acetone-methanol. Chromatography of this product on a silicic acid chromatostrip showed the presence of a small quantity of coumestrol. The crystalline product was, therefore, suspended in dilute aqueous potassium carbonate. The undissolved 7-O-methyl compound was collected and recrystallized from acetone-methanol. 7-O-Methylcoumestrol was thereby obtained in slightly yellow needles, m.p. 274° (0.8 g.).

Anal. Calcd. for C$_{16}$H$_{10}$O$_5$: C, 68.1; H, 3.83; 1 MeO—, 11.0. Found: C, 68.2; H, 3.63; MeO—, 11.0.

The pure 7-O-methylcoumestrol (0.1 g.) was reacetylated by heating it with acetic anhydride and fused sodium acetate for 1 min. Water was added, the solid was collected and crystallized from acetone-ethanol. The pure 7-O-methylcoumestrol acetate separated in colorless glistening needles, m.p. 208°.

TABLE I
ULTRAVIOLET SPECTRA OF COUMESTROL DERIVATIVES

Compound	EtOH	λ max, mμ EtOH–NaOAc	0.002M NaOEt
Coumestrol	343	362	387
	304	312	321
	244	264[a]	281
		243	260[a]
7-O-methylcoumestrol	342	342	380
	303	303	318
	243	243	270
7-O-benzylcoumestrol	343	343	380
	303	304	318
	244	244	271
4'-O-methylcoumestrol	341	377	377
	303	362	
	243	311	311
		303	
		265	266
		243	243
4'-O-methyl-7-O-benzylcoumestrol	341		
	303		
	243		
Coumestrol diacetate	342		
	327		
	297		
	236		
7-O-methylcoumestrol acetate	348		
	333		
	299		
	240		
7-O-benzylcoumestrol acetate	348		
	333		
	298		
	240		
4'-O-methylcoumestrol acetate	337		
	302		
	243		

[a] Inflection.

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.7; H, 3.73; 1 MeO—, 9.63; 1 CH_3CO—, 13.3. Found: C, 66.8; H, 3.82; MeO—, 9.59; CH_3CO—, 13.5.

7-O-Benzylcoumestrol. Coumestrol diacetate (3.0 g.) was refluxed with a mixture of benzyl chloride (30.0 ml.), potassium iodide (4.0 g.), anhydrous potassium carbonate (10.0 g.), and dry acetone (160 ml.) for 20 hr. The filtered acetone solution was evaporated to an oil. Warm hexane (100 ml.) was added, the mixture was cooled, and the crystalline precipitate was collected. It was purified by dissolving it in acetone (500 ml.). The filtered solution was concentrated to about 50 ml. and diluted with methanol (50 ml.). The colorless product (2.8 g.; m.p. 203°) was collected and recrystallized twice more from acetone-methanol. 7-O-Benzylcoumestrol acetate separated in colorless fluffy needles, m.p. 205°.

Anal. Calcd. for $C_{24}H_{16}O_6$: C, 72.0; H, 4.03; 1 CH_3CO—, 10.8. Found: C, 72.0; H, 4.09; CH_3CO—, 11.1.

A solution of the above acetate (2.6 g.) in acetone (400 ml.) was treated with ethanol (100 ml.), water (20 ml.), and concentrated hydrochloric acid (20 ml.). The mixture was heated on a steam bath for 1 hr., most of the acetone being allowed to evaporate during this period. Crystallization of the product then began. Water (80 ml.) was slowly added and the solid was collected. Recrystallized from acetone-methanol (charcoal), 7-O-benzylcoumestrol separated in colorless needles, m.p. 211° (1.8 g.). It dissolved instantly in cold aqueous sodium hydroxide to give a yellow solution.

Anal. Calcd. for $C_{22}H_{14}O_5$: C, 73.7: H, 3.94. Found: C, 73.7; H, 4.02.

Reacetylation of the 7-O-benzylcoumestrol gave 7-O-benzylcoumestrol acetate, m.p. 205°.

4'-O-Methyl-7-O-benzylcoumestrol. A mixture of the 7-O-benzylcoumestrol (1.4 g.), methyl iodide (15.0 ml.), anhydrous potassium carbonate (6.0 g.) and dry acetone (50 ml.) was refluxed for 2.5 hr. The filtered acetone solution was evaporated. The crystalline residue was washed with cold dilute aqueous sodium hydroxide and then recrystallized from acetone-methanol. 4'-O-Methyl-7-O-benzylcoumestrol was obtained in colorless felted needles, m.p. 187° (1.1 g.).

Anal. Calcd. for $C_{23}H_{16}O_5$: C, 74.2; H, 4.33; 1 MeO—, 8.39. Found: C, 74.2; H, 4.39; MeO—, 8.23.

4'-O-Methylcoumestrol. A solution of the 4'-O-methyl-7-O-benzylcoumestrol (1.0 g.) in glacial acetic acid (200 ml.) and concentrated hydrochloric acid (100 ml.) was heated on a steam bath for 15 min. Water (500 ml.) was added and the precipitated ether was collected. Recrystallized from acetone, 4'-O-methylcoumestrol separated in colorless needles, m.p. 337° (0.55 g.).

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.1; H, 3.83; MeO—, 11.0. Found: C, 68.3; H, 3.77; MeO—, 10.7.

The 4'-O-methylcoumestrol was acetylated by boiling it with acetic anhydride and sodium acetate for 1 min. 4'-O-methylcoumestrol acetate crystallized from acetone-methanol in colorless needles, m.p. 240° (with sintering at 234°).

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.7; H, 3.73; 1 MeO—, 9.63; 1 CH_3CO—, 13.3. Found: C, 66.9; H, 3.89; MeO—, 9.58; CH_3CO—, 13.3.

Some Urethans Derived from 3-Amino-1-propanol[1]

ELIZABETH DYER AND ROBERT E. READ

Previous publications[2,3] have shown that 3-amino-1-propanol and ethylene carbonate are convenient starting materials for preparing the cyclic urethan tetrahydro-2H-1,3-oxazin-2-one, now known[4,5] to be convertible to a polyurethan. In the course of a restudy[6] of the preparation and polymerization of this cyclic urethan, several hitherto unreported derivatives of 3-amino-1-propanol were prepared.

The immediate product from the reaction of 3-amino-1-propanol with ethylene carbonate at a temperature below 50° is a viscous liquid, identified by Delaby and coworkers[3] as 2-(hydroxyethyl)-N-3'-(hydroxypropyl)-urethan (I). The yield of this product, not given by previous workers,[2,3] was shown to be practically quantitative by conversion to the dicarbanilate (VI). Heating the viscous liquid gives the cyclic urethan (II).

Another route to the cyclic urethan involved N-3-hydroxypropyl-N'-phenylurea (III), which was obtained by the reaction of 3-amino-1-propanol with phenyl isocyanate under mild conditions. The urea (III) was converted to the urethan (II) by applying Weickmann's method of ring closure.[7] The structure of the urea (III) was indicated by its amide carbonyl absorption at 1625 cm.$^{-1}$ and at 1541–1600 cm.$^{-1}$ with the absence of absorption characteristic of the urethan carbonyl. By treatment of the urea (III) with phenyl isocyanate in the presence of triethylamine, a quantitative yield of the 3-phenylurethan (VII) was obtained. This compound showed urethan carbonyl absorption at 1653 cm.$^{-1}$ in addition to the amide absorption bands of compound (III).

The cyclic urethan (II) gave a γ-phenylallophanate, (V), when treated with phenyl isocyanate during heating.

In agreement with recent work[4,5] and contrary to our previous statement,[2] the cyclic urethan (II) polymerized on heating, to give the polyurethan

(1) From the M.S. thesis of R. E. Read, University of Delaware, 1957.

(2) E. Dyer and H. Scott, *J. Am. Chem. Soc.*, **79**, 672 (1957).

(3) R. Delaby, R. Damiens, and G. d'Huyteza, *Compt. rend.*, **239**, 674 (1954).

(4) E. K. Drechsel, U. S. Patent **2,701,246**, Feb. 1, 1955; *Chem. Abstr.*, **50**, 2686 (1956); and U. S. Patent **2,744,897**, May 8, 1956; *Chem. Abstr.*, **51**, 498 (1957).

(5) H. K. Hall, Jr., and A. K. Schneider, *J. Am. Chem. Soc.*, **80**, 6409 (1958).

(6) The authors were then unaware of the work in ref. (4) and (5).

(7) A. Weickmann, Ger. Patent **858,402**, Dec. 8, 1952; *Chem. Abstr.*, **47**, 11255 (1953).

(IV). Barium oxide speeded the reaction. By heating I in such a way as to cause elimination of ethylene glycol, II or IV or mixtures of II and IV could be obtained, depending on the conditions. Pyrolysis of the polyurethan gave the cyclic urethan (in 9% yield), carbon dioxide, and water-soluble degradation products.

EXPERIMENTAL

2-Hydroxyethyl-N-3'-hydroxypropylurethan (I) *and its dicarbanilate* (VI). To 3.52 g. (0.040 mol.) of ethylene carbonate[8] (b.p. 79° at 0.2 mm.) was added 3.00 g. (0.040 mol.) of 3-amino-1-propanol[9] (b.p. 54–56° at 1 mm.) with cooling to keep the temperature below 50°. To 6.21 g. (0.040 mol.) of the presumed 2-hydroxyethyl-N-3'-hydroxypropylurethan (I) was added 9.00 g. (0.065 mol.) of distilled phenyl isocyanate and the mixture warmed gently. The product, isolated by solution in boiling methanol and precipitation with water, consisted of 15.0 g. (a 98.6% yield) of solid, m.p. 116–118°. The infrared spectrum of the compound in KBr showed strong infrared absorption bands at 1700 cm.$^{-1}$ (C=O) and at 3333 cm.$^{-1}$ (N—H) characteristic of linear urethans.[10]

Anal. Calcd. for $C_{20}H_{23}N_3O_6$: C, 59.83; H, 5.73; N, 10.52. Found: C, 60.50; H, 5.78; N, 10.32.

N-3-Hydroxypropyl-N'-phenylurea (III). Treatment of 5.00 g. (0.067 mol.) of 3-amino-1-propanol with 14.40 g. (0.121 mol.) of phenyl isocyanate in 40 ml. of dry xylene at room temperature gave a 98% yield of III, m.p. 108–110°. After recrystallization from chloroform–petroleum ether, the compound melted at 110–111°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.89; H, 7.20; N, 14.43. Found: C, 62.00; H, 7.30; N, 14.32.

3-Phenylurethan of N-3-hydroxypropyl-N'-phenylurea (VII). By refluxing an ether solution of 0.400 g. (0.002 mol.) of III, 7.50 g. (0.063 mol.) of phenyl isocyanate, and three drops of triethylamine, a 99% yield of VII was obtained, m.p. 148–150°. After recrystallization from chloroform the substance melted at 149–150°.

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.18; H, 6.07; N, 13.47. Found: C, 64.90; H, 5.97; N, 13.16.

Tetrahydro-2H-1,3-oxazin-2-one (II).[2–5] Heating for 3 hr. under nitrogen at 0.5–1.0 mm. the viscous I from 0.298 mol. of 3-amino-1-propanol and 0.299 mol. of ethylene carbonate, and then distilling, gave ethylene glycol and a 74% yield of II.

Compound II was also obtained in 76% yield by treating 20.0 g. (0.268 mol.) of 3-amino-1-propanol with 12.0 g. (0.103 mol.) of phenyl isocyanate during cooling, heating the mixture in the presence of 0.5 g. of potassium carbonate at 160° for 3 hr., and distilling at 0.4 mm. under nitrogen. Fractions contained aniline (0.077 mol.) identified through the phenyl thiourea,[11] and II (0.077 mol.).

γ-Phenylallophanate of tetrahydro-2H-1,3-oxazin-2-one (V). A mixture of 1.26 g. (0.012 mol.) of II and 11.9 g. (0.100 mol.) of phenyl isocyanate was heated at 125° for 15 hr. After removal of excess isocyanate by distillation under reduced pressure, the resulting solid weighed 1 g., m.p. 118–120° (38% yield). After washing with ether and recrystallizing from chloroform-ligroin, the compound melted at 120–122° and depressed the melting point of VI; λ_{max}^{KBr} 1695, 1640, 1594, 1550–1525 cm.$^{-1}$

(8) Kindly supplied by Jefferson Chemical Company.

(9) Kindly supplied by American Cyanamid Company.

(10) H. K. Hall, Jr., and R. Zbinden, *J. Am. Chem. Soc.*, **80**, 6428 (1958).

(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, Fourth Ed., J. Wiley and Sons, Inc., New York, 1956, p. 288.

Anal. Calcd. for $C_{11}H_{13}N_2O_3$: C, 59.71; H, 5.88; N, 12.73. Found: C, 60.15; H, 5.53; N, 12.71.

Polyurethan (IV). Extended heating of II, especially in the presence of barium oxide, caused partial conversion to a low polymer. Unchanged monomer was removed by its solubility in acetone. The polymer melted at 125–131° and showed typical absorption[2] for a polyurethan.

Anal. Calcd. for $(C_4H_7NO)_n$: N, 13.87. Found: N, 13.87; mol. wt. (ebullioscopic), 1500; [η], 0.0659 (in dimethyl formamide at 25°).

The polyurethan was also prepared directly from I. When I was heated under nitrogen at 145° for 14 hr. at about 1 mm., ethylene glycol was distilled and the pot residue contained a 23% yield of polyurethan. Extending the initial heating to 29 hr. gave 30% of the cyclic urethan and 31% of the polyurethan. But advancing the heating to 107 hr. at 140–170° gave only degradation products.

When a sample of the polyurethan was heated for 14 hr. at 160–180° at 1 mm., a 9.3% yield of II and an equivalent amount of carbon dioxide were formed, together with unidentified, water-soluble substances.

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Preparation of Anhydrous Sodium Peracetate and Sodium Perbutyrate

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Kolesnikov[2] has described the isolation of anhydrous sodium performate by trituration of green barley leaves with sodium phosphate.

In the present investigation, it has been our purpose to develop a more general method for the preparation of anhydrous metal salts of aliphatic percarboxylic acids. Thus, the two salts, sodium peracetate and sodium perbutyrate, have been prepared.

For this purpose, we first required a solution of peracetic acid in an inert solvent as free as possible from acetic acid, as even small amounts of acetic acid will contaminate the final product with sodium acetate.

A convenient method for obtaining such a solution was found using commercially available peracetic acid[3] which contains 39% of acetic acid and 1% of sulphuric acid as impurities.

As peracetic acid is very weakly acidic, having a pK of 8.2,[4] it was possible by neutralization to a pH of 8.0 followed by extraction to obtain almost pure peracetic acid in an inert solvent.[5] The

(1) Present address: Ayerst, McKenna & Harrison, Ltd. Montreal, Canada.

(2) P. A. Kolesnikov, *Chem. Abstr.*, 4730 (1949); *Doklady. Akad. Nauk. S.S.S.R.*, **64**, 99 (1949).

(3) Becco Chemical Division of FMC, Buffalo, New York.

(4) A. J. Everett and G. J. Minkoff, *Trans. Farad. Soc.*, **49**, 410 (1953).

(5) Subsequent to the completion of this work, another method has been described for obtaining solutions of peracetic acid in inert solvents. B. Phillips, F. C. Frostick, and P. S. Starcher; *J. Am. Chem. Soc.*, **79**, 5982 (1957).

sodium salt was then obtained by precipitation with alkali.

For the preparation of sodium perbutyrate, perbutyric acid was prepared from butyric acid and 90% hydrogen peroxide[6] and the salt was prepared as in the case of sodium peracetate.

The salts so obtained were found to contain one atom of active oxygen which could be analyzed iodometrically.

In the analysis of the active oxygen content, it was found that on treating with acidified potassium iodide solution, in neither case was liberation of iodine instantaneous; thus in the case of sodium peracetate, iodine liberation was complete only after 30 min. at room temperature and in the absence of light while sodium perbutyrate required 75 min. under the same conditions.

Sodium peracetate decomposes at 55° leaving a residue which contains no active oxygen. On standing at room temperature for 3 days in a moist atmosphere, a sample of sodium peracetate lost all of its active oxygen content and when a sample was stored *in vacuo* at room temperature, the active oxygen content had decreased by 66% after 24 hr. and by 93% after 7 days.

EXPERIMENTAL

Note: The use of a safety shield is recommended in carrying out the following reactions.

Sodium Peracetate. A saturated solution of sodium carbonate was added with constant stirring to "Becco" peracetic acid[3] (50 ml.) at 8–10° until a pH of 8.0 was obtained as indicated by a pH meter. The resulting mixture was extracted with ether (5 × 50 ml.) and the extracts dried over magnesium sulfate. Analysis of an aliquot showed that the combined extracts contained 5.94 g., of peracetic acid. To the ethereal solution was added at 0°, sodium hydroxide (3.13 g.) dissolved in water (5 ml.) and 95% ethanol (70 ml.), causing an immediate precipitate. It was allowed to stand for 15 min. The salt was separated by filtration, washed with ethanol, then with ether and dried *in vacuo* at room temperature.

The sodium peracetate was analyzed for active oxygen iodometrically and for sodium gravimetrically as the sulfate.[7] Found: active O, 16.42; Na, 24.31% CH_3CO_3Na requires: active O, 16.32; Na, 23.46%.

Sodium perbutyrate. To an aqueous solution of perbutyric acid at 0° was added a saturated solution of sodium carbonate until a pH of 8.0 was obtained as indicated by a pH meter. To the pure peracid (2.7 gm.) in ethyl acetate was added at 0°, sodium hydroxide (1.05 gm.) dissolved in 95% alcohol. On standing at 0° for 2 hr., sodium perbutyrate precipitated. It was filtered off, washed and dried *in vacuo* at room temperature and analyzed for active oxygen iodometrically. Found: active O, 12.80% $C_4H_7O_3Na$ requires: active O, 12.68%.

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(6) J. D'Ans and W. Frey, *Ber.*, **45**, 1845 (1912).

(7) A similar preparation of several grams of dry sodium peracetate exploded violently, while sitting in a flask at room temperature. Caution is recommended in handling this compound.

A New Technique in Preparing 2,4-Dinitrophenylhydrazones. III. Two Examples of Hitherto Unobtainable Simple Derivatives: Diacetone Alcohol and Methyl Vinyl Ketone

HENRY J. SHINE

Recently[1] the convenient use of diglyme (dimethylether of diethylene glycol) solutions of 2,4-dinitrophenylhydrazine for preparing 2,4-dinitrophenylhydrazones was described. It was suggested at that time that the new technique might be usable for preparing 2,4-dinitrophenylhydrazones of sensitive compounds. This suggestion has now been found to be valid, and in view of the interest that has been shown in the earlier publication[1a] we are prompted to illustrate the further usefulness of the new technique with two examples. We have been able to prepare for the first time the true derivative of diacetone alcohol and the derivative of methyl vinyl ketone.

Diacetone alcohol. The 2,4-dinitrophenylhydrazone, melting point 203°, that is everywhere listed as the derivative of diacetone alcohol, is really the derivative of mesityl oxide. The conventional methods of preparation[1a] of the 2,4-dinitrophenylhydrazone cause the acid-catalyzed dehydration of the ketol to mesityl oxide.

If a solution of diacetone alcohol in a diglyme solution of 2,4-dinitrophenylhydrazine is acidified with acetic acid, however, the orange derivative, I, formed is that of diacetone alcohol and has a melting point of 157–159°. If, instead of acetic acid, hydrochloric acid is used, or if I is dissolved in ethanol and acidified with hydrochloric acid, the dark red derivative of mesityl oxide is obtained.

Methyl Vinyl Ketone. The only report of the reaction of 2,4-dinitrophenylhydrazine with this simple ketone is that of I. N. Nazarov and co-workers.[2] These authors report a compound with a melting point of 217°, the carbon analysis of which was 2.3% low for the expected derivative. They do not appear to have accepted their derivative as authentic. We have prepared the authentic derivative of this ketone; it has a melting point of 139.5–140.5°. It was prepared first in these laboratories by the diglyme technique using hydrochloric acid for catalysis. If attempts were made to prepare this derivative by conventional methods, using ethanol as solvent, the derivative was not obtained, but one of the products obtained was the derivative of 4-ethoxybutanone-2, melting point 92–93°. If methanol were used as a solvent, the derivative of 4-methoxybutanone-2 was obtained,

(1) (a) H. J. Shine, *J. Org. Chem.*, **24**, 252 (1959); (b) H. J. Shine, *J. Chem. Ed.*, **36**, 575 (1959).

(2) I. N. Nazarov, L. A. Kazitsyna and I. I. Zaretskaya, *Zhur. Obshchei Khim.*, **27**, 606 (1957).

melting point 88–90°. Thus, it is apparent that the solvent used is important in determining the final products of reaction. We found, indeed, that the derivative of methyl vinyl ketone can also be obtained if tetrahydrofuran and *tert*-butyl alcohol are used as solvents. In the latter case the derivative precipitates quickly and addition of the alcohol to the double bond does not take place. In the former case, as in the diglyme solutions, the solvent cannot react with the ketone or its derivative. Our work with methyl vinyl ketone has led us to begin investigating in some detail the products that are formed from the derivative of methyl vinyl ketone and of the alkoxybutanones in acidic solutions. We shall report on this investigation at a later date. It is quite apparent to us at this stage that attempts to make the derivatives of these ketones by conventional methods very often lead to products that are not the expected derivatives.

EXPERIMENTAL

Diacetone alcohol 2,4-dinitrophenylhydrazone. One milliliter of vacuum distilled diacetone alcohol was added to 20 ml. of a diglyme solution containing 0.8 g. of 2,4-dinitrophenylhydrazine. To this was added 3 ml. of acetic acid. The solution was allowed to stand at room temperature for 2 hr. and was then placed in the refrigerator for 24 hr. Water was added to the cold solution until it became turbid and the solution was again refrigerated until crystallization occurred. The orange product, m.p. 137–147°, was recrystallized twice from ethanol and then twice from benzene, giving glistening orange plates, m.p. 157–9°; λ_{max} (CHCl₃): 370 mmμ; λ_{max} (ligroin): 351 mmμ; ϵ_{max} (CHCl₃): 23,250.

Anal. Calcd. for $C_{12}H_{16}N_4O_5$: C, 48.65; H, 5.44; N, 18.9. Found[3]: C, 48.59; H, 5.36; N, 18.69.

A small amount of the derivative was dissolved in ethanol and acidified with concentrated hydrochloric acid. A red precipitate formed overnight. Crystallization from diglyme gave m.p. 203°. The melting point of the derivative of mesityl oxide was 203°.

Methyl vinyl ketone 2,4-dinitrophenylhydrazone. To a solution of 0.2 ml. of methyl vinyl ketone (Matheson, Coleman and Bell, technical, used without purification) in 10 ml. of the diglyme reagent solution was added 3 drops of concentrated hydrochloric acid. The solution stood overnight at room temperature. Addition of water gave an orange product, m.p. 137–8°. Several recrystallizations from ethanol gave long orange needles, m.p. 139.5–140.5°; λ_{max} (CHCl₃): 370 mmμ; λ_{max} (ligroin): 352 mmμ; ϵ_{max} (CHCl₃): 24.670.

Anal. Calcd. for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.03; N, 22.38. Found[3]: C, 48.07; H, 4.24; N, 22.62.

4-Ethoxybutanone-2 2,4-dinitrophenylhydrazone. This was obtained first when attempting to make the 217° product from methyl vinyl ketone by the described[2] procedure. A solution was made by boiling 1 g. of 2,4-dinitrophenylhydrazine in a mixture of 45 ml. of ethanol, 5 ml. of dioxane (freshly purified) and 1 ml. of concentrated hydrochloric acid. The cool solution was filtered from solid that had crystallized and was added to a solution of 1 ml. of methyl vinyl ketone in 2 ml. of ethanol. A small amount of an orange yellow solid precipitated, m.p. 202–8°. Dilution of the filtrate with water gave a flocculent yellow precipitate, m.p. 84–87°. Several crystallizations from ethanol gave light

orange crystals, m.p. 92–3°; (literature: 89–90°[4]; 100–1°[5]); λ_{max} (CHCl₃): 362 mmμ; λ_{max} (ligroin): 344 mmμ; ϵ_{max} (CHCl₃): 21,570.

Anal. Calcd. for $C_{12}H_{16}N_4O_5$: C, 48.65; H, 5.44; N, 18.90. Found[6]: C, 48.38; H, 5.30; N, 18.80.

4-Methoxybutanone-2 2,4-dinitrophenylhydrazone. The procedure described above was used. Again, the solution precipitated a yellow orange solid, m.p. 208–210°. Treatment of the filtrate as above gave a yellow product, m.p. 97–100°. Several crystallizations from methanol gave blunt, dark yellow needles, m.p. 88–90°; (literature[5]: 85–86°) λ_{max} (CHCl₃): 364 mmμ; λ_{max} (ligroin): 345 mmμ; ϵ_{max} (CHCl₃): 21,520.

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.84. Found:[4] C, 46.64; H, 4.89; N, 19.70.

Ultraviolet spectra. A Beckman DK-2 instrument was used. The ligroin used was Eastman Kodak's permanganate purified, b.p. 66–75°. Because of the unexpectedly high values of λ_{max} of the diacetone alcohol derivative the corresponding λ_{max} of mesityl oxide were determined. They were 383 mmμ (CHCl₃) and 365 mmμ (ligroin). The λ_{max} (isooctane) given[2] for mesityl oxide was 364 mmμ; while the λ_{max} (isooctane) calculated[2] for methyl vinyl ketone was 354 mmμ.

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(4) N. A. Milas, et al., *J. Am. Chem. Soc.*, **70**, 1597 (1948).

(5) I. N. Nazarov, S. G. Matsoyan, and V. N. Zhamagortsyan, *Zhur. Obshchei Khim.*, **23**, 1986 (1953).

(6) Geller Laboratories, Bardonia, N. Y.

Isomeric Bis(trimethylsilyl)xylylenes

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In a recent article[1] we described the synthesis of *m*- and *p*-bis(trimethylsilyl)xylylenes from coupling the respective xylylene dihalides and trimethylchlorosilane with magnesium in tetrahydrofuran. We wish to report the successful preparation of the remaining isomer, bis(trimethylsilyl)-*o*-xylylene, to complete the series and an additional dichloro-derivative of the *p*-isomer, bis(dimethylchlorosilyl)-*p*-xylylene. The physical properties of the three isomeric compounds are summarized in Table I and the infrared absorption spectrum of the *o*-isomer is reproduced in Fig. 1.
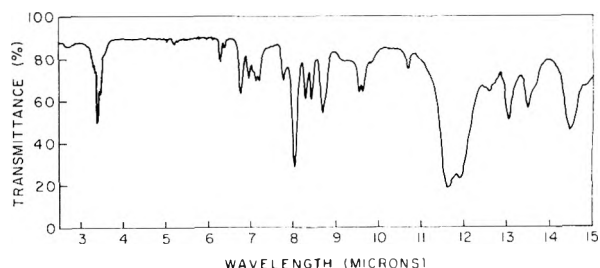

Fig. 1. Bis(trimethylsilyl)-*o*-xylylene

(1) G. R. Wilson, G. M. Hutzel, and A. G. Smith, *J. Org. Chem.*, **24**, 381 (1959).

(3) Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

TABLE I

PHYSICAL PROPERTIES OF ISOMERIC BIS(TRIMETHYLSILYL)-XYLYLENES

Isomer	M.P., °C.	B.P., °C./mm.	d_4^t	n_D^{20}
ortho	2–3	75–6/0.55	0.8686[25]	1.4950
meta	4.0	73–4/0.6	0.8595[24.7]	1.4919
para	61–3	73–4/0.3	...	...

EXPERIMENTAL

Bis(trimethylsilyl)-o-xylylene. This compound was prepared according to the procedure described in a previous article[1] from 0.75 mol. of o-xylylene dibromide, 6.0 mol. of trimethylchlorosilane and 1.64 mol. of magnesium. The material collected at 75–6° (0.55 mm.) was identified as bis(trimethylsilyl)-o-xylylene, m.p., 2–3; d_4^{25} 0.8686 and n_D^{20} 1.4950.

Anal. Calcd. for $C_{14}H_{26}Si_2$: C, 67.13; H, 10.46; Si, 22.40. Found: C, 67.28, 67.22; H, 10.02, 10.13; Si, 22.45, 22.40.

Bis(dimethylchlorosilyl)-p-xylylene. This compound was also prepared by the same procedure[1] from 70.0 g. (0.40 mol.) of p-xylylene dichloride, 113.8 g. (1.05 mol.) of dimethyldichlorosilane and 23.5 g. (0.97 g.-atom) of magnesium in tetrahydrofuran. Distillation yielded 35.8 g. (33% yield) of bis(dimethylchlorosilyl)-p-xylylene, m.p. 74–77°; b.p. 110–112° (0.47 mm.).

Anal. Calcd. for $C_{12}H_{20}Si_2Cl_2$: C, 49.47; H, 6.92; Si, 19.26; Cl, 24.34. Found: C, 49.35, 49.47; H, 7.07; 7.11; Si, 19.26, 19.34; Cl, 24.41, 24.32.

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Reactions of Sulfoxides with Organic Halides. Preparation of Aldehydes and Ketones

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The increasing interest[2–5] in the unusual behavior of organic halides in the presence of dimethyl sulfoxide prompts us to publish preliminary results of an investigation being carried out in this laboratory.[6]

In striking contrast to the reaction of arene- and alkane-sulfonates of secondary alcohols with dimethyl sulfoxide to yield olefins,[7] the sulfonates of primary alcohols react with dimethyl sulfoxide to yield, instead of the expected olefin, a mixture of aldehyde, acetal, and the alcohol derived from the starting ester. For example, hexyl tosylate gave hexanal, the methyl hexyl acetal of hexanal, and 1-hexanol. The corresponding aldehydes were also identified as products from the reaction of butyl and octyl benzenesulfonates in dimethyl sulfoxide. Heating the alcohol or aldehyde with or without the sulfonic acid did not give the same reaction products.

The reaction was then extended to the production of aldehydes from primary alkyl or aralkyl halides and dimethyl sulfoxide or other sulfoxides. It was also found that ketones could be obtained in fair yield in certain cases, e.g., benzophenone from diphenylmethyl chloride. Representative examples are given in Table I. During the course of this investigation the preparation of p-nitrobenzaldehyde by reaction of p-nitrobenzyl chloride with dimethyl sulfoxide was reported.[2]

The reaction of sulfonates and halides with sulfoxides can be carried out conveniently at temperatures in the range 100–160° in an excess of the sulfoxide as solvent, with or without an acid acceptor such as sodium bicarbonate. With dimethyl sulfoxide, low-boiling products are formed which

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(2) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).

(3) R. T. Major and H. J. Hess, *J. Org. Chem.*, **23**, 1563 (1958).

(4) J. M. Tien and I. M. Hunsberger, Abstracts of Papers, A. C. S. 134th Meeting, Chicago, Illinois, September, 1958, page 75P; Chem. and Ind. (London), 88 (1959).

(5) S. G. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958).

(6) U. S. Patent 2,888,488 (May 26, 1959).

(7) H. R. Nace, *Chem. & Ind. (London)*, 1629 (1958).

TABLE I

PREPARATION OF ALDEHYDES AND KETONES[a]

$$R_1R_2CHX + R_3SR_3 \longrightarrow R_1R_2\overset{O}{\overset{\uparrow}{C}}O \quad (R_1R_2CO)$$

R_1	R_2	R_3	X	Reaction Temp.	Reaction Time-hr.	% Yield
$n\text{-}C_3H_7$	H	CH_3	$-OSO_2C_6H_5$	100	2.0	..
$n\text{-}C_5H_{11}$	H	CH_3	$-OSO_2C_6H_5$	100	2.0	Approx. 20
C_6H_5	H	CH_3	$-Cl$	100	10.0	58
C_6H_5	H	C_6H_5	$-Cl$	114–125	6.0	66
$p\text{-}CH_3\text{--}C_6H_4$	H	CH_3	$-Br$	90–161	3.5	63
C_6H_5	C_6H_5	CH_3	$-Cl$	100	2.25	44

[a] Slight excess of sodium bicarbonate (based on halide) used as acid acceptor.

include dimethyl sulfide, methyl mercaptan and dimethyl disulfide. If an acid acceptor is not used, large amounts of formaldehyde are also formed. With diphenyl sulfoxide, a high-boiling residue, presumably diphenyl sulfide, is formed.

The formation of aldehyde can be conveniently accommodated by the following scheme:

$$O \uparrow$$

$$R_1CH_2X + CH_3SCH_3 \longrightarrow R_1CH_2O^+S(CH_3)_2 + X^-$$
$$\longrightarrow R_1CHO + (CH_3)_2S + HX.$$
$$X = R_2SO_3^- \text{ or halogen.}$$
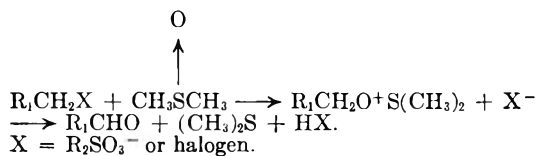
Evidence for the existence of the intermediate salt has already been presented,[5] and Hunsberger and Tien have proposed a similar mechanism for ethyl bromoacetate with dimethyl sulfoxide.[4]

Complete details, including a study of reaction variables and experiments with other halides and sulfonates, will be reported later.

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meso- and dl-9,10-Octadecanediols[1]

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Received May 15, 1959

The 9,10-octadecanediols were desired as examples of secondary glycols. Stereochemically definitive syntheses of the meso- and dl-9,10-octadecanediols, by performic acid treatment of the corresponding trans- and cis-octadecenes, have been reported by Criegee and co-workers.[3]

Other workers[4,5] had reported the preparation of the "high-melting" forms of such glycols by catalytic hydrogenation of acyloins, but had experienced difficulty in isolating the "low-melting" forms in a pure state. Our own experience with platinum oxide hydrogenation of nonyloin was similar.

A more convenient method of preparation was found to be the reduction of nonyloin with sodium borohydride, which proceeded almost quantitatively to a mixture of the two forms. Separation by crystallization from aqueous ethanol gave yields of 42% of the meso and 56% of the dl modification.

Identities were confirmed by independent preparation of the meso form by cis-hydroxylation[6] of cis-octadecene[7] with hydrogen peroxide–osmium tetroxide and of the dl form by ring opening, with Walden inversion,[8] performed on cis-9,10-epoxy-octadecane.[7]

Since greater solubility has been correlated with lower melting point and dl or threo configuration in the case of stilbene dibromide[9] and various esters of the isomeric 9,10-dihydroxystearic acids,[10,11] it was interesting to make solubility measurements (Table I) on the present diols and two related compounds.

TABLE I

Solubility of 9,10-Disubstituted Octadecanes, Stearic Acids and Octadecanols

Compound	M.P.	Solvent	Solubility, g./l. of Soln. at 25°
meso-Octadecanediol	130°	95% EtOH	11.9
dl-Octadecanediol	78°	95% EtOH	30.2
meso-Octadecanediol	130°	Benzene	2.6
dl-Octadecanediol	78°	Benzene	13.7
erythro-Dihydroxy-stearic acid[a]	131°	95% EtOH	8.8
threo-Dihydroxystearic acid[a]	95°	95% EtOH	69.8
Dichloroocta-decanol[b]	31°	95% EtOH	19.0[d]
Dichloroocta-decanol[c]	12°	95% EtOH	843.[d]

[a] Ref. (8). [b] Presumably erythro since made by chlorination of elaidyl alcohol.[12] [c] Presumably threo since made by chlorination of oleyl alcohol.[12] [d] Measurements made at 0°.

In each case the dl or threo modification is considerably more soluble, as well as lower melting.

EXPERIMENTAL

meso-9,10-Octadecanediol by hydrogenation of nonyloin. Hydrogenation at room temperature of 10 g. of nonyloin over PtO$_2$, gave a 30% yield of 9,10-octadecanediol, m.p. 130.0–130.4° (reported[5] 127°,[3] 127.5–128°). On admixture this substance did not change the melting point of meso-9,10-octadecanediol reference compound. Its infrared spectrum measured on a KBr disk was superimposable on that of the reference compound.

meso- and dl-Octadecanediols by sodium borohydride reduction of nonyloin. In 235 ml. of 95% alcohol 18.7 g. of nonyloin was reduced by treatment with 1.24 g. of sodium boro-

(1) Presented at the 135th National Meeting of the American Chemical Society, Boston, Massachusetts, April 6, 1959.

(2) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture, Eastern Regional Research Laboratory, Philadelphia 18, Pa.

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hydride. Crystallization from aqueous alcohol at room temperature gave 2.5 g. of meso-9,10-octadecanediol, m.p. 129.8–131.0° (reported[5] 127°,[3] 127.5–128°); on admixture it did not change the melting point of meso-9,10-octadecanediol reference compound. The infrared spectrum of this compound measured on a KBr disk was also superimposable upon that of the reference compound.

After the mother liquor had stood at 0°, a second crop of 5.4 g. of meso-9,10-octadecanediol was obtained of m.p. 129.2–131.0°. The total yield of the meso-diol was 7.9 g. (42%).

The filtrate from crop 2 on standing at −20° afforded 10.5 g. (56% yield) of dl-9,10-octadecanediol, m.p. 76.8–78.0° (reported[13] >70°,[3] 76–77°); on admixture with dl-9,10-octadecanediol reference compound the melting point was unchanged. The infrared spectra of this substance measured both on a KBr disk and on a CS₂ solution were superimposable on those of the reference compound.

meso-9,10-Octadecanediol, reference compound. Following the procedure of Woodward et al,[6] 1.2 g. of cis-9-octadecene[7] was cis-hydroxylated by treatment in ether solution for 48 hr. with hydrogen peroxide and a little osmium tetroxide. Crystallization at −20° yielded 0.541 g. of the impure product and, after recrystallization from 95% ethyl alcohol and from ligroin at −20°, 0.185 g. of meso-9,10-octadecanediol, m.p. 127.4–129.0° (reported[5] 127°,[3] 127.5–128°).

dl-9,10-Octadecanediol, reference compound. Following the procedure of Swern,[3] 1.07 g. of cis-9,10-epoxyoctadecane,[7] heated 1 hr. at 100° in 25 ml. of anhydrous formic acid, yielded after saponification and two recrystallizations at −20° from ethanol 0.35 g. of dl-9,10-octadecanediol, m.p. 75.8–77.6° (reported[13] >70°,[3] 76–77°).

Solubility determinations. Twenty-five ml. portions of saturated solutions of the 9,10-octadecanediols, dihydroxystearic acids, and dichlorooctadecanols were freed of solvent by evaporation under an air jet and heating for 1.5 hr. at 50° and 1 mm. pressure. The weights of the residues permitted calculation of the solubilities reported in Table I.

Acknowledgment. The authors are grateful to Dr. L. L. Gelb for pure samples of cis-9-octadecene and cis-9,10-epoxyoctadecane and to Dr. C. R. Eddy for infrared determinations.

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Preparation of O-Phenyl-DL-homoserine and of DL-Homoserine from α-Phthalimido-γ-butyrolactone

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In previous studies[1,2,3] it was shown, that α-amino-γ-butyrolactone, in its free and masked

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forms, can be converted into the corresponding γ-substituted α-amino acids.

As polymerization of O-phenyl-DL-homoserine resulted in high molecular, fiber-forming polypeptides,[4] it was of interest to obtain the starting material by a simpler method than hitherto[5] known. The easy availability of α-phthalimido-γ-butyrolactone[3] renders this compound a useful intermediate in the synthesis of O-phenyl-DL-homoserine. As direct opening of α-phthalimido-γ-butyrolactone proved successful, the following procedure has been worked out: by reaction of α-phthalimido-γ-butyrolactone with sodium phenoxide α-phthalimido-γ-phenoxybutyric acid (I) was prepared. Removal of the phthaloyl group was carried out by hydrolysis with 18% hydrochloric acid and α-amino-γ-phenoxybutyric acid hydrochloride isolated, from which the free O-phenyl-DL-homoserine (II) was obtained by treatment with triethylamine. Overall yield based on α-phthalimido-γ-butyrolactone was 42-45%, on γ-butyrolactone 27–29%.

Previously[2] we have described the synthesis of α-amino-γ-iodobutyric acid hydroiodide from α-bromo-γ-butyrolactone and aqueous ammonia. Some difficulties are encountered in the removal of the admixed salts from the intermediate α-amino-γ-butyrolactone hydroiodide. These are avoided in the present synthesis by employing α-phthalimido-γ-butyrolactone, which reacts with 55% hydroiodic acid, yielding α-amino-γ-iodobutyric acid hydroiodide (III) without any opportunity of its contamination by inorganic salts. From α-benzamido-γ-butyrolactone,[1] the hydroiodide (III) was prepared in a similar manner.

Hydrolysis of α-phthalimido-γ-butyrolactone with 24% hydrobromic acid gave α-amino-γ-butyrolactone hydrobromide (IV), as expected,[2] without opening of the lactone ring.

The convenient preparation of α-phthalimido-γ-butyrolactone and its ready hydrolysis by sulphuric acid renders this compound also an advantageous intermediate for a smooth synthesis of DL-homoserine. Overall yield was 50–55% of recrystallized homoserine based on γ-butyrolactone.

EXPERIMENTAL

α-Phthalimido-γ-phenoxybutyric acid (I). Clean sodium (4.6 g., 0.2 mole) was cautiously added in portions, and with occasional shaking, to an excess of molten phenol, placed in a flask fitted with an air condenser and a drying tube containing calcium chloride, the rate of addition being sufficient to keep the phenol molten. The mixture was finally heated until the sodium was dissolved, then gently refluxed for 5 min., and allowed to cool. After addition of α-phthalimido-γ-butyrolactone[3] (46 g., 0.2 mole), heating to reflux for ¹/₂ hr., and subsequent cooling, the solidified mixture was triturated with 250–300 ml. of ether, and the crude sodium

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$$\begin{array}{ccccc}
\underset{\underset{\text{O}\text{---}\text{CO}}{|\quad\quad|}}{CH_2CH_2CHN(CO)_2C_6H_4} & & \underset{\underset{N(CO)_2C_6H_4}{|}}{PhOCH_2CH_2CHCOOH} & & \underset{\underset{NH_2\cdot HCl}{|}}{PhOCH_2CH_2CHCOOH} \\
\downarrow & \searrow & I & \longrightarrow & \downarrow \\
\underset{\underset{\text{O}\text{---}\text{CO}\ \ IV}{|\quad\quad|}}{CH_2CH_2CHNH_2\cdot HBr} & \searrow & \underset{\underset{NH_2\cdot HI}{|}}{ICH_2CH_2CHCOOH} & & \underset{\underset{NH_2}{|}}{PhOCH_2CH_2CHCOOH} \\
& & III & II &
\end{array}$$
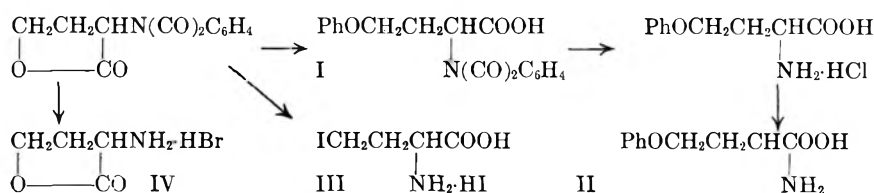
salt filtered off as a dark hygroscopic mass, which was dissolved in water and purified by repeated treatments with Norit and filtrations. 18% hydrochloric acid was introduced dropwise under cooling and stirring within two hours into the filtrate, to acidic reaction. The reaction mixture containing an oily, heavy precipitate was kept in the refrigerator for 1 day. After decantation, the semisolid acid (I) was purified by solution in boiling acetic acid, addition of a small amount of water, and treatment with Norit. To the cooled, vigorously stirred filtrate water was added slowly, causing precipitation of the acid (I). The dried crystals weighed 40 g. (62%), m.p. 122°. On recrystallisation from benzene–petroleum ether, m.p. 124°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 66.5; H, 4.6; N, 4.3. Found: C, 66.6; H, 4.7; N, 4.3.

*O-Phenyl-*DL-*homoserine hydrochloride (α-amino-γ-phenoxybutyric acid hydrochloride).* 300 ml. of 18% hydrochloric acid was added to a solution of α-phthalimido-γ-phenoxybutyric acid (I) (13 g., 0.04 mole) in 10 ml. of acetic acid, and the mixture refluxed for 3 hr. After concentration and cooling, phthalic acid was filtered off and the solution purified by treating with Norit. The crude hydrochloride, obtained on evaporation in vacuo, was dissolved in a small amount of water, freed from the rest of the phthalic acid by filtration and the solution concentrated again in vacuo. The dry residue was dissolved in water-ethanol, precipitated with ether, and dried in vacuo (P_2O_5). The almost colourless crystals (7 g., 76%) melted at 214°.

Anal. Calcd. for $C_{10}H_{14}NO_3Cl$: C, 51.7; H, 6.1; N, 6.1; Cl, 15.3. Found: C, 51.5; H, 6.3; N, 6.2; Cl, 15.5.

*O-Phenyl-*DL-*homoserine (α-amino-γ-phenoxybutyric acid) (II).* Triethylamine was added dropwise to a solution of O-phenyl-DL-homoserine hydrochloride (1 g., 0.0043 mole) in 10 ml. of 50% aqueous ethanol until pH 7–8. The precipitated free acid (II) was filtered off and washed with portions of ethanol. After drying in vacuo (P_2O_5), the crystals (0.8 g., 95%) melted at 230°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.5; H, 6.7; N, 7.2. Found: C, 61.3; H, 6.9; N, 7.2.

*N-Benzoyl-O-phenyl-*DL-*homoserine.* The N-benzoyl derivative was prepared in the usual way by benzoylation of the acid hydrochloride in 3N sodium hydroxide. After recrystallization from ethyl acetate–petroleum ether it melted at 145°.

Anal. Calcd. for $C_{17}H_{17}NO_4$: N, 4.7. Found: N, 4.6.

α-Amino-γ-iodobutyric acid hydroiodide (III). (a) From α-phthalimido-γ-butyrolactone: Powdered α-phthalimido-γ-butyrolactone[3] (23 g., 0.1 mole) was refluxed with 110 ml. of 55% hydroiodic acid during 2 hr. 500 ml. of toluene was added and refluxing continued for 3 hr. The aqueous hydroiodic acid was removed from the stirred mixture by azeotropic distillation. After cooling, the toluenic layer, containing the phthalic acid, was removed by decantation and the residue of crude, dark hydroiodide (III) was washed with ether. White yellow crystals (35 g., 98%) were obtained by extraction with dry ether in a Soxhlet apparatus, m.p. 195–198°.

Anal. Calcd. for $C_4H_9NO_2I_2$: N, 3.9; I, 71.1; Found: N, 4.0; I, 71.2. Since hydrolysis and γ-iodination of α-phthalimido-γ-butyrolactone proceeds quantitatively, the yield of the hydroiodide (III) equalled that of α-phthalimido-γ-butyrolactone (75–80%), prepared from α-bromo-γ-butyrolactone. Uncrystallized lactone could be used giving similar yield; overall yield based on γ-butyrolactone *via* α-bromo-γ-butyrolactone and α-phthalimido-γ-butyrolactone was 64–

72%. *(b) From α-benzamido-γ-butyrolactone:* α-benzamido-γ-butyrolactone[1] (20.5 g., 0.1 mole) was refluxed with 110 ml. of 55% hydroiodic acid. The mixture was worked up as described above, yielding 95% of the hydroiodide (III); based on γ-butyrolactone via α-bromo-γ-butyrolactone and α-benzamido-γ-butyrolactone the yield was 48–51%.

Anal. Found: N, 4.0; I, 71.3.

α-Amino-γ-butyrolactone hydrobromide (IV). Powdered α-phthalimido-γ-butyrolactone (2.3 g., 0.01 mole) was refluxed with 50 ml. of 24% hydrobromic acid for 3 hr. The solution was cooled and the phthalic acid which separated out was filtered off. The mother liquor was evaporated in vacuo; the dry residue was dissolved in 10 ml. of water and freed from traces of phthalic acid by filtration. Water was distilled off and the product washed with ethanol-ether. After drying in vacuo (P_2O_5), the crystals (1.7 g., 93%) melted at 225°.

Anal. Calcd. for $C_4H_8O_2NBr$: N, 7.7; Br, 43.9. Found: N, 7.6; Br, 44.1.

DL-*Homoserine (α-amino-γ-hydroxybutyric acid).* Powdered α-phthalimido-γ-butyrolactone (9.2 g., 0.04 mole) was dispersed in 50 ml. of 50% sulphuric acid, and the mixture refluxed for 3 hr. to dissolution of the lactone. The solution was left to cool to room temperature, then in ice-water. The phthalic acid was filtered off and the solution, containing the α-amino-γ-butyrolactone sulphate, was diluted, treated with Norit and filtered. 45 g. of calcium hydroxide was added and the mixture stirred on a steam bath for 1 hr. Calcium sulphate was filtered off and the solution, containing the calcium salt of DL-homoserine, concentrated to 20–25 ml. Diluted sulphuric acid was dropped in until neutral, and precipitated calcium sulphate filtered off. The solution was purified with Norit, the filtrate concentrated in vacuo to 10–15 ml., 20 ml. of ethanol, followed by 100 ml. of acetone were added and the mixture was kept in the freezer until complete separation of crude DL-homoserine (4.3 g., 91%). When recrystallized from a small amount of water and an excess of 1:5 ethanol-acetone, the crystals (3.8 g., 80%) melted at 182–183°.

Anal. Calcd. for $C_4H_9NO_3$: C, 40.3; H, 7.6; N, 11.8. Found: C, 40.1; H, 7.6; N, 11.7.

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The Synthesis of Nitroestradiols[1,2]

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As part of an investigation concerned with the relationship of molecular structure to estrogenic activity, new compounds are being synthesized by introducing substituents at various positions

(1) Presented before the Organic Chemistry Division, American Chemical Society, 133rd National Meeting, San Francisco, California, April, 1958.

(2) Supported by a grant, CY-2873, from the National Cancer Institute, U. S. Public Health Service.

on the estradiol-17β [1,3,5(10)-estratriene-3,17β diol] molecule. It is the purpose of this note to report the synthesis of 2-nitroestradiol-17β (I), 4-nitroestradiol-17β (II), and 2,4-dinitroestradiol-17β (III). Two routes were investigated for the synthesis of the mononitroestradiols.

The first route involved the direct nitration of estrone to 2-nitroestrone and 4-nitroestrone by a known procedure[3] followed by the selective reduction of the pure compounds to the corresponding mononitroestradiols I and II, respectively. Sodium borohydride was chosen as the reagent for the reduction, because it is known to reduce estrone stereospecifically to estradiol-17β[4] and because it does not attack nitro groups under the mild conditions required for the reduction of a carbonyl group.[5] The products required only recrystallization for purification.

The second route involved the direct nitration of estradiol-17β. The products were separated by chromatography. The nitroestradiols, I and II, obtained by this procedure were identical to the products obtained by the sodium borohydride reduction of 2-nitroestrone and 4-nitroestrone, respectively. Although the first method involved two steps (nitration of estrone followed by reduction), it is preferred over the second method, because the 2- and 4-nitroestrones are more easily separated than a mixture of 2- and 4-nitroestradiols.

The sodium borohydride reduction of 2,4-dinitroestrone which was synthesized by the dinitration of estrone[3] gave III. The infrared spectrum[6] and physical properties were identical to those reported for the product obtained from the nitration of estradiol-17β with 2 moles of nitric acid.[7]

EXPERIMENTAL[8]

Reduction of nitroestrones. A solution of sodium borohydride (200 mg.) in 30 ml. methanol was poured into a solution of the nitroestrone (500 mg.) in 30 ml. of methanol and 0.2 ml. 20% sodium hydroxide. After standing overnight at room temperature, the solution was poured into 150 ml. of water and acidified with 6N hydrochloric acid. The precipitate was collected by filtration and recrystallized from ethanol.

2-Nitroestrone[3] (m.p. 180–182°; *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 68.55; H, 6.71; N, 4.44; Found: C, 68.74; H, 6.73; N, 4.48) gave the diol I, m.p. 164–167°. Yield: 480 mg. (96%). Recrystallization from ethanol gave the pure product, m.p. 167–168°, λ_{max}^{EtOH} 293 mμ (ϵ 8100), 364–366 mμ (ϵ 3690), and λ_{max}^{KBr} 2.85 (17—OH), 3.04 (3—OH), 6.12, 6.37, 6.56 (aromatic NO_2), 7.63, and 11.05 μ (isolated ring H).

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(7) H. Werbin, *J. Org. Chem.*, **21**, 1532 (1956).

(8) Melting points are uncorrected. The author wishes to acknowledge the assistance of Almeria Thompson for the ultraviolet spectra.

Anal. Calcd. for $C_{18}H_{23}O_4N$: C, 68.11; H, 7.30; N, 4.41. Found: C, 68.08; H, 7.21; N, 4.48.

4-Nitroestrone[3] (m.p. 272–278°; *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.57; H, 6.89; N, 4.40) gave 490 mg. (98%) of diol II, m.p. 253–254°. Recrystallization from ethanol gave the pure product, m.p. 255° (dec.); λ_{max}^{EtOH} 278 mμ (ϵ 1810), and λ_{max}^{KBr} 2.81 (17—OH), 3.16 (3—OH); 6.14, 6.32, 6.55 (aromatic NO_2), 7.26, 12.16 μ (two adjacent ring H).

Anal. Calcd. for $C_{18}H_{23}O_4N$: C, 68.11; H, 7.30; N, 4.41. Found: C, 68.11; H, 7.21; N, 4.49.

2,4-Dinitroestrone[3] (m.p. 183–185°; *Anal.* Calcd. for $C_{18}H_{20}O_6N_2$: C, 59.99; H, 5.59; N, 7.78. Found: C, 60.26; H, 5.62; N, 7.77) gave 425 mg. (85%) of diol III, m.p. 255° (dec.); λ_{max}^{EtOH} 277 mμ (ϵ 6490), 352 mμ (ϵ 3430), 430 mμ (ϵ 1040), and λ_{max}^{KBr} 2.80 (17—OH), 3.16 (3—OH), 6.15, 6.35, 6.47 (aromatic NO_2), 7.60, and 11.03 μ (isolated ring H).

Anal. Calcd. for $C_{18}H_{22}O_6N_2$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.88; H, 6.05; N, 7.58.

Direct nitration of estradiol. Estradiol (1.5 g.) was dissolved in 45 ml. of hot acetic acid and allowed to cool to 45°. Then 0.34 ml. of nitric acid (sp. gr. 1.42) was added dropwise with stirring. After 24 hr. at room temperature it was poured slowly into 250 ml. of water with stirring. The mixture of mononitroestradiols was filtered, dried, and chromatographed on Merck alumna (acid washed). The column was eluted with benzene and benzene: acetic acid (99:1, 98:2, and 95:5, successively). The 4-nitroestradiol came off of the column first. Both products were recrystallized from 80% ethanol to give 490 mg. (28%) II, m.p. 255° (dec.) and infrared spectrum identical to II obtained by the reduction of 4-nitroestrone, and 512 mg. (29%) I, m.p. 166–167° and infrared spectrum identical to that of I obtained by the other procedure.

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Epoxidation of Butadiene Sulfone

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The reaction of performic acid (generated *in situ* from formic acid and hydrogen peroxide) with an olefin almost invariably gives the α-glycol or its monoformate as the final product.[1] Only a handful of compounds have been oxidized by this strongly acidic reagent to an isolatable epoxide.[2-4] We have found that butadiene sulfone reacts with a mixture of formic acid and hydrogen peroxide under fairly strenuous conditions (formic acid at 50°) to give the epoxide (I) as the only product in 30% yield. The structure of I was established by the sequence of reactions outlined below. It is interesting to note

(1) D. Swern, Chapter on "Oxidation of Olefins with Peracids," in *Org. Reactions*, Vol. **VII**, John Wiley & Sons, Inc., New York, 1951.

(2) A. Byers and W. J. Hickinbottom, *J. Chem. Soc.*, 1328 (1948).

(3) U. S. Patent, 2,485,160 (W. D. Niederhauser and J. E. Koroky, to Rohm & Haas).

(4) G. Storck, *et al.*, *J. Am. Chem. Soc.*, **73**, 3546, 4496 (1951).

that the performic oxidation yielded the epoxide, while peracetic acid has been reported to oxidize butadiene sulfone to the 3,4-dihydroxytetramethylene sulfone, VII,[5,6] a fact we have verified experimentally. This is the reverse of what might be expected, since formic acid is considered to be much more destructive of the epoxide ring system, to form α-glycol derivatives,[1] than is acetic acid.
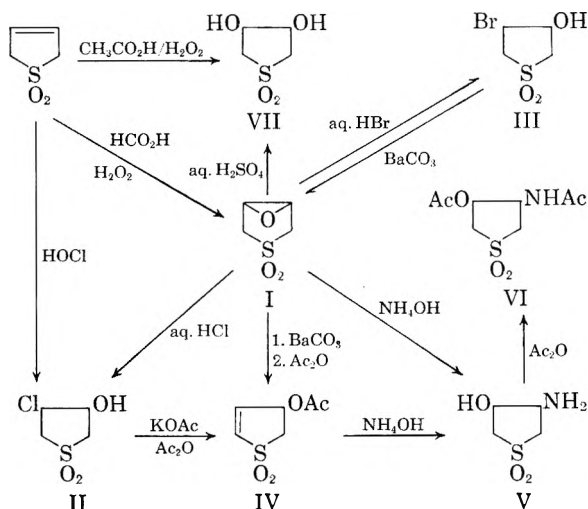
The epoxide I was refluxed with dilute hydrochloric acid to give a chlorohydrin II, identical with that from the addition of hypochlorous acid to butadiene sulfone. Reaction of II with potassium acetate in acetic anhydride gave the cyclic olefin–sulfone acetate, IV, by elimination of HCl. Compound IV, when warmed for one hour with aqueous ammonia, gave the same amino alcohol, V, that resulted from I by the action of aqueous ammonia at room temperature for 24 hours. Epoxide I reacted with hydrobromic acid to give the bromohydrin, III, which regenerated I by treatment with barium carbonate. Refluxing 10% sulfuric acid converted the epoxide I to the same diol, VII, as obtained by peracetic acid oxidation of butadiene sulfone. (All disubstituted compounds are believed to be *trans* isomers from the known stereochemical course of most of the reactions involved.)

The epoxide I has been described previously as having been prepared from the 3-hydroxy-4-bromotetramethylene sulfone (III) by the action of pyridine.[7] The reported melting point was 130°. The melting point of I as we obtained it was 159–160°, which, strangely enough, is exactly that of the diol VII. A mixed melting point between our I and VII was depressed 50°. Analysis and chemical reactivity clearly showed that each had the structure assigned to it. Our epoxide I gave a negative test with

(5) E. deR. van Zuydewijn, *Rec. trav. chim.*, **57**, 445 (1938).

(6) S. F. Birch and D. T. McAllan, *J. Chem. Soc.*, 2556 (1951).

(7) O. E. van Lohuizen and H. J. Backer, *Rec. trav. chim.*, **68**, 1137 (1949).

periodic acid, was recovered unchanged from refluxing acetic anhydride, and showed no hydroxyl absorption in the infrared. The diol VII, prepared by either route, gave a positive periodic acid test, a diacetate from acetic anhydride, and strong hydroxyl absorption. The 130° melting point reported for I[7] is thought to be in error.[8]

EXPERIMENTAL

Epoxide I. Reaction of butadiene sulfone with formic acid and hydrogen peroxide. To 850 ml. of 98% formic acid was added 170 g. of purified butadiene sulfone, m.p. 64–65°, (recrystallized from chloroform-ether). Then 214 g. of 30% hydrogen peroxide was added. Considerable heat was evolved and the reaction was cooled in ice to keep the temperature at 50°. The reaction was allowed to stand at room temperature over a weekend. Excess ferrous ammonium sulfate was added to destroy the remaining peroxides, and the solution distilled at water aspirator pressure. When most of the solvent had been removed, a solid began to form. This was filtered, triturated with water to remove the red iron salts, and recrystallized from acetone to give shiny needles, m.p. 159.5–160°, after thorough drying. The yield was 56.5 g. (30%).

Anal. Calcd. for $C_4H_6O_3S$: C, 35.82; H, 4.47; S, 23.89. Found: C, 35.9, 35.8; H, 4.6, 4.5; S, 24.4, 24.4.

Reaction of I with HCl (II). Two grams of I was refluxed 8 hr. with 44 ml. of 9% hydrochloric acid. On cooling, 2.4 g. (95% yield) of white crystals were obtained, which, after washing with water and drying without further purification, melted sharply at 167–168°. On admixture with I, a depression of the m.p. to 140–144° occurred. With authentic 3-chloro-4-hydroxy-tetramethylene sulfone, prepared below, no melting point change occurred. [Ref. (7) reports the m.p. of II as 160°].

Anal. Calcd. for $C_4H_7ClO_3S$: C, 28.23; H, 4.11. Found: C, 28.6, 28.50; H, 4.1, 4.2.

3-Chloro-4-hydroxy-tetramethylene sulfone (II). To a stirred, ice-cooled solution of 59 g. butadiene sulfone in 300 ml. water was added a solution of HOCl, as prepared in *Org. Syntheses*, **Coll. Vol. 1**, 158, until no more HOCl was taken up (KI-HCl test). A solid separated during the course of the addition, which, after filtering, was recrystallized from acetone and then methanol, followed by vacuum drying. It had a m.p. of 167–168°; the m.p. was not depressed by the product from the preceding paragraph. The yield was 68 g.

(8) Since this paper was submitted, M. Prochaska and V. Horak, *Coll. Czech. Chem. Comm.*, **24**, 1509 (1959), have reported the preparation of epoxide I by the method of Ref. (7). They obtained a melting point of 124.5–6°. They also describe a number of derivatives of the epoxide which correspond in melting point to those reported here and in Ref. (7). In addition, Prochaska and Horak find that treatment of their epoxide with barium carbonate gives the olefin-alcohol corresponding to IV, above, which is then acetylated to IV. We find that our epoxide, I, melting at 159–160°, undergoes the same sequence of reactions, leading to IV, identical to the compound obtained from the potassium acetate/acetic anhydride treatment of the chlorohydrin II. Prochaska and Horak report almost exactly the same reaction of the chlorohydrin, with sodium acetate and acetic anhydride in two steps, to give IV also. It is difficult to explain the wide variance in melting point of epoxide I between that reported in Ref. (7) (130°) and by Prochaska and Horak (124.5–126°), and that found by us (159–160°). It may be a matter of two crystalline modifications; thus far, we have been unable to transform the 159–160° melting compound to any other form by recrystallization from various solvents.

(77%) of crude product. Only a slight loss occurred on re-crystallization.

Reaction of I with HBr (III). Five g. I was refluxed with 39 ml. 10% HBr for 8 hr. On cooling, the solid which formed was of high apparent purity, and on washing with water and drying it melted sharply at 192–193°. The yield was 5.5 g. (69%).

Anal.: Calcd. for $C_4H_7BrO_3S$: C, 22.3; H, 3.25; Br, 37.2. Found: C, 22.5, 22.3; H, 3.2, 3.2; Br, 37.2, 37.8.

Reaction of III with BaCO₃. Five and two-tenths g. of the bromohydrin from above was heated for 2 hr. on the steam bath with 2.4 g. BaCO₃ in 20 ml. water. The solution became almost completely clear. It was filtered of some residual solid and the filtrate cooled in ice. The solid that formed was re-crystallized from ethanol/ethyl acetate; m.p. 158–159°, yield, 2.1 g. (65%). On admixture with Compound I there was no depression of melting point.

Anal.: Calcd. for C_4HO_3S: C, 35.88; H, 4.51; S, 23.89. Found: C, 35.6, 35.9; H, 4.2, 4.3; S, 24.5, 24.41.

Reaction of I with Ammonia (V). In 250 ml. of 28% aqueous ammonia was placed 10 g. of I. It was allowed to stand at room temperature for 24 hr. A small amount of a crystalline solid was filtered off that melted (dec.) at 260°. The filtrate was evaporated, and the solid residue triturated with ether, acetone, and ethyl acetate. After drying, it had a m.p. of 198–199°; yield, 7.4 g. (64%).

Anal.: Calcd. for $C_4H_8NO_3S$: C, 31.81; H, 5.92; N, 9.28; S, 21.20. Found: C, 31.9, 31.9; H, 6.3, 6.1; N, 9.4, 9.3; S, 21.4, 21.4.

Acetylation of V (VI). To a mixture of 50 ml. acetic anhydride and 3 ml. acetic acid was added 2.5 g. of V. The mixture was refluxed for 3 hr. The excess anhydride and acid was distilled under vacuum and the residual solid recrystallized from methanol; m.p. 149–150° after drying; yield 3.8 g. (93%).

Anal.: Calcd. for $C_8H_{13}NO_5S$: C, 40.85; H, 5.53; N, 5.95; S, 13.59. Found: C, 40.5, 40.5; H, 5.6, 5.5; N, 5.8, 5.8; S, 13.3, 13.2.

Reaction of II with acetic anhydride and potassium acetate (IV). Seventeen g. of II was added to a solution of 10.0 g. KOAc in 200 ml. Ac₂O and 20 ml. HOAc. This mixture was heated on the steam bath overnight, then refluxed 2 hr. further. An inorganic solid was filtered, the filtrate evaporated under vacuum and the solid residue taken up in methanol. Again, some inorganic solid was filtered. The methanol solution was cooled and the crystalline solid recrystallized from methanol. The product weighed 12 g. (68%); m.p. 110–111°.

Anal.: Calcd. for $C_6H_8O_4S$: C, 40.85; H, 4.55; S, 18.18. Found: C, 40.9, 41.1; H, 4.6, 4.67; S, 18.5, 18.7.

Reaction of IV with ammonia (V). A mixture of 5.5 g. IV and 90 ml. 28% aq. ammonia was heated on the steam bath for 1 hr. The liquid was distilled under vacuum and the residue recrystallized from ethanol-water after trituration with ethyl acetate; m.p. 197–198°, yield 2.5 g. (48%). Mixed melting point with V from I plus NH₄OH was not depressed.

Reaction of I with aqueous H₂SO₄ (VII). A solution of 10 g. of I in 50 ml. of 10% H₂SO₄ was refluxed overnight. The acid was neutralized with solid sodium carbonate and the mixture evaporated to dryness. The solid residue was taken up in absolute alcohol, filtered, and the alcohol filtrate cooled. The solid that separated was recrystallized twice from absolute alcohol. After drying it had a m.p. of 159–160°. It depressed the melting point of starting material almost 50° on admixture. It did not depress the m.p. of authentic 3,4-dihydroxytetramethylene sulfone, prepared below.

Dihydroxylation of butadiene sulfone (VII). Butadiene sulfone was dihydroxylated according to the method of Ref. (6) (where 2,5-dihydrothiophene was the starting material) using peracetic acid. The diol VII was the product in 75% yield. It was identical with VII prepared from I by acid hydrolysis (above). The procedure involves finally refluxing the acetic acid solution for 3 hr. to destroy excess peroxide.

When I is refluxed in 98% formic acid for 3 hr., it is recovered unchanged.

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Lithium Aluminum Alkoxide Catalyzed Transesterification of Primary Alcohols with Ethyl Acetate

P. R. STAPP AND NORMAN RABJOHN

In the course of another investigation, it was necessary to convert 3-butyl-3-propyloctanoic acid (I) to 3-butyl-3-propyl-1-octanol (II). The reduction was carried out by using an excess of lithium aluminum hydride, followed by destruction of the excess hydride with ethyl acetate, prior to hydrolysis, according to conventional procedures.[1-3]

Upon examining the reaction mixture, it was found that extensive transesterification had taken place, and that a mixture of the expected alcohol (II) and 3-butyl-3-propyl-1-octyl acetate (III) was obtained. Reduction of I to pure II was accomplished successfully by the procedure of Nystrom and Brown[4] by destroying the excess lithium aluminum hydride with dilute sulfuric acid.

As no particular care had been taken to hydrolyze the original reduction mixture immediately after the excess lithium aluminum hydride had been destroyed with the ethyl acetate, it was interesting to examine the reaction system further. A series of *reductions of the acid (I) was carried out* in which variations were made in the period of time which the reaction mixtures were allowed to stand in contact with a large excess of ethyl acetate before hydrolysis. The mixtures of alcohol (II) and acetate (III) were analyzed by gas chromatography and the results are summarized in Table I. It is noteworthy that even when the reaction mixture was acidified immediately following the introduction of the ethyl acetate, 31% of ester (III) was obtained. The rapidity of the transesterification appeared to be unusual because of the low temperatures involved and the hindered structure of the alcohol (II).

In order to determine if the observed rate of transesterification were peculiar to the structure of the alcohol (II), four reductions of caprylic acid

(1) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956, p. 1010.

(2) W. G. Brown, *Org. Reactions*, VI, 488 (1951).

(3) R. S. Moffett, *Org. Syntheses*, **33**, 82 (1953).

(4) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1197 (1947).

were performed under comparable conditions with somewhat similar results as is shown in Table I. The relative proportions of n-octyl acetate obtained were lower, but still quite significant. In the last experiment shown in the table, only 1.1 g. (0.0125 mole) of ethyl acetate was used in excess, and the product was contaminated by 16% of ester.

TABLE I

TRANSESTERIFICATION OF LITHIUM ALUMINUM HYDRIDE REDUCTION MIXTURES IN THE PRESENCE OF EXCESS ETHYL ACETATE[a]

Acid	Time (hrs.)[b]	% Acetate in Reaction Product	Yield of Acetate, %
I	0	44	31[d]
I	3	71	51[d]
I	24	74	51[d]
n-C$_7$H$_{15}$CO$_2$H	0	35	24[d]
n-C$_7$H$_{15}$CO$_2$H	3	52	37[d]
n-C$_7$H$_{15}$CO$_2$H	16	55	40[d]
n-C$_7$H$_{15}$CO$_2$H	3	16[c]	74[e]

[a] The excess lithium aluminum hydride was destroyed with 25 ml. of ethyl acetate. This amounts to a fourfold (.20 mole) excess. [b] Time between addition of ethyl acetate and hydrolysis with 10% sulfuric acid. [c] An excess of only 0.0125 mole of ethyl acetate was employed in this experiment. [d] Per cent yield of ester based on starting acid. [e] Per cent yield of ester based on the ethyl acetate in excess of that required to destroy the excess lithium aluminum hydride.

In Table II are recorded the results of an experiment which was designed to show that ester interchange occurs readily between alkoxides of the type (RO)$_4$LiAl and ethyl acetate. The preformed alkoxide, (n-C$_8$H$_{17}$O)$_4$LiAl, in ether and an ether solution of ethyl acetate were equilibrated at 29.1°, mixed, samples removed at timed intervals, quenched by addition to dilute acid and worked up. The samples were analyzed by gas chromatography.

TABLE II

REACTION OF (n-C$_8$H$_{17}$O)$_4$LiAl WITH ETHYL ACETATE[a]

Time after Mixing (mins.)	% n-Octyl Acetate In mixture	% Yield of n-Octyl acetate[b]
1	0.55	2
3	0.66	3
5	0.74	3
10	1.2	5
15	1.3	5
20	1.8	7
30	2.1	8
45	3.1	12
60	3.6	14
120	4.8	19
180	6.5	26

[a] Equimolar amounts of reactants employed. [b] Based on ethyl acetate.

Although the amount of transesterification was less under these conditions, it was still quite significant considering the fact that the ethyl acetate

was present in only one-fourth the equivalent quantity required.

The possibility of ester interchange of the lithium aluminum alkoxide of a secondary alcohol with ethyl acetate was considered. When 5-nonanone was reduced with lithium aluminum hydride under conditions similar to those described previously, and the reaction mixture was allowed to stand for 16 hr. with a large excess of ethyl acetate, only the expected carbinol was obtained. Larger highly branched ketones which were reduced previously under essentially the same conditions also gave only carbinols.[5]

EXPERIMENTAL[6]

Materials. Caprylic acid and n-octyl alcohol were redistilled Distillation Products Inc. White Label products. Lithium aluminum hydride was purchased from Metal Hydrides, Inc. The 3-butyl-3-propyloctanoic acid (I) was prepared by the method of Rabjohn, Phillips, and DeFeo.[5] 5-Nonanone was obtained by the potassium dichromate oxidation of 5-nonanol.[7]

Reduction of 3-butyl-3-propyloctanoic acid (I). In a 2-l. three necked flask fitted with a condenser protected by a drying tube, a mercury-sealed stirrer, and an addition funnel, were placed 11.4 g. (.30 mole) of lithium aluminum hydride and 500 ml. of dry ether, and the mixture was stirred until a uniform slurry was obtained. A solution of 48.4 g. (.20 mole) of 3-butyl-3-propyloctanoic acid in 150 ml. of dry ether was added dropwise over a period of 2 hr., stirred for an additional 4 hr. and allowed to stand overnight. The excess hydride was destroyed by the dropwise addition of 200 ml. of a 50% solution of ethyl acetate in dry ether. The mixture was hydrolyzed with 500 ml. of 10% sulfuric acid, the layers separated, and the aqueous layer extracted with ether. The combined ether layers were washed with water, 10% sodium bicarbonate solution, again with water, dried over magnesium sulfate, and filtered. The ether was removed at atmospheric pressure and the residue distilled under reduced pressure through a short Vigreux column. There was obtained 47.4 g. of a colorless oil b.p. 115–117.5° (1 mm.), n_D^{25} 1.4448, whose infrared spectrum indicated a mixture of a primary alcohol and an ester.

Separation of the above mixture. In a 500-ml. round-bottomed flask were placed 25.0 g. (.107 mole) of 3,5-dinitrobenzoyl chloride, 42.9 g. of the mixture of alcohol and ester, and 250 ml. of dry pyridine. The mixture was refluxed gently for 2 hr. and allowed to stand overnight. The dark red solution was poured into 400 ml. of 5% sodium hydroxide solution and the resulting mixture was shaken occasionally while standing for 1 hr. The mixture was extracted with ether, the ether extracts washed with water, 10% hydrochloric acid, again with water, 10% sodium bicarbonate solution, again with water, and dried over magnesium sulfate. The solution was filtered, the ether removed at atmospheric pressure, and the residue was distilled under reduced pressure. There was obtained 29.4 g. (68.5%) of III as a colorless oil, b.p. 135–137° (1.5 mm.), n_D^{23} 1.4440.

Anal. Calcd. for C$_{17}$H$_{34}$O$_2$: C, 75.50; H, 12.67. Found: C, 75.48; H, 12.39.

(5) Norman Rabjohn, L. V. Phillips, and R. J. DeFeo, Unpublished results.

(6) All melting points are uncorrected. The carbon-hydrogen analyses were performed by Weiler and Strauss of Oxford, England. The gas chromatographic analyses were performed with the assitance of W. M. Lamkin on a Perkin-Elmer Model 154 Vapor Fractometer.

(7) G. H. Coleman and D. Craig, *Org. Syntheses*, **Coll. Vol. II**, 179 (1943).

The dark, tarry residue from the distillation was extracted with 200 ml. of 95% ethanol, decolorized with carbon, filtered, and concentrated to one-half the original volume. After standing overnight in a refrigerator, there was obtained 22.5 g. (28.4%) of 3-butyl-3-propyl-1-octyl 3,5-dinitrobenzoate (IV) in the form of yellowish crystals, m.p. 42–45°. An analytical sample was obtained from 95% ethanol as fluffy, colorless needles, m.p. 44.5–45°.

Anal. Calcd. for $C_{22}H_{34}O_6N_2$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.60; H, 8.03; N, 6.56.

Saponification of IV. In a 500-ml. three necked flask equipped with a mechanical stirrer and a reflux condenser were placed 20.3 g. (.31 mole) of 85% potassium hydroxide pellets, 200 ml. of 95% ethanol, and 50 ml. of water, and the mixture was stirred until the potassium hydroxide went into solution. To the alkali solution was added 15.4 g. (.037 mole) of IV and the mixture was refluxed for 25 hr. It was allowed to cool and 1-l. of water was added. The mixture was extracted four times with ether, the ether removed, and the residue distilled under reduced pressure. There was obtained 7.1 g. (84.5%) of II as a viscous, colorless oil, b.p. 131–132° (1.5 mm.), n_D^{25} 1.4517.

Anal. Calcd. for $C_{15}H_{32}O$: C, 78.87; H, 14.12. Found: C, 78.85; H, 13.82.

Identification of III. A solution of 20 g. (.30 mole) of 85% potassium hydroxide in 50 ml. of water and 100 ml. of 95% ethanol was refluxed with 10.9 g. of III for 36 hr., cooled, and transferred to a distillation flask. The ethanol was removed by distillation, and after adding 150 ml. of water, the mixture was extracted four times with ether. The combined ether extracts were washed with water, dried over magnesium sulfate, filtered, and the ether removed. The residue was distilled under reduced pressure and 7.8 g. of a colorless, viscous oil, b.p. 139–140° (2.0 mm.), n_D^{25} 1.4519, was obtained whose infrared spectrum was identical with that of 3-butyl-3-propyl-1-octanol (II). Its 3,5-dinitrobenzoate was prepared, m.p. 43–44°, and the melting point was not depressed on admixture with authentic 3-butyl-3-propyl-1-octyl 3,5-dinitrobenzoate (IV).

The aqueous solution was evaporated to dryness and the crude potassium salt was converted to its *p*-bromophenacyl ester, m.p. 84–85°; lit.[8] m.p. 85°.

Preparation of pure II by reduction of I. The reduction of 22.6 g. (.094 mole) of I was acccomplished successfully with 3.8 g. (.10 mole) of lithium aluminum hydride followed by destruction of the excess hydride with 100 ml. of 10% sulfuric acid. After work up, there was obtained 18.4 g. (86.4%) of pure II, b.p. 141–142° (2 mm.), n_D^{25} 1.4520.

Preparation of III from II. A mixture of 8.4 g. (.037 mole) of II, 21.6 g. (.212 mole) of acetic anhydride, 20 ml. of dry thiophene-free benzene, and 2 drops of concentrated sulfuric acid was boiled gently for 3 hr. The solution was cooled, poured into 200 ml. of cold, 10% sodium carbonate solution, and allowed to stand for 2 hr. with occasional stirring. The layers were separated, the aqueous layer extracted with benzene, and the combined benzene solutions washed twice with water. The benzene was removed at atmospheric pressure and the residue distilled under reduced pressure. There was obtained 8.7 g. (87.9%) of III, b.p. 140–142° (2 mm.), n_D^{25} 1.4440, whose infrared spectrum was identical with that of the acetate obtained from the separation of the original reaction mixture.

Anal. Calcd. for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67. Found: C, 75.46; H, 12.92.

Treatment of lithium aluminum hydride reduction mixtures with excess ethyl acetate. The reductions listed in Table I were all carried out in the following manner: A solution of .10 mole of the appropriate acid in 100 ml. of dry ether was added dropwise to a slurry of 3.8 g. (.10 mole) of lithium aluminum hydride in 75 ml. of dry ether, and the mixture was

refluxed gently for 3 hr. after addition was complete. It was cooled in an ice bath and 50 ml. of a 50% solution of ethyl acetate in ether was added as rapidly as possible, and the mixture allowed to stand for the indicated time. The complex was hydrolyzed by addition of 100 ml. of 10% sulfuric acid and the mixture was worked up and distilled through a short Vigreux column. In the last run a total of 3.3 g. (.0375 mole) of ethyl acetate in 10 ml. of ether was added, this corresponds to an excess of .0125 mole over that required for destruction of the excess hydride. The mixtures obtained after distillation were analyzed by gas chromatography.

Transesterification of ethyl acetate by $(C_8H_{17}O)_4LiAl$. In a 500-ml. three necked flask fitted with a mercury-sealed stirrer, a condenser protected by a drying tube, and a dropping funnel, were placed 0.95 g. (.025 mole) of lithium aluminum hydride and 50 ml. of dry ether, and the mixture was stirred vigorously for 30 minutes. The flask was placed in a constant temperature bath held at 29.1 ± .05°, and 15 g. (.115 mole) of *n*-octyl alcohol in 75 ml. of dry ether added and the mixture was stirred for an additional 2 hr. to insure temperature equilibrium. A solution of 2.2 g. (.025 mole) of ethyl acetate in 10 ml. of dry ether, which had been equilibrated for 2 hr. in the constant temperature bath, was added in one portion. At timed intervals, 5 ml. portions were pipetted from the reaction mixture, quenched with 10 ml. of cold 10% sulfuric acid, and worked up in the usual fashion. Each sample was analyzed by gas chromatography, and the results obtained are given in Table II.

Reduction of 5-nonanone. The reduction of 28.4 g. (.20 mole) of 5-nonanone in 200 ml. of dry ether was carried out using 5.7 g. (.15 mole) of lithium aluminum hydride in 125 ml. of dry ether. The excess hydride was destroyed with 100 ml. of 50% ethyl acetate in ether, the mixture was allowed to stand for 16 hr., and then was hydrolyzed with 150 ml. of 10% sulfuric acid. After work up, there was obtained 23.7 g. (82.3%) of 5-nonanol, b.p. 90–92° (20 mm.), n_D^{23} 1.4360, whose infrared spectrum showed no traces of carbonyl adsorption.

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Non-lability of the α-Hydrogen during Ninhydrin Oxidation of Alanine[1]

JACK G. KAY AND F. S. ROWLAND

Recent studies of the reactions of recoil tritium with L(+)-alanine required a degradation method which would remove tritium radioactivity from the α-hydrogen position without affecting any radioactivity in the β-positions.[2] An examination of the proposed mechanism for the oxidation of α-amino acids by ninhydrin showed the original condensation reaction (1), followed by enolization (2) and subsequent hydrolysis (3):[3]

(1) Research supported by A.E.C. Contract No. AT-(11-1)-407.

(2) J. G. Kay, R. P. Malsan, and F. S. Rowland, *J. Am. Chem. Soc. in press.*

(3) A. Schönberg and R. Moubasher, *Chem. Revs.*, 50, 261 (1952). R. Moubasher and M. Ibrahim, *J. Chem. Soc.*, 702 (1949). A. Schönberg, R. Moubasher, and A. Mostafa, *J. Chem. Soc.*, 176 (1948). F. G. Baddar, *J. Chem. Soc.*, S, 163 (1949).

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., J. Wiley and Sons, Inc., New York, 1956, p. 276.

(1), (2), (3)
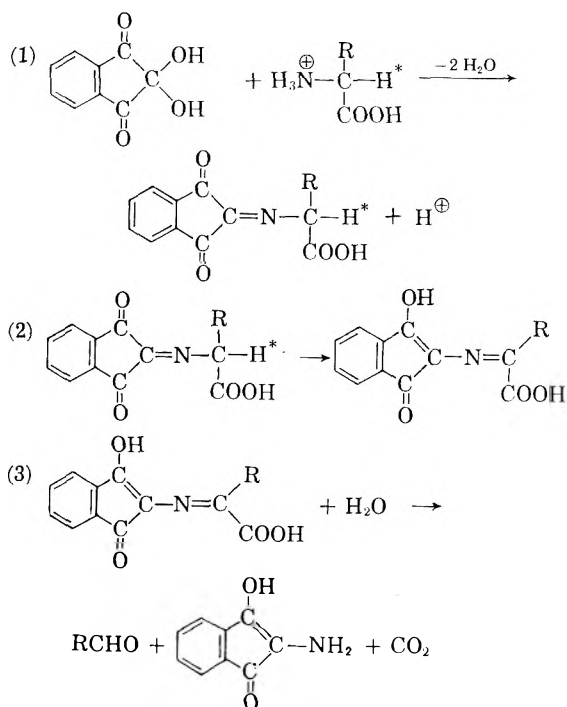
As shown above, any tritium activity in the α-position of the amino acid would be exchanged with the solvent and lost during tautomerization; the radioactivity of the resulting acetaldehyde (or derivative) would then serve as a measure solely of the original β-hydrogen radioactivity. However, actual experiments with recoil labeled DL-alanine showed only a minor loss of tritium activity during the reaction sequence from alanine to acetaldehyde derivative, as shown in Table I (a). (Degradation of another aliquot of the same labeled alanine to thallous acetate demonstrated that a large percentage of the tritium activity was originally present in the α-position.)

An additional experiment was then performed in which unlabeled dl-alanine was oxidized in the presence of high activity HTO. The resulting derivative
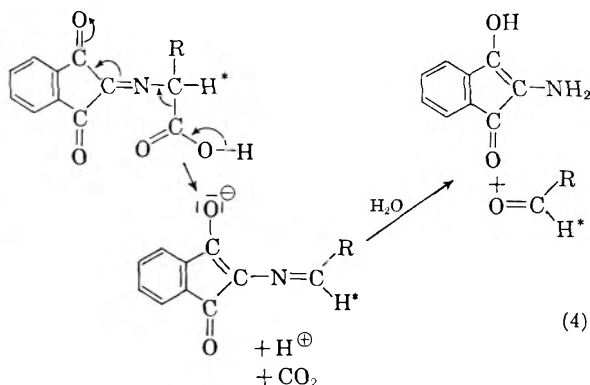
TABLE I

RADIOACTIVITY OF ALANINE AND DERIVATIVES
$(DPM/\mu$ MOLE$)$

	(a)	(b)
Alanine	1.32×10^3	0
Water	...	740
Acetaldehyde,-2,4-dinitro-phenylhydrazone	1.16×10^3	<0.3
Acetaldehyde dimedone	1.22×10^3	...
Thallous acetate	0.48×10^3	...

of acetaldehyde was essentially non-radioactive [Table I (b)], showing that the α-hydrogen is non-labile throughout the entire reaction. The small loss of original activity in part (a) of Table I is consistent with previously measured exchange rates for formation of these derivatives.[4]

(4) W. J. Hoff, Jr., and F. S. Rowland, *J. Am. Chem. Soc.*, **79**, 4867 (1957).

Under these reaction conditions the mechanism of the ninhydrin oxidation cannot involve tautomeric forms, as in (2), which require hydrogen loss from the α-carbon. The reactions shown in (4) are consistent with this requirement.

(4)

EXPERIMENTAL

A 50-mg. sample of the purified tritium-labeled alanine [Table I(a)] was reacted with ninhydrin according to the method of Van Slyke[5] and Wolf[6] using citrate buffer and sweeping the solution with nitrogen while warming on the steam bath. The nitrogen stream swept the acetaldehyde from the reaction into the bottom of an ice-cooled solution of 2,4-dinitrophenylhydrazine dissolved in CH_3OH and HCl. The acetaldehyde-2,4-dinitrophenylhydrazone produced in the alcohol solution was then purified by recrystallization to constant specific activity from methanol-water solutions. This procedure was repeated, substituting a solution of 5,5-dimethylcyclohexane-1,3-dione in 50% aqueous methanol in place of the dinitrophenylhydrazine solution previously used. The dimedone derivative was formed by adding one drop of pyridine and boiling for 30 sec. and was then purified by recrystallization from methanol-water mixtures to constant specific activity.

Another sample (289 mg.) of the purified tritiated alanine was similarly reacted with ninhydrin, sweeping the acetaldehyde product into an ice cooled solution of CrO_3 in M H_2SO_4. After the ninhydrin reaction was complete and all of the acetaldehyde had been swept from the solution, the chromic acid solution was allowed to stand at room temperature overnight in order to complete the oxidation of acetaldehyde to acetic acid. The acetic acid was then removed by steam distillation and titrated with thallous hydroxide according to the method of Wolf and coworkers.[7] The thallous acetate was recrystallized to constant specific activity from methanol-acetone mixtures.

A 68 mg. sample of non-tritium-labeled DL-alanine [Table I(b)] was submitted to the ninhydrin oxidation in the presence of 100 ml. of tritium-labeled water (sp. act = 740 DPM/μ mole), forming acetaldehyde-2,4-dinitrophenylhydrazone from the aldehyde produced and purifying as before.

All specific activities were measured by combustion of a few mg. of the solid according to the method of Wilzbach, Kaplan, and Brown[8] and counting in a silver-walled glass proportional counter with propane as the counter gas.

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(5) D. D. Van Slyke, R. T. Dillon, D. A. MacFadyen, and P. Hamilton, *J. Biol. Chem.*, **141**, 627 (1941).

(6) A. P. Wolf, private communication.

(7) A. P. Wolf, C. S. Redvanly, and R. C. Anderson, *J. Am. Chem. Soc.*, **79**, 3717 (1957).

(8) K. Wilzbach, L. Kaplan, and W. G. Brown, *Science*, **118**, 522 (1953).

Reactivity of Aryl Isocyanates

F. H. BROCK

The rate constants reported in the literature for the reactions of several aryl isocyanates and di-isocyanates with various alcohols under different experimental conditions have been correlated successfully by means of the Hammett linear free-energy relationship,[1] $\log k/k_0 = \rho \Sigma \sigma$. In this equation, ρ is the reaction series constant and $\Sigma \sigma$ is the sum of the substituent constants. Based on limited data, ρ is calculated to be 1.69.

In Table I are listed the reaction series and rate constants. Figures 1 to 3 are plots of $\log k/k_0$
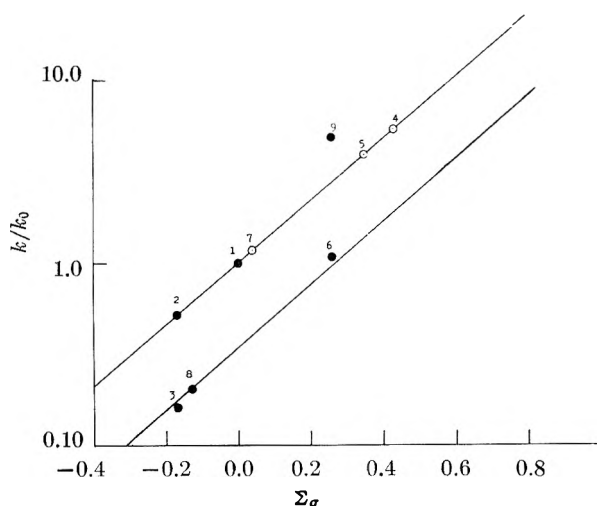

Fig. 1. Plot of $\log k/k_0$ vs. $\Sigma\sigma$; series I: $\bigcirc$, used to evaluate σ values. Numbers refer to compounds in Table I
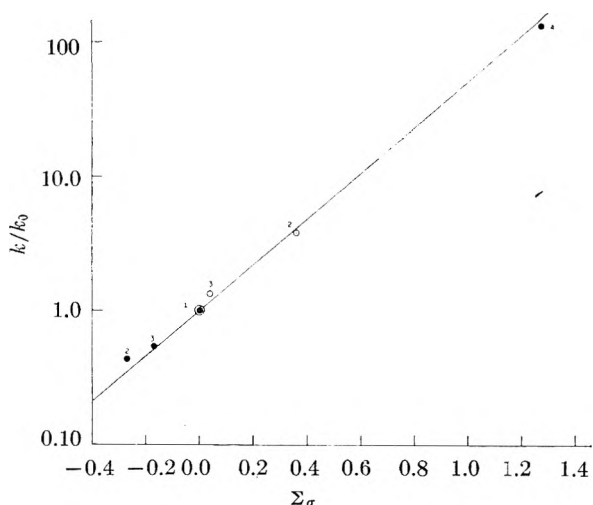

Fig. 2. Plot of $\log k/k_0$ vs. $\Sigma\sigma$; $\bigcirc$, series II; $\bullet$, series III. Numbers refer to compounds in Table I

(1) L. P. Hammett, *Physical Organic Chemistry*, McGraw Hill Co., New York, 1940, p. 184; also, R. W. Taft, Jr., in M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, 1956, p. 570.
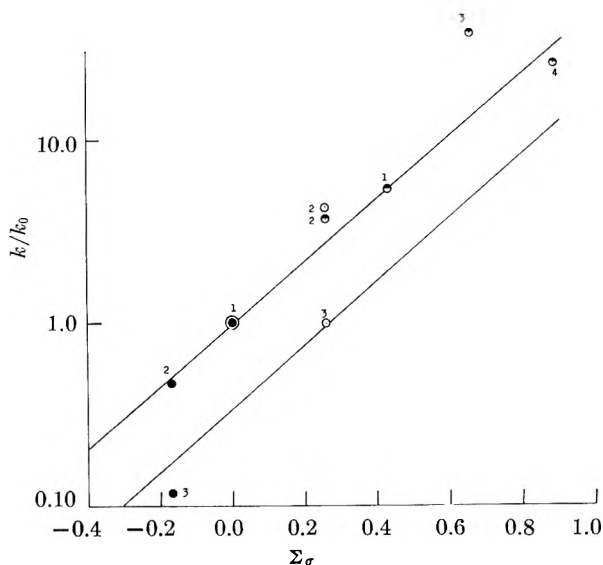

Fig. 3. Plot of $\log k/k_0$ vs. $\Sigma\sigma$; $\bullet$, series IV; $\bigcirc$, series V; $\ominus$, series VI. Numbers refer to compounds in Table I

vs. $\Sigma\sigma$, where the k values designated as k_1 in Table I, refer to the reaction of the first isocyanato group. In every series the rate constants for the phenyl isocyanate reactions are taken as k_0.

TREATMENT OF RATE DATA

The number of data available in every series is limited, and each series was run at a different temperature. Hence, the assumption was made that the ρ and σ values are independent of temperature. The experimental rate constants for the symmetrical diisocyanates were divided by 2 in order to evaluate the reactivity of one isocyanato group.

Series I.[2] Fig. 1 shows a plot of the data of series I using a ρ value of 1.69, the values of k/k_0 for compounds 4, 5, and 7 being plotted on this line. The σ values obtained for the substituents of these compounds are presented in Table II. Although these values were used for the appropriate compounds in this and in the other series and appear to be applicable in these particular reactions, they are considered to be preliminary, since no other confirmatory data are available. Also listed in Table II are other σ values derived from these reactions together with the literature values of those required in this paper. The points for the compounds that have an o-CH$_3$ group, namely 3, 6, and 8 define a line parallel to that of the sterically unhindered compounds, the σ values of the p-substituents of compounds 7 and 8 being considered equal to each other.

Series II[3] and III[4]: In Fig. 2 are presented the data for these series. All the σ values are known

(2) J. Burkus and C. F. Eckert, *J. Am. Chem. Soc.*, **80**, 5948 (1958).

(3) L. L. Ferstandig and R. A. Scherrer, *Am. Chem. Soc. Div. Petrol. Chem. Symposium* 1 (Chemicals from Petroleum) Gen. Papers No. 2, 69 (1956).

(4) J. W. Baker, and J. B. Holdsworth, *J. Chem. Soc.*, 713 (1947).

TABLE I
SUMMARY OF RATE DATA

Series I: Reaction with 1-Butanol in Toluene, 0.0313M
Triethylamine Catalyst, at 39.69°

Monoisocyanates	k_1	$k_2(1 \text{ mol.}^{-1} \text{ min.}^{-1})$
1. Phenyl	0.406	...
2. p-Tolyl	0.210	...
3. o-Tolyl	0.0655	...
Diisocyanates		
4. m-Phenylene	4.34	0.517
5. p-Phenylene	3.15	0.343
6. 2,6-Tolylene	0.884	0.143
7. 4,4′-Diphenylmethane	0.960	0.33
8. 3,3′-Dimethyl-4,4′ diphenylmethane	0.165	0.070
9. 2,4-Tolylene	1.98	0.166

Series II: Reaction with Ethanol in Toluene, 30°

	$k_1 \cdot 10^2$	$k_2 \cdot 10^2$ units unknown
1. Phenyl isocyanate	2.39	...
2. 3,5-Tolylene diisocyanate	9.20	0.362
3. 4,4′-Diphenylmethane	6.24	2.25

Series III: Reaction with Methanol in Di-n-butyl Ether,
0.0306N Triethylamine Catalyst, at 20°

	$k_1 10^2(1 \text{ mol.}^{-1} \text{ min.}^{-1})$
1. Phenyl isocyanate	22.6
2. p-Methoxyphenyl isocyanate	9.06
3. p-Tolyl isocyanate	12.25
4. p-Nitrophenyl isocyanate	~3,000

Series IV: Reaction with Ethanol in Carbon Tetrachloride,
0.072N Triethylamine catalyst, at 28°

	$k_1 10^4(1 \text{ mol.}^{-1} \text{ sec.}^{-1})$
1. Phenyl isocyanate	43.30
2. p-Tolyl isocyanate	18.42
3. o-Tolyl isocyanate	5.16

Series V: Reaction with Ethanol in Carbon Tetrachloride,
at 28°

	$k_1 10^4(1 \text{ mol.}^{-1} \text{ sec.}^{-1})$
1. Phenyl isocyanate	2.50
2. 2,4-Tolylene diisocyanate	10.70
3. 2,6-Tolylene diisocyanate	2.46

Series VI: Reaction with 1-Butanol in Toluene, at 25°

|	$k_1 10^3$	$k_2 10^3(1 \text{ mol.}^{-1} \text{ sec.}^{-1})$
1. m-Phenylene diisocyanate	1.7	0.17
2. 2,4-Tolylene diisocyanate	0.58	...
3. 4-Chloro-1,3-phenylene diisocyanate	5.8	0.75
4. 4,6-Dichloro-1,3-phenylene diisocyanate	8.4	0.92

for the compounds in series III, in which the rate constants vary by approximately 300 fold.

Series IV,[5] V[5] and VI.[6] Fig. 3 shows that the data of series IV and V are correlated within acceptable

(5) J. C. Kogon, *J. Org. Chem.*, **24**, 438 (1959).

precision by the parallel lines obtained from series I. Since the rate constant for phenyl isocyanate was not determined in series VI, the relative rate constant values were determined by use of the rate constant for m-phenelene diisocyanate in series VI and its relative rate constant in series I. The rate constants for the isocyanates with two ortho groups have been omitted.

TABLE II
SUBSTITUENT CONSTANTS

Substituent	σ Value	Source
m-NCO	0.43	Cmpd. I-4
p-NCO	0.35	I-5
p-(CH₂◯NCO)	0.04	I-7
m-NHCOOnBu	0.06	I-4
	0.01	I-6
	0.04	I-9
	0.02	VI-1
	0.05	VI-4
pNHCOOnBu	−0.05	I-5
p-(CH₂◯NHCOOnBu)	−0.05	I-7
p-(CH₂◯NHCOOC₂H₅)	0.01	II-3
o,p-CH₃	−0.17	Ref. 1
m-CH₃	−0.07	Ref. 1
o,p-Cl	0.23	Ref. 1
p-OCH₃	−0.27	Ref. 1
p-NO₂	1.27	Ref. 1

DISCUSSION

The data of the sterically unhindered aryl isocyanates in every reaction series follow the Hammett linear free-energy relationship with acceptable precision. An *ortho*-methyl group causes a decrease in the rate constant by a factor of approximately 0.34.

The data for 2,4-tolylene diisocyanate deserve special comment. Most authors[5-7] have assumed that the reactivity of the *para*-isocyanato group is about 10 times that of the *ortho* group, whereas others[2] have considered them to be of equal reactivity. These assumptions simplified the mathematical analyses of the rate data. It will now be shown that in the light of this paper, the *para*-isocyanato group is computed to be 2.67 times as reactive as the *ortho* group.

Considering the m- and p-σ values to consist of contributions of inductive and resonance effects,[8] the resonance effects of a *meta*-isocyanato group is

(6) J. J. Tazuma and H. K. Latourette, presented before the Division of Paints and Plastics at the 130th national meeting of the American Chemical Society, Atlantic City, N. J., September 1956.

(7) M. Morton and M. A. Deisz, presented before the Division of Paints and Plastics at the 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September 1956.

(8) R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958).

very small. Furthermore, the steric inhibition of resonance of the *ortho*-isocyanato group by the methyl group is considered to be negligible. Hence, the m-σ value that is used in the evaluation of the reactivity of the *para*-isocyanato group by the *ortho*-isocyanato group is unaffected by the presence of the methyl group. Therefore, the calculated k/k_0 value for the *para* group is 2.75 using the determined value of ρ and the appropriate σ values from Table II. The k/k_0 value for the *ortho* group is 1.03, using the average of the experimental data of compounds I-6 and V-3 (or 0.93 using the data from the "ortho" line of Fig. 1). Thus, the expected initial k/k_0 value for 2,4-tolylene diisocyanate is 3.78. A comparison of the experimental log k/k_0 values to the calculated one is shown in Table III.

TABLE III

VALUES OF RELATIVE RATE CONSTANTS FOR 2,4-TOLYLENE DIISOCYANATE

log k/k_0	Source
0.577	Calculated
0.688	Cmpd. I-9
0.631	Cmpd. V-2
0.562	Cmpd. VI-2

The agreement between the calculated and experimental values, which were derived under various conditions, is rather striking and within 0.1 log units which is the accepted limit of accuracy for this type of correlation. Thus, it is concluded that the ratio of reactivity of the *para* to the *ortho* group is about 2.67 to 1. The difference in reactivity of one order of magnitude that has been previously assumed does not apply to these groups, but is the ratio of the sum of the reactivities of both isocyanato groups compared to that of the *ortho*-isocyanato group when the *para*-substituent is a carbamide and not an isocyanato group.

Further corroboration for this approach lies in the similar explanation of the value for the rate constant of 4-chloro-1,3-diphenylene diisocyanate (compound VI-3). The difference between the experimental and calculated log k/k_0 values of 4,6-dichloro-1,3 phenylene diisocyanate (compound VI-4) is taken as the steric effect due to an *ortho*-chloro group. Hence, the expected k/k_0 values for the *para*- and *ortho*-isocyanato groups of compound VI-3 are 13.0 and 10.8, respectively, resulting in an initial relative rate constant of 23.8 (1.377 log units) *vs.* the experimental value of 36.5 (1.562 log units). Considering the scarcity of applicable data in this series, the agreement is quite good and again emphasizes the fact that the two isocyanato groups have reactivities of the same order of magnitude.

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Bisacylation of 4-Pyrones

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In a recent paper[1] a method describing the acylation of 4-pyrones under the catalytic influence of trifluoroacetic acid has been described. This contribution represents an elaboration of that method in which bisacylation is accomplished. The procedure, although relatively simple, produces the diketones in high yield and remarkably free of polymerized contaminants.

Bisacylation of 4-pyrones in the presence of trifluoroacetic acid appears to be nonspecific in the orientation and the acyl groups are apparently put on any position available on the pyrone nucleus.

The bisacylated compounds, I-A–G, are given in Table I. Several derivatives of compound I-A, a relatively simple substance and illustrative of the nature of this type of compound, are given in confirmation of its generalized structure as compounds III and IV.

Included in this communication are several instances in which either acid anhydrides or *p*-bromo phenacyl bromide have been induced to react with pyrones. These compounds are listed in Table II as the II-A–C Series.

Attempted reduction of compounds I-B, -D, -E, and -F under the conditions of the Meerwein-Pondorf-Verley reaction failed in every case. The analytical results indicated that the pyrone had been fragmented and the pyrone structure destroyed.

Reduction of compounds I-A, -D and -E and II-A and -B with potassium borohydride in absolute ethanol was fairly successful in that compounds I-D and II-B were reduced as expected. The three other compounds gave analytical results which could not be justified. Infrared data are given for most of the new compounds listed in Tables I and II in Table III.

EXPERIMENTAL[2]

Preparation of compounds I-A–G *series.* A mixture consisting of 0.2 mol. of the acyl halide, except in the case of I-E in which 0.3 mol. of benzoyl chloride was used, 0.1 mol. of the pyrone and 35 ml. trifluoroacetic acid was refluxed for 30 min. or sufficiently longer so that hydrogen chloride was no longer evolved. The mixture was then diluted with 150 ml. of water, cooled, and filtered. The sample was dried in air and the analytical sample obtained by recrystallizing the compound once from boiling heptane.

The isolation of compound I-G was handled somewhat differently in that after the reaction mixture was diluted with water the solution was neutralized with sodium bicarbonate and extracted with benzene. The substance was

(1) L. L. Woods and P. A. Dix, *J. Org. Chem.* **24**, 1126 (1959).

(2) All analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J. All melting points were determined on a Fisher-Johns melting point assembly.

TABLE I

Pyrone	Acyl Halide	Yield %	M.P.°	Formula	Calculated		Found	
					C	H	C	H
I-A 2,6-Dimethyl-4-pyrone	p-Tolyl chloride	96	177–178	$C_{23}H_{20}O_4$	76.64	5.59	76.29	5.29
I-B 2,6-Dimethyl-4-pyrone	Cinnamoyl chloride	85	120	$C_{25}H_{20}O_4$	78.10	5.24	77.64	5.51
I-C 2,6-Dimethyl-4-pyrone	Benzoyl chloride	99	111–113	$C_{21}H_{16}O_4$	75.89	4.85	76.11	4.98
I-D Kojic acid diacetate	Benzoyl chloride	100	119–120	$C_{24}H_{18}O_8$	66.35	4.17	66.09	4.35
I-E α-Chloro-α-deoxy kojic acid	Benzoyl chloride	100	110	$C_{27}H_{17}ClO_6$	68.57 Chlorine 7.49	3.59	68.87 7.27	3.38
I-F Benzodihydro-4-pyrone	Benzoyl chloride	61	115–117	$C_{23}H_{16}O_4$	77.51	4.52	77.07	4.74
I-G Kojic acid diacetate	Acetyl chloride	17	121	$C_{14}H_{14}O_8$	54.19	4.54	53.94	4.29

TABLE II

Pyrone	Anhydride or Phenacyl halide	Yield, %	M.P.°	Formula	Calculated		Found	
					C	H	C	H
II-A 2,6-Dimethyl-4 pyrone	Phthalic anhydride	60	133.5	$C_{16}H_{12}O_6$	66.17	4.44	66.42	4.12
II-B Kojic acid diacetate	Benzoic anhydride	96	144–145	$C_{17}H_{14}O_7$	61.81	4.27	61.57	4.40
II-C 2,6-Dimethyl 4-pyrone	p-Bromo phenacyl bromide	90	113	$C_{16}H_{13}O_3Br$	56.09	4.07	56.47	4.27

TABLE III

INFRARED DATA[a]

Sample	Wave Number cm.$^{-1b}$
I-A	2985, 2857, 1661 (B), 1610, 1577, 1422, 1319, 1282, 1183, 1117
I-B	3077 (VB), 1761, 1675 (B), 1621, 1488, 1445, 1418, 1339, 1307, 1282, 1222, 1070
I-D	2778 (VB), 1681 (B), 1600, 1577, 1449, 1418, 1321, 1290 (B), 1183, 925.
I-E	3067–2757 (VB), 1733 = shoulder, 1689 (B), 1603, 1449, 1422, 1321, 1285 (B), 1263, 1248, 1202, 934
I-F	3376, 3106, 2817, 2667, 2538, 1675 (B), 1600, 1580, 1449, 1420, 1321, 1287 (B), 1179, 935
II-A	2008, 1848, 1754 (VB), 1695 = shoulder, 1613, 1462, 1353, 1255 (B), 1109, 869
II-B	3067, 1730, 1661, 1631, 1597, 1431 = shoulder, 1427, 1370, 1333, 1252 (VB), 1215, 1143, 1053, 1021

[a] Significant absorption bands of some of the compounds listed in Tables I and II measured in wave number cm.$^{-1}$ on a Beckmann IR-5 instrument using KBr pellets. [b] B = broad, VB = very broad.

obtained by removal of the solvent over a steam bath then recrystallized twice from heptane.

Preparation of compounds of II-A-C series. The reactants were mixed in the same mol. proportions along with 25 ml. of trifluoroacetic acid. The reflux period for compounds II-A and -B was 1 hr. and for II-C was 5 hr. The procedure for the purification of the substances was accomplished by recrystallization first from ethanol then from heptane.

2,6-Dimethyl-3,5-di(p-tolyl)-4-pyridone (III). Four grams of I-A was placed in 15 ml. absolute alcohol and warmed to dissolve the compound. To this mixture 10 ml. of concentrated ammonium hydroxide was added. Storage of the solution overnight in the refrigerator produced crystals which

were filtered, dried in air, and recrystallized once from heptane, m.p. 158–159.

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 76.02; H, 5.88; N, 3.89. Found: C, 76.24; H, 5.69; N, 3.67.

Malononitrile derivative of I-A (IV).[3] Three grams of I-A along with 1.5 g. malononitrile was refluxed for 1 hr. in 25 ml. acetic anhydride then poured into 400 ml. of ice water. The precipitate, when dried in air, was recrystallized twice from heptane, m.p. 160.

Anal. Calcd. for $C_{32}H_{20}N_6O$: N, 16.65. Found: N, 16.49.

Reduction of compounds I-D and II-B with potassium borohydride. Three grams of the acylated compound was mixed with 30 ml. of ethanol and then 3 g. powdered potassium borohydride was gradually sifted in while the mixture was magnetically stirred. The retaining flask was then loosely stoppered with a cotton plug. After standing overnight the mixtures were each treated with 50 ml. of water to which 10 ml. of concentrated hydrochloric acid had been added. The mixtures were stored in the freezer overnight to produce a precipitate which when dried in air weighed 1.3 g. for II-B. Sample I-D did not form a precipitate, so the solution was extracted with ethyl acetate and the solvent removed over a steam bath to give nearly 4 g. of brown crystals. Both samples were purified by recrystallizing the crude compounds from boiling heptane: m.p. I-D, 112.5–114, m.p. II-B 153–155.

Anal. Calcd. for $C_{24}H_{22}O_8$ compound I-D: C, 65.74; H, 5.05. Found: C, 65.49; H, 4.82. Calcd. for $C_{17}H_{16}O_7$ compound II-B: C, 61.44; H, 4.85. Found: C, 61.27; H, 4.59.

(3) L. L. Woods, *J. Am. Chem. Soc.,* **80**, 1440 (1958).

Derivatives of Sulfenic Acids. XXXV. The Reaction of 2,4-Dinitrobenzenesulfenyl Chloride with Vinyl Acetate[1]

Norman Kharasch and Hans H. von Duesel

The reactions of 2,4-dinitrobenzenesulfenyl chloride (I) with olefins, acetylenes and numerous other reagents have now been studied in considerable detail,[2] but the reaction with vinyl esters has not been reported.

It has now been shown that the sulfenyl chloride (I) reacts with vinyl acetate to yield *trans*-1-acetoxy-2-(2'-4'-dinitrophenylthio)ethene, II, as the only isolatable product, in about 40% yield. The reaction was best carried out in glacial acetic acid as solvent. None of the 1:1 adduct was found, suggesting that the intermediate episulfonium ion is stabilized by electron release from the ether oxygen of the acetoxy group (compare Orr and Kharasch[3]). The relatively low yield of adduct appears to be caused by some attendant polymerization.

IIIA = semicarbazone
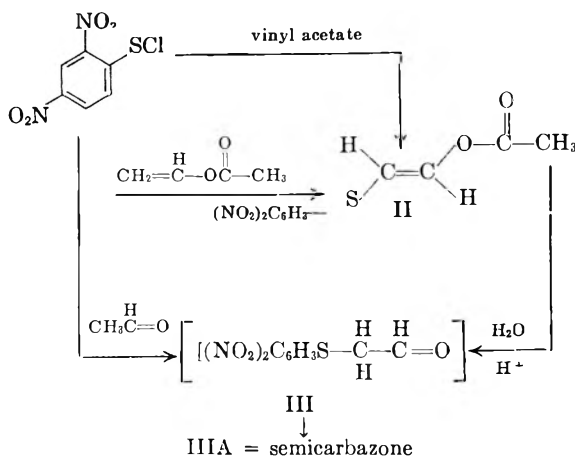
The proof of structure of II is based on (a) elementary analysis, (b) the infrared spectrum which showed the vinyl acetate absorption at 1755 cm.$^{-1}$ and the *trans*-hydrogen absorption at 965 cm.$^{-1}$, and (c) hydrolysis of II to the aldehyde, III, which was characterized as the semicarbazone III A (and also obtained via I and acetaldehyde).

While the reaction of I with numerous ketones gives excellently crystalline derivatives, III was generally obtained as an oil and could not be obtained as a good crystalline product. Preliminary experiments with several other aldehydes also

failed to give satisfactory solid derivatives—which is an unusual circumstance for the products derived from I.[4] The hydrolysis of II to III must be conducted in acid media, since in presence of alkali, III apparently undergoes rapid polymerization. An attempt to oxidize III to the corresponding acid with alkaline permanganate was not successful, as scission of the Ar-S bond occurred under the conditions attempted to give only dinitrophenol.

It was of interest to compare the rate of reaction of I with vinyl acetate, relative to that with cyclohexene, styrene, *etc.*[5] The reaction in dry acetic acid, at 35°, followed second-order kinetics and gave a rate constant (1. × mol.$^{-1}$ × min.$^{-1}$) of 2.94 × 10^{-4}, which shows it to be only about $^1/_{300}$ as fast as styrene, for which the corresponding k is 888 × 10^{-4} (1. × mol.$^{-1}$ × min.$^{-1}$), and approximately $^1/_{3000}$ that of cyclohexene,[5] under the same conditions. A qualitative run with vinyl *n*-butyl ether also showed this reaction to proceed slowly, indicating an inductive deactivation of the olefin bond by the alkoxy group.

EXPERIMENTAL

trans-(1-Acetoxy)-2(2',4'-dinitrophenylthio)ethene, II. —2,4-Dinitrobenzenesulfenyl chloride (23.4 g.; 0.01 mole), recrystallized from carbon tetrachloride, was dissolved in 35 ml. glacial acetic acid, and to this was added 8 ml. (0.09 mole) of vinyl acetate (Matheson Company, 99.5%, stabilized product). The mixture was let stand two days at room temperature, then evaporated to half volume, at room temperature and reduced pressure. The crude product (1.23 g., 43%) melted at 152°, and this was raised to 159°, by recrystallizing from a 1:1 mixture of 95% alcohol and ethyl acetate.

Anal. Calcd. for $C_{10}H_8O_6N_2S$: C, 42.3; H, 2.82. Found: C, 42.13; H, 3.02.

2,4-Dinitrophenylthioacetaldehyde. II (568 mg., 0.002 mole) was added to a solution made from 10 ml. water, 10 ml. 95% alcohol and 1 ml. concd. sulfuric acid. The mixture was heated at reflux until all of the insoluble material disappeared (about 1 hr.). The hot solution was filtered and cooled, whereupon formation of some oily layer was noted. The acidified aqueous solution was extracted with methylene chloride and the extract dried with anhydrous magnesium sulfate (calcium chloride as desiccant seemed to promote polymerization of III). After the solvent was evaporated, there remained a dark oily mass, which was re-extracted with ethanol. Evaporation of the alcohol left the aldehyde as a wax-like, yellow mass of crystals, 320 mg. (66%); m.p. 49°.

The aldehyde could not be obtained in analytically pure condition, as it was too subject to thermal decomposition to distill at reduced pressure, while recrystallization from other solvents gave only oily precipitates. The infrared spectrum showed the carbonyl band at 1730 cm.$^{-1}$

2,4-Dinitrophenylthioacetaldehyde semicarbazone. III (224 mg., 0.001 mole) was dissolved in 10 ml. ethanol and diluted with water until the solution became turbid. The turbidity was dispelled by adding a few drops of ethanol, then 1 g. of semicarbazide hydrochloride and 1.5 g. sodium acetate, with vigorous shaking of the reaction mixture. The reaction vessel was placed in a beaker of boiling water and left there

(1) This study was carried out under sponsorship of the Office of Ordnance Research, United States Army, Contract DA-04-495-Ord. 901.

(2) For a summary of references *Cf.* N. Kharasch, in Organic Sulfur Compounds, Vol. I., Pergamon Press, New York-London, 1960.

(3) W. L. Orr and N. Kharasch, *J. Am. Chem. Soc.*, 78, 1201 (1956).

(4) N. Kharasch, *J. Chem. Ed.*, 33, 585, 1956; also R. B. Langford and D. D. Lawson, 34, 510 (1957).

(5) D. R. Hogg and N. Kharasch, *J. Am. Chem. Soc.*, 78, 2728 (1956).

until it cooled to room temperature. Scratching and cooling induced precipitation of the product, which was collected by filtration and recrystallized from a mixture of methanol and water. Yield: 249 mg; 83%; m.p. (dec.) 202°.

Anal. Calcd. for $C_9H_9N_5O_6S$: N, 10.71. Found: N, 10.45.

Kinetic measurements of the reaction of I with vinyl acetate, in dry acetic acid, at 35°. The determination of the second order constant, k_2, was made in the manner described by Orr and Kharasch, in dry acetic acid at 35 ± .02°, and gave a value for k_2 (l. × mol^{-1} × min^{-1}) of 2.94 × 10^{-4} ± 4%.

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Alkyl 6-Alkoxytetrahydropyran-2-carboxylates[1]

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Received June 10, 1959

The preparation of ethyl 3,4-dihydro-2*H*-pyran-2-carboxylate[3] and the subsequent reaction with phenols to prepare ethyl 6-aryloxytetrahydropyran-2-carboxylates[4] have been reported. We wish to report the synthesis of several alkyl 6-alkoxytetrahydropyran-2-carboxylates (II) and the 2,5-dimethyl derivatives. These materials are prepared readily by the reaction of 7-oxo-6,8-dioxabicyclo [3.2.1.] octane (I) or its 1,4-dimethyl derivative with the appropriate alcohol in the presence of sulfuric acid as a catalyst and isopropyl ether as an entrainer to remove the coproduct water.
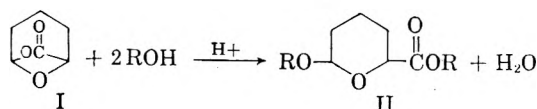
The starting lactones may be prepared from acrolein dimer or methacrolein dimer by oxidation with silver oxide[3] or oxygen,[5] by the Tishchenko reaction,[6] or by the Cannizzaro reaction.[7]

The reactant combinations that were used and the results that were obtained are shown in Table I. Good to excellent yields were obtained in all cases and the products from a single distillation were of high purity.

As a means of obtaining esters for which the alkyl groups of the ester and of the acetal functions

(1) Presented in part before the Southeastern Regional Meeting of the American Chemical Society at Gainesville, Fla., December 1958.

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(3) R. R. Whetstone and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5280 (1951).

(4) R. R. Whetstone, U. S. Patent **2,574,444** (1951).

(5) A. E. Montagna and L. V. McQuillen, British Patent **782,430**, (1957).

(6) C. W. Smith, U. S. Patent **2,537,921** (1957).

(7) G. G. Stoner and J. S. McNulty, *J. Am. Chem. Soc.*, **72**, 1531 (1950).

were different, two of the acetal-esters were subjected to base-catalyzed transesterification. The reactions were conducted in a standard manner and the equilibrium was shifted by removing the exchanged alcohol by distillation. The reactant combinations used and the results obtained are summarized in Table II.

Whetstone and Ballard[3] reported that, in their attempts to isolate the free 3,4-dihydro-2*H*-pyran-2-carboxylic acid (III) by acidification of the sodium salt and extraction with ether, a viscous, water-soluble product was obtained. The acid was unstable and resinified on standing but immediate distillation provided the lactone, 7-oxo-6,8-dioxabicyclo[3.2.1]octane (I). In addition to the extracted acid, these workers isolated also a viscous solid by evaporation of the aqueous solution. On the basis of the analytical results, this material was considered to be a mixture of the hydroxy acid (IV) and 5-formyl-2-hydroxypentanoic acid (V). These materials were presumed to have formed by the acid-catalyzed hydration of the unsaturated acid (III).
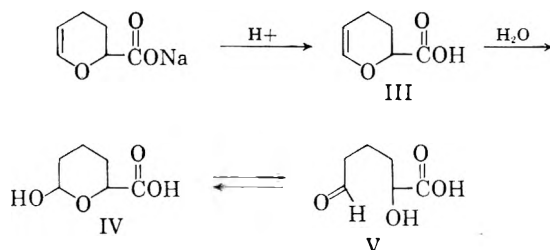
We have encountered this same problem in our work even when the unsaturated acid (III) was isolated from its sodium salt under conditions designed to minimize hydration of the acid (80% acidification at 0° with mineral acid and in the presence of solvent to immediately extract the unsaturated acid.) The isolated acid resinified rapidly to form a clear, tacky solid and appeared to be in major part a homopolymer of the unsaturated acid (III), based upon analyses (elemental, functional group, and infrared) and the fact that strong heating converted the polymer to the monomeric lactone.
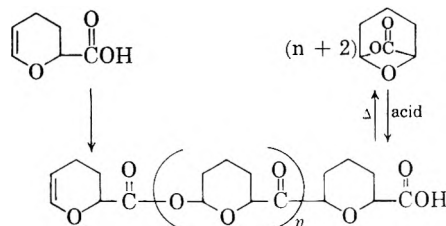
The lactone (I) polymerized in a few hours in the presence of ferric chloride or aluminum bromide to yield a water-insoluble polymer which appeared very similar to that obtained from the unsaturated acid (III).

The 6-hydroxytetrahydropyran-2-carboxylic acid (IV) was isolated in low yield from the aqueous solution remaining after the sodium salt had been acidi-

TABLE I

PREPARATION OF "SYMMETRICAL" ALKYL 6-ALKOXYTETRAHYDROPYRAN-2-CARBOXYLATES

Lactone, mol.	Alcohol, mol.	Reflux time, hrs.	Product Tetrahydropyran-2-carboxylate	Yield, %	B.P. °C./mm. Hg	n_D^{20}	Sp. Gr. 20/15.6°	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Sap. Equiv. Calcd.	Found
5.6[a]	Ethyl, 20.0	25	Ethyl 6-Ethoxy-	88.7	86/2.0	1.4405	1.046	59.4	59.4	9.0	9.1	202	201
1.4[b]	Ethyl, 3.7	...	Ethyl 6-Ethoxy-	85.0	...	...	...	...	...	...	...	...	...
3.0[a]	2-Ethylhexyl, 10.0	7.0	2-Ethylhexyl 6-(2-Ethylhexoxy)-	88.7	165/0.4	1.4528	0.9405	71.2	71.3	11.4	11.2	370	368
3.0[a]	OXO-decyl, 10.0	7.5	OXO-decyl 6-OXO-decyloxy-	91.1	205–220/0.7	1.4589	0.933	73.2	73.1	11.8	12.0	426	422
1.0[a]	Allyl, 8.0	30	Allyl 6-Allyloxy-	82.0	01/0.5	1.4618	1.0261	63.7	63.4	8.0	8.2	226	227
1.0[a]	Propargyl, 6.0	1.5	Propargyl 6-Propargyloxy-	81.5	128/1.0	1.4825	1.136	64.9	64.6	6.4	6.5	222	211
2.6[c]	Ethyl, 8.4	27	Ethyl 2,5-Dimethyl-6-ethoxy-	93.5	75/0.6	1.4366	1.001	62.6	62.5	9.6	9.8	230	230

[a] 7-Oxo-6,8-dioxabicyclo [3.2.1] octane. [b] Crude 3,4-dihydro-2H-pyran-2-carboxylic acid. [c] 1,4-Dimethyl-7-oxo-6,8-dioxabicyclo [3.2.1] octane.

TABLE II

PREPARATION OF "UNSYMMETRICAL" ALKYL 6-ALKOXYTETRAHYDROPYRAN-2-CARBOXYLATES

Starting tetrahydropyran-2-carboxylate, moles	Alcohol, mol.	Product Tetrahydropyran-2-carboxylate	Yield, %	B.p. °C./mm. Hg	n_D^{20}	Sp. Gr. 20/15.6°	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Sap. Equiv. Calcd.	Found
Ethyl 6-Ethoxy-, 0.5	2-Ethylhexyl, 3.0	2-Ethylhexyl 6-Ethoxy-	76.8	144/2.0	1.4482	0.974	67.1	67.5	10.6	10.7	286	282
Ethyl 6-Ethoxy-, 0.5	Allyl, 2.0	Allyl 6-Ethoxy-	68.5	85/1.0	1.4522	1.054	61.6	61.4	8.5	8.7	214	215
Allyl 6-Allyloxy-, 0.63	2-Ethylhexyl, 3.1	2-Ethylhexyl 6-Allyloxy-	58.8	141/1.0	1.4565	0.983	68.4	68.4	10.1	9.9	298	298
Allyl 6-Allyloxy-, 1.5	OXO-decyl, 4.5	OXO-decyl 6-Allyloxy	89.5	154/0.7	1.4599	0.973	69.9	69.5	10.5	10.7	326	321

fied (with excess mineral acid) and the unsaturated acid (III) had been removed by extraction. This same hydroxy acid was prepared in essentially quantitative yield by the acid-catalyzed hydration of 7-oxo-6,8-dioxabicyclo[3.2.1]octane.
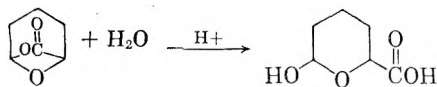
EXPERIMENTAL[8]

7-Oxo-6,8-dioxabicyclo[3.2.1]octane and 1,4-dimethyl-7-oxo-6,8-dioxabicyclo[3.2.1]octane. These materials were prepared *via* the silver-catalyzed oxidation with molecular oxygen of acrolein dimer and methacrolein dimer, respectively. The oxidation has been reported elsewhere,[5] and involves the oxidation of the aldehydes with molecular oxygen with a silver catalyst in an aqueous solution of sodium hydroxide. The products of the oxidation are the salts of the acids from which the lactones are recovered by acidification, extraction, and distillation.

Esterification procedure. For the preparation of the "symmetrical" acetal-esters, the lactone and alcohol were used in the quantities shown in Table I. These materials along with the sulfuric acid catalyst (0.5 to 0.75 weight %) were charged to the kettle of a distillation assembly which carried a liquid-liquid separating head. Sufficient isopropyl ether was added (200–400 ml.) to insure ready separation of the water of reaction during the reflux period. At the completion of the water removal, the mixtures were allowed to stand at room temperature for several hours, usually overnight. The sulfuric acid was neutralized with sodium ethoxide or sodium acetate and the mixtures distilled to recover the alkyl 6-alkoxytetrahydropyran-2-carboxylates.

Transesterification procedure. The transesterifications shown in Table II were conducted in a standard manner using sodium methoxide or sodium ethoxide as a catalyst. The acetal-ester and alcohol were mixed in the proportions shown in Table II and 0.5% catalyst (sodium methoxide or sodium ethoxide) by weight of the reactants was added. The mixtures were distilled to remove most of the lower boiling, exchanged alcohol at atmospheric pressure. The last traces of the exchanged alcohols were removed under reduced pressure followed by removal of the excess reactant alcohol and the product ester. For the last reactant combination shown in Table II, the mixture containing the catalyst was permitted to stand 16 hr. at room temperature. The coproduct allyl alcohol was then removed by distillation at essentially room temperature under reduced pressure. Inasmuch as distinctly superior results were obtained for this experiment as compared to the other reactant combinations, this may be the preferred method of performing this transesterification.

Poly(3,4-dihydro-2H-pyran-2-carboxylic acid). Four hundred g. of aqueous solution containing 100 g. of sodium 3,4-dihydro-2H-pyran-2-carboxylate which was neutral to phenolphthalein, was acidified with 26.2 g. of concentrated sulfuric acid (80% of theory) in 130 ml. of water. The acidification was conducted at 0° and in the presence of 300 ml. of ethyl ether. The aqueous layer was removed and extracted twice with 200 ml. of ether. The combined extracts were distilled (steam bath) under reduced pressure to remove the ether. The residue amounted to 59 g. and was a colorless, viscous liquid which was water-soluble and evolved carbon dioxide upon treatment with aqueous sodium bicarbonate. Immediate titration with standard base to a phenolphthalein end point gave a purity of approximately 50.5% as the monomeric acid. The value was somewhat uncertain due to the fading end point. Determination of the purity by bromina-

(8) All melting points are corrected, boiling points are uncorrected.

tion (0°) gave an approximate value of 45% purity. The infrared spectrum contained discrete absorption bands at 3.7, 5.7, 7.7, and 10.6μ characteristic of the carboxyl group and at 6.04μ characteristic of the unsaturation. In a few hours the material had resinified to a nonpourable state and was tacky.

Anal. Calcd. for $C_6H_8O_3$: C, 56.20; H, 6.29; Sap. Equiv., 128.1. Found: C, 56.70; H, 6.17; Sap. Equiv. 135.

After the polymer had stood for approximately 2 months, 31.8 g. was heated (oil bath at 160 to 200°) under 3 mm. of pressure. The vapors were passed through a gooseneck and condensed to provide 24 g. of a water-insoluble liquid. This material was identified as the lactone, 7-oxo-6,8-dioxabicyclo[3.2.1]octane, on the basis of its boiling point (65°/3 mm.; lit.[3] value is 63/3 mm.) and refractive index (n_D^{20} 1.4582; lit.[3] value is n_D^{20} 1.4587).

6-Hydroxytetrahydropyran-2-carboxylic acid. An aqueous solution of 430 ml. remaining from the acidification with excess sulfuric acid of the sodium 3,4-dihydro-2H-pyran-2-carboxylate and extraction with isopropyl ether was evaporated to dryness at room temperature. On the basis of the acid balance, the aqueous solution could have contained a maximum of 30 g. of the 6-hydroxytetrahydropyran-2-carboxylic acid. The light colored, tacky solid was extracted several times with ethyl ether and the extracts evaporated. The white solid was recrystallized from ethyl acetate to provide 2.5 g. of white prisms or needles believed to be 6-hydroxytetrahydropyran-2-carboxylic acid and which melted at 89.5–90.5°.

This same acid was prepared as follows: a suspension of 25.6 g. (0.2 mol.) of 7-oxo-6,8-dioxabicyclo[3.2.1]octane, 20 ml. of water, and 7.3 ml. of 0.5N sulfuric acid was shaken at room temperature. After several minutes the solution temperature increased to about 40° accompanied by a complete solution of the organic phase. The solution was neutralized with 7.3 ml. of 0.5N sodium hydroxide and the water evaporated below 30° using a vacuum desiccator to provide 29.2 g. of 6-hydroxytetrahydropyran-2-carboxylic acid of m.p. 89.0–90.5°. A melting point of 89.0–90.5° was observed for a mixture of the acids isolated from the two sources. The infrared spectrum contained no absorption for ethylenic unsaturation but did contain strong bands characteristic of the —OH and —COOH groups.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.3; H, 7.0; Neut. Equiv. 146. Found: C, 49.0; H, 7.0; Neut. Equiv., 147.

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The Preparation of Certain Amino-Substituted Perfluoroalkyl-s-Triazines

JOHN T. SHAW AND FRANK J. GROSS

As part of a study of cellulose-reactive materials, the preparation of a number of amino-substituted perfluoroalkyl-s-triazines was undertaken. It is known that the *N*-methylol derivatives of 2-alkyl-4,6-diamino-s-triazines can be used as crosslinking

TABLE I

PERFLUOROALKYL-s-TRIAZINES
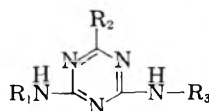
R$_1$	R$_2$	R$_3$	M.P. °C.	Calcd.			Found			Yield
				C	H	N	C	H	N	
H	CF$_3$	H	318–321^a	26.8	2.25	39.1	26.9	2.23	38.8	90
H	CF$_3$CF$_2$	H	255–256	26.2	1.76	30.5	26.2	1.75	30.7	73
H	CF$_3$(CF$_2$)$_6$	H	177–179	25.0	0.80	14.6	25.0	1.37	14.7	80
C$_6$H$_5$^{b}	CF$_3$	H	185–186	47.1	3.16	27.4	47.2	3.15	27.5	81
p-ClC$_6$H$_5$^{b,c}	CF$_3$	p-ClC$_6$H$_5$	182–185	49.2^d	3.75	14.5	49.1	3.55	14.3	20
H	—(CF$_2$)—$_3$	H	>320	29.2	2.18		28.8	2.50		68

^{a} Sublimed. ^{b} For each mole biguanide, 2 moles of methyl trifluoroacetate and 1 mole sodium methoxide used. ^{c} Reactants shaken in autoclave for 24 hours at 100° before drowning in H$_2$O. ^{d} Product recrystallized from dioxane and retained 1 mole of dioxane of crystallization, C$_{16}$H$_{10}$Cl$_2$F$_3$N$_5$·C$_2$H$_4$O$_2$; Calcd. Cl, 14.5; Found: Cl, 14.6.

agents for cotton. It was, therefore, of interest to determine the effect of replacing the hydrogen atoms attached to the alkyl group with fluorine. The only compound of this type reported in the literature, 6 - amino - 4 - anilino - 2 - trifluoromethyl - s - triazine, was prepared by Overberger, Michelotti and Carabateas.[1]

In preparing the s-triazine derivatives, the general method reported by Thurston and Kaiser[2] of reacting biguanides with esters was followed. The reaction of unsubstituted biguanide with methyl esters of various perfluorocarboxylic acids was extremely clear-cut, and good yields of pure materials were obtained. In contrast, the reaction of monosubstituted biguanides with methyl trifluoroacetate required not only longer times, but also, in some cases, the presence of sodium methoxide. The reaction of a disubstituted biguanide with methyl trifluoroacetate required even more vigorous conditions: cyclization of 1,5-bis-(p-chlorophenyl)biguanide to the corresponding s-triazine derivative necessitated heating the reactants in methanol in an autoclave at 100° in the presence of sodium methoxide for 24 hr.

EXPERIMENTAL[3]

Materials. Methyl trifluoroacetate,[4] methyl pentafluoropropionate,[5] methyl heptafluorobutyrate,[6] methyl pentadecafluorocaprylate,[6] and dimethyl hexafluoroglutarate,[7] were all prepared by methods given in the literature.

(1) C. G. Overberger, F. W. Michelotti and P. M. Carabateas, *J. Am. Chem. Soc.*, **79**, 941 (1957).

(2) J. T. Thurston and D. W. Kaiser, U.S. Patent **2,535,968**.

(3) Melting points are uncorrected.

(4) E. Gryszkiewicz and J. Wnuk, *Rec. trav. chim.*, **66**, 413 (1947).

(5) D. R. Husted and A. H. Ahlbrect, *J. Am. Chem. Soc.*, **75**, 1605 (1953).

(6) A. R. Diesslin, E. A. Kauck and J. H. Simons, U. S. Patent 2,567,011 [*Chem. Abstr.*, **46**, 1376 (1952)].

(7) A. L. Henne and W. J. Zimmerschied, *J. Am. Chem. Soc.*, **67**, 1236 (1945).

n-Butylbiguanide hydrochloride. A mixture of 27.3 g. (0.25 mole) of butylamine hydrochloride and 21.0 g. (0.25 mole) of cyanoguanidine was stirred on the steam bath until fusion occurred and then at 130 ± 5° for 4.5 hr.

The cooled melt was taken up in boiling acetone and allowed to reflux for 1 hr. and upon cooling, there separated 16.6 g. (34.6%) of white crystals, m.p. 152–164°. Recrystallization from benzene ethanol raised the m.p. to 176–177.

Anal. Calcd. for C$_6$H$_{15}$N$_5$·HCl: C, 37.2; H, 7.82; N, 36.2. Found: C, 37.3; H, 8.19; N, 36.2.

1,5-Bis-p-chlorophenylbiguanide hydrochloride. The method we report is simpler and less time consuming than that given in the literature.[8] To a stirred slurry of 63.0g. (0.49 mole) of p-chloroaniline, 44.5 g. (0.50 mole) of sodium dicyanamide and 500 ml. of water at 90° was added dropwise over a period of .5 hr., 100 ml. of 4.9M HCl. The gray precipitate which formed was chilled and filtered after first adjusting the pH to 3 with conc. HCl. The crude p-chlorophenyldicyandiamide, I, after drying at 60° for 24 hr., weighed 80.8 g. (83.5%), m.p. 204–207, and was used in the next step without further purification. A stirred slurry of 30.0 g. (0.15 mole) of I, 21.0 g. (0.16 mole) of p-chloroaniline, 50 ml. of Cellosolve, and 250 ml. water was treated dropwise at 97° ± 3 with 25 ml. of 6.6M HCl over a 20-minute period. After completion of the addition of the acid, the solution was refluxed for 1.5 hr. and the precipitate collected after cooling and adjusting the pH to 3; 40.8 g. (74%) m.p. 251–253, lit.,[8] 250°.

4,6-Diamino-2-heptafluorobutyl-s-triazine. The preparation of this compound was typical of the N-unsubstituted diaminoperfluoroalkyl-s-triazines listed in Table I. To a solution of 26.2 g. (0.26 mole) of biguanide and 100 ml. of absolute methanol at 35° was added portion-wise with stirring 68.4 g. (0.3 mole) of methyl heptafluorobutyrate. The temperature of the reaction rose rapidly to the boil, and the rate of addition was such as to maintain a gentle boil. Within a few minutes after all the fluoroester had been added, a heavy white precipitate formed. The reaction mixture was cooled to room temperature and allowed to stir overnight before chilling, filtering and air drying. There was obtained 45.7 g. of a white solid, m.p. 202–204°; concentration of the mother liquor yielded an additional 9.0 g., total yield 75.6%. After recrystallizing from methanol, the product melted 203–204°.

Anal. Calcd. for C$_6$H$_4$F$_7$N$_5$: C, 25.8; H, 1.44; N, 25.1. Found: C, 26.0; H, 1.64; N, 25.2.

6-Amino-4-n-butylamino-2-trifluoromethyl-s-triazine. The preparation of this compound is typical of the N-substituted

(8) A. F. Crowther, F. H. S. Curd, D. W. Richardson and F. L. Rose, *J. Chem. Soc.*, 1636 (1948).

diaminoperfluoroalkyl-s-triazines listed in Table I, unless otherwise noted. A mixture of 3.86 g. (0.02 mole) of n-butylbiguanide hydrochloride, 1.18 g. (0.02 mole) of sodium methoxide, 2.76 g. (0.022 mole) of methyl trifluoroacetate, and 75 ml. of methanol was stirred at room temperature for 4 days, and then drowned in an excess of water. The white crystalline solid which formed from the initial oil weighed 2.75 g. (58.5%) and melted 98–100 .

Anal. Calcd. for $C_8H_{12}F_3N_5$: C, 40.9; H, 5.14; N, 29.8. Found: C, 41.1; H, 5.19; N, 29.6.

Acknowledgment. The authors wish to thank R. K. Madison for his helpful assistance, J. L. Gove for the infrared absorption data and O. E. Sundberg and his associates for the microanalyses.

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Reduction of Allylic Halides by Lithium Aluminum Hydride[1]

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The lithium aluminum hydride reduction of an allylic halide to the corresponding hydrocarbon has been used as a means of identification and characterization of allylic halides, especially geometrical isomers.[3] There is retention of configuration and no allylic rearrangement with this reaction when the allylic halogen atom is terminal. It has been noted, however, that 2,3,3-trichloro-1-butene gives trans-2,3-dichloro-2-butene[4] and 3,4-dibromo-1-butene gives trans-2-butene.[5] DeWolf and Young have suggested that this reaction goes by an S_N2' mechanism[6] and the conformational implications of this mechanism have been discussed by Hatch, Gardner and Gilbert.[5] This reaction has now been extended to include 3,4-dichloro-1-butene and two secondary-mono-allylic halides (3-chloro-1-butene and 3-bromo-1-butene).

The reduction of 3,4-dichloro-1-butene by lithium aluminum hydride in tetrahydrofuran gave the expected trans-2-butene as indicated by gas-liquid partition chromatography. 3-Chloro-1-butene was prepared along with its allylic isomer, trans-1-chloro-2-butene, by the addition of hydrogen

chloride to butadiene using concentrated hydrochloric acid.[7] Lithium aluminum hydride reduction of this chloride produced a mixture of hydrocarbons containing cis-2-butene (5%), butadiene (8%), trans-2-butene (18%) and 1-butene (69%). A similar mixture was obtained from 3-bromo-1-butene. The 3-bromo-1-butene was prepared by allylic rearrangement of trans-1-bromo-2-butene.

From these data it would appear that the prediction that secondary allylic halides react by an S_N2' mechanism[5] must be modified. The present indications are that at least one other halogen atom is required to be in the vicinity of the secondary allylic halogen to cause the reaction to go exclusively by this mechanism. The other halogen atom or atoms are also required for the reaction to be stereospecific.[5] The butadiene was formed by dehydrohalogenation caused by the lithium aluminum hydride.

Both trans-1-chloro-2-butene (crotyl chloride) and trans-1-bromo-2-butene (crotyl bromide) give trans-2-butene on reduction with lithium aluminum hydride. 1,4-Dichloro-2-butene prepared by the addition of chlorine to butadiene also gave the expected trans-2-butene[8] but a purchased sample of 1,4-dichloro-2-butene formed a mixture of products containing 71% cis-2-butene and 29% trans-2-butene. This dichloride apparently was produced from 1,4-butynediol by catalytic hydrogenation followed by conversion of the diol to the corresponding dichloride.

EXPERIMENTAL

3,4-Dichloro-1-butene. This dichloride was purchased from Columbia Organic Chemicals, Inc., Columbia, S.C., and purified by distillation: b.p. 42° (40 mm.); n_D^{25} 1.4615. Lit.[9] b.p. 123° (766 mm.); n_D^{20} 1.4630.

1,4-Dichloro-2-butene. A sample of 1,4-dichloro-2-butene was purchased from Columbia Organic Chemicals, Inc., and distilled: b.p. 72.5° (39 mm.); n_D^{25} 1.4872.[8] cis isomer b.p. 152.5° (758 mm.), n_D^{25} 1.4887; trans isomer b.p. 155.5° (758 mm.), n_D^{25} 1.4871. trans-1,4-dichloro-2-butene was synthesized along with 3,4-dichloro-1-butene by the addition of chlorine (45 g., 0.64 mole) to butadiene (31 g., 0.58 mole) in 200 ml. of chloroform at ice bath temperature. The 1,4-dichloro-2-butene was separated from its isomer by distillation: b.p. 74° (40 mm.); n_D^{25} 1.4863.

3-Chloro-1-butene and 1-chloro-2-butene. A mixture of 3-chloro-1-butene and trans-1-chloro-2-butene (crotyl chloride) was obtained by the treatment of butadiene (54 g., 1.00 mole) with an excess of 37% hydrochloric acid saturated with hydrogen chloride.[7] The reaction was carried out in a sealed tube at 25° for 36 hr. The organic layer was washed with a dilute sodium bicarbonate solution, dried and distilled. 3-Chloro-1-butene: b.p. 64° (760 mm.); n_D^{27} 1.4111. Lit.[7] b.p. 63.7° (748 mm.); n_D^{20} 1.4151.

trans-1-Chloro-2-butene: b.p. 84° (760 mm.); n_D^{27} 1.4292. Lit.[7] b.p. 84.8° (752 mm.); n_D^{25} 1.4327.

3-Bromo-1-butene. 3-Bromo-1-butene was obtained as a mixture with trans-1-bromo-2-butene by permitting the

(1) Presented in part at the 136th meeting of the American Chemical Society, Atlantic City, September 13–18, 1959.

(2) Present address: The Dow Chemical Company, Freeport, Texas.

(3) L. F. Hatch and R. H. Perry, *J. Am. Chem. Soc.*, **71**, 3262 (1949).

(4) L. F. Hatch and J. J. D'Amico, *J. Am. Chem. Soc.*, **73**, 4393 (1951).

(5) L. F. Hatch, P. D. Gardner and R. E. Gilbert, *J. Am. Chem. Soc.*, **81**, 5943 (1959).

(6) R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 753 (1956).

(7) L. F. Hatch and S. S. Nesbit, *J. Am. Chem. Soc.*, **72**, 727 (1950).

(8) K. Mislow and H. M. Hellman, *J. Am. Chem. Soc.*, **73**, 244 (1951).

(9) L. N. Owen, *J. Chem. Soc.*, 241 (1949).

trans-1-bromo-2-butene to equilibrate at room temperature. The mixture had a refractive index of n_D^{25} 1.4690. This refractive index indicated a mixture containing 46% 1-bromo-2-butene and 54% 3-bromo-1-butene.[10] The infrared spectrum of the mixture indicated the presence of only these two isomers.

1-Bromo-2-butene. 1-Bromo-2-butene (crotyl bromide) was purchased from Columbia Organic Chemicals, Inc., and used without further purification. n_D^{25} 1.4788. Lit.[10] n_D^{25} 1.4794.

Lithium aluminum hydride reductions. The lithium aluminum hydride reduction procedure was similar to that previously described.[5] Tetrahydrofuran was the solvent for both the halide and the hydride. After the addition of the lithium aluminum hydride at room temperature, the reaction mixture was refluxed (67°) for 1 hr. The reaction products distilled into a cold trap (dry-ice acetone) as formed and were weighed and analyzed by gas-liquid partition chromatography. In nearly every reaction the material balance was approximately 100%.

Anal. The chromatography equipment consisted of a 10 ft. by $^1/_4$ in. copper tube containing dinonyl phthalate (30%) on 40–60 mesh fire brick (70%) as packing. The detector was a Gow-Mac thermal conductivity cell, helium was the carrier gas and the temperature was 30°. 3,4-Dichloro-1-butene: 100% *trans*-2-butene. 3-Chloro-1-butene: 5% *cis*-2-butene; 8% butadiene; 18% *trans*-2-butene; 69% 1-butene. 3-Bromo-1-butene (69%) and *trans*-1-bromo-2-butene: 26% *cis*-2-butene; 44% *trans*-2-butene; 30% 1-butene. 1,4-Dichloro-2-butene (purchased): 71% *cis*-2-butene; 29% *trans*-2-butene. 1,4-Dichloro-2-butene: (from butadiene): 100% *trans*-2-butene. *trans*-1-Chloro-2-butene: 100% *trans*-2-butene. *trans*-1-Bromo-2-butene: 100% *trans*-2-butene.

Acknowledgment. The authors wish to thank The Robert A. Welch Foundation for the financial support which made this research possible.

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(10) M. S. Kharasch, E. T. Margolis and F. R. Mayo, *J. Org. Chem.*, 1, 393 (1936).

DL-1,2-Diketo-*myo*-inositol Phenylosotriazole and 2-Phenyl-2,1,3-triazole-4,5-dicarboxaldehyde

LAURENS ANDERSON AND JOHN N. ARONSON[1]

Received June 11, 1959

An interest in procedures for the carbon-by-carbon degradation of *myo*-inositol[2] prompted us to study osotriazole formation[3] with the racemic phenylosazone obtained by treating *myo*-

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) The cyclitols mentioned in this note are named and numbered according to the system of H. G. Fletcher, Jr., L. Anderson, and H. A. Lardy, *J. Org. Chem.*, 16, 1238 (1951).

(3) E. G. V. Percival, *Advances in Carbohydrate Chem.*, 3, 37 (1948).

inosose-2 (I) with excess phenylhydrazine.[4] Magasanik and Chargaff[5] had reported that they were unable to obtain the osotriazole from one of the optically active forms of this osazone, D(+)-1,2-diketo-*myo*-inositol bisphenylhydrazone. However, we found that the racemic osazone could be converted to the osotriazole II, albeit in poor yield, by the usual treatment with acidic copper sulfate. The osotriazole was degraded to the hitherto unknown 2-phenyl-2,1,3-triazole-4,5-dicarboxaldehyde (III).
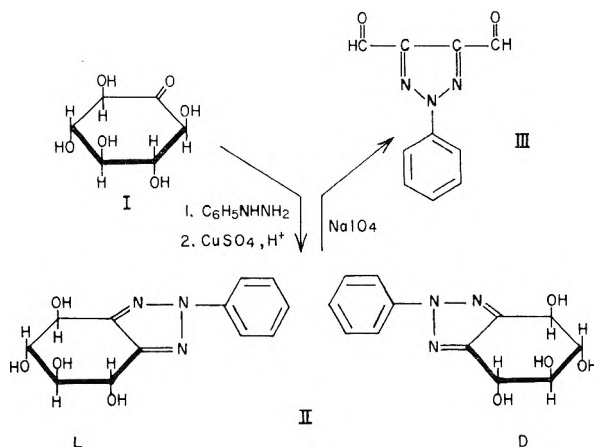
EXPERIMENTAL[6]

DL-1,2-Diketo-myo-inositol phenylosotriazole (II). Thirteen g. of crude DL-1,2-diketo-*myo*-inositol bisphenylhydrazone[4] was refluxed for 2 hr. with 940 ml. of acidic copper sulfate solution (33 g. CuSO$_4$·5H$_2$O per liter of 0.01 *N* H$_2$SO$_4$) and 625 ml. of isopropanol.[7] The osazone gradually went into solution. After the solution had cooled, the copper was precipitated with hydrogen sulfide and removed by filtration, and the filtrate, after treatment with charcoal, was concentrated under vacuum to less than 200 ml. On standing 3 hr. at room temperature, the concentrate deposited 1.2 g. (12%) of light brown solid. Several recrystallizations of this from pyridine-benzene, pyridine-ether, and water gave colorless prisms melting at 278–282° (dec.). Losses of material in the recrystallizations were moderate.

Anal. Calcd. for C$_{12}$H$_{13}$O$_4$N$_3$ (263.35): C, 54.8; H, 5.0. Found: C, 53.8; H, 5.3.

Attempts to isolate additional quantities of the osotriazole by concentrating the reaction liquors were fruitless, as were efforts to improve the yield by varying the proportions of the reactants, and by using methanol, 2-methoxyethanol and acetone as solvents.

Tetra-O-acetyl-DL-1,2-diketo-myo-inositol phenylosotriazole was obtained by treating the free osotriazole with acetic anhydride and pyridine on the steam bath. After recrystallization from warm acetone, the tetraacetate melted at 194–195°.

(4) H. E. Carter *et al.*, *J. Biol. Chem.*, 174, 415 (1948). The parent compound was called "*scyllo*-inosose" by these authors.

(5) B. Magasanik and E. Chargaff, *J. Biol. Chem.*, 174, 173 (1948).

(6) All crystalline compounds were recrystallized to constant melting point. Melting points were determined in capillary tubes. The thermometer used has been calibrated against Anschütz thermometers calibrated by the National Bureau of Standards. Microanalyses by the Micro-Tech Laboratories, Skokie, Illinois.

Anal. Calcd. for $C_{20}H_{21}O_8N_3$ (431.39): C, 55.7; H, 4.9. Found: C, 55.6; H, 5.0.

2-Phenyl-2,1,3-triazole-4,5-dicarboxaldehyde (III). II (288 mg., 1.1 mmole) was shaken at room temperature with 10 ml. of aqueous sodium metaperiodate (755 mg., 3.55 mmole). During 24 hr., the silky needles of osotriazole changed to shorter, thicker crystals. The product, obtained by filtration, was cream white and had a perfume-like odor. (2-Phenyl-2,1,3-triazole-4-carboxaldehyde smells like geraniol.[7]) After two recrystallizations from ethanol-water, it weighed 164 mg. (75% yield) and melted at 145–147°. The compound sublimes readily.

Titration of aliquots of the original filtrate showed that slightly over 3 molar equivalents of periodate had been consumed with the production of exactly 2 molar equivalents of acid, as required for the removal of 2 carbon atoms from II to give a triazole dialdehyde.

The aldehyde gave a 2,4-dinitrophenylhydrazone (presumably the bis derivative) melting at 304–307° (dec.). Final identification of the aldehyde was made by oxidizing it with neutral permanganate to an acid which, after recrystallization from 30% acetic acid containing a few drops of conc. HCl, had the properties of the known *2-phenyl-2,1,3-triazole-4,5-dicarboxylic acid.* [Found: Neutral equivalent[8]; 126; m.p., 259–261° (dec.). Lit.:[9] Neutral equivalent, 116.5, m.p., 255–256° (dec.).]

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(7) R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.,* 66, 735 (1944).
(8) The authors thank R. M. Bock and D. D. Gilboe for performing the electrometric microtitration.
(9) O. Baltzer and H. von Pechmann, *Ann. Chem.,* 262, 302 (1891).

Some Reactions Leading to 8-Aminocaffeine

HANS ZIMMER AND JOSEPH B. METTALIA, JR.

8-Aminocaffeine is an important intermediate in the preparation of certain pharmacologically useful compounds. It has been prepared previously by three different methods and each method has certain disadvantages. The earliest and still most widely used method is due to Fischer,[1] who prepared this compound by heating 8-bromocaffeine with ammonia under pressure. Yields are excellent, but the method is not convenient for the laboratory preparation of moderate amounts of compound. Two other reports exist in the literature for the preparation of 8-aminocaffeine. The second is by Brooks and Rudner,[2] who reported that caffeine reacts with chloramine to give a low yield of a product which was thought to be 8-aminocaffeine; and

the third is by Burgison and Wilson,[3] who obtained 8-aminocaffeine by reducing 8-nitrotheophylline to 8-aminotheophylline. Methylation of this compound yielded 8-aminocaffeine. The over-all yield for this latter method has not been reported.

We have prepared 8-aminocaffeine by two different routes. The first was by a Gabriel synthesis from 8-bromocaffeine using dimethylformamide as a solvent. This, in itself, would not be an improvement over the Fischer synthesis of this compound, as, generally, the N-substituted phthalimides have to be hydrolyzed in a sealed tube. In this case, however, hydrolysis was effected very easily by heating the N-(8-caffeinyl)phthalimide for a short period of time with dilute acid at atmospheric pressure. The second method consisted in heating 8-caffeinylhydrazine in either phenol or dimethylformamide solution. This latter reaction was discovered when an attempt to prepare 1,6-di(8-caffeinyl)-1,2,5,6-tetrazahexane from the reaction of 8-caffeinylhydrazine with ethylene bromide led unexpectedly to the formation of 8-aminocaffeine.

Although the yields in these reactions are not high, they do represent relatively simple laboratory methods of preparing 8-aminocaffeine. The second method is considered preferable since 8-caffeinylhydrazine can be obtained in quantitative yield from the reaction of 8-bromocaffeine with hydrazine hydrate and 8-caffeinylhydrazine can be converted to 8-aminocaffeine in 40–43% yield while the Gabriel synthesis resulted in only a 24% yield of 8-aminocaffeine.

EXPERIMENTAL

Gabriel Reaction. A mixture of 82 g. of 8-bromocaffeine (0.3 m.), 88 g. of phthalimide (0.6 m.). 56 g. of potassium carbonate and 500 ml. of dimethylformamide was refluxed for 18 hr. During this time the mixture became red and a yellow precipitate formed. The yellow precipitate was then dissolved in dilute hydrochloric acid and the solution refluxed for 15 min. After cooling and making the solution basic a white precipitate was obtained which was recrystallized from an ethanol-acetic acid mixture. The yield was 15 g. (24%) of white powder, m.p. >320°.

Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30. Found: C, 45.95; H, 5.55.

Reaction of 8-caffeinylhydrazine in dimethylformamide. A solution of 3.5 g. of 8-caffeinylhydrazine in 100 ml. of dimethylformamide was refluxed for 14 hr. The solution became dark red in color. After cooling to −20°, 1.3 g. of a green precipitate were collected which after recrystallization from an ethanol-acetic acid mixture gave 0.7 g. of a tan product, m.p. >320°. This compound was identified as 8-aminocaffeine by the characteristic triplet peak it exhibited in the N—H region of the infrared and conversion to the known 8-diacetamidocaffeine. The yield was 40% before recrystallization.

(1) E. Fischer, *Ann.,* 215, 253 (1882).
(2) M. E. Brooks and B. Rudner, *J. Am. Chem. Soc.,* 78, 2339 (1956).

(3) R. M. Burgison and H. F. Wilson, Abstract of a paper presented before the Medicinal Chemistry Division at the 131st meeting of the American Chemical Society, Miami, April, 1957.

Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.98; H, 5.39; N, 33.44.

Diacetyl derivative, m.p. 137–142°; mixture m.p. with authentic 8-diacetamidocaffeine, 137–142°.

Reaction of 8-Caffeinylhydrazine with ethylene bromide. A stream of nitrogen was passed through a solution of 10 g. of 8-caffeinylhydrazine (0.045 m.) in 350 ml. of dimethylformamide as it was heated to reflux and while it was refluxing. To this refluxing solution was added 4.5 g. of ethylene bromide (0.024 m.) in 30 ml. of dimethylformamide over a period of 1.5 hr. A green precipitate formed after the addition was complete and the solution darkened. The solution was refluxed for 11 hr. and then cooled in an ice-salt bath. A mixture of green and brown precipitates was collected. The combined precipitate was treated with 500 ml. of boiling ethanol. The green precipitate (2.5 g.) remained undissolved and treatment of the ethanol filtrate with hexane gave 1.4 g. of a white precipitate. The green precipitate showed no N—H peak in the infrared and an acid solution of the compound exhibited a peak at 348 mμ in the ultraviolet. This compound was thought to be 1,2-bis(8-caffeinylazo)ethane, m.p. >320°.

Anal. Calcd. for $C_{18}H_{22}N_{12}O_4$: C, 45.95; H, 4.71; N, 35.73. Found: C, 45.99, H, 4.76; N, 35.22.

The tannish-white precipitate was identified as 8-aminocaffeine by its elemental analysis, the characteristic triplet peak it exhibited in the N—H region of the infrared and conversion to the known 8-diacetamidocaffeine. Yield was 15%.

Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.59; H, 5.55; N, 32.67.

Diacetyl derivative, m.p. 143–146°; mixture m.p. with authentic 8-diacetamidocaffeine, 142–145°.

When this reaction was repeated using phenol as a solvent 8-aminocaffeine was obtained in 43% yield. No 1,2-bis(8-caffeinylazo)ethane was found.

Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 46.37; H, 5.80; N, 32.98.

Diacetyl derivative m.p. 143–145°; mixture m.p. with authentic 8-diacetamidocaffeine, 142–145°.

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Versatility and Temperature Range of Silicone Grease as Partitioning Agent for Gas Chromatography

JAMES CASON AND WILLIAM T. MILLER

Although high vacuum silicone grease has been used rather extensively as partitioning agent in gas chromatography, and column packings containing this material are readily available commercially, there appears to have been published no description of the processing we have found necessary in order to realize the full potential of this partitioning agent. It may be claimed, with some justification, that a properly prepared column containing high vacuum silicone grease as partitioning

agent easily surpasses all others as regards temperature range and variety of compounds that may be satisfactorily chromatographed. Chief limitation to the separations possible is that resolution is based largely on differences in vapor pressure. Major structural differences and differences in functional groups do have significant effects on retention times; however, subtle structural differences and degree of unsaturation usually have little effect on retention times. Even this limitation sometimes becomes an asset when separations on silicone grease are combined with separations on other agents where minor structural differences have larger effects on solubility in the partitioning agent.

There is considerable variation between different commercial[1] lots of high vacuum silicone grease, as regards its performance as a partitioning agent before being conditioned or "cured" at high temperature. Some lots have initially given such extremely long retention times and broad chromatography bands as to be of little use. In all cases, the grease must be heated for a period of at least 50 hours at temperatures above 300° in order to bake out volatile materials. All lots of grease which have been examined have become highly satisfactory as a partitioning agent after being cured as described in the Experimental section. A typical, but by no means maximum, variation between two lots of silicone grease is illustrated in Table I.

TABLE I

CHROMATOGRAPHY OF METHYL ESTERS OF FATTY ACIDS ON SILICONE GREASE[a]

Partitioning Agent	Temp. for Chromatog.	Retention Times (min.) for Esters of Acids		
		C_{16}	C_{17}	C_{18}
Lot I, uncured	320°	6.9	8.5	10.4
Lot II, uncured	305°	4.9	6.0	7.5
Lot I, cured[b]	310°	5.1	6.3	7.7
Lot II, cured[b]	305°	3.1	3.8	4.6

[a] The partitioning agents were prepared as described in the Experimental section. Chromatography was in a Pyrex glass column, 8 mm. × 2.5 m.; helium flow was approximately 190 ml./min. [b] Lot I was cured by heating for 8 days at 325–335°; Lot II similarly for 5 days.

The cured silicone grease packing is stable indefinitely when used at temperatures below about 275°. Packings used for several thousand hours have shown essentially constant retention times and unimpaired resolving power. At temperatures near 300°, there is a slow decrease in retention times, and after two thousand hours or longer, resolving power becomes impaired. Most samples of cured grease may be used at 325° for more than 200 hours before the resolving power deteriorates

(1) The silicone grease to which reference is made in this report was purchased from the Dow Corning Corporation, under the name "High Vacuum Grease," during the period 1956–1959.

TABLE II

GAS CHROMATOGRAPHY ON HIGH VACUUM SILICONE GREASE

Compound	Column Temp., °C.	Column Length,[a] m.	Retention Time,[b] min.:sec.
6-Hexadecanone[c]	190°	2	9:50
	220°	4	33:30
6-Heptadecanone[c]	190°	2	14:10
	220°	4	46:00
Dodecyl alcohol	200°	2	1:50
Tetradecyl alcohol	200°	2	2:45
Hexadecyl alcohol	200°	2	4:32
Octadecyl alcohol	200°	2	7:40
Methyl stearate	285°	3	13
Methyl tetracosanoate	285°	3	57
	305°	3	36
Methyl hexacosanoate	285°	3	95
	305°	3	54
Methyl 4-methylocta-decanoate[d]	200°	2	33
	260°	4	40
Methyl nonadecanoate[d]	200°	2	39
	260°	4	47
Dimethyl suberate	155°	2	4:10
Dimethyl sebacate	155°	2	8:26
Methallyl bromide	60°	2	2:00[e]
Crotyl bromide	60°	2	2:50[e]
Nitrobenzene	110°	2	8:40
Nitrosobenzene	110°	2	3:00
Aniline	110°	2	4:50
N-Phenylhydroxyl-amine	110°	2	f
cis-Dimethylsuccinic anhydride	145°	2	5:50
	145°	3	17:10
trans-Dimethylsuccinic anhydride	145°	2	4:50
	145°	3	13:30
Ester I	190°	1.5	15:55[g]
Ester III	190°	1.5	13:15[g]
Dibutyl ether	85°	2	9:35
Butyl alcohol	85°	2	3:40
Butyl acetate[h]	85°	2	6:10
Butyl propionate	85°	2	10:55
Butyl butyrate	85°	2	20:00

[a] Columns were made of Pyrex glass, 8 or 9 mm. o.d., except for the 3- and 4-m. columns, which were 15 mm. o.d. A spiral column of 20-mm. tubing gave relatively poor resolution. [b] Rate of helium flow was 145–160 ml./min. for the 8- and 9-mm. columns, 160–190 ml./min. for the 15-mm. columns, except as otherwise noted. Pressure required to give these rates of gas flow was in the range 12–22 cm. of mercury. [c] In the 2-m. column at 190°, recorder tracing barely touched baseline between the hexadecanone and heptadecanone bands; in the 4-m. column at 220°, tracing was at baseline between the bands for 7 min. [d] Nonadecanoate and 4-methyloctadecanoate boil about 3.5° apart at 3 mm. pressure. In the 2-m. column, tracing did not quite reach baseline between bands; in the 4-m. column, tracing touched baseline between bands. [e] Helium flow rate in these runs was about 30 ml./min. [f] Apparently N-phenylhydroxylamine disproportionates extremely rapidly at 110° in a helium atmosphere to nitrosobenzene and aniline, for injection of this substance gave excellent bands at 3:10 and 4:50

(observation of Dr. R. J. Fessenden). [g] With a second lot of packing cured in the same manner (12 days), retention times in the same column at 200° were respectively 4:42 and 3:57, and the peaks of the bands were barely resolved. Resolution was improved only slightly at lower temperature. [h] A quantity of 0.01 μl. of butyl acetate could be detected in presence of 1.0 μl. of butyl alcohol. With di-2-ethylhexyl phthalate as partitioning agent, the bands for these compounds were closer together and butyl acetate could be detected only when present in a ratio of at least 1:50.

to the point of ineffectiveness. Below 275°, contamination of chromatographed samples by "bleeding" of partitioning agent from the column is essentially nil; at 300° there is minor but observable contamination from bleeding until the column has been used for a thousand hours or longer.

The versatility of silicone grease as partitioning agent is illustrated in part by the data assembled[2] in Table II. Among other compounds successfully chromatographed are lactones, nitrogen heterocycles, saturated hydrocarbons up to C_{36}, oximes,[3] esters of fatty acids up to C_{32}, alkylphosphonic esters, and other organophosphorus compounds,[4] alkylnaphthalenes, and complex reaction mixtures containing hydroxy nitriles.[5] The iodides from a Zeisel analysis may be readily identified, both qualitatively and quantitatively as methyl, ethyl, isopropyl or n-propyl iodides. Among the very few types of compounds not successfully chromatographed are alkanediols. No signal could be observed after injection of decanediol. Esters of dibasic acids, including diethyl malonate and diethyl oxalate, are readily separated. Among compounds chromatographed satisfactorily but not separated are: 2- and 3-bromopentanes, methyl stearate and methyl oleate, 2- and 3-octadecanones, the isomeric half esters of methylsuccinic acid.
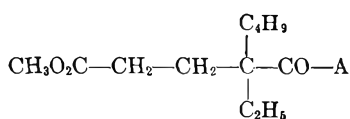
Perhaps one of the more interesting entries in Table II is the separation of the isomeric half esters, I and III, of α-butyl-α-ethylglutaric acid. In fractional distillation, there has been detected no difference in the boiling points of these compounds. The isomeric keto esters, II and IV, were not separable on silicone grease but were separable on Reoplex-400 (Geigy). Also of interest is the separation on silicone grease of the cis- and trans-isomers of sym-dimethylsuccinic anhydride. Although fatty acids may be chromatographed quite satisfactorily,

(2) These data have been excerpted from those accumulated in various investigations in these laboratories. Principal contributors have been R. E. Bozak, Joan S. Fessenden, R. J. Fessenden, E. R. Harris, R. B. Hutchison, K. W. Kraus, F. J. Schmitz, and P. Tavs.
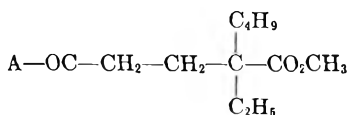
(3) Although di-2-ethylhexyl phthalate was used for separation of oximes in work recently published [J. Cason and E. R. Harris, J. Org. Chem., 24, 676 (1959)], silicone grease is equally effective.

(4) J. Cason and W. N. Baxter, J. Org. Chem., 23, 1302 (1958).

(5) J. Cason, K. W. Kraus, and W. D. MacLeod, Jr., J. Org. Chem., 24, 392 (1959).

$$CH_3O_2C-CH_2-CH_2-\underset{\underset{C_2H_5}{|}}{\overset{\overset{C_4H_9}{|}}{C}}-CO-A$$

I. A = OH
II. A = C₄H₉

$$A-OC-CH_2-CH_2-\underset{\underset{C_2H_5}{|}}{\overset{\overset{C_4H_9}{|}}{C}}-CO_2CH_3$$

III. A = OH
IV. A = C₄H₉

the corresponding esters give sharper bands and larger signals with a thermal detector. Strangely enough, for equal weights of half esters I and III, a significantly larger signal is received from ester III. This is a definite exception to the report[6] that signal is a function of square root of molecular weight. Lower molecular weight acids, including formic and acetic acids may be separated on the silicone grease; however, broad unsymmetrical bands of somewhat variable retention times are obtained. The separation of branched-chain and normal fatty acid esters has been reported.[7]

EXPERIMENTAL

Preparation of column packing. There were used 4 parts of silicone grease[1] to 10 parts by weight of 30–60-mesh Celite (Johns-Manville "Chromosorb" or Celite firebrick which had been pulverized and sieved). The grease was dispersed by warming and stirring in 7–8 parts by weight of chloroform. A few minutes of vigorous mixing and stirring by hand are required for complete dispersion. The Celite, moistened with chloroform, was added to the stirred dispersion of grease, and the resultant mixture was shaken vigorously for a few minutes. The chloroform was removed at reduced pressure and the packing material was dried at 100° in a vacuum. Such packing material is just short of becoming sticky and has an appearance similar to the Celite before impregnation.

The packing material is cured by heating in a slow stream of nitrogen at 325–335°; higher temperatures tend to impair resolution and give too rapid a curing for satisfactory control. In large batches, an exothermic reaction may be noticeable as the temperature approaches 300° and this may necessitate turning off the heater for a few minutes. Heating may be accomplished[8] in a Pyrex tube, on which an electric heating wire has been wound. The heated tube should be placed in a vertical position with a short (20 mm.) outlet tube at the bottom of not less than 10 mm. o.d. During the first 30–50 hr. of heating, both a volatile, low-melting solid and a mobile liquid are swept from the tube; care must be exercised that the outlet is not plugged by the solid.

After 50–70 hr. of heating, when evolution of solid material has nearly ceased, heating should be discontinued, and

(6) R. H. Eastman, *J. Am. Chem. Soc.*, **79**, 4243 (1957).
(7) J. Cason and P. Tavs, *J. Biol. Chem.*, **234**, 1401 (1959).
(8) Commercial models of gas chromatography apparatus usually are not designed to permit heating above 300°; however, if one has apparatus which will withstand temperatures up to 340°, heating is conveniently done in the chromatography tube, where retention time may be checked by simply lowering the temperature to a suitable value. Heating may then be resumed as indicated.

the packing material should be tested for retention times of suitable compounds.[8] For some lots of silicone grease, this initial heating period has been sufficient. A retention time of 2–4 min. for methyl decanoate at 180° in a 1.5-m. column, helium pressure of 15–20 cm. of mercury, is in the range that is satisfactory. A representative rate of decrease of retention time with heating may be noted in Table I. The grease described as Lot II in this table gave, at 305° in the 2.5-m. column, a retention time for ethyl 10-methyltetracosanoate of 34 min. before curing, 22 min. after curing. A curing period of 5–8 days is normal, and the longest period that has been used was 12 days. If very high molecular weight materials are to be chromatographed, retention times may be shortened by extending the heating period, but deterioration of resolution eventually occurs. It is usually better to reduce retention times by decreasing the content of grease on the packing.

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Thermal Decomposition of Di-*n*-butyl Maleate

WILLIAM R. MILLER AND H. M. TEETER

During work on the addition of maleic acid derivatives to unsaturated fatty acids,[1] it was found that di-*n*-butyl maleate undergoes a decomposition reaction which has not been previously reported. The decomposition appears to be related to the well known pyrolysis of esters to form alkenes.[2] It may also be related to the decarboxylation of diaryl fumarates to form, first, aryl cinnamates and, then, stilbenes.[3] It differs from these reactions and is unusual in that decomposition is initiated at the relatively low temperature of 265°, the boiling point of dibutyl maleate. Another unusual feature of the decomposition is formation of 1-butanol.

When di-*n*-butyl maleate is heated to 260–265°, the liquid turns deep red, the refractive index rises, and there is loss in weight. Heating for 2.5 hr. transforms about 40% of the ester into higher boiling material. 1-Butanol is found in the cold trap when this material is distilled under vacuum. If the ester is swept with nitrogen while being heated, 1-butene can be trapped from the off-gas. Attempts to distill dibutyl maleate at atmospheric pressure result in a slow distillation of butanol and evolution of butene. Low weight recoveries in these experiments indicated the presence of another volatile product, shown to be carbon dioxide.

Beside volatile products, there is a considerable residue of dark, viscous tar. This residue could be

(1) W. R. Miller, E. W. Bell, H. M. Teeter, and J. C. Cowan. Presented before the 32nd Fall Meeting of American Oil Chemists' Society, October 1958, Chicago, Ill.
(2) W. J. Bailey and W. N. Turek, *J. Am. Oil Chemists' Soc.*, **33**, 317 (1956).
(3) L. B. Flett and W. H. Gardner, *Maleic Anhydride Derivatives*, John Wiley and Sons, New York, 1952, p. 248.

separated into an ethanol-soluble viscous oil and an insoluble charcoal-like solid. Nothing was characterized in the residue except minute quantities of succinic and fumaric acids. A quantitative study of the volatile products (Table I) was undertaken to learn more about the nature of this decomposition.

TABLE I

THERMAL DECOMPOSITION OF DI-n-BUTYL MALEATE AND FUMARATE

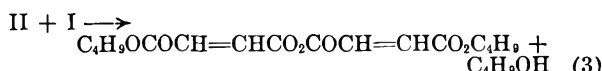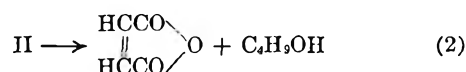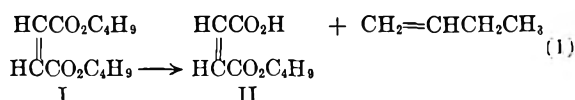| Ester	Charge mmols.	Product, mmols.			Molar ratio		
		Bu-tanol	Bu-tene	CO_2	Bu-tanol	Bu-tene	CO_2
Maleate[a]	438	287	145	234	1.87	1	1.61
	110	91	50	68	1.82	1	1.36
	175	173	86	...	2.02	1	..
Maleate[b]	175	124	71	116	1.75	1	1.63
	175	162	82	107	1.97	1	1.31
Fumarate	175	165	93	127	1.78	1	1.37

[a] Prepared with H_2SO_4 catalyst. [b] Prepared without catalyst.

Butanol and butene were in a molar ratio of 2 to 1. The amount of carbon dioxide evolved was less on a molar basis than that of butanol but more than that of butene. For each mole of ester a maximum of about 1 mole of butanol was formed, with corresponding quantities of the other components.

An explanation for the ease of this decomposition was sought. The ester had been prepared from maleic anhydride and butanol, using concentrated sulfuric acid as catalyst. It was postulated that some acidic sulfur group, carried through the preparation and distillation of the dibutyl maleate, might have catalyzed the decomposition. Accordingly, dibutyl maleate was prepared without acid catalyst. This ester decomposed in exactly the same manner as did the ester prepared with acid catalyst. Di-n-butyl fumarate also was subjected to the same conditions. Results were identical, except that the butanol contained some water and high-boiling material while butanol from the maleic ester was pure.

It is not difficult to suggest reactions that would account qualitatively for the products. The evolution of butene suggests pyrolysis of the butyl ester (Eq. 1). The acid moiety so produced could react with another ester group on the same (Eq. 2) or on a different molecule (Eq. 3) to form an anhydride and butanol.[4] Again, the acid might decarboxylate to form butyl acrylate (Eq. 4). The diester might eliminate carbon dioxide in the manner of the diaryl fumarates,[3] to give in turn butyl β-butylacrylate and 5-decene (Eq. 5). In the latter case, the amount of carbon dioxide formed would be independent of the mechanism of ester pyrolysis and anhydride formation.

(4) W. Nagel and R. H. Abelsdorff, *Wiss. Veroffentl Siemens-Konzern.* **5**, 193 (1926).

$$\begin{array}{cc} HCCO_2C_4H_9 & HCCO_2H + CH_2{=}CHCH_2CH_3 \\ \| & \| \\ HCCO_2C_4H_9 \longrightarrow & HCCO_2C_4H_9 \\ I & II \end{array} \quad (1)$$

$$II \longrightarrow \begin{array}{c} HCCO \\ \| \quad \searrow O + C_4H_9OH \\ HCCO \nearrow \end{array} \quad (2)$$

$$II + I \longrightarrow$$
$$C_4H_9OCOCH{=}CHCO_2COCH{=}CHCO_2C_4H_9 + $$
$$C_4H_9OH \quad (3)$$

$$II \longrightarrow H_2C{=}CHCO_2C_4H_9 + CO_2 \quad (4)$$

$$I \longrightarrow C_4H_9CH{=}CHCO_2C_4H_9 + CO_2$$
$$\searrow C_4H_9CH{=}CHC_4H_9 + CO_2 \quad (5)$$
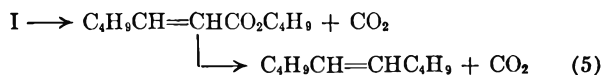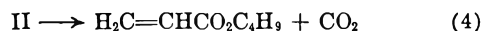
On the basis of these reactions, the relatively nonvolatile products of the decomposition should include at least some of the following: Butyl hydrogen maleate, maleic anhydride and/or a more complex ester anhydride, butyl acrylate, butyl β-butylacrylate, 5-decene, further degradation products, and the geometric isomers of the maleic derivatives. Only a little fumaric acid was found. The acrylic derivatives would probably be polymerized very readily, possibly copolymerizing with the maleic derivatives.

Quantitatively these reactions require a butanol: butene ratio of 1:1, whereas the observed ratio was 2:1. If the carbon dioxide resulted from decarboxylation of the half ester (Eq. 4), there should be proportionately more butene than butanol formed. If the carbon dioxide came from the diester (Eq. 5), it should not affect the butanol:butene ratio significantly. Thus reactions in Equations 1–3 must not represent the true course of the decomposition.

Other reactions can be postulated, but all run into the same objection or require unprecedented vinyl hydrogen reactivity in the maleic ester. A molecule of butanol possibly could be split out of the ester with formation of a ketene, but this seems most unlikely. If it did happen, for each two ester groups that react in this manner, a third would have to react by a different route to split out butene. There seems to be no cogent reason for this sort of variation. Further, there is one piece of inconclusive evidence, based on an incomplete decomposition, that butene is evolved before, or faster than, butanol.

Work on the kinetics of this decomposition and investigation of the reactions of related esters might serve to elucidate the mechanism. Because further study of this decomposition is beyond the scope of our program, we shall be glad to have others explain the true course of this unusual decomposition.

EXPERIMENTAL

Di-n-butyl maleate was prepared from maleic anhydride and 1-butanol and redistilled before use. An analytically pure sample of the ester had n_D^{30} 1.4412. The maleate used in the experiments had n_D^{30} 1.4409–1.4411. Use of sulfuric acid catalyst in the synthesis had no effect on the properties of the ester. Di-n-butyl fumarate was prepared from fumaric acid and 1-butanol using dry HCl as catalyst, n_D^{30} 1.4420.

Decompositions were carried out in a flask fitted with a nitrogen ebullator; a thermometer; and an absorption train consisting of a water-cooled condenser with receiver, a trap cooled by an ice salt freezing mixture, another trap containing concentrated sulfuric acid and finally, a U-tube containing Ascarite.[5] Typically the pot containing the ester was heated to about 265°, at which temperature the ester would start to boil. A slow stream of nitrogen was used to sweep out the decomposition products. A liquid, n_D^{30} 1.3950, was collected in the receiver of the water-cooled condenser. This was identified as 1-butanol by preparation of an α-naphthylurethan which melted at 69–70.5° and did not depress the melting point of an authentic sample. Butene was absorbed in the sulfuric acid and carbon dioxide in the Ascarite. In preliminary experiments butene was identified by condensation in a cold trap, the liquid was evaporated, and the gas passed into a solution of bromine in carbon tetrachloride to give a liquid boiling at 164°; n_D^{30} 1.507; d^{29} 1.76. These values are in reasonable agreement with literature values[6] for 1,2-dibromobutane: B.P. 166°, n_D^{20} 1.5125, d^{25} 1.787. These data indicate that the butene is primarily 1-butene, although there may have been some rearrangement. Decomposition was continued until evolution of volatile material had stopped.

Acknowledgment. The authors acknowledge their appreciation to J. L. O'Donnell for preparation of the esters.

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NORTHERN UTILIZATION RESEARCH AND DEVELOPMENT
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(5) Mention of firm names or trade products are furnished for convenience, and this information does not constitute an endorsement of them or their products by the Department of Agriculture.

(6) R. T. Dillon, W. G. Young, and H. J. Lucas, *J. Am. Chem. Soc.*, **52**, 1954 (1930); N. A. Lange, *Handbook of Chemistry*, Seventh Edition, Handbook Publishers, Inc., Sandusky, Ohio, 1946, p. 446.

Iodination of Benzoic Acid in Acetic Acid–Sulfuric Acid Mixture Containing Iodate
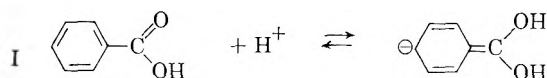
ROBERT S. AJEMIAN AND A. J. BOYLE

The direct halogenation of benzoic acid is inhibited by the deactivating influence of the carboxyl group. It is possible however, to obtain yields of *m*-chlorobenzoic acid as high as 50% by the use of potassium permanganate, hydrochloric acid, and benzoic acid in aqueous medium.[1] The iodination of benzoic acid was attempted in acidified aqueous medium in the presence of iodide and iodate. Perchloric, nitric, sulfuric, and acetic acids, respectively, failed to produce even the slightest yield of *m*-iodobenzoic acid.

The use of 1:1 glacial acetic and sulfuric acids containing benzoic acid and sodium iodate produces a 70% yield of *m*-iodobenzoic acid when sodium iodide, dissolved in glacial acetic acid, is added

dropwise over a period of one hour to the heated (85°) mixture. Subsequently, it was determined that a mixture of 45% glacial acetic and 55% sulfuric acids by volume proved to be the most effective environment. Sodium iodide in acetic acid, or iodine plus sodium iodide, presented a convenient way in which to introduce iodine. The latter combination makes possible the solution of 20 g. of iodine in 50 ml. of acetic acid.

It would appear that in the presence of glacial acetic and sulfuric acids the benzoic acid is rather basic and may be considered a proton acceptor.[2] Acquiring a proton, the carboxyl group now permits more negativity at the *meta-* position (I), a situa-

tion which seems to facilitate iodination. The presence of water in this system provides a much stronger base than benzoic acid and thus hydronium ion is formed which effectively prevents a proton combination with the carboxyl group. The reaction (II) is most rapid in the presence of a slight excess of iodate and free iodine which is liberated on the addition of iodide as described above. The acetic acid solubilizes both iodine and benzoic acid which enhances the rate of reaction.
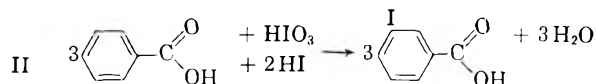
A temperature above 100° promptly stops the reaction. Lowering the temperature at this point does no good. Above 100° elemental sulfur (III) appears

$$III \quad H_2SO_4 + 6HI \xrightarrow{>100°} 3I_2 + S + 4H_2O$$
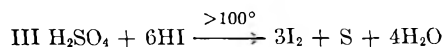
on the colder parts of the reaction flask. At the optimum temperature for the reaction to proceed, an excess of iodide over the equivalent of iodate will stop the iodination. Iodate must always be in slight excess over the iodide added. The addition of more iodate when iodide is in excess will restore the iodination process.

EXPERIMENTAL

Benzoic acid (12.0 g.) was placed in a 3-necked flask, with condenser, along with glacial acetic acid (90 ml.) and stirred to dissolve the benzoic acid. Concentrated sulfuric acid (110 ml.) was added slowly with stirring. To this mixture was added sodium iodate (6.0 g.). The mixture was maintained at 85° throughout the reaction. Acetic acid (50 ml.), containing sodium iodide (10 g.), was added dropwise while the mixture was vigorously stirred mechanically. The free iodine concentration was permitted to be in considerable excess. As the reaction progresses the iodine color disappears and more iodide must be added to keep the rate optimum. In these circumstances the time required is approximately 50 min.

The mixture was decolorized by the use of sodium sulfite. The addition of water equivalent to 3 times the volume of the

(1) H. Y. Yee and A. J. Boyle, *J. Chem. Soc.*, 4139 (1955).

(2) L. P. Hemmet, *Chem. Revs.*, **16**, 67 (1935).

final mixture effectively brings down the *m*-iodobenzoic acid. The product recovered was recrystallized from glacial acetic acid by diluting the solution with water yielding 18.0 grams (75%) of pure product. M.p. and mixed m.p. 181–183°.

*Anal.* Calcd. for $C_7H_5O_2I$: 248. Found: Equiv. 246.

DETROIT 1, MICH.

Heterocyclic Vinyl Ethers. XV. The Thermal Stability of 1,4-Dithiadiene and Its Reaction with Chlorine.[1]

WILLIAM E. PARHAM, BRIAN GADSBY, AND RICHARD A. MIKULEC

We now wish to report some terminal experiments with the heterocycle 1,4-dithiadiene, including an improved method of synthesis, its thermal stability, and its reaction with chlorine.

The preparation of 1,4-dithiadiene (II), by the vapor phase dealkoxylation of 2,5-diethoxy-1,4-dithiane (I) on alumina, has been re-examined. The reaction temperature was accurately measured
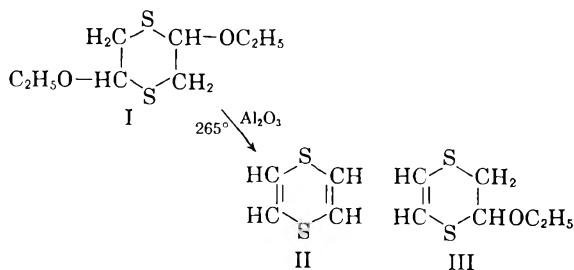

and carefully controlled. Optimum yields of II (47–60%) were obtained when molten I, in the absence of solvent, was reacted on alumina at 260–265°. The use of higher temperatures (310°), as previously reported,[2] gave only viscous oils and neither II nor III could be isolated.

1,4-Dithiadiene was previously reported[2] to decompose at its boiling point (181°/735 mm.). We have subsequently found that the thermal stability of II is quite dependent upon its purity. Pure 1,4-dithiadiene can be distilled at atmospheric pressure under nitrogen with no apparent decomposition. A sample of pure II was maintained at the reflux temperature in a nitrogen atmosphere for 50 minutes with no evidence of decomposition; however, after that time a rapid decomposition initiated. The infrared spectra of the crude decomposition residue, and of the more volatile material obtained from the pyrolysis reaction in the preparation of II, did not reveal bands char-

acteristic of thiophene. Indophenine color tests for thiophene were also negative. Thus, the thermal stability of 1,4-dithiadiene is in contrast with that of 2,5-diphenyl-1,4-dithiadiene (IV). The latter decomposes at 180° to give 68% yields of 2,4-diphenylthiophene and sulfur.[3]
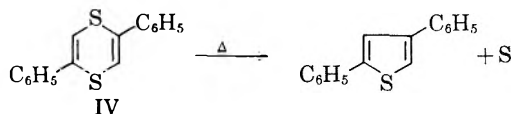

The reaction of 1:4-dithiadiene, in carbon tetrachloride at zero degrees, with one molar equivalent of chlorine, resulted in the formation of two solid products: (A) m.p. 104.5–105.5° (22%), and (B) m.p. 157–158° dec. (29%).
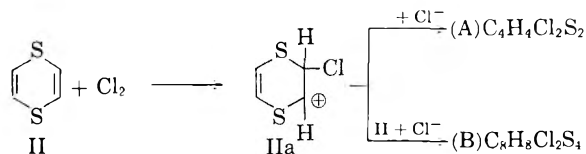
(A) is relatively unstable in air, becoming first brown and then dark purple. Elemental analysis and molecular weight determinations established the molecular formula $C_4H_4Cl_2S_2$. Elemental analysis of (B) gave the empirical formula $C_4H_4ClS_2$, although attempts to determine the exact molecular weight were not successful, because of its very low solubility in suitable solvents at low temperatures, and of its thermal instability at higher temperatures. An approximate value obtained suggested the molecular formula $C_8H_8Cl_2S_4$.

Possible structures for (A) were considered to be V or VI, and for (B) the structure VII, or a product related to VI. Product VI could form, as shown in the above equations (IIa → IIb → VI),
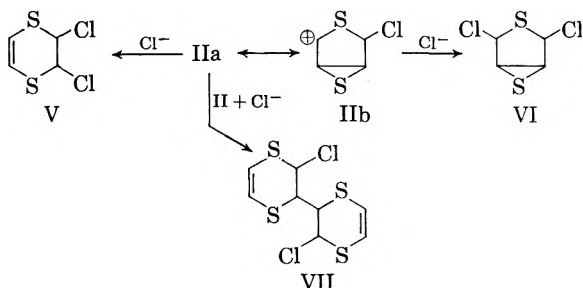
a process related to that postulated for the thermal degradation of diaryl dithiadienes.[3,4] The product (A) reacted readily with potassium iodide in acetone to liberate iodine; however, 1,4-dithiadiene disulfone could not be recovered from the acetone solution subsequent to oxidation with hydrogen peroxide. Failure to isolate the disulfone from such mixtures was subsequently shown to be of little

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(1) This work was supported by the Office of Ordnance Research, U. S. Army, Contract No. DA-11-022 ORD 2616.

(2) W. E. Parham, H. Wynberg and F. Ramp, *J. Am. Chem. Soc.*, **75**, 2065 (1953).

(3) W. E. Parham and V. J. Traynelis, *J. Am. Chem. Soc.*, **76**, 4960 (1954).

(4) W. E. Parham and V. J. Traynelis, *J. Am. Chem. Soc.*, **77**, 68 (1955).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF CYCLIC AND ALICYCLIC BIS-MERCAPTOETHYLENES

Solvent	Compound	λ	ϵ	λ	ϵ	λ	ϵ	ref.
95% Ethanol	n-C$_4$H$_9$SCH=CHSC$_4$H$_9$-n			251	11348	268[a]	6560	5
	cis t-C$_4$H$_9$S—CH=CHS—C$_4$H$_9$-t	230[a]	5897	250	9192	263[a]	5377	5
	cis n-C$_4$H$_9$-—SCH=CH—C$_4$H$_9$-n	232[a]	5062	257	8474	269	7638	5
	n-C$_4$H$_9$SCH=CHSCH$_3$	226	5392	252	9717	275[a]	3749	5
	cis CH$_3$SCH=CHSCH$_3$	228	4917	253	9051	270–300[a]		5
	trans CH$_3$SCH=CHSCH$_3$	230	5096	254	8863	270[a]	5143	5
	C$_6$H$_5$SCH=CHSC$_4$H$_9$-n	217[a]	9924			271	12991	5
	C$_6$H$_5$SCH=CHSC$_4$H$_9$-t	217[a]	11043			273	14104	5
	n-C$_4$H$_9$SCH=CHOC$_2$H$_5$	215	8534	248	3928			5
	t-C$_4$H$_9$SCH=CHOC$_2$H$_5$	215	8534	248	3928			5
	1,4-dithiadiene			262	5400	266–270	5280	2
	2,5-dimethyl-1,4-dithiadiene			262	4131	269	4102	7
	2,5-diphenyl-1,4-dithiadiene			259	22100	309	8900	3
	1,4-dithiene					282	4365	6
	bis-1,2(ethylmercapto)cyclohexene			263	4750			
	C$_2$H$_5$SC(CH$_3$)=CHSC$_2$H$_5$			225	1730			
	2-methoxy-1,4-dithiene-5	221	3320			272	4580	
	2-ethoxy-1,4-dithiene-5	220				273		
	3-ethoxy-2,5-dimethyl-1,4-dithiene-5	232	4300			268	4000	7
	3-n-butoxy-2,5-dimethyl-1,4-dithiene-5	232	4330			268	4080	7
	2,3-dihydro-4H-thiopyran	208	3000	225	4400	247	2200	
Chloroform	2,3-dichloro-1,4-dithiene-5 (V)			243	3784	281	4351	
	Compound VII			245	7429	282	7995	
	2-ethoxy-1,4-dithiene-5			246	5466	275	7076	
	n-C$_4$H$_9$SCH=CHSCH$_3$					261	2140	
	t-C$_4$H$_9$SCH=CHSC$_4$H$_9$-t			243[a]	4760	272	7470	

[a] Pt. of inflection.

consequence, for only small yields (<10%) of 1,4-dithiadienedisulfone could be isolated from similar mixtures containing authentic 1,4-dithiadiene and iodine.

More compelling evidence for the structures V and VII was obtained by comparison of their spectra with those of related compounds. The infrared spectrum of (A) (KBr disk) showed characteristic absorption at: 650 cm.$^{-1}$ (strong), 680 cm.$^{-1}$ (strong), 1220 cm.$^{-1}$ (medium) and 1555 cm.$^{-1}$ (strong); the higher melting solid (B) (KBr disk): 645 cm.$^{-1}$ (strong), 665 cm.$^{-1}$ (strong), 680 (in chloroform, weak), 1215 cm.$^{-1}$ (medium), 1550 cm.$^{-1}$ (strong). These spectra were compared with those of seven available compounds (from table I), both cyclic and alicyclic, possessing the group R—S—CH=CH—S—R. These compounds show characteristic absorption in the regions: 670–685 cm.$^{-1}$ (medium to strong), 1212–1240 cm.$^{-1}$ (medium to strong), and 1537–1550 cm.$^{-1}$ (medium to strong). The bands at 1537–1550 cm.$^{-1}$ are not present in compounds with the grouping R—S—CH=CH—OR, but are replaced by new bands at 1615–1620 cm.$^{-1}$ (strong) and 1720–1725 cm.$^{-1}$ (weak); consequently, it was concluded from these comparisons that both products (A) and (B) contained the R—S—C=C—S—R structure, and that V and VII were the most probable structures.

It can be seen from Table I that the absorption observed for V is consistent with the substituted dithiene structure. Furthermore, similar absorption noted for VII, with twice the molar extinction coefficient, establishes the relationship of structures proposed.

Attempts were made to oxidize 1,4-dithiadiene to the monosulfoxide by means of equimolar amounts of 40% peracetic acid,[8] iodosobenzene,[9] and 40% hydrogen peroxide.[10] In all cases only recovered 1,4-dithiadiene was finally obtained. The infrared spectrum of the crude reaction products, however, contained bands which could be associated with the sulfoxide group (1052–1022 cm.$^{-1}$).[11] There was no evidence for the formation of thiophene in these reactions. The oxidation of II with excess hydrogen peroxide readily gives the mono- or disulfone[2] in high yield. Thus, toward oxidation, 1,4-dithiadiene behaves in a manner

(5) W. E. Parham, R. F. Motter and G. L. O. Mayo, J. Am. Chem. Soc., 81, 3386 (1959).

(6) W. E. Parham, J. Heberling and H. Wynberg, J. Am. Chem. Soc., 77, 1173 (1955).

(7) W. E. Parham, G. L. O. Mayo and B. Gadsby, J. Am. Chem. Soc., 81, 5993 (1959).

(8) H. H. Szmant and L. M. Alfonso, J. Am. Chem. Soc., 79, 205 (1957).

(9) A. H. Ford-Moose, J. Chem. Soc., 2126 (1949).

(10) O. Hinsberg, Ber., 43, 289 (1910).

(11) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., 295 (1954). (b) Organic Sulfur Compounds, "Infrared Spectra of Organic Sulfur Compounds," N. Kharasch, ed., Vol. 1, Chap. 3, L. J. Bellamy. Pergamon Press Inc. (in press), New York 22, N. Y.

quite different from the diaryl-dithiadienes. 2,5-Diphenyl-1,4-dithiadiene (IV) readily gives a monosulfoxide which decomposes, or is subsequently decomposed,[3] to a thiophene in high yield.

Attempts were made to nitrate 1,4-dithiadiene by the action of nitric acid in acetic acid, cupric nitrate in acetic anhydride, and tetranitromethane. In all cases the final products were tars plus a small amount of amorphous acidic material. There were some indications, however, that unstable intermediates were being formed. In the tetranitromethane reaction a dark red amorphous solid was isolated which rapidly turned a tar.

EXPERIMENTAL

1,4-Dithiadiene (II). The procedure previously described[2] for the conversion of 2,5-diethoxy-1,4-dithiane to 1,4-dithiadiene, by reaction in ethanol with alumina at 310° could not be successfully repeated. The reaction variables were studied and the following procedure was found to afford I in consistent yields of 47–60%.

Alumina pellets (60 g., Harshaw Chemical Co., T $^1/_8''$) were heated for 48 hr. at 310° in a vertical glass tube (2 × 30 cm.). The temperature was lowered to 265° and molten[12] 2,5-diethoxy-1,4-dithiane (36.0 g., 0.173 mole) was passed through the tube at 8 drops per minute with dry nitrogen gas at 0.5 l. per minute, followed by absolute ethanol (10 ml.). The crude product, collected in a dry ice cold trap, was dissolved in ether (150 ml.) and the solution washed with water (10 ml.), saturated sodium chloride (2 × 15 ml.) and dried over magnesium sulfate. Distillation of the product through an 8" spiral wire column yielded impure 1,4-dithiadiene (12.0 g., 60%), b.p. 77–79°/15 mm., $n_D^{23.6}$ 1.6318. The product was further purified by chromatography as before[2] to give pure 1,4-dithiadiene, b.p. 71.5°/17 mm., $n_D^{25.8}$ 1.6343.

When a saturated ethanolic solution of 2,5-diethoxy-1,4-dithiane was pyrolysed at 260°, only 2-ethoxy-1,4-dithiene-5 (56%) was obtained.

Thermal Stability of 1,4-Dithiadiene. Distillation. A sample of 1,4-dithiadiene (2.0 g., $n_D^{20.7}$ 1.6347) was distilled slowly at atmospheric pressure under dry nitrogen. The distillate was a yellow-orange liquid $n_D^{20.7}$ 1.6348–1.6355 and the residue consisted of a dark red brown tar (0.06 g.).

Refluxing. A 1.0 g. sample could be heated under reflux in the presence of nitrogen for a period of 50 minutes. There was little evidence of decomposition, as indicated by only a slight darkening in color. After this time the material appeared to undergo a sudden decomposition, emitting a cloud of white smoke through the condenser and leaving a black tarry residue, possessing a strong odor of hydrogen sulfide. The reflux condenser was rinsed with thiophene free benzene and the resulting solution tested for thiophene by the indophenine reaction.[13] No blue color could be detected.

During preparation. An attempt was made to isolate any thiophene present in the material obtained as a forerun in the preparation of 1,4-dithiadiene as the 2-chloromercuri-derivative: 0.82 g. of liquid forerun was diluted with ethanol (2 ml.) and treated with 4M sodium acetate solution (8 ml.) and 0.25M mercuric chloride solution (40 ml.). The dark yellow precipitate thus formed could not be recovered from an aqueous ethanolic solution.

The infrared spectra of crude pyrolyses products did not show any bands which could be used to identify thiophene.

Reaction of 1,4-Dithiadiene with Chlorine. To a solution of 1,4-dithiadiene (11.6 g., 0.1 mole) in carbon tetrachloride (125 ml.) was added, at 0° with stirring, a solution of chlorine (7.1 g., 0.1 mole) in carbon tetrachloride (125 ml.) during one hour. The mixture was stirred at 0° for an additional 15 minutes and then at room temperature for 2 hr. There was filtered off a purple solid (4.41 g., 29% of $C_8H_8Cl_2S_4$), recrystallization of which gave compound B as colorless prisms, m.p. 157–158° (dec.).

Anal. Calcd. for $C_8H_8Cl_2S_4$: C, 31.68; H, 2.66; Cl, 23.38; S, 42.29; mol. wt. 303. Found: C, 31.57; H, 2.57; Cl, 23.24; S, 43.11; mol. wt. 486° (benzene).[14]

The filtrate was evaporated under reduced pressure, and the residue was recrystallized from petroleum ether B to give compound A (V) as colorless needles (4.15 g., 22% of $C_4H_4Cl_2S_2$) m.p. 104.5–105.5°. Compound A slowly decomposed in air and was therefore stored under nitrogen.

Anal. Calcd. for $C_4H_4Cl_2S_2$: C, 25.67; H, 2.15; Cl, 37.90; S, 34.27; mol. wt., 187. Found: C, 25.66; H, 2.07; Cl, 37.66; S, 35.30; mol. wt. (f.p. benzene), 171, 186, 186.

Reaction of Compound A with Sodium Iodide in Acetone. A solution of sodium iodide (4.80 g., 32 mmole) in acetone (10 ml.) was added to a solution of compound A (0.75 g., 4 mmole) in acetone (10 ml.), and the mixture was allowed to stand for periods varying from 30 minutes to 16 hr. The formation of iodine was evident within a few minutes. The solution was diluted with ether (25 ml.) and saturated aqueous sodium chloride (20 ml.), and the resulting mixture treated with aqueous sodium sulfite (5%) until the dark red iodine color was removed. The ether solution was diluted with glacial acetic acid (10 ml.) and 10 ml. of 30% hydrogen peroxide added. The solution obtained was heated at 70° for two days. The precipitate (0.25 g.) was identified as "acetone superperoxide" ($C_6H_6O_4$, m.p. and mixed m.p. 131.5°), formed by reaction of acetone with hydrogen peroxide.[15] 1,4-Dithiadiene disulfone could not be isolated from the filtrate.

Similar reactions were carried out using 1,4-dithiadiene instead of compound A. Iodine, of course, was not formed and 1,4-dithiadiene disulfone[2] was isolated from the final reaction mixture in 39% yield (m.p. 241–242° dec.); however, when iodine was added to the original reaction mixture, the yield of disulfone was very low (<10%).

Attempted Conversion of 1,4-Dithiadiene to the Monosulfoxide or to Thiophene by Oxidation. The procedures used were essentially identical to those previously described for the conversion of 2,5-diphenyl-1,4-dithiadiene to 2,5-diphenyl-1,4-dithiadiene monosulfoxide and to 2,4-diphenyl-thiophene.[8,3,4] In addition, attempts were made to effect these transformations by oxidation with iodosobenzene.[9] The crude products showed a strong broad infrared absorption band in the region 1022–1052 cm.$^{-1}$, which suggested the possible presence of sulfoxide.[11] They did not show any infrared absorption characteristic of thiophene, and the indophenine[13] test for thiophene was negative in all cases. When the crude products were processed, only unchanged 1,4-dithiadiene was recovered (16 to 30% yield).

Attempted Nitration of 1,4-Dithiadiene. The procedures used, employing nitric acid in acetic acid,[4,16] cupric nitrate

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(12) Preheating of the diethoxy compound I (∼80°) was necessary in order to obtain a homogeneous mixture of its solid and liquid isomers. This was achieved by using an infrared lamp.

(13) H. D. Hartough, "Thiophene and Derivatives," Interscience Publishers Inc., 1952, p. 16.

(14) This molecular weight is based on a freezing point depression of only 0.022°. During the determination, some of the solid came out of solution and, therefore, the value would be expected to be somewhat higher than would have been observed otherwise.

(15) Pastureau, *Comp. rend.*, 140, 1592 (1905).

(16) W. E. Parham, T. M. Roder and W. R. Hasek, *Comp. rend.*, 75, 1647 (1953).

in acetic anhydride,[17] and tetranitromethane[18] were similar to those previously reported. In all cases, tars plus small amounts of acidic material were isolated. With tetranitromethane, an amorphous red solid was obtained but this rapidly decomposed.

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(17) A. G. Anderson, J. A. Nelson and J. J. Tazuma, Comp. rend., 75, 4980 (1953).
(18) G. G. Fritz, Ph.D. Thesis, Univ. of Washington, p. 62 (1956).

Characterization of Several n-Alkyl Esters of Gibberellin A₃ and Their Comparative Biological Activity[1,2]

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The gibberellins, metabolic products of the fungus *Gibberella fujikuroi*, some of which are also native to higher plants,[3,4] have been shown to alter markedly plant behavior.[5,6] As with other growth regulators, some derivatives are biologically active. Takahashi, *et al.*[7] reported that the methyl ester of gibberellin A₃ (gibberellic acid) was inactive but did not specify the bioassay used. Esterification of the hydroxyl group of gibberellin A₃ had no significant effect on biological activity, while esterification of the carboxyl group resulted in compounds which were inactive when applied to the leaves but were slightly active when applied to the root medium.[8] The response from root treatment may have resulted from hydrolysis of the ester in the culture solution.

These results prompted further study of the n-alkyl esters of gibberellin A₃. The synthesis, physical, and chemical properties, and biological activ-

ity of the methyl through the n-decyl esters are described in this report.

EXPERIMENTAL

Esterification of the carboxyl group of gibberellin A₃ was accomplished with the appropriate alkyl iodide similar to the procedure described in the Australian patent of Imperial Chemical Industries Limited.[8] A mixture of 1.5 g. of gibberellin A₃, 6.5 g. of anhydrous potassium carbonate, 3.5 ml. of allkyl iodide, and 60 ml. of dry acetone was refluxed at 62° for 48 hr. with mechanical stirring. After esterification the acetone was removed by distillation *in vacuo* and the residue washed with water. The esters were further purified by recrystallization from a mixture of ethyl acetate and benzene. All esters were recrystallized to a constant melting point and subjected to carbon and hydrogen analysis. The chemical and physical properties are given in Table I.

BIOLOGICAL ACTIVITY

The comparative biological activities of the esters of gibberellin A₃ in stimulating germination of lettuce seed in the dark, parthenocarpic growth of tomato ovaries, and stem elongation of the bean were determined.

Solutions were prepared by dissolving the appropriate ester in a few drops of ethanol and diluting to the desired volume with distilled water. One hundred lettuce seeds (var. Grand Rapids) were placed in a Petri dish on Whatman No. 1 filter paper, and 5 ml. of the ester solution ($3 \times 10^{-5} M$) were added to each dish. Seeds similarly treated with five milliliters of distilled water and a comparable concentration of ethanol were used as a control. Seeds were germinated in an incubator at $26 \pm 0.5°$ for 96 hr. Each treatment was replicated five times and the experiment performed twice. In parthenocarpic fruit growth the esters were applied in lanolin paste in concentrations of 3×10^{-3} to $3 \times 10^{-6} M$ directly to emasculated ovaries of the Michigan-Ohio Hybrid tomato variety. The diameter of the ovaries was measured 5 days after the treatment. Comparative stimulation of stem elongation was determined with Blue Lake beans. Ten ml. of a 3×10^{-5} or $3 \times 10^{-6} M$ solution was applied to the epicotyl apex and stem elongation (distance from cotyledon to epicotyl apex) was determined after 48 hr.

Methyl, ethyl, n-propyl, n-butyl, n-amyl, n-hexyl, and n-heptyl gibberellates significantly increased the per cent of lettuce seed that germinated in the dark (Table I) with the methyl, ethyl, n-propyl, n-butyl, and n-amyl gibberellates equal to or approaching the activity of gibberellin A₃. Germination was not significantly enhanced by the n-octyl, n-nonyl, or n-decyl gibberellates. Parthenocarpic development of tomato ovaries and stem elongation in the bean were not significantly stimulated by any of the esters of the carboxyl grouping of gibberellin A₃. The promotive responses obtained from methyl, ethyl, n-propyl, n-butyl, n-amyl, n-hexyl, and n-heptyl gibberellates in lettuce seed germination in

(1) Journal Article No. 2462 from the Michigan Agricultural Experiment Station, East Lansing.
(2) This research was supported by the Horace H. Rackham Research Endowment.
(3) J. MacMillan and P. J. Suter. *Die Naturwiss.*, 45, 1 (1958).
(4) C. A. West and K. H. Murashige, *Plant Physiol.*, Suppl., 33, 38 (1958).
(5) B. B. Stowe and T. Yamaki, *Science*, 129, 807 (1959).
(6) S. H. Wittwer and M. J. Bukovac, *Econ. Bot.*, 12, 213 (1958).
(7) N. Takahashi, H. Kitamura, A. Kawarda, V. Seta, M. Takai, S. Tamura, and Y. Sumiki, *Bull. Agri. Chem. Soc. Japan*, 19, (4), 267 (1955).
(8) Pat. Appl. Imperial Chemical Industries, Ltd., Q 11504 A 11656 A Commonwealth of Australia 28.6.55.10190. (1955).

TABLE I

CHEMICAL AND PHYSICAL PROPERTIES OF SEVERAL n-ALKYL ESTERS OF GIBBERELLIN A_3 AND THEIR COMPARATIVE EFFECT ON GERMINATION OF LETTUCE SEED IN THE DARK
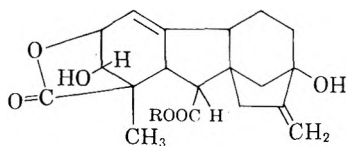
R	Empirical Formula	Carbon %		Hydrogen %		M.P., °C.	Germination of Lettuce Seed, %
		Calcd.	Found	Calcd.	Found		
Control							41.2[b]
H (Gibberellin A_3)							80.6
Methyl	$C_{20}H_{24}O_6$	66.6[a]	66.2	6.7	6.6	202	63.5
Ethyl	$C_{21}H_{26}O_6$	67.4[a]	67.7	7.0	7.1	155	78.4
n-Propyl	$C_{22}H_{28}O_6$	68.0	67.9	7.3	7.5	138	68.9
n-Butyl	$C_{23}H_{30}O_6$	68.6[a]	68.5	7.5	7.6	145	83.7
n-Amyl	$C_{24}H_{32}O_6$	69.2	69.0	7.7	7.7	165–66	79.1
n-Hexyl	$C_{25}H_{34}O_6$	69.7	69.5	7.9	7.9	188–89	56.8
n-Heptyl	$C_{26}H_{36}O_6$	70.2	70.1	8.2	8.2	181–82	57.2
n-Octyl	$C_{27}H_{38}O_6$	70.7[a]	70.6	8.4	8.4	157–58	48.0
n-Nonyl	$C_{28}H_{40}O_6$	71.2	71.5	8.5	8.9	131–32	46.7
n-Decyl	$C_{29}H_{42}O_6$	71.6	71.6	8.7	8.8	102.5–108.5	40.0

[a] Cf. ref. (8). [b] L.S.D. at p. 05: 11.7. L.S.D. at p. 01: 16.4.

the dark may have resulted from hydrolysis of the esters to the acid (gibberellin A_3) in the aqueous germinating medium or hydrolysis within the seed or seedling after imbibition.

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Chloromethylation of 1,2,4-Trimethylbenzene

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Previous investigators[1,2] of the chloromethylation of 1,2,4-trimethylbenzene (I) reported the product to be 2,4,5-trimethylbenzyl chloride (II). We have found the product, obtained in 78% yield, to be a mixture of 75% of 2,4,5-trimethylbenzyl chloride (II), 22% of 2,3,6-trimethylbenzyl chloride (III) and 2% of 2,3,5-trimethylbenzyl chloride (IV). The mixture boiled over a range of 3° and all fractions showed essentially identical refractive indices and infrared spectra. The mixture was nonseparable by vapor phase chromatography.

(1) L. I. Smith and C. W. MacMullen, *J. Am. Chem. Soc.*, **58**, 629 (1936).

(2)(a) G. Vavon and J. Bolle, *Compt. rend.*, **204**, 1826 (1937); *Bull. soc. chim.* (5), **6**, 1025 (1939). (b) W. John and P. Günther, *Ber.*, **74B**, 879 (1941) report that chloromethylation of pseudocumene under conditions similar to our own, gives in addition to the main product (b.p. 98–108°/1 mm.), a by-product, $C_{11}H_{14}Cl_2$, b.p. 120–130°/1 mm., m.p. 99–101°. The latter is presumably an isomeric α,α'-dichloropentamethylbenzene.
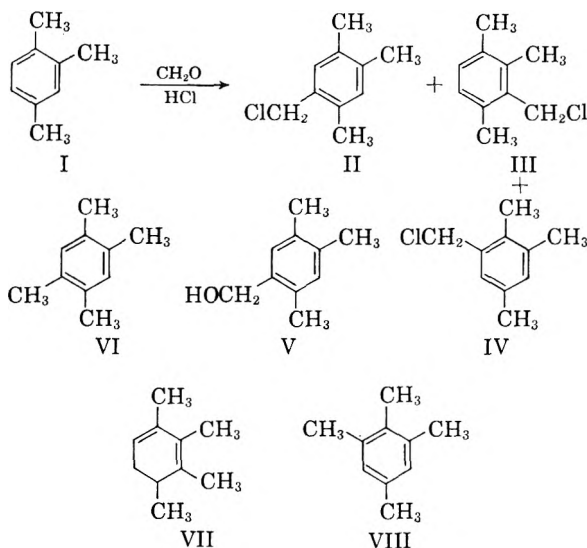
From the hydrolyzed chloride mixture was isolated 2,4,5-trimethylbenzyl alcohol (V, m.p. 81–82°) whose identity was confirmed by reduction to 1,2,4,5-tetramethylbenzene (VI). Authentic 2,4,5-trimethylbenzyl chloride (II) obtained from 2,4,5-trimethylbenzyl alcohol (V) showed a refractive index which was similar, but an infrared spectrum which was different, from that of the original mixture. Using authentic II as standard, the infrared spectrum of the original mixture indicated the presence of 74% of II.

The chloride mixture was further characterized by catalytic reduction to a mixture of tetramethylbenzenes whose infrared spectrum showed the presence of 76% of 1,2,4,5-tetramethylbenzene (VI), 22% of 1,2,3,4-tetramethylbenzene (VII) and 2% of 1,2,3,5-tetramethylbenzene (VIII). The analytical value for VI was obtained by direct com-

parison with the spectrum of an authentic sample. The values for VII and VIII were obtained using bands corresponding to those of published spectra,[3] assuming the mixture to contain only VI, VII, and VIII, as evidenced by elemental analysis and molecular weight.

Permanganate oxidation of the initial mixture of benzyl chlorides gave 1,2,4,5-benzenetetracarboxylic acid in 36% yield.

EXPERIMENTAL

The melting and boiling points are uncorrected.

Chloromethylation of 1,2,4-trimethylbenzene.[4] A mixture of 240 g. (2.0 mol.) of 1,2,4-trimethylbenzene (I), 178 g. (2.2 mol.) of formalin and 1250 ml. of concentrated hydrochloric acid was stirred for 6 hr. at 60–65° in the presence of a slow stream of hydrogen chloride. The product was extracted with petroleum ether (b.p. 40–45°) and the extract washed successively with water, aqueous bicarbonate and water, dried, and concentrated. The concentrate was distilled through a 13-cm. Vigreux column, and the major fraction (289 g., b.p. 40–105°/1.1 mm.) redistilled through a 50-cm. Vigreux column to yield 264 g. (78%) of trimethylbenzyl chloride; b.p. 106–109°/6 mm., n_D^{25} 1.5410 (lit.[1] b.p. 111–116°/6 mm.).

Anal. Calcd. for $C_{10}H_{13}Cl$: C, 71.21; H, 7.77; Cl, 21.02. Found: C, 71.43; H, 7.81; Cl, 20.99.

A solid fraction (31.5 g., 7% yield, b.p. 99–112°/0.05 mm.) obtained in the first distillation was crystallized from *n*-hexane to give 8.0 g. of white solid (m.p. 83–83.5°), presumably an α,α′-dichloropentamethylbenzene.[2b]

Anal. Calcd. for $C_{11}H_{14}Cl_2$: C, 60.84; H, 6.50; Cl, 32.66; mol. wt., 217.1. Found: C, 60.90; H, 6.71; Cl, 32.76; mol. wt., 213.

2,4,5-Trimethylbenzyl alcohol (V). A mixture of 16.9 g. (0.10 mol.) of trimethylbenzyl chloride, 11.0 g. (0.10 mol.) of sodium carbonate and 100 ml. of water was refluxed for 12 hr. The crude product which separated on cooling (14.5 g., 97% yield, m.p. 51–75°) was crystallized from *n*-hexane to yield 5.2 g. (35%) of silky white needles of 2,4,5-trimethylbenzyl alcohol (V, m.p. 83–83.5°, lit.[1] m.p. 83–83.5°).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.40. Found: C, 79.92; H, 9.17.

2,4,5-Trimethylbenzyl N-phenylcarbamate. The carbamate, m.p. 98–99°, was obtained as white needles by crystallization from petroleum ether (b.p. 40–45°).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.02; H, 7.16; N, 5.22.

Bis-trimethylbenzyl ether. Concentration of the mother liquor from the crystallization of 2,4,5-trimethylbenzyl alcohol yielded 7.7 g. of semisolid, 2.0 g. of which was chromatographed on a silica gel column to give 1.0 g. of a chloroform-eluted fraction, m.p. 80–90°. Crystallization of the eluate from *n*-hexane gave white plates, m.p. 99.5–100.5°, presumably a bis-trimethylbenzyl ether.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.05; H, 9.28. Found: C, 84.82; H, 9.37.

The remaining fractions were oily and the only identified product isolated therefrom was 0.10 g. of 2,4,5-trimethylbenzyl alcohol.

Reduction of 2,4,5-trimethylbenzyl alcohol to 1,2,4,5-tetramethylbenzene. To a suspension of 3.76 g. (0.025 mol.) of

2,4,5-trimethylbenzyl alcohol in 100 ml. of liquid ammonia and 3.5 g. of absolute ethanol was added, during 45 min., 1.8 g. (0.075 g.-atom) of sodium. After evaporation of the ammonia the product was decomposed with ice and extracted with ether. The extract was concentrated and the residue washed with ethanol. The product (2.70 g., 81% yield) was crystallized from ethanol; melting point and mixture melting point with an authentic specimen 80–81° (lit.[5] m.p. 80°).

2,4,5-Trimethylbenzyl chloride (II). (A). A mixture of 6.81 g. (0.045 mol.) of 2,4,5-trimethylbenzyl alcohol (V) and 150 ml. of concentrated hydrochloric acid was stirred for 0.5 hr. at 25° followed by extraction with petroleum ether (b.p. 40–45°). The extract was washed, dried, concentrated, and the residue distilled to yield 6.47 g. (85%) of 2,4,5-trimethylbenzyl chloride (II); b.p. 108–109°/6.3 mm., n_D^{25} 1.5400.

(B) A warm solution of 6.81 g. (0.045 mol.) of 2,4,5-trimethylbenzyl alcohol (V) in 50 ml. of benzene was added during 20 min. to a solution of 6.50 g. (0.054 mol.) of thionyl chloride and 5.4 g. (0.068 mol.) of pyridine in 25 ml. of benzene. After refluxing for 1 hr. the benzene layer was decanted from a small semisolid residue, washed successively with water, aqueous bicarbonate and water, dried and concentrated. Distillation of the residue yielded 5.12 g. (68%) of 2,4,5-trimethylbenzyl chloride (II); b.p. 111–112°/6.8 mm., n_D^{25} 1.5399. The infrared spectra of the products obtained by methods A and B were identical.

Anal. Calcd. for $C_{10}H_{13}Cl$: C, 71.21; H, 7.77; Cl, 21.02. Found: C, 71.06; H, 7.57; Cl, 20.86.

Reduction of trimethylbenzyl chloride mixture. A solution of 16.8 g. (0.10 mol.) of the above mixture in 100 ml. of dioxane was hydrogenated at 25° under an initial pressure of 60 p.s.i. in the presence of 14.5 g. (0.12 mol.) of dimethylaniline and 0.5 g. of 10% palladiumized charcoal. The theoretical hydrogen uptake was reached in 2 hr. Dimethylaniline hydrochloride (16.6 g., 105% of theory, m.p. 82.5–86.5°) was recovered from the filtrate. The filtrate was concentrated and the residue dissolved in petroleum ether (b.p. 40–45°). The solution was washed successively with dilute hydrochloric acid, water, aqueous bicarbonate, dried, concentrated, and the residue distilled to yield 9.55 g. (71%) of a mixture of tetramethylbenzenes, b.p. 105–111°/49 mm.

Anal. Calcd. for $C_{10}H_{14}$: C, 89.49; H, 10.51; mol. wt., 134.2. Found: C, 89.49; H, 10.57; mol. wt., 137.

Quantitative infrared analysis of the tetramethylbenzene mixture showed 76% of VI, 22% of VII, and 2% of VIII. The bands appearing at 868, 804, and 847 cm.$^{-1}$ were used. These correspond to the literature values[3] of 867, 805, and 848 cm.$^{-1}$ for VI, VII, and VIII, respectively.

Crystallization of the mixture of tetramethylbenzenes from ethanol yielded colorless plates of 1,2,4,5-tetramethylbenzene (VI); melting point and mixture melting point with an authentic specimen 79–80° (lit.[5] m.p. 80°).

1,2,4,5-Benzenetetracarboxylic acid. A mixture of 8.43 g. (0.05 mol.) of the initial trimethylbenzyl chloride product, 5.3 g. (0.05 mol.) of sodium carbonate and 250 ml. of water was stirred and refluxed for 10 hr. while 79.0 g. (0.50 mol.) of potassium permanganate was added. Manganese dioxide was removed by filtration and excess permanganate in the filtrate destroyed with bisulfite. The filtrate, acidified with hydrochloric acid, was concentrated to 75 ml. and cooled to yield 8.66 g. of white crystals, m.p. >360°. Recrystallization of the product from dilute hydrochloric acid yielded 5.18 g. (36%) of 1,2,4,5-benzenetetracarboxylic acid dihydrate; m.p. 262–265°, lit.[6] m.p. 264°. Water of hydration was determined by heating to constant weight at 65°/0.05 mm.

(3) American Petroleum Institute, Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pa., *Catalog of Infrared Spectral Data*, Ser. No.'s 1592, 1295, 1591.

(4) Obtained from A. D. Little Co., 95.5% pure by ultraviolet analysis.

(5) L. I. Smith, *Org. Syntheses*, Coll. Vol. II, 248 (1943).

(6) G. Schroeter, *Ber.*, 57, 2003 (1924).

Anal. Calcd. for $C_{10}H_6O_8 \cdot 2H_2O$: H_2O, 12.42. Found: H_2O, 12.40. Calcd. for $C_{10}H_6O_8$: Neut. eq., 63.5. Found: Neut. eq., 63.8.

Acknowledgment. This work was done by the Monomers Fellowship, sustained by Koppers Co., Inc. The assistance of Messrs. Harry Nelson, William Baer, and Robert Massey in performing some of the analytical work is gratefully acknowledged.

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New Synthesis of α-Keto Esters

JOHN P. SCHAEFER AND E. J. COREY[1]

The importance of α-keto acids and their derivatives as vital biochemical intermediates[2] makes a direct and efficient synthesis of these compounds particularly desirable. We have accomplished this objective by making use of the remarkable ability of selenium dioxide to oxidize active methylene groups.[3,4]

We have found that the reaction of selenium dioxide with an α-bromo ketone of the type $RCOCH_2Br$ in an anhydrous alcohol as solvent produces the corresponding α-keto ester in high yield. From α-bromoacetophenone in absolute ethanol a 70% yield of ethyl benzoylformate was obtained. When methanol was employed as the solvent, the methyl ester was formed in 80% yield.

The reaction path probably involves conversion of the α-halomethyl group to an acid bromide. This would then react rapidly with the solvent to produce the keto ester. The mechanism of the oxidation step is probably the same as that recently postulated by Corey and Schaefer[5] for the reaction of selenium dioxide with a ketone of the type $RCOCH_2R$ to produce an α-diketone.

EXPERIMENTAL

Ethyl benzoylformate. To 9.0 grams (0.074 mol.) of selenium dioxide dissolved in 75 ml. of boiling absolute ethanol was added 15.0 g. of α-bromoacetophenone; the resulting solution was refluxed for 12 hr. The extracts were then poured into water, extracted with ether, dried over magnesium sulfate, and distilled to give 9.2 g. (70% yield) of the desired ester, b.p.₂ 97–98°.[6]

(1) Address all inquiries to E. J. Corey, Department of Chemistry, Harvard University, Cambridge, Mass.

(2) H. A. Krebs, *Advances in Enzymology*, **3**, 191 (1943).

(3) H. L. Riley, J. F. Morley, and N. A. C. Friend, *J. Chem. Soc.*, 1875 (1932).

(4) N. Rabjohn, *Org. Reactions*, V, 331 (1947).

(5) E. J. Corey and J. P. Schaefer, *in press*. See also abstracts of the Sixteenth National Organic Chemistry Symposium of the American Chemical Society, p. 65 (1959).

(6) B. B. Corson, R. A. Dodge, S. A. Harris, and R. K. Hazen, *Org. Syntheses*, VIII, 68 (1928).

Methyl benzoylformate. The same procedure was used to form the methyl ester with the exception that methanol was used as the solvent. The yield was 80%, b.p.₁₄ 137°.[7]

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(7) I. Heilbron, *Dictionary of Organic Compounds*, Vol. I, 262 (1953).

Simplified Zinc-Copper Couple for Use in Preparing Cyclopropanes from Methylene Iodide and Olefins

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It has been recently found that olefins react with methylene iodide and zinc-copper couple to give cyclopropanes.[1] This elegant reaction is quite general in that it is applicable to olefins which are hindered and are either electronegatively- or electropositively-substituted. The method for preparing the zinc-copper couple is important with respect to its reactivity with methylene iodide and its reproducibility for preparing cyclopropanes. The zinc (90%)-copper (10%) couple which has been used most effectively previously is prepared by reaction of zinc dust, cupric oxide, and hydrogen at 500°[1,2] and is subsequently activated by iodine. For purposes of synthesis, this method of obtaining the couple is inconvenient; the activity of the couple is also affected by the temperature at which it is prepared. Couples derived from granulated zinc and copper powder do give cyclopropanes but in erratic yields; those obtained by thermal decomposition of cupric citrate in the presence of zinc dust react with methylene iodide with difficulty.[1]

We would like to report a simple zinc-copper couple which is satisfactory for effecting reaction of methylene iodide with olefins to give cyclopropanes. The couple is prepared simply and rapidly by successive washing of zinc powder with hydrochloric acid (3%), aqueous copper sulfate (2%), water, ethanol, and ethyl ether, respectively.[3] The results obtained for reaction of methylene iodide and the zinc-copper couple in ethyl ether with 1-octene, cyclohexene, (+)-limonene and dihydropyran are

(1) (a) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **80**, 5323 (1958). (b) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **81**, 4256 (1959). (c) The present authors should like to acknowledge the private communications of the previous investigators concerning the scope and details of their experimental studies.

(2) F. L. Howard, *J. Research Natl. Bur. Standards*, **24**, 677 (1940); F. R. Buck, B. B. Elsner, E. J. Forbes, S. H. Morrell, J. C. Smith, and E. R. Wallsgrove, *J. Inst. Petroleum*, **34**, 339 (1948).

(3) The method of preparing the zinc-copper couple is essentially that of G. F. Hennion and J. J. Sheehan, *J. Am. Chem. Soc.*, **71**, 1964 (1949).

TABLE I
REACTIONS OF OLEFINS WITH METHYLENE IODIDE/ZINC-COPPER COUPLE

Olefin	Olefin (mol.)	CH$_2$I$_2$ (mol.)	Zn(Cu) (mol.)	Reaction Time (hr.)	Product	Yield, %
1-Octene[a]	0.40	0.20	0.30	19	n-hexylcyclopropane[b]	55[c,d]
1-Octene[a]	0.40	0.20	0.30	67	n-hexylcyclopropane[b]	50[c]
1-Octene[e]	0.40	0.20	0.25	30	n-hexylcyclopropane[b]	48[c]
1-Octene[a]	0.40	0.25	0.20	48	n-hexylcylcopropane[b]	47[c]
1-Octene[a]	0.40	0.20	0.50	41	n-hexylcyclopropane[b]	38[c]
Cyclohexene[a]	0.30	0.15	0.22	67	bicyclo [4.1.0]-heptane[f]	50[c,d]
Cyclohexene[a]	0.40	0.20	0.30	64	bicyclo [4.1.0]-heptane[f]	47[c]
(+)-Limonene[a]	0.15	0.30	0.33	70	1-methyl-4-(1-methyl-cyclopropyl)cyclohexene[g]	51[d]
Dihydropyran[e,h]	0.15	0.25	0.33	20	2-oxabicyclo [4.1.0] heptane[e]	66[c]

[a] Reaction was effected by adding a mixture of olefin, methylene iodide, and ether to zinc-copper couple. [b] B.p. 148–150°, n_D^{25} 1.4173; lit.[1] b.p. 148°, n_D^{25} 1.4160. [c] Yield computed by gas chromatographic methods. [d] The reaction product was rectified. [e] Reaction was effected by first initiating reaction of zinc-copper couple, methylene iodide, and iodine (0.0006 mol) in ether and then adding the olefin in ether. [f] B.p. 116°, n_D^{25} 1.4542; lit.[1] b.p. 116.5°, n_D^{25} 1.4546. [g] B.p. 69.5–70.2° (8 mm.), n_D^{25} 1.4687; lit.[1] b.p. 73° (8.5 mm), n_D^{25} 1.4679. [h] The reaction mixture was filtered, washed with excess ammonium hydroxide and then with water until neutral, dried, and distilled.

summarized in Table I. The couple may be prepared in large quantity and compares favorably in general for purposes of synthesis with that obtained by the more elaborate methods. The couple is sufficiently active that it will usually react in ether upon addition of the mixture of olefin and methylene iodide. Reaction could not be initiated in this manner with dihydropyran and methylene iodide. The addition could be executed satisfactorily however by first heating an ether solution of methylene iodide and zinc-copper couple in the presence of iodine and then adding a mixture of dihydropyran in ether. The latter technique has been used successfully with the other olefins and is recommended for use in the Simmons-Smith reaction.

EXPERIMENTAL

Preparation of the zinc-copper couple. Zinc powder (32.8 g., 0.5 mol., Mallinckrodt Analytical Reagent) was washed successively with hydrochloric acid (3%, 4 × 25 ml.), distilled water (4 × 30 ml.), aqueous copper sulfate (2%, 2 × 50 ml.), distilled water (4 × 30 ml.), absolute ethanol (4 × 30 ml.) and absolute ether (5 × 25 ml.).[4] The couple was finally transferred to a Buchner funnel, washed with additional anhydrous ether, covered tightly with a rubber dam, and suction-dried until it reached room temperature. The zinc-copper couple is ready for immediate use in preparation of cyclopropanes.

n-Hexylcyclopropane. A typical procedure for preparing n-hexylcyclopropane from 1-octene is described (see Table I). This procedure has also been adapted to the synthesis of the other cyclopropanes of the present study.

Methylene iodide (53.6 g., 0.20 mol.) and iodine (0.15 g.,

(4) The washings were performed conveniently by stirring a mixture of the zinc powder and each wash solution with a porcelain spatula in an open beaker and then decanting the supernatant liquid. (b) The washings with hydrochloric acid should be done rapidly to avoid adsorption of hydrogen on the zinc which makes subsequent washings more difficult. (c) The absolute ethanol and absolute ether washings were decanted directly on a Buchner funnel to prevent loss of the couple.

0.0006 mol.) were added to a mixture of zinc-copper couple (16.3 g. of zinc, 0.25 mol.) and anhydrous ether (165 ml.) in a flask equipped with a stirrer and an efficient water condenser fitted with a calcium chloride tube. The iodine color disappeared immediately; the initial gray-colored mixture was then refluxed for 30 min.[5] During this period the mixture turned darker; the color change was accompanied by a gentle exothermic reaction. External heating was discontinued and 1-octene (44.8 g., 0.4 mol.) in anhydrous ether (25 ml.) was added dropwise in 30 min. During the addition the mixture continued to reflux. Heating was resumed and the mixture refluxed for 30 hr.[6] The reaction mixture was cooled and filtered through a Super Cel pad on a Buchner funnel. The residue was washed thoroughly with ether. The ether solution was extracted with hydrochloric acid (5%, 3 × 50 ml.; to remove dissolved zinc iodide), aqueous sodium bicarbonate (3 × 50 ml.), and saturated aqueous sodium chloride. The aqueous washings were washed with ether; the combined ether extract was filtered through anhydrous magnesium sulfate. After the ether had been removed through a packed column, a mixture (47.7 g.) of 1-octene and n-hexylcyclopropane remained.[7] Analysis by gas-phase chromatography (40% polyethylene glycol column, 50°; carrier gas, nitrogen, 17 cm. pressure) revealed that n-hexylcyclopropane was obtained in 48% yield. Rectification of an aliquot of the reaction mixture in a Nester spinning band column allowed separation of n-hexylcyclopropane in ~50% yield, b.p. 148–150°, n_D^{25} 1.4173, infrared absorption for a cyclopropane ring at 9.88μ, no absorption for an olefin at 6.08μ: lit.[1] b.p. 148°, n_D^{25} 1.4160.

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(5) The minimum time for effecting initiation has not been determined.

(6)(a) The reaction is essentially complete after 4–6 hours of refluxing. At this time the mixture assumes a dark red-brown color and precipitation of white zinc iodide is apparent. (b) The presence of active reagent from methylene iodide–zinc–copper can be determined conveniently by adding an aliquot to water and noting the volume of gases produced. (c) There were no differences apparent when these reactions were conducted under nitrogen or in the presence of air.

(7) The infrared spectra of the mixture indicated the absence of any methylene iodide.

# Potential Anticancer Agents.[1] XXV. Monofunctional Alkylating Agents Derived from 2-Methylbenzimidazole

W. A. Skinner, Marc G. M. Schelstraete,
and B. R. Baker

In a recent hypothesis[2] it was suggested that some nitrogen mustard derivatives derived from substrates might operate as irreversible inhibitors by fitting the enzyme site for the substrate, then combining irreversibly with the enzyme by alkylation. If such were the case, then only one alkylating group, rather than the usual two alkylating groups of the bis-nitrogen mustards, would be necessary for irreversible inhibition. One way of evaluating this hypothesis is to synthesize and test monofunctional alkylating analogs of nitrogen mustards derived from carriers that are substrates or substrate inhibitors. Since benzimidazole can act as an antagonist of adenine in some systems,[3-5] and since 2 - [bis(2 - chloroethyl)aminomethyl]benzimidazole (IX) is a mustard with antitumor activity[6] against *Ehrlich ascites carcinoma, Adenocarcinoma* 755, *Adenocarcinoma* EO-771, and *Sarcoma* 180, the synthesis and testing of four "one-armed" mustards related to IX were undertaken.

2-(Chloromethyl)benzimidazole (I)[7] reacted with 2-ethylaminoethanol in boiling ethanol to yield crystalline 2-[N-ethyl-N-(2-hydroxyethyl)aminomethyl]benzimidazole (II) in 52% yield. Treatment of II with thionyl chloride in boiling chloroform yielded the "one-armed" mustard as its dihydrochloride (III) in 26% yield.

Ethylenimine reacted readily with 2-(chloromethyl)-benzimidazole (I) in ethanol at room temperature using potassium carbonate as an acid acceptor. The substituted ethylenimine (IV) was obtained in 71% yield as an unstable oil. Higher temperatures for the reaction were unsuccessful, since the product (IV) was noticeably unstable above 50°. When a solution of IV in chloroform was treated with anhydrous hydrogen chloride, a solid precipitated in 80% yield which proved to be 2-[(2-chloroethyl)-aminomethyl]benzimidazole dihy-

drochloride (V). That the ethylenimine group of IV had opened to a 2-chloroethylamine (V) was unequivocally proven by the presence of three chlorines in the product, since of the possible products only V could accommodate three chlorines per mole.
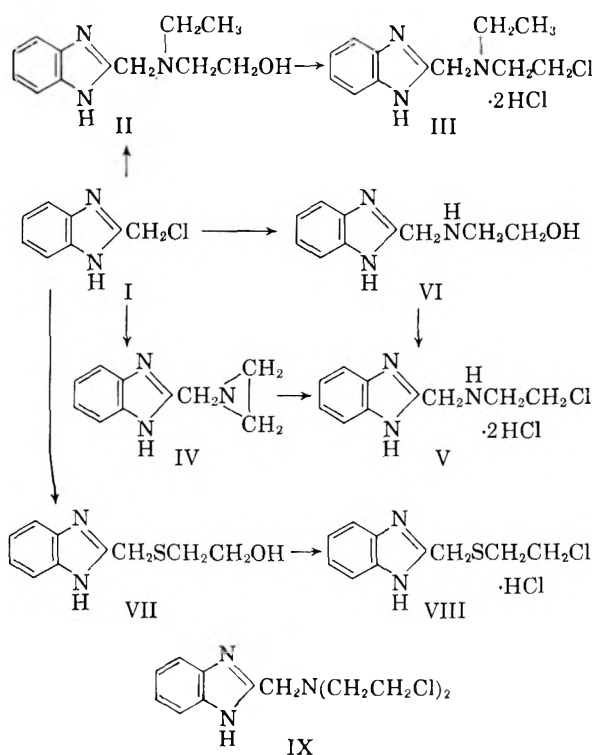
A second route to V appeared to be less promising. 2 - [(2 - Hydroxyethyl)aminomethyl]benzimidazole (VI), prepared in 72% yield from 2-aminoethanol and I, readily reacted with thionyl chloride. However, chlorine analyses of the various crystalline preparations inconsistently indicated between two and three chlorine atoms per molecule.

A hemi-sulfur mustard derivative (VIII) of 2-methylbenzimidazole was also synthesized from 2-(chloromethyl)benzimidazole (I). Reaction of I with an excess of potassium 2-hydroxyethylmercaptide in absolute ethanol at room temperature gave a 45% yield of 2-[(2-hydroxyethyl)thiomethyl]benzimidazole (VII) as an oil, characterized as its crystalline picrate. If higher temperatures and lower ratios of the mercaptide were employed, then a bis-benzimidazole derivative of 2-mercaptoethanol was obtained. Replacement of the hydroxyl group of VII with chlorine proceeded smoothly with thionyl chloride in boiling chloroform, the crystalline hydrochloride (VIII) being obtained in 81% yield.

Biological results. The four "one-armed" mustards were evaluated[8] against *Sarcoma* 180, *Carcinoma* 755, *Leukemia* L-1210 and *Ehrlich ascites*. With *Leukemia* L-1210, only V (9 mg./kg.) showed a positive response, giving borderline activity. Only VIII showed activity against *Carcinoma*

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* J. DeGraw, L. Goodman, R. Koehler, and B. R. Baker, *J. Org. Chem.,* **24,** 1629 (1959).

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(6) E. Hirschberg, A. Gellhorn, and W. S. Gump, *Cancer Research,* **17,** 904 (1957).

(7) A. Bloom and A. R. Day, *J. Org. Chem.,* **4,** 14 (1939).

(8) We wish to thank Dr. Joseph Greenberg and staff of this Institute for the test data, performed under contract with the Cancer Chemotherapy National Service Center.

755, being borderline[9] at 60 mg./kg. All four compounds were inactive against *Sarcoma* 180. However, both III (18 mg./kg.) and VIII (60 mg./kg.) gave a 47% extension of life of mice bearing *Ehrlich ascites;* V (18 mg./kg.) gave a less significant 28% extension.

The "two-armed" mustard, 2-[bis(2-chloroethyl)-aminomethyl]benzimidazole (IX) has been reported[6] to give, at 8 mg./kg., a 94% life extension of mice bearing *Ehrlich ascites*, near borderline activity[9] on *Carcinoma* 755 and no activity with *Leukemia* L-1210 or *Sarcoma* 180.[9]

Comparison of the data obtained with the four "one-armed" mustards to that of the "two-armed" mustard (IX) does not allow an unequivocal conclusion on whether the "two-armed" mustard (IX) can or cannot act as an irreversible enzyme inhibitor. Nevertheless, the sought-for increased effectiveness of "one-armed" mustards in the benzimidazol series was not found, except perhaps for *Leukemia* L-1210.

EXPERIMENTAL

2-[N-Ethyl-N-(2-hydroxyethyl)aminomethyl]benzimidazol (II).[10] To a suspension of 75 g. (0.45 mol.) of 2-(chloromethyl)benzimidazole (I)[7] in 175 ml. of absolute ethanol, stirred in an ice bath, was added 112 ml. (1.15 mol.) of 2-ethylaminoethanol. The resulting mixture was heterogeneous, but upon slight heating became homogeneous. The solution was refluxed for 16 hr., cooled, then poured into 500 ml. of 4N aqueous sodium hydroxide solution. This solution was evaporated *in vacuo* and the residue partitioned between 200 ml. of distilled water and 500 ml. of chloroform. The aqueous phase was extracted with chloroform (2 × 100 ml.). After being dried with anhydrous magnesium sulfate, the combined chloroform solutions were evaporated *in vacuo*, yielding 98.7 g. of a yellow, tacky solid. The solid was dissolved in methanol, clarified with Norit, and crystallized by the addition of benzene; yield 51.4 g. (52%), m.p. 149–150.0°; $\lambda_{max(\mu)}^{KBr}$ 3.52, (NH), 9.55 (C—OH), 13.40 (o-disubstituted benzene); $\lambda_{max(\mu)}^{ethanol}$ 276 (ϵ7600), 282 (ϵ820C). The compound moved as a single spot (R_f 0.73) on paper[11] as detected by its ultraviolet absorption spectrum.

Anal. Calcd. for $C_{12}H_{17}N_3O$: C, 65.7; H, 7.81; N, 19.2. Found: C, 65.9; H, 8.05; N, 19.0.

2-[N-Ethyl-N-(2-chloroethyl)aminomethyl]benzimidazole dihydrochloride (III). A solution of 21.9 g. (0.10 mol.) of 2-[N-ethyl-N-(2-hydroxyethyl)aminomethyl]benzimidazole (II) in 200 ml. of chloroform was added with shaking to a solution of 100 ml. (1.4 mol.) of thionyl chloride in 150 ml. of chloroform. The system was refluxed for 4 hr. and allowed to remain overnight at room temperature. The solution was evaporated *in vacuo* (bath 40–50°). The solid residue was dissolved in methanol, clarified with Norit, and concentrated *in vacuo* until an oil began to separate. Benzene (200 ml.) was added and the solution again concentrated

(9) Borderline activity is defined as a ratio of tumor weights in treated animals to tumor weights in control animals (T/C) of 0.38–0.54. Above 0.54 is considered inactive; *cf. Cancer Chemotherapy Reports,* No. 1, p. 60 (1959), published by the Cancer Chemotherapy National Service Center, Bethesda, Md.

(10) This compound was first prepared by Dr. S. Fuqua of these laboratories.

(11) Paper chromatograms were run by the descending technique on Whatman No. 1 paper with butanol-acetic acid-water (5/2/3).

in vacuo until crystals appeared; yield 8.02 g. (26%), m.p. >160° (dec.); $\lambda_{max(\mu)}^{KBr}$ 3.60–3.75 (NH), 4.15 (NH$^+$), 6.20 (aryl), absence of C—OH, 9.55.

Anal. Calcd. for $C_{12}H_{16}ClN_3 \cdot 2HCl$: C, 46.4; H, 5.84; Cl, 34.2. Found: C, 46.0; H, 5.47; Cl, 34.0.

2-(Ethyleniminomethyl)benzimidazole (IV). To a solution of 5.01 g. (0.030 mol.) of 2-(chloromethyl)benzimidazole (I) in 200 ml. of absolute methanol were added in rapid succession 3.11 g. (0.020 mol.) of finely powdered anhydrous potassium carbonate and 7.80 ml. (0.15 mol.) of ethylenimine. The reaction mixture was stirred vigorously for 6 hr. at room temperature, filtered, and the filtrate evaporated *in vacuo* (bath 25°) to give 8.63 g. of a semisolid residue. The residue was partitioned between 50 ml. of water and chloroform. The chloroform layer was evaporated to dryness *in vacuo* (bath 25°) to yield 5.10 g. (71%) of a pale amber liquid; $\lambda_{max(\mu)}^{liquid}$ 6.15 (aryl), 6.25 (C=N), 6.95, 7.85 (benzimidazole ring), 13.40 (o-disubstituted benzene). All attempts to crystallize this liquid have failed.

This compound was characterized by treatment with hydrogen chloride to yield V.

2-[(2-Chloroethyl)aminomethyl]benzimidazole dihydrochloride (V). A solution of 2.0 g. (0.012 mol.) of the oily imine derivative IV in 50 ml. of chloroform was cooled in an ice bath and gaseous hydrogen chloride was bubbled through the solution over a period of 1 hr. The white solid which separated was collected on a filter; yield 2.61 g. (80%) of product, m.p. 228–231° (dec.). Recrystallization of this compound from methanol saturated with hydrogen chloride by the addition of benzene gave a product, m.p. 231–238° (dec.); $\lambda_{max(\mu)}^{Nujol}$ 3.75, 3.92 (NH$^+$), 6.20 (C=N), 13.35 (o-disubstituted benzene), absence of C—OH, 9.55.

Anal. Calcd. for $C_{10}H_{12}ClN_3 \cdot 2HCl$: C, 42.5; H, 5.00; Cl, 37.6. Found: C, 42.7; H, 5.00; Cl, 37.1, 36.5, 35.9. The percentage of chloride decreased upon standing, as shown by the three consecutive analyses.

2-[(2-Hydroxyethyl)aminomethyl]benzimidazole (VI). A solution of 14.4 g. (0.086 mol.) of I and 8.0 g. (0.13 mol.) of 2-aminoethanol in 90 ml. of absolute ethanol was refluxed for 4 hr. The solvent was removed *in vacuo* (bath 50°), yielding a yellow semisolid, which was dissolved in 20 ml. of hot methanol and added to 400 ml. of water and 100 g. of ice; yield 11.8 g. (72%) of white solid, m.p. 101–115°. Recrystallization from aqueous ethanol gave an analytical sample, m.p. 117°; $\lambda_{max(\mu)}^{KBr}$ 3.15, 3.55, 6.50 (NH), 6.20 (C=N), 6.70–7.05 (benzimidazole structure), 9.70 (C—OH), 13.40 (o-disubstituted benzene). The compound traveled on paper[11] as a primary spot at R_f 0.85 with a secondary trace spot at R_f 0.82.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.8; H, 6.85; N, 21.9. Found: C, 62.7; H, 6.42; N, 21.3.

Attempts to convert VI to V with thionyl chloride in boiling chloroform, as described for the preparation of III, gave an unidentified crystalline hydrochloride, m.p. 216–217°, that did not give proper combustion values for V.

Anal. Found: C, 51.6, 51.8; H, 5.02, 4.86; Cl, 24.7; N, 16.1.

2-[(2-Hydroxyethyl)thiomethyl]benzimidazole (VII). To a solution of 350 ml. of absolute ethanol and 14 g. (0.25 mol.) of potassium hydroxide was added with stirring 19.5 g. (0.25 mol.) of 2-mercaptoethanol. When solution was complete, 8.32 g. (0.05 mol.) of finely powdered 2-(chloromethyl)benzimidazole (I) was added over a period of 15 min. After the addition was complete, the system was stirred for another 3.5 hr. at room temperature.

The reaction mixture was cooled in an ice bath and the potassium chloride (3.54 g., 95%) which had separated was removed by filtration. The filtrate was evaporated *in vacuo* (bath 60°) to a volume of 50 ml., poured into 600 ml. of water, and the resultant solution acidified to pH 3 with dilute hydrochloric acid. The acidified solution was extracted 3 times with 100 ml. of ether. The aqueous layer was brought to pH 7–8 and extracted 4 times with chloroform. The combined chloroform extracts were evaporated to yield 4.66 g.

(45%) of a viscous oil. This material traveled as a single spot on Whatman No. 1 paper, R_f 0.80 in n-butanol saturated with water. In a larger scale preparation, VII crystallized, m.p. 122–124°.

A crystalline picrate of this oil was prepared by adding a saturated solution of picric acid in ethanol to a 10% solution of the oil in ethanol, m.p. 187.5–188.5°; $\lambda_{max(\mu)}^{Nujol}$ 2.82 (OH), 3.48 (NH$^+$), 6.18 (aryl), 6.51 (NO$_2$), 9.40 (C—OH).

Anal. Calcd. for $C_{10}H_{12}N_2OS \cdot C_6H_3N_3O_7$: C, 43.9; H, 3.45; N, 16.0; S, 7.33. Found: C, 44.1; H, 3.71; N, 16.1; S, 7.11.

2-[(2-Chloroethyl)thiomethyl]benzimidazole hydrochloride (VIII). To a solution of 4.66 g. (0.023 mol.) of VII in 60 ml. of chloroform was added dropwise with stirring a solution of 22.8 ml. (0.32 mol.) of thionyl chloride in 35 ml. of chloroform. After the addition was complete, the reaction mixture was refluxed for 4 hr., then allowed to stand overnight at room temperature. The system was filtered to yield 4.76 g. (81%) of product, m.p. 177–179°.

An analytical sample was prepared by recrystallization of the crude product from methanol saturated with hydrogen chloride at 40° by the addition of hot benzene, m.p. 180–182°; $\lambda_{max(\mu)}^{Nujol}$ 6.10, 6.35 (aryl, C=N), 13.35 (o-disubstituted benzene), no C—OH near 9.40 nor OH near 2.8.

Anal. Calcd. for $C_{10}H_{11}ClN_2S \cdot HCl$: C, 45.6; H, 4.59; Cl, 26.9, S, 12.2. Found: C, 45.7; H, 4.70; Cl, 27.3; S, 11.7.

Acknowledgments. The authors wish to thank Dr. Peter Lim for interpretation of the infrared absorption spectra and his staff for the paper chromatography and spectrophotometry. The authors are also indebted to Mr. O. P. Crews, Jr., and staff for large-scale preparation of certain intermediates.

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Piper Methysticum Forst. II. The Synthesis of *dl*-Methysticin and *dl*-Dihydromethysticin

M. W. KLOHS, F. KELLER, AND R. E. WILLIAMS

In a previous paper from these laboratories[1] the results of a chemical and pharmacological investigation of *Piper methysticum* Forst were reported. On the basis of ability to antagonize strychnine convulsions and potentiate barbiturate sleep time in mice, it was found that methysticin I and

I

II

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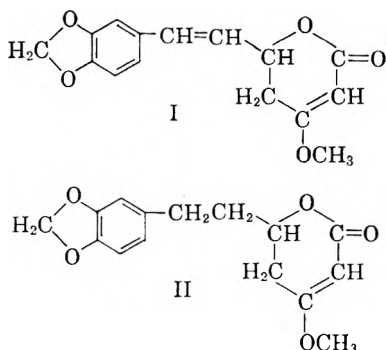
(1) M. W. Klohs, F. Keller, R. E. Williams, I. M. Toekes and G. E. Cronheim, *Journal of Medicinal and Pharmaceutical Chemistry,* 1, 95 (1959).

dihydromethysticin II possessed a greater degree of activity than the other constituents, kawain, dihydrokawain, yangonin, and desmethoxyyangonin,[2] isolated from this plant. The significant physiological activity evidenced by methysticin and dihydromethysticin on the central nervous system made it of interest to obtain sufficient quantities of these α-pyrone derivatives for further pharmacological studies. Because of the inherent difficulties attendant in securing these compounds from their natural source, a means for obtaining them synthetically was desirable.

The synthesis of kawain[3] and yangonin[4] have been recorded by previous investigators, but the synthesis of methysticin, the first of this class of compounds to be isolated from this plant[5] and its dihydro derivative have not been reported, although their structures have been known since 1929.[6]

Our approach to the synthesis of *dl*-methysticin was by the Reformatsky condensation of 3,4-methylenedioxycinnamaldehyde and methyl γ-bromo-β-methoxycrotonate using tetrahydrofuran as the reaction medium. The condensation proceeded smoothly and *dl*-methysticin was readily obtained by direct crystallization of the product. A comparison of the infrared and ultraviolet spectra of this compound with those of natural methysticin showed them to be indistinguishable. Further evidence for confirming their structural identity was obtained by removing the center of asymmetry at C$_6$ in the α-pyrone ring of methysticin, by basic hydrolysis, thereby forming methysticic acid which proved to be identical with the acid obtained in the same manner from *dl*-methysticin.

Catalytic reduction of *dl*-methysticin afforded *dl*-dihydromethysticin which exhibited the same infrared and ultraviolet spectra as those of the naturally occurring material.

EXPERIMENTAL[7]

6-(3',4'-Methylenedioxystyryl)-4-methoxy-5,6-dihydro-2-H-pyran-2-one. 3,4-Methylenedioxycinnamaldehyde (58.6 g.;

(2) This substance had been referred to as compound A in our earlier paper, pending final identification. Compound A has now been compared with a synthetic sample of desmethoxyyangonin [J. Cieślak, *Roczniki Chemii,* 32, 837 (1958) and references therein kindly supplied by Dr. Jerzy Cieślak and they have been found to be identical. This represents the first recorded occurrence of desmethoxyyangonin in *P. methysticum.* Since the completion of this work a publication has appeared citing the presence of this compound in *Aniba firmula* Mez. [Otto Richard Gottlieb and Walter B Mors, *J. Org. Chem.,* 24, 17–18 (1959)].

(3) D. Kosterman, *Nature,* 166, 787 (1950); D. Kosterman, *Rec. Trav. Chim.* 70, 79 (1951); E. M. P. Fowler and H. B. Henbest, *J. Chem. Soc.,* 3642 (1950).

(4) W. Borsche and C. K. Bodenstein, *Ber.* 62, 2515 (1929).

(5) Gobley and O'Rorke, *J. de Pharmacie et Chimi,* 598 (1860), M. Cuzent, *Compt. rend.* 205 (1861).

(6) W. Borsche and W. Peitzsch, *Ber.,* 62, 360 (1929).

(7) All microanalyses by H. V. Tashinian, Microchemical Specialties Company, Berkeley 3, California.

0.33 mole) and methyl-γ-bromo-β-methoxortcyonate,[8] (70 g.; 0.33 mole) were dissolved in 1 liter of tetrahydrofuran (tetrahydrofuran was distilled from calcium hydride and mineral oil and stored over sodium prior to use). This solution was added dropwise through a dropping funnel into a dry 3-neck round bottom flask, equipped with stirrer and reflux condenser and containing finely cut zinc sheet metal (25 g.; 0.38 mole); the zinc metal, immediately prior to the reaction, was sanded, cut into small strips and washed consecutively with 25% hydrochloric acid, water, methanol, acetone and ether, and then dried at 100°. A small crystal of iodine was added to help initiate the reaction and the solution was refluxed with stirring for 5 hr. At the end of this time the reaction mixture (reddish-brown in color) was cooled to room temperature and added to a saturated solution of ammonium chloride (2.5 l.) with stirring. The mixture was extracted twice with CHCl₃ (1500 ml. portions) and the combined CHCl₃ extracts were washed once with water (500 ml.), filtered through anhydrous sodium sulfate and concentrated on the steam bath *in vacuo* to a resinous mass which on standing overnight at room temperature formed a solid mass of crystals. The material was triturated with ether (500 ml.), filtered and recrystallized from methanol (350 ml.) to give 35 g. (38%) of *dl*-methysticin, m.p. 132–134°. The ultraviolet spectrum showed $\lambda_{max}^{alc.}$ (log ϵ): 226 mμ (4.40), 267 mμ (4.14), 306 mμ (3.93); $\lambda_{min}^{alc.}$ (log ϵ): 218 mμ (4.37), 253 mμ (4.09), 284 mμ (3.80).

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.59; H, 5.15; —OCH₃, 11.23; M.W., 274. Found: C, 65.56; H, 5.25; —OCH₃, 11.35; M.W. (Rast), 285.

A comparison of the ultraviolet and infrared absorption spectra of this material with those of an authentic sample of natural methysticin showed them to be identical.

7-(3',4'-methylenedioxyphenyl)-3-methoxy-2,4,6-heptatrienoic acid-1. dl-Methysticin was hydrolyzed by the procedure employed by Borsche and co-workers for the hydrolysis of natural methysticin,[9] giving a nearly quantitative yield of methysticic acid. The light yellow crystalline product was recrystallized from hot methanol; m.p. 196–197°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.54; H, 5.31.

Upon admixture with an authentic sample of methysticic acid, no depression of melting point was observed. The infrared and ultraviolet absorption spectra were identical.

6-(3',4'-Methylenedioxy-β-phenethyl)-4-methoxy-5,6-dihydro-2-H-pyran-2-one. dl-Methysticin (300 g.) was dissolved in tetrahydrofuran (1.2 l.) and 10% Pd on carbon catalyst (10 g.) was added. The mixture was hydrogenated on a modified Parr apparatus at a pressure of 35 p.s.i., the uptake being completed within one hour. The solution was filtered free of suspended catalyst and the filtrate was taken to dryness *in vacuo* yielding crystals. The crude product was recrystallized from isopropyl alcohol (1.5 l.) to give needles (270 g.), m.p. 110–111°.

Anal. Calcd. for: $C_{15}H_{16}O_5$: C, 65.21; H, 5.84; —OCH₃, 11.23. Found: C, 64.99; H, 5.85; —OCH₃, 11.74.

The infrared and ultraviolet absorption spectra of this material were identical with those of an authentic sample of natural dihydromethysticin.

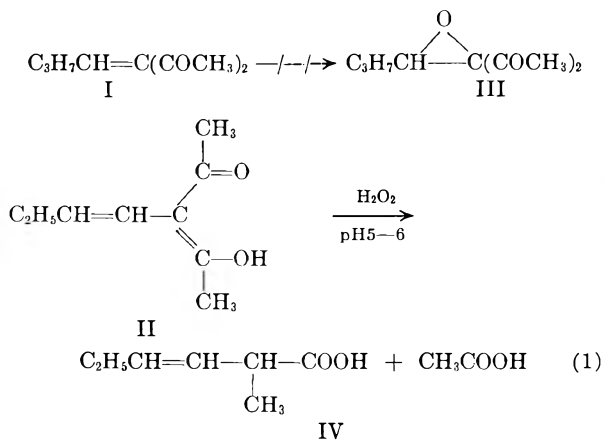(8) F. Kogl and O. A. de Bruin, *Rec. Trav. Chim.* **69**, 729 (1950) *Chem. Abs.* **45**, 2416 (1951).

(9) W. Borsche, C. H. Meyer, and W. Peitzsch, *Ber.*, **60**, 2113 (1927).

Novel Rearrangement in the Oxidation of 3-Butylideneacetylacetone by Hydrogen Peroxide

GEORGE B. PAYNE

As part of a general survey concerned with the mode of reaction of various unsaturated materials with hydrogen peroxide under controlled *p*H conditions, the product from the condensation of *n*-butyraldehyde with acetylacetone was investigated. It was initially assumed that this product, 3-butylideneacetylacetone, would have structure I, and that it would probably afford the corresponding epoxy diketone (III) on treatment with hydrogen peroxide at the appropriate *p*H.

$$C_3H_7CH{=}C(COCH_3)_2 \xrightarrow{\ /{-}/{-}/\ } C_3H_7CH\overset{O}{\overbrace{\quad}}C(COCH_3)_2$$

I   III

$$C_2H_5CH{=}CH{-}\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{\overset{C{=}O}{\underset{C{-}OH}{C}}}} \xrightarrow[\text{pH5--6}]{H_2O_2}$$

II

$$C_2H_5CH{=}CH{-}\underset{\underset{CH_3}{|}}{CH}{-}COOH + CH_3COOH \quad (1)$$

IV

Surprisingly, *2-methyl-3-hexenoic acid* (IV) rather than III was obtained in 70% yield by the action of hydrogen peroxide at *p*H 5–6 and 38–40° for 1 hr. In view of this result, perhaps the structure of the starting material was not correctly described.

That II, 3-acetyl-2,4-heptadien-2-ol, should better represent this structure was indicated by analogy with the products obtained earlier from the reactions of propionaldehyde[1] and isovaleraldehyde[2] with acetylacetone. This belief was confirmed by infrared analysis which showed the condensation product to possess a highly enolized β-diketone system.[3]

Structure IV was established on the basis of physical constants and analysis as well as by direct comparison of its anilide and saturated anilide with authentic samples.

Confirmation of the position of the double bond in IV was obtained by treatment with iodine-sodium bicarbonate[4] to give the iodo lactone (V) in 87%
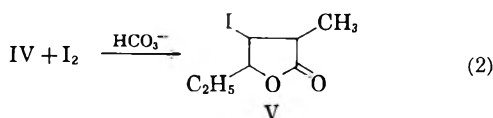
(1) M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957).

(2) F. Tiemann and P. Krüger, *Ber.*, **28**, 2121 (1895).

(3) L. J. Bellamy, "Infrared Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, 1954, p. 123.

(4) R. P. Linstead and C. J. May, *J. Chem. Soc.*, 2565 (1927).

yield. α,β-Unsaturated acids are reported[4] not to react by the procedure employed.

$$\text{IV} + \text{I}_2 \xrightarrow{\text{HCO}_3^-} \underset{\text{V}}{\overset{\displaystyle \text{I} \quad \text{CH}_3}{\underset{\text{C}_2\text{H}_5 \quad \text{O} \quad \text{O}}{\bigg|}}} \tag{2}$$

A few related experiments with II and hydrogen peroxide were carried out with the hope of learning something about the mechanism of the reaction. It was found, for example, that the reaction at pH 5–6 was exceedingly more rapid that at "ambient pH". Indeed, the uncatalyzed reaction in ethanol required 2 days at room temperature for 95% reaction or about 4 hr. at reflux. From the latter reaction, IV was secured in 62% yield.

The sulfuric acid-catalyzed reaction proceeded exothermally at 35° but with a consumption of peroxide greater than theory. Compound IV was obtained in 41% yield based on an 85% conversion of II.

That the reaction did not proceed via the enolate anion of II was indicated by a very slow reaction when II and 1 molar equivalent of alkali were treated with hydrogen peroxide. After 3 days at room temperature, the reaction was still only 70% complete; it was not further investigated.

Of the several possible mechanisms considered for this unusual reaction, the following is considered most reasonable. The initial driving force for the
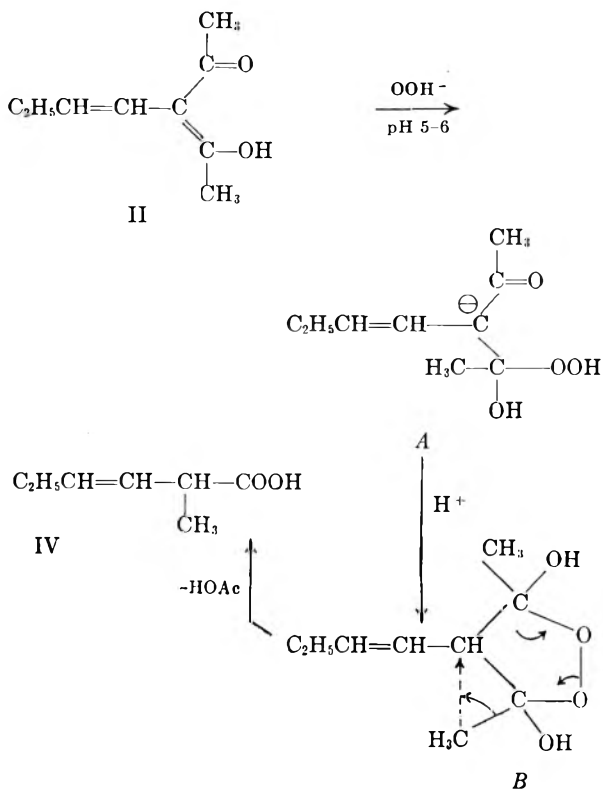
reaction would be the formation of carbanion A, resonance stabilized by both ethylenic and carbonylic linkages. A might reasonably be expected

to form the symmetrical dihydroxy peroxide B,[5] with simultaneous addition of a proton. Peroxide cleavage with methyl migration in the manner indicated would then afford the observed product.

EXPERIMENTAL

3-Butylideneacetylacetone. To a solution of 443 g. (4.43 moles) of acetylacetone (n_D^{20} 1.4514) in 700 ml. of acetic acid was added a solution of 22 g. of piperidine in 100 ml. of acetic acid. This mixture was stirred at 35–40° while 319 g. (4.43 moles) of freshly distilled n-butyraldehyde was added over 1 hr. After an overnight stand at room temperature, the mixture was poured into 2 liters of water and extracted with two 500 ml. portions of chloroform. The combined chloroform was washed with sodium bicarbonate and then with water. Distillation of the dried solution through a 10-tray Oldershaw column gave 78 g. of recovered diketone, b.p. 30° (10 mm), n_D^{20} 1.4490, and 420 g. (75% yield based on unrecovered acetylacetone) of 3-butylideneacetylacetone, b.p. 83–84° (8 mm), n_D^{20} 1.4840.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.1. Found: C, 70.0; H, 9.2.

Infrared analysis showed a broad band centered at 6.25 μ, characteristic of enolized β-diketones.[3] The sample also gave a characteristic[1] deep purple color with ferric chloride.

Reaction of 3-butylideneacetylacetone with hydrogen peroxide at pH 5–6. To a 1-liter, 5-neck round-bottom flask equipped with stirrer, thermometer, pH electrodes and dropping funnel, were charged 75 g. (0.49 mole) of 3-butylideneacetylacetone (3-acetyl-2,4-heptadiene-2-ol), 300 ml. of methanol and 42 g. (0.61 mole) of 50% hydrogen peroxide. The mixture was stirred at 38–40° and maintained at a meter pH of 5.1–5.3 (true pH of 5–6 by indicator paper) by the addition of $3N$ sodium hydroxide; ice bath cooling was required. After 45 minutes, 100 ml. of alkali had been added and an iodometric titration indicated the presence of 0.16 mole of peroxide. Another 25 ml. of alkali raised the pH from 5.2 to 5.4, indicating a strongly buffered solution. No further consumption of peroxide was observed during an additional 0.5 hr. at 30–35°. Another 75 ml. of caustic solution brought the pH to 5.7, while 100 ml. more caused the meter pH to rise to 9. The total alkali consumed amounted to 0.90 equivalent.

After concentration under vacuum to a volume of about 250 ml., the concentrate was acidified with 30% sulfuric acid and extracted with three 100 ml. portions of chloroform. After a water wash, the chloroform extract was concentrated on the steam bath and then distilled through a 0.7×50 cm. glass spiral-packed column at 5 mm. pressure. Slow takeoff was required at first for the removal of 6.6 g. of pre-cut, b.p. 80–95°. There was then secured 43.6 g. (70% yield) of 2-methyl-3-hexenoic acid, b.p. 95–96°, n_D^{20} 1.4388 (lit.[6] values: b.p. 121–122° (24 mm); n_D^{25} 1.4382).

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4; neut. equiv., 129. Found: C, 65.6; H, 9.4; neut. equiv., 128.

Acid chloride was prepared from 12 g. of acid by dissolving it in 50 ml. of benzene and adding 25 g. of oxalyl chloride. After standing at ambient temperature for 1 hr., the mixture was allowed to reflux for 2 hr. Claisen distillation afforded 9.7 g. (70% yield) of product, b.p. 150–155°.

Anilide was prepared from the acid chloride by dissolving the latter (9.7 g., 0.066 mole) in 50 ml. of benzene and adding 12.3 g. (0.132 mole) of aniline. The mixture was brought to a boil on the steam bath and held there for 10 minutes. After cooling, this mixture was washed successively with water, dilute acid, dilute alkali and water. After concentration to a volume of 50 ml., 100 ml. of Skellysolve B was added and the

(5) A cyclic hydroxy peroxide was recently isolated from the alkaline epoxidation of mesityl oxide; see G. B. Payne, *J. Org. Chem.*, **23**, 310 (1958).

(6) A. C. Cope and C. M. Hofmann, *J. Am. Chem. Soc.*, **63**, 3456 (1941).

solution chilled to precipitate 9.0 g. of anilide, m.p. 94–95°. Recrystallization did not alter the melting point.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.8; H, 8.4. Found: C, 76.7; H, 8.5.

The anilide (2.03 g.) was *hydrogenated* in 50 ml. of ethanol using 500 mg. of 10% palladium on charcoal catalyst and 50 pounds of hydrogen. One molar equiv. of hydrogen was absorbed in 20 minutes and the product was isolated by precipitation from the concentrated (10 ml.) ethanol solution, m.p. 95–96°.

Authentic samples of both the unsaturated and saturated anilides were prepared as above from authentic 2-methyl-3-hexenoic acid[6] and melted at 94–95° and 95–96°, respectively. The respective mixed melting points were not depressed.

Reaction of 3-butylideneacetylacetone with hydrogen peroxide in ethanol. A solution of 98 g. (0.64 mole) of diketone and 80 g. (0.70 mole) of 30% hydrogen peroxide in 300 ml. of ethanol was allowed to reflux gently for 4.5 hr. and then concentrated to low volume on the steam bath. Distillation of the residue through a 0.7 × 50 cm. glass spiral-packed column gave 13 g. of crude recovered starting material, b.p. 60–90° (5 mm) and 50 g. (62% yield based on ketone charged) of 2-methyl-3-hexenoic acid, b.p. 79–80° (2 mm); n_D^{20} 1.4393.

When the above reaction was carried out at room temperature, 2 days were required for 95% consumption of the theoretical amount of peroxide and after 5 days the mixture was vacuum-flashed *at room temperature* to give 65 mole % of volatile acid. The latter was identified as acetic by means of the *p*-bromophenacyl ester, m.p. and mixed m.p. 83–84°. Claisen distillation of the residue from the flashing operation gave a 70% yield of crude product, b.p. 105–115° (20 mm); the purity was 87% by neut. equiv.

Reaction of 2-methyl-3-hexenoic acid with iodine. The procedure used was that described in the literature.[4] A 2.19 g. (0.0171 mole) sample of unsaturated acid was dissolved in 25 ml. of saturated sodium bicarbonate solution and treated with 3 gram-atoms of iodine (from a solution made from 25 g. of iodine, 40 g. of potassium iodide and 125 ml. of water). After 2 hr. at room temperature, the solution was treated with 5 g. of sodium carbonate and extracted with ether. The ether extract was washed with dilute sodium thiosulfate solution, water, and dried. Concentration under vacuum gave 3.78 g. (87% yield) of crude solid product. Recrystallization from petroleum ether afforded 2-methyl-3-iodo-4-hexanolactone, m.p. 28–30°.

Anal. Calcd. for $C_7H_{11}IO_2$: C, 33.1; H, 4.4; I, 49.9; sapon. equiv., 254. Found: C, 33.2; H, 4.3; I, 49.0; sapon. equiv., 260.

EMERYVILLE, CALIF.

### 7-Phenyl-2:6:8-trioxaspiro(3,5)nonane: A High Yield Reduction with Lithium Aluminum Hydride[1]

RIYAD F. NASSAR AND COSTAS H. ISSIDORIDES[2]

In recent years, several reports have appeared in the literature on the reductive cleavage of oxetanes by lithium aluminum hydride. In 1954,

Büchi[3] prepared 2-phenyl-3,3,4-trimethyl oxetane and attempted to reduce it with lithium aluminum hydride, but reported that no detectable reaction took place even at elevated temperatures. The stability of a highly substituted 1,3 oxide to lithium aluminum hydride has also been noticed by Allen.[4] The first successful reductive cleavage of oxetanes was reported almost simultaneously by this laboratory[5] and by Searles, Pollart and Lutz.[6] In their excellent and thorough study of ten oxetanes having two or fewer alkyl substituents, Searles and his coworkers found that the ease of cleavage was markedly affected by substitution, particularly by *gem*-dialkyl substitution at position 3, which caused marked deactivation. This deactivation was attributed to two factors: The Thorpe-Ingold effect and the relatively low basicity of such oxetanes.

In conjunction with other work carried out in this laboratory on derivatives of pentaerythritol, we had the opportunity to prepare 7-phenyl-2:6:8-trioxaspiro (3,5) nonane (I). Since this oxetane has a spirocyclic structure in addition to having two substituents at position 3, we thought it of interest to study its response to lithium aluminum hydride. The reaction proceeded smoothly in tetrahydrofuran, giving 5-methyl-5-hydroxymethyl-2-phenyl-1,3-dioxane (II) in excellent yield (90%).
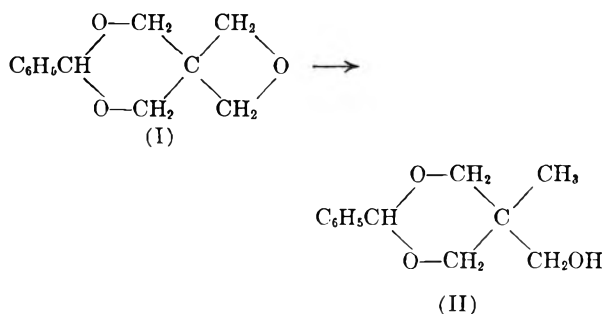
The structure of (II) was proved by independent synthesis from benzaldehyde and trimethylolethane.

In view of the strong deactivation associated with 3,3 dialkyl substitution in the reaction of oxetanes with lithium aluminum hydride, it is remarkable that (I) is cleaved by this reagent in nearly quantitative yield. The reason why the spirocyclic compound is so vulnerable to this reagent is not entirely clear. One possible explanation lies in the fact that in (I) the substituents at position 3 are "held back" by the six membered ring thus failing to diminish the distortion of the

(1) Abstracted in part from the M.S. thesis of Riyad F. Nassar, American University of Beirut, June 1959.

(2) To whom requests for reprints should be addressed.

(3) G. Büchi, C. G. Inman, and E. S. Lipinsky, *J. Am. Chem. Soc.*, 76, 4327 (1954).

(4) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, 77, 4784 (1955).

(5) C. H. Issidorides and N. S. Aprahamian, *J. Org. Chem.*, 21, 1534 (1956).

(6) S. Searles, K. A. Pollart, and E. F. Lutz, *J. Am. Chem. Soc.*, 79, 948 (1957).

internal bond angles of the oxetane ring.[7] We are at present preparing a series of other spirocyclic oxetanes and will report on their reductive cleavage later.

EXPERIMENTAL[8]

7-Phenyl-2:6:8-trioxaspiro (3,5) nonane (I). A solution of 20 g. (0.07 mol.) of monobenzal pentaerythrityl monobromide[9] in 50 ml. of absolute ethanol was treated with 5.6 g. (0.1 mol.) of potassium hydroxide in 50 ml. of ethanol and refluxed with stirring for 3 hr. The mixture was cooled, filtered, and evaporated under reduced pressure to dryness. The residue was treated with cold water to dissolve the excess potassium hydroxide, and the mixture immediately extracted with ether. Evaporation of the ether gave a pale yellow solid which was dissolved in the minimum amount of benzene and chromatographed on a column of alumina. Elution with petroleum ether (30–60°) and benzene (2:1, 1:1, 1:2, 3:7) gave 9.4–11.0 g. (65–75%) of product melting at 74–77°. After one recrystallization from petroleum ether, the melting point was raised to 78–79°. The analytical sample melted at the same temperature.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.05; H, 6.85.

Lithium aluminum hydride reduction of (I). In a three necked flask, fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser protected with a calcium chloride tube, were placed 3 g. (0.079 mol.) of lithium aluminum hydride and 40 ml. of dry tetrahydrofuran. To the well stirred mixture at reflux was added 4.1 g. (0.02 mol.) of (I) in 40 ml. of tetrahydrofuran in the course of 1 hr. The mixture was refluxed for 4 more hr. and the excess lithium aluminum hydride was destroyed carefully with water. A 20% solution of sodium hydroxide was added to dissolve the aluminum hydroxide, and the alkaline suspension was extracted with ether. Evaporation of the ether extracts gave 3.9 g. (94%) of (II) melting at 95–98°. One recrystallization from a mixture of one part benzene to two parts of hexane raised the melting point to 100–101° (recovery above 90%), undepressed upon admixture with an authentic sample. The analytical sample, obtained after three recrystallizations, melted at the same temperature.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.28; H, 7.79.

5-Methyl-5-hydroxymethyl-2-phenyl-1,3-dioxane (II). A solution of 12 g. (0.1 mol.) of trimethylolethane (Heyden Newport Chemical Corp.) in 40 ml. distilled water and 0.6 ml. of concentrated hydrochloric acid was heated to 70–80°, treated with 10.6 g. (0.1 mol.) of benzaldehyde and shaken mechanically for 3 hr. at room temperature. The precipitate was collected on a Buchner funnel, washed successively with dilute sodium carbonate and water, dried, and recrystallized from benzene-hexane giving 12.5 g. (60%) of (II) melting at 99–100°.

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(7) For a discussion see ref. (6) and references cited therein.

(8) Melting points are not corrected. Alumina used for chromatography was neutral, grade I, "Woelm," to which 3% water was added. Microanalyses are by Pascher Mikroanalytisches Laboratorium, Bonn, Germany.

(9) C. H. Issidorides, R. C. Gulen, and N. S. Aprahamian, *J. Org. Chem.*, 21, 997 (1956).

Carboxylation of Rosin and Oleic Acid

D. R. LEVERING

The synthesis of esters from olefins, carbon monoxide, and alcohols using metal carbonyls, particularly nickel carbonyl, was reported by Reppe and Kroper[1] in the work done on carbon monoxide chemistry.

This particular reaction gave very poor yields of the desired products. Natta and his associates[2] who have been active in the field of carbon monoxide chemistry discovered that cobalt catalysts were much more effective than those based on nickel. They reported that simple olefins were converted to methyl esters in fair yields (up to 60%). However, complications arose in going to higher alcohols and substituted olefins.[2b,c]

Recently the oxonation of rosin, in which a hydroxymethyl group was added to a hindered double bond, has been reported to proceed with good conversion.[3] It has now been found that carbon monoxide and methanol can be added across the double bond of some of the unsaturated components of rosin. The latter reaction is the subject of this note.

N-wood rosin[4] reacts with carbon monoxide and methanol at 6000 p.s.i.g. and 220° in the presence of dicobalt octacarbonyl as catalyst. The reaction results in the addition of carbomethoxy (CH_3OC-, with an O double-bonded to C) groups to the double bonds of the rosin acids to give a viscous, amber-colored liquid product. During the reaction the original carboxyl groups on the rosin acids are largely esterified. Conversions of 60% to diesters have been obtained. The completely saturated tetrahydroabietic acid

(1) W. Reppe and H. Kroper, *Ann.*, 582, 38 (1953).

(2) (a) G. Natta, P. Pino, and E. Mantica, *Gazz. chim. ital.*, 80, 680 (1950); (b) P. Pino, R. Ercoli, and S. Mantica, *Gazz. chim. ital.*, 80, 635 (1951); (c) R. Ercoli, M. Avanzi, and G. Moretti, *Chim. e ind. (Milan)*, 38, 865 (1955). (d) G. Natta, P. Pino, and R. Ercoli, *J. Am. Chem. Soc.*, 74, 4496 (1952).

(3) D. R. Levering and A. L. Glasebrook, *Ind. Eng. Chem.*, 50, 317 (1958).

(4) Rosin consists of a mixture of the following components:[5]

A. Abietic Type: 50 ± 6% abietic, neoabietic acid, and palustric acids; 6 ± 5% dihydroabietic; 11 ± 2% dehydroabietic acid; 6 ± 5% tetrahydroabietic acid; 2 ± 2% oxidized acids.

B. Pimaric Type: 7 ± 5% pimaric acid; 7 ± 5% isopimaric acid.

C. Neutrals: 11 ± 2%.

(5) (a) G. C. Harris, Wood Rosins; L. E. Wise, E. C. Johns, eds., Wood Chemistry, 2nd ed., Vol. I, pp. 590–617, Reinhold, New York, 1952. (b) V. M. Loeblich, D. E. Baldwin, R. V. Lawrence, *J. Am. Chem. Soc.*, 77, 2823 (1955).

TABLE I

CARBOXYLATION OF N-WOOD ROSIN AND OLEIC ACID[a]

Olefin	Weight, g.	CH₃OH, g.	[Co(CO₄)]₂, g.	Time, hr.	Wt. of Product, g.	Acid No.	Sapon. No.	Iodine No.	Conversion to Dibasic Esters, %
N-Wood rosin	Starting material			...	...	167	172	...	...
N-Wood rosin	250	230	10	11.3	265	36	214	...	60.5
N-Wood rosin	250	200	27	10.0	265	43	210	...	56.0
Oleic acid	250	418	32	3.0	280	6	260	Nil	68.8
Oleic acid	200	400	29	1.0	261	17	276	Nil	79.3
Oleic acid	Starting material			...	...	199	200	90	...

[a] Reactions were carried out at 220° and 6000 p.s.i g. of CO.

and the aromatic dehydroabietic acid, as well as some of the neutrals, are, of course, unable to undergo reaction. Thus, a maximum conversion of about 75% can be expected. This is a second example of the preparation of difunctional derivatives from rosin using carbon monoxide.

The reaction of rosin with carbon monoxide and methanol is much slower than that with carbon monoxide and hydrogen (oxo reaction), taking about 10 hr. vs. 1 to 2 hr. for oxo reaction. The temperature of 220° was found to be optimum. At higher temperatures decomposition of the product occurred. Highest conversions were obtained using solid dicobalt octacarbonyl as the catalyst.

Under conditions similar to those for rosin, freshly distilled oleic acid (Darling and Company) reacts readily to give the methyl esters of dibasic acids in 60 to 80% yields. The reaction rate is much faster for oleic acid than for rosin (1 hour vs. 10 hr.). The remaining 20% of the product is probably methyl stearate since it contains no residual unsaturation or new functional groups, such as hydroxyl or carbonyl.

EXPERIMENTAL

Some examples of typical experiments are shown in Table I. The experiments were all carried out as follows:

A 1000-ml. stainless steel pressure vessel was charged with 250 g. of N-wood rosin (Hercules Powder Company), 200 g. of absolute methanol (Merck and Company), and 27 g. of dicobalt octacarbonyl.[6] The pressure was raised to 2000 p.s.i.g. of carbon monoxide and the autoclave was heated to 220°. The pressure was maintained at 6000 to 5000 p.s.i.g. during the reaction. After no more gas was absorbed, the reactor was cooled, vented, and the product removed.

The catalyst was removed by diluting the product with ether and extracting the ether solution with 6N hydrochloric acid. The cobalt-free solution was washed until neutral, dried, and the solvent removed by distillation. The total product was analyzed for acid and ester in the usual manner.

HERCULES POWDER COMPANY
HERCULES RESEARCH CENTER
WILMINGTON, DEL.

(6) I Wender, H. Greenfield, and M. Orchin, J. Am. Chem. Soc., 73, 2656 (1951).

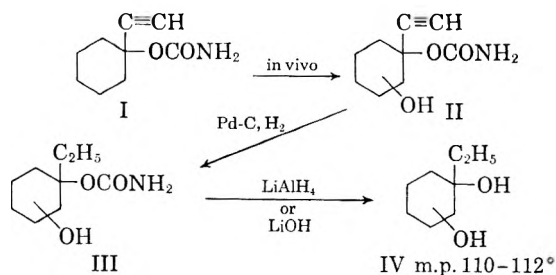## In Vivo Hydroxylation of 1-Ethynylcyclohexyl Carbamate,[1] II. The Orientation of Hydroxylation

ROBERT E. McMAHON

The human urinary metabolite of 1-ethynylcyclohexyl carbamate (I) has been shown to be 1-ethynyl-4-hydroxycyclohexyl carbamate by transformation to one of the isomers of 1-ethylcyclohexane-1,4-diol. The preparation and properties of the isomeric 1-ethynylcyclohexane-1,4-diols and 1-ethylcyclohexane-1,4-diols are reported.

In an earlier report[2] the metabolism of the central nervous system depressant, ethinamate [1-ethynylcyclohexyl carbamate, (I)], was described. In that study the major human metabolite was isolated in pure form and shown to be hydroxyethinamate (II). However, the ring position of the hydroxyl group in the metabolite was not established. Although biological hydroxylation at a saturated carbon atom in a carbocyclic ring is well known in the steroid field, the present case represents the first reported instance of enzymatic hydroxylation of a simple cyclohexane derivative.

For this reason, it was of importance to establish the position of hydroxylation. The proof of structure is described in this paper.

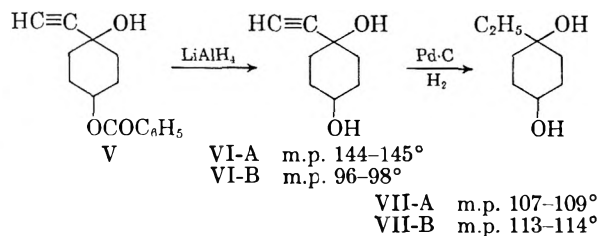Direct conversion of II to the corresponding 1-ethynylcyclohexanediol by hydrolytic procedures

(1) Eli Lilly and Company Trademark, VALMID®, ethinamate, Lilly.
(2) R. E. McMahon, J. Am. Chem. Soc., 80, 411 (1958).

failed to produce a pure, isolable product. However, after catalytic reduction of the metabolite to its saturated analog (III), the carbamate grouping was easily removable. Degradation of III either by warming with aqueous lithium hydroxide or by refluxing with lithium aluminum hydride in benzene yielded the diol (IV). This diol was a white crystalline product, m.p. 110–112°, which was easily purified by vacuum sublimation at 65°. The infrared spectrum was quite consistent with the expected structure, *i.e.* a 1-ethylcyclohexanediol (IV).

The position of the second hydroxyl group in IV was established by synthesis. Since II had been found to be optically inactive,[2] it was tentatively assumed that hydroxylation had occurred in the four position. Synthetic efforts were therefore undertaken in this direction. The preparation of the pure *cis* and *trans* isomers of 1-ethylcyclohexane-1,4-diol (VII) was achieved through synthesis of the corresponding 1-ethynylcyclohexyl-1,4-diols (VI).

HC≡C OH $\xrightarrow{\text{LiAlH}_4}$ HC≡C OH $\xrightarrow[\text{H}_2]{\text{Pd-C}}$ C₂H₅ OH

OCOC₆H₅   OH   OH

V	VI-A	m.p. 144–145°
	VI-B	m.p. 96–98°

VII-A   m.p. 107–109°
VII-B   m.p. 113–114°

Jones and Sondheimer[3] have reported the preparation of 1-ethynyl-4-benzoyloxycyclohexanol (V) and its conversion to 1-ethynylcyclohexane-1,4-diol (VI). However, both of these materials were a mixture of the *cis* and *trans* isomers and were not separated. In the present work V was prepared by the method of Jones[3] and was converted to a mixture of the diols (VI-A and VI-B) by reduction with lithium aluminum hydride. The mixture so obtained was then separated into the pure isomers. One isomer (VI-A, m.p. 144–145°) was obtained directly by crystallization from benzene solution. Chromatography of the mother liquors on alumina yielded the second isomer (VI-B, m.p. 96–98°) by elution with a 4:1 benzene-ether mixture. By elution with a more polar solvent (99:1 ether-methanol) more of isomer A was obtained. The ratio in yields of isomer A to isomer B was about 4:1. The relative geometrical configuration of VI-A and of VI-B have not as yet been established.[4]

The desired 1-ethylcyclohexane-1,4-diols (VII-A and VII-B) were obtained readily from the acetylenic analogs by catalytic hydrogenation. Reduction of VI-A yielded the corresponding saturated diol

VII-A, m.p. 107–109°, while VI-B yielded VII-B. m.p. 113–114°.

By a comparison of physical properties, the ethylcyclohexanediol (IV), obtained through transformation of the human metabolite (II), was shown to be identical with VII-B, the higher melting isomer of 1-ethylcyclohexane-1,4-diol. The metabolite II is thus shown to be 1-ethynyl-4-hydroxycyclohexyl carbamate. In this simple case, therefore, enzymatic hydroxylation has occurred at the position in the ring furthest removed from steric interference. These results have led to a study of the effect of ring substitution upon the pharmacological properties of ethinamate analogs.

EXPERIMENTAL[5]

1-Ethynylcyclohexane-1,4-diols. Isomer VI-A. Fifty-six g. of 4-benzoyloxycyclohexanone[6] was converted to 1-ethynyl-4-benzoyloxycyclohexanol by the method of Jones and Sondheimer.[3] The crude product, which was a red oil, was obtained in 76% (48 g.) yield. This was not distilled but was converted directly to the mixed 1-ethynylcyclohexane-1,4-diols by dissolving in 500 ml. of ether and adding dropwise to a stirred suspension of 8.5 g. of lithium aluminum hydride in a mixture of 400 ml. of ether and 300 ml. of benzene. When addition was complete, 1N NaOH was added dropwise until the precipitate became granular and settled. The solution was then filtered, and the filtrate was evaporated to dryness. The residue was taken up in warm benzene. Upon cooling 6.4 g. (23.2% yield) of crystalline 1-ethynyl-cyclohexane-1,4-diol (VI-A) separated. After recrystallization from benzene–petroleum ether the product melted at 144–145°.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.80.

The 3,5-dinitrobenzoate was prepared by the method of Brewster and Ciotti,[7] m.p. 197–199°.

Anal. Calcd. for $C_{22}H_{16}O_{12}N_4$: N, 10.60. Found: N, 10.67.

Isomer VI-B. Isomer B was obtained by alumina chromatography of the filtrate after removal of isomer A. From the fractions eluted with 4:1 benzene-ether was obtained 3.5 g. (12.7% yield) of VI-B, m.p. 96–98°.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.40; H, 8.66.

The 3,5-dinitrobenzoate of isomer B melted at 213–215°.
Anal. Calcd. for $C_{22}H_{16}O_{12}N_4$: N, 10.60. Found: N, 10.32.

From the fractions eluted with ether and 99:1 ether-methanol was obtained an additional 2.4 g. of VI-A bringing the total yield of this isomer to 8.8 g. (32%).

1-Ethylcyclohexane-1,4-diol. Isomer VII-A. One-half gram of 1-ethynylcyclohexane-1,4-diol (VI-A) was converted quantitatively to the corresponding 1-ethylcyclohexane-1,4-diol by hydrogenation at atmospheric pressure using palladium on calcium carbonate as a catalyst. The product was purified by sublimation at 65° (0.1 mm.), m.p. 107–109°.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.90; H, 11.06.

Isomer VII-B. 1-Ethynylcyclohexane-1,4-diol (VI-B) was reduced to the corresponding saturated diol in the same

(3) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).

(4) It would seem reasonable, however, to suppose that of the two isomers, the *cis* would be the more firmly bound on the alumina. Consequently, VI-A would be *cis*-1-ethynyl-cyclohexane-1,4-diol and VI-B would be the *trans* isomer.

(5) All melting points are corrected.

(6) D. A. V. Denny and D. A. H. Taylor, *J. Chem. Soc.*, 1922 (1957).

(7) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).

manner. After sublimation the product melted at 113–114°

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.45; H, 11.29.

Degradation of hydroxyethylcyclohexyl carbamate (III) *to 1-ethylcyclohexane-1,4-diol* (VII-B). This conversion was carried out by two different methods, refluxing for 1 hr. with excess lithium aluminum hydride in benzene and by basic hydrolysis with lithium hydroxide. The identical product was obtained in each case. The latter procedure is described here:

Ten milligrams of hydroxyethylcyclohexylcarbamate (III), prepared from the human metabolite as described previously,[2] was refluxed for 10 min. with 1*N* lithium hydroxide. After cooling, the reaction mixture was extracted with ether, and the ether extract was evaporated to dryness. Sublimation of the residue at 65° (0.1 mm.) gave a crystalline solid, m.p. 110–112°. When mixed with 1-ethylcyclohexane-1,4-diol (VII-A), the melting point was depressed to 76–81°. Upon admixture with VII-B, however, the melting point was not depressed (112–113°). The X-ray crystallographic pattern and infrared spectrum were identical to that of 1-ethylcyclohexane-1,4-diol (isomer VII-B).

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Some Reactions of 1-Methoxypyridinium Salts and a Color Test for *N*-Oxides

N. A. COATS AND A. R. KATRITZKY

1-Alkyloxypyridinium salts react (*cf.* structure I) with hydroxide ion to give pyridine and an aldehyde,[1-3] but many reactions are known in which pyridine 1-oxide derivatives are attacked in the α- or γ- positions of the ring by nucleophilic reagents,[4] as in *e.g.*, structure II. In an attempt to effect a reaction of this type, 1-methoxypyridinium toluene-*p*-sulfonate was treated with a series of nucleophilic reagents.* Sodium ethoxide and sodium phenoxide gave pyridine in good and poor yield, respectively. Sodium acetate, benzyl mercaptan, morpholine, aniline, hydroxylamine, semicarbazide, and phenyl magnesium bromide gave pyridine 1-oxide in 15–56% yield. The 1-methoxypyridinium ion acts here as a methylating agent (structure III) and *N*-methylaniline was isolated as the toluene-*p*-sulfonamide from the reactions with aniline. This appears to be the first time that 1-alkoxylpyridinium salts have been dealkylated without concomitant loss of the *N*-oxide oxygen atom.
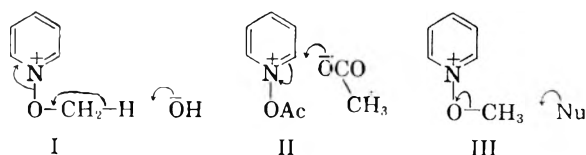

Treatment of pyridine with benzoyl chloride and dimethylaniline yields 4-(*p*-dimethylaminophenyl) pyridine (IV),[5] probably by addition of dimethylaniline to V followed by aromatization of VI. It appeared that an analogous reaction could occur with pyridine 1-oxide; however, this compound behaved as an oxidizing agent and gave crystal violet probably admixed with methyl violet by releasing formaldehyde or its equivalent from dimethylaniline which then combined with further molecules of dimethylaniline. When pyridine 1-oxide hydrochloride and dimethylaniline were heated together, the same blue color was formed.
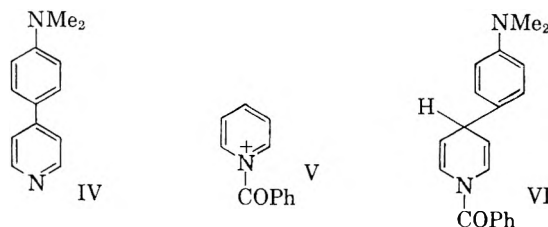
The production of a blue color on gently heating with dimethylaniline and hydrochloric acid was found to be a convenient color test for *N*-oxides and also for nitro compounds. Crystal violet is formed from dimethylaniline, *via* an oxidative dealkylation to formaldehyde, by many inorganic oxidizing agents,[6-8] *e.g.*, $KClO_3$, Mn_3O_4, $Cu(NO_3)_2$, H_2O_2. Of organic compounds, benzene sulfonyl chlorides react slowly.[9] Peroxides give colors with dimethylaniline.[10] Nitro compounds, and especially polynitrocompounds, form yellow or orange-red charge transfer complexes with dimethylaniline.[11,12]

Methyl ketones give a violet coloration with *m*-dinitrobenzene and methanolic alkali[13]; this reaction is also given by α-methyl-chromones and -pyrones.[14] Neither 2-, 3-, or 4-methylpyridines nor their 1-oxides gave a similar coloration under these conditions; however, 1,2- (VII) and 1,4-, but not 1,3-dimethylpyridinium ions and 1-methoxy-2- (VIII) and 1-methoxy-4-methylpyridinium ions showed a positive reaction.

(1) E. Ochiai, M. Katada, and T. Naito, *J. Pharm. Soc. Japan*, 64, 210 (1944); *Chem. Abstr.*, 45, 5154 (1951).

(2) A. R. Katritzky, *J. Chem. Soc.*, 2404 (1956).

(3) W. Feely, W. L. Lehn, and V. Boekelheide, *J. Org. Chem.*, 22, 1135 (1957).

(4) A. R. Katritzky, *Quart. Rev.*, 10, 395 (1956).

* Note added in proof: Reactions of this type between 1-methoxypyridinium salts and cyanide ions leading to 2- and 4-cyanopyridines have recently been described by T. O. Kamoto and H. Tani, *Chem. and Pharm. Bulletin (Japan)*, 7, 130 (1959); and by W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, 81, 4004 (1959).

(5) E. Koenigs and E. Ruppelt, *Ann.*, 509, 142 (1934).

(6) Beilstein, Hauptwerk, XII, 153.

(7) A. W. Hofmann, *Ber.*, 6, 352 (1873).

(8) F. T. Naylor and B. C. Saunders, *J. Chem. Soc.*, 3519 (1950).
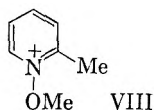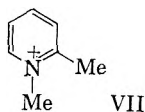
(9) L. Horner and H. Nickel, *Ann.*, 597, 20 (1955).

(10) I. de Paoline, *Gazz. Chim. Ital.*, 60, 859 (1930).

(11) J. Walter, *Zeit. für Fabenindustrie*, 10, 49; *Chem. Zentr.*, 1, 1411 (1911).

(12) B. Dale, R. Foster, and D. L. Hammick, *J. Chem. Soc.*, 3986 (1954).

(13) B. von Bitto, *Ann.*, 269, 377 (1892).

(14) A. Schönberg and M. M. Sidky, *J. Org. Chem.*, 21, 476 (1956).

EXPERIMENTAL

Reactions of 1-methoxypyridinium toluene–p-sulfonate (IX).
(a) IX (2.65 g., prepared by the lit. method[2]) and ethanolic
sodium ethoxide (from 0.23 g. sodium and 10 cc. ethanol)
were refluxed for 1 hr., cooled in methanol–Dry Ice, and
filtered; hot ethanolic picric acid (2.29 g.) added to the fil-
trate gave pyridine picrate (3.1 g., 81%), m.p. and mixed
m.p. 163–164° after recrystallization from ethanol.

(b) Ethanolic sodium phenoxide gave pyridine (20%,
isolated as the picrate).

(c) IX (2.65 g.), hydroxylamine hydrochloride (1.4 g.),
and anhydrous sodium carbonate (5.3 g.) were refluxed
for 1 hr. in 10 cc. of water, and filtered at 0°. Evaporation
of the filtrate at 100°/30 mm., extraction of the residue
with ethanol (20 cc.), and treatment of the extracts with
picric acid (2 g.) gave pyridine 1-oxide picrate (3.2 g., 55%),
m.p. and mixed m.p. 178.5–179° (lit.[15] m.p. 179.5°).

(d) IX (2.65 g.) and aniline (2.8 g.) were heated at 120°
for 16 hr., treated with aqueous potassium hydroxide (4.4
cc., 30%), and the organic layer separated and distilled. The
fraction which boiled below 80°/0.1 mm. was heated for
10 min. at 100° with pyridine (1 cc.) and toluene-p-sulfonyl
chloride (1 g.), aqueous sodium hydroxide was added and
the oily layer removed and acidified to give N-methyl

(15) J. Meisenheimer, *Ber.*, **59**, 1848 (1926).

toluene–p-sulfonanilide (15%), m.p. and mixed m.p. 95–
96°. The fraction which boiled above 80°/0.1 mm. with
ethanolic picric acid gave pyridine 1-oxide picrate, m.p.
and mixed m.p. 177–178.5°.

(e) Under conditions similar to those described in (a),
(c), or (d), pyridine 1-oxide picrate was obtained from 1-
methoxypyridinium toluene–p-sulfonate with the following
reagents in the yields indicated: ethanolic sodium benzyl
mercaptide, 35%; sodium acetate in acetic acid, 30%;
morpholine, 23%; aqueous semicarbazide, 28%; and
ethereal phenyl magnesium bromide, 15%.

*Reaction of pyridine 1-oxide hydrochloride with dimethyl-
aniline.* Pyridine 1-oxide hydrochloride (6.5 g.) and di-
methylaniline (1.5 g.) were heated for 1 hr. at 165° and
chromatographed in benzene-chloroform on alumina. Elution
with chloroform-ethanol and rechromatographing gave
crystal violet (identified by infrared spectrum).

Color test for N-oxides. General procedure: dimethyl-
aniline (0.2 cc.), concentrated hydrochloric acid (0.05 cc.),
and the material to be tested (0.1 g.) were boiled in a test
tube for 1 min. Ethanol (1 cc.) was added to the cooled
residue; if positive an intense blue color developed.

The following substituted pyridine 1-oxides gave a posi-
tive result: 2-, 3-, and 4-methyl, 2-, 3-, and 4-cyano, 3-
and 4-nitro, 2-amino, and 2- and 3-hydroxy, 2,6-dimethyl,
2,4,6-trimethyl, 3-methyl-4-nitro, 4-ethoxy-3-nitro. Quin-
oline 1-oxide, nitrobenzene, and m-dinitrobenzene also gave
a positive result.

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Communications TO THE EDITOR

Conversion of Phthalic Anhydride into Biphthalyl by Trialkyl Phosphites[1]

Sir:

We should like to report the conversion of phthalic anhydride into biphthalyl (I) by trialkyl phosphites, a novel reaction which may have wide synthetic applications.

A mixture of phthalic anhydride (74 g.) and *triethyl phosphite* (166 g.) was kept 37 hr. at reflux temperature, under nitrogen. From the mixture, 44 g. (65% yield) of biphthalyl (I),[2] m.p. 352–354°, separated on cooling. I, whose m.p. did not change upon recrystallization from xylene, was characterized by elemental analysis, saponification equivalent, and ultraviolet and infrared spectra; it was also compared with a sample of biphthalyl prepared from phthaloyl chloride in very low yield.[3]

The yield of biphthalyl (I) is considerably lower when *trimethyl phosphite* is used. Using 2 mol. of trimethyl phosphite per mol. of phthalic anhydride, approximately 74% of the latter was recovered unchanged after 20 hr. at reflux temperature. Biphthalyl (I) was obtained in *ca.* 5% yield and, in addition, dimethyl methylphosphonate, $CH_3P(O)(OCH_3)_2$, trimethyl phosphate $(CH_3O)_3PO$, and dimethyl phthalate were produced. No phosphite was left unchanged.

It is attractive to postulate an intermediate of type II in this reaction. From II, either an α-oxophosphonate ester[4] (III) or a species with pentacovalent phosphorus (IV) could be produced. The latter might be the precursor of biphthalyl *via* the diketene (V) and the carbene (VI). This, as well as other mechanistic schemes, is under study, and the scope of the reaction of phosphite esters with anhydrides[4] is under investigation.
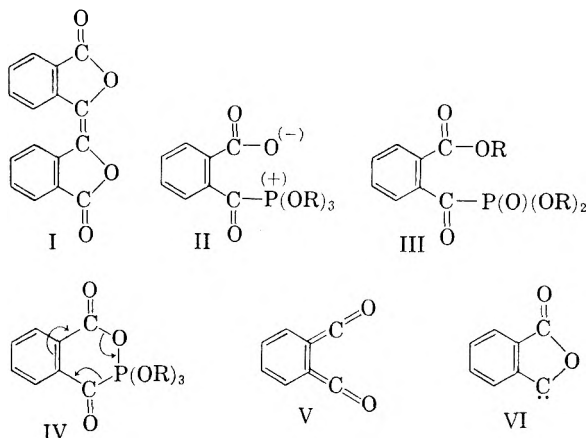
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(1) These studies are being supported by the Public Health Service (Grants CY-3250 and RG 6136A) and by the National Science Foundation (Grant NSF-G9917).

(2) *Beilstein Handbuch der organishen Chemie*, 4th ed., Vol. 19, 176 (I 688), (II 192), J. Springer, Berlin, 1918.

(3) We are grateful to Dr. J. C. Sauer of E. I. du Pont de Nemours & Co. for a sample of biphthalyl prepared in 3% yield from unsymmetrical phthaloyl chloride. *Cf.* P. Karrer, W. Wehrli, E. Biederman, and M. dalla Vedova, *Helv. Chem. Acta*, 11, 233 (1928).

(4) The formation of carboxylic esters and acylphosphonates from trialkyl phosphites and certain anhydrides has been reported. *Cf.* G. Kamai and V. A. Kukhtin *Akad. Nauk, S.S.S.R.*, Trudy 1-Oi Konferents, 1955, 91–97 *Chem. Abstr.*, 52, 241 (1958).