

the corresponding 2,4-dinitrophenylhydrazones and *p*-nitrophenylhydrazones showed no depression in melting points.

5-Chloromercuri-2,4-diphenylthiophene.—2,4-Diphenylthiophene (500 mg., 2.1 mmoles) gave a 93% yield of 5-chloromercuri-2,4-diphenylthiophene (m.p. 219.5–221°) by reaction with mercuric chloride and sodium acetate according to the conditions described by Bogert and Herrera.⁹

Chloromercuration of 2,5-diphenyl-1,4-dithiadene was attempted using the same condition; however, only unchanged starting material was recovered.

Pyrolysis of 2,5-Diphenyl-1,4-dithiadene.—A 6-inch test-tube, with side-arm, was fitted with a stopper, containing a thermometer which extended to the bottom of the tube, and a nitrogen inlet tube. 2,5-Diphenyl-1,4-dithiadene (997 mg., 3.72 mmoles) was placed in the tube and nitrogen was passed through the system for ten minutes. The tube was inserted into an oil-bath at 200°, and after two minutes (temperature of the melt was 190°) a vigorous reaction took place which caused the temperature of the yellow melt to rise to 250°. The tube was removed from the oil-bath and cooled under a stream of nitrogen. The pyrolysate was purified by chromatography with a 3.5 × 30 cm. column which contained 100 g. of Alcoa Activated Alumina F-20. Petroleum ether (30–60°) eluted 80 mg. (67%) of monoclinic sulfur, m.p. 121–123°. A mixture melting point with authentic sample was not depressed.

Anal. Calcd. for S: S, 100. Found: S, 96.8.

2,4-Diphenylthiophene (598 mg., 69%, m.p. 121–122.5°) was eluted with 10% benzene in petroleum ether (30–60°). The infrared and ultraviolet spectra of this product were identical to those previously obtained for pure III; a mixture melting point with pure III was not depressed.

Oxidation of 2,5-Diphenyl-1,4-dithiadene, Compound (I).¹—A mixture of 2,5-diphenyl-1,4-dithiadene (4.0 g., 0.015 mole), 30% hydrogen peroxide (1.8 g., 0.016 mole)

and 50 ml. of glacial acetic acid was heated on a steam-bath for one hour. After the solution was diluted with water, the solid was filtered and recrystallized from acetone. The yellow solid (1.5 g., m.p. 126–129°) melted at 127–129° (1.2 g., 33%) after recrystallization from ethyl acetate. This product previously³ was shown to have the empirical formula C₂₂H₂₄S₃.

The structure of the product (m.p. 127–129°) obtained by oxidation of I was shown to be a molecular complex of 2,4-diphenylthiophene (III) and 2,5-diphenyl-1,4-dithiadene (I). (a) The ultraviolet spectrum of this product ($\lambda_{258\text{ m}\mu}^{\text{max}}$ (ϵ 58,500), $\lambda_{305\text{ m}\mu}^{\text{plateau}}$ (ϵ 16,400)) was essentially identical to the sum of the spectra of I ($\lambda_{258\text{ m}\mu}^{\text{max}}$ (ϵ 22,100), $\lambda_{309}^{\text{max}}$ (ϵ 8900)) and III ($\lambda_{257\text{ m}\mu}^{\text{max}}$ (ϵ 34,700), $\lambda_{308}^{\text{inflection}}$ (ϵ 8800)).

(b) The oxidation product (288 mg., 0.57 mmole) readily gave 5-chloromercuri-2,4-diphenylthiophene (98 mg., 36%, m.p. and mixed m.p. 219.5–221°) by reaction (6 days at room temperature) with saturated aqueous mercuric chloride (25 g.) and sodium acetate (5 g., 33% in water) in 95% ethanol (150 ml.). The precipitate that originally formed was washed with petroleum ether (60–68°) and the insoluble chloromercuri derivative was recrystallized from 95% ethanol. From the petroleum ether extract there was obtained 86 mg. (30%) of unchanged starting material (m.p. 126–127°).

(c) An equimolar mixture of I (m.p. 118–119°) and III (m.p. 121.5–123°) was recrystallized from ethyl acetate. The product (94% yield) melted at 128–129° and caused no depression in melting point when admixed with the product obtained by oxidation of I. The ultraviolet spectrum of this product ($\lambda_{258\text{ m}\mu}^{\text{max}}$ (ϵ 56,400), $\lambda_{305\text{ m}\mu}^{\text{max}}$ (ϵ 16,200)) was essentially identical to the product obtained by oxidation of I.

Anal. Calcd. for C₂₂H₂₄S₃: C, 76.14; H, 4.79. Found: C, 75.97; H, 5.05.

MINNEAPOLIS, MINNESOTA

(9) M. T. Bogert and P. P. Herrera, *THIS JOURNAL*, **45**, 240 (1923).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

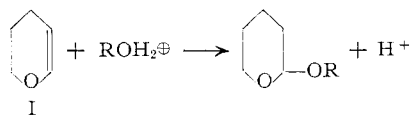
Protection of Hydroxyl Groups. II. Preferential Pyranylation

BY WILLIAM E. PARHAM AND DALE M. DELAITSCH¹

RECEIVED APRIL 28, 1954

The approximate rate of addition of phenol, ethyl mercaptan and thiophenol to dihydropyran has been determined and the following order of reactivity has been established: C₆H₅OH >>> C₂H₅SH > C₆H₅SH. Although thiophenol reacts at an appreciably slower rate with dihydropyran than does phenol, the latter serves as a catalyst for the pyranylation of the former, and, consequently, thiophenol is preferentially pyranylated in competitive reactions with phenol. Studies of the monopyranylation of 4-substituted pyrocatechols show that a carbethoxy group, but not a methyl group, in the 4-position, causes preferential pyranylation of the least acidic hydroxyl group.

Dihydropyran (I), a typical vinyl ether, readily adds aliphatic and aromatic hydroxyl groups in the presence of acid catalysts, and this reaction has been employed as a method of protecting hydroxyl groups for reactions conducted in basic media.²



In order that additional information concerning this reaction might be gained, the relative rates of reaction of I with phenol, ethyl mercaptan, and thiophenol have been determined. Also, a study has been made of the monopyranylation of 4-substituted pyrocatechols.

For the reactions of I with ethanol, phenol,

ethyl mercaptan and thiophenol identical experimental conditions were employed.³ It was observed that the rate of reaction of dihydropyran with compounds containing hydroxyl groups was much more rapid than with compounds containing sulfhydryl groups. Furthermore, ethanol appeared⁴ to react more rapidly than did phenol.

It can be seen from Tables I, II and III (Experimental section) that phenol was 50% consumed in less than seven minutes, whereas ethyl mercaptan and thiophenol were 50% consumed in approximately eight and twenty-one hours, respectively. Under the conditions employed, the rates of reaction were related to the basicity of the addendum—the most basic compounds reacting the fastest.

Although thiophenol reacts at an appreciably

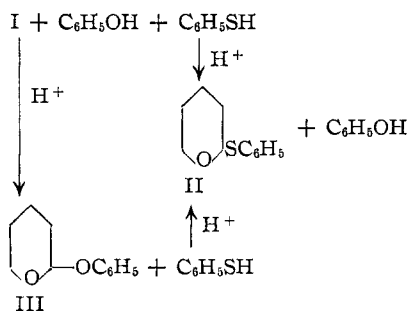
(3) RXH (0.25 mole), I (0.50 mole), hydrogen chloride (0.00058 mole) in ether (0.50 ml.) at 28°.

(4) The reaction with ethanol was studied qualitatively only; however, the reaction was very fast and an 82% yield of addition product was isolated after the reaction had progressed for seven minutes.

(1) From the Ph.D. Thesis of D. M. DeLaitsch, University of Minnesota, 1950.

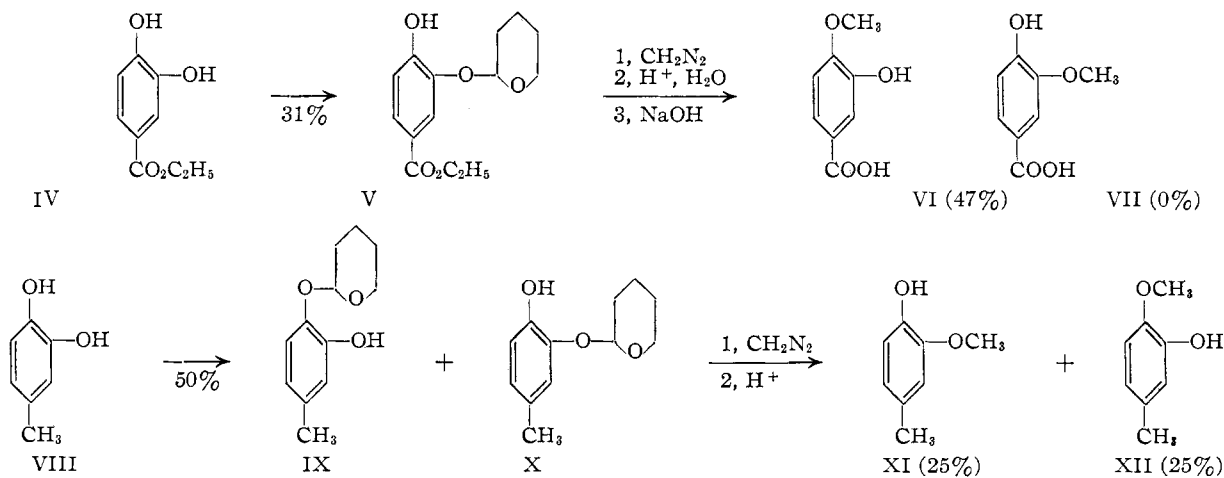
(2) Cf. W. E. Parham and E. L. Anderson, *THIS JOURNAL*, **70**, 4187 (1948).

slower rate with dihydropyran than does phenol, phenol serves as a catalyst for the pyranylation of thiophenol, and, consequently, the former cannot be preferentially pyranylated in the presence of the latter. In fact, the opposite situation obtains. When an equimolar mixture of dihydropyran, phenol, and thiophenol was allowed to stand for 20 minutes in the presence of a catalytic quantity of ethereal hydrogen chloride, a 68% yield of pure phenyl-2-tetrahydropyranyl sulfide (II) was obtained.



Phenol was recovered in 71% yield, and only small amounts (1–3%) of thiophenol and phenyl-2-tetrahydropyranyl ether (III) were obtained. These results indicated that the initial reaction product III underwent a rapid acetal interchange with thiophenol, and this was found to be the case. Distillation of the reaction product obtained when a mixture of III, thiophenol and ethereal hydrogen chloride was allowed to stand for 20 minutes, gave a 78% yield of II and a 79% yield of phenol.

In view of the results described above, it was anticipated that the reaction of dihydropyran with 4-substituted pyrocatechols might result in mono-



pyranylated derivatives in which the least acidic hydroxyl group was converted into an acetal function. Two such cases, ethyl protococatechuate (IV) and 4-homopyrocatechol (VIII) have been studied. Our results show that: (a) a carboxy group in the 4-position does give a monopyranylated product in which only the least acidic hydroxyl group is involved, and (b) a methyl group in the 4-position has no apparent effect in controlling the preferential pyranylation of either hydroxyl group.

The methods employed are summarized in the following equations—details are found in the Experimental section of the report.

During the course of this work it was shown that phenyl-2-tetrahydropyranyl sulfide (II) is quite resistant to acid hydrolysis. II can be recovered in high yield (86%) after prolonged treatment (7 hr.) with a hot (100°) mixture of concentrated hydrochloric acid, water and acetone (1:1:10). This behavior is in sharp contrast to the reported sensitivity of aliphatic pyranyl sulfides to acid hydrolysis.⁵

This work is being extended to include a study of the rate of pyranylation of substituted phenols and alcohols.

Experimental

Phenyl 2-Tetrahydropyranyl Sulfide (II).—The procedure used was essentially identical to that previously reported² for the pyranylation of aliphatic alcohols; however, the reaction mixture was heated to the reflux temperature for nine hours. From 55 g. (0.5 mole) of thiophenol there was obtained 69 g. (71% yield) of II, b.p. 130–131° (4 mm.), n_D^{25} 1.5700.

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{OS}$: C, 67.77; H, 7.26. Found: C, 67.83; H, 7.51.

Ethyl 2-tetrahydropyranyl sulfide,⁵ b.p. 84–86° (20 mm.), n_D^{25} 1.4850, was obtained in 66% yield by the same procedure as described for II, above; however, in this case the reaction mixture was allowed to stand (under a reflux condenser) for two days at room temperature.

Rate of Reaction of Thiophenol with Dihydropyran.—Thiophenol (27.5 g., 0.25 mole) was mixed with dihydropyran (42.0 g., 0.50 mole) in a three-necked flask fitted with a stirrer and reflux condenser equipped with a drying tube. The flask was submerged in a large-volume water-bath which was maintained at $28 \pm 1^\circ$. Diethyl ether (0.50 ml.) containing anhydrous hydrogen chloride (0.00058 mole) was added. At various time intervals, a 5.00-ml. portion (4.83 g.) of the reaction mixture was removed and added to excess aqueous sodium hydroxide. The alkaline solution was washed with ether, and then acidified and ex-

tracted with benzene. The amount of thiophenol in the

(5) F. Kipnis and J. Ornfelt, *THIS JOURNAL*, **73**, 822 (1951), report that aliphatic pyranyl sulfides are decomposed easily by action of dilute acid to "5-hydroxypentenal" and mercaptans. The reported basis for this conclusion was the positive test for aldehyde and mercaptan obtained after these sulfides were treated with acid. It is of interest to note that titration of the initial hydrolysis mixture of II (described above) gave the following values for $\text{C}_6\text{H}_5\text{SH}$: (a) after 7 min. at 28°, 3.7%; (b) after 180 min. at 100°, 3.1%; (c) after 720 min. at 100°, 4.9%. These data suggest that a positive test for aldehyde and mercaptan is not an adequate criterion for evaluation of the ease of hydrolysis of the pyranyl sulfides.

benzene extract was determined by the method of Sampey and Reid.⁶ Blank determinations using known concentrations of thiophenol gave values which were 99% of the theoretical. Typical values of thiophenol concentrations at various time intervals are recorded in Table I.

TABLE I

Time, min.	Thiophenol consumed, %		Average
	Run I	Run II	
15	0.8	1.9	1.3
45	2.4	3.4	2.9
105	4.3	5.7	5.0
1200	45.5	44.8	45.1
2800	82.9	69.5	76.2

Reaction of Ethyl Mercaptan with Dihydropyran.—The molar ratio of reactants, and the procedure employed, were identical to those described above for thiophenol.

TABLE II

Time, min.	Ethyl mercaptan consumed, %			Average
	Run I	Run II	Run III	
7	0.4	3.0	0.8	1
15	0.6	7.2	1.5	3
45	7.5	10.9	5.9	8
105	17.8	22.6	13.1	18
540	54.5	54.5
1200	71.7	87.6	88.0	82
2800	96	96

Reaction of Phenol with Dihydropyran.—The conditions for the reaction, and the ratio of reactants, were identical to those previously described for thiophenol and ethyl mercaptan. The 5.00-ml. aliquot (5.00 g.) was added to excess aqueous sodium hydroxide and the resulting mixture was extracted with ether. The alkaline solution was made strongly acidic with concentrated hydrochloric acid and the resulting solution was diluted to exactly 250 ml. with water. The phenol was determined by the method of Koppescharr.⁷

Weighed amounts of phenol, when carried through similar treatment, gave values which were $93 \pm 0.5\%$ of the theoretical. Consequently, a correction factor has been included in the results.

TABLE III

Time, min.	Phenol consumed, %		Average
	Run I	Run II	
7	82.7	84.6	84
15	87.8	87.2	88
45	92.5	93.2	93
105	94.2	94.1	94
1200	99.3	99.0	99

Competitive Reaction between Dihydropyran, Phenol and Thiophenol.—Phenol (18.8 g., 0.2 mole), thiophenol (22.0 g., 0.2 mole), and dihydropyran (16.8 g., 0.2 mole) were mixed, and ethereal hydrogen chloride (0.50 ml. containing 0.00058 mole of acid) was added. An exothermic reaction occurred. After 20 minutes, one-half of the total reaction mixture (28.8 g.) was processed in the usual way.² There was obtained: phenyl 2-tetrahydropyranyl sulfide (13.2 g., 68% yield, b.p. 166–169° (24 mm.), n_D^{25} 1.5680), phenol (6.67 g., 71% yield, b.p. 178–180° (760 mm.)), thiophenol (0.14 g., 1.3% calculated from the weight of its lead salt), and impure 2-tetrahydropyranyl ether (0.50 g., 2.8%, b.p. 145–147° (24 mm.), n_D^{25} 1.5480).

Reaction of Phenyl 2-Tetrahydropyranyl Ether (III) with Thiophenol.—Phenyl 2-tetrahydropyranyl ether² (17.8 g., 0.1 mole) and thiophenol (12.5 g., 0.113 mole) were mixed and 2 ml. of 6% ethereal hydrogen chloride was added. The reaction mixture was allowed to stand for 20 minutes and then processed in the usual way. There was obtained 15.15 g. (78%) of phenyl 2-tetrahydropyranyl sulfide, b.p. 166–169° (25 mm.), n_D^{25} 1.5688.

Ethyl protocatechuate (IV) was prepared from protocate-

chuic acid⁸ by esterification with ethyl alcohol and sulfuric acid; m.p. 130–131.5° (reported m.p. 134°).

Conversion of Ethyl Protocatechuate into Isovanillic Acid (VI).—Preliminary experiments showed that neither the mono- or dipyranylated derivative of ethyl protocatechuate could be distilled without decomposition. The following procedure was developed to: (a) ensure high conversion of IV into pyranlyated products, and (b) to eliminate the possibility that VI and/or VII could be formed by methylation of unchanged IV.

Ethyl protocatechuate (18.2 g., 0.1 mole) was mixed with dihydropyran (50.4 g., 0.6 mole) and one drop of concentrated hydrochloric acid was added. The reaction was only mildly exothermic and the original ester was completely dissolved after two hours. The reaction mixture was allowed to stand for 24 hours, and then ether was added and the mixture was extracted with cold 5% sodium hydroxide. The ether extract, containing dihydropyran, dipyranylated IV and polymers of dihydropyran, was discarded. Dry Ice was added to the alkaline solution and the organic layer, which separated, was extracted with ether. From the dry ethereal extract there was obtained 8.4 g. (31%) of a viscous oil which was principally V, contaminated, perhaps, with a small quantity of unchanged IV. This product was dissolved in ether, and a large excess of diazomethane, in ether, was added. The resulting solution was allowed to stand for 24 hours, and was then extracted with cold, dilute sodium hydroxide.¹⁰ The ether was removed from the dried solution containing the methylated derivative of V, and the residual oil was treated with dilute hydrochloric acid (one-half hour at the reflux temperature followed by 12 hours at room temperature) to hydrolyze the acetal linkage. The resulting mixture was extracted with ether and the phenolic material was separated from the ether extract by extraction with aqueous sodium hydroxide. The alkaline solution was heated at the reflux temperature for ten minutes (to complete the hydrolysis of the ester group), acidified, and the resulting solution was cooled. There was obtained 2.5 g. of isovanillic acid (m.p. 243–246, 249–251° after recrystallization¹¹). No vanillic acid, m.p. 207°,⁸ was found.

Conversion of 4-Homopyrocatechol (VIII) into XI and XII.—4-Homopyrocatechol (15 g., 0.121 mole, m.p. 65–66°¹²) was treated with dihydropyran (30.6 g., 0.363 mole) and acid as described for IV above. The dipyranylated derivative of VIII was purified by distillation, b.p. 171–176° (3 mm.), n_D^{25} 1.5200, with subsequent recrystallization (ethanol) of the distillate; m.p. 65–67°.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.30 (liq.), 69.56 (solid); H, 8.39 (liq.), 8.23 (solid).

The monopyranlyated derivative (obtained by carbonation of the alkaline extract) was purified by distillation. There was obtained 12.9 g. (51% yield, 15–25% on subsequent runs) of product boiling at 150–158° (3 mm.). The sample used for analysis boiled at 150–151° (3 mm.), n_D^{25} 1.5291.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.01; H, 7.92.

The mixture of IX and X was treated with excess diazomethane according to the procedure described in the preceding section. The mixture of creosol and isocresol was obtained as an oil (51.5%) boiling at 112–115° (24 mm.).¹³

The approximate concentration of XI and XII in the product was determined in the following way. A sample of the mixture (0.40 g.) was treated with excess benzenesulfonyl chloride in pyridine and the mixture of benzenesulfonates (0.72 g. 89% yield, m.p. 49–59°) was obtained. This mixture was dissolved in cold alcohol, and water was added in small portions over a period of two days. There was obtained 0.70 g. (97.2% recovery) of the mixed creosol and iso-

(8) J. A. Pearl, *THIS JOURNAL*, **68**, 2180 (1946).

(9) O. Hesse, *Ann.*, **114**, 295 (1860).

(10) This step was included to insure the absence of any VI or VII in the final product which might be derived by mono-methylation of unchanged starting material.

(11) Isovanillic acid is reported to melt at 250°; K. V. Matsumoto, *Ber.*, **11**, 126 (1878).

(12) M. O. DeVries, *Rec. trav. chim.*, **28**, 278 (1909).

(13) The reported boiling points of creosol and isocresol are 221–222° (765 mm.) or 113.5° (22.5 mm.) and 222–223° (760 mm.), respectively. Cf. ref. 12 and W. H. Perkin, *J. Chem. Soc.*, **69**, 1185 (1896).

(6) J. R. Sampey and E. E. Reid, *THIS JOURNAL*, **54**, 3404 (1932).

(7) W. F. Koppescharr, *Z. anal. Chem.*, **15**, 233 (1876).

creosol benzenesulfonates (m.p. 50–71°). This procedure was repeated two additional times; the melting ranges for the mixtures were: (a) 50–71°, (b) 49–68° and (c) 49.5–59°.

Anal. Calcd. for $C_{14}H_{14}O_4S$: C, 60.42; H, 5.07. Found: C, 60.52; H, 5.37.

Pure creosol benzenesulfonate (m.p. 65–66.5°) and pure isocresol benzenesulfonate (m.p. 88–89°)¹⁴ were prepared

(14) Isocresol, b.p. 112° (23 mm.), was prepared from *p*-toluidine, by modifications of the procedure previously reported by M. O. DeVries, *Rec. trav. chim.*, **28**, 289 (1909). Isocresol benzenesulfonate was prepared by standard procedures from isocresol, and recrystallized

and a mixed melting point diagram was made up from known mixtures of the pure components. The melting points of the mixtures of sulfonates obtained from VIII (a, b, c above), correspond to mixtures of creosol and isocresol benzenesulfonates in the ratios 45:55, 48:52 and 56:44, respectively.

to constant melting point (m.p. 88–89°) from alcohol–water. A Von Wacek and A. Von Beyard, *Ber.*, **74B**, 845 (1941), report the melting point of isocresol benzenesulfonate to be 94°.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

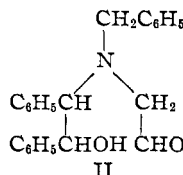
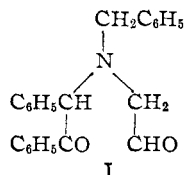
Ring-Chain Relationships in the 2-(N-Acetal-N-benzylamino)-1,2-diphenylethanone and Ethanol Series¹

By ROBERT E. LUTZ AND CLAIBOURNE E. GRIFFIN

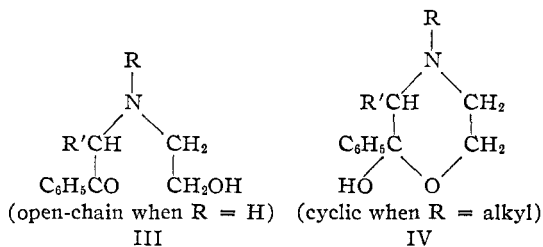
RECEIVED MARCH 29, 1954

N-Acetal-N-benzylamino-1,2-diphenylethanone and the two stereoisomeric ethanols have been prepared; their structures were shown by ultraviolet absorptions and by reduction of the former to one of the latter by aluminum isopropoxide. Hydrolyses gave corresponding dihydroxy and monohydroxy-morpholines by irreversible cyclization through the aldehyde group; the cyclic structures were shown by ultraviolet absorptions and by reduction characteristics. Acid-catalyzed etherifications and transesterifications of both open-chain and cyclic compounds were easily effected in absolute alcohols. A small amount of water was necessary to effect cyclizations under these conditions, however; and this is explained in terms of hydrolysis first to the hemiacetal or free aldehyde. Dehydration of the dihydroxymorpholine gave irreversibly a hydroxydihydroxazine, the structure of which was shown by its stilbene type ultraviolet absorptivity. Lithium aluminum hydride reduction proceeded one stage to an enolate-alkoxide which only upon subsequent hydrolysis gave the then further reducible 2-hydroxymorpholine.

This investigation deals with the two β,β' -dioxymorpholines I and II which have been obtained only in the open-chain or cyclic acetal or cyclic hemiacetal forms; it is a part of the study of the



effect of structural modifications of certain types of amino alcohol and amino ketone systems on pharmacological activity and on the ring-chain relationships of the type III–IV²; and it is essentially an



extension of early and limited work on diacetalamine³ and acetalethanolamine⁴ which have been converted into the cyclic acetal-ketal and the cyclic acetal of types IX and XXII, respectively.

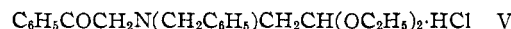
(1) This investigation was supported by a grant from the Eli Lilly Company.

(2) Cf. (a) R. E. Lutz, J. A. Freek and R. S. Murphey, *THIS JOURNAL*, **70**, 2015 (1948); (b) R. E. Lutz and R. H. Jordan, *ibid.*, **71**, 996 (1949).

(3) L. Wolff, *Ber.*, **21**, 1481 (1888); L. Wolff and R. Marburg, *Ann.*, **363**, 169 (1908).

(4) L. Knorr, *Ber.*, **32**, 729 (1899).

In preliminary experiments in this field⁵ α -(N-benzyl-N-acetalamino)-acetophenone was obtained as an unstable hydrochloride V. The N-benzyl-



1,2-diphenyl series, however, was chosen for the first extended study because of the greater stability and good melting points of the compounds involved, for the structural analogy to the previously studied 1,2-diphenylamino alcohols and hydroxymorpholines III–IV, and in order to obtain new pharmacologically interesting compounds in this series in which there has been found a high incidence of necrotizing activity against mammalian tumors.⁶

2-(N-2,2-Diethoxyethyl-N-benzylamino)-1,2-diphenylethanone (VIIIa) which is related to I, was obtained in good yield by direct condensation of desyl chloride VI with α -benzylaminoacetal (VII); the hydrogen chloride liberated was removed as the hydrochloride of the reagent VII which was used in sufficient excess for the purpose. Transesterification of this diethylacetal VIIIa to and from the corresponding dimethylacetal VIIIb without cyclization was readily accomplished by the action of the appropriate absolute alcohol and hydrogen chloride.

That these compounds VIIIa and b are open-chain as written was demonstrated as follows: the ultraviolet molecular absorptivities in the 240–250 μ region (ϵ 12.4–12.7 $\times 10^3$) are of the character-

(5) Carried out in this Laboratory by Dr. R. H. Jordan.

(6) Cf. (a) J. L. Hartwell and S. R. L. Kornberg, *THIS JOURNAL*, **67**, 1606 (1945); (b) J. L. Hartwell and M. J. Shear, *Am. Assoc. Cancer Research*, 38th meeting, May 16–17, 1947 (*cf. Cancer Research*, **7**, 716 (1947)); (c) M. J. Shear, V. Downing, J. L. Hartwell, *et al.*, *Am. Assoc. Cancer Research*, 40th meeting, April 16–17, 1949 (*cf. Cancer Research*, **9**, 625 (1949)).