The methylene chloride soluble fraction yielded 2.8 g. (64%) of 2-ethylmethylamino-5-phenyl-2-oxazolin-4-one, m.p. 90–97°. An analytical sample was recrystallized twice from ethyl acetate, m.p. 104–107°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.78. Found: C, 65.89, H, 6.62; N, 12.78.

2-*N*-Methylanilino-5-phenyl-2-oxazolin-4-one (XIII).—5-Phenyl-2-phenylimino-4-oxazolidinone (XII, 6.9 g.)[18] was methylated exactly as in the examples above and yielded 8.0 g. of a crystallizable oil. Ordinary recrystallization (from ethyl acetate or methylene chloride–ether) of similar material from other experiments gave samples melting within a 1° range with consistently low (0.6–0.9%) analytical values for carbon. Accordingly, 4.0 g. of this oil was subjected to partition chromatography by the procedure above except that a cyclohexane–dioxane–water system (80:20:8) was used and absorption of the eluate at 235 mμ was observed. Concentration of the major fraction (second and third h.b.v.) yielded a solid. Recrystallization from ethyl acetate afforded 1.4 g. (39%) of 2-*N*-methylanilino-5-phenyl-2-oxazolin-4-one (XIII), m.p. 109–109.4°, which, after drying at 65° for 1 hr. *in vacuo* had m.p. 107–107.5°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.31. Found: C, 71.26; H, 5.10.

5-Phenyl-2,4-oxazolidinedione was eluted from similar columns in the same position and may have been a contaminant.

Hydrolysis of 75 mg. in 2 ml. of 10% hydrochloric acid for 0.5 hr. at 90–100° yielded 25 mg. (50%) of 5-phenyl-2,4-oxazolidinedione, m.p. 110–111°, which was identified by its infrared spectrum. The acidic mother liquor was treated with 0.28 g. of sodium hydroxide and 0.11 g. of *p*-toluenesulfonyl chloride.[32] The solid obtained (99 mg.) was recrystallized from aqueous ethanol to yield 34 mg. (46%) of *N*-methyl-*p*-toluenesulfonanilide, m.p. 95–97° (lit.,[32] m.p. 94°). The infrared spectrum matched that of the crude material and that of an authentic sample; mixed m.p. 94–96°.

3-Methyl-5-phenyl-2-phenylimino-4-oxazolidinone (XIV).—A solution of 13 g. of α-chlorophenylacetyl chloride and 10.3 g. of 1-methyl-3-phenylurea in 40 ml. of benzene was heated under reflux for 5 hr. exactly as described by Aspelund[36] and yielded 13.1 g. (71%) of recrystallized 3-methyl-5-phenyl-2-phenylimino-4-oxazolidinone (XIV), m.p. 90–92° (lit.,[36] m.p. 90–91°).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.31; N, 10.52. Found: C, 71.83; N, 5.32; N, 10.63.

Hydrolysis of 0.53 g. of XIV in 5.8 ml. of 10% hydrochloric acid at 95–100° for 0.5 hr. yielded 0.31 g. (82%) of sublimed 3-methyl-5-phenyl-2,4-oxazolidinedione, m.p. 112–113° as reported.[36] The infrared spectrum of this sample was identical with that of authentic material.

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(32) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, 1956, pp. 103 and 285.

A Rearrangement of 5-Aryl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one 4-Oxides[1]

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5-Aryl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one 4-oxides were shown to rearrange to 3-acyloxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ones upon treatment with acylating agents. Hydrolysis of the acyl groups gave 3-hydroxy analogs. Upon treatment with alkali, 7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one rearranged to 7-chloro-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepine-2,3(1*H*)-dione and 6-chloro-4-phenyl-3,4-dihydro-2-quinazolinecarboxylic acid.

The action of acetic anhydride upon 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one 4-oxide[2] (I) has led to the formation of 3-acetoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (II). The course of this rearrangement is similar to that observed upon treatment of an aromatic *N*-oxide with acetic anhydride. Pyridine 1-oxide, for example, affords 2-acetoxypyridine.[3] In II, however, the acetoxy group is found on a saturated carbon atom. The formation of II would appear, therefore, to be more closely related to the proposed formation of acetylated carbinolamines as intermediates in the Polonovski reaction.[4] As an example of this reaction, *N*,*N*-dimethylaniline *N*-oxide is converted by acetic anhydride into *N*-methylacetanilide with *N*-acetoxymethyl-*N*-methylaniline as the suggested intermediate. In contrast to these proposed intermediates, II appears to be stable.

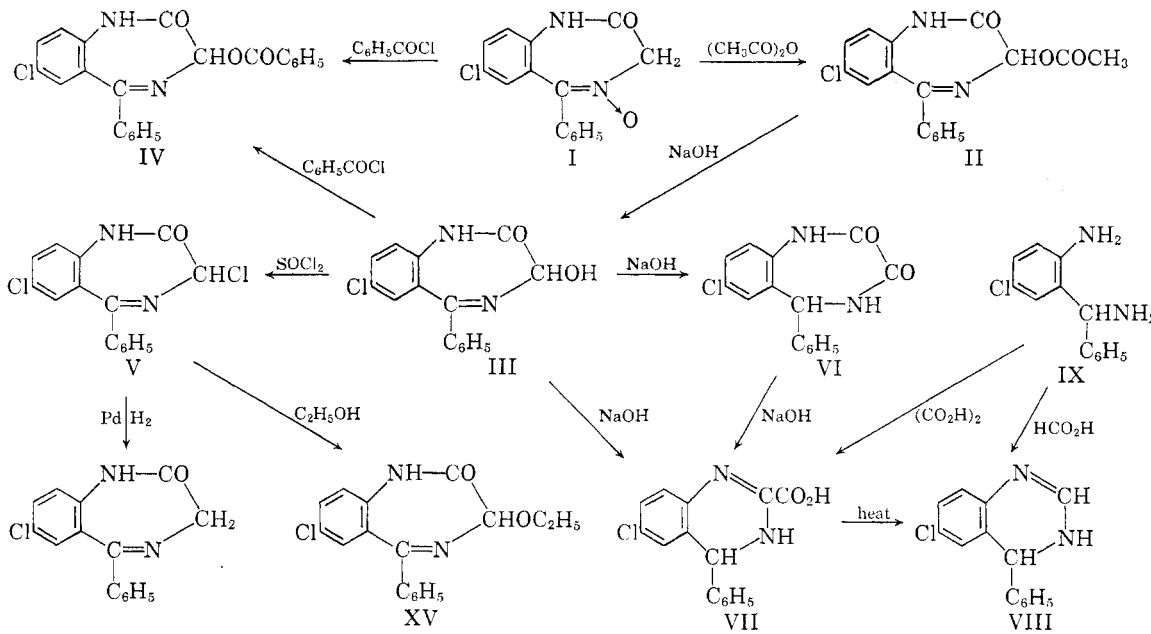
The acetyl group of II was easily hydrolyzed with one equivalent of sodium hydroxide, affording 7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (III). This product was benzoylated in pyridine solution to afford 3-benzoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (IV), identical with material prepared by treating I with benzoyl

(1) Presented at the National Meeting, American Chemical Society, Washington, D. C., March, 1962.

(2) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

(3) M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947).

(4) R. Huisgen, F. Bayerlein, and W. Heydkamp, *Chem. Ber.*, **92**, 3223 (1959), and W. Walter, M. Steffen, and K. Heyns, *Chem. Ber.*, **94**, 2462 (1961).



chloride. The retention of the seven-membered ring following the treatment of II with sodium hydroxide was demonstrated by treating III with thionyl chloride to give 3,7-dichloro-5-phenyl-1,3-dihydro - 2*H* - 1,4 - benzodiazepine - 2 - one (V). Removal of the 3-chloro substituent by catalytic reduction afforded the known 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one.[2]

Compound III, upon further treatment with sodium hydroxide, gave a new compound having the same empirical formula as III. This new product appears to be 7-chloro-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepine-2,3(1*H*)-dione (VI). The assignment of a cyclic diamide structure was made on the basis of the isomerism with III, the increase of almost 100° in the melting point and the ultraviolet and infrared absorption spectra. The absorption spectrum of III (Fig. 1) shows a band at

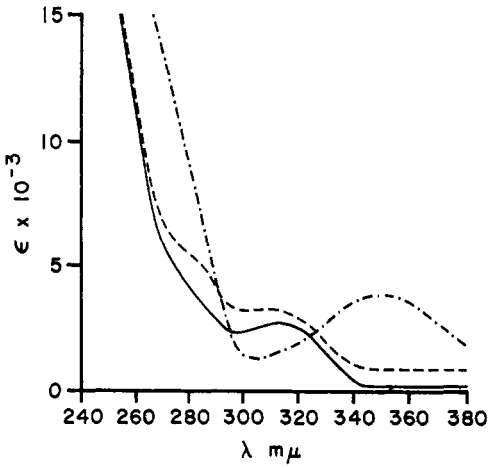


Fig. 1.—Absorption spectrum of III in 95% ethanol: ———, neutral; — — —, 0.1 *N* HCl; — · —, 0.1 *N* NaOH

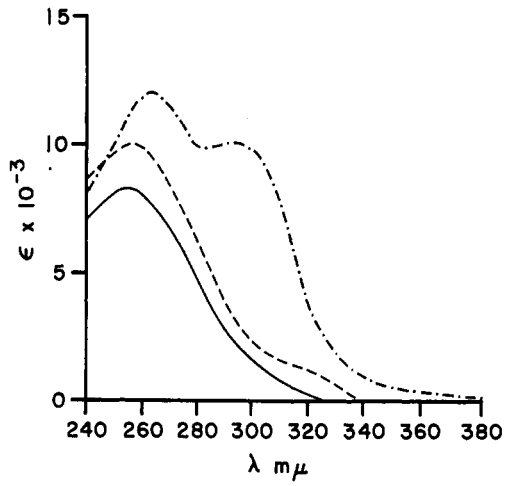


Fig. 2.—Absorption spectrum of VI in 95% ethanol: ———, neutral; — — —, 0.1 *N* HCl; — · —, 0.1 *N* NaOH

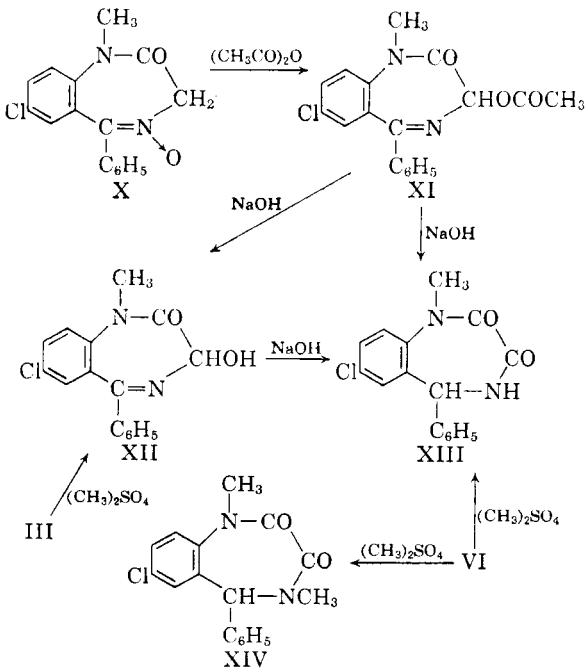
314 mμ attributable to the $C_6H_5C{=}N$ chromophore at positions 4 and 5. No such band occurs in the absorption spectrum of VI (Fig. 2). The absorption spectrum of neither compound is much affected by 0.1 *N* hydrochloric acid, but the spectra of both compounds are changed appreciably in 0.1 *N* sodium hydroxide. Compound VI shows a new band at 291 mμ attributable to the chromophore $(C_6H_5\overset{\ominus}{N}{-}C{=}O \rightleftharpoons C_6H_5N{=}C{-}\overset{\ominus}{O})$ arising from the ionization at position 1. A similar ionization in base takes place in III resulting in a bathochromic shift to 349 mμ of the band found at 314 mμ in neutral solution.

Both II and III have an absorption band in the infrared at 6.23 μ that may be attributable to >C=N— stretching. This band is absent in VI.

There are two carbonyl stretching bands in III (5.84, 5.91 μ) as well as in VI (5.92, 6.05 μ).

The formulation of VI as 7-chloro-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepine-2,3(1*H*)-dione was supported by a second rearrangement undergone by either III or VI upon more strenuous treatment with sodium hydroxide to afford a compound that was again isomeric with III. The product VII was soluble in sodium bicarbonate solution and lost carbon dioxide on heating to give a compound that was identified as 6-chloro-4-phenyl-3,4-dihydroquinazoline (VIII) by direct comparison with a sample prepared from 2-amino-5-chlorobenzhydrylamine (IX) and formic acid. Compound VII was therefore identified as 6-chloro-4-phenyl - 3,4 - dihydro - 2 - quinazolinecarboxylic acid. The identification was confirmed by the preparation of VII from IX and oxalic acid. The contraction from a seven-membered to a six-membered ring can occur by opening of the ring between the 1- and 2-positions or between the 3- and 4-positions of VI followed by recyclization to a dihydroquinazoline structure.

The rearrangement with acetic anhydride, followed by reaction with sodium hydroxide, was also carried out with 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one 4-oxide (X) and 1-methyl compounds (XI, XII, and XIII) related to II, III, and VI resulted. Methylation of III and VI in basic solution took place at the 1-position, as shown by the identity of the products XII and XIII with those prepared from X. It was possible to introduce two methyl groups into VI to give 7-chloro-1,4-dimethyl-5-phenyl-4,5-dihyhydro - 2*H* - 1,4 - benzodiazepine - 2,3(1*H*) - dione (XIV).



The rearrangement of I to 3-acyloxy derivatives was accomplished with benzoyl chloride, acetyl chloride, chloroacetic anhydride, and chloroacetyl chloride in addition to acetic anhydride. There was an unexpected by-product in the reaction of I with benzoyl chloride. Upon treatment of the reaction mixture with ethanol, 3-ethoxy-7-chloro-5-phenyl - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepine-2-one (XV) was obtained along with IV. Compound XV probably arises through the intermediate production of V. The reaction between ethanol and V would then give XV. Compound V was found to react wth ethanol to give XV whereas IV did not.

3-Chloroacetoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XVI) reacted with morpholine in anhydrous ethanol to give the corresponding 3-morpholinoacetoxy analog, which was obtained as a water-soluble hydrochloride (XVII).

Three additional analogs of II were synthesized: 3-acetoxy-5-phenyl-, 3-acetoxy-7-bromo-5-(*p*-chlorophenyl)-, and 3-acetoxy-7-chloro-5-(2-thienyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XVIII, XIX, and XX). The 3-acyloxy- and 3-hydroxy compounds exhibited potent effects on the central nervous system.

Experimental[5]

The benzodiazepine-2-one 4-oxides used as starting materials are described in ref. 2.

3-Acetoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (II).—A suspension of 10 g. of I in 100 ml. of acetic anhydride was stirred and heated on a steam bath for 20 min., a clear solution resulting. Upon cooling the solution there was obtained 9.8 g. of analytically pure II, m.p. 242–243°.

Anal. Calcd. for $C_{17}H_{13}ClN_2O$: C, 62.09; H, 3.98; N, 8.52 Found: C, 62.06; H, 4.13; N, 8.30.

The following 3-acetoxy compounds were similarly prepared from the corresponding 4-oxides:

3-Acetoxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XVIII), m.p. 229–231°.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.39; H, 4.80; N, 9.51. Found: C, 69.30; H, 4.91; N, 9.64.

3-Acetoxy-7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XI), m.p. 262–263°.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; Cl, 10.34; N, 8.17. Found: C, 63.16; H, 4.57; Cl, 10.25; N, 8.22.

3-Acetoxy-7-bromo-5-(*p*-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XIX), m.p. 256–257°.

Anal. Calcd. for $C_{17}H_{12}BrClN_2O_3$: C, 50.07; H, 2.97; Cl, 8.70; N, 6.86. Found: C, 50.08; H, 3.08; Cl, 8.51; N, 6.77.

3-Acetoxy-7-chloro-5-(2-thienyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XX), m.p. 269°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_3S$: C, 53.80; H, 3.31; N, 8.37. Found: C, 53.95; H, 3.41; N, 8.17.

7-Chloro-3-choloroacetoxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XVI). Method A.—A mixture of 5 g. of I and 10 g. of chloroacetic anhydride was heated for 10 min. on a steam bath. After a clear melt had formed, solidification occurred. The mixture was washed with carbon tetrachloride, and the residue was recrystallized from alcohol to give 4 g. of product, m.p. 230–231°.

(5) The melting points are uncorrected.

Method B.—Five grams of I was heated in a refluxing solution of 20 ml. of chloroacetyl chloride in 20 ml. of chloroform for 20 min. The solvent was removed *in vacuo* and the residue recrystallized as before to give 3.2 g. of product, m.p. 230–231°.

Anal. Calcd. for $C_{17}H_{12}Cl_2N_2O_3$: C, 56.06; H, 3.32; Cl, 19.47; N, 7.70. Found: C, 56.08; H, 3.42; Cl, 19.40; N, 7.43.

7-Chloro-3-morpholinoacetoxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one Hydrochloride (XVII).—A solution of 3 g. of XVI and 2.2 ml. of morpholine in 75 ml. of absolute alcohol was heated under reflux for 2 hr. Acidification of the cooled solution with alcoholic hydrogen chloride afforded 1 g. of product, m.p. 228–229°.

Anal. Calcd. for $C_{21}H_{19}ClN_3O_4 \cdot HCl$: C, 56.01; H, 4.48; Cl, 15.75; N, 9.33. Found: C, 55.35; H, 4.65; Cl, 15.70; N, 9.02.

7-Chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (III).—To a suspension of 3.4 g. of II in 80 ml. of alcohol was added 6 ml. of 4 *N* sodium hydroxide. After complete solution had taken place, a solid precipitated that redissolved upon the addition of 80 ml. of water. The solution was acidified with acetic acid to give 2.4 g. of white crystals. After recrystallization from alcohol, the compound melted at 203–204°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.81; H, 3.84; Cl, 12.37; N, 9.77. Found: C, 62.57; H, 3.93; Cl, 12.30; N, 9.59.

7-Chloro-3-hydroxy-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XII). Method A.—A mixture of 4 g. of III, 4 ml. of 4 *N* sodium hydroxide, and 1.4 ml. of dimethyl sulfate in 200 ml. of 50% alcohol was stirred for 2 hr., and evaporated to dryness *in vacuo*. Water and ether were added and the ether layer was separated. The solvent was removed and the residue was recrystallized from cyclohexane to afford 1.9 g. of compound, m.p. 119–121°.

Method B.—To a suspension of 3.4 g. of XI in 50 ml. of alcohol was added with stirring during 2 hr. a solution of 2.5 ml. of 4 *N* sodium hydroxide and 20 ml. of water. Dilution with 100 ml. of water precipitated the product. Recrystallization from cyclohexane afforded 1.3 g. of product, m.p. 119–121°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.92; H, 4.36; Cl, 11.76; N, 9.32. Found: C, 63.78; H, 4.64; Cl, 11.30; N, 9.26.

7-Chloro-5-phenyl-4,5-dihydro-2*H*-benzodiazepine-2,3-(1*H*)-dione (VI).—A suspension of 6 g. of III (or II) in 200 ml. of 50% alcohol and 20 ml. of 4 *N* sodium hydroxide was heated for 30 min. on a steam bath. The mixture was cooled and diluted with 200 ml. of water. Some insoluble matter was removed, and the solution was acidified with acetic acid to precipitate the product. After two recrystallizations from alcohol there was obtained 2.0 g. of VI, m.p. 297–298°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.81; H, 3.83; Cl, 12.37; N, 9.77. Found: C, 62.90; H, 3.94; Cl, 12.35; N, 9.41.

7-Chloro-1-methyl-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepine-2,3(1*H*)-dione (XIII). Method A.—One gram of XI (or XII) was suspended in 50 ml. of alcohol and 2.5 ml. of 4 *N* sodium hydroxide solution. The mixture was stirred until solution was complete (1 hr.). Addition of 50 ml. of water and acidification with hydrochloric acid gave a solid which was recrystallized from ethanol to give 0.3 g. of white, fibrous crystals, m.p. 224–225°, resolidifying and remelting at 234–235°.

Method B.—To a solution of 1 g. of VI in 50 ml. of 50% alcohol containing 1 ml. of 4 *N* sodium hydroxide was added 0.45 g. of dimethylsulfate. After several minutes a solid separated. The solid was collected and recrystallized from alcohol giving 0.5 g. of product, identical with the material prepared by method A.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.92; H, 4.36; Cl, 11.79; N, 9.32. Found: C, 63.75; H, 4.46; Cl, 11.79; N, 9.46.

7-Chloro-1,4-dimethyl-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepine-2,3(1*H*)-dione (XIV) was prepared in a yield of 50% by treating 1 g. of VI in a solution of 50 ml. of 50% alcohol and 4 ml. of 4 *N* sodium hydroxide with 1 g. of dimethyl sulfate. The product precipitated. It was recrystallized from alcohol as a white solid, m.p. 266–268°.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.25; N, 8.91. Found: C, 64.80; H, 4.68; Cl, 11.00; N, 9.20.

6-Chloro-3,4-dihydro-2-quinazolinecarboxylic acid (VII). Method A.—A solution of 1.3 g. of III in 10 ml. of alcohol and 10 ml. of 4 *N* sodium hydroxide was heated under reflux for 2 hr. The solution was cooled and 0.15 g. of sodium oxalate was filtered off. Ether extraction gave a small amount of 2-amino-5-chlorobenzophenone. Acidification of the aqueous portion afforded 0.8 g. of VII, m.p. 168–169° (reprecipitated).

Method B.—The reduction at 50–60° of a solution of 25 g. of 2-amino-5-chlorobenzophenone oxime in 500 ml. of alcohol and 40 ml. of 6 *N* hydrochloric acid in the presence of 5 g. of 10% palladium–charcoal afforded 21 g. of 2-amino-5-chlorobenzhydrylamine (IX) dihydrochloride, m.p. 221–223° (from methanol–acetonitrile).

Anal. Calcd. for $C_{13}H_{13}ClN_2 \cdot 2HCl$: C, 51.10; H, 4.95; Cl, 34.81; N, 9.17. Found: C, 51.18; H, 4.83; Cl, 34.70; N, 9.06.

A solution of 1 g. of IX·2HCl, 1 g. of sodium oxalate, and 10 g. of oxalic acid in 100 ml. of 50% alcohol was heated for 3 hr. under reflux. When the solution was concentrated to 25 ml., there was obtained 0.3 g. of material that was identical with VII prepared by method A.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.81; H, 3.84; Cl, 12.37; N, 9.77. Found: C, 62.36; H, 3.91; Cl, 12.26; N, 9.72.

6-Chloro-4-phenyl-3,4-dihydroquinazoline (VIII). Method A.—Two grams of VII was decarboxylated by heating in dimethylformamide for 15 min. Addition of water precipitated VIII. Recrystallization from acetonitrile gave 0.6 g. of white crystals, m.p. 173–174°.

Method B.—A mixture of 1 g. of IX·2HCl, 1 g. of sodium formate, and 20 ml. of formic acid was heated under reflux for 2 hr. The solvent was removed, water was added, and the mixture was made basic to give 0.5 g. of a material, m.p. 173–175°, identical with VIII prepared by method A.

Anal. Calcd. for $C_{14}H_{11}ClN_2$: C, 69.28; H, 4.57; N, 11.55. Found: C, 69.57; H, 5.28; N, 11.95.

Hydrochloride, m.p. 267–268°.

Anal. Calcd. for $C_{14}H_{11}ClN_2 \cdot HCl$: C, 60.45; H, 4.35; Cl, 25.49; N, 10.03. Found: C, 60.03; H, 4.86; Cl, 25.70; N, 10.08.

3-Benzoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (IV).—A suspension of 5 g. of I in 20 ml. of benzoyl chloride was warmed on the steam bath until the solid dissolved (about 10 min.). The solution was diluted with cyclohexane to precipitate a solid. The solid was separated and washed with warm ethanol and the washings were reserved for further work-up. The washed solid was recrystallized from aqueous alcohol to afford 1.8 g. of IV, m.p. 251–252°.

Anal. Calcd. for $C_{22}H_{15}ClN_2O_3$: C, 67.63; H, 3.87; Cl, 9.07; N, 7.17. Found: C, 67.57; H, 4.05; Cl, 9.05; N, 6.93.

Compound IV could also be prepared by adding one equivalent of benzoyl chloride to a pyridine suspension of III. The material so obtained was identical with the product prepared by treating I with benzoyl chloride.

7-Chloro-3-ethoxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XV) was produced by diluting with water the ethanol washings from the preceding treatment of I with benzoyl chloride. The precipitate was recrystallized from acetonitrile to yield 2 g. of XV, m.p. 225–227°.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.25; N, 8.90. Found: C, 64.45; H, 4.69; Cl, 11.20; N, 8.88.

3,7-Dichloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (V).—One gram of III was finely powdered and treated with 1 ml. of thionyl chloride. An immediate reaction took place with the formation of a yellow solid. Anhydrous ether was added and the solid was collected and washed free of thionyl chloride. From analytical values the product, m.p. 151–153° dec., appeared to be a partial hydrochloride. It was suspended in 25 ml. of methylene chloride and 1 g. of Amberlite IRA-400 (OH) and 1 g. of barium oxide were added. The yellow color was discharged and the insoluble matter was immediately removed. The solution was treated with charcoal and slowly diluted with hexane to afford 0.5 g. of V, m.p. 179° dec.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2O$: C, 59.03; H, 3.30; Cl, 23.24; N, 9.18. Found: C, 59.57; H, 3.22; Cl, 22.05; N, 9.51.

The poor analysis was attributed to the extreme reactivity of V. Mere warming in alcohol afforded XV, identical with the compound obtained as a by-product in the preparation of IV.

Catalytic hydrogenation (1 mole) of V in dimethoxyethane over 5% palladium–charcoal gave 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one, m.p. 214–216°, undepressed upon mixing with an authentic sample.[2]

Acknowledgment.—We are indebted to Dr. Gordon Ellis and his associates for the microanalyses and to Mr. Bruce Hofmann for helpful discussions of the spectra. Mr. Carl Gochman gave valuable technical assistance.

New Derivatives of 2,2,6,6-Tetramethylpiperidine

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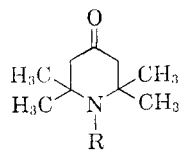
A number of new derivatives of 2,2,6,6-tetramethylpiperidine have been prepared for testing as ganglionic and neuromuscular blocking agents. Many of these are bisamines and are represented by both symmetrical and unsymmetrical types.

Interest in the chemistry and pharmacology of highly methylated derivatives of piperidine has been stimulated in recent years by the discovery[1–4] that 1,2,2,6,6-pentamethylpiperidine (Ia) is a potent ganglionic blocking agent. Further work has shown that such activity is not very specific



IIa. R = H
b. R = CH_3

but is associated with a certain optimum degree of shielding of the nitrogen atom of a secondary or tertiary amine by nearby substituents, particularly alkyl groups.[5] Ganglionic blocking agents of this type are characterized by excellent absorption from the gastrointestinal tract combined with moderately rapid excretion.[6] Ganglionic blockers of the quaternary type, on the other hand, are characterized by erratic gastrointestinal absorption. Usually the activity can be increased by incorporating two quaternary centers into a single molecule. The distance between the quaternary centers determines whether the compounds are predominantly ganglionic blocking or neuromuscular blocking.[7,8]

The present work was undertaken to ascertain whether bis-tertiary amines of the polymethylpiperidine type would show a structure-activity relationship similar to the quaternary amines while still retaining the favorable absorption properties of the tertiary amines. Thus we undertook the preparation of a series of compounds in which the separation of the amine nitrogens was six to ten methylene groups. These separations have been approximate maxima for ganglionic and neuromuscular blocking agents, respectively, in the bisquaternary series.

In Table I are listed the monobasic amines which were prepared. Most of these were studied for activity and were also used to prepare the bis structures shown in Table II. Miscellaneous compounds are listed in Table III.

The principal starting material for this work was triacetonamine (IIa) prepared by the method of Francis[9] from acetone, calcium chloride, and ammonia. The triacetonamine was usually isolated in the crude anhydrous form by fractional distillation of the reaction mixture rather than *via* the hydrate as described by Francis.

Contrary to the literature[10a] the *N*-methyl deriv-

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