was treated with 204 mg. of 2,4-dinitrophenylhydrazine in 30 ml. of 2 *N* hydrochloric acid and 10 ml. of methanol. The resulting 2,4-dinitrophenylhydrazone was removed by extraction with benzene and purified by chromatography through a deactivated alumina column.[6] Further purification was achieved by chromatography on a silicic acid–Celite (2:1) column.[7] The main fraction, eluted with 5% ether in petroleum ether, yielded 60 mg. of product, which was recrystallized three times from *n*-heptane to give 6.8 mg. of orange crystals, m.p. 45–48°.[8] An additional 16 mg. of crystals, m.p. 45–51°, was obtained similarly from the mother liquor.

Anal. Calcd. for $C_{18}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04. Found: C, 53.37; H, 6.42; N, 18.87.

Ozonolysis of Streptimidone (Ia).—Ozone was passed through a solution of 866 mg. (2.95 mmoles) of crystalline streptimidone in 20 ml. of ethyl acetate (distilled three times from 2,4-dinitrophenylhydrazine) at −80° for 45 minutes. The blue color of ozone appeared after 5 minutes of ozonization. The ethyl acetate solution was concentrated *in vacuo* to approximately 10 ml., then mixed with 10 ml. of methanol, 1 g. of ferrous sulfate and 175 ml. of water. The mixture was steam distilled (525 ml. of distillate) into a 2 *N* hydrochloric acid solution saturated with 2,4-dinitrophenylhydrazine (DNP mixture).

The precipitate from the DNP mixture was filtered, washed with methanol and dried to give 67 mg. (5.2%) of a rust colored precipitate, which was crystallized first from dimethylformamide–water and then from dimethylformamide to give 31 mg. (2.4%) of pyruvaldehyde bis-2,4-dinitrophenylhydrazone, identified by comparison with an authentic sample (no mixed melting point depression; identical ultraviolet and infrared spectra).

(6) Alcoa F-20 alumina was adjusted to *p*H 5 with dilute sulfuric acid and then dried for 4 hours at 200°.

(7) B. E. Gordon, F. Wopat, Jr., H. D. Burnham and L. C. Jones, Jr., *Anal. Chem.*, **23**, 1754 (1951).

(8) M. C. Chiang [*J. Chinese Chem. Soc.*, **18**, 65 (1951); *cf. C. A.*, **46**, 4472 (1952)] reported 45–47° as the melting range of 4-methyl-2-hexanone 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{15}H_{12}N_8O_8$: C, 41.67; H, 2.80; N, 25.92. Found: C, 41.68; H, 2.70; N, 26.11.

The filtrate and washings from the DNP mixture were extracted with chloroform. The extract was evaporated to dryness *in vacuo*, and a benzene solution of the residue was percolated through a deactivated alumina[6] column to remove 2,4-dinitrophenylhydrazine. Evaporation of the effluent to dryness yielded 137 mg. of crystals, which was recrystallized from methanol to give 75 mg. (12.1%) of formaldehyde 2,4-dinitrophenylhydrazone, m.p. 158–163°, identified by its infrared spectrum and by paper chromatography, using *n*-heptane saturated with methanol.[9] Paper chromatography showed that the mother liquor from above contained an additional 53 mg. of formaldehyde 2,4-DNP (8.5%) and 9 mg. of acetaldehyde 2,4-DNP (1.4%).

As a control experiment, employing completely identical isolation procedures, ozonolysis of the C-9 ketone from dihydrostreptimidone (streptimidone with one olefinic linkage catalytically reduced[1]) yielded methyl ethyl ketone (39%) as the major product.

The reagent grade ethyl acetate used in the isolation procedures in some of the previously reported ozonolysis experiments[1] was shaken with 2 *N* hydrochloric acid saturated with 2,4-dinitrophenylhydrazine. The weight of the resulting methyl ethyl ketone 2,4-dinitrophenylhydrazone isolated indicated that the ethyl acetate contained methyl ethyl ketone at approximately 40 μg./ml. Thus, in the ozonolysis experiments of the present investigation, meticulous removal of any ketones and aldehydes from all solvents was performed, by repeated distillation from solid 2,4-dinitrophenylhydrazine.

Acknowledgment.—The authors wish to express their appreciation to Dr. H. E. Machamer and associates for supplying pilot plant quantities of culture filtrates and crude concentrates; to Dr. D. H. Szulczewski and associates for ultraviolet and infrared determinations; and to Mr. C. E. Childs and associates for microanalyses.

(9) D. F. Meigh, *Nature*, **170**, 579 (1952).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION, CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.]

Investigations in Heterocycles. X.[1] The Synthesis of Tetrahydro-1,3-benzodiazepines, a New Heterocyclic System

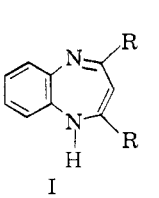
BY GEORGE DESTEVENS AND MARYLOU DUGHI

RECEIVED FEBRUARY 6, 1961

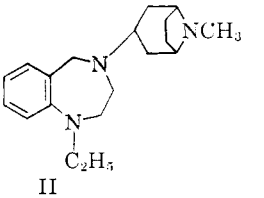
A method has been developed for the preparation of 3-substituted-1,2,4,5-tetrahydro-1,3-benzodiazepines. The structure of these compounds has been rigorously proved by means of chemical transformations and spectral data.

Within the past decade the synthesis of seven-membered ring compounds containing two nitrogen atoms has attracted considerable attention. Ried[2] and co-workers have enlarged significantly upon the early findings of Thiele[3] and Steinmig concerning the synthesis of 2,4-disubstituted-1H-1,5-benzodiazepines (I), whereas the preparation of 1-ethyl-4-(3-tropanyl)-tetrahydro-1H-1,4-benzodiazepine (II) and its derivatives has been the subject of a report by Archer, *et al.*[4]

Finally, another member of this group, 1-H-1,3-benzodiazepine, has recently been described only in derivative form by Plieninger[5] and Nogradi.



I



II

They have found that the autoxidation of the lactone β-(*o*-acetamidophenyl)-α-amino-γ-hydroxycrotonic acid (III) gives rise to the lactone of 5-hydroxymethyl-2-methyl-1H-1,3-benzodiazepine-4-carboxylic acid (IV).

Our interest in seven-membered heterocycles of the 1,3-benzodiazepine class was confined to the study of the completely saturated system, 1,2,4,5-tetrahydro-3-methyl-1,3-benzodiazepine (V) and its analogs.

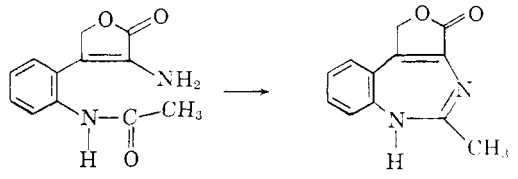
(1) For part IX in this series see G. deStevens, A. Halamandaris, P. Wenk and L. Dorfman, *J. Am. Chem. Soc.*, **81**, 6292 (1959).

(2) W. Ried and A. Draisbach, *Chem. Ber.*, **92**, 949 (1959); W. Ried and E. Torinus, *ibid.*, **92**, 2902 (1959).

(3) J. Thiele and G. Steimmig, *ibid.*, **40**, 955 (1907).

(4) S. Archer, J. R. Lewis, M. J. Unser, J. O. Hoppe and H. Lape, *J. Am. Chem. Soc.*, **79**, 5783 (1957).

(5) H. Plieninger and I. Nogradi, *Ber.*, **88**, 1965 (1955).



III IV

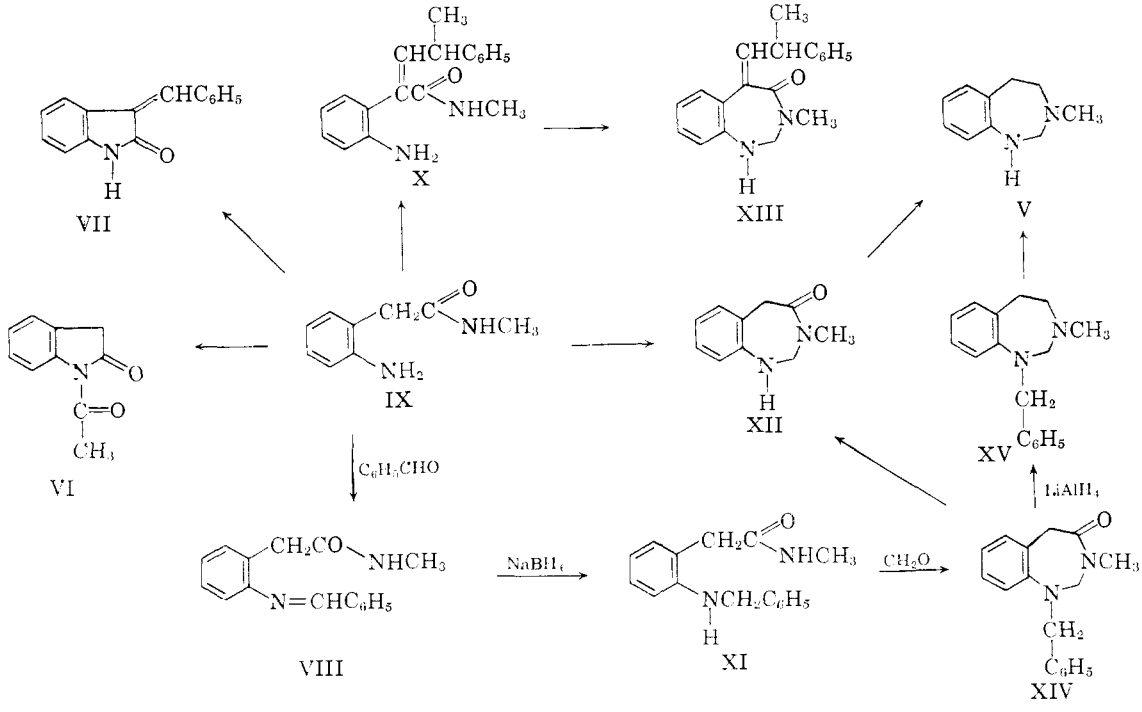
It appeared that the most facile path to these compounds would be through the amides of *o*-aminophenylacetic acid. However, it had already been amply demonstrated first by Baeyer[6] and then by Neber[7] that *o*-aminophenylacetic acid and its amide are readily converted to oxindole under the influence of traces of mineral acid or at elevated temperatures. Moreover, König[8] and Reissert had shown that reduction of 2-(*o*-nitrophenyl)-N-phenylacetamide with stannous chloride and hydrochloric acid also yielded oxindole. Thus, these and numerous other reports[9] emphasize the propensity of *o*-aminophenylacetic acid and its derivatives to form the five-membered heterocycle. A re-study of some of this work has now been carried out in our laboratory and in Scheme I is outlined the various reactions leading to the preparation of V and its derivatives.

2 - (*o* - Aminophenyl) - N - methylacetamide (IX), prepared according to a modification of the Baumgarten[10] procedure, was treated with one molecular equivalent of formaldehyde and heated at 60° in 90% aqueous ethyl alcohol containing catalytic amounts of alkali. A similar procedure had been employed previously by us for the preparation of 3,4 - dihydrobenzothiadiazine - 1,1-dioxides,[11] and by Feldman and Wagner[12] in the synthesis of 1,2,3,4-tetrahydro-4-quinazolinones. Although most of the substance isolated was identified as oxindole, it was possible to isolate a small amount of crystalline compound whose elemental analysis corresponds to XII. However, when this condensation reaction was carried out in the absence of base, a 78% yield of XII was obtained.

It was next of interest to condense IX with benzaldehyde. Initially, the reaction was carried out at the reflux temperature of diethylene glycol dimethyl ether (190°), but this resulted only in the formation of 3-benzylideneoxindole (VII). This was identical with an authentic sample prepared according to Wahl and Bagard.[13] However, when IX was allowed to react with benzaldehyde in ethylene glycol dimethyl ether at 95° a quantitative yield of VIII was secured. Evidence for the benzylidene structure VIII in preference to the desired 2-benzyl-2,5-dihydro-3-methyl-1H-1,3-benzodiazepine-4-one was obtained by ultraviolet absorption spectrum measurements. Compound VIII gives maxima at 260 mμ (ε 15,760) and 320 mμ (ε 6540). These wave lengths and extinction coefficients correspond closely to the data for benzylidene-*o*-toluidine.[14]

This then left open the possibility that the product from the condensation of IX with formalde-

SCHEME I

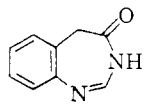


(6) A. v. Baeyer, *Ber.*, **11**, 582 (1878).
(7) P. W. Neber, *ibid.*, **55**, 826 (1922).
(8) A. König and A. Reissert, *ibid.*, **32**, 782 (1889).
(9) A thorough critique on this subject is presented by P. Julian in R. C. Elderfield's "Heterocyclic Compounds," Vol. III, J. Wiley and Sons, Inc., New York, N. Y., 1952, pp. 126–186; see also G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955).
(10) H. E. Baumgarten, P. J. Creger and R. L. Zey, *ibid.*, **82**, 3977 (1960).
(11) L. A. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman and G. deStevens, *ibid.*, **82**, 1161 (1960).
(12) J. R. Feldman and E. C. Wagner, *J. Org. Chem.*, **7**, 31 (1942).
(13) A. Wahl and P. Bagard, *Compt. rend.*, **148**, 716 (1909).
(14) F. W. Holly and A. C. Cope, *J. Am. Chem. Soc.*, **66**, 1875 (1944).

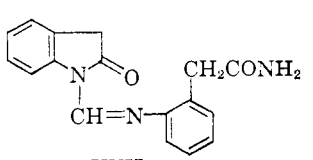
hyde could have the azomethine structure rather than that represented by XII, since it exhibited ultraviolet absorption maxima at 252 mμ (ε 8080) and 297 mμ (ε 2280). Holly and Cope had also demonstrated that 1,2-dihydro-3,1,4-benzoxazine absorbs at 246 and 290 mμ, thus casting some doubt on the correctness of the postulated tetrahydrobenzodiazepine formulation. The region of N–H stretching in the infrared showed one strong band at 3325 cm.$^{-1}$ for XII and 3300 cm.$^{-1}$ for VIII and the amide absorption region was not decisive. To establish unequivocally the product of this condensation reaction, an unambiguous route to 2,5-dihydro - 3 - methyl - 1H - 1,3 - benzodiazepine-4-one (XII) was carried out. Compound VIII was reduced with sodium borohydride to 2-(*o*-benzylaminophenyl)-N-methylacetamide (XI) which in turn was allowed to react with formaldehyde. It was found that this condensation could only be effected in refluxing ethylene glycol dimethyl ether after several hours. Lower reaction temperatures only gave back starting material. Elemental analysis and the absence of absorption bands in the –N–H region of the infrared served to confirm structure XIV. Hydrogenolysis of the benzyl group in XIV yielded the dihydro-1,3-benzodiazepine-4-one (XII) which was identical in all respects with the substance obtained directly from condensation of IX with formaldehyde. The preparation of 1,2,4,5-tetrahydro-3-methyl 1,3-benzodiazepine (V) in turn was accomplished through reduction of XII with lithium aluminum hydride. By a similar sequence XIV was converted to V *via* XV.

In passing it is noteworthy that α-phenylpropionaldehyde condensed with the α-methylene group of IX instead of with the amino group to yield X. Strong supporting evidence for this assignment was furnished firstly by the strong single ultraviolet absorption maximum at 317 mμ (ε 28,750) and secondly by its infrared absorption characteristics A distinct aromatic primary amine band is present at 3420 cm.$^{-1}$ with the amide N–H band at 3228 cm.$^{-1}$. The amide carbonyl absorption band is elicited at 1636 cm.$^{-1}$ with a secondary amide band at 1517 cm.$^{-1}$ which is more typical of a conjugated amide. The strong band at 1603 cm.$^{-1}$ is attributed to the ethylene and the aromatic groups. Conversion of X to the dihydro-1.3-benzodiazepine (XIII) was accomplished with formaldehyde.

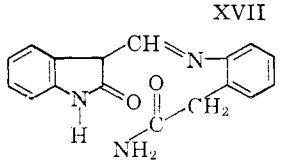
Finally, an attempt was made to prepare 3,5-dihydro-1,3-benzodiazepine-4-one (XVI). Treatment of *o*-aminophenylacetamide with excess formic acid or formamide at their reflux temperatures only gave rise to oxindole. Similarly, IX was converted to N-acetyloxindole (VI) in refluxing acetic anhydride. Finally, *o*-aminophenylacetamide was allowed to react with ethyl orthoformate under controlled conditions.[15] A yellow crystalline substance, m.p. 227–228°, was isolated. Its elemental analysis, molecular weight and infrared absorption spectrum suggest either structure XVII or XVIII. The structure of the dimer was determined unequivocally by synthesis. Condensation of *o*-aminophenylacetamide with 3-hydroxymethylene oxindole gave a product which was identical with XVIII.



XVI



XVII



XVIII

Acknowledgment.—The authors wish to take this opportunity to thank Dr. E. Schlittler for his interest and encouragement. They are also indebted to Mrs. Halina Lukaszewski for the preparation of some of the intermediates and to Mr. Louis Dorfman and his associates for the microanalytical and spectral data.

Experimental[16]

Preparation of *o*-Amino-N-substituted-phenylacetamides.—These intermediates were prepared according to a modification of the Baumgarten[10] method. Whereas the latter procedure utilizes methanol as the solvent in the catalytic reduction of *o*-nitro-N-substituted-phenylacetamides, the present method incorporates use of ethyl methyl ketone. The much greater solubility of the amides in the latter solvent allows for the processing of more material per reduction. The following procedure serves as a general method.

2-(*o*-Aminophenyl)-N-methylacetamide (IX).—*o*-Nitro-N-methylphenylacetamide (10.0 g., 0.052 mole)[17] was dissolved in 150 ml. of ethyl methyl ketone. To this was added 0.75 g. of 10% palladium-on-carbon catalyst and the mixture reduced under 47 lb. per in.^{2} of hydrogen pressure at room temperature. The molar equivalent of hydrogen (13.4 lb.) was taken up within a 7-minute period. After filtering off the catalyst, the filtrate was distilled *in vacuo* leaving a thick residue which was recrystallized twice from benzene. The yield of pure amine, m.p. 85–86°, was 84%.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.81; H, 7.35; N, 16.83.

2-(*o*-Aminophenyl)-N-ethylacetamide, m.p. 78–80°, was obtained in 82% yield.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.21; H, 7.80; N, 16.01.

2-(*o*-Aminophenyl)-N-propylacetamide, m.p. 58–60°, was obtained in 94% yield.

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.58. Found: C, 68.66; H, 8.43; N, 19.63.

2-(*o*-Aminophenyl)-N-benzylacetamine, m.p. 129–130°, was obtained in 33% yield.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.65. Found: C, 75.20; H, 6.51; N, 11.46.

2-(*o*-Benzylideneaminophenyl)-N-methylacetamide (VIII).—A mixture of 25.0 g. (0.15 mole) of 2-(*o*-aminophenyl)-N-methylacetamide and 16.2 g. (0.15 mole) of benzaldehyde dissolved in 200 ml. of ethylene glycol dimethyl ether was heated at 95° for 4 hours. The solution was then evaporated to dryness. The yellow residue was recrystallized from ethyl alcohol to give 37.5 g. of yellow needles, m.p. 124°; $\lambda_{max}^{C_2H_5OH}$ 260 mμ (ε 15,760), 320 mμ (ε 6540); infrared spectrum: 3300 cm.$^{-1}$ (—NH), 1641 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.25; H, 6.35; N, 11.10. Found: C, 76.36; H, 6.49; N, 11.10.

(15) U. M. Teotino and G. Cignarella, *J. Am. Chem. Soc.*, **81**, 4935 (1959).

(16) The melting points reported herein are uncorrected. The infrared absorption spectra were run as Nujol mulls in a Perkin-Elmer model 21 spectrophotometer.

(17) A. B. Neill, Belgian Patent 582,941, March 23, 1960.

When the above reaction was carried out in refluxing diethylene glycol dimethyl ether, only 3-benzylideneoxindole, m.p. 175.5–176°, could be isolated.

2-(*o*-Benzylaminophenyl)-N-methylacetamide (XI).—Sodium borohydride (4.16 g., 0.11 mole) was added in portions with stirring to 27.5 g. (0.11 mole) of VIII dissolved in 200 ml. of methanol; 50 ml. of water was added to the cloudy solution. After standing in the refrigerator overnight, the white solid was collected on a filter and recrystallized from ethyl alcohol–water (5:1). A white crystalline substance, m.p. 96–98°, was obtained in 95% yield; $\lambda_{max}^{C_2H_5OH}$ 247 mμ, (ε 12,200), 296 mμ (ε 3090); infrared: 3363, 3213, 3099 cm.$^{-1}$ (all bands are medium strong; —NH of amine and amide), 1638 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.77; H, 7.13; N, 11.02. Found: C, 75.40; H, 7.33; N, 10.85.

1-Benzyl-2,5-dihydro-3-methyl-1,3-benzodiazepine-4-one (XIV).—Three grams (0.012 mole) of 2-(*o*-benzylaminophenyl)-N-methylacetamide (XI) dissolved in 40 ml. of ethylene glycol dimethyl ether was treated with 1.6 ml. of 37% aqueous formaldehyde. The solution was then heated at reflux temperature for 2 hours. After removal of the solvent at the water-pump, the solid residue was recrystallized twice from ethyl alcohol–water (1:1) to give 2.4 g. of product, m.p. 118–120°; $\lambda_{max}^{C_2H_5OH}$ 256 mμ (ε 7602), 297 mμ (ε 2246); infrared spectrum: 1658 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.67; H, 6.81; N, 10.52. Found: C, 76.71; H, 6.80; N, 10.29.

2,5-Dihydro-3-methyl-1H-1,3-benzodiazepine-4-one (XII). Method A.—A mixture of 1.62 g. (0.01 mole) of 2-(*o*-aminophenyl)-N-methylacetamide and 1 ml. of 37% aqueous formaldehyde dissolved in 20 ml. of ethyl alcohol was allowed to stand at room temperature for 1 hour. The solution was then refluxed on the steam-bath for 3 hours. After removing the solvent *in vacuo* on the water-bath, the viscous residue was taken up in 100 ml. of boiling water. After standing in the refrigerator overnight, the white crystals were collected and dried *in vacuo* at 40°. Another recrystallization from water gave 1.4 g. of pure substance, m.p. 150°; $\lambda_{max}^{C_2H_5OH}$ 252 mμ (ε 8080), 297 mμ (ε 2280); infrared: 3325 cm.$^{-1}$ (–NH), 1646 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.82; N, 15.90. Found: C, 68.15; H, 6.99; N, 16.00.

The following 3-substituted tetrahydro-1,3-benzodiazepines were prepared according to the above-described method.

3-Ethyl-2,5-dihydro-1H-1,3-benzodiazepine-4-one, m.p. 144–145°. *Anal.* Calcd. for $C_{11}H_{14}N_2O$: C, 69.39; H, 7.36; N, 14.73. Found: C, 69.40; H, 7.54; N, 15.00.

2,5-Dihydro-3-*n*-propyl-1H-1,3-benzodiazepine-4-one, m.p. 128.5–130°. *Anal.* Calcd. for $C_{12}H_{16}N_2O$: C, 70.60; H, 7.84; N, 13.72. Found: C, 70.66; H, 8.09; N, 13.56.

3-Benzyl-2,5-dihydro-1H-1,3-benzodiazepine-4-one, m.p. 192°. *Anal.* Calcd. for $C_{16}H_{16}N_2O$: N, 11.10. Found: N, 11.16.

Method B.—To 1 g. of XIV dissolved in 50 ml. of ethyl alcohol there was added 0.5 g. of 10% palladium-on-carbon and 2 drops of glacial acetic acid. The mixture was shaken at room temperature under 48 lb. per in.^{2} hydrogen pressure for 20 hours. Finally, the temperature was increased to 40° and shaking was continued for an additional 4 hours. After separating the catalyst by filtration, the alcohol was removed *in vacuo* and the residue was recrystallized from water. The resulting white crystals (0.55 g.), m.p. 150°, gave no melting point depression when mixed with the substance obtained by method A and the infrared absorption spectra of the two samples were virtually superimposable.

1,2,4,5-Tetrahydro-3-methyl-1,3-benzodiazepine (V) Method A.—A solution of 2.4 g. (0.0136 mole) of 2,5-dihydro-3-methyl-1H-1,3-benzodiazepine-4-one (XII) dissolved in 30 ml. of tetrahydrofuran was added slowly with stirring to 1.6 g. of lithium aluminum hydride dissolved in 100 ml. of tetrahydrofuran. The mixture was refluxed for 18 hours. The hydride complex was decomposed with 9.2 ml. of water under cooling. After filtering off the solids, the filtrate was dried over $MgSO_4$. The maleic acid salt of this substance was prepared. After one recrystallization from ethyl acetate, it melted at 99–101°; $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ε 12,242), 296 mμ (ε 2,822).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.10; H, 6.88; N, 9.91.

Method B.—Five grams (0.019 mole) of XIV dissolved in 30 ml. of tetrahydrofuran was added dropwise to 50 ml. of tetrahydrofuran containing 1.43 g. of lithium aluminum hydride. The mixture was refluxed for 18 hours and then the complex was decomposed under cooling with 6.8 ml. of water. After filtering off the salts, the filtrate was dried over $MgSO_4$. Removal of the solvent at 50° *in vacuo* gave a yellow-brown oil which could not be crystallized. It was found that attempts to prepare mineral acid salts of this oil only led to dark green or purple tars. The oil also readily decomposed upon attempted distillation at 0.05 mm. The decomposition temperature was about 80°. An infrared absorption spectrum of the crude oil revealed that reduction of the amide carbonyl had indeed occurred. Consequently, 1.5 g. of this oil was dissolved in ethyl alcohol containing 0.5 g. of palladium-on-carbon. After shaking for 24 hours at room temperature under 47 lb. per in.^{2} of hydrogen, the catalyst was filtered off, and the alcohol filtrate was evaporated almost to dryness *in vacuo*. The oil was taken up in ether and this solution was treated with an ethanolic solution of maleic acid. The corresponding maleate salt was found to be identical with the substance obtained by method A.

***o*-Amino-N-methyl-(α-phenylpropylidene)-phenylacetamide (X).**—A solution of 3.2 g. (0.02 mole) of *o*-amino-N-methylphenylacetamide, 2.8 g. (0.02 mole) of α-phenylpropionaldehyde and 15 ml. of ethylene glycol dimethyl ether was heated at 95° for 2 hours after which time one-half the solvent was removed *in vacuo*. White crystals, obtained on chilling, were collected and recrystallized from ethyl alcohol to give 2.3 g. of white flat plates, m.p. 144–145°; $\lambda_{max}^{C_2H_5OH}$ 317 mμ (ε 28,750); infrared spectrum: 3421 cm.$^{-1}$ (—NH_2, —NH), 3228 cm.$^{-1}$ (NH), 1636 cm.$^{-1}$ (amide C=O), 1603 cm.$^{-1}$ (—C=C—, phenyl), 1517 cm.$^{-1}$ (conjugated amide). Similar absorption bands were obtained in Nujol mulls and chloroform solutions.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.09; H, 7.19; N, 10.00. Found: C, 77.04; H, 7.19; N, 10.21.

1,2-Dihydro-3-methyl-5-(α-phenylpropylidene)-1,3-benzodiazepine-4-one (XIII).—The amide X (0.56 g., 0.002 mole) was dissolved in 15 ml. of ethyl alcohol containing 0.3 ml. of 37% aqueous formaldehyde. The solution was refluxed for 2 hours on the steam-bath. Removal of the solvent *in vacuo* gave rise to a viscous oil which was triturated with ethyl alcohol–water (1:1). The resulting white powder was recrystallized from ethyl alcohol–water (1:2) to give a 20% yield of XIII, m.p. 45–46°.

Anal. Calcd. for $C_{19}H_{20}N_2O$: N, 9.57. Found: N, 9.38.

Attempted Preparation of 3,5-Dihydro-1,3-benzodiazepine-4-one (XVI).—Three grams of *o*-aminophenylacetamide was heated with 20 ml. of formic acid under reflux for 1 hour. After removing the excess formic acid at 90° at the water-pump, the residue was triturated with water. The solid material was collected on a Büchner funnel and dried *in vacuo*. One recrystallization from benzene gave 1.2 g. of pure substance which gave no mixture melting point depression with an authentic sample of oxindole. Using formamide in place of formic acid also gave rise to oxindole. Heating IX with acetic anhydride at reflux temperature yielded only N-acetyloxindole, m.p. 125°, which was identical with an authentic sample.

One gram of *o*-aminophenylacetamide was dissolved in 7 ml. of propylene glycol. To this there was added 7 ml. of ethyl orthoformate and the resulting solution was heated at 118–120° for 6 hours. A distillation apparatus was connected to the reaction flask so that ethyl alcohol could be removed during the heating process. The remaining solvent was removed on the steam-bath *in vacuo*. The residue was then triturated with 100 ml. of water. The precipitate was collected and recrystallized twice from ethyl alcohol-water (1:1) to give 0.5 g. of yellow crystals, m.p. 227–228°; infrared spectrum: 3375, 3160 cm.$^{-1}$ (—N—H); 1690 cm.$^{-1}$, (oxindole C=O); 1655, 1625 cm.$^{-1}$ (amide C=O and —C=N—); molecular weight by Rast procedure, 307. These data suggest the dimeric oxindole structure XVII or XVIII.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.32. Found: C, 69.28; H, 5.25; N, 14.19.

The above substance was identified as XVIII by synthesis.

3-Hydroxymethylene oxindole[18] (1.6 g., 0.01 mole) and 1.5 g. (0.01 mole) of *o*-aminophenylacetamide were dissolved in 10 ml. of ethyl alcohol and the solution was refluxed on the steam-bath for 15 minutes. Within that time a copious yellow precipitate was obtained. One recrystallization from ethyl alcohol gave 1.0 g. of yellow crystals, m.p. 227°. This substance gave no depression in melting point when mixed with XVIII and their infrared absorption spectra were virtually superimposable.

(18) E. Wenkert, N. K. Bhattacharyya, T. L. Reid and T. H. Stevens, *J. Am. Chem. Soc.*, **78**, 797 (1956).

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE, RENSSELAER, N. Y.]

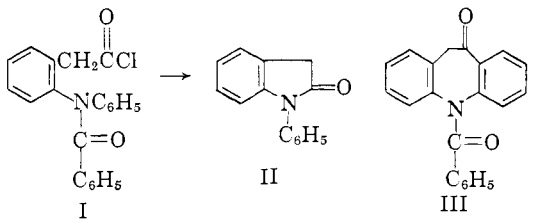
An Unusual Base-catalyzed Cyclization

BY JOHN W. SCHULENBERG AND S. ARCHER

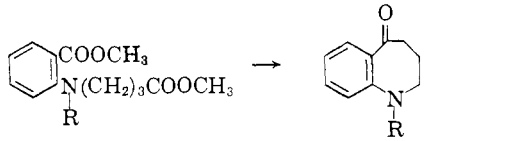
RECEIVED FEBRUARY 28, 1961

The reaction between N-benzoyl-*o*-carbomethoxy-*o'*-(carbomethoxymethyl)-diphenylamine (XIV) and sodium methoxide gave 3-benzoyl-1-(*o*-carbomethoxyphenyl)-oxindole (XX) and a related indole, probably 1-(*o*-carbomethoxyphenyl)-2-phenyl-3-indolecarboxylic acid (XXXV), instead of the expected Dieckmann product XVII. Similarly, methyl *o*-(N-benzoylanilino)-phenylacetate (XXVIII) furnished 3-benzoyl-1-phenyloxindole (XXIX) and methyl 1,2-diphenyl-3-indolecarboxylate (XXXI), the structures of which were proved by independent syntheses.

In our previous paper,[1] we reported that treatment of *o*-(N-benzoylanilino)-phenylacetyl chloride (I) with aluminum chloride yielded 1-phenyloxindole (II) instead of the desired dihydrodibenzazepinone (III). Astill and Boekelheide had encountered the same problem in attempting to prepare a tetrahydrobenzazepinone. They finally synthesized the desired product (VI) by Dieckmann ring closure of the appropriate diester IV.[2] Similarly, Proctor and Thomson converted the analogous tosyl derivative V into VII by the Dieckmann reaction, previous attempts to prepare an azepinone by Friedel-Crafts and acyloin reactions having failed.[3] It therefore appeared that the most promising route to III was *via* cyclization of a suitable diester.



I II III



IV, R = CH_3
V, R = *p*-$C_7H_7SO_2$

VI, R = CH_3
VII, R = *p*-$C_7H_7SO_2$

One of the best methods for preparing unsymmetrically substituted diphenylamines is the Chapman rearrangement.[4] While two imino-ethers, XII and XVI, could give the desired product XIV, only the former would be expected to rearrange smoothly. The imino-ether derived from methyl salicylate and benzanilimino chloride has been reported to rearrange in high yield to methyl N-benzoyl-N-phenylanthranilate[5] while the higher homolog XXVI prepared from methyl *o*-hydroxyphenylacetate gave a mixture containing the normal product and a compound (XXVII) resulting from a competing base-catalyzed cyclization.[1] Although a base-catalyzed reaction of XII to methyl salicylate and methyl 2-phenyl-3-indolecarboxylate is conceivable, it would not be expected to proceed at a rate sufficient to compete with the normal Chapman rearrangement which is accelerated by *meta*-directing groups *ortho* to the ether linkage.[4]

Methyl *o*-benzamidophenylacetate (VIII)[6] was therefore converted into the imino-chloride X. This was treated with the sodium salt of methyl salicylate to furnish the imino-ether XII in good yield. Pyrolysis of XII then afforded the desired diester XIV, apparently uncontaminated by abnormal Chapman products. The analogous ethyl ester XV was prepared similarly *via* IX, XI and XIII.

When the dimethyl ester XIV was treated with sodium methoxide in boiling benzene or toluene, 3-benzoyl-1-(*o*-carbomethoxyphenyl)-oxindole (XX) was obtained instead of the desired β-ketoester (XVII). When the corresponding ethyl ester XV was treated with sodium ethoxide in toluene, the homologous oxindole XXI was obtained. Compounds XX and XXI undoubtedly exist largely in the enolic form. Both cyclization products gave strong ferric chloride tests and had infrared spectra compatible with both the azepinone and oxindole structures.

When the ethyl ester XXI was refluxed for two hours with 5% aqueous potassium hydroxide, a dibasic acid was obtained. This was shown to be *o*-(2-carboxyanilino)-phenylacetic acid (XXIII) by its identity with material obtained by vigorous alkaline hydrolysis of our Chapman product (XIV). It is not surprising that the benzoyl group in XXI is cleaved readily by base, followed by saponification and ring-opening. However, the formation of XXIII can also be rationalized in terms of struc-

(1) J. W. Schulenberg and S. Archer, *J. Am. Chem. Soc.*, **82**, 2035 (1960).

(2) B. D. Astill and V. Boekelheide, *ibid.*, **77**, 4079 (1955).

(3) G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 2302, 2312 (1957).

(4) (a) A. W. Chapman, *ibid.*, **127**, 1992 (1925); (b) F. Möller in "Methoden der Organische Chemie," Band XI/1, Vierte Auflage, Georg Thieme Verlag, Stuttgart, pp. 910–913; (c) K. B. Wiberg and B. I. Rowland, *J. Am. Chem. Soc.*, **77**, 2205 (1955).

(5) M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, 1954 (1937).

(6) P. W. Neber, *Ber.*, **55**, 826 (1922).