Quinazolines and Benzodiazepines. XV.[1] 7-Nitro- and 7-Trifluoromethyl-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepines and Their Transformations

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Received May 15, 1963

Condensation of 2-chloro-5-nitro- or 2-chloro-5-trifluoromethylbenzophenones with ethylenediamine gave the 7-nitro- or 7-trifluoromethyl-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepines (Va,b), respectively. The trifluoromethyl derivative Vb was hydrolyzed to the corresponding carboxylic acid IX. The 1-methyl-7-nitro derivative VIa was converted into the 7-amino derivative which, *via* a Sandmeyer reaction, gave the 7-chloro, 7-bromo, and 7-cyano derivatives, respectively.

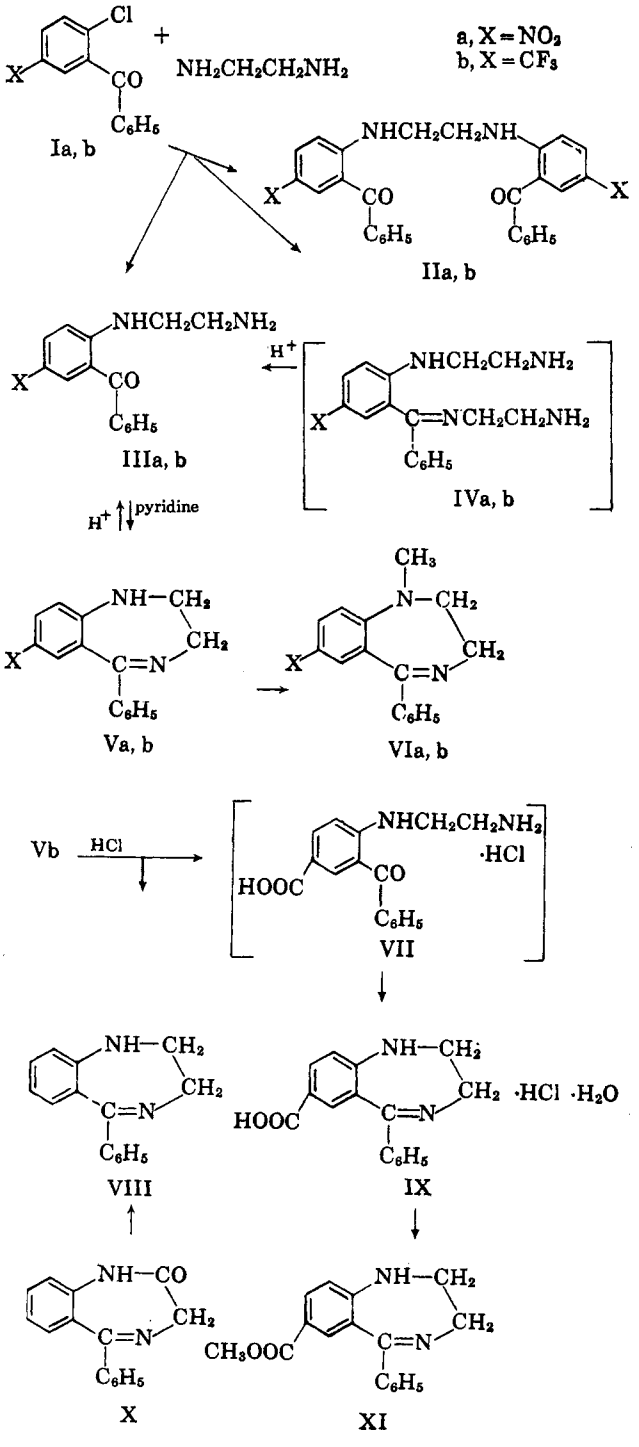
In continuation of our studies of 2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepines,[2] we sought synthetic methods leading to 7-nitro- and 7-trifluoromethyl derivatives. As starting materials, we chose the chlorobenzophenones Ia (X = NO_2)[3a] and Ib (X = F_3C),[3b] which on treatment with ethylenediamine, were expected to undergo nucleophilic displacement to form compounds of type III. In view of the marked tendency for formation of the benzodiazepine ring system,[2,4] we expected that these diamines would cyclize readily to form the desired benzodiazepines Va,b.

Heating compounds of type I with an excess of ethylenediamine in pyridine indeed resulted in replacement of the chlorine atom, and concomitant cyclization of the primary reaction products of type III, to the 2,3-dihydrobenzodiazepines Va[5] and Vb, respectively.[6,7]

The nitro compound Va was obtained in a 60% yield directly from the reaction mixture. Acid hydrolysis of the mother liquors followed by treatment with refluxing pyridine, yielded an additional amount of Va (30%). This seems to indicate that the reaction mixture contained, in addition to Va, an appreciable amount of the Schiff base IVa which was, however, not isolated in crystalline form.

In the case of Vb, the reaction mixture (Ib, ethylenediamine, and pyridine) was, after concentration, treated with cold acid to hydrolyze any Schiff base IVb which might be present. This yielded a small amount of crystalline IIIb and finally, after cyclization in pyridine, the desired Vb in 61% yield. Compound IIIa was best obtained by acid hydrolysis of Va. The "open" compounds III were relatively stable and did not show such a pronounced tendency to cyclize as the corresponding chloro derivatives discussed in our earlier paper.[2]

Vigorous treatment of Vb with hydrochloric acid resulted in hydrolysis of the trifluoromethyl to a carboxylic acid group, and also in partial decarboxylation. A compound which was most probably the hydrochloride VII crystallized from the reaction mixture; it could, however, not be purified due to its great tendency to cyclize. The crude hydrochloride



(1) Paper XIV: R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, in press.

(2) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).

(3) (a) K. Fries, K. Eishold, and B. Vahlberg, *Ann.*, **454**, 287 (1927); (b) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 226 (1962).

(4) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

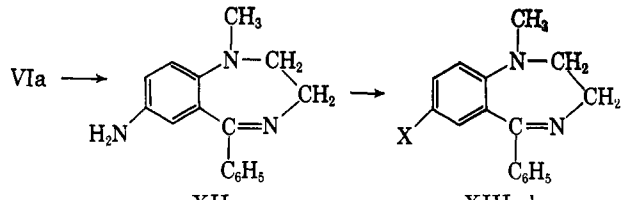
(5) While our work was in progress J. A. Hill, A. W. Johnson, and T. J. King [*J. Chem. Soc.*, 4430 (1961)] reported the isolation of Va as a by-product in the reaction of 6-(2-benzoyl-4-nitrophenoxy)podocarpan-6-ol with ethylenediamine, and proved its structure by synthesis from Ia and ethylenediamine.

(6) Small amounts of compounds of type II could also be isolated from the reaction mixture. Compound IIa was the major reaction product when a smaller excess of ethylenediamine was used.

(7) 2,5-Dichlorobenzophenone yielded, under similar conditions, the corresponding 7-chlorobenzodiazepine (V, X = Cl) in about 10% yield.

was, therefore, treated with boiling pyridine to cyclize it completely to the benzodiazepine. The product was isolated as the hydrochloride monohydrate IX,[8] and was characterized by conversion into the methyl ester XI. On treatment with alkali, the mother liquors from the acid hydrolysis yielded the decarboxylation product VIII. This compound was identified by direct comparison with a sample prepared from the benzodiazepinone X[4] by lithium aluminum hydride reduction.[2]

Compounds of type V were readily methylated,[2,9] *via* sodio derivatives, to yield the 1-methyl derivatives VIa and b. The nitro compounds Va and VIa were catalytically reduced to the corresponding 7-amino-2,3-dihydrobenzodiazepines.



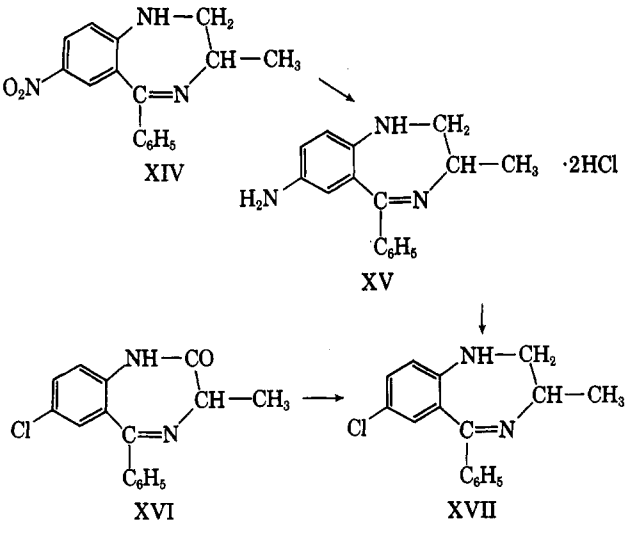
XII XIIIa,b,c

a, X = Cl
b, X = Br
c, X = CN

The 7-amino derivative XII was a useful intermediate for the preparation of compounds bearing a halogen or a cyano group in the 7-position. Benzodiazepines of this type were, as discussed previously,[2] not readily available by the lithium aluminum hydride reduction of the corresponding benzodiazepin-2-ones.

The Sandmeyer reactions leading to the 7-chloro or 7-bromo derivatives XIIIa,b proceeded in the normal way, but the 7-cyano derivative XIIIc could not be obtained by the conventional method; use of dimethylformamide as solvent, however, gave the desired product XIIIc, although in low yield (22%).

A homolog of Va was prepared by the reaction of Ia with propylenediamine. The structure of the product XIV was established by reduction to XV, followed by a Sandmeyer reaction, to give the chloro derivative XVII which, in turn, was prepared from the known benzodiazopinone XVI,[4] by lithium aluminum hydride reduction.[2]



XIV XV XVI XVII

The formation of compound XIV, in which the sterically less hindered amino group is attached to the aromatic nucleus, indicates that in the reaction sequence leading to 2,3-dihydrobenzodiazepines of type V or XIV, the first step is the nucleophilic exchange of the activated halogen atom, which is then followed by cyclization to the benzodiazepine.

Experimental

All melting points are corrected. The infrared absorption spectra of starting materials and products were compared whenever necessary, in order to establish structural changes. Identity of compounds was proved by mixture melting point determination and by comparison of infrared spectra. The spectra were determined in 1–5% chloroform solution, or in potassium bromide pellets.

2,3-Dihydro-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (Va).—A solution of 860 g. of 2-chloro-5-nitrobenozophenone (Ia) in a mixture of 2 l. of pyridine[10] and 800 ml. of ethylenediamine was refluxed for 5 hr., then the reaction mixture was concentrated *in vacuo* to dryness. The residue was crystallized by addition of methanol, to give almost pure reaction product in 60% yield (527 g.). The mother liquors were concentrated *in vacuo*, and the oily residue, consisting probably mostly of the Schiff base IVa was hydrolyzed by treatment for 2.5 hr. with an excess of boiling 1.5 *N* hydrochloric acid (2 l.). The mixture was then made alkaline and extracted with methylene chloride. The methylene chloride solution was dried, concentrated *in vacuo*, and the residue was cyclized by refluxing for 2.5 hr. in 1.1 l. of pyridine. Concentration *in vacuo* to a small volume, and addition of methanol yielded 266 g. of crystalline Va. This, together with 527 g. obtained from the original reaction mixture, resulted in a total yield of 90%.[11] After recrystallization from acetone, the product formed yellow needles melting at 211–212°.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.42; H, 4.90; Found: C, 67.36; H, 4.90.

2,2′′-Ethylenediiminobis(5-nitrobenzophenone) (IIa).—A solution of 26.1 g. (0.1 mole) of 2-chloro-5-nitrobenzophenone and 8 ml. (0.12 mole) of ethylenediamine in 75 ml. of pyridine was refluxed for 2 hr. and then concentrated *in vacuo*. The residue was dissolved in methylene chloride and the solution was washed with water and concentrated *in vacuo*. Methanol was added, and the crude crystalline reaction product (6.9 g.) was separated by filtration. It was dissolved in methylene chloride and washed with dilute hydrochloric acid and dilute sodium hydroxide. The organic layer was dried, concentrated *in vacuo*, and then diluted with ether. The precipitated crystalline reaction product (5.7 g.) was separated by filtration, and recrystallized from a mixture of methylene chloride and ether. It formed yellow needles melting at 217–218°; the melting point was depressed on admixture with Va.

Anal. Calcd. for $C_{28}H_{22}N_4O_6$: C, 65.87; H, 4.34; N, 10.98. Found: C, 65.88; H, 4.69; N, 11.30.

2-(2-Aminoethylamino)-5-nitrobenzophenone (IIIa) Hydrochloride.—A solution of 2 g. of Va in a mixture of 20 ml. of ethanol and 20 ml. of 3 *N* hydrochloric acid was refluxed for 18 hr. The solution was concentrated *in vacuo*, and the residue crystallized from methanol to yield 1.8 g. of the crude hydrochloride of IIIa. After recrystallization from a mixture of methanol and ether, yellow needles were obtained, melting at 225–227° dec.

Anal. Calcd. for $C_{15}H_{16}ClN_3O_3$: C, 55.99; H, 5.01. Found: C, 56.40; H, 4.96.

Base IIIa.—The hydrochloride was treated with aqueous alkali and the resulting free base was extracted with methylene chloride. Crystallization from ether gave yellow prisms melting at 118–119°. Treatment with boiling pyridine resulted in recyclization to Va.

(8) Heating *in vacuo* removed the mole of water of crystallization; exposure to moist air caused the reformation of the hydrate.

(9) The products VIa,b were obtained in much higher yields than in the case of the 7-chlorobenzodiazepine (VI, X = Cl), discussed in paper XI.[2] This is probably due to the effects of the strongly electron withdrawing groups (NO_2, CF_3) in the *para* position to the amino groups in Va and b, resulting in greater ease of formation of the corresponding sodio derivatives.

(10) See ref. 5. Hill and co-workers did not use pyridine in this reaction. We have found that the use of pyridine considerably increased the yield of Va.

(11) The mother liquors yielded small amounts (about 1%) of compound IIa.

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30. Found: C, 63.40; H, 5.22.

2,3-Dihydro-1-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (VIa).—To a solution of 160 g. of Va in 1.6 l. of N,N-dimethylformamide was added 35.6 g. of sodium methoxide. The resulting mixture was stirred at room temperature for 1 hr., then 62.5 ml. of dimethyl sulfate was added, and the stirring continued for an additional 2 hr. The reaction mixture was then diluted with water and extracted with methylene chloride. The organic solution was concentrated *in vacuo*, and the residue crystallized from a mixture of methylene chloride and ether to give yellow prisms melting at 187–188°. The yield was 128.5 g. (76%).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38. Found: C, 68.32; H, 5.04.

2,3-Dihydro-5-phenyl-7-trifluoromethyl-1*H*-1,4-benzodiazepine (Vb) and 2-(2-Aminoethylamino)-5-trifluoromethylbenzophenone (IIIb).—A solution of 200 g. of Ib and 210 g. of ethylenediamine in 250 ml. of anhydrous pyridine was refluxed for 5 hr., and then concentrated *in vacuo*. The residue was dissolved in methylene chloride and the solution was washed with dilute sodium carbonate and concentrated. The residue was dissolved in 200 ml. of methanol and added, with stirring, to 4 l. of ice-cold aqueous 1 *N* hydrochloric acid. The mixture was stirred during an additional 5 hr. at room temperature, and the resulting yellow precipitate was filtered off and washed with ether. Evaporation of the ether extract gave 51 g., (25% recovery) of starting material Ib. The precipitate remaining on the funnel was combined with the acid aqueous layer. The mixture was made basic with 5 *N* sodium hydroxide and extracted with methylene chloride. Concentration of this extract gave a mixture of bases, from which, by repeated fractional crystallizations from hexane, a small amount of IIIb could be obtained. It formed yellow prisms, m.p. 71–73°.

Anal. Calcd. for $C_{16}H_{15}F_3N_2O$: C, 62.33; H, 4.91; N, 9.09. Found: C, 62.38; N, 5.06; N, 8.90.

The remainder of the crude mixture containing IIIb and Vb was evaporated, and the residue was dissolved in 600 ml. of pyridine, and refluxed for 3 hr. to achieve complete cyclization to Vb. The mixture was then concentrated, and the residue was dissolved in methylene chloride and purified by filtration through a bed of activated alumina. The product, obtained after concentration of the filtrate, crystallized from a mixture of benzene and hexane as yellow prisms melting at 116–118°, or from hexane as long yellow needles melting at 110–111°.[12] The yield was 61% based on unrecovered 2-chloro-5-trifluoromethylbenzophenone (Ib).

Anal. Calcd. for $C_{16}H_{13}F_3N_2$: C, 66.19; H, 4.51; N, 9.65. Found (prisms): C, 65.88; H, 4.63; N, 9.62. Found (needles): C, 66.10; H, 4.47; N, 9.71.

The hydrochloride was prepared in methanol–ether with the calculated amount of methanolic hydrochloric acid. It formed yellow prisms, m.p. 283–285°.

Anal. Calcd. for $C_{16}H_{14}ClF_3N_2$: C, 58.81; H, 4.32; N, 8.57. Found: C, 58.64; H, 4.72; N, 8.44.

2,2′′-Ethylenediimimobis(5-trifluoromethylbenzophenone) (IIb).—The mother liquors from the crystallization of Vb yielded IIb, which was readily separated by means of its very low solubility in dilute hydrochloric acid. It formed yellow needles (from ethanol), m.p. 184–185°.

Anal. Calcd. for $C_{30}H_{22}F_6N_2O_2$: C, 64.75; H, 3.99; N, 5.04. Found: C, 64.69; H, 4.05; N, 5.13.

2,3-Dihydro-1-methyl-5-phenyl-7-trifluoromethyl-1*H*-1,4-benzodiazepine (VIb).—The product was prepared in the same way as VIa, using sodium hydride instead of sodium methoxide, to form the sodio derivative. After recrystallization from benzene–hexane and from hexane, pale yellow prisms (51% yield) were obtained melting at 151–152°.

Anal. Calcd. for $C_{17}H_{15}F_3N_2$: C, 67.09; H, 4.97; N, 9.21. Found: C, 67.16; H, 4.96; N, 9.46.

The hydrochloride was prepared in ether by addition of the calculated amount of methanolic hydrogen chloride. It formed orange prisms, melting at 261–262°.

Anal. Calcd. for $C_{17}H_{16}ClF_3N_2$: C, 59.91; H, 4.73; Cl, 10.41. Found: C, 59.88; H, 4.69; Cl, 10.38.

2,3-Dihydro-5-phenyl-*H*-1,4-benzodiazepine-7-carboxylic Acid Hydrochloride (IX) and 2,3-Dihydro-5-phenyl-1*H*-1,4-benzodiazepine (VIII) from Vb.—A solution of 60 g. of Vb in 600 ml. of 3 *N* hydrochloric acid was refluxed for 10 hr., and then cooled to 0°. The resulting yellow precipitate was filtered off, and washed successively with 3 *N* hydrochloric acid and ether, to give 48.3 g. of yellow crystals (probably VII), which melted at 185–187° with gas evolution, resolidified, and melted again at 315°. This crude hydrochloride was cyclized by heating in 500 ml. of refluxing pyridine for 3 hr. The solvent was evaporated, and the residue recrystallized from water to give IX as yellow prisms (41.3 g., 62% yield), m.p. 315–316° dec.[13]

Anal. Calcd. for $C_{16}H_{15}ClN_2O_2 \cdot H_2O$: C, 59.89; H, 5.34; Cl, 11.06. Found: C, 59.88; H, 5.37; Cl, 11.28.

After drying at 118° *in vacuo*, the color changed to deep orange, and analysis of product agreed with that of anhydrous salt.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99. Found: C, 63.26; H, 5.42.

Short exposure to moist air reconverted the product to the yellow monohydrate.

The hydrochloric acid filtrate and washings obtained in the preparation were made basic with sodium hydroxide solution, and extracted with methylene chloride to give a 24% yield of VIII. It formed yellow plates (from dilute alcohol or petroleum ether), m.p. 145–147°.

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35. Found: C, 81.12; H, 6.39.

The product was identical with the compound prepared by lithium aluminum hydride reduction of the benzodiazepinone X.[4] This reduction was carried out in the same manner as described[2] for the 7-chloro derivative.

2,3-Dihydro-5-phenyl-1*H*-1,4-benzodiazepine-7-carboxylic Acid Methyl Ester (XI).—A solution of IX in methanol was treated in the customary way with an excess of diazomethane in ether. After crystallization from methylene chloride–petroleum ether (b.p. 40–60°) and dilute alcohol, pale yellow prisms were obtained, melting at 191–193°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75. Found: C, 72.75; H, 5.43.

The **hydrochloride** was prepared in methanol–ether, and formed yellow prisms, m.p. 251–252° dec.

Anal. Calcd. for $C_{17}H_{17}ClN_2O_2$: C, 64.45; H, 5.41; Cl, 11.20. Found: C, 64.74; H, 5.45; Cl, 11.25.

7-Amino-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (XII) Dihydrochloride.—A suspension of 126.5 g. (0.45 mole) of VIa in 2.2 l. of methanol was hydrogenated at room temperature and atmospheric pressure in the presence of 130 g. (5 tablespoons) of Raney nickel. After the absorption of 1.35 moles of hydrogen (3 hr.) the catalyst was filtered off, and the filtrate acidified with an excess of methanolic hydrogen chloride. Part of the methanol was removed *in vacuo*, ether was added to the residual suspension, and the precipitated product (125 g.) was filtered. After recrystallization from a mixture of methanol and ether the product formed orange prisms melting at 267–268°.

Anal. Calcd. for $C_{16}H_{19}Cl_2N_3$: C, 59.26; H, 5.91. Found: C, 59.26; H, 6.22.

Base.—An ice-cold aqueous solution of the dihydrochloride of XII was made alkaline with potassium hydroxide. The base was extracted with methylene chloride and recrystallized from ether to form yellow prisms melting at 158–159°.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82. Found: C, 76.11; H, 7.03.

Acetyl Derivative.—A solution of 1.6 g. of the dihydrochloride of XII in a mixture of 20 ml. of pyridine and 10 ml. of acetic anhydride was left at room temperature for 60 hr. The precipitated crystalline hydrochloride of the reaction product (1 g.) was separated by filtration, and dissolved in ice–water. The base was liberated by treatment with dilute sodium hydroxide, and extracted with methylene chloride. The organic layer was dried and concentrated *in vacuo*, and the residue was crystallized from a mixture of methylene chloride and petroleum ether, to form yellow prisms melting at 176–177°.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53. Found: C, 73.51; H, 6.57.

7-Amino-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine dihydrochloride was prepared from Va, and crystallized in the same manner as the hydrochloride of XII. It formed yellow needles unmelted at 250°.

(12) The higher melting prisms were the more stable form. Both crystalline modifications had identical infrared spectra in chloroform solution, and yielded the same hydrochloride.

(13) The infrared spectrum, run as a 3% solution in piperidine–chloroform, showed a sharp band at 3630 cm.$^{-1}$ which is probably due to the O–H stretching frequency of the water of crystallization. Comparison with the spectrum of the anhydrous hydrochloride was impossible, owing to the extremely hygroscopic nature of the latter compound.

Anal. Calcd. for $C_{15}H_{17}Cl_2N_3$: C, 58.07; H, 5.52. Found: C, 58.23; N, 5.81.

The corresponding base was not obtained in crystalline form.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine Hydrochloride (XIIIa.)—To a cooled (−10°), stirred solution of 12.4 g. (0.038 mole) of 7-amino-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine dihydrochloride in 40 ml. of 1 *N* hydrochloric acid, was added 40 ml. of 1 *N* aqueous sodium nitrite. The temperature was allowed to rise to 10°. The resulting diazonium chloride solution was added over a period of 10 min. to a stirred solution of 7 g. of cuprous chloride in 40 ml. of concentrated hydrochloric acid, which had been diluted with 20 ml. of water. The mixture was diluted with 100 ml. of water and heated for 3 hr. to 35–40°. It was then cooled to 10°, and the precipitated orange-red copper complex (m.p. 168–169°) was separated by filtration and decomposed by treatment with 35 ml. of 10% aqueous ammonia at 40°. Compound XIIIa was extracted with methylene chloride, the extract was washed with water, dried, and concentrated *in vacuo*, and the residue was dissolved in acetone. The solution was filtered and treated with an excess of a solution of hydrogen chloride in isopropyl alcohol to give the hydrochloride of XIIIa (58%). The product was in every respect identical with the compound formerly described.[2]

7-Bromo-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (XIIIb).—This compound was made in the same manner as XIIIa. It formed orange-yellow prisms (from hexane), m.p. 104–105°.

Anal. Calcd. for $C_{16}H_{15}BrN_2$: C, 60.96; H, 4.80; N, 8.89. Found: C, 60.94; H, 5.11; N, 8.78.

The **hydrochloride** was prepared in methanol–ether, and formed orange-yellow prisms, m.p. 257–258° dec.

Anal. Calcd. for $C_{16}H_{16}BrClN_2$: C, 54.64; H, 4.58; N, 7.97. Found: C, 54.60; H, 4.66; N, 7.75.

7-Cyano-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (XIIIc).—To a cooled (0°–5°), stirred solution of 12.4 g. (0.038 mole) of the dihydrochloride of XII in 40 ml. of 1 *N* hydrochloric acid was added 40 ml. of 1 *N* sodium nitrite. The resulting diazonium chloride solution was added to a hot (80–90°), stirred suspension of 8 g. of cuprous cyanide in 300 ml. of N,N-dimethylformamide.[14] The reaction mixture was cooled to 60°, diluted with 200 ml. of 25% aqueous ammonia, and extracted with benzene. The organic layer was dried and concentrated *in vacuo*, and the residue was extracted with boiling ether. The ether extract was concentrated to 80 ml. and purified by chromatography on a column of 140 g. of Woelm grade I alumina. Elution with 750 ml. of ether yielded 5 g. of material which was crystallized from a mixture of ether and petroleum ether to give 2.2 g. of XIIIc (22%). Recrystallization from ether gave slightly yellow plates, melting at 149–150°.

Anal. Calcd. for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.19; H, 5.79; N, 16.36.

(14) Experiments using the conventional Sandmeyer method (addition of the diazonium chloride solution to a solution of cuprous cyanide in aqueous sodium cyanide) yielded only a red, crystalline, unidentified compound.

2,3-Dihydro-3-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (XIV) was prepared from Ia in the same manner as compound Va, using propylenediamine instead of ethylenediamine. The yield was 80%.

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38. Found: C, 68.24; H, 5.71.

This compound was hydrolyzed to the aminoethylamino ketone as described for Va.

The base, **2-(2-aminopropylamino)-5-nitrobenzophenone**, after crystallization from a mixture of methylene chloride and ether, formed yellow needles melting at 98–99°.

Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72. Found: C, 64.55; H, 5.79.

The **hydrochloride** formed yellow prisms from methanol–ether, melting at 204–205°.

Anal. Calcd. for $C_{16}H_{18}ClN_3O_3$: C, 57.40; H, 5.40. Found: C, 57.29; H, 5.78.

7-Chloro-2,3-dihydro-3-methyl-5-phenyl-1*H*-1,4-benzodiazepine (XVII). A. From 2,3-Dihydro-3-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (XIV) *via* 7-Amino-2,3-dihydro-3-methyl-5-phenyl-1*H*-1,4-benzodiazepine Dihydrochloride (XV).—Compound XIV was hydrogenated in the same manner as VIa to yield XV as yellow prisms (from ethanol–ether), melting at 277–280° dec.

Anal. Calcd. for $C_{16}H_{19}Cl_2N_3$: C, 59.26; H, 5.91. Found: C, 59.39; H, 5.97.

This compound was converted *via* a Sandmeyer reaction into the 7-chloro compound. To a cooled stirred solution of 6.4 g. of XV in 30 ml. of 6 *N* hydrochloric acid was added 20 ml. of 1 *N* sodium nitrite solution, while the temperature was kept below 5°. The solution was then added at room temperature to a stirred solution of 4 g. of cuprous chloride in 40 ml. of concentrated hydrochloric acid. The mixture was heated to 40° for 30 min., then to 85–90° for 20 min., cooled, treated with an excess of aqueous ammonia, and extracted with methylene chloride. The organic layer was dried and concentrated *in vacuo;* the residue was dissolved in 40 ml. of ether, and adsorbed on to 60 g. of Woelm alumina grade I. Elution with 250 ml. of ether gave 0.7 g. of material, which on crystallization from a mixture of ether and petroleum ether, yielded 0.3 g. of XVII. Further recrystallization gave pale yellow prisms, melting at 127–128°.

Anal. Calcd. for $C_{16}H_{15}ClN_2$: C, 70.97; H, 5.58. Found: C, 71.25; H, 5.51.

B. From 7-Chloro-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XVI).—Reduction of XVI[4] with lithium aluminum hydride as described for the 3-demethyl derivative,[2] gave a 70% yield of XVII, which was in every respect identical with the product obtained by method A.

Acknowledgment.—We are indebted to Dr. A. Motchane and Mr. S. Traiman for determination of the infrared spectra, and to Dr. Al Steyermark and his staff for the microanalyses. Mr. L. A. Dolan was helpful in the preparation of larger quantities of starting materials and intermediates.