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Benzodiazepines. V.[1] A Novel Synthesis of a 7-Nitro-1,4-benzodiazepine Derivative

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The synthesis of 1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (XVII) is described. 5-Nitro-3-phenylindole-2-carboxylic acid (X) was prepared by several methods and one of the most convenient methods was the treatment of *p*-nitrophenylhydrazine (VIII) with azlactone (V). A by-product isolated from the synthesis of XVII was shown to be 2-(2-benzoyl-4-nitroanilino)-N-methylacetamide (XVIII) by a comparison with an authentic sample prepared by independent synthesis.

In previous papers of this series,[1,3] a new method for the synthesis of 1,4-benzodiazepin-2-one derivatives has been reported. As a continuation of this work we have prepared 7-nitro-substituted 5-phenyl-1,4-benzodiazepin-2-one derivative XVII.

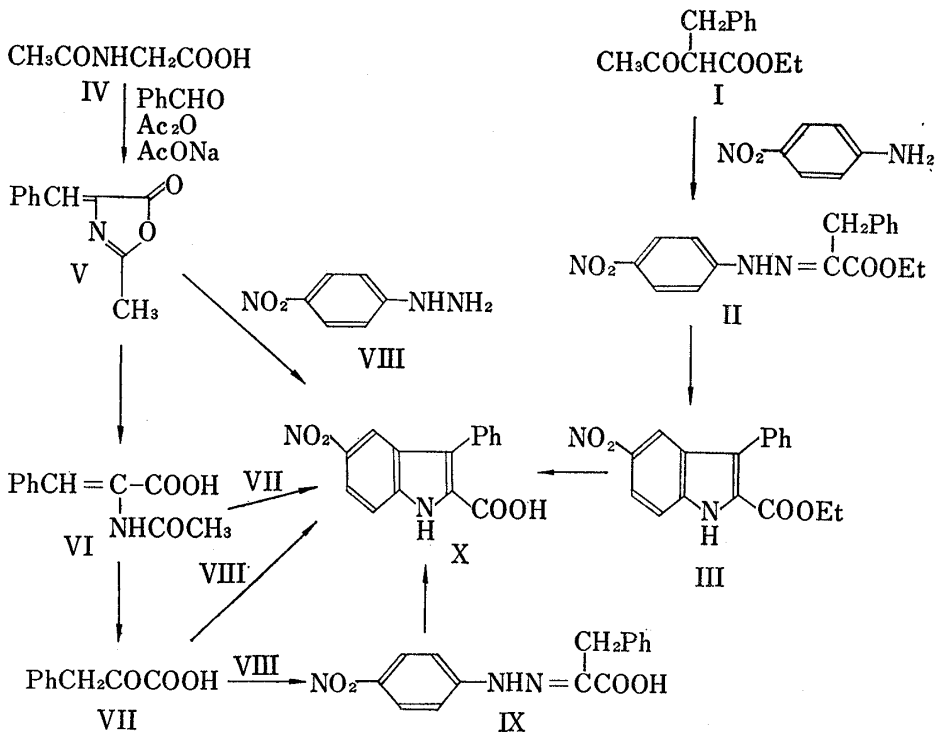


Chart 1

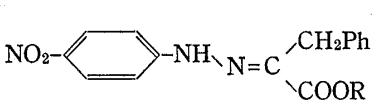
The starting compound X was prepared according to methods as showin in Chart 1.

The Japp–Klingemann reaction of α-benzylacetoacetate (I) with *p*-nitrobenzenediazonium chloride gave ethyl phenylpyruvate *p*-nitrophenylhydrazone(II) which consisted mainly of the

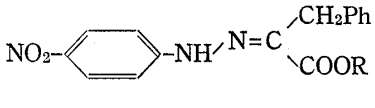
1) Part IV: S. Inaba, K. Ishizumi and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 263 (1971).
2) Location: *2-1, Takatsukasa-4-choma, Takarazuka-shi, Hyogo.*
3) *a*) H. Yamamoto, S. Inaba, T. Hirohashi and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968); *b*) S. Inaba, T. Hirohashi and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1263 (1969).

anti isomer(*anti*-II). Treatment of the crude hydrazone II with ethanolic hydrogen chloride led not to indole ring closure but to formation of the *syn* isomer(*syn*-II).[4]

Reaction of phenylpyruvic acid(VII) with *p*-nitrophenylhydrazine VIII in ethanol yielded a mixture of two isomers of phenylpyruvic acid *p*-nitrophenylhydrazone(IX). The *anti* isomer (*anti*-IX) was similarly converted to the *syn* isomer (*syn*-IX) by the action of ethanolic hydrogen chloride.



anti form



syn form

II: R=C_2H_5
IX: R=H

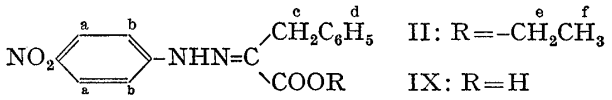
The structural assignment of the hydrazone II and IX as stereoisomers about the C=N linkage was based on their infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra(Table I). The IR spectra showed intramolecular hydrogen bonding in the *syn*-hydrazones with the lower frequency shift of the carbonyl band. In the NMR spectra, the NH protons of the *syn*-hydrazones were shifted to lower field compared with those of the *anti* isomers due to hydrogen bonding.[5]

Table I. IR and UV Spectra of Hydrazones (II and IX)

Compd.	mp (decomp.) (°C)	IR ν_{N-H} (cm^{-1}) in $CHCl_3$[a]	IR ν_{N-H} (cm^{-1}) in nujol	$\nu_{C=O}$ (cm^{-1}) in $CHCl_3$[a]	$\nu_{C=O}$ (cm^{-1}) in nujol	UV λ_{max} mμ (ε)
anti-II	110—114	3335	3320	1705	1720	375 (29,900)
syn-II	125.5—129.5	3258	3210	1686	1687	378 (30,600)
anti-IX	185	3332	3295	1758	1716	372 (28,800)
syn-IX	191—192	3240	3255	1685	1661	382 (31,100)

a) 0.2 w/v % in $CHCl_3$

Table II. NMR Spectra of Hydrazones (II and IX) in DMSO-d_6



II: R=$-CH_2CH_3$
IX: R=H

Compd.	NH (1H, s) τ	a-Protons (2H, d, J=9.5 cps) τ	b-Protons (2H, d, J=9.5 cps) τ	c-Protons (2H, s) τ	d-Protons (5H, s) τ	e-Protons (2H, q, J=7.0 cps) τ	f-Protons (3H, t, J=7.0 cps) τ
anti-II	−1.05	1.77	2.49	5.81	2.69	5.74	8.73
syn-II	−2.15	1.82	2.58	6.14	2.70	5.74	8.77
anti-IX	−0.97	1.75	2.43	5.84	2.69	—	—
syn-IX	−2.10	1.83	2.66	6.14	2.69	—	—

Both II and IX could be induced to undergo the Fischer indole cyclization by refluxing in a mixture of conc. hydrochloric acid and acetic acid to yield ethyl 5-nitro-3-phenylindole-2-carboxylate(III) and the acid X. Compound X was obtained in one step by subjecting an

4) G. K. Hughes, F. Lions and E. Ritchle, *J. Proc. Roy. Soc. New South Wales*, **72**, 209 (1939).
5) *a*) F. A. Isherwood and L. Jones, *Nature*, **175**, 419 (1955); *b*) R. M. Silverstein and J. N. Shoolery, *J. Org. Chem.*, **25**, 1355 (1960).

equimolar mixture of VII and VIII directly to the same indolization condition. Further study of this reaction showed that X could be more conveniently obtained by similar treatment of α-acetaminocinnamic acid(VI) or azlactone(V) instead of VII. Hydrolysis of III also afforded X.

5-Nitro-3-phenylindole-2-carboxamide(XI) was prepared from X, *via* the acid chloride. Dehydration of XI with phosphorous oxychloride, followed by methylation with dimethyl sulfate afforded 1-methyl-5-nitro-3-phenylindole-2-carbonitrile(XIII). 1-Methyl-5-nitro-3-phenylindole-2-carboxylic acid(XIV) and 1-methyl-5-nitro-3-phenylindole-2-carboxamide(XV), obtained by methylation of X and XI, were converted to XV and XIII in the same way as the corresponding indole N-unsubstituted derivatives.

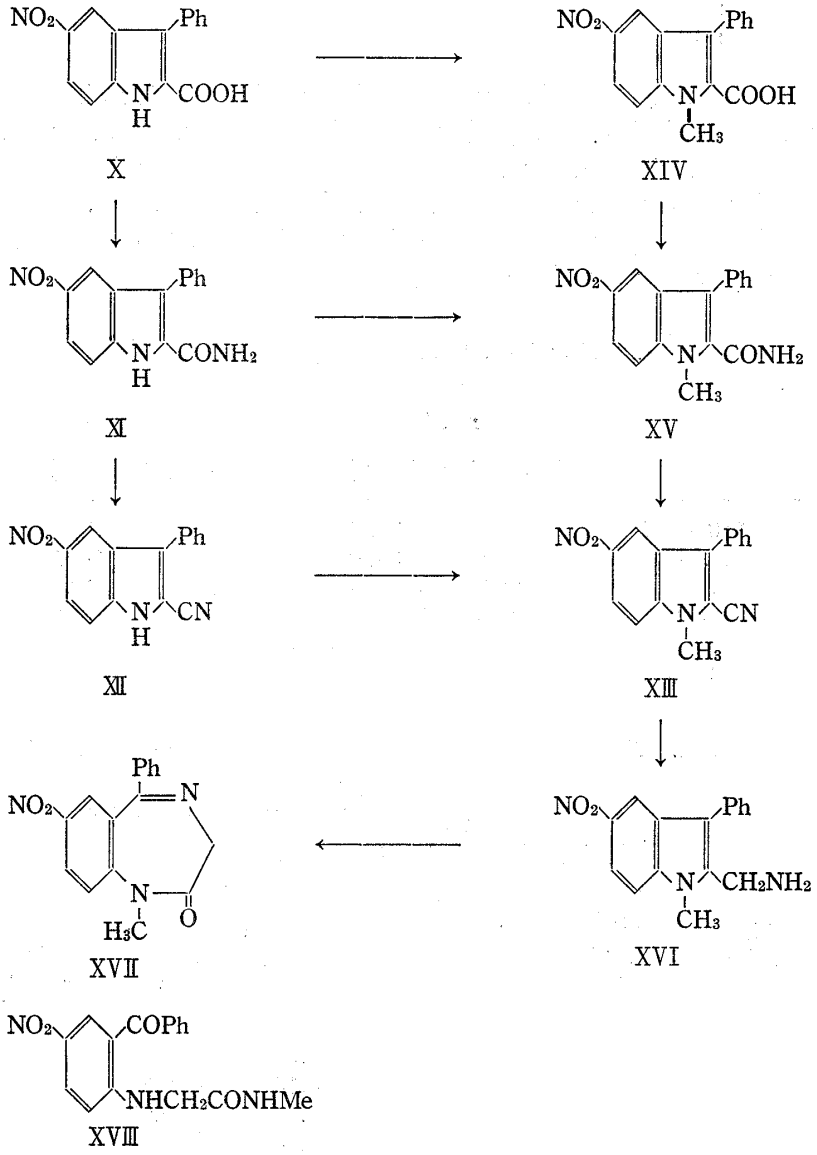


Chart 2

It has been reported that diborane was effective for the selective reduction of nitrile to amine in the presence of the nitro group.[6] Attempted reduction of XIII in tetrahydrofuran (THF), using diborane generated externally, was unsuccessful and only starting material was recovered. However, when the reduction was carried out by adding 88 mmoles of boron tri-

6) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960).

fluoride etherate to a suspension of 80 mmoles of sodium borohydride and 80 mmoles of XIII in THF, 2-aminomethyl-1-methyl-5-nitro-3-phenylindole (XVI) was obtained in 87% yield.

We repeated the experiment by adding 100 mmoles of XIII to a mixture of 120 mmoles of boron trifluoride and 260 mmoles of sodium borohydride in THF. Unexpectedly, the use of an excess of sodium borohydride resulted in only a 40% yield of XVI.

Finally, it was observed that the addition of 2 mmoles of sodium borohydride to a suspension of 10 mmoles of diborane and 10 mmoles of XIII in THF brought about a smooth reduction.

From these results it is clear that the reducing properties of diborane is greatly increased by the presence of catalytic quantities of sodium borohydride.

The aminomethylindole XVI, on treatment with chromium trioxide in acetic acid, underwent a ring enlargement to give the expected benzodiazepine XVII. This compound was shown to be identical with an authentic sample prepared by methylation of nitrazepam.[7]

A by–product isolated from the reaction of XVI with chromic acid was 2-(2-benzoyl-4-nitroanilino)-N-methylacetamide XVIII.[8]

The structure of XVIII was confirmed by the series of reactions outlined in Chart 3.

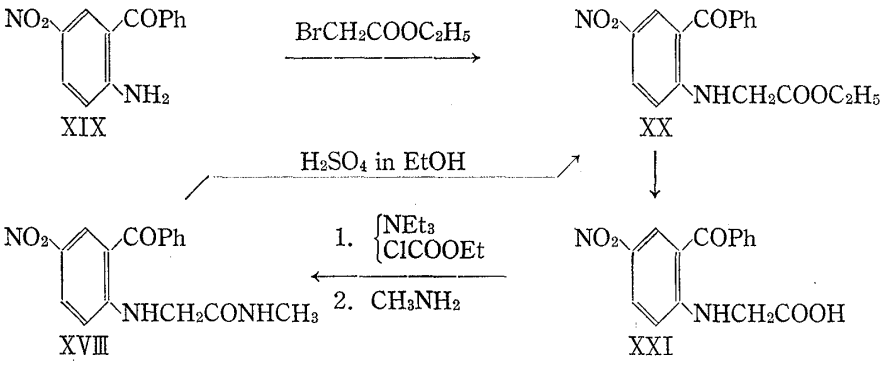


Chart 3

When the hydrochloride of XVI was used in the oxidation, XVII could be readily purified by isolating the crystalline precipitated salt of XVII directly from the reaction mixture.

This salt $C_{16}H_{13}O_3N_3 \cdot HClCrO_3$ was made basic with ammonium hydroxide to give the free base of XVII and shown to be identical with a sample prepared by treatment of the hydrochloride of XVII, $C_{16}H_{13}O_3N_3 \cdot HCl$ with CrO_3 under the same condition as the oxidation of XVI. These facts indicated that this salt was the complex of chromium trioxide, hydrogen chloride and XVII.

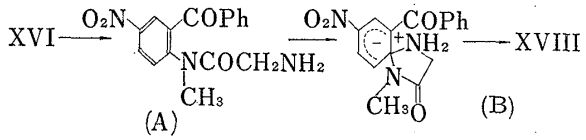
The pharmacological properties of XVII will be described in the future.

Experimental

All melting points are uncorrected. IR spectra were measured on a Perkin Elmer 125 spectrophotometer; UV spectra on a Shimadzu SV-50-AL Spectrophotometer, and NMR spectra on a Varian A-60-D

7) L. H. Strenbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

8) The formation of XVIII from XVI can be explained by a mechanism such as that shown below. Thus XVI is oxidized to form the intermediate (A), which immediately rearranges to XVIII through a cyclic transition state (B) by intramolecular nucleophilic attack of the amino group on the aromatic ring.



The mechanism will be reported in detail in near future.

instrument at 60 Mc and given in the τ scale with reference to tetramethylsilane as the internal standard. Following abbreviations are used for the representation of NMR data: s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. Mass spectra were determined on a Hitachi RMU-6E instrument with the direct sample inlet system; ionizing potential at 70 eV. Solvents used for extraction were dried over anhydrous Na_2SO_4 after extraction, and removed under reduced pressure.

Ethyl Phenypyruvate *p*-Nitrophenylhydrazone (II)——To an ice cold solution of I (77.5 g) in EtOH (380 ml) was added with vigorous stirring 50% aq. KOH (122 ml) and then ice water (720 ml), followed immediately by a solution of *p*-nitrobenzendiazonium chloride prepared from *p*-nitroaniline (49.6 g) and conc. HCl (143 ml), H_2O (215 ml) and $NaNO_2$ (24.8 g) which had been cooled to 0°. After further stirring for 5 min, a resulting oil was extracted with ether (four 500 ml portions). The extract was washed with H_2O, dried and evaporated leaving 111 g (96.6 %) of the crude hydrazone II as a red brown oil. The *anti* isomer of II was separated as crystals from this oil by allowing it to stand at room temperature. A small part was recrystallized from EtOH to give orange needles, mp 110—114°.[9] *Anal.* Calcd. for $C_{17}H_{17}O_4N_3$: C, 62.38; H, 5.24; N, 12.83. Found: C, 62.35; H, 5.14; N, 12.73.

To a solution of the crude hydrazone II (111 g) in EtOH (400 ml), dry HCl gas was passed over a period of 40 min. The precipitated *syn* isomer of II (49.8 g, 44.8%), mp 121.5—124°, was filtered after cooling and recrystallized from EtOH to yield orange needles, mp 125.5—129.5. *Anal.* Calcd. for $C_{17}H_{17}O_4N_3$: C, 62.38; H, 5.24; N, 12.83. Found: C, 62.44; H, 4.93; N, 12.64.

Ethyl 5-Nitro-3-phenylindole-2-carboxylate (III)——The crude hydrazone II (32.2 g) was prepared as above from I (22.0 g) and dissolved in a mixture of AcOH (60 ml) and conc. HCl (60 ml). This solution was heated with stirring at 95—100° for 2 hr. After cooling the precipitated product was collected by filtration and washed with a mixture of *n*-hexane and iso-PrOH (1:1). It was suspended in H_2O (100 ml), filtered and washed with H_2O. The dried solid, mp 227—230°, weighed 15.3 g (49.3% from I). Recrystallizations from EtOH gave yellow prisms, mp 243—244°. IR ν_{max}^{Nujol} cm^{-1}: 3300 (indole NH), 1678 (ester CO). *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C,65.80; H, 4.55; N, 9.02. Found: C, 65.71; H, 4.60; N, 9.07.

***α*-Acetaminocinnamic Acid (VI), Azlactone (V) of VI and Phenylpyruvic Acid (VII)**——V, VI and VII were prepared by the method of Herbst and Shemin.[10]

Phenylpyruvic Acid *p*-Nitrophenylhydrazone (IX)——A mixture of VII (22.5 g) and VIII (21 g) in EtOH (500 ml) was refluxed for 30 min. The reaction mixture was concentrated to 350 ml and cooled. The precipitated *syn* isomer of IX (12 g, 26.8%), mp 186—187° (decomp.), was collected by filtration and washed with cold EtOH. Recrystallizations from EtOH afforded orange needles, mp 187—188° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}O_4N_3$: C, 60.19; H, 4.38; N, 14.04. Found: C, 59.90; H, 4.27; N, 13.93.

The mother liquor was evaporated and the residue was washed with cold EtOH to give 28 g (62.5%) of *anti*-IX, mp 177—179° (decomp.). Recrystallizations from benzene afforded yellow needles, mp 185—186° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}O_4N_3$: C, 60.19; H, 4.38; N, 14.04. Found: C, 60.16; H, 4.28; N, 14.05. *Anti*-IX was converted to *syn*-IX by treatment with EtOH–HCl.

5-Nitro-3-phenylindole-2-carboxylic Acid (X)——a) From IX: To a solution of a mixture of *anti*- and *syn*-IX (190 g) in AcOH (1.9 liter) was added conc. HCl (1.9 liter). The mixture was then refluxed for 50 min and cooled. The precipitated product was collected by filtration, washed with H_2O and EtOH, and dried. Yield, 111 g (62.1%), mp 291° (decomp.). Washing with hot EtOH gave yellow small needles, mp 296—297° (decomp.) (reported[11] 275—295°). IR ν_{max}^{Nujol} cm^{-1}: 3315 (indole NH), 3225 (carboxylic acid OH), 1683 (carboxylic acid CO). *Anal.* Calcd. for $C_{15}H_{10}O_4N_2$: C, 63.83; H, 3.57; N, 9.92. Found: C, 64.02; H, 3.56; N, 9.97.

b) From VII: A mixture of VII (119 g) and VIII (112 g) in AcOH (2 liter)–conc. HCl (2 liter) was refluxed for 1 hr. Workup as above gave 168 g (83%) of X, mp 287° (decomp.).

c) From VI: A solution of VI (158 g) and VIII (112 g) in AcOH (2 liter) conc. HCl (2 liter) was refluxed for 1 hr and worked up as above to give 161 g (77.5%) of X, mp 293—294° (decomp.).

d) From V: A solution of V (161 g) and VIII (127 g) in AcOH (1.5 liter)–conc. HCl (1.5 liter) was refluxed for 1.5 hr. Yield, 159 g (69.0%), mp 289° (decomp.).

The IR spectra of products obtained in b)—d) were identical with that of the sample obtained in a).

e) From III: A solution of III (6.2 g) and KOH (2.7 g) in iso-PrOH (50 ml)–H_2O (1 ml) was refluxed for 4.5 hr. The reaction mixture was diluted with H_2O (150 ml) and acidified with conc. HCl. The precipitate was filtered, washed with H_2O and dried to yield 5.5 g (97.5%) of small prisms, mp 287° (decomp.).

The IR spectrum in nujol of this compound (B) was different with that of the sample (A) obtained in a)—d) (IR ν_{max}^{Nujol} cm^{-1}: 3220 (indole NH), 3080—2480 (carboxylic acid OH), 1700, 1654). However, it was recrystallized from a mixture of AcOEt, AcOH and DMF to yield small needles, mp 289—290° (decomp.), which had the same IR spectrum as that of material (A). The compound A was converted to B by dissolving

9) The IR and NMR spectra indicated that this *anti*-hydrazone II contained approximately 22% of the *syn* isomer.

10) R. M. Herbst and D. Shemin, "Organic Syntheses," Coll. Vol. II, ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 1 and 519.

11) R. I. Fryer, J. V. Earley and L. H. Sternbach, *J. Org. Chem.*, 32, 3798 (1967).

it in hot 1.3% aq. KOH, followed by acidification with conc. HCl. This fact indicated that two crystalline forms were polymorphic modifications of the same compound.

5-Nitro-3-phenylindole-2-carboxamide (XI)——A mixture of X (220 g) and $SOCl_2$ (930 g) was refluxed for 1 hr. After removal of excess $SOCl_2$, the solid residue was powdered and suspended in toluene (2.5 liter). Excess NH_3 gas was then passed in the stirred mixture at 50° over a period of 1 hr. The reaction mixture was cooled in an ice bath and the precipitated product was filtered, washed with H_2O and MeOH, and dried. Yield, 179 g (81.6%), mp 288—291° (decomp.). Recrystallizations from MeOH afforded yellow small pillars, mp 302° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3480 (indole NH), 3345, 3310, 3255 (amide NH), 1672 (amide CO). *Anal.* Calcd. for $C_{15}H_{11}O_3N_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.98; H, 4.19; N, 14.64.

5-Nitro-3-phenylindole-2-carbonitrile (XII)——A mixture of XI (179 g) and $POCl_3$ (780 g) was refluxed for 30 min. The cooled reaction mixture was poured with stirring into ice–water and the resulting precipitate (144 g, 86.0%), mp 253—257°, was collected by filtration and washed thoroughly with H_2O. Recrystallizations from MeOH gave pale yellow needles, mp 263—264°. IR ν_{max}^{Nujol} cm^{-1}: 3318 (indole NH), 2224 (CN). *Anal.* Calcd. for $C_{15}H_9O_2N_3$: C, 68.44; H, 3.45; N, 15.95. Found: C, 68.61; H, 3.07; N, 16.19.

1-Methyl-5-nitro-3-phenylindole-2-carboxylic Acid (XIV)——Me_2SO_4 (25.2 g) was added dropwise to a stirred solution of X (28.2 g) in a mixture of acetone (160 ml) and 50% aq. KOH (45 g). The mixture was refluxed for 2 hr and cooled. The precipitated potassium salt was collected by filtration, washed with cold acetone (two 70 ml portions) and dissolved in hot water (600 ml). The solution was filtered while hot and acidified with conc. HCl (18 ml). The mixture was cooled and the white precipitate was filtered, washed with H_2O and dried. Yield, 27.2 g (91.6%), mp 253—254° (decomp.). Recrystallizations from a mixture of acetone, AcOEt and AcOH gave yellow prisms, mp 253—254°. IR ν_{max}^{Nujol} cm^{-1}: 1680 (carboxylic acid CO). *Anal.* Calcd. for $C_{16}H_{12}O_4N_2$: C, 64.86; H, 4.08; N, 9.46. Found: C, 65.02; H, 4.03; N, 9.67.

1-Methyl-5-nitro-3-phenylindole-2-carboxamide (XV)——a) From XIV: This compound was prepared in 64.2% yield from XIV in the same manner as described for the preparation of XI. Recrystallizations from a mixture of acetone and DMF gave yellow prisms, mp 250.5—251.5° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3479, 3115, 3165 (amide NH), 1683, 1651 (amide CO). *Anal.* Calcd. for $C_{16}H_{13}O_3N_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.40; H, 4.48; N, 14.25.

b) From XI: To a stirred solution of XI (28.1 g) in a mixture of acetone (100 ml) and 50% aq. KOH (23 g) was added dropwise Me_2SO_4 (18.9 g) at 42—58°. After refluxing for 1 hr, the reaction mixture was cooled and the precipitate (19.3 g, 65.4%), mp 248—249°, was collected by filtration and washed with H_2O. This product was identical with one obtained in a).

1-Methyl-5-nitro-3-phenylindole-2-carbonitrile (XIII)——a) From XII: This compound was prepared in 94.7% yield in the same manner as described for methylation of XI. Recrystallizations from MeOH gave yellow plates, mp 222.5—223.5°. IR ν_{max}^{Nujol} cm^{-1}: 2220 (CN). *Anal.* Calcd. for $C_{16}H_{11}O_2N_3$: C, 69.30; H, 4.00; N, 15.16. Found: C, 68.96; H, 3.72; N, 14.78.

b) From XV: Dehydration of XV, by the same procedure as that used for dehydration of XI, gave XIII in almost quantitative yield. Its IR spectrum was identical with that of the sample obtained above.

Reduction of XIII to 2-Aminomethyl-1-methyl-5-nitro-3-phenylindole (XVI)——a) With $NaBH_4BF_3$, ether (1:1.1): To a well-stirred suspension of XIII (22.2 g, 80 mmoles) and powdered $NaBH_4$ (3.04 g, 80 mmoles) in dry THF (140 g) was added dropwise a solution of BF_3, ether (12.5 g, 88 mmoles) in dry THF (15 g) over a period of 26 min. The mixture was stirred at room temperature for 1 hr and refluxed for 3 hr. The excess hydride in the reaction mixture was destroyed by adding 7% aq. HCl (7.5 g) and the mixture was diluted with H_2O (160 ml). After evaporation of THF at atmospheric pressure, conc. HCl (32 g) was added dropwise at 70° and the resulting mixture was heated to 80° for 1 hr and then cooled. The precipitated hydrochloride (24.4 g), mp 269—270° (decomp.). was collected by filtration and washed with H_2O. The purity of this compound was shown to be 87.4% by comparison of the UV absorption intensity at 280 mμ of a sample, purified by the preparative TLC[12] as the base, with that of an analytically pure sample. Net yield, 83.9%.

The crude hydrochloride (20 g) was suspended in $CHCl_3$ (200 ml) and made basic with 40% aq. NaOH. After stirring for 4 hr, $CHCl_3$ layer was separated, washed with H_2O and dried. The residue was solidfied and washed with EtOH to yield the free base of XVI (16.9 g), mp 156—159°. The crude free base was chromatographed over silica gel. Elution with EtOH–$CHCl_3$ and recrystallizations of the eluate from EtOH yielded the pure base XVI as orange prisms, mp 159—160°. UV λ_{max}^{MeOH} mμ (ε): 266 (20300), 280 (21600), 334 (7400). NMR ($CDCl_3$) τ: 8.63 (2H, s, NH_2), 6.08 (3H, s, CH_3), 5.92 (2H, s, $-CH_2-$), 2.70 (1H, d-d, $J_0=9$ cps, $J=2.5$ cps, C_7-H), 2.56 (5H, s, $-C_6H_5$), 1.82 (1H, d-d, $J_0=9$ cps, $J_m=2$ cps, C_6-H), 1.50 (1H, d, $J_m=2$ cps, C_4-H). Mass Spectrum *m/e*: 281 (47%, M^+), 265 (43), 264 (44.5, $M-NH_3$), 234 (21), 219 (65) 218 (100, $M-NO_2-NH_3$), 217 (57.5), 204 (50). *Anal.* Calcd. for $C_{16}H_{15}O_2N_3$: C, 68.31; H, 5.38; N,14.94. Found: C, 68.21; H, 5.16; N, 14.70.

The pure base XVI (5.63 g) was treated with an excess of EtOH–HCl, yielding 6.15 g of hydrochloride, mp 276—278° (decomp.). Recrystallizations from DMF gave yellow needles, mp 278—280° (decomp.).

12) Silica gel HF_{254} (E. Merck AG), solvent $CHCl_3$–EtOH(50:15).

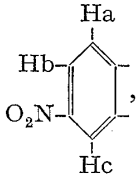
Anal. Calcd. for $C_{16}H_{16}O_2N_3Cl$: C, 60.48; H, 5.08; N, 13.22; Cl, 11.16. Found: C, 60.53; H, 5.09; N, 13.41; Cl, 11.01.

b) With $NaBH_4$–BF_3·Ether (2.6:1.2): To a stirred suspension of $NaBH_4$ (9.9 g, 260 mmoles) in THF (175 g) was added a solution of BF_3·ether (17.0 g, 120 mmoles) in THF (17 g) at room temperature over a period of 30 min. After stirring at the same temperature for 1 hr and refluxing for 1.5 hr, XIII (27.8 g, 100 mmoles) was added under cooling. The resulting mixture was stirred at room temperature for I hr, refluxed for 2.5 hr and worked up as above. The quantity of XVI in the crude product (27.0 g), based on TLC–UV analysis, was 12.5 g; net yield, 39.8%.

c) With B_2H_6–$NaBH_4$ (1:0.2): To a suspension of XIII (2.77 g, 10 mmoles) in THF (20 ml) was added 18 ml (10 mmoles) of a 0.555 M solution of B_2H_6 in THF,[13] followed by the addition of $NaBH_4$ (0.076 g, 2 mmoles). The mixture was stirred at room temperature for 4.5 hr and 20% aq. HCl (10 ml) was added under cooling. The precipitated product (2.3 g), mp 278—280° (decomp.), was collected by filtration and dried. From mother liquor another crop (1.0 g), mp 269—273° (decomp.), was obtained.

Oxidation of XVI to 1, 3-Dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (XVII)——a) From the Free Base of XVI: To a stirred suspension of the crude free base XVI (6.5 g) in AcOH (65 ml) was added a solution of CrO_3 (6.5 g) in H_2O (6.5 ml) at 20°. The mixture was stirred at room temperature for 20 hr, diluted with H_2O (200 ml) and made basic with 28% aq. NH_4OH (100 ml). The precepitate was collected by filtration and washed with H_2O. Crystallization of the solid (5.9 g), mp 135—140°, from EtOH gave a mixture of yellow plates (A) (3.8 g, 55.7%), mp 153—156°, and pale yellow needles (B) (0.15 g, 2.1%), mp 223—229°, which were mechanically separated and recrystallized from EtOH. The former A (3.4 g, 49.8%), mp 156—156.5°, was further recrystallized to yield pure XVII as pale yellow plates, mp 156.5—157.5°, identical with an authentic sample.[7] IR ν_{max}^{Nujol} cm^{-1}: 1680 (CO), 1615. UV λ_{max}^{MeOH} mμ (ε): 259 (15, 800), 308 (9,600). NMR ($CDCl_3$) τ: 6.55 (3H, s, CH_3), 6.22 and 5.11 (2H, ABq, J=11 cps, -CH_2-), 2.70—2.33 (5H, m, C_6H_5-), 2.49 (1H, d, J_o=9 cps, C_9-H), 1.84 (1H, d, J_m=2.5 cps, C_6-H), 1.60 (1H, d-d, J_o=9 cps, J_m=2.5 cps, C_8-H). Mass Spectrum *m/e*: 295 (51%, M^+), 294 (65), 268 (92), 267 (100, M-CO), 248 (65, M-1-NO_2), 221 (54), 220 (73). *Anal.* Calcd. for $C_{16}H_{13}O_3N_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.09; H, 4.26; N, 14.08.

Compound B (0.10 g, 1.4%), mp 239—241°, was identified as XVIII. Two more recrystallizations raised the melting point to 242—243°. IR ν_{max}^{Nujol} cm^{-1}: 3290, 3090, 1656, 1638, 1609. UV λ_{max}^{MeOH} mμ (ε): 364 (19500). NMR (DMSO) τ: 7.30 (3H, d, J=5 cps, CH_3), 5.90 (2H, d, J=5 cps, -CH_2-), 3.18 (1H, d, J=10 cps, Ha), 2.34 (5H, s, C_6H_5), 1.95—1.80 (3H, m, Hb, Hc and CONHMe)



, 0.56 (1H, t, J=5 cps, D_2O exchangeable, -NHCH$_2$-). Mass Spectrum *m/e*: 313 (9%, M^+), 255 (100, M–CONHMe), 209 (32). *Anal.* Calcd. for $C_{16}H_{15}O_4N_3$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.12; H, 4.50; N, 13.01.

b) From the Hydrochloride of XVI: A suspension of the pure hydrochloride XVI (4.77g) in AcOH (40 ml) was treated with a solution of CrO_3 (4.5 g) in H_2O (4 ml). The mixture was stirred at room temperature for 23 hr and the precipitated orange salt of XVII (5.54 g), mp 186—189° (decomp.), was separated by filtration and washed successively with AcOH and hexane. The analysis sample was recrystallized by removal of acetone from a solution of the product in a mixture of AcOH and acetone. It formed orange pillars, mp 186—189° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1757 (small), 1693 (CO), 1617, 958, 938 (CrO). *Anal.* Calcd. for $C_{16}H_{14}O_6N_3ClCr$: C, 44.51; H, 3.27; N, 9.73; Cl, 8.21; Cr, 12.04. Found: C, 44.20; H, 3.42; N, 9.38; Cl, 7.61; Cr, 11.6.

The crude salt was suspended in H_2O (50 ml) and made basic with 28% aq. NH_4OH. The precipitate (3.51 g), mp 156—158°, was filtered and washed with H_2O. Recrystallization from iso-PrOH gave 2.98 g of XVII mp 157—159°, which was identified with the sample obtained in a).

The AcOH mother liquor obtained after the separation of the crude salt was diluted with H_2O and made basic with 28% aq. NH_4OH. The precipitate (0.66g) was separated and chromatographed over 30 g of silica gel. Elution with AcOEt afforded 0.55 g of XVII, mp 152—157°, and 13 mg of XVIII, mp 238—242°. Total yield of XVII was 4.06 g (91.7%).

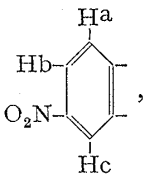
Hydrochloride of XVII——A hot solution of the pure base XVII (3.0 g) in EtOH (100 ml) was treated with 16% EtOH–HCl (20 ml). The precipitate (3.2 g), mp 243—247° (decomp.), was collected and washed with EtOH. *Anal.* Calcd. for $C_{16}H_{14}O_3N_3Cl$: C, 57.93; H, 4.25; N, 12.67; Cl, 10.69. Found: C, 58.00; H, 4.20; N, 12.67; Cl, 11.01.

$HClCrO_3$ Salt of XVII——From the Hydrochloride of XVII: A solution of CrO_3 (0.81 g) in H_2O (0.8 ml) was added to a suspension of the hydrochloride XVII (1.0 g) in AcOH (10 ml). The mixture was stirred at

13) G. Zweifel and H. C. Brown, "Organic Reactions," Vol. 13, John Wiley and Sons, Inc., New York, N. Y., 1963, Chapter 1.

room temperature for 6 hr. The precipitate (1.09 g), mp 178—180° (decomp.), was filtered, washed with AcOH and purified as described for the sample obtained by the oxidation of XVI, yielding orange pillars, mp 185—188° (decomp.). Its IR spectrum was identical with that of the sample obtained from XVI. *Anal.* Calcd. for $C_{16}H_{14}O_6N_3ClCr$: C, 44.51; H, 3.27; N, 9.73; Cl, 8.21; Cr 12.04. Found: C, 44.41; H, 3.47; N, 9.33; Cl, 7.53; Cr, 12.1.

Ethyl N-(2-Benzoyl-4-nitrophenyl) glycinate (XX)——a) From XVIII: A solution of XVIII (1.0 g) in a mixture of conc. H_2SO_4 (10 ml) and EtOH (30 ml) was refluxed for 10 hr. The mixture was cooled and the precipitated product (0.83 g, 79.2%) was separated by filtration and washed with EtOH. Recrystallizations from EtOH yielded pale yellow needles, mp 134—135°. IR ν_{max}^{Nujol} cm^{-1}: 3318 (NH), 1737 (ester CO), 1635 (CO). NMR (C_5D_5N) τ: 8.81 (3H, t, J=7 cps, CH_3), 5.75 (2H, q, J=7 cps, CH_2Me), 5.62 (2H, d, J=6 cps, $>NCH_2$-), 3.09 (1H, d, J_o=9 cps, Ha), 2.60—2.15 (5H, m, C_6H_5), 1.65 (1H, d-d, J_o=9 cps, J_m=3 cps, Hb), 1.38 (1H, d, J_m=3 cps, Hc)



, 0.90 (1H, t, J=5 cps, NH). *Anal.* Calcd. for $C_{17}H_{16}O_5N_2$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.31; H, 4.74; N, 8.40.

b) From XIX: A mixture of XIX (0.5 g) and ethyl bromoacetate (5 ml) was refluxed for 20 hr. Excess ethyl bromoacetate was evaporated *in vacuo* and the residue was chromatographed over 30 g of silica gel. Elution with benzene gave 0.4 g (76.3%) of XX, mp 124—126°. Recrystallization from EtOH yielded pale yellow needles, mp 133—134°, identical with the sample obtained in a).

N-(2-Benzoyl-4-nitrophenyl) glycine (XXI)——A solution of XX (1.6 g) in a mixture of 2% aq. NaOH (20 ml) and EtOH (30 ml) was refluxed for 10 min. After evaporation of EtOH, the reaction mixture was acidified with conc. HCl and the precipitate was collected by filtration, washed with H_2O and dried. Recrystallization from aq. iso-PrOH gave 1.0 g (68.3 %)of yellow pillars, mp 204—207°. Further recrystallization raised the melting point to 207—208.5°. IR ν_{max}^{Nujol} cm^{-1}: 3250 (NH), 1765 (carboxylic acid CO), 1631 (CO), 1602. *Anal.* Calcd. for $C_{15}H_{12}O_5N_2$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.93; H, 3.92; N, 9.47.

2-(2-Benzoyl-4-nitroanilino)-N-methylacetamide (XVIII)——A solution of ClCOOEt (0.15 g) in THF (5 ml) was added dropwise to a cold solution of XXI (0.3 g) and NEt_3 (0.15 g) in THF (15 ml). After stirring for 30 min, the mixture was added under stirring and cooling to 30% aq. $MeNH_2$(20 ml) over a period of 5 min. The reaction mixture was stirred at room temperature for 1 hr and THF was removed *in vacuo*. The precipitated product (0.25 g, 79.9%), mp 233—239°, was filtered and washed with H_2O. Recrystallization from EtOH gave pale yellow needles, mp 242—244°, which was identical with the sample of XVIII obtained by the oxidation of XVI.