

Benzodiazepine. XIII.¹⁾ Syntheses of 1,4-Benzodiazepine DerivativesSHIGEHO INABA, MITSUHIRO AKATSU, TOSHIYUKI HIROHASHI,
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Oxidation of 3-methyl- or benzyl-substituted or unsubstituted 2-aminomethylindole was described.

1,4-Benzodiazepin-2-one derivatives (VIIa—c) were synthesized by oxidative ring enlargement of corresponding 2-aminomethylindole derivatives (VIa—c). Also, oxidation of VIa and VIc with O₃ gave 1,4-benzodiazepin-2,5-dione derivatives VIIIa and VIIIc, respectively, oxidation of VIa with CrO₃ gave isatin derivative IX and oxidation of VIc with H₂O₂ afforded 2-oxindole derivative X as unexpected product.

In previous publications³⁾ of this series, the oxidative ring enlargement of 2-aminomethyl-3-phenylindoles to the corresponding 5-phenyl-1,4-benzodiazepin-2-ones have been reported. We wish to report now on the oxidation of 2-aminomethyl-3-methyl or benzyl substituted- or unsubstituted-indoles.

2-Aminomethylindoles (VIa—c) were prepared from the indole esters as shown in Chart 1.

Ethyl 5-chloroindole-2-carboxylate (Ia) was methylated with sodium hydride and methyl iodide to give N-methylindole ester (IIa), which was hydrolysed with base to afford acid (IIIa). Methylation of ethyl 3-benzyl-5-chloroindole-2-carboxylate (Ib) with aqueous potassium hydroxide and dimethyl sulfate in acetone gave N-methyl-indole-2-carboxylic acid (IIIb) directly. N-Phenylation of ethyl 5-chloro-3-methylindole-2-carboxylate (Ic) with bromobenzene in the presence of potassium carbonate and cuprous bromide gave N-phenylindole ester (IIc) as a pale yellow oil, whose infrared (IR) spectrum showed a band at 1710 cm⁻¹ (ester C=O) but no absorption band corresponding to NH group. Hydrolysis of oily IIc gave a crystal acid (IIIc).

The acid IIIa was converted to amide (IVa) by the mixed anhydride method.⁴⁾ The acid IIIb and IIIc were converted to the corresponding amides IVb and IVc, respectively, *via* acid chloride by treatment with thionyl chloride followed by ammonia. The amides (IIIa, IIIb and IIIc) were converted to the desired 2-aminomethylindoles (VIa, VIb and VIc) by reduction with lithium aluminum hydride. 2-Aminomethyl-5-chloro-3-methyl-1-phenyl indole (VIc) was also prepared by dehydration of IVc with phosphorous oxychloride, followed by reduction with lithium aluminum hydride.

Oxidation of 2-aminomethylindoles (VIa, VIb and VIc) gave the following results shown in Table I.

Oxidation of VIa (free base) with ozone in acetic acid at 15—20° for 1 hour afforded a mixture of expected 7-chloro-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VIIa) (0.5%) and the neutral product 7-chloro-1-methyl-3H-1,4-benzodiazepin-2,5(1H,4H)-dione (VIIIa)

1) Part XII: S. Inaba, K. Ishizumi, T. Okamoto, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 3279 (1975).

2) Location: 2-1, Takatsukasa-4-chome, Takarazuka-shi, Hyogo.

3) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968); S. Inaba, T. Hirohashi, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1263 (1969); S. Inaba, K. Ishizumi, and H. Yamamoto, *ibid.*, **19**, 263 (1971); S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *ibid.*, **19**, 722 (1971).

4) N.F. Albertson, "Organic Reactions," Vol. 12, John Wiley and Sons, Inc., New York, N.Y. 1962.

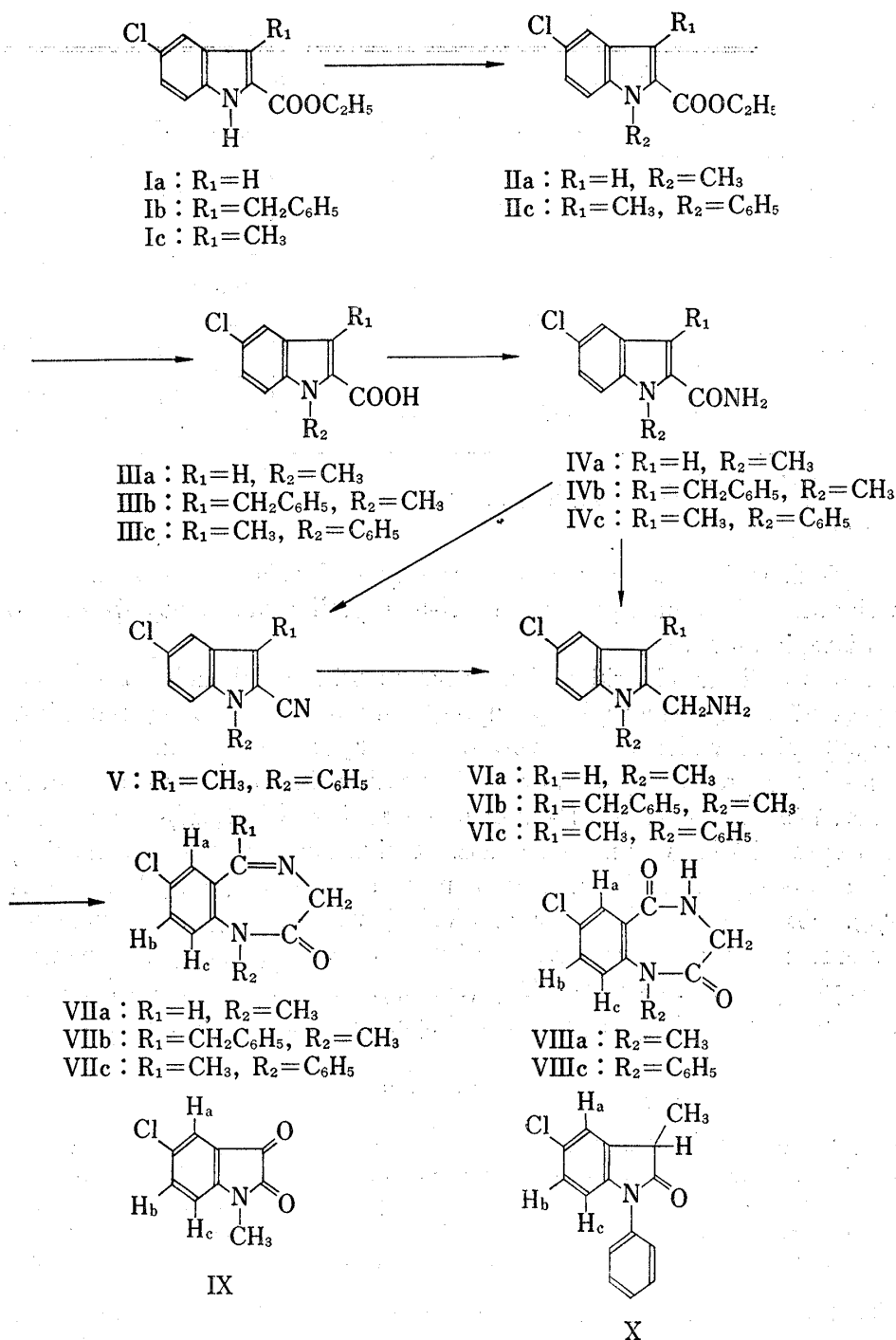


Chart 1

(1.4%). The structures of compounds (VIIa and VIIIa) were supported by the IR, nuclear magnetic resonance (NMR) spectra and analytical values.

In case of the oxidation of VIa (hydrochloride) with chromic acid in acetic acid at room temperature for 3.5 hours did not give the expected 1,4-benzodiazepin-2-one VIIa but 5-chloro-1-methylisatin (IX) in 13% yield. Reaction of IX with thiosemicarbazide gave thiosemicarbazone.⁵⁾

Oxidation of VIb (free base) with ozone in acetic acid at 15–20° for 2 hours afforded the expected 5-benzyl-7-chloro-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VIIb) as an

5) The IR spectrum was similar to that of N-Methylisatin-3-thiosemicarbazone (=Marboran).

TABLE I. Oxidation of 2-Aminomethylindole (VI)

| Compd. No. ^{a)} | Condition | | Time (hr) | Product | | Yield (%) |
|--------------------------|---------------------|------------------|-----------|--------------------------|------|-----------|
| | Agent ^{b)} | Temp. | | Compd. No. ^{a)} | | |
| VIa (F) | A | 15—20° | 1 | { VIIa (F) | 6.5 | |
| | | | | { VIIIa | 1.4 | |
| VIa (H) | B | RT ^{c)} | 3.5 | IX | 13 | |
| VIb (F) | A | 15—20° | 2 | VIIb (F) | 61.9 | |
| VIc (H) | B | 25—30° | 3 | VIIc (F) | 60.3 | |
| VIc (F) | A | 15—20° | 5/6 | VIIIc | 28.3 | |
| VIc (H) | A | 15—20° | 2 | { VIIc (F) | 16.1 | |
| | | | | { VIIIc | 11.8 | |
| VIc (H) | C | RT ^{c)} | 22 | { VIIc (F) | 27.9 | |
| | | | | { X | 26.6 | |

a) (F): free base, (H): hydrochloride.

b) A: O₃-AcOH, B: CrO₃-AcOH, C: H₂O₂-AcOH.

c) room temp.

oil⁶⁾ in 61.9% yield, which was converted to the hydrochloride, mp 214—216° (decomp.) and identical with authentic sample prepared by N-methylation of 5-benzyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one.⁷⁾

Oxidation of VIc (hydrochloride) with chromic acid in acetic acid at 25—30° for 3 hours gave the expected 7-chloro-5-methyl-1-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VIIc) as an oil in 60.3% yield, which was converted to the hydrochloride, mp 202—204° (decomp.). The oxidation of VIc (free base) with ozone in acetic acid 15—20° for 50 minutes yielded a neutral product, 7-chloro-1-phenyl-3H-1,4-benzodiazepin-2,5-(1H,4H)-dione (VIIIc) in 28.3% yield and the expected VIIc was not obtained. Oxidation of VIc (hydrochloride) with ozone in acetic acid at 15—20° for 2 hours gave a mixture of VIIc (16.1%) and neutral product VIIIc (11.8%). Oxidation of VIc (hydrochloride) with hydrogen peroxide in acetic acid at room temperature for 22 hours gave a mixture of VIIc (27.9%) and neutral substance, 5-chloro-3-methyl-1-phenyl-2-oxindole (X) (26.6%). The structures of compounds VIIc, VIIIc and X were supported by IR, and NMR spectra, and the analytical values.

Experimental

All melting points were determined in open capillary tubes and are uncorrected. IR spectra were measured on a Hitachi Model EPI-G3 spectrophotometer and NMR spectra on a Varian A-60-D instrument at 60 Mc and given in the τ scale with reference to tetramethylsilane as an internal standard. Mass spectra were determined on a Hitachi RMU-7 instrument with direct sample inlet system; ionizing potential at 70 eV. Solvents for extraction were dried over anhydrous Na₂SO₄ after extraction, and removed under reduced pressure.

Ethyl 5-Chloroindole-2-carboxylate (Ia)—Prepared according to B. Heath-Brown and P.G. Philpott,^{8b)} in 82% yield. Recrystallized from EtOH in pale yellow needles, mp 167—168°. (lit.^{8a)} mp 167—168°.

Ethyl 3-Benzyl-5-chloroindole-2-carboxylate (Ib)—A mixture of 8.41 g of *p*-chloroaniline, 16 ml of conc. hydrochloric acid and 16 ml of water was heated into a solution, and then cooled to 0°. To the mixture was added dropwise a solution of 4.5 g of NaNO₂ in 6 ml of water with stirring. Then the mixture, was stirred at 0° for additional 20 minutes, and 7.38 g of AcONa was added thereto. The resulting mixture was added dropwise to a cooled mixture of 15 g of ethyl α -phenethylacetoacetate, 12.8 g of anhydrous AcOK and 64 ml of MeOH, with stirring, while the reaction mixture was maintained below 5° by external cooling. After stirring continued at 3° for 3 hr, the reaction mixture was extracted with ether. The ethereal extracts were combined and dried, and the ether was removed. The oily residue was heated with 100 ml of EtOH and 10 ml of conc. H₂SO₄ on a steam bath. The mixture was refluxed for 3.5 hr. After cooling, the pre-

6) lit.⁷⁾ mp 113°.

7) J. Schmitt (Etablissements Clin-Byla), Fr. Patent 1391752 (1965) [*Chem. Abstr.*, 63, 4316 (1965)].

8) a) H.N. Rydon and J.C. Tweddle, *J. Chem. Soc.*, 1955, 3499; b) B. Heath-Brown and P.G. Philpott, *ibid.*, 1965, 7185.

precipitate was collected by filtration, washed well with water and dried to give 10.8 g of Ib. Recrystallization from benzene afforded colorless needles, mp 192.5–194°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3280 (NH), 1685 (ester C=O). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{16}\text{O}_2\text{NCl}$: C, 68.90; H, 5.14; N, 4.46; Cl, 11.30. Found: C, 68.80; H, 4.81; N, 4.38; Cl, 11.25.

Ethyl 5-Chloro-3-methylindole-2-carboxylate (Ic)—A mixture of 31 g of *p*-chloroaniline, 60 ml of conc. HCl and 60 ml of water was heated into a solution, and then cooled to 0°. To the mixture was added dropwise a solution of 18.2 g of NaNO_2 in 45 ml of water at 3–5° with stirring. The resulting mixture was added to a chilled mixture of 31.6 g of ethyl α -ethylacetoacetate, 82 g of AcONa and 70% aqueous EtOH with stirring under cooling (0–3°). After addition, the mixture was stirred at 0–5° for 4 hr. The reaction mixture was extracted with ether. The ethereal extracts were combined and dried, and the solvent was removed. The residue was refluxed with 20% ethanolic H_2SO_4 for 5 hr. After cooling, the precipitate was collected by filtration, washed successively with water and small amount of petroleum ether, and dried to give 15.7 g of Ic. Recrystallization from benzene afforded colorless needles, mp 162–163°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3330 (NH), 1670 (ester C=O). NMR (CDCl_3) τ : 1.03 (1H, br.s, >NH), 2.30–2.41 (1H, m, aromatic protons), 2.66–2.76 (2H, d, $J=1.5$ Hz, aromatic protons), 5.55 (2H, q, $J=7$ Hz, $-\text{COOCH}_2\text{CH}_3$), 7.46 (3H, s, >C- CH_3) and 8.67 (3H, t, $J=7$ Hz, $-\text{COOCH}_2\text{CH}_3$). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_2\text{NCl}$: C, 60.62; H, 5.08; N, 5.89; Cl, 14.92. Found: C, 60.53; H, 4.93; N, 5.84; Cl, 14.79.

Ethyl 5-Chloro-1-methylindole-2-carboxylate (IIa)—To a stirred solution of the ester Ia (10 g) in 60 ml of dimethylformamide was added 1.77 g of 63% NaH oil dispersion. To this mixture was added dropwise a solution of 6.4 g of methyl iodide in 60 ml of dimethylformamide at 10° with stirring over a half hour period, and then the reaction mixture was poured into ice-water, extracted with ether. The ethereal extracts were combined and dried, and ether was removed. The residue was crystallized from EtOH-petroleum benzene to give 8.4 g (78.4%) of colorless needles, mp 85.5–86.5°. Recrystallization from EtOH raised the melting point to 87.5–88.5°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1720 (ester C=O). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{NCl}$: C, 60.63; H, 5.09; N, 5.89; Cl, 14.91. Found: C, 60.50; H, 4.75; N, 5.61; Cl, 14.68.

5-Chloro-1-methylindole-2-carboxylic Acid (IIIa)—A solution of the ester IIa (7.4 g) in 100 ml of MeOH was refluxed with 4 g of KOH for 3 hr. After evaporation of the solvent, the residue was dissolved in water and acidified with conc. HCl under cooling. The resulting white precipitate was filtered off, washed with water and dried to give 6.51 g (99.7%) of IIIa as colorless powder, mp 242–243° (decomp.). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1665 (COOH). This IIIa was insoluble in organic solvents.

3-Benzyl-5-chloro-1-methylindole-2-carboxylic Acid (IIIb)—To a solution of the ester Ic (8.5 g) in 135 ml of acetone was added a solution of 7.4 g of KOH in 7 ml of water. To the mixture was added dropwise 5.1 g of dimethyl sulfate. The mixture was heated under reflux for 5 hr. After cooling the reaction mixture was concentrated, and the residue was dissolved in water and filtered. The filtrate was acidified with conc. HCl under cooling. The precipitate was collected by filtration, washed with water and dried to give 8.1 g (100%) of IIIb as a colorless solid, mp 223–224° (decomp.). Recrystallization from benzene gave colorless small needles, mp 223.5–224° (decomp.). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1670 (COOH). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_2\text{NCl}$: C, 68.12; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 68.04; H, 4.65; N, 4.56; Cl, 11.45.

5-Chloro-3-methyl-1-phenylindole-2-carboxylic Acid (IIIc)—A mixture of the ester Ic (1 g), 1 g of anhydrous K_2CO_3 , 15 ml of bromobenzene and 0.1 g of cuprous bromide was heated under reflux for 3.5 hr. The reaction mixture was cooled and filtered, and the residue was washed with benzene. The filtrate and washings were combined, and the solvent was removed. The residue was dissolved in CHCl_3 and chromatographed on silica gel,⁹⁾ eluting with CHCl_3 to give 0.9 g of the ester IIc as a pale yellow oil. IR ν_{\max}^{film} cm^{-1} : 1710 (ester C=O). NMR (CDCl_3) τ : 2.30 (1H, d, $J_m=2.5$ Hz, $\text{C}_4\text{-H}$), 2.40–2.90 (6H, m, >N- C_6H_5 and $\text{C}_6\text{-H}$), 3.40 (1H, d, $J_o=9$ Hz, $\text{C}_7\text{-H}$), 5.82 (2H, q, $J=7$ Hz, $-\text{COOCH}_2\text{CH}_3$), 7.40 (3H, s, >C- CH_3) and 8.92 (3H, t, $J=7$ Hz, $-\text{COOCH}_2\text{CH}_3$). After N-phenylation of the ester Ic (3 g) as above, the crude ester IIc was dissolved in 150 ml of 10% KOH-EtOH solution and allowed to stand at room temperature overnight. The mixture was diluted with water and washed with CHCl_3 . The aqueous layer was acidified with conc. HCl under cooling. The precipitate was collected by filtration to give 2.8 g (80%) of the carboxylic acid IIIc. Recrystallization from benzene-ether gave colorless prisms, mp 241–242°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1680 (COOH). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{12}\text{O}_2\text{NCl}$: C, 67.26; H, 4.23; N, 4.90; Cl, 12.41. Found: C, 67.39; H, 4.11; N, 5.03; Cl, 12.25.

5-Chloro-1-methylindole-2-carboxamide (IVa)—A solution of the carboxylic acid IIIa (6 g) and 2.89 g of triethylamine in 200 ml of dry tetrahydrofuran was cooled at -8° . To the solution was added dropwise a solution of 3.1 g of ethyl chloroformate in dry tetrahydrofuran with stirring. The resulting mixture was stirred at -8° for 0.5 hr. Excess NH_3 gas was passed into the cooled mixture with stirring for 0.5 hr. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The colorless solid was yielded and crystallized from benzene to give 3.1 g (52%) of the amide IVa as colorless needles, mp 199–203°. Recrystallization from EtOH raised the melting point to 202–204°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3370, 3160 (CONH_2), 1646 (amide C=O). *Anal.* Calcd. for $\text{C}_{10}\text{H}_9\text{N}_2\text{OCl}$: C, 57.56; H, 4.34; N, 13.42; Cl, 16.99. Found: C, 57.59; H, 4.28; N, 13.18; Cl, 16.86.

9) Mullinckrodt Silicic Acid AR 100 mesh.

5-Chloro-3-methyl-1-phenylindole-2-carboxamide (IVc)—A mixture of the carboxylic acid IIIc (19 g) and 60 ml of SOCl_2 was heated under reflux for 1.5 hr. The excess SOCl_2 was removed under reduced pressure. The residue [crude acid chloride, mp 99–101°. IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 1735 (COCl)] was dissolved in 200 ml of anhydrous ether and cooled. NH_3 gas was bubbled into the cooled solution with stirring for 1 hr. The reaction mixture was cooled in an ice bath for 1 hr. The precipitate was collected by filtration, washed with water and dried to give 18.2 g (97%) of the amide IVc as a colorless solid, mp 232–234°. Recrystallization from MeOH–Acetone gave colorless needles, mp 245–247°. IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 3400, 3200 (CONH_2), 1645 (amide C=O). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{13}\text{ON}_2\text{Cl}$: C, 67.49; H, 4.60; N, 9.84; Cl, 12.45. Found: C, 67.20; H, 4.51; N, 9.73; Cl, 12.68.

3-Benzyl-5-chloro-1-methylindole-2-carboxamide (IVb)—The amide IVb was obtained from IIIb as above in 92% yield and recrystallized from benzene to give colorless needles, mp 215–217°. IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 3330, 3160 (CONH_2), 1640 (amide C=O). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{15}\text{ON}_2\text{Cl}$: C, 68.34; H, 5.06; N, 9.38; Cl, 11.87. Found: C, 68.59; H, 4.83; N, 9.55; Cl, 11.86.

5-Chloro-3-methyl-1-phenylindole-2-carbonitrile (V)—A mixture of the amide IVc (17 g) and 27.6 g of POCl_3 in 170 ml of toluene was stirred at 65–75° for 4 hr. After cooling the solution was diluted with 130 ml of water and extracted with toluene. The extracts were combined, washed with water and dried. The solvent was removed to give 14.4 g (90.6%) of the nitrile V. Recrystallization from *n*-hexane–ether gave colorless prisms, mp 120.5–122°. IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 2220 ($\text{C}\equiv\text{N}$). NMR (CDCl_3) τ : 2.35–2.80 (8H, m, aromatic protons), 7.50 (3H, s, $\text{C}_3\text{-CH}_3$). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{11}\text{N}_2\text{Cl}$: C, 72.05; H, 4.16; N, 10.50; Cl, 13.44.

2-Aminomethyl-5-chloro-1-methylindole (VIa)—To a stirred suspension of 1 g of LiAlH_4 in 100 ml of dry ether was added the amide IVa (2.4 g). The mixture was stirred under reflux for 4 hr. After cooling, 20 ml of water was added dropwise carefully to the mixture with stirring under cooling. The ethereal layer was separated, dried and evaporated. The residue was dissolved in 20 ml of EtOH and to this solution was added 5 ml of 25% HCl–EtOH. After cooling the resulting precipitate was filtered off and dried to give 1.65 g (61.7%) of the hydrochloride of VIa, as reddish brown crystals, mp 269° (decomp.). IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 2590–3100 (N^+H_3). *Anal.* Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{Cl}\cdot\text{HCl}$: C, 51.96; H, 5.23; N, 12.12; Cl, 30.68. Found: C, 52.41; H, 5.00; N, 12.04; Cl, 30.45.

This hydrochloride was treated with NH_4OH to give free base. IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 3350 (NH_2).

2-Aminomethyl-3-benzyl-5-chloro-1-methylindole (VIb)—The reduction of the amide IVb was carried out as described for reduction of IVa. The hydrochloride of VIb was obtained in 73.2% as a colorless solid, mp 249–251° (decomp.). Recrystallization from EtOH gave colorless prisms, mp 255° (decomp.). IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 2580–3100 (broad, N^+H_3). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{Cl}\cdot\text{HCl}$: C, 63.56; H, 5.65; N, 8.72; Cl, 22.07. Found: C, 63.72; H, 5.31; N, 8.86; Cl, 22.09.

This hydrochloride was treated with NaOH solution to give free base as a pale yellow viscous oil. NMR (CDCl_3) τ : 2.58–2.90 (8H, m, aromatic protons), 5.95 (2H, s, $-\text{CH}_2\text{-C}_6\text{H}_5$), 6.08 (2H, s, $-\text{CH}_2\text{NH}_2$), 6.30 (3H, s, $>\text{N-CH}_3$), 8.83 (2H, br.s, $-\text{CH}_2\text{NH}_2$). The signal of τ 6.08 was broader slightly than that of τ 5.95.

2-Aminomethyl-5-chloro-3-methyl-1-phenylindole (VIc)—i) From the Amide IVc: The reduction of the amide IVc was carried out as described above for reduction of IVa. The oily product was crystallized by treating with ethereal HCl to give the hydrochloride of VIc in 83%. Recrystallization from acetone–MeOH gave colorless needles, mp 227–229° (decomp.). IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 2700–3100 (broad, N^+H_3). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{Cl}\cdot\text{HCl}$: C, 62.55; H, 5.25; N, 9.14; Cl, 23.08. Found: C, 62.35; H, 5.35; N, 9.04; Cl, 22.89.

ii) From the Nitrile V: To a suspension of 9.1 g of LiAlH_4 in 300 ml of dry ether was added the nitrile V (12.8 g). After refluxing for 4.5 hr, water was added dropwise carefully to the mixture under cooling. The ethereal layer was separated, dried and evaporated. The residue was crystallized to give 12.5 g (96.2%) of pale yellow crystals. Recrystallization of this free base VIc from *n*-hexane–ether afforded colorless prisms, mp 83–85°. IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 3350 (NH_2). NMR (CDCl_3) τ : 2.36–3.16 (8H, m, aromatic protons), 6.16 (2H, s, $-\text{CH}_2\text{NH}_2$), 7.68 (3H, s, $\text{C}_3\text{-CH}_3$), 8.80 (2H, s, $-\text{CH}_2\text{NH}_2$). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{Cl}$: C, 70.98; H, 5.58; N, 10.35; Cl, 13.09. Found: C, 70.91; H, 5.53; N, 10.20; Cl, 12.88.

The free base was treated with ethereal HCl to give the hydrochloride in 98.2% as a colorless crystalline solid. This was identical with the one obtained from IVc through admixture and IR spectra comparison.

Oxidation of VIa—i) Ozonized oxygen was bubbled into a solution of the free base VIa (1.3 g) in 20 ml of AcOH at 15–20° for 1 hr. The reaction mixture was poured into 200 ml of water, neutralized with 28% aq. NH_4OH and extracted with CH_2Cl_2 . The extracts were combined, washed with water and dried. The solvent was removed. The residue in CHCl_3 was chromatographed on silica gel using $\text{CHCl}_3\text{-AcOEt}$ (4:1^{v/v}) as eluent. First elution gave 90 mg (6.5%) of VIIa, which was crystallized and recrystallized from EtOH–cyclohexane to give pale brown prisms, mp 105–107°. IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 1667 (amide C=O), 1637 (C=N). NMR (CDCl_3) τ : 1.44 (1H, s, $-\text{CH}=\text{N}-$), 2.46 (1H, d.d, $J_{bc}=9 \text{ Hz}$, $J_{ab}=2.5 \text{ Hz}$, Hb), 2.56 (1H, d, $J_{ab}=2.5 \text{ Hz}$, Ha), 2.75 (1H, d, $J_{bc}=9 \text{ Hz}$, Hc), 5.73 (2H, br.s, $-\text{COCH}_2\text{N}=\text{N}$), 6.60 (3H, s, $>\text{N-CH}_3$). *Anal.* Calcd. for $\text{C}_{10}\text{H}_9\text{ON}_2\text{Cl}$: C, 57.56; H, 4.34; N, 13.42; Cl, 16.99. Found: C, 57.37; H, 3.88; N, 13.23; Cl, 17.18. Mass spectrum was shown in Table II.

Further elution of the column with the same solvent gave 20 mg (1.4%) of VIIIa, which was crystallized and recrystallized from EtOH–cyclohexane to give pale brown prisms, mp 170–172°. IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 3350

(CONH), 1680, 1660 (amide C=O). NMR (CDCl_3) τ : 2.10 (2H, br.d, $J=2.5$ Hz, $-\text{CONH}-$ and Ha), 2.45 (1H, d.d, $J_{bc}=9$ Hz, $J_{ab}=2.5$ Hz, Hb), 2.80 (1H, d, $J_{bc}=9$ Hz, Hc), 6.14 (2H, d, $J=6$ Hz, $-\text{NHCH}_2\text{CO}-$), 6.61 (3H, s, $>\text{N}-\text{CH}_3$). *Anal.* Calcd. for $\text{C}_{10}\text{H}_9\text{O}_2\text{N}_2\text{Cl}$: C, 53.46; H, 4.03; N, 12.43; Cl, 15.78. Found: C, 52.79; H, 3.78; N, 11.93; Cl, 16.39. Mass spectrum was shown in Table II.

TABLE II. Principal Peaks Present in the Mass Spectra of VIIa, VIIc, VIIIa and VIIIc.

| | VIIa m/e (%) ^a | VIIc m/e (%) ^a | VIIIa m/e (%) ^a | VIIIc m/e (%) ^a |
|------|--------------------------------|--------------------------------|---------------------------------|---------------------------------|
| M+2 | 210(23.8) | 286(20.3) | 226(19.1) | 288(11.8) |
| M | 208(74.6) | 284(60.2) | 224(60.7) | 286(41.6) |
| M-26 | 182(36.8) | 258(15.3) | 198(10.0) | 260(10.5) |
| M-27 | 181(82.2) | 257(35.6) | 197(23.6) | 259(10.5) |
| M-28 | 180(100) | 256(35.6) | 196(27.0) | 258(26.3) |
| M-29 | 179(75.7) | 255(100) | 195(67.4) | 257(18.8) |
| M-43 | 165(27.0) | | | |
| M-55 | | | 169(12.8) | 231(42.9) |
| M-56 | 152(11.4) | | 168(20.2) | |
| M-57 | | 227(5.1) | 167(36.0) | 229(100) |
| M-83 | 125(17.8) | | | |
| M-84 | | | 140(36.0) | |
| M-85 | | | 139(100) | 201(11.4) |
| M-86 | | | 138(73.0) | |

a) relative intensity

ii) Oxidation of VIa (hydrochloride) with CrO_3 : To a solution of the hydrochloride of VIa (1 g) in 30 ml of AcOH was added dropwise a solution of 1.56 g of CrO_3 in 1.56 ml of water. The mixture was stirred at room temperature for 3.5 hr. The reaction mixture was neutralized with 30% aq. NaOH, diluted with 80 ml of water and extracted with 1,2-dichloroethane. The extracts were combined, dried and evaporated. The residue (0.39 g) was chromatographed on silica gel. Elution with $\text{AcOEt}-\text{CHCl}_3$ (1:1^{vol.}) gave 0.11 g (13%) of IX as red crystals, mp 170—171.5°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1750 (C=O), 1730 (C=O). NMR (CDCl_3) τ : 2.32—2.53 (2H, m, Ha, Hb), 3.13 (1H, d, $J_{bc}=9$ Hz, Hc), 6.75 (3H, s, $>\text{N}-\text{CH}_3$). Mass Spectrum m/e : 195 (M^+ , 94.7), 167 (57.9), 139 (base peak). *Anal.* Calcd. for $\text{C}_9\text{H}_6\text{O}_2\text{NCl}$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.25; H, 2.91; N, 7.11. Reaction with thiosemicarbazide gave thiosemicarbazone as yellow needles, mp 259° (decomp.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3390 (NH), 3230, 3150 (CSNH_2), 1690 (C=O). *Anal.* Calcd. for $\text{C}_{10}\text{H}_9\text{ON}_4\text{ClS}$: C, 44.70; H, 3.38; N, 20.85; Cl, 13.19; S, 11.93. Found: C, 44.63; H, 3.34; N, 20.58; Cl, 13.02; S, 11.65. Mass Spectrum m/e : 268 (M^+).

5-Benzyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VIIb)—i) Ozonolysis: Ozonized oxygen was bubbled into a solution of the free base VIIb (2 g) in 30 ml of AcOH at 15—20° for 2 hr. Work up as above in (i). The oily residue was chromatographed on silica gel using $\text{AcOEt}-\text{CHCl}_3$ (1:1^{vol.}) as eluent to give 1.3 g (61.9%) of VIIb as an oil. The oily product was treated with EtOH-HCl to give the hydrochloride of VIIb as a solid. Recrystallization from MeOH-benzene gave colorless prisms, mp 214—216° (decom.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2350, 1970, 1940 ($=\text{NH}$), 1695 (amide C=O), 1665 (amide C=O and $\text{C}=\text{N}$). NMR¹⁰ (CDCl_3) τ : 1.90—2.95 (8H, m, aromatic protons), 5.34, 6.35 (2H, d.d, $J=11$ Hz, $-\text{COCH}_2\text{N}$), 5.90 (2H, s, $-\text{CH}_2-\text{C}_6\text{H}_5$), 6.79 (3H, s, $-\text{NCH}_3$). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{15}\text{ON}_2\text{Cl}\cdot\text{HCl}$: C, 60.91; H, 4.81; N, 8.36; Cl, 21.15. Found: C, 60.67; H, 5.01; N, 8.40; Cl, 20.87.

ii) From 5-Benzyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one: To a solution of 5-benzyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one⁷ (1.2 g) in 20 ml of DMF was added 0.2 g of 56% NaH-mineral oil at 5°. The mixture was stirred at 5° for 15 min. To the mixture was added 0.71 g of CH_3I , and then the mixture was stirred at 5° for 20 min. The reaction mixture was poured into 200 ml of water, extracted with ether. The extracts were combined, washed with water, dried and evaporated. The residue was treated with HCl-EtOH to give 1.4 g (99.4%) of the hydrochloride of VIIb. Recrystallization from MeOH-benzene gave colorless prisms, mp 215—217° (decomp.). This compound was identical with the sample obtained from VIIb through IR spectra comparison.

Oxidation of VIc—(a) Oxidation of VIc (hydrochloride) with CrO_3 : To a solution of the hydrochloride of VIc (1 g) in 15 ml of AcOH was added dropwise a solution of 0.98 g of CrO_3 in 1 ml of water at 15—20°. The mixture was stirred at 25—30° for 3 hr. The reaction mixture was neutralized with 30% aq. NaOH,

10) Free base of VIIb.

diluted with 100 ml of water and extracted with ether. The extracts were combined, dried and evaporated. The residue (0.7 g) was chromatographed on neutral alumina.¹¹⁾ Elution with AcOEt-benzene (1:1^{vol.}) gave 0.56 g (60.3%) of VIIc as an oil. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1680 (amide C=O), 1620 (C=N). NMR (CDCl₃) τ : 2.50 (1H, d, $J_{ab}=2.5$ Hz, Ha), 2.52–3.00 (6H, m, >N-C₆H₅ and Hb), 3.18 (1H, d, $J_{bc}=9$ Hz, Hc), 5.79 (2H, br.d, $J=40$ Hz, -COCH₂N=), 7.43 (3H, s, >C-CH₃). This free base in ether was treated with ethereal HCl under cooling. The precipitate was collected and dried to give the hydrochloride of VIIc as a colorless solid. Recrystallization from MeOH-acetone gave colorless needles, mp 202–204° (decomp.). IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 2350, 2100, 2000, 1930 (=NH), 1695, 1680 (amide C=O), 1660 (C=N). NMR (CF₃COOD) τ : 1.93–2.83 (8H, m, aromatic protons), 5.21 (2H, br.s, -COCH₂=NH-) 6.77 (3H, s, >C-CH₃). Anal. Calcd. for C₁₆H₁₃ON₂Cl·HCl: C, 59.86; H, 4.40; N, 8.73; Cl, 22.09. Found: C, 59.86; H, 4.32; N, 8.74; Cl, 22.32. Mass spectrum was shown in Table II.

(b) Oxidation of VIc (free base) with Ozone: Ozonized oxygen was bubbled into a solution of the free base VIc (1 g) in 20 ml of AcOH at 15–20° for 50 min. The mixture was poured into ice water, neutralized with NH₄OH and extracted with ether. The extracts were combined and dried. The solvent was removed and the residue in benzene was chromatographed on alumina.¹¹⁾ Elution with EtOH-AcOEt (1:9^{vol.}) gave 0.3 g (28.3%) of VIIIc as a viscous oil, which was crystallized from *n*-hexane and recrystallized from iso-PrOH-isopropyl ether to give colorless prisms, mp 199–201°. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3150 (CONH), 1675 (amide C=O). NMR (CDCl₃) τ : 1.90 (1H, t, $J=6$ Hz, -CONHCH₂-), 2.10 (1H, d, $J_{ab}=2.5$ Hz, Ha), 2.35–3.20 (6H, m, >N-C₆H₅ and Hb), 3.25 (1H, d, $J_{bc}=9$ Hz, Hc), 6.11 (2H, d, $J=6$ Hz, -NHCH₂CO-). Anal. Calcd. for C₁₅H₁₁O₂N₂Cl: C, 62.84; H, 3.87; N, 9.77; Cl, 12.37. Found: C, 62.54; H, 4.16; N, 9.57; Cl, 11.90. Mass Spectrum was shown in Table II.

(c) Oxidation of VIc (hydrochloride) with Ozone: A solution of the hydrochloride of VIc (1 g) in 20 ml of AcOH was ozonized at 15–20° for 2 hr. Work-up as above afforded 0.4 g of oil as a residue. The residue was chromatographed on alumina.¹¹⁾ Elution with AcOEt gave 0.15 g (16.1%) of VIIc as an oil. Further elution with AcOEt-EtOH (9:1^{vol.}) gave 0.11 g (11.8%) of VIIIc.

(d) Oxidation of VIc (hydrochloride) with H₂O₂: To a solution of the hydrochloride of VIc (1 g) in 20 ml of AcOH was added dropwise 1.7 ml of 30% H₂O₂ under cooling. The mixture was stirred at room temperature for 22 hr. The reaction mixture was poured into 100 ml of water, basified with NH₄OH and extracted with CH₂Cl₂. The extracts were combined, dried and evaporated. The residue (0.86 g) was chromatographed on silica gel. Elution with AcOEt-CHCl₃ (1:1^{vol.}) gave 0.22 g (26.6%) of X as colorless prisms, mp 106–107°. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1710 (amide C=O). NMR (CDCl₃) τ : 2.46–2.95 (7H, m, >N-C₆H₅, Ha, Hb), 3.24 (1H, d, $J_{bc}=8$ Hz, Hc), 6.40 (1H, q, $J=7.5$ Hz, >CH-CH₃), 8.45 (1H, d, $J=7.5$ Hz, >CH-CH₃). Mass Spectrum *m/e*: 257 (M⁺, base peak), 229 (32.8), 228 (82.0), 214 (76.1). Anal. Calcd. for C₁₅H₁₂ONCl: C, 69.91; H, 4.69; N, 5.43; Cl, 13.85. Found: C, 69.54; H, 4.62; N, 5.38; Cl, 13.85. Further elution with AcOEt gave 0.26 (27.9%) of expected VIIc as an oil.

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11) Woelm neutral grade II.