[Chem. Pharm. Bull. 19(5) 982—989 (1971)]

UDC 547.751.07 : 615.277.3.011.5

Synthesis of 1*H*-Pyrrolo[1,2-*a*]indole Derivatives. II.[1] Synthesis of 7-Nitro-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles

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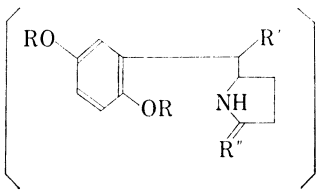
(Received November 28, 1970)

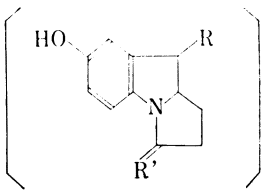
In connection with synthesis of the ring system of mitomycins, 1*H*-pyrrolo[1,2-*a*] indoles (III to VI) were synthesized. Indole (XVIII) was synthesized by the reaction of aminodiester (XVII) and 2-chloro-5-nitrobenzaldehyde in one step. Dieckmann reaction of XVIII afforded pyrroloindole (III). By the carbene cyclization reaction, tosylhydrazone (XX) of aldehyde (XIX) gave the compound IV in poor yield, and tosylhydrazones (XXV and XXX) of ketones (XXIV and XXVIII) afforded the desired pyrroloindoles (V and VI) in good yield, respectively.

The preceding paper of this series[1] reported the synthesis of 2-hydroxy-6*H*-isoindolo[2,1-*a*]indole (I) and its 10b,11-dihydro derivative (II) in connection with synthesis of the ring system of mitomycins. In the present work, 1*H*-pyrrolo[1,2-*a*]indoles (III to VI) were synthesized for the same purpose.[3] Very recently, Yamada and Matsui[4] reported the synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole ring system.

Mitomycins contain an indoloquinone skeleton which can be derived from 5-hydroxyindoles by oxidation.[5] Considering this point, synthesis of 2,5-dihydroxybenzylpyrrolidines (VII) was examined in order to prepare 7-hydroxy-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]-indoles (VIII). If the synthetic method[1] for I and II be followed, VII might be regarded as the potential precursor of VIII.



VII: R=Me or H
R'=COOEt or CH_2OH
R''=O or H_2



VIII: R=COOEt or CH_2OH
R'=O or H_2

Ethyl 2,5-dimethoxyphenylacetate (IX) was derived to ethyl 2,5-dimethoxyphenylmalonate (X) and the latter was saponified with the calculated amount of potassium hydroxide to the malonic monoester (XI) of mp 75°. The method of Ireland and Marshall[6] was used for the reaction of isopropylmagnesium bromide and β-ethoxycarbonylpropionyl chloride to obtain diethyl α-(2,5-dimethoxyphenyl)-β-oxoadipate (XII) but the product obtained here proved to be the cyclized lactone compound (XIII) as a pale yellowish green oil of bp 148° (2 mmHg).

1) Part I: T. Takada and S. Ohki, *Chem. Pharm. Bull.* (Tokyo), **19**, 977 (1971).
2) Location: *No. 600, Kashiwagi 4-Chome, Shinjuku-ku, Tokyo, 160, Japan.*
3) Paper read at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.
4) Y. Yamada and M. Matsui, *Agr. Biol. Chem.* (Tokyo), **34**, 724 (1970).
5) G.R. Allen, J. F. Poletto, and M.J. Weiss, *J. Org. Chem.*, **30**, 2897 (1965).
6) R.E. Ireland and J.A. Marshall, *J. Am. Chem. Soc.*, **1959**, 2907.

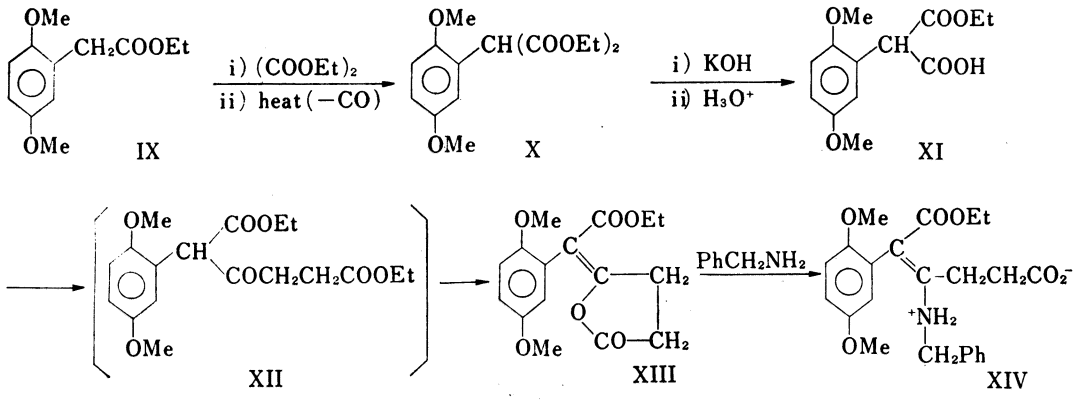
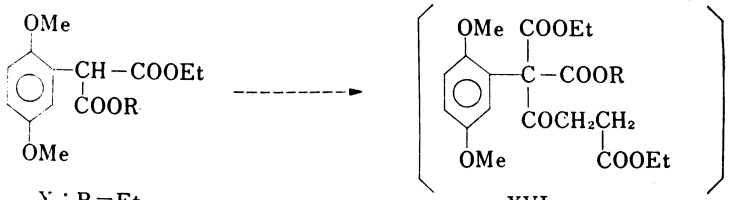


Chart 1 Ph=phenyl

XIII easily reacted with amines and its reaction with benzylamine gave needles, mp 155°, which was thought to take the betaine (XIV) structure from its elemental analytical values and from ultraviolet (UV) and infrared (IR) spectra. Although XIII and XIV should come in *cis-trans* stereoisomers, both were obtained as a single unity.

Reduction of the carbon-carbon double bond in XIV and its cyclization to the pyrrolidone ring were attempted in order to derive XIV into VII[7] but all attempts under various conditions failed. Reduction of the double bond in XIII also did not materialize. In order to avoid the formation of an *exo*-double bond lactone like XIII, synthesis of phenyl-ethoxycarbonyl-propionylmalonate (XVI) from X or *tert*-butyl ethyl phenylmalonate (XV) and β-ethoxycarbonylpropionyl chloride was also attempted but this also ended fruitless.



The synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles by Yamada and Matsui[4] involved Nenitzescu's indole synthesis and the formation of a VII-type compound as an intermediate was suggested.

Since the synthesis of VII-type compounds did not give the desired product, compounds III to VI were synthesized from the consideration that 5-nitroindoles could be used in place of 5-hydroxyindoles as a potential precursor of indoloquinones. Reaction of glycine ester and ethyl β-bromopropionate afforded ethyl N-ethoxycarbonylmethyl-β-aminopropionate (XVII) which was heated with 2-chloro-5-nitrobenzaldehyde in dimethylformamide, in the presence of triethylamine, on which condensation-cyclization proceeded in one step to give ethyl 1-(2-ethoxycarbonyl-ethy)-5-nitro-2-indolecarboxylate (XVIII) as yellow needles, mp 98—100°. Dieckmann reaction of XVIII afforded 7-nitro-1-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (III) as pale yellow crystals, mp 135°.

7) *cf.* P. Ruggli and A. Maeder, *Helv. Chim. Acta*, **25**, 936 (1942).

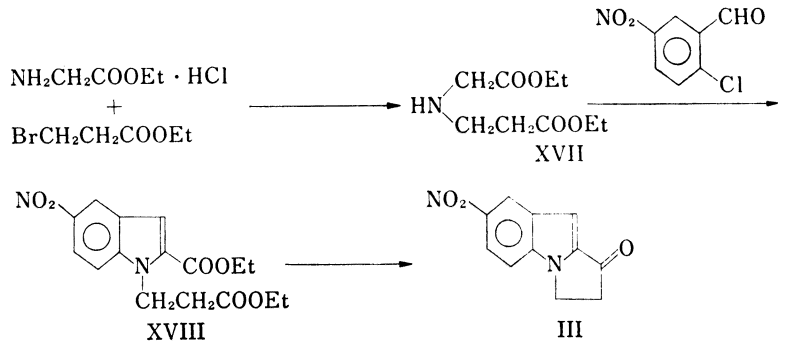


Chart 2

XVIII was treated with zinc dust and phosphoric acid by the method of Dolby and Gribble[8] to prepare its 2,3-dihydro compound but only partially saponified 2-carboxylic acid compound was obtained.

Garner[9] had obtained indolines and benzoindolizidines by treatment of benzaldehyde tosylhydrazones with substituted tertiary amino group in the *ortho* position with sodium methoxide in diglyme, and this method was applied for the synthesis of 7-nitro-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (IV).

Condensation of 2-chloro-5-nitrobenzaldehyde and pyrrolidine gave 5-nitro-2-(1-pyrrolidino)benzaldehyde (XIX) whose tosylhydrazone (XX) was treated in the same way as used by Garner. The objective compound (IV) was obtained as yellow crystals, mp 35°, but in a poor yield of 7.8% and the main product (70% yield) was the sulfone compound (XXI).

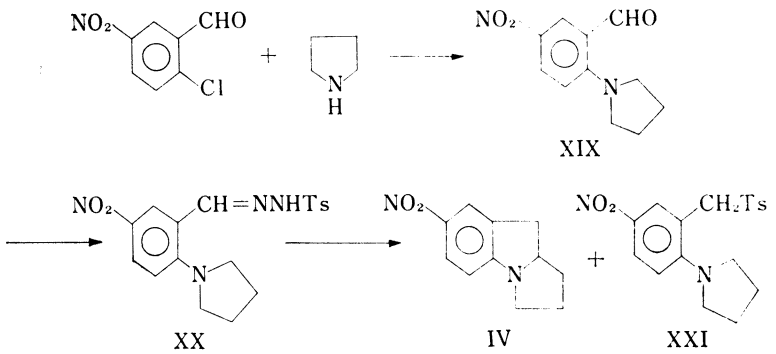


Chart 3

This carbene reaction differs from the case of Garner and a reaction with the sulfone group seems to have occurred preferentially over cyclization to the fused five-membered rings. Therefore, the above reaction was carried out with the synthesized 5-nitro-2-(1-pyrrolidino) acetophenone (XXIV), expecting some inhibition of the reaction with the sulfone group. Synthesis of XXIV followed the route shown in Chart 4. Synthesis of *o*-nitroacetophenone (XXII) by the direct nitration of acetophenone[10] is accompanied by the formation of *meta* isomer (formation ratio of *ortho* to *meta*, 1:3) and the separation of these products is difficult,

8) L.J. Dolby and G.W. Gribble, *J. Heterocyclic Chem.*, **3**, 124 (1966).
9) R. Garner, *Tetrahedron Letters*, **1968**, 221.
10) N.J. Leonard and S.N. Boyd, Jr., *J. Org. Chem.*, **11**, 406 (1946).

and the synthesis was attempted with *o*-nitrobenzoic acid[11] as a starting material. 2-Bromo-5-nitroacetophenone[10] (XXIII) was derived to 5-nitro-2-(1-pyrrolidino)acetophenone (XXIV), and its tosylhydrazone (XXV) was obtained in two kinds of crystals, one of mp 224—227° (decomp.) and the other of mp 217—219°(decomp.). These are considered to be *syn* and *anti* isomers with respect to the azomethine double bond. The carbene cyclization reaction gave the desired pyrroloindole (V) from both isomers as yellow needles, mp 84.5°, in 85% yield. This structure was confirmed from elemental analytical values and from IR, UV, and nuclear magnetic resonance (NMR) spectra. Although the presence of diastereoisomers can be considered for V, only a single substance was obtained.

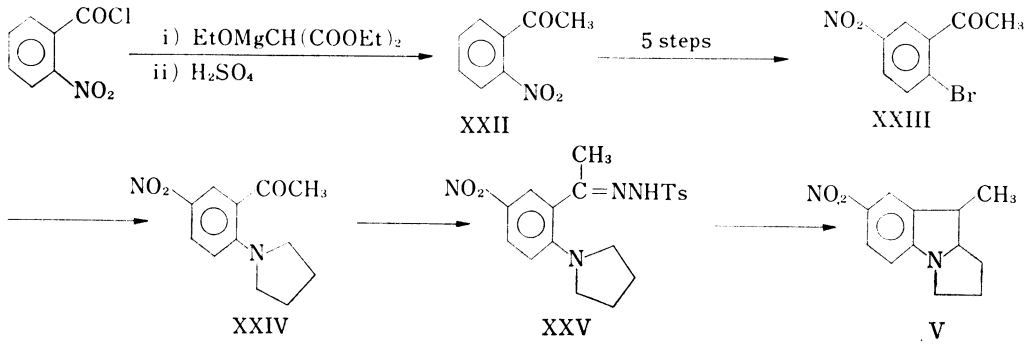


Chart 4

For closer approach to the structure of mitomycins, 6,9-dimethyl-7-nitro-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (VI) was synthesized. Synthesis of the starting compound, 2-chloro-4-methyl-5-nitroacetophenone was described by Borsche and others[12] a long time ago and this method was followed, starting with *m*-chlorotoluene. Chloro-methyl-acetophenone (XXVI) and chloro-methyl-nitroacetophenone (XXVII), having the same boiling and melting points as those reported in literature, were obtained but these were expected to be a mixture of isomers and the condensation products of XXVII and pyrrolidine (XXVIII and XXIX) were submitted to column chromatography. The main product came as orange-yellow prisms, mp 128°, and a minor one as yellow prisms, mp 184°, in a formation ratio of 3:1. The NMR spectra of both showed two singlets for two protons which did not show any coupling in the aromatic ring proton region so that they are XXVIII and XXIX. Comparison of their melting points and UV spectra with those of the afore-mentioned pyrrolidino-acetophenones (XIX and XXIV) suggested that the substance of mp 184° is the objective XXVIII and that of mp 128°would be its isomer (XXIX). In fact, the tosylhydrazone (XXX) of the product of mp 184° afforded the cyclized product (VI) in 86% yield, proving experimentally this assumption. This tosylhydrazone (XXX) also came in two isomers as the above-mentioned, one of mp 223—225° (decomp.) and the other of mp 217—220° (decomp.), and both formed the same cyclized product (VI). VI was obtained as yellow prisms, mp 88°, and its structure was confirmed from its elemental analytical values, and from UV, IR and NMR spectra. VI was also obtained as a single unity, as in the case of V.

The product (XXIX) of mp 128° also formed two kinds of tosylhydrazone (XXXI). Its carbene reaction under the same conditions as for XXX resulted in a syrupy substance whose elemental analysis and UV, IR and NMR spectra proved it to be an ether compound (XXXII).

11) K. Fukui and T. Shimakura, "Syntheses of Organic Compounds," Vol. 9, ed. by Yuki Gosei Kyokai, Gihodo, Inc., Tokyo, 1966, pp. 75—79.
12) W. Borsche, L. Stackmann, and J. Makaroff-Semljanski, *Chem. Ber.*, **49**, 2222 (1916).

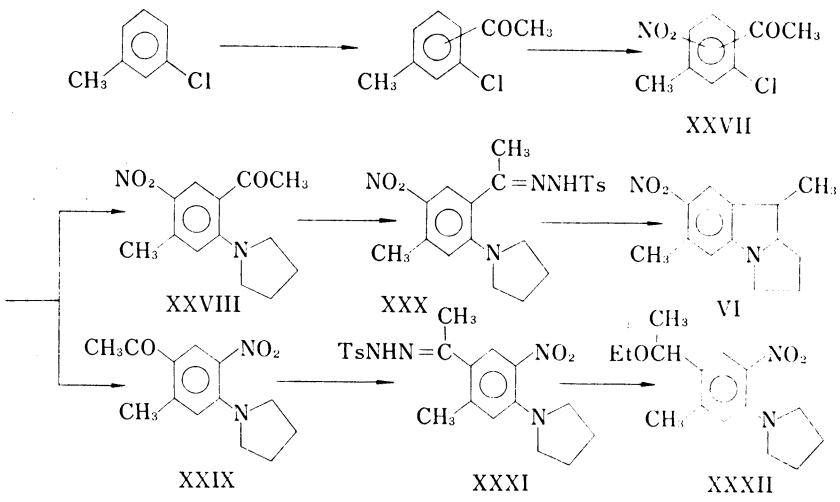


Chart 5

Thus, synthesis of 1*H*-pyrrolo[1,2-*a*]indole derivatives was carried out by the three foregoing methods and studies are now under way for further approach to mitomycin structure by their derivation to indoloquinones.

Experimental[13]

Ethyl 2,5-Dimethoxyphenylmalonate (X)——To a solution of 1.38 g of Na dissolved in 30 ml of anhyd. EtOH, 8.76 g of diethyl oxalate was added in one portion while stirring the solution at 60°, followed by 14.25 g of ethyl 2,5-dimethoxyphenylacetate[14] (XI). The mixture was allowed to stand for 1 hr, EtOH was evaporated under a reduced pressure, and the syrupy residue was dissolved in cold H_2O. This solution was acidified with HCl, the separated viscous oil was extracted with $(C_2H_5)_2O$, and the solvent was evaporated from the extract after drying over Na_2SO_4. The residue was refluxed for 6 hr under a reduced pressure (9 mmHg) to effect decarbonylation, and the fraction of bp 190—193°(7 mmHg) was collected. Yield, 11.94 g (63.6%). IR $\nu_{max}^{liq.film}$: 1735 cm^{-1}(C=O).

Ethyl Hydrogen 2,5-Dimethoxyphenylmalonate (XI)——To a solution of 1.68 g of KOH dissolved in 48 ml of 50% EtOH, 8.89 g of X was added, shaken for some time until in homogeneous solution, and the mixture was allowed to stand for 18 hr at room temperature. The solvent was evaporated under a reduced pressure, H_2O was added to the residue, and the oily substance (X) that separated out was extracted with $(C_2H_5)_2O$. The aqueous phase was acidified with HCl and the oil that separated out was extracted with $(C_2H_5)_2O$. The extract was dried over Na_2SO_4, the solvent was evaporated, and the residue was recystallized from a mixture of CH_2Cl_2 and petr. ether to colorless plates, mp 75°. Yield, 6.02 g (75%). *Anal.* Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 57.78; H, 5.91. IR ν_{max}^{KBr} cm^{-1}: 1760 (carboxylic acid C=O), 1735 (ester C=O).

2-(α-Ethoxycarbonyl-2,5-dimethoxybenzylidene)-5-oxotetrahydrofuran (XIII)——To a solution of *iso*-PrMgBr, prepared from 0.97 g (0.04 g·atom) of Mg, 4.92 g (0.04 mole) of *iso*-PrBr, and 10 ml of tetrahydrofuran, a solution of 5.13 g (0.02 mole) of X dissolved in 10 ml of tetrahydrofuran was added dropwise with stirring. The mixture was then chilled to 0°, a solution of 3.29 g (0.02 mole) of β-ethoxycarbonylpropionyl chloride dissolved in 10 ml of tetrahydrofuran was added dropwise and the temperature was raised gradually by which the reaction progressed with vigorous evolution of CO_2. After completion of the reaction, tetrahydrofuran was evaporated under a reduced pressure, saturated NH_4Cl solution and $(C_2H_5)_2O$ were added, and insoluble matter was collected. This was treated with 5% HCl and the blue oily substance that formed was extracted with $(C_2H_5)_2O$. The extract was dried over Na_2SO_4, the solvent was evaporated, and the

13) All melting points are uncorrected. NMR spectra were measured by JNM 4H-100 (100 Mc) spectrophotometer and tetramethylsilane was used as internal reference. IR and UV spectra were measured on a JASCO DS-301 IR spectrophotometer and on a Hitachi EPS-3 UV spectrophotometer, respectively.

14) G. Leaf and A. Neuberger, *Biochem. J.*, **43**, 606 (1948).

residue was distilled under a reduced pressure to collect pale yellow oil, bp 148° (2 mmHg). Yield, 0.65 g (11%). This substance colored violet to $FeCl_3$ reagent. UV λ_{max}^{EtOH} mμ: 264, 288, 310. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1810 (lactone C=O), 1735 (ester C=O).

4-Benzylamino-5-ethoxycarbonyl-5-(2,5-dimethoxyphenyl)-4-pentenoic Acid (XIV)——To a solution of 306 mg of XIII dissolved in 3 ml of $(C_2H_5)_2O$, 107 mg of benzylamine was added dropwise by which white crystals separated out immediately. The crystals were collected, washed with $(C_2H_5)_2O$, and recrystallized from MeOH to 332 mg (80.5%) of XIV as colorless needles, mp 155°. *Anal.* Calcd. for $C_{23}H_{27}O_6N$: C, 66.81; H, 6.58; N, 3.39. Found: C, 67.00; H, 6.35; N, 3.25. UV λ_{max}^{EtOH} mμ: 261, 283, 305. IR ν_{max}^{KBr} cm^{-1}: 1690 (ester C=O), 1575 and 1400 (carboxylate).

Ethyl N-Ethoxycarbonylmethyl-β-aminopropionate (XVII)——To a saturated aqueous solution of 13.8 g (0.1 mole) of ethyl aminoacetate hydrochloride and 13.8 g (0.1 mole) of K_2CO_3 dissolved in a small quantity of H_2O, a solution of 18.1 g (0.1 mole) of ethyl β-aminopropionate dissolved in 30 ml of EtOH was added dropwise while stirring the solution and the mixture was refluxed for 5 hr. EtOH was evaporated under a reduced pressure, the oily substance that separated out was extracted with benzene, and the solvent was evaporated under a reduced pressure after drying over K_2CO_3. The residue was distilled under a reduced pressure to collect the fraction of bp 153° (20 mmHg). Yield, 10 g (50%). The substance showed a single spot in thin-layer chromatography. IR ν_{max}^{NaCl} cm^{-1}: 3413 (NH), 1761, 1751 (C=O), 1196, 1036 (COO).

Ethyl 1-(2-Ethoxycarbonylethyl)-5-nitro-2-indolecarboxylate (XVIII)——To a solution of 0.7 g (0.04 mole) of 2-chloro-5-nitrobenzaldehyde dissolved in 5 ml of dimethylformamide, 0.82 g (0.04 mole) of XVII and 0.4 g (0.004 mole) of Et_3N were added and the mixture was refluxed for 15 hr. When cooled, $Et_3N\cdot$HCl was filtered off, the solvent was evaporated under a reduced pressure, and the residue was acidified with HCl and extracted with benzene. The extract was dried over Na_2SO_4, benzene was evaporated, and the residue was treated with hexane to collect the soluble portion. This product was recrystallized from EtOH to yellow needles, mp 98—100°. Yield, 0.8 g (60%). *Anal.* Calcd. for $C_{16}H_{18}O_6N_2$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.31; H, 5.69; N, 8.41. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O), 1530, 1350 (NO_2). NMR ($CDCl_3$) τ: 1.39 (1H, doublet, J=3 cps, C_4–H), 1.78 (1H, doublet of doublet, $J_{6,7}$=9 cps, $J_{6,4}$=3 cps, C_6–H), 2.45 (1H, doublet, J=9 cps, C_7–H), 8.53 (1H, singlet, C_3–H), 5.11 (2H, triplet, J=8 cps, N–CH_2–), 5.62 (2H, quartet, J=8 cps, $CH_2CH_2COOCH_2CH_3$), 5.93 (2H, quarte, J=8 cps, ⫽—$COOCH_2CH_3$), 7.13 (2H, triplet, J=8 cps, N–CH_2CH_2–), 8.55 (3H, triplet, J=8 cps, $CH_2CH_2COOCH_2CH_3$), 8.82 (3H, triplet, J=8 cps, ⫽—$COOCH_2CH_3$).

Ethyl 7-Nitro-1-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (III)——To a solution of 0.2 g (0.0006 mole) of XVIII dissolved in 5 ml of abs. benzene, 0.026 g (0.0011 mole) of Na was added and the mixture was refluxed for 4 hr. After standing over night, H_2O was added to this mixture to decompose Na, the aqueous layer was acidified with 10% HCl and extracted with benzene. The extract was dried over Na_2SO_4, benzene was evaporated, and residual yellow crystals were recrystallized from EtOH to 0.1 g (58%) of crystals, mp 135°. *Anal.* Calcd. for $C_{14}H_{12}O_5N_2$: C, 58.38; H, 4.20; N, 9.73. Found: C, 58.30; H, 4.86; N, 9.98. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O), 1695 (C=O), 1517, 1335 (NO_2).

Reduction of Ethyl 1-(2-Ethoxycarbonylethyl)-5-nitro-2-indolecarboxylate (XVIII)——A solution of 0.8 g (0.0024 mole) of XVIII dissolved in 5 ml of CH_2Cl_2 was added dropwise into a mixture of 0.47 g (0.007 g·atom) of Zn powder in 15 ml of 85% H_3PO_4, while stirring and passing N_2 gas, and the mixture was heated at 85—90° for 10 hr. H_2O was added to the mixture which was extracted with AcOEt. The extract was dried over Na_2SO_4, the solvent was evaporated, and the crystalline residue was recrystallized from EtOH to 0.1 g of crystals, mp 179—181°. *Anal.* Calcd. for $C_{14}H_{14}O_6N_2$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.71; H, 4.62; N, 8.80. NMR ($CDCl_3$) τ: 1.36 (1H, doublet, J=3 cps, C_4–H), 1.77 (1H, doublet of doublet, $J_{6,7}$=9 cps, $J_{4,6}$=3 cps, C_6–H), 2.43 (1H, doublet, J=9 cps, C_7–H), 8.53 (1H, singlet, C_3–H), 5.12 (2H, triplet, J=8 cps, N–CH_2–), 5.59 (2H, quartet, J=8 cps, $CH_2CH_2COOCH_2CH_3$), 7.06 (2H, triplet, J=8 cps, N–CH_2CH_2–), 8.58 (3H, triplet, J=8 cps, $CH_2CH_2COOCH_2CH_3$). Mass Spectrum *m/e*: 306(M^+), $C_{14}H_{14}O_6N_2$; 278 ($M^+-C_2H_4$), $C_{12}H_{10}O_6N_2$; 247 ($M^+-C_2H_3O_2$), $C_{12}H_{11}O_4N_2$; m* 199.4 (306→247); 219 (247−C_2H_4), $C_{10}H_7O_4N_2$; m* 194.2(247→219). These spectral data proved that this product is 1-(2-ethoxycarbonylethyl)-5-nitroindolecarboxylic acid.

5-Nitro-2-(1-pyrrolidino)benzaldehyde (XIX)——To a solution of 3.7 g (0.02 mole) of 2-chloro-5-nitrobenzaldehyde dissolved in 20 ml of EtOH, 1.4 g (0.04 mole) of pyrrolidine was added dropwise and the mixture was refluxed for 4 hr. After standing over night, the yellowish brown crystals that separated out were collected by filtration and recrystallized from EtOH to 3.3 g (75%) of XIX, mp 132—134°. *Anal.* Calcd. for $C_{11}H_{12}O_3N_2$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.73; H, 5.52; N, 12.81. IR ν_{max}^{KBr} cm^{-1}: 1672 (C=O), 1490, 1312 (NO_2).

Tosylhydrazone (XX) of XIX——A solution of 1.86 g (0.01 mole) of tosyl hydrazide dissolved in 10 ml of EtOH was added to a solution of 2.20 g (0.01 mole) of XIX dissolved in 10 ml of EtOH and the mixture was warmed on a water bath for 10 min. The yellow crystals that separated out were collected by filtration and recrystallized from EtOH to yellow needles, mp 213—215°. Yield, 3.4 g (88%). *Anal.* Calcd. for $C_{18}H_{20}O_4N_4S$: C, 55.65; H, 5.20; N, 14.44. Found: C, 55.99; H, 5.27; N, 14.51. IR ν_{max}^{KBr} cm^{-1}: 1160 (SO).

7-Nitro-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (IV)——To a solution of 3.00 g (0.008 mole) of the tosylhydrazone (XX) dissolved in 30 ml of diglyme, 0.43 g (0.008 mole) of MeONa was added and the mixture was refluxed for 1 hr. Crystals of MeONa were removed by filtration and diglyme was evaporated.

H_2O was added to the residue and extracted with benzene. The extract was dried over Na_2SO_4, benzene was evaporated, and the residue was purified by column chromatography over Al_2O_3. Indoline (IV) was obtained as yellow crystals, mp 35°, in 0.127 g (7.8%) yield, and 5-nitro-2-pyrrolidinobenzyl-*p*-tolyl sulfone (XXI) of mp 180—182° in a yield of 2.00 g (70%). *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$ (IV): C, 64.69; H, 5.92; N, 13.71. Found: C, 64.27; H, 6.03; N, 13.72. NMR ($CDCl_3$) τ: 1.96 (1H, doublet, $J=9$ cps, C_6-H), 2.12 (1H, singlet, C_8-H), 3.58 (1H, doublet, $J=9$ cps, C_5-H), 5.80—6.20 (1H, multiplet), 6.30—7.20 (4H, multiplet), 7.85—8.93 (4H, multiplet). *Anal.* Calcd. for $C_{18}H_{20}O_4N_2S$ (XXI): C, 60.05; H, 5.04; N, 7.78. Found: C, 59.75; H, 5.55; N, 8.26. NMR ($CDCl_3$) τ: 2.02 (1H, doublet of doublet, $J_{3,4}=9$ cps, $J_{4,6}=3$ cps, C_4-H), 2.39 (1H, doublet, $J_{6,4}=3$ cps, C_6-H), 2.53 (2H, doublet, $J=9$ cps, $C_{2'}$-H, $C_{6'}$-H), 2.76 (2H, doublet, $J=9$ cps, $C_{3'}$-H, $C_{5'}$-H), 3.41 (1H, doublet, $J=9$ cps, C_3-H), 5.45 (2H, singlet, S-CH_2-), 6.61 (4H, multiplet, CH_2-N-CH_2), 7.61 (3H, singlet, CH_3), 8.07 (4H, multiplet, -CH_2CH_2-).

5-Nitro-2-(1-pyrrolidino)acetophenone (XXIV)——To a solution of 300 mg of 2-bromo-5-nitroacetophenone[10] (XXIII) dissolved in 0.5 ml of EtOH, 175 mg of pyrrolidine was added dropwise by which exothermic reaction occurred at once. The mixture was warmed on a water bath for 1hr, EtOH was evaporated under a reduced pressure, and the residue was diluted with H_2O. This solution was basified with NaOH, insoluble matter was collected by filtration, washed with H_2O, and recrystallized from EtOH to yellow prisms, mp 163°. Yield, 258 mg (89.8%). *Anal.* Calcd. for $C_{12}H_{14}O_3N_2$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.73; H, 6.01; N, 12.05. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 1480, 1325 (NO_2).

Tosylhydrazones (XXV) of XXIV——A mixture of 768 mg of XXIV, 660 mg of tosyl hydrazide, and 4 ml of EtOH was refluxed for 8 hr, cooled, and crystals sparingly soluble in EtOH were collected. This product was submitted to column chromatography over silica gel in $CHCl_3$ solution and the following two kinds of product were obtained.

XXVa: Recrystallized from EtOH to yellow needles, mp 217—219°. Yield, 593 mg (44.9%). *Anal.* Calcd. for $C_{19}H_{22}O_4N_4S$: C, 56.71; H, 5.51; N, 13.92. Found: C, 57.13; H, 5.43; N, 13.92. UV λ_{max}^{EtOH} mμ: 394. IR ν_{max}^{KBr} cm^{-1}: 1565 (C=N), 1483, 1323 (NO_2), 1274, 1167 (SO_2).

XXVb: Recrystallized from EtOH to yellow needles, mp 224—227° (decomp.). Yield, 462 mg (35.0%). *Anal.* Calcd. for $C_{19}H_{22}O_4N_4S$: C, 56.71; H, 5.51; N, 13.92. Found: C, 56.91; H, 5.50; N, 14.10.

9-Methyl-7-nitro-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (V)——To a solution of MeONa prepared from 38 mg of Na, 500 mg of XXVa and 10 ml of diglyme were added and the mixture was heated at 160—165° (bath temp.) for 1 hr. Diglyme was evaporated under a reduced pressure, on a water bath, and the residue was dissolved in $(C_2H_5)_2O$. This $(C_2H_5)_2O$ solution was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography over silica gel ($CHCl_3$) and 230 mg (85%) of crude crystals of V was obtained. Recrystallization from dil. EtOH gave yellow needles, mp 84.5°. *Anal.* Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.02; H, 6.43; N, 12.77. UV λ_{max}^{EtOH} mμ: 388. IR ν_{max}^{KBr} cm^{-1}: 1490, 1330 (NO_2). NMR ($CDCl_3$) τ: 1.93 (1H, doublet of doublet, $J_{5,6}=9$ cps, $J_{6,8}=3$ cps, C_6-H), 2.12 (1H, doublet, $J=3$ cps, C_8-H), 3.58 (1H, doublet, $J=9$ cps, C_5-H), 5.80—6.10 (1H, multiplet), 6.30—7.00 (3H, multiplet), 7.90—8.50 (4H, multiplet, =CH-CH_2CH_2-), 8.65 (3H, doublet, $J=8$ cps, CH_3).

XXVb also reacted in exactly the same manner as XXVa and formed V which was confirmed from the mp, analytical values, and UV, IR, and NMR spectra of the produt.

4-Methyl-5-nitro-2-(1-pyrrolidino)acetophenone (XXVIII) and 2-Methyl-5-nitro-(1-pyrrolidino)acetophenone (XXIX)——To a solution of 4200 mg (0.02 mole) of chloro-methyl-nitroacetophenone[12] (XXVII) dissolved in 14 ml of EtOH, 2846 mg (0.02 mole) of pyrrolidine was added and the mixture was warmed on a water bath for 2 hr. EtOH was evaporated under a reduced pressure and purification of the residue by column chromatography over silica gel (benzene) afforded 570 mg of XXVIII and 1416 mg of XXIX.

XXVIII: Recrystallized from EtOH to yellow prisms, mp 184°. *Anal.* Calcd. for $C_{13}H_{16}O_3N_2$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.64; H, 6.45; N, 11.24. UV λ_{max}^{EtOH} mμ: 229, 380. IR ν_{max}^{KBr} cm^{-1}: 1678 (C=O), 1535, 1305 (NO_2). NMR ($CDCl_3$) τ: 1.51 (1H, singlet, C_6-H), 3.44 (1H, singlet, C_3-H), 6.78 (4H, multiplet, $-CH_2$-N-CH_2-), 7.35 (3H, singlet, $COCH_3$), 7.38 (3H, singlet, CH_3), 8.01 (4H, multiplet, -CH_2CH_2-).

XXIX: Recrystallized from EtOH to orange-yellow prisms, mp 128°. *Anal.* Calcd. for $C_{13}H_{16}O_3N_2$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.95; H, 6.53; N, 11.32. UV λ_{max}^{EtOH} mμ: 245, 317, 405. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O), 1540, 1355 (NO_2). NMR ($CDCl_3$) τ: 1.71 (1H, singlet, C_6-H), 3.32 (1H, singlet, C_3-H), 6.71 (4H, multiplet, $-CH_2$-N-CH_2-), 7.14 (3H, singlet, $COCH_3$), 7.48(3H, singlet, CH_3), 8.00 (4H, multiplet, -CH_2CH_2-).

Tosylhydrazones (XXX) of XXVIII——A mixture of 745 mg (0.003 mole) of XXVIII, 1115 mg (0.006 mole) of tosyl hydrazide, and 30 ml of EtOH was refluxed for 24 hr, cooled, and the solvent was evaporated. Substance insoluble in $(CH_3)_2CO$ was collected and submitted to column chromatography over silica gel ($CHCl_3$), affording two kinds of crystals.

XXXa: Recrystallized from EtOH to orange-yellow crystals, mp 223—225° (decomp.). Yield, 494 mg. *Anal.* Calcd. for $C_{19}H_{24}O_4N_4S$: C, 57.67; H, 5.81; N, 13.45. Found: C, 58.02; H, 5.73; N, 13.53. UV λ_{max}^{EtOH} mμ: 392. IR ν_{max}^{KBr} cm^{-1}: 1545 (C=N), 1512, 1325 (NO_2), 1278, 1164 (SO_2). NMR (d_6-DMSO) τ: 2.26 (2H, doublet, $J=9$ cps, $C_{2'}$-H, $C_{6'}$-H), 2.28 (1H, singlet, C_6-H), 2.62 (2H, doublet, $J=9$ cps, $C_{3'}$-H,

$C_{5'}$-H), 3.44 (1H, singlet, C_3-H), 7.08 (4H, multiplet, $-CH_2-\underset{|}{N}-CH_2$), 7.61 (3H, singlet, CH_3), 7.87 (3H, singlet, CH_3), 8.37 (4H, multiplet, $-CH_2CH_2-CH=$). One of the CH_3 signals near 7.5 τ is hidden by the DMSO signals.

XXXb: Recrystallized from EtOH to yellow prisms, mp 217—220° (decomp.). Yield, 74 mg. *Anal.* Calcd. for $C_{19}H_{24}O_4N_4S$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.55; H, 6.08; N, 13.41. UV λ_{max}^{EtOH} mμ: 388. IR ν_{max}^{KBr} cm^{-1}: 1549 (C=N), 1482, 1325 (NO_2), 1309, 1170 (SO_2). NMR ($CDCl_3$) τ: 2.22 (2H, doublet, J=9 cps, $C_{2'}$-H, $C_{6'}$-H), 2.32 (1H, singlet, C_6-H), 2.68 (2H, doublet, J=9 cps, $C_{3'}$-H, $C_{5'}$-H), 3.47 (1H, singlet, C_3-H), 6.85 (4H, multiplet, $-CH_2-\underset{|}{N}-CH_2-$), 7.37 (3H, singlet, CH_3), 7.54 (3H, singlet, CH_3), 7.72 (3H, singlet, CH_3), 8.11 (4H, multiplet, $-CH_2CH_2-CH=$).

6,9-Dimethyl-7-nitro-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (VI)——To MeONa prepared from 25 mg of Na, 417 mg (0.001 mole) of XXXa and 8 ml of diglyme were added and the mixture was heated at 160—165°(bath temp.) for 1 hr. Diglyme was evaporated under a reduced pressure, on a water bath, the residue was dissolved in $(C_2H_5)_2O$, and the solution was washed with H_2O. After drying over Na_2SO_4, $(C_2H_5)_2O$ was evaporated and the residue was purified by column chromatography over silica gel ($CHCl_3$) to 199 mg (86%) of crude VI. Recrystallization from dil. EtOH gave yellow prisms, mp 88°. *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.33; H, 7.07; N, 11.95. UV λ_{max}^{EtOH} mμ: 388. IR ν_{max}^{KBr} cm^{-1}: 1493, 1316 (NO_2). NMR ($CDCl_3$) τ: 2.6 (1H, singlet, C_8-H), 3.71 (1H, singlet, C_5-H), 5.80—6.10 (1H, multiplet), 6.35—7.00 (3H, multiplet), 7.40 (3H, singlet, Ar-CH_3), 7.85—8.45 (4H, multiplet, =CH-CH_2CH_2-), 8.67 (3H, doublet, J=8 cps, =CH-CH_3).

XXXb reacted exactly the same as XXXa and afforded VI which was confirmed from mp, analytical values, and UV, IR, and NMR spectra.

Tosylhydrazones (XXXI) of XXIX——A mixture of 248 mg (0.001 mole) of XXIX, 200 mg (0.0011 mole) of tosyl hydrazide, and 6 ml of EtOH was refluxed for 5 hr, cooled, and crystals that separated out were collected by filtration and submitted to column chromatography over silica gel in $CHCl_3$ solution and the following two kinds of product were obtained.

XXXIa: Recrystallized from EtOH to orange-yellow prisms, mp 212° (decomp.). Yield, 66 mg. *Anal.* Calcd. for $C_{20}H_{24}O_4N_4S$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.72; H, 6.02; N, 13.31. UV λ_{max}^{EtOH} mμ: 261, 420. IR ν_{max}^{KBr} cm^{-1}: 1548 (C=N), 1495, 1337 (NO_2), 1275, 1167 (SO_2). NMR ($CDCl_3$) τ: 2.23 (2H, doublet, J=9 cps, $C_{2'}$-H, $C_{6'}$-H), 2.63 (1H, singlet, C_6-H), 2.77 (2H, doublet, J=9 cps, $C_{3'}$-H, $C_{5'}$-H), 3.24 (1H, singlet, C_3-H), 6.77 (4H, multiplet, $-CH_2-\underset{|}{N}-CH_2-$), 7.54 (3H, singlet, CH_3), 7.88 (3H, singlet, CH_3), 7.91 (3H, singlet, CH_3), 7.98 (4H, multiplet, $-CH_2CH_2-CH=$).

XXXIb: Recrystallized from EtOH to orange-yellow prisms, mp 195°. Yield, 218 mg. *Anal.* Calcd. for $C_{20}H_{24}O_4N_4S$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.96; H, 6.03; N, 13.32. UV λ_{max}^{EtOH} mμ: 300, 424. IR ν_{max}^{KBr} cm^{-1}: 1545 (C=N), 1500, 1340 (NO_2), 1280, 1167 (SO_2). NMR ($CDCl_3$) τ: 212 (2H, doublet, J=9 cps, $C_{2'}$-H, $C_{6'}$-H), 2.44 (1H, singlet, C_6-H), 2.70 (2H, doublet, J=9 cps, $C_{3'}$-H, $C_{5'}$-H), 3.37 (1H, singlet, C_3-H), 6.79 (4H, multiplet, $-CH_2-\underset{|}{N}-CH_2-$), 7.58 (3H, singlet, CH_3), 7.74 (3H, singlet, CH_3), 7.89 (3H, singlet, CH_3), 8.04 (4H, multiplet, $-CH_2CH_2-CH=$).

2-(1-Ethoxyethyl)-1-methyl-4-nitro-5-(1-pyrrolidino)benzene (XXXII)——To MeONa prepared from 8 mg of Na, 104 mg (0.00025 mole) of XXXIb and 2 ml of diglyme were added and the mixture was heated at 160—165° (bath temp.) for 1 hr. Diglyme was evaporated under a reduced pressure, on a water bath, the residue was dissolved in $(C_2H_5)_2O$, and the solution was washed with H_2O. After drying over Na_2SO_4, $(C_2H_5)_2O$ was evaporated and the residue was purified by column chromatography over silica gel ($CHCl_3$) to 46 mg of orange-yellow syrupy substance. S was not found by the Na fusion test. UV λ_{max}^{EtOH} mμ: 254, 425. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1545, 1330 (NO_2), 1267 (-O-). NMR ($CDCl_3$) τ: 2.24 (1H, singlet, C_3-H), 3.34 (1H, singlet, C_6-H), 5.48 (1H, quartet, J=8 cps, =CH-CH_3), 6.63 (2H, quartet, J=8 cps, -O-CH_2-CH_3), 6.79 (4H, multiplet, $-CH_2-\underset{|}{N}-CH_2-$), 7.67 (3H, singlet, Ar-CH_3), 8.05 (4H, multiplet, $-CH_2CH_2-$), 8.60 (3H, doublet, J=8 cps, =CH-CH_3), 8.81 (3H, triplet, J=8 cps, $-CH_2-CH_3$).

Acknowledgement The present work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education which is gratefully acknowledged. The authors are indebted to Mrs. Y. Nakaoka and Mrs. E. Kawashima for technical assistance, to Mrs. Y. Baba, Mrs. A. Shimada, and Mr. Wakamatsu for elemental analyses, and to Mr. T. Ono for NMR spectral measurement.