Summary

3-Substituted 5-nitrosotropolone (IIIa～c), 7*H*-cyclohepta[*b*]pyrazin-7-one oxime (VIIIa,b), 8*H*-cyclohepta[*b*]quinoxalin-8-one oxime (IXa～c), 9*H*-cyclohepta[*b*]naphtho[2,3-*e*]pyrazin-9-one oxime (X), 5-nitrosotropolone guanidine adduct (XI), 2-(2-acetylhydrazino)-5-nitrosotropone (XII and its analogues) and 2-(2-troponylhydrazino)-5-nitrosotropone (XIV) were synthesized according to the schemes shown in Chart 1, 2, and 3. In addition, some reactions related to IIIa and IIIc were described. Among these derivatives, 2-(2-isonicotinoylhydrazino)-5-nitrosotropone and its N-oxide showed remarkable anti-tumor activities on ascitic and solid forms of Ehrlich tumor and Sarcoma 180.

(Received June 1, 1963)

[Chem. Pharm. Bull. 11 (11) 1431 ~ 1440]

UDC 547.517.07

224. Yasunobu Sato: Studies on Seven-membered Ring Compounds. X.*1 Nitration of 5-Hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one Derivatives and their Rearrangement Reaction to Indole Derivatives.

(*Takamine Research Laboratory, Sankyo Co., Ltd.**2)

In the preceding paper,[1] the author reported the syntheses of 5-hydroxycyclohepta-[*b*]pyrrol-6-(1*H*)-one derivatives from 5-tropolonylhydrazone derivatives which were obtained from 5-aminotropolone (I) in single step by the application of Japp-Klingemann method. The present work was carried out to examine the chemical reactivities of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives and to investigate the rearrangement reactions of their nitro-derivatives to indole derivatives. 3-Aryl-5-hydroxycyclohepta-[*b*]pyrrol-6(1*H*)-ones were also synthesized in a similar manner as described earlier.

The application of the Japp-Klingemann reaction of I with ethyl 2-benzylacetate afforded ethyl phenylpyruvate 5-tropolonylhydrazone (IIa), which on methylation with diazomethane gave ethyl phenylpyruvate 2-methoxy-5-troponylhydrazone (IIc). Cyclization of IIa with concentrated sulfuric acid in ethylene glycol afforded 2-(2-hydroxyethoxy)carbonyl-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (IIIa) whose analytical values corresponded to the composition of $C_{18}H_{15}O_5N$. The hydrolysis of ester (IIIa) with 2*N* ethanolic potassium hydroxide furnished 2-carboxy-3-phenyl-5-hydroxycyclohepta-[*b*]pyrrol-6(1*H*)-one (IVa), whose esterification with absolute ethanol afforded 2-ethoxycarbonyl-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (Va). In a similar manner, Japp-Klingemann reaction of I with ethyl 2-(*p*-chlorobenzyl)acetoacetate afforded ethyl 2-(*p*-chlorophenyl)pyruvate 5-tropolonylhydrazone (IIb), from which could by obtained 2-(2-hydroxyethoxy)carbonyl- (IIIb), 2-carboxy- (IVb) and 2-ethoxycarbonyl-3-(*p*-chlorophenyl)-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (Vb).

An attempted decarboxylation of IVa with hydrobromic acid failed to give desired compound, but with copper powder in quinoline afforded 3-phenyl-5-hydroxycyclohepta-[*b*]pyrrol-6(1*H*)-one (VIa). A similar decarboxylation of IVb afforded 3-(*p*-chlorophenyl)-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (VIb).

---

*1 Part IX. Y. Sato: Ann. Rept. Takamine Lab., **15** (1963)

*2 Nishi-shinagawa, Shinagawa-ku, Tokyo (佐藤裕信).

1) Part IV. G. Sunagawa, Y. Sato: Yakugaku Zasshi, **82**, 414 (1962).

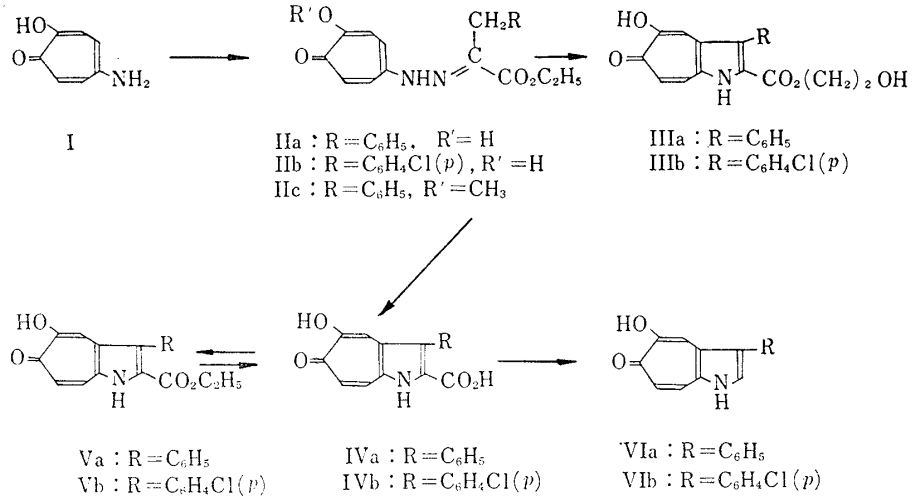


Chart 1.

Next, in order to investigate their electrophilic substitution, the nitration of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives was carried out, which is fundamentally important. Since VIa did not possess a substituent at the 2-position and it was susceptible to resinification during nitration, VII whose cyclohepta[*b*]pyrrolon ring was assumed to be stabler being in ethyl indole-2-carboxylate was nitrated to yield mononitro compound, which gave a positive ferric chloride reaction, and showed the characteristic ultraviolet spectrum of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivative, as shown in Fig. 1.

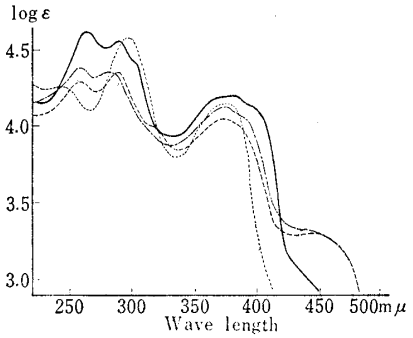


Fig. 1. Ultraviolet Absorption Spectra of 5-Hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one Derivatives (in EtOH)

——— Va - - - - - - VIIIa
..... VIa —·—·— VIIIb

As regards its infrared spectrum, absorption bands due to nitro group were observed at 1543 and 1376 cm^{-1}. It had been known that mononitration of tropolone derivatives having a substituent in the 5-position give 3-nitrotropolone derivatives.[2] Therefore, if the nitration takes place similarly in tropolone ring of VII, the above-mentioned mononitro compound (VIIIa) is assumed to be either 4- or 7-nitro-2-ethoxycarbonyl-3-methyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one. Analogously, the nitration product (VIIIb) of Va is assumed to be either 4- or 7-nitro-2-ethoxycarbonyl-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one, and catalytic reduction of this compound afforded the corresponding amino compound after the absorption of 3 molar equivalents of hydrogen.

When VIIIb was hydrolysed with 10% aqueous sodium hydroxide, orange brown needles, m.p. over 300° were obtained. Judging from the hydrolysis of Va to IVa by alkali, the author expected that the product would be the corresponding carboxylic acid. However, the product showed ultravilet absorption maxima bands only at 244 and 312

2) T. Nozoe, T. Mukai, M. Kunori, T. Muroi, K. Matsui : Sci. Repts. Tohoku Univ. I, 35, 242 (1951).

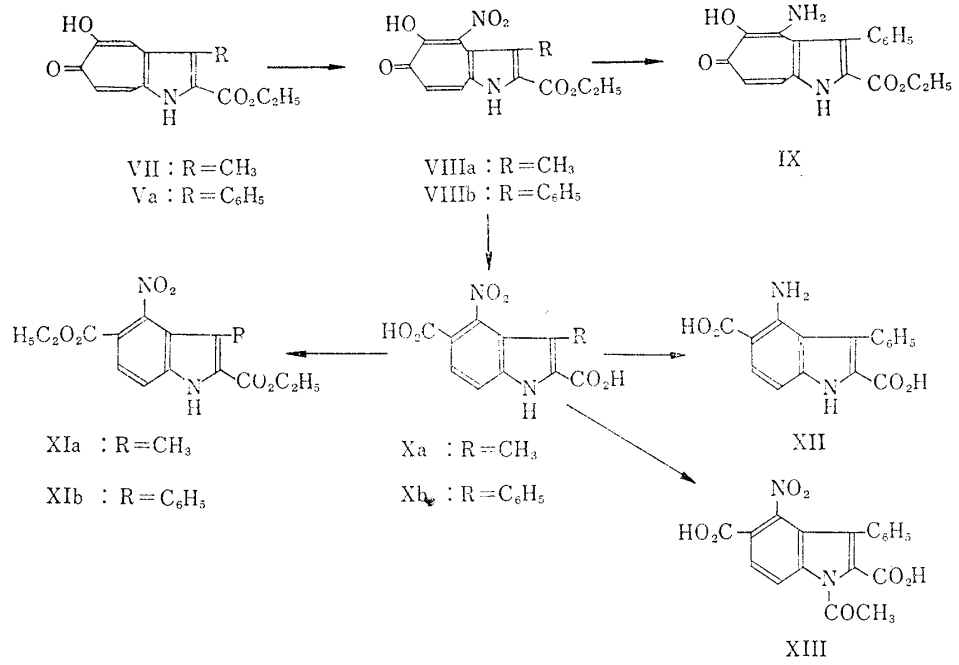


Chart 2.

mμ, as shown in Fig. 2, and gave negative ferric chloride reaction. Furthermore, it was interesting to note that the same product was obtained, when VIIIb was allowed to stand in 10% aqueous sodium hydroxide at room temperature. Consequently, this product was conceived to be different from the expected one. Among a number of rearrangement reactions of tropolone derivatives to benzene derivatives, it had been known that tropolones having an electron-withdrawing group such as nitro group are converted into nitrobenzoic acids more easily.[2] Therefore, if the rearrangement reaction of the nitration product of Va took place analogously, above-mentioned product (Xb) was presumed to be either 4- or 6-nitro-3-phenylindole-2,5-dicarboxylic acid. The analytical values corresponded to the composition of $C_{16}H_{12}O_7N_2$. As regards the infrared spectrum, absorption bands due to ν_{OH} (hydrate), ν_{NH}, $\nu_{C=O}$ (carboxylic acid) and nitro groups were observed at 3663, 3268, 1689, 1553, and 1376 cm^{-1}. Furthermore, the author confirmed that Xb had two carboxyl and one nitro groups by the following reactions. The esterification of Xb afforded the corresponding diethyl ester, m.p. 224~225°, which showed absorption bands at 1736 and 1684 cm^{-1} comparable to those at 1706 and 1681 cm^{-1} of carbonyl groups of diethyl 3-phenylindole-2,5-dicarboxylate.[3] The reduction and acetylation of Xb afforded the corresponding amino and monoacetyl compounds, respectively. These findings supported the author's assumption concerning the structure of Xb. In a similar manner, the reaction of VIIIa with alkali afforded crystals which were esterified to form pale yellow needles, m.p. 186~187°. The compound was considered to be diethyl 3-methyl-4(or 6)-nitroindole-2,5-dicarboxylate (XIa), which showed a similar curve to that of the diethylester of Xb, in the ultraviolet spectrum as shown in Fig. 2.

As stated above, the rearrangement reaction of mononitro compounds of VII and Va to indole derivatives was reasonably suggested, and consequently their structures were established by deciding upon the structures of the indole derivatives. For this purpose, the diethylester of Xb was synthesized by Fischer indole synthesis. Phenyl pyruvic acid 4-carboxy-3-nitrophenylhydrazone (XVIa) was obtained by condensation reaction of phenylpyruvic acid with 4-hydrazino-2-nitrobenzoic acid (XVa) which was prepared by

3) G.K. Hughes, F. Lions, *et al.*: J. Proc. Roy. Soc. N.S. Wales, **71**, 475 (1938) (C.A. **33**, 588 (1939)).

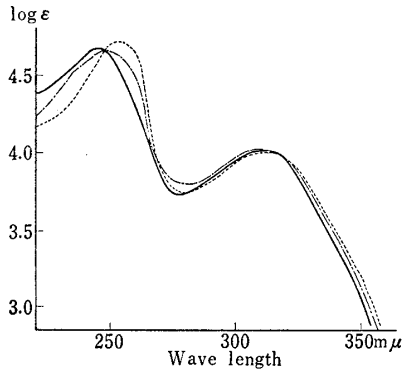


Fig. 2. Ultraviolet Absorption Spectra of 4-Nitroindole-2,5-dicarboxylic Acid Derivatives (in EtOH)

——— Xb
····· XIa
– – – – XIb

diazotization followed by reduction of 4-amino-2-nitrobenzoic acid (XIV).[4] Cyclization of the hydrazone (XVIa) with concentrated sulfuric acid in ethanol gave pale yellow needles, m.p. 224~225° and pale yellow needles, m.p. 204~205° which were established, respectively to be diethyl 4-nitro- (XIb) and diethyl 6-nitro-3-phenylindole-2,5-dicarboxylate (XVIIIa) by the following manner. On the other hand, the infrared spectrum of the compound, m.p. 224~225° was identical to that of the diethyl ester of Xb, but the position of its nitro group still remained undetermined.

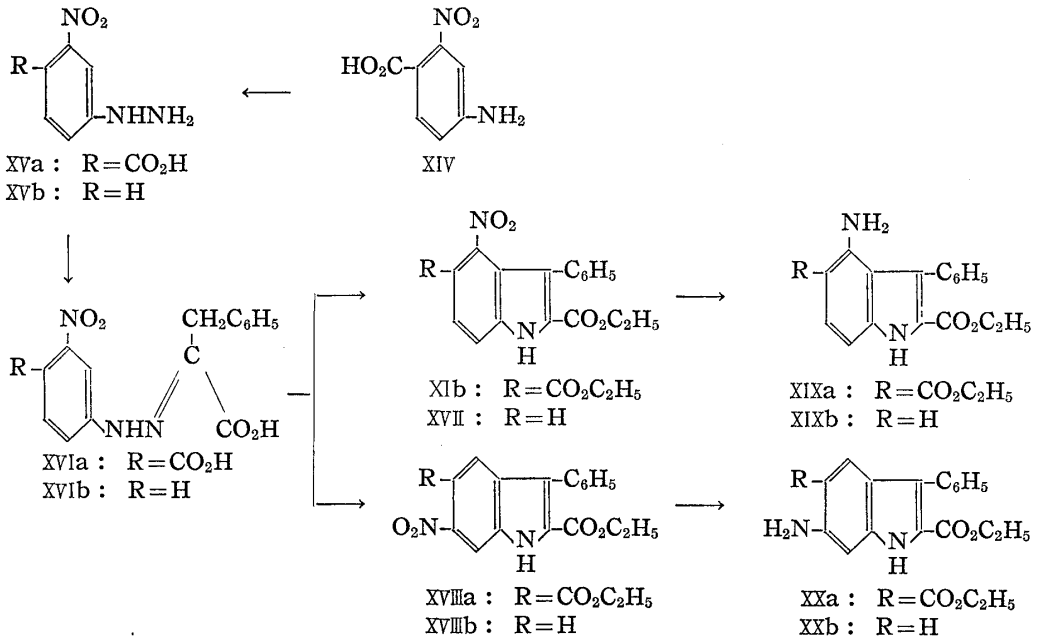


Chart 3.

First, in order to determine the positions of the nitro groups of the above-mentioned cyclization products by means of infrared spectra, the author attempted to synthesize ethyl 4-nitro- (XVII) and ethyl 6-nitro-3-phenylindole-2-carboxylate (XVIIIb) for comparison. The condensation of phenylpyruvic acid and 3-nitrophenylhydrazine afforded phenylpyruvic acid 3-nitrophenylhydrazone (XVIb), which was cyclized with concentrated sulfuric acid in ethanol to ethyl 4(or 6)-nitro-3-phenylindole-2-carboxylate, m.p. 176~177°, and its isomer, m.p. 197~198°.

Then, out-of-plane deformation vibrations of amino indole derivatives obtained from the nitroindole derivatives were examined, because nitro group substitution has been

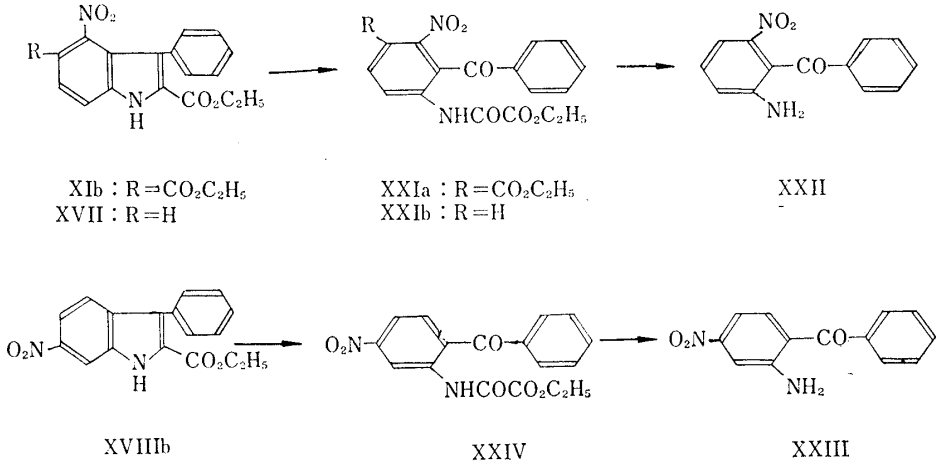
4) M. T. Bogert, A. H. Kropff : J. Am. Chem. Soc., **31**, 841 (1909).

shown to shift the vibration out of the expected range.[5] The results, as shown in Table I, suggested that the compounds, m.p. 224~225° and m.p. 204~205° obtained by cyclization of XVIa were XIb and XVIIIa, respectively, while compounds, m.p. 176~177° and m.p. 197~198° were ethyl 4-nitro- (XVII) and ethyl 6-nitro-3-phenylindole-2-carboxylate (XVIIIb), respectively.

Table I. Out-of-plane Deformation Vibrations of Aminoindoles (in Nujol)

Compound	One isolated hydrogen atom (cm^{-1})	Two adjacent hydrogen atoms (cm^{-1})
4-Amino-3-phenylindole-2,5-dicarboxylic acid (XII)	—	806
Diethyl 4-amino-3-phenylindole-2,5-dicarboxylate (XIXa)	—	803
Diethyl 6-amino-3-phenylindole-2,5-dicarboxylate (XXa)	820	—
Ethyl 4-amino-3-phenylindole-2-carboxylate (XIXb)	—	—
Ethyl 6-amino-3-phenylindole-2-carboxylate (XXb)	830	807

Furthermore, the structures deduced by the investigation of their infrared spectra were further confirmed by following reactions. Oxidation of XIb with chromic anhydride afforded colorless prisms, m.p. 123~124°. The compound was established to be ethyl 3-benzoyl-4-ethoxylamino-2-nitrobenzoate (XXIa) by hydrolysis and decarboxylation to 2-amino-6-nitrobenzophenone (XXII) which had been obtained by Schofield, *et al.*[6] Thus, product XIb was shown to be diethyl 4-nitro-3-phenylindole-2,5-dicarboxylate. In a similar



XIb : R=$CO_2C_2H_5$
XVII : R=H

XXIa : R=$CO_2C_2H_5$
XXIb : R=H

XXII

XVIIIb

XXIV

XXIII

Chart 4.

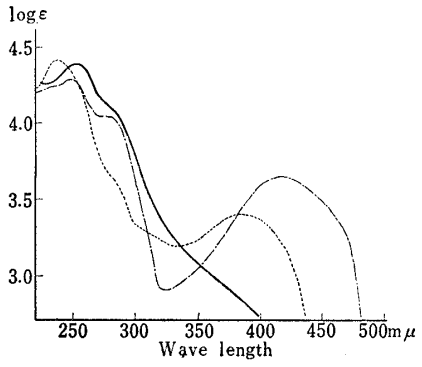


Fig. 3. Ultraviolet Absorption Spectra of Benzophenone Derivatives (in EtOH)

——— XXIa
····· XXII
– – – – XXIII

5) L. J. Bellamy : "The Infra-red Spectra of Complex molecules" (1958). John Wiley & Son, Inc., New York.
6) K. Schofield, R. S. Theobald : J. Chem. Soc., **1950**, 1505.

manner, XVII and XVIIIb were established, respectively to be ethyl 4-nitro- and ethyl 6-nitro-3-phenylindole-2-carboxylate by successive oxidation and hydrolysis to XXII and 2-amino-4-nitrobenzophenone (XXIII).

Consequently, it was confirmed that Xb was 4-nitro-3-phenylindole-2,5-dicarboxylic acid and VIIIb was 2-ethoxycarbonyl-4-nitro-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one. Hence, it could be recognized that XIa was diethyl-3methyl-4-nitroindole-2, 5-dicarboxylate and VIIIa was 2-ethoxycarbonyl-3-methyl-4-nitro-5-hydroxycyclohepta[*b*] pyrrol-6(1*H*)-one. Furthermore, the above-mentioned reduction product of VIIIb was established to be 4-amino-2-ethoxycarbonyl-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (XI), which showed the out-of-plane deformation vibration ascribable to two adjacent troponoid hydrogen atoms at 830 cm^{-1}.[7]

From the hitherto-stated results, it was clarified that 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives were nitrated in the 4-position and their nitration products were rearranged easily to the indole derivatives. Regarding the mechanism of this interesting rearrangement reaction appeared that the reaction underwent through benzilic acid rearrangement *via* their tautomeric structures as follows :

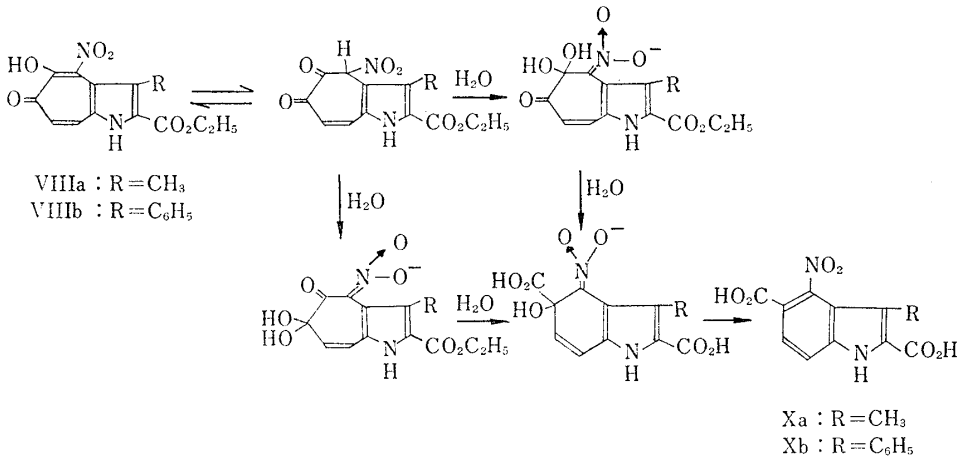


Chart 5.

Experimental

Ethyl Phenylpyruvate 5-Tropolonylhydrazone (IIa)——To a solution of 1 g. of I in 7.5 ml. of H_2O and 7.5 ml. of dioxane, 1.2 ml. of conc. H_2SO_4, a solution of 800 mg. of $NaNO_2$ in 5 ml. of H_2O was added dropwise at −5~0°. The diazonium sulfate solution was added dropwise to a mixture of 1.62 g. of ethyl 2-benzylacetoacetate, 2.2 g. of NaOH, 50 ml. of EtOH and 50 ml. of H_2O at −8~−2°. After stirring the mixture for 2 hr., it was adjusted to pH 4 and extracted with $CHCl_3$. The extract was evaporated and the solid residue was recrystallized from 70% EtOH to give 622 mg. of yellow prisms, m.p. 174~175°. *Anal.* Calcd. for $C_{18}H_{18}O_4N_2$: C, 66.24; H, 5.56; N, 8.58. Found : C, 66.52; H, 5.62; N, 8.53. UV λ_{max}^{EtOH} mμ (log ε) : 226 (4.42), 283 (3.97), 384 (4.55). IR ν_{max}^{Nujol} 867 cm^{-1}(troponoid adjacent 2H).

Ethyl (*p*-Chlorophenyl)pyruvate 5-Tropolonylhydrazone (IIb)——Hydrazone (IIb) was prepared from I and ethyl 2-*p*-chlorobenzylacetoacetate by the similar manner as in the case of IIa. The product was recrystallized from MeOH to give yellow scales, m.p. 176~177°. *Anal.* Calcd. for $C_{18}H_{17}O_4N_2Cl$: C, 59.92; H, 4.75; N, 7.76. Found : C, 59.53; H, 4.67; N, 7.71. UV λ_{max}^{EtOH} mμ (log ε) : 225 (4.56), 285 (4.07), 382 (4.59).

Ethyl Phenylpyruvate 2-Methoxy-5-tropolonylhydrazone(IIc)——A solution of excess of CH_2N_2 in Et_2O was added to 600 mg. of IIa and the mixture was allowed to stand over night. The solid separated was recrystallized from dioxane to give 380 mg. of yellow crystals, m.p. 203~204°. *Anal.* Calcd. for

7) Y. Kitahara : Sci. Repts. Tohoku Univ. I, **39**, 275 (1956); Y. Ikegami : "Kagaku no Ryoiki Extra No. 8" p. 79 (1959).

$C_{19}H_{20}O_4N_2$: C, 67.04; H, 5.92; N, 8.23. Found : C, 66.89; H, 6.21; N, 8.17. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.36), 281 (4.02), 376 (4.50).

2-(2-Hydroxyethoxy)carbonyl-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (IIIa)——A mixture of 260 mg. of IIa, 0.4 ml. of conc. H_2SO_4 and 4 ml. of ethylene glycol was heated at 190° for 40 min., and then poured into ice-water and adjusted to pH 4 with 10% NaOH. The solid (200 mg.) separated was collected by filtration. The analytical sample was recrystallized from 80% MeOH to give yellow crystals, m.p. 257°. *Anal.* Calcd. for $C_{18}H_{15}O_5N$: C, 66.45; H, 4.65; N, 4.31. Found : C, 66.04; H, 4.62; N, 4.54. UV λ_{max}^{EtOH} mμ (log ε) : 263 (4.45), 292 (4.43), 304 (4.34) (shoulder), 380 (4.14), 400 (4.00) (shoulder).

2-(2-Hydroxyethoxy)carbonyl-3-(*p*-chlorophenyl)-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (IIIb)——Preparation of IIIb from IIb was carried out by the similar manner as in the case of IIIa. The product was recrystallized from EtOH to give orange yellow crystals, m.p. 260°(decomp.), but the further purification was difficult.

2-Carboxy-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (IVa)——A mixture of 500 mg. of IIa and 10 ml. of 2*N* aq. EtOH-KOH was refluxed for 1 hr. and adjusted to pH 4 with 10% HCl. The solid (200 mg.) separated was recrystallized from MeOH to give pale yellow needles, m.p. 290°(decomp.). *Anal.* Calcd. for $C_{16}H_{11}O_4N$: C, 68.32; H, 3.94; N, 4.98. Found : C, 68.06; H, 4.21; N, 5.31. UV λ_{max}^{EtOH} mμ (log ε) : 261 (4.43), 292 (4.46), 303 (4.35) (shoulder), 380 (4.15).

The material was obtained also by hydrolysis of 2-ethoxycarbonyl-3-phenyl-5-hydroxycyclohepta-[*b*]pyrrol-6(1*H*)-one (Va).

2-Carboxy-3-(*p*-chlorophenyl)-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (IVb)——The similar treatment adopted for IVa was applied to IIIb, and the product was recrystallized from MeOH to give pale yellow needles, m.p. 285°(decomp.). *Anal.* Calcd. for $C_{16}H_{10}O_4NCl$: C, 60.86; H, 3.19; N, 4.43. Found: C, 60.73; H, 3.45; N, 4.83. UV λ_{max}^{EtOH} mμ (log ε) : 262.5 (4.55), 291 (4.56), 379 (4.23).

2-Ethoxycarbonyl-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1-*H*)-one (Va)——A mixture of 100 mg. of IVa, 5 ml. of abs. EtOH and 0.5 ml. of conc. H_2SO_4 was refluxed for 6 hr., poured into ice-water and then adjusted to pH 7 with 10% NaOH. The solid (80 mg.) separated was recrystallized from 70% EtOH to give yellowish brown needles, m.p. 234~235°. *Anal.* Calcd. for $C_{18}H_{15}O_4N$: C, 69.89; H, 4.89; N, 4.53. Found : C, 69.52; H, 4.72; N, 4.74. UV λ_{max}^{EtOH} mμ (log ε) : 263 (4.61), 291 (4.45), 303 (4.40), 380 (4.21), 400 (4.11).

2-Ethoxycarbonyl-3-(*p*-chlorophenyl)-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (Vb)——The similar treatment adopted for Va was applied to IVb, and the product was recrystallized from 50% EtOH to give yellow needles, m.p. 234~235°. *Anal.* Calcd. for $C_{18}H_{14}O_4NCl$: C, 62.89; H, 4.11; N, 4.07. Found: C, 62.93; H, 4.14; N, 4.24. UV λ_{max}^{EtOH} mμ (log ε) : 264 (4.55), 283 (4.47) (shoulder), 302 (4.31) (shoulder), 376 (4.14), 396 (4.06) (shoulder).

3-Phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (VIa)——A mixture of 900 mg. of IVa and 150 mg. of Cu powder in 9 ml. of quinoline was heated and maintained at 230~235° for 1 hr. The Cu powder was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH and adjusted to pH 3 with 10% HCl. The solid separated was recrystallized from 80% MeOH to give 130 mg. of yellowish brown needles, m.p. 236~237°. *Anal.* Calcd. for $C_{15}H_{11}O_2N$: C, 75.93; H, 4.67; N, 5.90. Found : C, 75.65; H, 4.76; N, 6.12. UV λ_{max}^{EtOH} mμ (log ε) : 243 (4.25), 295 (4.57), 376 (4.10).

3-(*p*-Chlorophenyl)-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (VIb)——The similar treatment adopted for VIa was applied to IVb, and the product was recrystallized from dimethylformamide-water mixture to give brown crystals, m.p. 310°(decomp.). *Anal.* Calcd. for $C_{15}H_{10}O_2NCl$: C, 66.31; H, 3.71; N, 5.16; Cl, 13.05. Found : C, 66.37; H, 3.89; N, 4.96; Cl, 12.72.

2-Ethoxycarbonyl-3-methyl-4-nitro-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (VIIIa)——To a solution of 1 g. of VII in 100 ml. of AcOH, a mixture of 0.7 ml. of conc. HNO_3(sp. gr. 1.50) and 5 ml. of AcOH was added dropwise at about 30°. After stirring the mixture at room temperature for 2.5 hr., 400 ml. of water was added and the mixture was allowed to stand over night. The brown crystals, m.p. 220° (decomp.) separated were collected and washed with H_2O and EtOH. Yield, 413 mg. The material gave positive $FeCl_3$ reaction. *Anal.* Calcd. for $C_{13}H_{12}O_6N_2$: N, 9.59. Found : N, 9.85. UV λ_{max}^{EtOH} mμ (log ε): 257 (4.31), 287 (4.41), 371 (4.18), 435 (3.30) (shoulder). IR ν_{max}^{Nujol} cm^{-1} : 1543, 1376 (NO_2).

2-Ethoxycarbonyl-4-nitro-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (VIIIb)——Preparation from Va was carried out by the similar manner as in the case of VIIIa. *Anal.* Calcd. for $C_{18}H_{14}O_6N_2$: C, 61.01; H, 3.98; N, 7.91. Found : C, 61.83; H, 4.15; N, 7.88. UV λ_{max}^{EtOH} mμ (log ε) : 258 (4.38), 283 (4.36), 372 (4.12), 435 (3.34) (shoulder). IR ν_{max}^{Nujol} cm^{-1} : 1681 (ester C=O), 1538, 1370 (NO_2).

4-Amino-2-ethoxycarbonyl-3-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (IX)——Four hundred and thirty milligrams of VIIIb was catalytically reduced in 50 ml. of EtOH over 35 mg. of PtO_2. After 80 ml. of H_2 was absorbed, the catalyst was removed by filtration. The filtrate was evaporated and the residue was recrystallized from MeOH to give yellowish brown crystals, m.p. 250°. Yield, 40 mg. *Anal.* Calcd.

for $C_{18}H_{16}O_4N_2$: C, 66.67; H, 4.97; N, 8.64. Found : C, 66.96; H, 5.12; N, 8.07. UV λ_{max}^{EtOH} mμ (log ε): 289.5 (4.64), 300 (4.80), 340 (4.94), 400 (3.80). IR : ν_{max}^{Nujol} 830 cm^{-1}(troponoid adjacent 2H).

Rearrangement Reaction of 2-Ethoxycarbonyl-3-methyl-4-nitro-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (VIIIa)——A mixture of 413 mg. of VIIIa and 15 ml. of 10% NaOH was allowed to stand at room temperature for 24 hr., and adjusted to pH 3 with 10% HCl. The solid separated was collected by filtration and dried. The solid was heated with 0.2 ml. of conc. H_2SO_4 in 2 ml. of abs. EtOH for 6 hr. and the mixture was neutralized with 10% NaOH. The solid separated was recrystallized from H_2O-EtOH to give diethyl 3-methyl-4-nitroindole-2,5-dicarboxylate (XIa) as pale yellow needles, m.p. 186 ~187°. *Anal.* Calcd. for $C_{15}H_{16}O_5N_2$: C, 56.25; H, 5.04; N, 8.75. Found : C, 56.32; H, 5.22; N, 9.06. UV λ_{max}^{EtOH} mμ (log ε) : 251 (4.72), 313 (3.99).

Rearrangement Reaction of 2-Ethoxycarbonyl-4-nitro-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (VIIIb) to 4-Nitro-3-phenylindole-2,5-dicarboxylic Acid (Xb)——A mixture of 200 mg. of VIIIb and 15 ml. of 10% NaOH was heated on water bath for 3 hr. and adjusted to pH 3 with 10% HCl. The solid (80 mg.) separated was recrystallized from 40% EtOH to give orange brown needles, m.p. >300°. The material gave negative $FeCl_3$ reaction. *Anal.* Calcd. for $C_{16}H_{12}O_7N_2 \cdot H_2O$: C, 55.82; H, 3.51; N, 8.14. Found : C, 55. 38; H, 3.61; N, 7.94. UV λ_{max}^{EtOH} mμ (log ε) : 224 (4.67), 312 (4.01). IR ν_{max}^{Nujol} cm^{-1} : 3663, 3268, 1689, 1553, 1376. When a mixture of 280 mg. of VIIIb and 25 ml. of 10% NaOH was allowed to stand at room temperature for 22 hr. Yield, 130 mg.

4-Amino-3-phenylindole-2,5-dicarboxylic Acid (XII)——A suspension of 800 mg. of Xb in 25 ml. of EtOH and 10 ml. of *N* NaOH was heated at 50° and treated with a solution of 2.5 g. of sodium hydrosulfite in 12 ml. of 0.5*N* NaOH. After shaking the mixture for 10 min., inorganic precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and the solid separated was recrystallized from H_2O-EtOH to give pale brown crystals, m.p. 205~206° (decomp.). *Anal.* Calcd. for $C_{16}H_{12}O_4N_2$: N, 9.46. Found : N, 9.47.

1-Acetyl-4-nitro-3-phenylindole-2,5-dicarboxylic Acid (XIII)——To a solution of 430 mg. of Xb and 150 mg. of KOH in 5 ml. of water, 0.1 ml. of AcCl was added and the mixture was shaken for 2 hr. The solid separated was recrystallized from H_2O-EtOH to give yellow crystals, m.p. 300°. *Anal.* Calcd. for $C_{18}H_{12}O_7N_2$: C, 58.70; H, 3.28; N, 7.61. Found : C, 58.83; H, 3.30; N, 8.23.

Diethyl 4-Nitro-3-phenylindole-2,5-dicarboxylate (XIb). i) Esterification of 4-Nitro-3-phenylindole-2,5-dicarboxylic Acid (Xb)——A mixture of 290 mg. of Xb, 10 ml. of abs. EtOH and lml. of conc. H_2SO_4 was refluxed for 6 hr., then poured into ice-water and neutralized with 10% NaOH. The solid (290 mg.) separated was recrystallized from EtOH to give pale yellow needles, m.p. 224~225°. *Anal.* Calcd. for $C_{20}H_{18}O_6N_2$: C, 62.82; H, 4.75; N, 7.33. Found : C, 62.75; H, 4.79; N, 7.65. UV λ_{max}^{EtOH} mμ (log ε): 248 (4.65), 313 (4.02). IR ν_{max}^{Nujol} cm^{-1} : 1736, 1684 (ester C=O), 1550, 1370 (NO_2).

ii) Fischer Synthesis of Phenylpyruvic Acid 4-Carboxy-3-nitrophenylhydrazone (XVIa)——A mixture of 1.8 g. of XVIa, 2 g. of conc. H_2SO_4 and 20 ml. of EtOH was refluxed for 5.5 hr., poured into ice-water and neutralized with 10% NaOH. The solid separated was recrystallized from EtOH to give 800 mg. of yellow crystals, m.p. 186~224°. Repeated fractional recrystallization of the crystals gave pale yellow needles, m.p. 224~225°, whose IR was identical with that of XIb obtained in (i) and whose melting point did not depress upon admixture. *Anal.* Calcd. for $C_{20}H_{18}O_6N_2$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.78; H, 4.75; N, 7.08.

Diethyl 6-Nitro-3-phenylindole-2,5-dicarboxylate (XVIIIa)——The alcoholic mother liquor from recrystallization of the crude isomer (XIb) was concentrated under reduced pressure. The solid separated was repeatedly recrystallized from 70% EtOH to give pale yellow needles, m.p. 204~205°. *Anal.* Calcd. for $C_{20}H_{18}O_6N_2$: C, 62.82; H, 4.75; N, 7.33. Found : C, 62.94; H, 4.59; N, 7.20. UV λ_{max}^{EtOH} mμ (log ε) :248 (4.47), 310 (4.03) (shoulder). IR ν_{max}^{Nujol} cm^{-1} : 1727, 1695 (ester C=O), 1538, 1370 (NO_2).

4-Hydrazino-2-nitrobenzoic Acid (XVa)——To a suspension of 7.6 g. of XIV in 12 ml. each of conc. HCl and H_2O, a solution of 3.5 g. of $NaNO_2$ in 6 ml. of H_2O and then 30% NaOH was added dropwise until pH reached to 3 at −2~0°. Insoluble crystals were removed by filtration and the filtrate was added to a solution of 20 g. of $(NH_4)_2SO_3 \cdot 3H_2O$ in 4.7 ml. of conc. aq. NH_3 and 23 ml. of H_2O at −2~0°. After stirring the mixture for 30 min., 40 ml. of conc. HCl was added and the mixture allowed to stand over night. The solid separated was heated in 12 ml. of conc. HCl and the separated solid was dissolved in hot H_2O. The solution was filtered while hot and the filtrate was adjusted to pH 3 with a saturated solution of AcONa. The crystals separated were recrystallized from 60% MeOH to give 3.7 g. of yellowish brown needles, m.p. 190°(decomp.). *Anal.* Calcd for $C_7H_7O_4N_3 \cdot H_2O$: C, 39.07; H, 4.22; N, 19.53. Found : C, 39.32; H, 4.16; N, 19.43.

Phenylpyruvic Acid 4-Carboxy-3-nitrophenylhydrazone (XVIa)——A mixture of 1.5 g. of XVa, 1.25 g. of phenylpyruvic acid, 70 ml. of MeOH and 10 ml. of EtOH was refluxed for 15 min. After evaporation of the reaction mixture, small amount of water was added and the solid (2.2 g.) separated was recrystallized from H_2O-EtOH to give orange yellow crystals, m.p. 218°(decomp.). *Anal.* Calcd. for $C_{16}H_{13}O_6N_3$: C, 55.98; H, 3.82; N, 12.24. Found : C, 55.99; H, 3.73; N, 12.27. UV : λ_{max}^{EtOH} 333 mμ (log ε, 4.47).

Phenylpyruvic Acid 3-Nitrophenylhydrazone (XVIb)——Preparation of XVIb from XVIb·HCl and phenylpyruvic acid was carried out by the similar manner as in the case of XVIa. The product was recrystallized from 60% EtOH to give yellow prisms, m.p. 160~161° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}O_4N_3$: C, 60.19; H, 4.38; N, 14.04. Found: C, 60.13; H, 4.47; N, 13.77. UV: λ_{max}^{EtOH} 310 mμ (log ε, 4.39).

Ethyl 6-Nitro-3-phenylindole-2-carboxylate (XVIIIa)——A mixture of 10 g. of XVIb, 10 g. of conc. H_2SO_4 and 90 ml. of EtOH was refluxed for 5 hr., neutralized with 10% NaOH and the solid separated was fractionally recrystallized from 80% EtOH to give 1.7 g. of pale yellow scales, m.p. 197~198°. *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55; N, 9.05. Found: C, 65.90; H, 4.47; N, 9.05. UV λ_{max}^{EtOH} mμ (log ε): 224 (4.31), 283 (4.26), 319 (4.19), 370 (3.80) (shoulder).

Ethyl 4-Nitro-3-phenylindole-2-carboxylate (XVII)——The mother liquor from the recrystallization of the crude isomer (XVIIIb) was concentrated. The solid residue was recrystallized from benzene to give 1.5 g. of yellow prisms, m.p. 176~177°. *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55; N, 9.08. Found: C, 65.77; H, 4.53; N, 9.07. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.60), 317 (3.94).

Diethyl 4-Amino-(XIXa) and Diethyl 6-Amino-3-phenylindole-2,5-dicarboxylate (XXa) and Ethyl 4-Amino-(XIXb) and Ethyl 6-Amino-3-phenylindole-2-carboxylate (XIXb)——Reductions of XIb, XVIIIa, XVII and XVIIIb were carried out, using the same method as described for XII. The aminoindole derivatives synthesized are listed in Table II.

Table II.

Compound No.	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	UV λ_{max}^{EtOH} mμ (log ε)
XIXa	210~211	$C_{20}H_{20}O_4N_2$	68.17	5.72	7.95	67.55	5.48	8.14	224(4.43), 274(4.66), 329(3.94)
XXa	189~190	$C_{20}H_{20}O_4N_2$	68.17	5.72	7.95	67.76	5.39	8.06	254(4.57), 271(4.59), 370(3.93)
XIXb	159~160	$C_{17}H_{16}O_6N_2$	72.84	5.75	9.99	72.48	5.56	10.30	249(4.43), 298(4.09), 344(4.86)
XXb	145~146	$C_{17}H_{16}O_6N_2$	72.84	5.75	9.99	72.34	5.75	9.61	223(4.41), 254(4.39), 330(4.26)

Ethyl 3-Benzoyl-4-ethoxalylamino-2-nitrobenzoate (XXIa)——A suspension of 1 g. of XIb in 50 ml. of AcOH was treated with 1 g. of CrO_3 in 2 ml. of H_2O. After 48 hr. at room temperature, the mixture was diluted with 100 ml. of H_2O. The crystals separated were recrystallized from 50% MeOH to give colorless prisms, m.p. 123~124°. Yield, 705 mg. *Anal.* Calcd. for $C_{20}H_{18}O_8N_2$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.09; H, 4.39; N, 6.68. UV: λ_{max}^{EtOH} 250 mμ (log ε, 4.39).

2-Amino-6-nitrobenzophenone (XXII) i) Reaction of Ethyl 3-Benzoyl-4-ethoxalylamino-2-nitrobenzoate (XXIa) with Hydrobromic Acid——A mixture of 200 mg. of XXIa and 2 ml. of 48% HBr was refluxed for 6 hr., adjusted to pH 3 with 10% NaOH. The solid separated was recrystallized from 85% EtOH to give 30 mg. of yellow scales, m.p. 172~173°, showing no depression in melting point upon admixture with authentic sample. The IR and UV spectra of the material were identical with those of the authentic sample. *Anal.* Calcd. for $C_{13}H_{10}O_3N_2$: C, 64.46; H, 4.16; N, 11.57. Found: C, 63.84; H, 3.83; N, 11.56. UV λ_{max}^{EtOH} mμ (log ε): 237 (4.42), 384 (3.42). Benzoylation of this material afforded 2-benzoylamino-6-nitrobenzophenone.

ii) Reaction of 2-Ethoxalylamino-6-nitrobenzophenone (XXIb) with Hydrobromic Acid——A mixture of 247 mg. of XXIb and 3 ml. of 48% HBr was refluxed for 5.5 hr., then neutralized with 10% NaOH and the solid separated was recrystallized from 80% EtOH to give yellow scales, m.p. 172~173°, whose IR spectrum was identical with that of the authentic sample. *Anal.* Calcd. for $C_{13}H_{10}O_3N_2$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.26; H, 4.19; N, 11.48.

2-Ethoxalylamino-6-nitrobenzophenone (XXIb)——A suspension of 2 g. of XVII in 60 ml. of AcOH was treated with 2 g. of CrO_3 in 2 ml. of H_2O. After leaving 3 days at room temperature, the mixture was diluted with 150 ml. of H_2O. The crystals separated were recrystallized from MeOH to give 347 mg. of colorless needles, m.p. 115°. *Anal.* Calcd. for $C_{17}H_{14}O_6N_2$: C, 59.65; H, 4.12; N, 8.18. Found: C, 59.76; H, 4.15; N, 8.21. UV λ_{max}^{EtOH} 249 mμ (log ε, 4.40).

2-Ethoxalylamino-4-nitrobenzophenone (XXIV)——The similar treatment adopted for XXIb was applied to 400 mg. of XVIIIb, and the product was recrystallized from MeOH to give 470 mg. of colorless scales, m.p. 150~151°. *Anal.* Calcd. for $C_{17}H_{14}O_6N_2$: C, 59.65; H, 4.12; N, 8.18. Found: C, 59.12; H, 4.07; N, 8.27. UV λ_{max}^{EtOH} mμ (log ε): 265 (4.35), 340 (4.14).

2-Amino-4-nitrobenzophenone (XXIII)——The similar treatment adopted for XXII was applied to 400 mg. of XXIV, and the product was recrystallized from 90% EtOH to give 185 mg. of yellow scales, m.p. 180~181° (literature 172~173°) whose melting point was not depressed upon admixture with the authentic sample, and whose IR and UV spectra were identical with those of the authentic sample. *Anal.* Calcd. for $C_{13}H_{10}O_3N_2$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.29; H, 4.08; N, 11.58. UV λ_{max}^{EtOH} mμ (log ε): 250 (4.30), 280 (4.07), 417 (3.67).

The author is deeply grateful to Prof. Tetsuo Nozoe, Prof. Yoshio Kitahara and Prof. Shuichi Seto of Tohoku University, Mr. Munetoshi Matsui, Director of this Laboratory and Dr. Genshun Sunagawa, Assistant Director of this Laboratory, for guidance and encouragements, throughout the course of this work. The measurement of infrared and ultraviolet spectra were carried out by Messrs. N. Higosaki and H. Higuchi and T. Fujimura and Miss N. Sawamoto, and microanalyses were performed by Messrs. K. Ono and H. Nagashima and Misses Y. Saito and N. Gonda.

Summary

3-Aryl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one were synthesized by the similar manner as previously described. Nitration of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives (Ⅶ and Ⅴa) gave mononitro derivatives (Ⅷa and Ⅷb). The properties of the mononitro derivatives (Ⅷa and Ⅷb) were examined and it was discovered that Ⅷa and Ⅷb underwent rearrangement by aqueous alkali to 4-nitroindole derivatives (Xa and Xb). In order to determine the structure of the products being obtained by the rearrangement reaction, the cyclization of phenylpyruvic acid 4-carboxy-3-nitrophenylhydrazone (XIVa) was investigated. Moreover, the nitro groups of the products were proved to be in 4-potition by infrared spectra analysis and oxidative degradations. Therefore, above-mentioned mononitro derivatives were established to be 4-nitro-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives.

(Received June 1, 1963)

[Chem. Pharm. Bull. 11 (11) 1440 ~ 1445]

UDC 547.517.07

225. Yasunobu Sato : Studies on Seven-membered Ring Compounds. XI.*1 Bromination of 5-Hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one Derivatives and Synthesis of 3-(2-Aminoethyl)-2-carboxy-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one.

(*Takamine Research Laboratory, Sankyo Co., Ltd.**2)

In the preceding paper,*1 the author reported the nitration of 5-hydroxycyclohepta-[*b*]pyrrol-6(1*H*)-one derivatives to afford the corresponding 4-nitro compounds. The present paper describes bromination of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives, and synthesis of a seven-membered ring compound having a similar structure to serotonin, 3-(2-Aminoethyl)-2-carboxy-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one.

Firstly, the bromination of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives whose 2-positions were occupied by a ethoxycarbonyl group, was investigated. Treatment to 2-ethoxycarbonyl-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ib) with 1 molar equivalent of bromine in acetic acid afforded monobromo compound, which showed a similar ultraviolet absorption curve of Ib, with a characteristic bathochromic shift of bromo substituted tropolone derivatives,[1] as shown in Fig. 1. The monobromo compound was considered to be 4-bromo-2-ethoxycarbonyl-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6-(1*H*)-one (Ⅱb) whose out-of-plane deformation vibration due to two adjacent tropolone ring

---

*1 Part X. Y. Sato : This Bulletin, **11**, 1431 (1963).
*2 Nishi-shinagawa, Shinagawa-ku, Tokyo (佐藤裕信).
1) M. Tsuboi : Bull. Chem. Soc. Japan, **25**, 369 (1952).