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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.

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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.

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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

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*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).

hydrogen atoms was observed at 825 cm^{-1}.*[1,2] The monobromo derivative (IIb) was obtained by the bromination of Ib with 1 molar and 2 molar equivalent of bromine in two solvents, chloroform and acetic acid, respectively and in latter case no dibromo compound was reported.

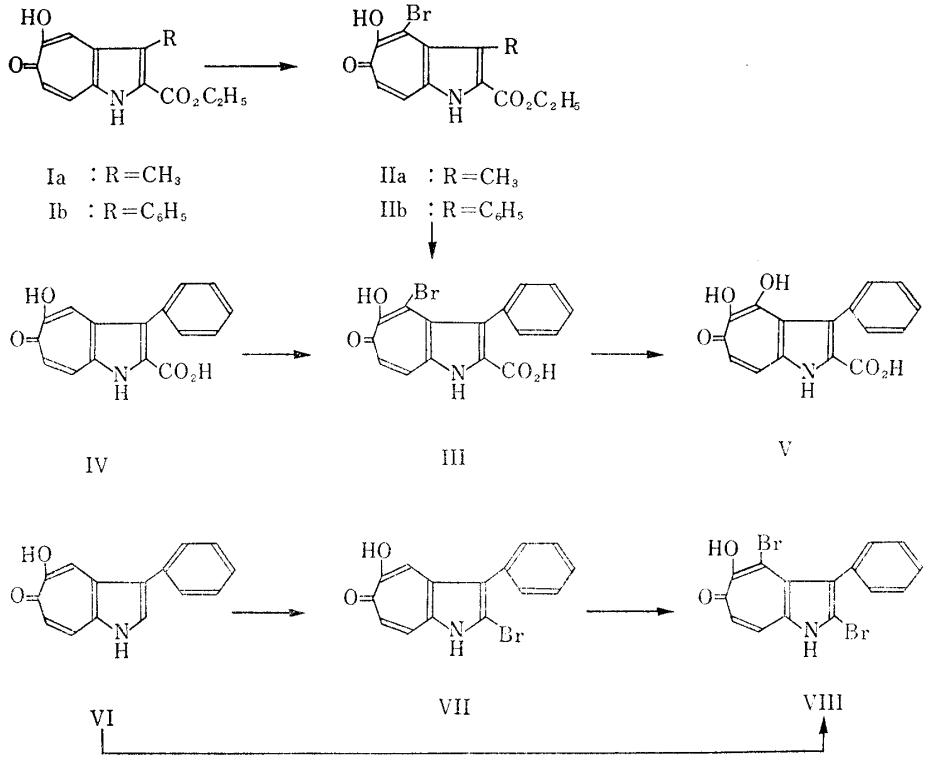

Chart 1.

A similar bromination of 2-ethoxycarbonyl-5-hydroxy-3-methylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ia) using 1 molar equivalent of bromine afforded 4-bromo-2-ethoxycarbonyl-5-hydroxy-3-methylcyclohepta[*b*]pyrrol-6(1*H*)-one (IIa).

Heating of IIb in aqueous ethanolic solution of potassium hydroxide afforded yellow crystals, m.p. 270° (decomp.), which showed characteristic ultraviolet spectrum of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivative, as shown in Fig. 1. On the other hand, it exhibited identical infrared absorption bands, that of monobromo compound obtained from 2-carboxy-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (IV). Therefore, the resulting compound was 4-bromo-2-carboxy-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (III), which proves that IIb does not undergo the rearrangement reaction with aqueous ethanolic alkali.

When III was heated in 28% aqueous ammonia, yellow needles, m.p. 280° (decomp.) were obtained. The product gave negative Beilstein reaction to suggest that substitution of amino group for bromine atom of III took place. However, it was shown to be 2-carboxy-4,5-dihydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (V), on the basis of its analytical values, $C_{16}H_{11}O_5N$. As regards its infrared spectrum, the out-of-plane deformation vibration due to two adjacent tropolone ring hydrogen atoms was observed at 848 cm^{-1}.

Next, the bromination of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivative whose 2-position was vacant, was examined. Treatment of 5-hydroxy-3-phenylcyclohepta[*b*]-

2) Y. Kitahara : Sci. Repts. Tohoku Univ. I, **39**, 275 (1956); Y. Ikegami : "Kagaku no Ryoiki, Extra No. 38" p. 79 (1959).

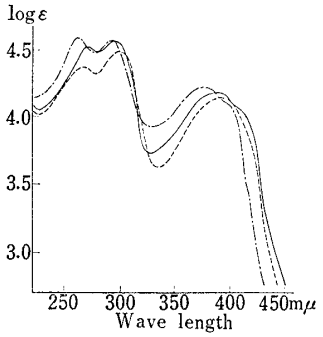

Fig. 1. Ultraviolet Absorption Spectra of 4-Bromo-2-ethoxycarbonyl-5-hydroxy-, 4-Bromo-2-carboxy-5-hydroxy- and 2-Carboxy-4,5-dihydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (in EtOH)

——— IIb
..... III
– – – – – V

pyrrol-6(1*H*)-one (VI) with 1 molar equivalent of N-bromosuccinimide in chloroform afforded monobromo compound. It did not show bathochromic shift towards longer wave lengths region in ultraviolet spectrum as shown in Fig. 2. In this case, therefore, it is considered that bromination in tropolone ring of VI did not take place. The out-of-plane deformation vibrations due to isolated and two adjacent tropolone ring hydrogen atoms and five adjacent benzene ring hydrogen atoms were observed at 880, 840, 763, and 697 cm^{-1}, respectively. Recently, it has been known that bromination of 3-methylcyclohepta[*b*]pyrrol-8(1*H*)-one, analogous to VI, takes place first in the 2-position and then 5 and 7-positions.[3] From these facts, the monobromo compound was considered to be 2-bromo-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (VII). The treatment of VII with 1 molar equivalent of bromine afforded an expected dibromo compound, which showed the characteristic bathochromic shift in ultraviolet spectrum.[1] Its infrared spectrum showed the out-of-plane deformation vibration at 826 cm^{-1} due to two adjacent tropolone ring hydrogen atoms, but the band due to isolated tropolone ring hydrogen atom did not appear. Consequently, the dibromo compound was considered to be 2,4-dibromo-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (VIII). Treatment of VI with 2 molar equivalents of bromine in acetic acid afforded also VIII.

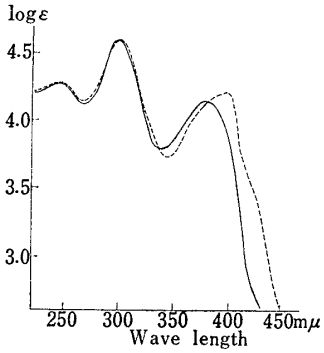

Fig. 2. Ultraviolet Absorption Spectra of 2-Bromo- and 2,4-Dibromo-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (in EtOH)

——— VII
..... VIII

From these results, it was confirmed that 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives whose 2-positions were occupied by a substituent, were brominated only in the 4-position, and one whose 2-positions were vacant were brominated in the 2-, 4-positions.

Thus, the author has discovered a new synthetic method and investigated the properties of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives, a type of seven-membered ring compound corresponding to 5-hydroxyindole, and further investigation was made on the synthesis of seven-membered ring compound analogous to serotonin, 3-(2-aminoethyl)-2-carboxy-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one hydrochloride (XI), which was the primary object of the present studies, in the following manner.

3) G. Sunagawa, N. Soma, H. Nakao, Y. Matsumoto : Yakugaku Zasshi, **81**, 1799 (1961).

Although XI may be synthesized from 2-(2-hydroxyethoxy)carbonyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one, but the yield was unsatisfactory as previously reported.[4] Hereupon an attempt was made to synthesize the 5-hydroxycycolhepta[*b*]pyrrol-6(1*H*)-one derivatives analogous to ethyl indole-3-carboxylate, indole-3-acetonitrile and 3-diethylaminomethylindole, which were used generally to synthesize indoles having a side chain in the 3-position. Ethyl 4-cyano-2-oxobutyrate (Xb), ethyl 4-diethylamino-2-oxobutyrate (Xc) and 5-phthalimido-2-oxoglutarate 5-tropolonylhydrazone (Xd), respectively as the starting materials, were prepared by the application of Japp-Klingemann reaction of 5-aminotropolone (IX) with ethyl 2-(2-cyanoethyl)-, ethyl 2-(2-diethylaminoethyl)- and ethyl 2-(3-phthalimidopropyl)acetoacetate.

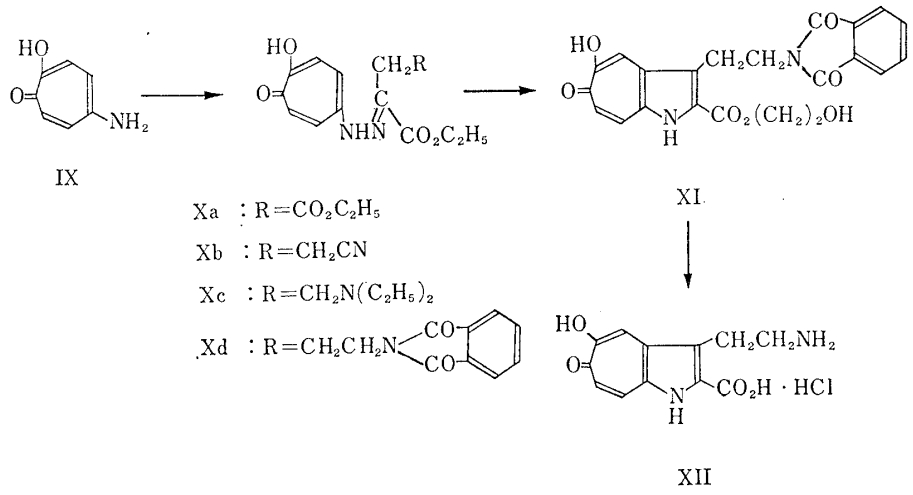

Chart 2.

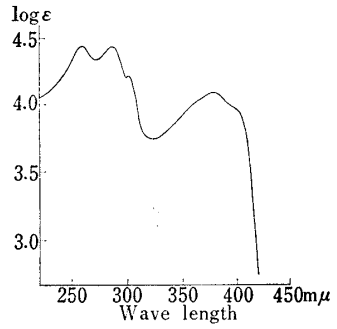

Fig. 3. Ultraviolet Absorption Spectrum of 3-(2-Aminoethyl)-2-carboxy-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one Hydrochloride (XII)

An attempted cyclization reaction of diethyl 2-oxosuccinate 5-tropolonylhydrazone (Xa),[4] Xb and Xc with concentrated sulfuric acid in ethylene glycol or polyphosphoric acid ended in failure, contrary to author's expectation. However, the cyclization reaction of Xd was accomplished by the following manner. Heating of Xd with concentrated sulfuric acid in ethylene glycol afforded yellowish brown crystals, m.p. 280° (decomp.), which showed absorption maxima bands at 259, 288, 378 mμ in the ultraviolet spectrum. Hence, cyclization seemed to have ocourred to give 2-(2-hydroxyethoxy)carbonyl-5-hydroxy-3-(2-phthalimidoethyl)cyclohepta[*b*]pyrrol-6(1*H*)-one (XI), which was subjected to hydrolysis without purification. The ultraviolet spectrum of the hydrolysis product showed the characteristic absorptions of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives, and its analytical values agreed with a composition of $C_{12}H_{17}O_6N_2Cl$. Consequently,

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

it was established to be 3-(2-aminoethyl)-2-carboxy-5-hydroxycyclohepta-[*b*]-pyrrol-6(1*H*)-one hydrochloride (XIII) dihydrate.

Experimental

4-Bromo-2-ethoxycarbonyl-5-hydroxy-3-methylcyclohepta[*b*]pyrrol-6(1*H*)-one (IIa)——To a solution of 100 mg. of Ia in 20 ml. of AcOH, 80 mg. of Br_2 was added, the mixture was allowed to stand at room temperature for 24 hr., and then refluxed for 1 hr. After cooling the mixture, the solid separated was recrystallized from AcOH to give 40 mg. of yellow scales, m.p. 290~291°(decomp.). *Anal.* Calcd. for $C_{13}H_{12}O_4NBr$: C, 47.82; H, 3.70; N, 4.29. Found : C, 47.82; H, 3.88; N, 4.30. UV λ_{max}^{EtOH} mμ (log ε) : 267 (4.35), 296 (4.59), 389 (4.20), 410 (4.03) (shoulder). IR : ν_{max}^{Nujol} 828 cm^{-1}(troponoid adjacent 2H).

4-Bromo-2-ethoxycarbonyl-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (IIb). i) Reaction of 2-Ethoxycarbonyl-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ib) with Br_2 in AcOH——To a solution of 154 mg. of Ib in 25 ml. of AcOH, 80 mg. of Br_2 in 4 ml. of AcOH was added, the mixture was allowed to stand at room temperature for 24 hr., and then refluxed for 1 hr. After cooling the mixture, the solid separated was recrystallized from AcOH to give 100 mg. of yellow crystals, m.p. 287° (decomp.). *Anal.* Calcd. for $C_{18}H_{14}O_4NBr$: C, 55.69; H, 3.64; N, 3.61; Br, 20.59. Found : C, 56.04; H, 3.60; N, 4.11; Br, 20.90. UV λ_{max}^{EtOH} mμ (log ε) : 270 (4.52), 295 (4.56), 390 (4.20), 410 (4.06) (shoulder). IR : ν_{max}^{Nujol} 825 cm^{-1}(troponoid adjacent 2H). Heating Ib with 2 molar equivalents of Br_2 in AcOH for 10 hr., afforded IIb, and dibromo compound was not obtained.

ii) Reaction of 2-Ethoxycarbonyl-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ib) with Br_2 in $CHCl_3$——A mixture of 90 mg. of Ib and 46 mg. of Br_2 in 90 ml. of $CHCl_3$ was allowed to stand at room temperature for 3 days, and the solvent evaporated to afford a solid residue which exhibited absorption maxima bands at 270, 295, 390, 410 mμ (shoulder). The solid was recrystallized from AcOH to give yellow crystals, m.p. 287°(decomp.). The IR and UV spectra were identical with those of IIb obtained in i).

4-Bromo-2-carboxy-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (III). i) Saponification of 4-Bromo-2-ethoxycarbonyl-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (IIb)——A solution of 90 mg. of IIb in 5 ml. of 2*N* aq. EtOH of KOH was refluxed for 1 hr., the reaction mixture was concentrated under reduced pressure and adjusted to pH 3. The solid separated was recrystallized from AcOH to give 80 mg. of yellow crystals, m.p. 270°(decomp.). *Anal.* Calcd. for $C_{16}H_{10}O_4NBr \cdot H_2O$: C, 50.81; H, 3.20; N, 3.70. Found : C, 50.36; H, 3.25; N, 3.98. UV λ_{max}^{EtOH} mμ (log ε) : 266 (4.38), 298 (4.51), 390 (4.16). IR : ν_{max}^{Nujol} 826 cm^{-1}(troponoid adjacent 2H).

ii) Bromination of 2-Carboxy-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (IV)——To a solution of 281 mg. of IV in 100 ml. of AcOH, 160 mg. of Br_2 was added and the similar treatment adopted for IIb was carried out. The product was recrystallized from AcOH to give yellow crystals, m.p. 270°(decomp.), whose IR and UV spectra were identical with those of III obtained in i).

2-Carboxy-4,5-dihydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (V)——A mixture of 500 mg. of III and 8 ml. of 28% aq. NH_3 was heated in sealed tube at 100° for 7 hr., adjusted to pH 3 and the solid separated was collected by filtration. The solid was heated in MeOH and a resinous material was filtered off. The filtrate was concentrated to a small volume under reduced pressure and the crystals separated were recrystallized from H_2O-EtOH to give yellow silky needles, m.p. 280°(decomp.). Yield, 25 mg. *Anal.* Calcd. for $C_{16}H_{11}O_5N$: C, 64.64; H, 3.73; N, 4.71. Found : C, 64.21; H, 4.08; N, 4.65. UV λ_{max}^{EtOH} mμ (log ε) : 260 (4.60), 291 (4.59), 377 (4.25). IR : ν_{max}^{Nujol} 848 cm^{-1}(troponoid adjacent 2H).

2-Bromo-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one(VII)——To a solution of 237 mg. of VI in 80 ml. of $CHCl_3$, 178 mg. of NBS and 5 mg. of benzoylperoxide were added and the mixture was refluxed for 2 hr. After cooling, the mixture was filtered and the filtrate was concentrated under reduced pressure. The solid residue was recrystallized from AcOH to give 210 mg. of greenish yellow crystals, m.p. 265°. *Anal.* Calcd. for $C_{15}H_{10}O_2NBr$: C, 56.98; H, 3.19; N, 4.43. Found : C, 57.23; H, 3.16; N, 4.69. UV λ_{max}^{EtOH} mμ (log ε) : 243 (4.28), 298 (4.60), 378 (4.16)) IR ν_{max}^{Nujol} cm^{-1} : 880, 840, 763, 697.

2,4-Dibromo-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (VIII). i) Bromination of 2-Bromo-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (VII)——A mixture of 290 mg. of VII and 147 mg. of Br_2 in 40 ml. of AcOH was allowed to stand at room temperature for 24 hr. and then refluxed for 1 hr. After cooling the mixture, the solid separated was recrystallized from AcOH to give yellow crystals, m.p. 296°. *Anal.* Calcd. for $C_{15}H_9O_2NBr$: C, 45.60; H, 2.29; N, 3.54. Found : C, 45.83; H, 2.34; N, 3.78. UV λ_{max}^{EtOH} mμ (log ε) : 244 (4.27), 298 (4.60), 390 (4.20), 398 (4.21), 425 (3.39) (shoulder). IR : ν_{max}^{Nujol} 826 cm^{-1}(troponoid adjacent 2H).

ii) Bromination of 5-Hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (VI)——A mixture of 71 mg. of VI and 100 mg. of Br_2 in 2 ml. of AcOH was allowed to stand at room temperature for 15 hr., and then refluxed for 1 hr. After cooling the mixture, the solid separated was recrystallized from AcOH

to give yellow crystals, m.p. 296° whose IR and UV spectra were identical with those of Ⅷ obtained in i).

Ethyl 4-Cyano-2-oxobutyrate 5-Tropolonylhydrazone (Xb)——Hydrazone (Xb) was prepared from Ⅸ and ethyl 2-(2-cyanoethyl)acetoacetate by the similar manner as described in preceding paper.[4] The product was recrystallized from MeOH to give yellow needles, m.p. 166~167°. *Anal.* Calcd. for $C_{14}H_{15}O_4N_3$: C, 58.12; H, 5.23; N, 14.53. Found: C, 58.43; H, 5.18; N, 14.33. UV λ_{max}^{EtOH} mμ (log ε): 230 (4.31), 280 (3.81), 394 (4.46). IR: ν_{max}^{Nujol} 855 cm^{-1} (troponoid adjacent 2H).

Ethyl 4-Diethylamino-2-oxobutyrate 5-Tropolonylhydrazone (Xc)——Hydrazone (Xc) was prepared from Ⅸ and ethyl 2-(2-diethylaminoethyl)acetoacetate by the similar manner as in the case of Xb. The product was recrystallized from benzene to give orange needles, m.p. 150~151°. *Anal.* Calcd. for $C_{17}H_{25}O_4N_3$: C, 60.88; H, 7.51; N, 12.53. Found: C, 61.07; H, 7.09; N, 12.52. UV λ_{max}^{EtOH} mμ (log ε): 230 (4.40), 286 (3.96), 392 (4.53). IR: ν_{max}^{Nujol} 840 cm^{-1} (troponoid adjacent 2H).

Picrate: Orange silky needles, m.p. 185~186°. *Anal.* Calcd. for $C_{23}H_{28}O_{11}N_6$: C, 48.93; H, 5.00; N, 14.89. Found: C, 49.13; H, 4.85; N, 14.64.

Ethyl 5-Phthalimido-2-oxoglutarate 5-Tropolonylhydrazone (Xd)——Hydrazone (Xd) was prepared from Ⅸ and ethyl 2-(3-phthalimidopropyl)acetoacetate by the similar manner as in the case of Xb. The product was recrystallized from 70% MeOH to give yellowish brown crystals, m.p. 153~154° (decomp.). *Anal.* Calcd. for $C_{22}H_{21}O_6N_3$: N, 9.93. Found: N, 9.63. UV λ_{max}^{EtOH} mμ (log ε): 225.5 (4.45), 276 (3.90), 390 (4.38).

2-(2-Hydroxyethoxy)carbonyl-5-hydroxy-3-(2-phthalimidoethyl)cyclohepta[*b*]pyrrol-6(1*H*)-one (XI)——A mixture of 500 mg. of Xd, 0.6 ml. of conc. H_2SO_4 in 6 ml. of ethylene glycol was heated at 180° for 1 hr., and then poured into ice-water and adjusted to pH 4 with aq. 10% NaOH. The solid separated was collected by filtration. Yield, 120 mg. The solid was recrystallized from EtOH to give yellowish brown crystals, m.p. 280° (decomp.), but further purification was difficult.

3-(2-Aminoethyl)-2-carboxy-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one Hydrochloride (XII)——After 1.4 g. of XI was refluxed in 15 ml. of 2*N* KOH aq. EtOH, 10% HCl was added to adjust to pH 6. The solid (360 mg.) separated was collected by filtration. The solid was refluxed in 20 ml. of aq. 10% HCl, the mixture was filtered while hot and the filtrate was concentrated under reduced pressure. The solid residue was recrystallized from 2% HCl to give 50 mg. of yellow crystals, m.p. 290° (decomp.). *Anal.* Calcd. for $C_{12}H_{12}O_4N_2 \cdot HCl \cdot 2H_2O$: C, 44.93; H, 5.34; N, 8.73; Cl, 11.06. Found: C, 45.42; H, 5.19; N, 8.48; Cl, 10.89. UV λ_{max}^{EtOH} mμ (log ε): 225.5 (4.45), 276 (3.90), 390 (4.38). IR: ν_{max}^{Nujol} 838 cm^{-1} (troponoid adjacent 2H).

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Summary

Bromination of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one was examined. Namely, bromination of 2-ethoxycarbonyl-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ib) afforded only 4-bromo-2-ethoxycarbonyl-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ⅱb), and 5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ⅵ) afforded 2-bromo (Ⅷ), and 2,4-dibromo-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ⅷ). Hydrolysis of Ⅱb with alkali afforded 4-bromo-2-carboxy-5-hydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ⅲ) without rearrangement reaction. Reaction of Ⅲ with aqueous ammonia afforded 2-carboxy-4,5-dihydroxy-3-phenylcyclohepta[*b*]pyrrol-6(1*H*)-one (Ⅴ). A seven-membered ring compound having a similar structure to serotonin, 3-(2-aminoethyl)-2-carboxy-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one hydrochloride (XII) was prepared.

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