Chem. Pharm. Bull. 13(3) 300~303 (1965)

UDC 615.782-012

38. Tetsuji Kametani, Kazuo Kigasawa,*1 and Tetsutaro Hayasaka*2 : Azabenzomorphane and Related Compounds. III.*3 A Synthesis of 1,2,3,4,5,6-Hexahydro-2,6-methanobenzo[*e*][1,4]diazocine.*4

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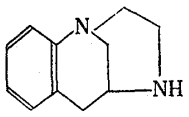
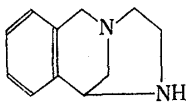
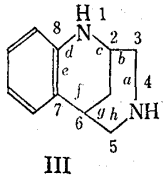
In the preceding papers*3, 1) two kinds of azabenzomorphane derivaties (I) and (II) were synthesized. In this paper will be described some results of synthetical experiments of 1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (III), which appeared to have some analgesic activity.



I



II



III

Since the skeleton of the compound (III) as above has not been known yet, synthetic procedures were investigated by using 2,4-quinolinedicarboxylic acid (V)[2] as a starting material, which was obtained from isatin (IV) and pyuric acid. Esterification of V with ethanol and methanol gave, respectively, ethyl ester (VIa) and methyl ester (VIb).[3] Ammonolysis of VIa in methanol at 50° gave an unexpected methyl 2-carbamylcinchoninate (VIIb), which was obtained by transesterification. Infrared spectrum of this compound (VIIb) was found to be identical with that of an authentic sample which was synthesized by an usual ammonolysis of VIb in methanol according to Renshaw, *et al.*[2] Both specimen showed no depression of melting point on admixture with the above one. Ammonolysis of VIa in ethanol gave ethyl ester (VIIa) under the same conditions as above.

Catalytic hydrogenation of VIIb in acetic acid with platinum oxide gave methyl 2-carbamyl-1,2,3,4-tetrahydrocinchoninate (VIII). Reduction of VIII with lithium aluminum hydride in dioxane gave a mixture of an objective 2-aminomethyl-1,2,3,4-tetrahydro-4-quinolinemethanol (IX), and 1,2,3,4-tetrahydro-4-quinolinemethanol (X), the latter of which was obtained as by-products by decarbamylation during hydrogenation and, furthermore, determined as its benzoyl derivative (XII). The former compound (IX) was furthermore recognized as 1-acetyl-2-acetamidomethyl-1,2,3,4-tetrahydro-4-quinoline methanol acetate (XI), m.p. 140~140.5°, which was obtained by acetylation of IX with acetic anhydride. The latter compound (X) was also identical with an authentic sample, which was prepared from the acid (V) by decarboxylation, esterification and reduction.[4~6]

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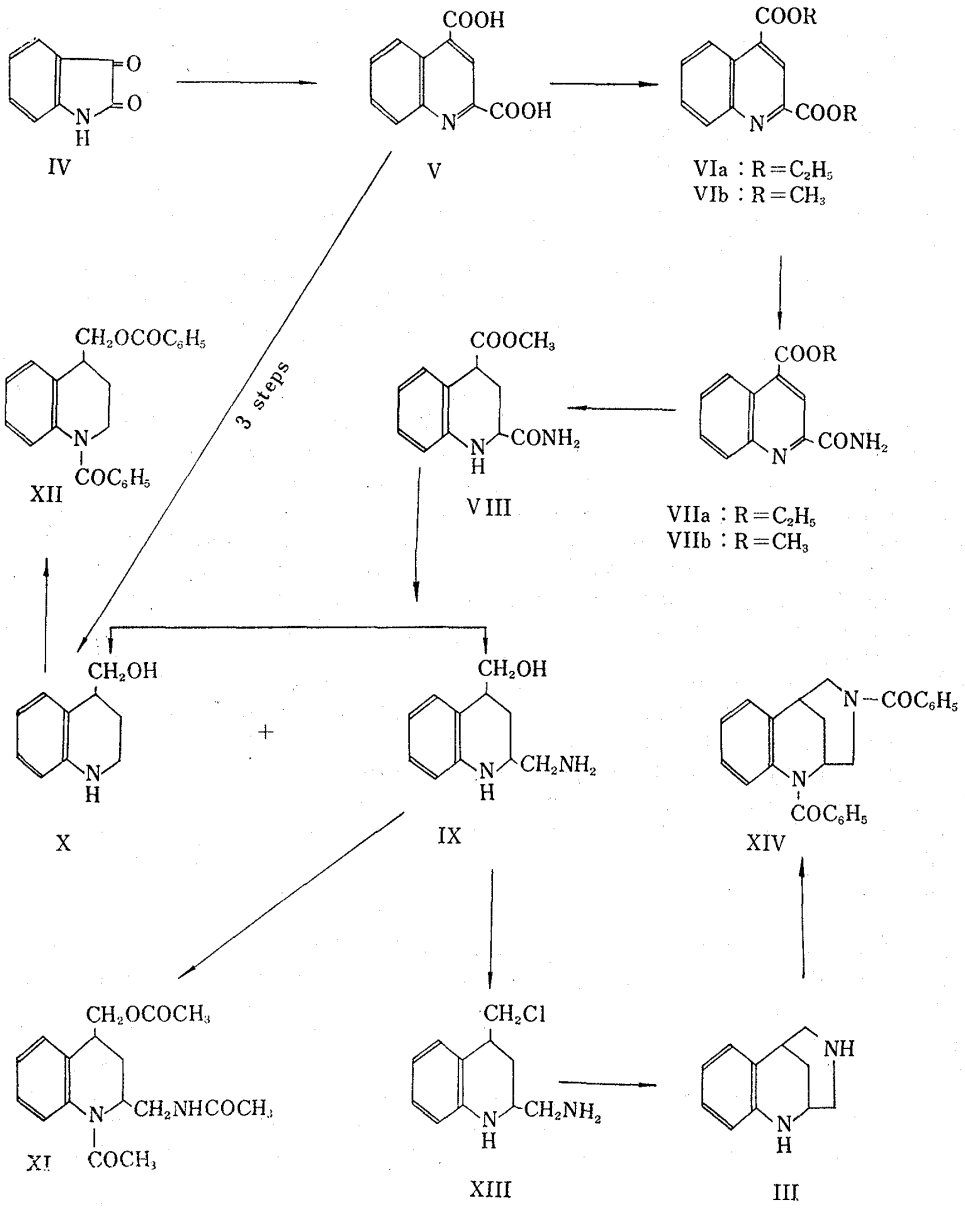
*3 Part II. T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru : This Bulletin, **13**, 295 (1965).
*4 This forms Part CVII of "Studies on the Syntheses of Heterocyclic Compounds" by Tetsuji Kametani.

1) T. Kametani, K. Kigasawa, H. Hiiragi, T. Hayasaka, T. Iwata : Yakugaku Zasshi, **84**, 405 (1964).
2) W. Pfitzinger : J. prakt. Chem., [2] **56**, 283 (1897).
3) R. R. Renshaw, H. L. Friedmann : J. Am. Chem. Soc., **61**, 3320 (1939).
4) W. Pfitzinger : J. prakt. Chem., [2] **56**, 311 (1897).
5) H. Decker, P. Pemfry : *Ibid.*, [2] **79**, 345 (1909).
6) J. Braun, G. Lenke : Ann., **478**, 176 (1930).

Chlorination of IX with phosphoryl chloride gave 2-aminomethyl-4-chloromethyl-1,2,3,4-tetrahydroquinoline (XIII) as its hydrochloride, whose free base (XIII) was used in the following reaction without purification. Intramolecular dehydrochlorination of XIII by refluxing in xylene in the presence of potassium carbonate afforded 1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (III), which was extremely labile. Recrystallization of its hydrochloride gave the diazocine (III) as pale blue crystals, m.p. 250.5~251° (decomp.), which was also so labile and hygroscopic that pale blue crystals rapidly change to dark-blue resinous substance. Accordingly, benzoylation of XIII with benzoyl chloride was carried out, to give a comparatively stable dibenzoyl derivative (XIV), m.p. 152.5~155.5°, with the correct analysis.



Experimental

Methyl 2-Carbamylcinchoninate (VIIb)——a) A mixture of 8.7 g. of VIa[3] and 100 ml. of MeOH containing 11 g. of liq. NH_3 was warmed at 50° for 6 hr. The reaction mixture was cooled to separate crystals. Filtration and recrystallization of the crude (VIIb) from AcOH gave 6.6 g. (90%) of colorless

needles, m.p. 222～224°. *Anal.* Calcd. for $C_{12}H_{10}O_3N_2$: C, 62.60; H, 4.38; N, 12.17. Found : C, 62.67; H, 4.04; N, 11.86.

b) Ammonolysis of 1 g. of VIb[3] under the same conditions as above also gave 0.92 g. of VIIb as colorless needles, m.p. 222～223°, whose IR spectrum was identical with that of the compound (VIIb) as above. Yield, 97.9%. *Anal.* Calcd. for $C_{12}H_{10}O_3N$: C, 62.61; H, 4.35; N, 12.17. Found : C, 62.13; H, 4.60; H, 12.02. IR ν_{max}^{KBr} cm^{-1} : 3400 (NH); 1725 (ester C=O); 1695 (amide C=O).

Ethyl 2-Carbamylcinchoninate (VIIa)——A mixture of 3 g. of VIa and 100 ml. of EtOH containing 3.3 g. of NH_3 was heated on a water bath at 50° for 6 hr. To the reaction mixture was added H_2O and the precipitates were filtered. Recrystallization from benzene gave 2.3 g. (86.1%) of VIIa as colorless leaflets, m.p. 155～157°. *Anal.* Calcd. for $C_{13}H_{12}O_3N_2$: C, 63.92; H, 4.95; N, 11.47. Found : C, 63.57; H, 5.31; N, 11.67. IR ν_{max}^{KBr} cm^{-1} : 3400 (NH); 1725 (ester C=O); 1700 (amide C=O).

Methyl 2-Carbamyl-1,2,3,4-tetrahydrocinchoninate (VIII)——The above compound (VIIb) (2.5 g.) in 200 ml. of AcOH was hydrogenated with H_2 over 0.3 g. of Adams Pt on warming, 500 ml. (Calcd. 448 ml.) of H_2 being absorbed. Concentration of the filtrate from the catalyst gave a soild, which was recrystallized from EtOH to afford 2.1 g. (84%) of VIII as colorless prisms, m.p. 139～139.5°. *Anal.* Calcd. for $C_{12}H_{14}O_3N_2$: C, 61.54; H, 5.98; N, 11.96. Found : C, 61.69; H, 5.87; N, 12.13. IR ν_{max}^{KBr} cm^{-1} : 3360 (NH); 1730 (ester C=O); 1670 (amide C=O).

2-Aminomethyl-1,2,3,4-tetrahydro-4-quinolinemethanol (IX) and 1,2,3,4-Tetrahydro-4-quinolinemethanol (X) (Reduction of VIII with $LiAlH_4$)——A solution of 10 g. of the preceding amide (VIII) in 100 ml. of dioxane was dropwise added to a stirred suspension of 15 g. of $LiAlH_4$ in 500 ml. of dioxane on heating at 90～100°. After the addition of the above solution, the mixture was heated at 90～100° for an additional 4 hr., and the solvent was distilled off at atmospheric pressure. To the above residue was added benzene, and the mixture was decomposed with H_2O. The solvent layer was then separated, washed with H_2O, and dried on K_2CO_3. Removal of the solvent gave 3 g. (46.9%) of a pale yellowish-brown viscous oil, b.p_2 158～160°, and 3 g. (36.6%) of a colorless viscous oil, b.p_2 196～198°, which solidified on being allowed to stand.

Recrystallization of the latter compound from benzene gave 2-aminomethyl-1,2,3,4-tetrahydro-4-quinolinemethanol (IX) as colorless needles, m.p. 117～120°. *Anal.* Calcd. for $C_{11}H_{16}ON_2$: C, 68.75; H, 8.33; N, 14.58. Found : C, 68.58; H, 8.17; N, 14.45. IR : ν_{max}^{KBr} 3300 cm^{-1} (OH).

Recrystallization of HCl salt of the former compound from EtOH gave 1,2,3,4-tetrahydro-4-quinolinemethanol (X) as colorless prisms, m.p. 151.5～153.5°, which was proved by mixed melting point test and IR spectrum to be identical with an authentic sample,[5] m.p. 151.5～153.5°. *Anal.* Calcd. for $C_{10}H_{13}ON \cdot HCl$: C, 60.15; H, 6.56 ; N, 7.02. Found : C, 59.69; H, 7.20; N, 6.83. IR : ν_{max}^{KBr} 3400 cm^{-1} (OH).

1-Acetyl-2-acetaminomethyl-1,2,3,4-tetrahydro-4-quinolinemethanol Acetate (XI)——A mixture of 1 g. of Xa and an excess of acetic anhydride was refluxed for 1 hr. The reagent was distilled off, and the residue was extracted with $CHCl_3$. The extract was washed with 10% HCl and H_2O. Removal of the dried (Na_2SO_4) solvent gave a solid, which was recrystallized from benzene to give 1.3 g. (77.8%) of 1-acetyl-2-acetaminomethyl-1,2,3,4-tetrahydro-4-quinolinemethanol acetate (XI) as colorless cubes, m.p. 140～140.5°. *Anal.* Calcd. for $C_{17}H_{22}O_4N_2$: C, 64.13; H, 6.97; N, 8.80. Found : C, 63.60; H, 6.80; N, 8.38.

1-Benzoyl-1,2,3,4-tetrahydro-4-quinolinemethanol Benzoate (XII)——Schotten-Baumann reaction of 0.5 g. of the above compound (X) with 4 g. of benzoyl chloride in benzene gave a crystalline solid according to an usual procedure. Recrystallization from AcOEt-petr. ether afforded 0.8 g. (73%) of 1-benzoyl-1,2,3,4-tetrahydro-4-quinolinemethanol benzoate (XII) as colorless cubes, m.p. 80～83°. *Anal.* Calcd. for $C_{24}H_{21}O_3N$: C, 77.61; H, 5.70; N, 3.37. Found : C, 77.12; H, 6.21; N, 3.71. IR ν_{max}^{KBr} cm^{-1} : 1710 (ester C=O); 1640 (amide C=O).

2-Aminomethyl-4-chloromethyl-1,2,3,4-tetrahydroquinoline (XIII)——A mixture of 0.5 g. of IX and 10 ml. of $POCl_3$ was gently refluxed for 2 hr. About 5 volumes of petr. ether was added to the reaction mixture, and the mixture was then allowed to stand overnight. A clear upper solution was removed by decantation and the residue was dissolved in 10% HCl. After filtration, the filtrate was basified with 10% NaOH and extracted with ether. HCl gas was introduced into the above dried (K_2CO_3) solvent, to yield HCl salt of XIII, which was recrystallized from MeOH to give 0.3 g. (46.9%) of colorless cubes, m.p. 226～227° (decomp.). On its exposure in air, white color of this HCl salt becomes blue. *Anal.* Calcd. for $C_{11}H_{15}N_2Cl \cdot HCl$: C, 53.45; H, 6.53; N, 11.34. Found : C, 53.59; H, 6.81; N, 11.38. IR : ν_{max}^{KBr} 3300 cm^{-1} (OH).

1,2,3,4,5,6-Hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (III)——A mixture of the chloride (XIII), obtained by chlorination of 3 g. of IX with 30 ml. of $POCl_3$, and 10 g. of K_2CO_3 in xylene was in an oil bath for 2 hr. The cooled reaction mixture was extracted with 10% HCl. An acidic solution was basified with 10% NaOH and extracted with ether. Removal of the dried (K_2CO_3) solvent gave 1 g. (40%) of an oil, b.p_2 164～166°, whose halogen test was negative. This compound was hygroscopic and changed blue on exposure in air. *Anal.* Calcd. for $C_{11}H_{14}N_2 \cdot \frac{1}{3}H_2O$: C, 73.33; H, 8.14; N, 15.56. Found : C, 73.43; H, 8.44; N, 16.23. Recrystallization of its hydrochloride of III from MeOH afforded pale blue prisms, m.p. 250.5～251°

(decomp.). The hydrochloride of Ⅲ rapidly colored dark-blue on its exposure in air and was also hygroscopic. *Anal.* Calcd. for $C_{11}H_{14}N_2 \cdot 2HCl \cdot 1.5H_2O$: C, 48.18; H, 6.98; N, 10.22. Found : C, 47.72; H, 7.01; N, 9.92. The free base and its hydrochloride were so hygroscopic that it was furthermore recognized as the benzoyl derivative as follows.

1,4-Dibenzoyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (XIV)——Benzoylation of 0.5 g. of Ⅲ in benzene with 4 g. of benzoyl chloride in benzene gave the solid, which was recrystallized from EtOH to give 0.5 g. (45.5%) of XIV as colorless cubes, m.p. 152.5~155.5°. *Anal.* Calcd. for $C_{25}H_{22}O_2N_2$: C, 78.51; H, 5.80; N, 7.33; mol. wt.*5 382. Found : C, 78.34; H, 5.93; N, 7.29; mol. wt. 359. IR ν_{max}^{KBr} cm^{-1} : 1655, 1640 (amide C=O).

We thank President Y. Yanagisawa, Vice-president A. Yanagisawa, and Grelan Pharmaceutical Co. Ltd., for their grateful assistance. We also thank Miss S. Oizumi for the IR spectra, and Miss E. Sugahara and Miss N. Nanjo for the microanalyses.

Summary

In order to test the analgesic action of 1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*]-[1,4]diazocine (Ⅲ), tetrahydroquinoline derivative (Ⅷ) was synthesized from 2,4-quinolinedicarboxylic acid (Ⅴ) as a starting material. Reduction of Ⅷ with lithium aluminum hydride in dioxane gave a mixture of an objective 2-aminomethyl-1,2,3,4-tetrahydro-4-quinolinemethanol (Ⅸ) and 1,2,3,4-tetrahydro-4-quinolinemethanol (Ⅹ), the latter of which was identical with an authentic sample prepared from the acid (Ⅴ). Chlorination of Ⅸ with phosphoryl chloride, followed by cyclization with potassium carbonate in xylene, gave the objective compound (Ⅲ), which was derived to XIV by benzoylation.

(Received September 25, 1964)

*5 Molecular weight determination was done by Rast's method.