(0.6 g., 29%) which was identical with quinazoline by admixture of its picrate with an authentic sample, m.p. 188~189°.

Reaction of Diacetone Alcohol with Benzaldehyde——A solution of 1.0 g. of diacetone alcohol, 4 ml. of 10% NaOH and 4.0 g. of benzaldehyde in 4 ml. of MeOH was treated similarly as described above. 1,5-Diphenyl-3-pentadienone (Ⅶ) (2.4 g., 61%) was obtained.

Reaction of I with 3-Pentanone——A solution of 1.3 g. of I, 1.4 g. of 3-pentanone and NaOH solution (0.5 g. of NaOH in 0.5 ml. of H_2O) in MeOH was treated similarly as described in the reaction of I with acetone, already reported.[1] I (0.6 g.) was recovered.

The authors are indebted to Mr. K. Narita and Miss N. Yamazaki for microanalytical data and to Miss K. Asahina for ultraviolet spectral measurements in this college.

The expenses for this work was defrayed by a Grant-in-Aid for Individual Research in 1963 from the Ministry of Education, for which is gratefully acknowledged.

Summary

The structures of the reaction products, Ⅲ, Ⅳ, and V, obtained in the interaction between quinazoline and acetone, 2-butanone and cyclohexanone in the presence of hydroxide anion at room temperature, were determined to be 1-(3,4-dihydro-4-quinazolinyl)-4-hydroxy-4-methyl-2-pentanone (Ⅲ), 1-(3,4-dihydro-4-quinazolinyl)-4-hydroxy-3,4-dimethyl-2-hexanone (Ⅳ) and 2-(3,4-dihydro-4-quinazolinyl)-6-(1-hydroxycyclohexyl)-cyclohexanone (V).

The possible mechanism for this reaction was suggested in Chart 4 in the text.

(Received September 24, 1964)

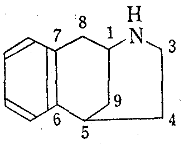
Chem. Pharm. Bull.
13(3) 295~299 (1965)

UDC 615.782-012

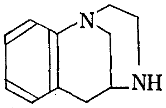
37. **Tetsuji Kametani, Kazuo Kigasawa, Mineharu Hiiragi,**[*1] **and Haruhide Ishimaru**[*2] : Azabenzomorphane and Related Compounds. II.[*3] A Synthesis of 1,2,3,4-Tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine.[*4]

(*Pharmaceutical Institute, Tohoku University School of Medicine,*[*1] *and Research Laboratories, Grelan Pharmaceutical Co., Ltd.*[*2])

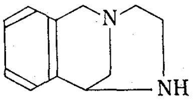
In a previous paper[*3] 3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*e*][1,4]diazocine (Ⅱ), into which one nitrogen was introduced instead of tertiary carbon atom at 5 position of benzomorphane ring (I), was synthesized using a quinoline as a starting material. The purpose of the present investigation was to synthesize 1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (Ⅲ) in order to test its analgesic activity.



I



II



III

[*1] Kita-4-bancho, Sendai (亀谷哲治, 気賀沢和雄, 柊木峯治).

[*2] Shinmachi-3-chome, Setagaya-ku, Tokyo (石丸春秀).

[*3] Part I. T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, T. Iwata : Yakugaku Zasshi, 84, 405 (1964).

[*4] This forms Part CVI of "Studies on the Syntheses of Heterocyclic Compounds" by Tetsuji Kametani.

Since the skeleton of the compound (III) as above has not been synthesized yet, methods for its synthesis were examined using an isoquinoline as a starting material according to the procedures reported in the syntheses of morphane ring,[1,2] benzomorphane ring,[3,4] 9-azo-des-N-morphinan and azabenzomorphane (II).*3

Ammonolysis of 4-bromoisoquinoline (V),[6,7] which was obtained by bromination of isoquinoline with bromine and hydrobromic acid, gave 4-aminoisoquinoline (VI)[7] and its benzoylation was carried out to give 4-benzamidoisoquinoline (VII)[7].

Reduction of 2-(2-hydroxyethyl)-4-benzamidoisoquinolinium bromide (VIII) which was obtained by heating 4-benzamidoisoquinoline (VII) with ethylene bromohydrin at 140°, with tin and hydrochloric acid or sodium borohydride gave no objective compound (IX). However, catalytic hydrogenation of VIII with platinum oxide gave 4-benzamido-1,2,3,4-tetrahydro-3-isoquinolineëthanol (IX) with an excellent yield as an oil, which was recognized as a crystalline free base and its hydrobromide. Reduction of the free base (IX) with lithium aluminum hydride in dioxane afforded 4-benzylamino-1,2,3,4-tetrahydro-2-isoquinolineëthanol (X) which was characterized as its picrate, m.p 171~173° (decomp.).

The latter compound (X) was found to be identical with an authentic sample which was synthesized as follows. Catalytic hydrogenation with platinum oxide of 2-ethoxycarbonylmethyl-4-benzamidoisoquinolinium chloride (XI), which was obtained by condensation of VII and ethyl chloroacetate, gave ethyl 4-benzamido-1,2,3,4-tetrahydro-2-isoquinolineacetate (XII). Finally, this compound (XII) was derived to X by reduction with lithium aluminum hydride.

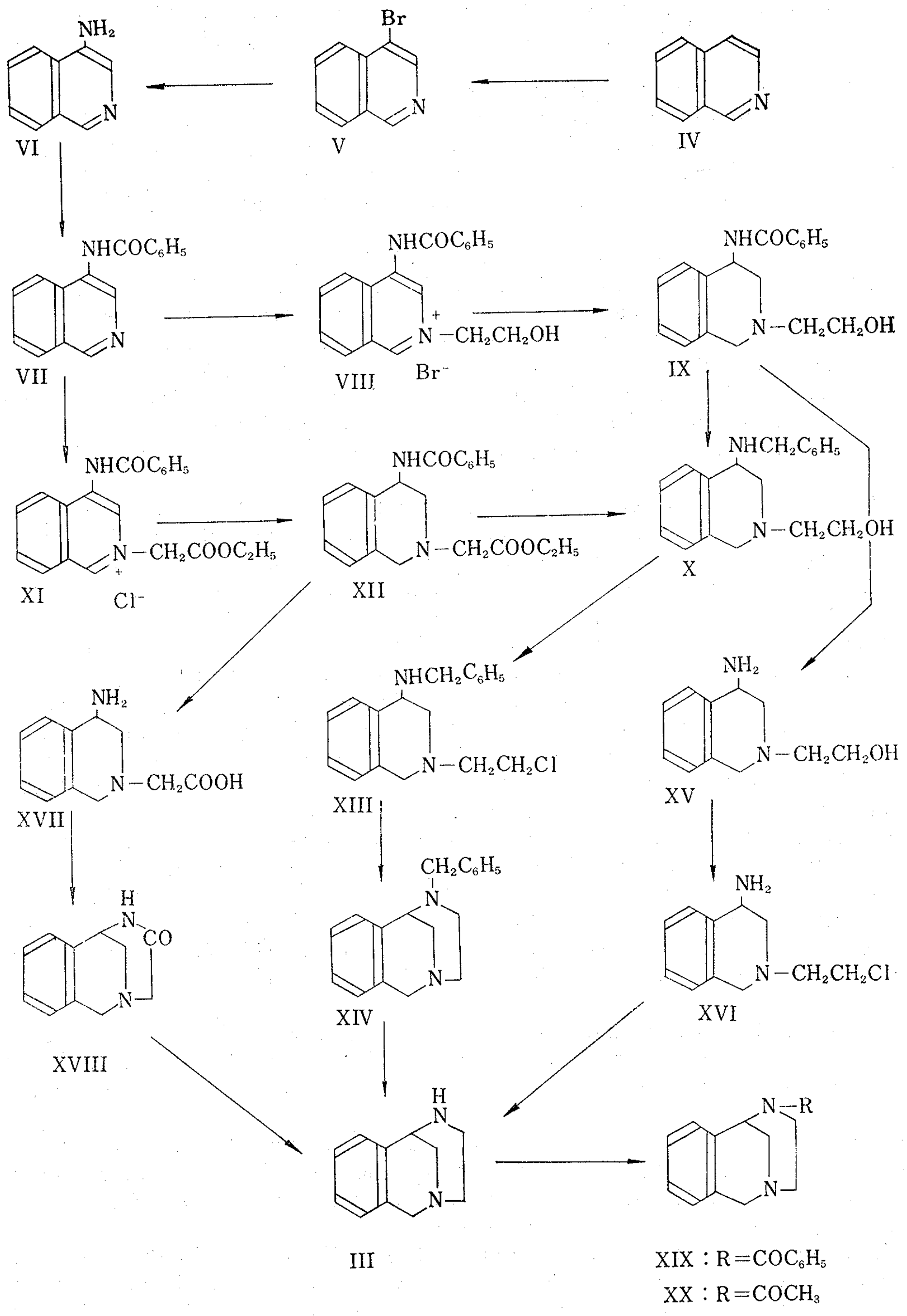
Attempted crystallization of an oily 2-(2-chloroethyl)-4-benzylamino-1,2,3,4-tetrahydroisoquinoline (XIII), which was obtained by chlorination of X with thionyl chloride, resulted in failure, but intramolecular condensation of XIII in xylene in the presence of potassium carbonate gave 2-benzyl-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (XIV), which was characterized as dihydrochloride, m.p. 252~253° (decomp.). Debenzylation of the compound (XIV) by catalytic hydrogenation with palladium-carbon yielded 1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (III).

On the other hand, III was also found to be identical with an authentic sample which was alternatively synthesized as follows. Chlorination with thionyl chloride at room temperature of 2-(2-hydroxyethyl)-4-amino-1,2,3,4-tetrahydroisoquinoline (XV), which was obtained by hydrolysis of IX, gave 2-(2-chloroethyl)-4-amino-1,2,3,4-tetrahydroisoquinoline (XVI), and intramolecular condensation by 8 hours' refluxing the latter compound in xylene in the presence of potassium carbonate afforded the same compound (III) as above, whose infrared spectrum was superimposable on that of the above authentic sample.

Furthermore, ring closure of 4-amino-1,2,3,4-tetrahydro-2-isoquinolineacetic acid (XVII), which was obtained by hydrolysis of XII, gave the lactam, 1,2-dihydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocin-3-(4*H*)-one (XVIII), m.p. 162~163°, whose infrared spectrum shows a maximum at 3200 (NH) and 1660 (C=O). Reduction of this lactam (XVIII) with lithium aluminum hydride in dioxane gave the same objective compound (III) as above. Benzoylation of III also gave 4-benzoyl derivative (XIX), m.p. 220~221° (decomp.). Acetylation of III with acetic anhydride yielded 2-acetyl-1,2,3,4-tetrahydro-6*H*-1,5-methano-

---

1) M. W. Cronyn: J. Org. Chem., **14**, 1013 (1949).
2) D. Ginsburg: *Ibid.*, **15**, 1003 (1950).
3) J. A. Barltrop: J. Chem. Soc., **1947**, 399.
4) E. L. May, J. G. Murphy: J. Org. Chem., **22**, 1957 (1957).
5) N. Sugimoto, H. Kugita: Yakugaku Zasshi, **75**, 184 (1955).
6) B. Rodda: J. Am. Chem. Soc., **62**, 3031 (1940).
7) J. J. Crig, W. E. Cass: *Ibid.*, **64**, 783 (1942).



benzo[*f*][1,4]diazocine (XX), which was charaterized as its hydrochloride, m.p. 266~267°.

Analgesic activity of these compounds is under investigation.

Experimental

2-(2-Hydroxyethyl)-4-benzamidoisoquinolinium Bromide (VIII)——A mixture of 3 g. of 4-benzamidoisoquinoline[7] (VII) and 1.5 g. of ethylene bromohydrin was heated at 140° for 2 hr. The reaction mixture which solidified was recrystallized from MeOH to give 4.1 g. of VIII as colorless cubes, m.p. 220° (decomp.). *Anal.* Calcd. for $C_{18}H_{17}O_2N_2Br$: C, 57.92; H, 4.59. Found : C, 57.82; H, 5.30. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 3500~3300 (OH or NH), 1695 (C=O); 1640 (C=N).

4-Benzamido-1,2,3,4-tetrahydro-2-isoquinolineëthanol (IX)——The above compound (VIII) (9 g.) in MeOH was hydrogenated with H_2 over Adams Pt (0.2 g.) on heating, 1140 ml. of H_2 being absorbed. Concentration of the filtrate from the catalyst gave a solid, which was recrystallized from EtOH to give colorless cubes. Recrystallization from benzene yielded colorless needles, m.p. 103~105°. *Anal.* Calcd. for $C_{18}H_{20}O_2N_2$: C, 72.92; H, 6.80; N, 9.45. Found : C, 73.05; H, 7.15; N, 9.65. IR ν_{max}^{KBr} cm^{-1} : 3400 (OH); 1640 (C=O).

4-Benzylamino-1,2,3,4-tetrahydro-2-isoquinolineëthanol (X)——a) A solution of 10 g. of the preceding amide (Ⅸ) in dry dioxane was dropwise added to a stirred suspension of 7 g. of $LiAlH_4$ in dioxane at room temperature. The mixture was then refluxed for 6 hr. After concentration of the solvent, 200 ml. of benzene was added and then cooled. The excess of reagent was decomposed by dropwise addition of H_2O. The above benzene layer was separated, and dried on Na_2SO_4. Evaporation of the solvent gave 9 g. of X as a viscous oil.

The picrate of X formed yellow cubes, m.p. 171~173°(decomp.), (from MeOH). *Anal.* Calcd. for $C_{18}H_{22}ON_2 \cdot 2C_6H_3O_7N_3$: C, 48.64; H, 3.81; N, 15.12. Found : C, 48.94; H, 4.17; N, 15.28.

b) A solution of 0.9 g. of Ⅻ described later in dioxane was dropwise added to a stirred suspension of 1 g. of $LiAlH_4$ in dioxane. The mixture was refluxed for 6 hr. The same treatment of the mixture as above gave an oily substance (X). Recrystallization of HCl salt of X from EtOH gave 0.4 g. of HCl salt as colorless prisms, m.p. 191~192°(decomp.). Recrystallization of the picrate from MeOH afforded the same crystals, m.p. 171~172°(decomp.), whose IR spectrum was identical with that of the authentic sample obtained by the procedure (a). This picrate also showed no depression of melting point on admixture with the above one.

2-(2-Ethoxycarbonylmethyl)-4-benzamidoisoquinolinium Chloride (XI)——A mixture of 18 g. of Ⅶ and 13 g. of ethyl chloroacetate was heated at 120° for 2 hr. The reaction mixture which solidified on cooling was recrystallized from BuOH to give 22 g. of pale reddish cubes, m.p. 210°(decomp.). *Anal.* Calcd. for $C_{20}H_{14}O_3N_2Cl \cdot H_2O$[*5]: C, 61.81; H, 5.44; N, 7.21. Found : C, 61.49, 62.04; H, 5.49, 5.33; N, 7.21, 7.41. IR $\nu_{max}^{KBr}cm^{-1}$: 1750 (ester C=O); 1670 (amide C=O); 1640 (C=N).

Ethyl 4-Benzamido-1,2,3,4-tetrahydro-2-isoquinolineacetate (XII)——The compound (Ⅺ) (22 g.) in MeOH was hydrogenated at atmospheric pressure in the presence of 0.5 g. of PtO_2, H_2 being absorbed quantitatively during 5 hr. Filtration and removal of the solvent gave crude hydrochloride of Ⅺ as a colorless powder, which was basified with 10% NaOH solution and extracted with benzene. Concentration of the dried (Na_2SO_4) solvent afforded a free base of Ⅻ from benzene gave 16.5 g. of pale yellow cubes, m.p. 99°. *Anal.* Calcd. for $C_{20}H_{22}O_3N_2$: C, 70.98; H, 6.55; N, 8.18. Found : C, 71.01; H, 6.65; N, 8.44. IR ν_{max}^{KBr} cm^{-1} : 2320 (NH); 1745 (ester C=O); 1650 (amide C=O).

2-(2-Chloroethyl)-4-benzylamino-1,2,3,4-tetrahydroisoquinoline (XIII)——A mixture of 10 g. of X and 20 g. of $SOCl_2$ was allowed to stand overnight and, after benzene had been added to it, the mixture was heated at 50° for 0.5 hr. The reaction mixture was then cooled and the solvent layer was separated by decantation. The residue was dissolved in H_2O, and filtered. The acidic filtrate was basified with 10% NaOH and extracted with ether. Concentration of the dried (Na_2SO_4) solution gave ⅩⅢ as a viscous oil, whose recrystallization resulted in failure. The crude chloride was used in the following reaction without purification.

2-Benzyl-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (XIV)——A mixture of 10 g. of ⅩⅢ and 1 g. of K_2CO_3 in 400 ml. of xylene was refluxed for 10 hr. After the reaction mixture had been basified with saturated K_2CO_3 solution, the solvent which was separated from aqueous layer, was extracted with 10% HCl.

The above acidic solution was basified with 10% NaOH and extracted with ether. Introduction of HCl gas into the dried (Na_2SO_4) solvent gave the hydrochloride of XIV. Filtration and recrystallization from EtOH afforded 8.5 g. of colorless cubes, m.p. 252~253°(decomp.). *Anal.* Calcd. for $C_{18}H_{20}N_2 \cdot 2HCl$: C, 64.10; H, 6.57; N, 8.30. Found : C, 63.79; H, 6.87; N, 8.40.

4-Amino-1,2,3,4-tetrahydro-2-isoquinolineëthanol (XV)——To 10 ml. of 30% H_2SO_4 was added 12.8 g. of Ⅸ, and the mixture was refluxed for 5 hr. After the benzoic acid precipitated had been filtered off and the acidic filtrate washed with ether, the aqueous solution was basified with 10% NaOH, extracted with ether and dried on Na_2SO_4. HCl salt of XV was obtained by treatment of the above ethereal solution with HCl gas. Recrystallization from EtOH gave 6.8 g. of HCl salt of XV as colorless plates, m.p. 218~220°(decomp.). *Anal.* Calcd. for $C_{11}H_{16}ON_2 \cdot 2HCl$: C, 49.82; H, 6.84; N, 10.57. Found : C, 50.01; H, 6.68; N, 10.27.

2-(2-Chloroethyl)-4-amino-1,2,3,4-tetrahydroisoquinoline (XVI)——A mixture of 2.3 g. of HCl salt of XV and 8 g. of $SOCl_2$ was allowed to stand overnight at room temperature. After the crystals of XV had been once dissolved in $SOCl_2$, the crystalline substance again separated during the reaction. A suitable amount of benzene was added to the above reaction mixture in order to remove a soluble substance in solvent. Recrystallization from MeOH of the residue obtained by decantation of the solvent from the mixture gave 1.4 g. of HCl salt of XVI as colorless cubes, m.p. 229~230°(decomp.). *Anal.* Calcd. for $C_{11}H_{15}N_2Cl \cdot 2HCl$: C, 46.58; H, 6.04; N, 9.88. Found : C, 46.46; H, 5.92; N, 9.66.

4-Amino-1,2,3,4-tetrahydro-2-isoquinolineacetic Acid (XVII)——A mixture of 5 g. of Ⅻ and 50 ml. of conc. HCl was refluxed for 20 hr. After the benzoic acid which precipitated had been filtered off and the

---

[*5] This was dried over P_2O_5 at 50°(5 mm.) for 5 hr.

resultant filtrate was with ether, the acidic solution was evaporated to dryness *in vacuo.* Recrystallization of the residue from MeOH gave 3.0 g. of HCl salt of XVII as hygroscopic colorless cubes, m.p. 163~165° (decomp.). *Anal.* Calcd. for $C_{11}H_{14}O_2N_2\cdot 2HCl\cdot 1\frac{2}{3}H_2O$[*5] : C, 42.87; H, 6.32; N, 9.09. Found : C, 42.55; H, 6.37; N, 8.93. IR : ν_{max}^{KBr} 1730 cm^{-1} (C=O).

1,2-Dihydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocin-3(4*H*)-one (XVIII)——Fusion of 3.0 g. of HCl salt of XVII at 200~220° (bath) for 0.5 hr. yielded a solid, a severe gas evolution being observed. The mixture was then dissolved in H_2O. The acidic solution was basified with 10% NaOH and extracted with $CHCl_3$. Concentration of the dried (K_2CO_3) solvent gave a solid. Recrystallization from benzene 1.2 g. colorless scales, m.p. 162~164°. *Anal.* Calcd. for $C_{11}H_{12}ON_2$: C, 70.19; H, 6.43; N, 14.88. Found : C, 69.66; H, 6.65; N, 15.08. IR ν_{max}^{KBr} cm^{-1} : 3200 (NH); 1660 (C=O).

1,2,3,4-Tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (III)——a) The HCl salt of XIV (1.0 g.) in MeOH was hydrogenated with H_2 over 0.2 g. of 10% Pd-C, 70 ml. of H_2 being absorbed for 1 hr. Concentration of the filtrate from the catalyst and recrystallization of the residue from MeOH gave 0.4 g. of colorless cubes, m.p. >290°. *Anal.* Calcd. for $C_{11}H_{14}N_2\cdot 2HCl$: C, 53.43; H, 6.53; N, 11.34. Found : C, 53.33; H, 6.29; N, 11.30. Recrystallization of HCl salt of 4-benzoyl derivative (XIX) from MeOH gave colorless needles, m.p. 180°, which were very hygroscopic. *Anal.* Calcd. for $C_{11}H_{18}ON_2\cdot HCl\cdot H_2O$[*5] : C, 65.72; H, 7.00; N, 8.52. Found : C, 65.62; H, 6.43; N, 8.93.

b) A mixture of 3 g. of K_2CO_3, 300 ml. of xylene and the free base, which was obtained from 1.3 g. of HCl salt of XVI, was refluxed for 10 hr. The cooled reaction mixture was extracted with 10% HCl. The resultant acidic solution was basified with 10% NaOH and extracted with ether. Introduction of HCl gas into the above dried (Na_2SO_4) solvent gave HCl salt of III. Filtration and recrystallization from MeOH yielded 0.3 g. of colorless cubes, m.p. >290°, which was identical with the above one from the point of IR spectrum and mixed melting point test.

c) A solution of 1.0 g. of lactam (XVIII) in dioxane was dropwise added to a stirred suspension of 1.5 g. of $LiAlH_4$ in dioxane at room temperature. The mixture was refluxed for 10 hr., and the solvent was evaporated to dryness. After an excess of benzene (200 ml.) had been added, the excess of reagent was decomposed by dropwise addition of wet ether then H_2O. The mixture was basified with 20% NaOH and then extracted with benzene. The benzene extract was washed with H_2O, dried on Na_2SO_4 and distilled *in vacuo* to give 0.6 g. of an oily substance (III), which was again extracted with ether and derived to 0.2 g. of the HCl salt of III by treatment with HCl gas. Recrystallization of this HCl salt from MeOH afforded the same one of III as above, whose IR spectrum was superimposable on that of the compound (III) obtained by the method (a).

2-Acetyl-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (XX)——A mixture of 0.3 g. of III and 1 g. of Ac_2O was refluxed at 140° for 2 hr. Removal of an excess of Ac_2O gave a viscous oil, which was basified with 10% NaOH and extracted with ether. Removal of the washed and dried (Na_2SO_4) solvent gave an oily substance, whose HCl salt was recrystallized from EtOH to afford 0.3 g. of XX as colorless plates, m.p. 266~267°. *Anal.* Calcd. for $C_{13}H_{16}ON_2\cdot HCl$: C, 61.78; H, 6.78; N, 11.08. Found : C, 61.88; H, 6.82; N, 11.02.

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 2,3,4,5-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (III), methods for its synthesis were examined using various starting materials. Compounds (XIII, XVI, and XVII) were synthesized from isoquinoline (IV) *via* 4-aminoisoquinoline (VI). Cyclization of compounds (XIII, XVI, and XVII) gave the objective azabenzomorphane derivatives (XIV, III, and XVIII), respectively. Reduction of lactam (XVIII) with lithium aluminum hydride and debenzylation of XIV by catalytic hydrogenation in the presence of Adam's platinum afforded the same objective compound (III), which was also recognized as benzoyl and acetyl derivatives (XIV and XX).

(Received September 25, 1964)