Summary

Thirteen kinds of monohalogenoacyl substituted aromatic derivatives were synthesized and tested their antitrichophyton effect.

On anilide, Cl substitution of *p*-position is 30 times as strong as that of *o*-position, and Cl substitution is 33 times as strong as Br substitution. The double bond of acyl group of monohalogenoacyl substituted aromatic amide derivatives did not show strong fungical effect, and there was no difference of fungical effect between *cis* and *trans*.

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UDC 547.833.3.07 : 547.94.07

79. **Tetsuji Kametani and Kazuo Kigasawa** : Azabenzomorphane and Related Compounds. Ⅸ.*1 A Synthesis of 3-Benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*][1,3]diazocine. (Studies on the Synthesis of Heterocyclic Compounds. CXLI.*2)

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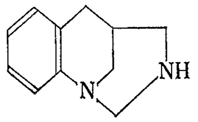
In the previous papers*1,1~5) several kinds of azabenzomorphane derivatives were synthesized. The purpose of the present investigation was to synthesize 3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*][1,3]diazocine (I), which appeared to have some analgesic activity.



I

Since the skeleton of compound (I) mentioned above has not yet been synthesized, methods for its synthesis were examined, using 3-cyanoquinoline (Ⅱ) as a starting material according to the procedures reported in the syntheses of imidazolidine and hexahydropyrimidine derivatives6~8) and 1,3-diazoadamantane derivatives9). Thus synthetic methods of 3-(N-benzylaminomethyl)-1,2,3,4-tetrahydroquinoline (Ⅵ), which was thought to be a key compound for synthesis of 3-benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*][1,3]diazocine (Ⅸa) and its 2-phenyl derivative (Ⅸb), were investigated according to the two methods as follows.

Hydrolysis of 3-cyanoquinoline (Ⅱ)10) which was obtained by the Rosenmund-von Braun reaction of 3-bromoquinoline10) gave quinoline-3-carboxylic acid (Ⅲ).11) Catalytic

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*1 Part Ⅷ : T. Kametani, K. Kigasawa, T. Hayasaka : This Bulletin, **13**, 1225 (1965).

*2 Part CXL : T. Kametani, *et al.* : Yakugaku Kenkyu, **37**, No. 2, 1 (1966).

*3 No. 85, Kita-4-bancho, Sendai (亀谷哲治, 気賀沢和雄).

1) T. Kametani, *et al.* : Yakugaku Zasshi, **84**, 405 (1964).

2) T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru : This Bulletin, **13**, 295 (1965).

3) T. Kametani, K. Kigasawa, T. Hayasaka : *Ibid.*, **13**, 300 (1965).

4) T. Kametani, K. Kigasawa, M. Hiiragi : *Ibid.*, **13**, 1225 (1965).

5) *Idem* : Yakugaku Zasshi, **85**, 871 (1965).

6) R.C. Elderfield : "Heterocyclic Compound," **6**, 314 (1957).

7) H.W. Wanzlick, W. Löckel : Chem. Ber., **86**, 1463 (1953).

8) J.H. Billmann, L.C. Dormann : J. Org. Chem., **27**, 2417 (1962).

9) H. Stetter, H. Hennig : Chem. Ber., **88**, 789 (1955).

10) E. Ochiai, S. Fujise : "Jikken Kagaku Koza," **21**, Ⅲ, 343 (Maruzen Co., Ltd.).

11) H. Gilman, S.M. Spatz : J. Am. Chem. Soc., **63**, 1553 (1941).

hydrogenation with platinum oxide of the amide (Ⅳ), which was obtained by condensation of Ⅲ with benzylamine in the presence of phosphoryl chloride, gave 3-benzylcarbamoyl-1,2,3,4-tetrahydroquinoline (Ⅴ). Reduction of the above carboxamide (Ⅴ) with lithium aluminum hydride gave 3-(N-benzylaminomethyl)-1,2,3,4-tetrahydroquinoline (Ⅵ) as a colorless syrup, which was characterized as its picrate.

Secondly, catalytic hydrogenation with platinum oxide of 3-aminomethylquinoline (Ⅶ), which in turn was obtained by hydrogenation of Ⅱ with Raney nickel, gave 3-aminomethyl-1,2,3,4-tetrahydroquinoline (Ⅷ). Catalytic hydrogenation with platinum oxide of a mixture of Ⅷ and benzaldehyde yielded the same compound (Ⅵ) as described above (method a), the infrared spectra of the two samples being also superimposable.

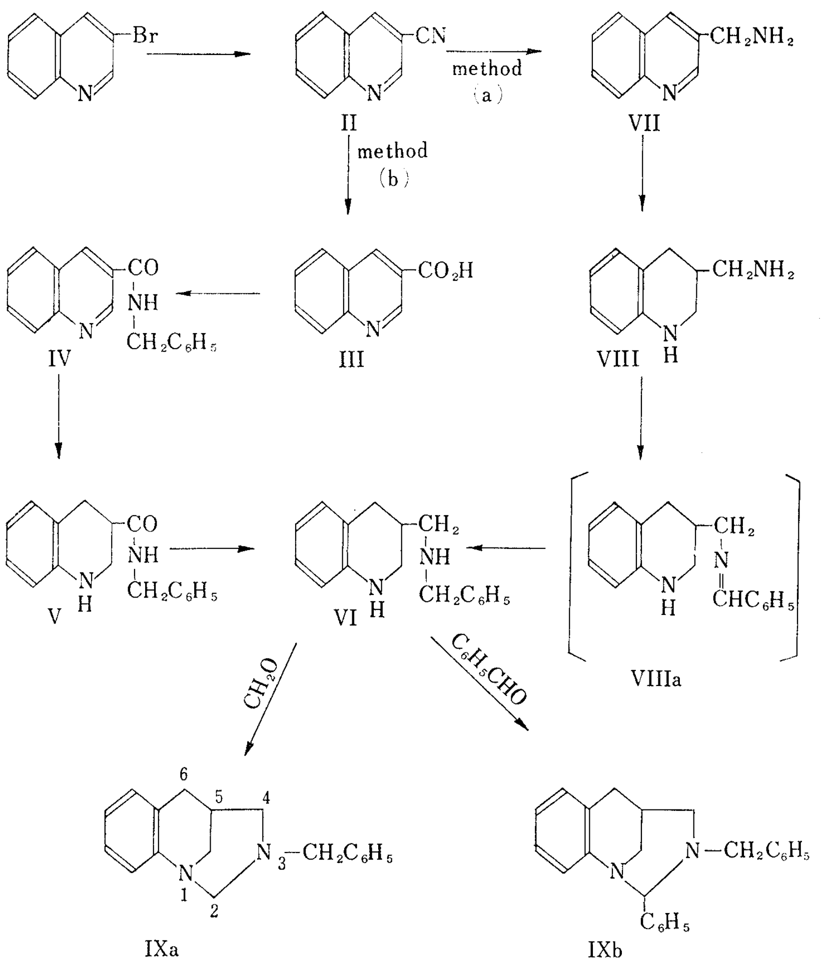
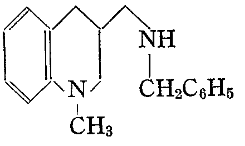


Chart 1.

Finally, ring closure with paraformaldehyde and benzaldehyde of compound (Ⅵ) gave 3-benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*] [1,3]diazocine (Ⅸa) and 2-phenyl-3-benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*] [1,3]diazocine (Ⅸb), respectively.

Both specimens (Ⅸa and Ⅸb) lack NH absorption band in the infrared spectrum. Furthermore, there was no change in the nuclear magnetic resonance (NMR) spectra of Ⅸa and Ⅸb even when both compounds were treated with deuterium oxide. These facts reveal that both compounds having the expected structure were obtained by ring closure of Ⅵ.

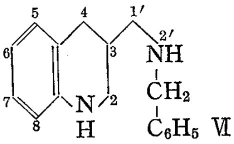
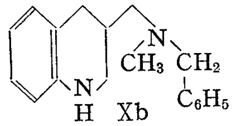
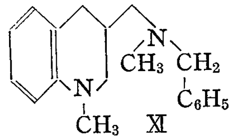
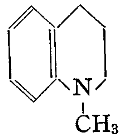
Catalytic hydrogenation of Ⅸa and Ⅸb with palladium oxide was investigated in order to obtain the final compound (I) by debenzylation. The compound (Ⅸa) in methanol was hydrogenated to give the N-methyl derivative, one mole of hydrogen being absorbed. In the NMR spectrum of the above product the protons of the N-methyl group appeared as a singlet at 7.82τ. This reveals that IXa was converted into Xa or Xb. Furthermore, the location of the N-methyl group in the rather high field of 7.82τ seems to indicate that a cleavage between the N_1- and C_2-position gave compound (Xb) by reductive alkylation. If the fission had occurred between C_2- and N_3 to form compound (Xa), the protons of the N-methyl group should appear at a lower field of 7.18τ as in the case of 1-methyl-1,2,3,4-tetrahydroquinoline.[12]


Xa

In fact, methylation of VI with dimethyl sulfate gave 1-methyl-3-(N-benzyl-N-methylaminomethyl)-1,2,3,4-tetrahydroquinoline (XI); in this compound, the N_1-methyl group of the quinoline nucleus showed up as a singlet at 7.18τ and that of the side-chain N_2-methyl group at 7.83τ The chemical shift of the former signal is identical to that of 1-methyl-1,2,3,4-tetrahydroquinoline (XII) at 7.18τ while the latter is comparable to that of Xb at 7.82τ.

The NMR spectra of VI, Xb, XI and XII are summarized in Table I.

Table I. Nuclear Magnetic Resonance Spectra*4 of Tetrahydroquinoline Derivatives

Structure	Aromatic protons		$N-C\underline{H}_2C_6H_5$	$>N\underline{H}$ $-C\underline{H}_2-$ $>C\underline{H}$	$N-C\underline{H}_3$	
	Benzyl group	Quinoline group			N_1-CH_3	$N_{2'}-CH_3$
 VI	2.75 (5H)	2.85∼3.75 (4H)	6.23 (2H)	6.40∼8.15 (9H)	—	—
 Xb	2.75 (5H)	2.85∼3.75 (4H)	6.55 (2H)	6.35∼8.15 (8H)	—	7.82 (3H)
 XI	2.75 (5H)	2.90∼3.66 (4H)	6.23 (2H)	6.35∼8.47 (7H)	7.18 (3H)	7.83 (3H)
 XII	—	2.90∼3.68 (4H)	—	6.68∼8.33 (6H)	7.18 (3H)	—

On the other hand catalytic hydrogenation of IXb gave an oil, the infrared and NMR spectra of which were identical with those of the above mentioned compound (VI). In this case two moles of hydrogen were absorbed. This fact is presumably due to the formation of toluene, but it could not be detected.

It is well known that methylenediamine type compounds such as imidazolidine derivatives are generally unstable to acid.[6~8] Therefore, the following experiments were examined in order to inspect the stability of IXa and IXb against acid. After compound (IXa) had been dissolved in 0.1 *N* hydrochloric acid, basification of the acidic

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*4 Nuclear magnetic resonance spectrum was determined on a Varian A-60 spectrophotometer with deuterochloroform as solvent and tetramethylsilane as internal reference. In this Table the signals are shown as the τ-value.

[12] P. J. Scheuer, W. I. Kimoto, K. Ohinata: J. Am. Chem. Soc., **75**, 3029 (1953).

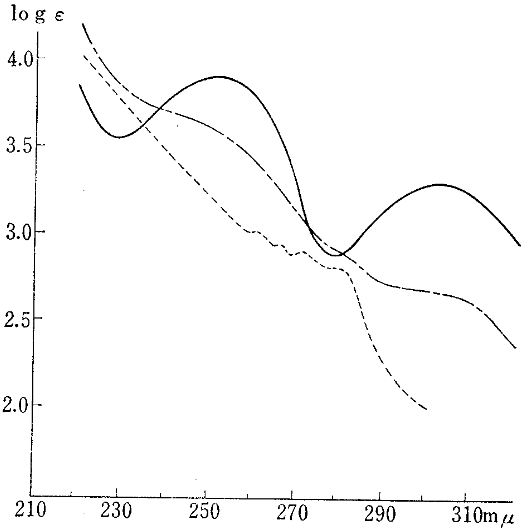

Fig. 1. Ultraviolet Spectra in Ethanol

—— VI ------- IXa
—·—·— IXb

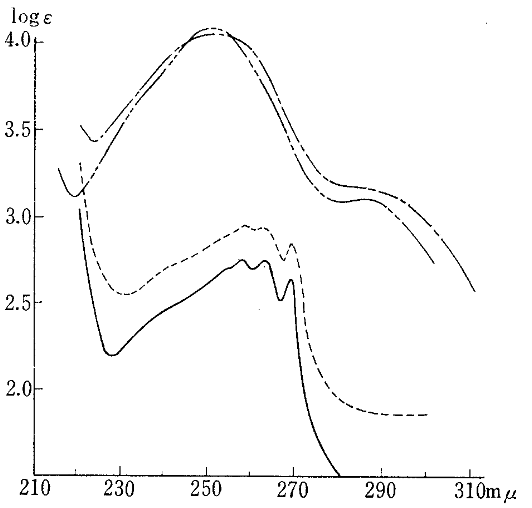

Fig. 2. Ultraviolet Spectra in 0.1*N* Hydrochloric Acid

—— VI ------- IXa
—·—·— IXb —··—·· C_6H_5CHO

solution with sodium hydroxide gave compound (VI), the infrared spectrum of which was superimposable on that of the specimen (VI) mentioned above. The same treatment of IXb with acid gave a mixture of VI and benzaldehyde. The UV spectra of IXa in ethanol (Fig. 1) and in 0.1 *N* hydrochloric acid (Fig. 2) were almost the same. On the other hand, the absorption curve of compound (IXb) in 0.1 *N* hydrochloric acid (Fig. 2) was similar to that of benzaldehyde; however, in ethanol no decomposition took place (Fig. 1).

Furthermore, IXb was found to be hydrolyzed by merely being refluxed in dilute ethanol to give compound (VI).

Experimental[*5]

3-Benzylcarbamoylquinoline (IV)——A mixture of 5 g. of quinoline-3-carboxylic acid (III),[11] 3.1 g. of benzylamine and 20 ml. of $POCl_3$ was heated under reflux for 1 hr. After cooling the resultant mixture was decomposed with ice-water, basified with aqueous Na_2CO_3 solution, and extracted with $CHCl_3$. The extract was dried on K_2CO_3 and distilled off, to give the amide (IV) as a crystalline substance, which was recrystallized from EtOH to give 6 g. (80%) of colorless needles, m.p. 143~144°. *Anal.* Calcd. for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.95; H, 5.51; N, 10.78. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH); 1660 (C=O).

3-(Benzylcarbamoyl)-1,2,3,4-tetrahydroquinoline (V)——The above amide (IV) (5.3 g.) in 100 ml. of MeOH was hydrogenated at atmospheric pressure in the presence of 2.1 ml. of conc. HCl and 250 mg. of PtO_2, a theoretical amount of H_2 (1008 ml.) being absorbed. After filtration and removal of the solvent, the residue was basified with 10% aq. NaOH solution and extracted with $CHCl_3$. The extract was washed with H_2O and dried on K_2CO_3. Evaporation of the solvent and recrystallization from EtOH gave 5.3 g. (89.8%) of V as colorless prisms, m.p. 143~144°. This compound showed the depression of melting point on admixture with the starting material (IV). *Anal.* Calcd. for $C_{17}H_{18}ON_2$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.80; H, 6.90; N, 10.50. IR ν_{max}^{KBr} cm^{-1}: 3420 (NH), 3300 (NH), 1615 (C=O).

3-(N-Benzylaminomethyl)-1,2,3,4-tetrahydroquinoline (VI). a) Reduction of V with Lithium Aluminum Hydride——A solution of 4.9 g. of the amide (V) in 30 ml. of dry dioxane was dropwise added to a stirred suspension of 2.1 g. of $LiAlH_4$ in 90 ml. of dioxane at 105~110°. The mixture was then refluxed for 4 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 by decantation, washed with H_2O, and dried on K_2CO_3. Evaporation of the solvent and distillation ***in vacuo*** gave 4.2 g. (90.5%) of VI as a colorless viscous oil, b.p$_1$ 220°. IR ν_{max}^{liquid} cm^{-1}: 3450 (NH), 3350 (NH) (shoulder). UV

[*5] All melting points are uncorrected.

λ_{max}^{EtOH} mμ (log ε): 252 (3.92), 304 (3.32). UV $\lambda_{max}^{0.1N\,HCl}$ mμ (log ε): 257 (2.75); 261.5 (2.75); 268 (2.63). The NMR spectrum is shown in Table I.

The picrate of VI formed yellow cubes (from AcOH), m.p. 169∼171° (decomp.). *Anal.* Calcd. for $C_{17}H_{20}N_2 \cdot 2C_6H_3O_7N_3$: C, 49.02; H, 3.69; N, 15.77. Found : C, 49.03; H, 3.76; N, 15.60.

b) **Reductive Benzylation of VIII**——After a mixture of 2.4 g. of VIII and 1.5 g. of benzaldehyde in 50 ml. of benzene was refluxed for 1 hr., the solvent was distilled off, to give VIIIa as a viscous syrup. The preceding base (VIIIa) (1 g.) was hydrogenated in 30 ml. of MeOH in the presence of 77 mg. of PtO_2, 90 ml. of H_2 being absorbed. Filtration and removal of the solvent gave an oil, whose picrate was recrystallized from AcOH to afford the same compound as above. IR spectrum of this picrate was identical with that of the above one.

3-Aminomethylquinoline (VII)——The compound (II) (5 g.) in 100 ml. of MeOH containing 2.6 g. of liq. NH_3 was hydrogenated in the presence of 19 ml. of Raney Ni, 1450 ml. of H_2 being absorbed. Filtration and distillation *in vacuo* afforded 3.3 g. (64.7%) of VII as a pale yellow oil. IR ν_{max}^{liquid} cm^{-1} : 3370 (NH); 3300 (NH). Recrystallization of the picrate from AcOH gave colorless needles, m.p. 215° (decomp.). *Anal.* Calcd. for $C_{10}H_{10}N_2 \cdot 2C_6H_3O_7N_3$: C, 42.86; H, 2.62; N, 18.17. Found : C, 43.15; H, 3.05; N, 18.21.

3-Aminomethyl-1,2,3,4-tetrahydroquinoline (**VIII**)——The compound (VII) (3 g.) in 80 ml. of MeOH was hydrogenated in the presence of 4 ml. of conc. HCl and 99.5 mg. of PtO_2, 850 ml. of H_2 being absorbed. Filtration and distillation of MeOH afforded the crude HCl salt of VIII quantitatively. The picrate formed yellow cubes (from AcOH), m.p. 182.5∼183° (decomp.). *Anal.* Calcd. for $C_{10}H_{14}N_2 \cdot 2C_6H_3O_7N_3$: C, 42.59; H, 3.25; N, 18.06. Found : C, 42.98; H, 3.67; N, 18.28. IR ν_{max}^{liquid} cm^{-1} (free base) : 3360 (NH), 3300 (NH). NMR (τ) : 2.75 (5H, singlet, aromatic protons of benzyl radical); 2.85∼3.75 (aromatic protons of quinoline); 6.23 (2H, singlet, -CH_2- of benzyl radical); 6.40∼8.15 (9H, 2NH, 3-CH_2-,=CH-).

3-Benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*][1,3]diazocine (**IXa**)——A mixture of 1 g. of VI and 3 g. of paraformaldehyde in 20 ml. of benzene was refluxed for 40 min. and then the excess of the reagent was filtered off. The benzene layer was washed with 10% aq. NaOH solution and dried on K_2CO_3. Evaporation of the solvent gave an oil, whose distillation *in vacuo* afforded 0.8 g. (76.2%) of IXa as a colorless viscous syrup, b.p$_{25}$ 190∼200°. *Anal.* Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found : C, 81.83; H, 7.83; N, 10.57. UV λ_{max}^{EtOH} mμ (log ε) : 269.5 (2.90). UV $\lambda_{max}^{0.1N\,HCl}$ mμ (log ε) : 257.5 (2.96), 261.5 (2.96), 268 (2.86). NMR (τ) : 2.67∼3.33 (9H, aromatic proton); 7.67∼6.08 (10H, 5-CH_2-), 8.05 (1H, multiplet, C_5-H). Treatment of IXa with D_2O gave no change in the above NMR spectrum.

2-Phenyl-3-benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*][1,3]diazocine (**IXb**)——After a mixture of 4.5 g. of VI and 1.88 g. of benzaldehyde in 50 ml. of benzene had been heated under reflux for 10 min., the solvent was removed at atmospheric pressure and the residue was extracted with petroleum ether. The extract was chromatographed on 30 g. of Al_2O_3. Evaporation of the first eluate (100 ml.) of petroleum ether gave 4 g. of a colorless solid, which was recrystallized from petroleum ether to yield 3.1 g. (76.5%) of IXb as a large colorless lump, m.p. 86∼88°. *Anal.* Calcd. for $C_{24}H_{24}N_2$: C, 84.66; H, 7.11; N, 8.23. Found : C, 84.53; H, 7.35; N, 8.35. UV $\lambda_{max}^{0.1N\,HCl}$ mμ (log ε) : 251 (4.07). NMR (τ) : 2.0∼3.58 (14H, aromatic proton); 6.2 (2H, methylene of benzyl radical), 6.3∼8.0 (8H, 3-CH_2- and 2$>$CH). Substitution of IXb with deuterium oxide gave no change in the NMR spectrum.

Evaporation of the second eluate (100 ml.) of ether recovered 1.5 g. of the starting material (VI).

Hydrolysis of IXa with 0.1*N* Hydrochloric Acid——After a solution of 50 mg. of IXa in 20 ml. of 0.1 *N* HCl had been allowed to stand for a short time, the mixture was basified with 10% aq. NaOH solution and extracted with ether. The extract was washed with H_2O and dried on K_2CO_3. Removal of the solvent gave the free base of VI, whose infrared spectrum was identical with that of the sample (VI).

Hydrolysis of IXb with 0.1*N* Hydrochloric Acid——After the same treatment of 0.3 g. of IXb with 50 ml. of 0.1*N* HCl solution, the mixture was extracted with ether. The solvent layer was separated and dried on K_2CO_3. Removal of the solvent gave benzaldehyde as an oil, whose 2,4-dinitrophenylhydrazone[13] was identical with that of an authentic sample, m.p. 237°. The above acidic aqueous solution was basified with 10% aq. NaOH solution and extracted with ether. The solvent layer was separated, washed with H_2O and dried on K_2CO_3. Removal of the solvent afforded VI as an oil, whose infrared spectrum was identical with that of the compound (VI) as above.

Hydrolysis of IXb with Water——A mixture of 0.1 g. of IXb, 0.5 ml. of H_2O and 10 ml. of EtOH was refluxed for 1 hr. Removal of the solvent and distillation *in vacuo* gave VI as an oil, whose infrared spectrum was identical with that of the above sample (VI).

Catalytic Hydrogenation of IXa——The compound (IXa) (1.24 g.) in 30 ml. of MeOH was hydrogenated in the presence of 50 mg. of PdO, 105 ml. of H_2 being absorbed. Filtration and evaporation of the solvent gave an oil, whose distillation *in vacuo* afforded 1.1 g. (93.3%) of the compound (Xb) as a colorless viscous oil, b.p$_{0.1}$ 170°. *Anal.* Calcd. for $C_{18}H_{22}N_2$: C, 81.16; H, 8.33. Found : C, 80.99; H, 8.60. The τ-values of NMR spectrum are shown in Table I.

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13) N. R. Campbell : Analyst, **61**, 392 (1936).

The picrate formed yellowish-green cubes (from AcOH), m.p. 162～163° (decomp.). *Anal.* Calcd. for $C_{18}H_{22}N_2 \cdot 2C_6H_3O_7N_3 \cdot H_2O$: C, 48.52; H, 4.07; N, 15.09. Found : C, 49.01; H, 4.01; N, 14.81.

Catalytic Hydrogenation of IXb——The compound (Ⅸb) (0.87 g.) in 50 ml. of MeOH was hydrogenated in the presence of 117 mg. of PdO, 107 ml. of H_2 being absorbed. Filtration and distillation of the solvent gave an oil, whose distillation *in vacuo* afforded 0.5 g. (78.1%) of Ⅵ as a colorless viscous oil, b.p$_1$ 220°. The infrared and NMR spectra were identical with those of Ⅵ.

1-Methyl-3-(N-benzyl-N-methylaminomethyl)-1,2,3,4-tetrahydroquinoline (XI)——Dimethyl sultate (0.66 g.) was added dropwise to 0.5 g. of Ⅵ on cooling, and the mixture was heated on a water-bath for 1 hr. After shaking with 10 ml. of 33% KOH solution, the reaction mixture was extracted with ether. The solvent layer was separated, washed with water and dried on K_2CO_3. Removal of the solvent gave an oil, whose distillation *in vacuo* b.p$_1$ 230～240° (bath) afforded 0.2 g. (36.4%) of Ⅺ as a pale yellow viscous oil, which was comparatively labile. Furthermore, characterization as its salts resulted in failure.

1-Methyl-1,2,3,4-tetrahydroquinoline (Kairoline) (XII)——Dimethyl sulfate (3.7 g.) was added dropwise to 3.5 g. of 1,2,3,4-tetrahydroquinoline[14] on cooling, and the mixture was warmed on a water-bath for 0.5 hr. After the above mixture had been shaken with 10 ml. of 33% KOH solution, it was extracted with ether. The solvent layer was separated, dried on K_2CO_3 and evaporated to give an oil, to which was added 5 ml. of Ac_2O. The mixture was heated under reflux for 1 hr. Removal of Ac_2O *in vacuo* gave an oil, which was dissolved in benzene. The benzene extract was washed with 10% NaOH solution and then 10% HCl solution. From the benzene layer 0.9 g. of neutral substance was obtained. The above acidic solution was basified with 10% NaOH solution and extracted with ether. The extract was dried on K_2CO_3 and evaporated to give an oil, whose distillation *in vacuo* gave 1.4 g. (43.7%) of Ⅻ as a colorless oil, b.p$_3$ 96°. The τ-values of NMR spectrum are shown in Table I.

Recrystallization of the picrate from EtOH gave yellow prisms, m.p. 125° (recorded 121°,[15] 123～124°[16] and 136～137°[17]).

We express our deep gratitude to Mr. T. Hayasaka of Grelan Pharmaceutical Co., Ltd., for his earnest experimental assistance. We also thank Mrs. F. Seto, Miss N. Nanjo and Miss R. Kobayashi for microanalyses, and Miss T. Oikawa for infrared spectra measurement.

Summary

In order to test the analgesic action of azabenzomorphane derivatives, 3-benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*][1,3]diazocine (Ⅸa) and its 2-phenyl derivative (Ⅸb) were synthesized by cyclization of 3-(N-benzylaminomethyl)-1,2,3,4-tetrahydroquinoline (Ⅵ) with paraformaldehyde and benzaldehyde. Both compounds were found to be extremely labile against acid.

Methods for synthesis of Ⅵ, which was used as a key intermediate, were also examined using 3-cyanoquinoline (Ⅱ) as a starting material according to two procedures, that is, a) reduction of 3-benzylcarbamoylquinoline (Ⅳ) and b) reductive benzylation of 3-aminomethyl-1,2,3,4-tetrahydroquinoline with benzaldehyde in the presence of hydrogen and platinum oxide.

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[14] E. Bamberger, F. Lengfeld : Ber., **23**, 1138 (1890).

[15] R. J. Schever, W. I. Kimoto, K. Ohinata : J. Am. Chem. Soc., **75**, 3029 (1953).

[16] F. H. Beilstein : "Handbuch der Organischen Chemie," Erstes Ergänzungswerk, Vol. 20, Vierte Auflage, Julius Springer, Berlin, 1935, p. 94～95.

[17] J. F. Thorpe, A. S. Wood : J. Chem. Soc., **1913**, 1611.