[Chem. Pharm. Bull. 13(10)1225~1230(1965)]

UDC 615.782-012 : 547.833.07

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Azabenzomorphane and Related Compounds. VIII.[*3]
A Synthesis of 4-Benzyl-3,4,5,6-tetrahydro-1*H*-2,6-methanobenzo[*e*][1,3]diazocine.[*4]

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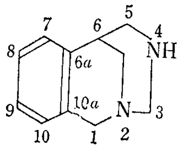
In the preceding papers,[*3],1~4) several kinds of azabenzomorphane derivatives were synthesized. The purpose of the present investigation was to synthesize 3,4,5,6-tetrahydro-1*H*-2,6-methanobenzo[*e*][1,3]diazocine (I) in order to test their analgesic activity.



I

Since the skeleton of the compound (I) as above has not been synthesized yet, methods for its synthesis were examined using 4-cyanoisoquinoline (Ⅱ) as a starting material according to the procedures reported in the syntheses of imidazolidine and hexahydropyrimidine derivatives,5~7) 1,3-diaza-adamanthane8) and azabenzomorphane derivatives.9) Thus, synthetic methods of 4-(benzylaminomethyl)-1,2,3,4-tetrahydroisoquinoline (Ⅵ), which was thought to be a key compound for syntheses of 4-benzyl-3,4,5,6-tetrahydro-1*H*-2,6-methanobenzo[*e*][1,3]diazocine (XVIa) and its 3-phenyl-derivative (XVIb), were investigated according to the three methods as follows.

Hydrolysis of 4-cyanoisoquinoline (Ⅱ)10) which was obtained by Rosenmund-von Braun reaction of 4-bromoisoquinoline11) gave 4-isoquinolinecarboxylic acid (Ⅲ).12) Catalytic hydrogenation with platinum oxide of the amide (Ⅳ), which was obtained by condensation of Ⅲ with benzylamine in the presence of phosphoryl chloride, gave 4-(benzylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline (Ⅴ). Reduction of the above carboxamide (Ⅴ) with lithium aluminum hydride gave 4-(benzylaminomethyl)-1,2,3,4-tetrahydroisoquinoline (Ⅵ), which was also characterized as its benzoyl derivative (Ⅶ).

In the second place, catalytic hydrogenation with platinum oxide of 4-aminomethylisoquinoline (Ⅷ),13) which was obtained by hydrogenation of Ⅱ with Raney nickel, did not give an expected 4-aminomethyl-1,2,3,4-tetrahydroisoquinoline (XV), but a mixture of ammonium chloride and 4-methylisoquinoline (Ⅸ). The latter compound (Ⅸ) was characterized as its picrate, whose melting point agreed with that of an authentic

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[*3] Part Ⅶ : This Bulletin, **13**, 1220 (1965).
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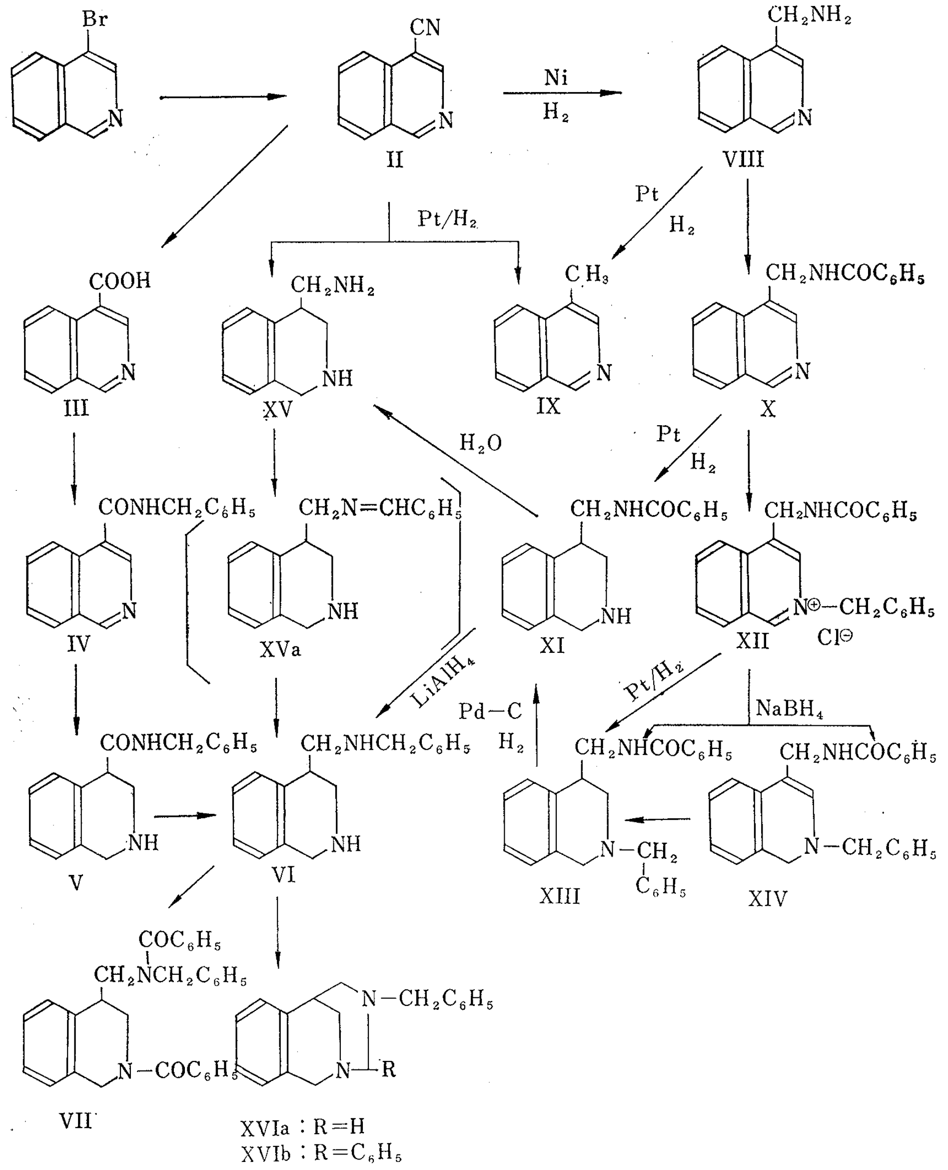

Chart 1.

sample (lit.,14) m.p. 202~203°). Furthermore, nuclear magnetic resonance spectrum of IX showed the methyl protons at $7.42\,\tau$.

Catalytic hydrogenation of the benzoyl derivative (X), which was obtained by benzoylation of VIII in order to prevent from deamination during hydrogenation, gave 4-(benzoylaminomethyl)-1,2,3,4-tetrahydroisoquinoline (XI), which was converted into an objective compound (VI). On the other hand, XI was also found to be identical with the compound which was also alternatively synthesized as follows. Catalytic hydrogenation with platinum oxide of 2-benzyl-4-(benzoylaminomethyl)isoquinolinium chloride (XII), which was obtained by the reaction between the compound (X) and benzyl chloride, afforded 2-benzyl-4-(benzoylaminomethyl)-1,2,3,4-tetrahydroisoquinoline (XIII). Debenzylation of XIII with 10% palladium-carbon at 50° (30 atm.) gave the same compound (XI) as above, whose infrared spectrum was superimposable on that of the above sample.

Furthermore, reduction of XII with sodium borohydride gave a mixture of the above compound (XIII) and 2-benzyl-4-(benzoylaminomethyl)-1,2-dihydroisoquinoline (XIV), the

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14) E. Späth, F. Burger, W. Kuntara: Chem. Ber., **63**, 134 (1930).

latter of which was so lavile in the air that colorless needles gradually change to a reddish substance. Further reduction of this compound (XIV) with sodium borohydride or by hydrogenation in the presence of platinum oxide also afforded the same compound (XIII) as above. Conversion of 2-methylisoquinolinium iodide to 2-methyl-1,2-dihydroisoquinoline by reduction with lithium aluminum hydride[15] is thought to be similar to this reaction.

At last, catalytic hydrogenation of II in acetic acid with platinum oxide gave a mixture of IX and 4-aminomethyl-1,2,3,4-tetrahydroisoquinoline (XV), but this reaction needed a large amount of platinum oxide and it took much time for hydrogen to be absorbed, giving the objective compound (XV) in 17.3% yield. The compound (XV) was also obtained by hydrolysis of XI. Catalytic hydrogenation with platinum oxide of a mixture of XV and benzaldehyde also yielded the same compound (VI) as above, whose infrared spectrum was identical with that of the above sample.

Finally, ring closure with paraformaldehyde and benzaldehyde of the compound (VI), which was obtained by three kinds of procedures as above, gave 4-benzyl-3,4,5,6-tetrahydro-1*H*-2,6-methanobenzo[*e*][1,3]diazocine (XVIa) and 3-phenyl-4-benzyl-3,4,5,6-tetrahydro-1*H*-2,6-methanobenzo[*e*][1,3]diazocine (XVIb) respectively. Attempted formation of XVIa by heating the compound (VI) with 37% formalin at 60° in methanol for 1 hr., resulted in failure.

All attempts to obtain our final objective compound (I) by catalytic hydrogenation of XVIa and XVIb with 10% palladium-carbon, palladium oxide, platinum oxide, or Raney nickel resulted in failure, giving a starting material (XVIa and XVIb). Furthermore, attempted derivation of both compounds as above to I with sodium in liquid ammonia also recovered the starting material.

It is well known that the compound of methylenediamine type like imidazolidine and hexahydropyrimidine derivatives is generally easy to be decomposable against acid.[5~7] Therefore, the following experiments were examined in order to inspect the stability of XVIa and XVIb against acid. After the compound (XVIa) had been dissolved in 0.1*N* hydrochloric acid, basification of the acidic solution with sodium hydroxide

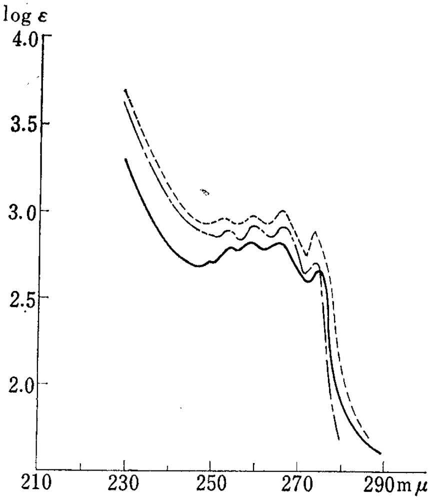

Fig. 1. Ultraviolet Spectra in Ethanol

———— VI
……………… XVIa
—·—·— XVIb

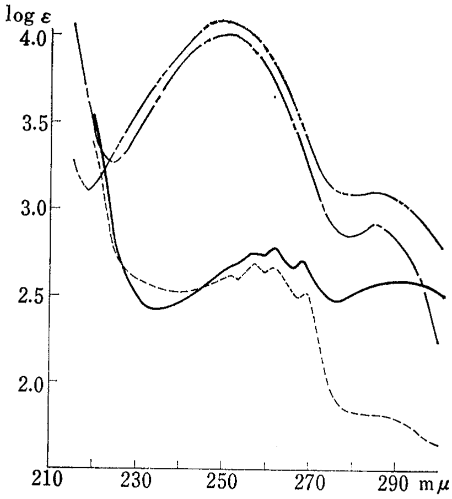

Fig. 2. Ultraviolet Spectra in 0.1*N* Hydrochloric Acid

———— VI
……………… XVIa
—·—·— XVIb
—··—··— C_6H_5CHO

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[15] H. Schmid, P. Karrer: Helv. Chim. Acta, **32**, 960 (1950).

gave the compound (VI), whose infrared spectrum was superimposable on that of the sample (VI) as above. The same treatment of XVIb with acid gave a mixture of VI and benzaldehyde. Ultraviolet spectra of XVIa in ethanol (Fig. 1) and in 0.1*N* hydrochloric acid (Fig. 2) were almost the same, but the absorption curve of the compound (XVIb) in 0.1*N* hydrochloric acid (Fig. 2) was similar to that of benzaldehyde, which is different from that of XVIb in ethanol (Fig. 1).

Furthermore, XVIb was found to be decomposed with picric acid. That is, treatment of XVIb with picric acid gave the picrate of VI.

Experimental[*5]

4-Benzylcarbamoylisoquinoline (IV)——A mixture of 10 g. of 4-isoquinolinecarboxylic acid (III)[12] and 6.2 g. of benzyl amine was heated at 160°. To the cooled mixture was added 13.2 g. of $POCl_3$. Soon after the mixture was gradually heated up to 130°, it was decomposed with ice-water, basified with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was dried on K_2CO_3 and distilled off, to give 14 g. of crystals (IV), whose recrystallization from EtOH afforded 9.5 g. (63.3%) of IV as colorless needles, m.p. 168.5~169.5°. *Anal.* Calcd. for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.38; N, 10.68. Found : C, 77.61; H, 5.43; N, 10.72. IR ν_{max}^{KBr} cm^{-1} : 3300 (NH); 1640 (C=O).

4-Benzylcarbamoyl-1,2,3,4-tetrahydroisoquinoline (V)——The compound (IV) (1.3 g.) in 50 ml. of MeOH was hydrogenated at atmospheric pressure in the presence of 0.5 ml. of conc. HCl and 350 mg. of PtO_2, 250 ml. of H_2 (Calcd., 224 ml.) being absorbed. Filtration and removal of the solvent gave crude hydrochloride of V as crystals, which 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. Concentration of the solvent afforded a free base of V, whose recrystallization from H_2O gave 1.05 g. (80.8%) of colorless needles, m.p. 107~108°. *Anal.* Calcd. for $C_{17}H_{18}ON_2$: C, 76.66; H, 6.81; N, 10.52. Found : C, 76.61; H, 6.81; N, 10.71.

4-Methylisoquinoline (IX)——A solution of 1.95 g. of VIII[13]·HCl in 80 ml. of MeOH was hydrogenated in the presence of 200 mg. of PtO_2, 221 ml. of H_2 (Calcd., 224 ml.) being absorbed. Filtration and removal of the solvent gave the residue, which was extracted with 15 ml. of hot EtOH in order to remove an inorganic substance. An insoluble NH_4Cl (0.3 g.) was collected by filtration and recognized by the test of $AgNO_3$ and Nessler reagent. The ethanolic filtrate was distilled off, basified with 10% aq. NaOH, and extracted with ether. The solvent was dried on K_2CO_3 and evaporated to give an oil, whose purification by distillation *in vacuo* gave 0.95 g. (66.5%) of IX, b.p$_3$ 106~108°. IR ν_{max}^{liquid} cm^{-1} : 1610 (C=N). Recrystallization of IX·HCl from EtOH gave colorless needles, m.p. 264~265° (decomp.). *Anal.* Calcd. for $C_{10}H_9N \cdot HCl$: C, 66.85; H, 5.61; N, 7.80. Found : C, 66.59; H, 5.74; N, 8.03.

4-(Benzamidomethyl)isoquinoline (X)——A solution of 2.4 g. of the preceding amine (VIII) in 50 ml. of $CHCl_3$ was treated with 5.4 ml. of benzoyl chloride in the presence of 30% aq. KOH. The solvent layer was separated, dried on K_2CO_3 and distilled off, to give the crude amide (X) as crystals, whose recrystallization from EtOH afforded 3.55 g. (88.7%) of colorless plates, m.p. 162~163°. *Anal.* Calcd. for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.60; H, 5.37; N, 10.52. IR ν_{max}^{KBr} cm^{-1}: 3250 (NH); 1640 (C=O).

4-(Benzamidomethyl)-1,2,3,4-tetrahydroisoquinoline (XI)——a) The above amide (X) (1.5 g.) in 80 ml. of MeOH was hydrogenated at atmospheric pressure in the presence of 0.5 ml. of conc. HCl and 400 mg. of PtO_2, H_2 being absorbed. After filtration and removal of the solvent, the residue was basified with 10% aq. NaOH 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 1.2 g. (80%) of XI as colorless needles, m.p. 128.5~129.5°, whose IR spectrum was identical with that of the compound obtained by the procedure (b). This compound also showed no depression of melting point on admixture with the substance described later.

b) The compound (XIII) (25 g.) in 150 ml. of MeOH was hydrogenated at 50 atm. in the presence of 17 g. of 10% Pd-C and 7 ml. of conc. HCl on heating at 50°, ca. 1600 ml. of H_2 being absorbed. After filtration and removal of the solvent, the residue was basified with 10% aq. NaOH, extracted with $CHCl_3$ and dried on K_2CO_3. Evaporation of the solvent gave 18 g. of the crude crystals, which were recrystallized from EtOH to afford 12 g. (64%) of XI as colorless needles, m.p. 128.5~129.5°. *Anal.* Calcd. for $C_{17}H_{18}ON_2$: C, 76.66; H, 6.81; N, 10.52. Found : C, 76.59; H, 7.02; N, 10.57. IR ν_{max}^{KBr} cm^{-1} : 3340 and 3280 (NH), 1640 (C=O).

2-Benzyl-4-(benzamidomethyl)isoquinolinium Chloride (XII)——A mixture of 25.4 g. of X and 13.5 g. of benzyl chloride was heated at 150°. After fusion the mixture soon solidified. Recrystallization from EtOH gave 36 g. (95.7%) of XII colorless cottonlike crystals, m.p. 228~229°. *Anal.* Calcd. for $C_{24}H_{21}ON_2Cl$: N, 7.20. Found : N, 6.76. IR ν_{max}^{KBr} cm^{-1} : 3400 (NH); 1640 (CO).

[*5] Melting points are not corrected.

2-Benzyl-4-(benzamidomethyl)-1,2,3,4-tetrahydroisoquinoline (XIII) and 2-Benzyl-4-(benzamidomethyl)-1,2-dihydroisoquinoline (XIV). a) Reduction of XII with Sodium Borohydride——To a solution of 34 g. of XII in 500 ml. of MeOH and 20 ml. of H_2O was added in small portions with shaking 33.3 g. of $NaBH_4$. The mixture was refluxed for 1 hr., distilled, and basified with 10% aq. KOH solution. The crystals separated were collected by filtration and recrystallization from ca. 100 ml. of EtOH gave 15.1 g. (48.9%) of XIV as colorless needles, m.p. 129～134° (it changes brown at 120°). *Anal.* Calcd. for $C_{24}H_{22}ON_2$: C, 81.32; H, 6.26; N, 7.90. Found : C, 81.10; H, 6.15; N, 7.97. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 3300 (NH); 1630 (C=O).

Concentration of the above filtrate in case of recrystallization gave 9.1 g. (29.4%) of XIII as colorless prisms, m.p. 99～100°. *Anal.* Calcd. for $C_{24}H_{24}ON_2$: C, 80.86; H, 6.79; N, 7.86. Found : C, 80.59; H, H, 6.83; N, 7.84. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 3350 (NH); 1640 (C=O).

b) **Catalytic Hydrogenation of XII**——The compound (XII) (1 g.) in 50 ml. of MeOH was hydrogenated at atmospheric pressure in the presence of 250 mg. of PtO_2, 116 ml. of H_2 (Calcd., 115 ml.) being absorbed. Filtration and removal of the solvent gave the crude crystals, which were basified with 10% aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O and dried on K_2CO_3. Concentration of the extract and recrystallization from EtOH afforded 0.7 g. (76.9%) of XIII as colorless prisms, m.p. 99～100°, whose IR spectrum was identical with that of the compound obtained by the procedure (a). This compound also showed no depression of melting point on admixture with the above one.

c) **Reduction of XIV with Sodium Borohydride**——To a solution of 11.8 g. of XIV in 300 ml. of MeOH containing 3 ml. of conc. HCl was added in small portions with shaking 4.3 g. of $NaBH_4$. The mixture was refluxed for 1 hr., distilled, and basified with 10% aq. KOH. Filtraiton of the crystals precipitated and recrystallization from EtOH gave 6.4 g. (54.2%) of XIII as colorless prisms, m.p. 99～100°, which were identical with the sample as above from IR spectrum and mixed melting point determination.

d) **Catalytic Hydrogenation of XIV**——Catalytic hydrogenation with H_2 of 0.3 g. of XIV in 50 ml. of MeOH and 0.1 ml. of conc. HCl in the presence of 50 mg. of PtO_2 gave 0.2 g. (66.7%) of the same compound (XIII) as above.

4-Aminomethyl-1,2,3,4-tetrahydroisoquinoline (XV). a) Catalytic Hydrogenation of II——The compound (II) (5.5 g.) in 100 ml. of AcOH was hydrogenated in the presence of 6 ml. of conc. HCl and 800 mg. of PtO_2, 3300 ml. of H_2 being absorbed. Filtration and distillation of AcOH *in vacuo* afforded the crude HCl salt of XV, which was dissolved in H_2O, basified with an excess of K_2CO_3 and extracted with $CHCl_3$. The extract was dried on K_2CO_3. Concentration of the solvent gave an oil, which was distilled *in vacuo* to give 1.7 g. (33.3%) of a colorless oil (IX), b.p$_3$ 106～108°, whose IR spectrum was identical with that of the sample (IX) described previously, and 1.0 g. (17.3%) of a pale yellow oil (XV), b.p$_3$ 150°. IR $\nu_{\max}^{\text{liquid}}$ cm^{-1} : 3400 and 3300 (NH). Recrystallization of XV·HCl from MeOH afforded colorless plates, m.p. >284°. *Anal.* Calcd. for $C_{10}H_{14}N\cdot 2HCl$: C, 51.07; H, 6.86; N, 11.91. Found : C, 51.01; H, 6.81; N, 12.00.

b) **Hydrolysis of XI**——After a mixture of 1.0 g. of XI and 15 ml. of conc. HCl had been heated under reflux for 4 hr., the mixture was cooled and benzoic acid separated was filtered off, the filtrate being extracted with ether.

Evaporation of the above aqueous filtrate and recrystallization of the residue from MeOH gave 0.6 g. (68.2%) of XV as colorless plates, m.p. >284°, whose IR spectrum was identical with that of the compound obtained by the procedure (a).

4-(N-Benzylaminomethyl)-1,2,3,4-tetrahydroisoquinoline (VI). a) Reduction of V with Lithium Aluminum Hydride——A solution of 0.5 g. of the amide (V) in 30 ml. of dry dioxane was dropwise added to a stirred suspension of 0.35 g. of $LiAlH_4$ in 50 ml. of dioxane at 100°. The mixture was then refluxed for 5.5 hr. After concentration of the solvent, an excess 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, washed with H_2O, and dried on K_2CO_3. Evaporation of the solvent and distillation *in vacuo* gave 0.4 g. (84.2%) of a colorless oil (VI), b.p$_{23}$ 194°. IR $\nu_{\max}^{\text{liquid}}$ cm^{-1} : 3300 (NH). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε) : 257.5 (2.76), 262 (2.80), 268 (2.72), 290 (5.59).

The picrate of VI formed yellow needles (from AcOH), m.p. 217° (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, 49.26; H, 3.81; N, 15.61.

b) **Reduction of XI with Lithium Aluminum Hydride**——A solution of 3.0 g. of XI in 80 ml. of dioxane was dropwise added to a stirred suspension of 2.5 g. of $LiAlH_4$ in 100 ml. of dioxane at 100°. The mixture was then refluxed for 2 hr. After concentration of the solvent at atmospheric pressure, 100 ml. of benzene was added and the excess of reagent was decomposed with H_2O. The benzene layer was separated, and dried on K_2CO_3. Evaporation of the solvent gave 0.28 g. of VI as an oil, whose picrate formed yellow needles, m.p. 217° (decomp.). IR spectra of free base and picrate were identical with those of the substance obtained by the procedure (a).

c) **Reductive Alkylation of XV**——After a mixture of 400 mg. of XV and 260 mg. of benzaldehyde in 10 ml. of MeOH was shaken at 60° for 10 min., the solvent was distilled off, to give XVa as a viscous syrup. The preceding base (XVa) (250 mg.) was hydrogenated in 20 ml. of MeOH in the presence of 100 mg. of PtO_2, 19 ml. of H_2 being absorbed. Filtration and removal of the solvent gave an oil, whose picrate was recrystallized from AcOH to afford 290 mg. (40.8%) of yellow needles, m.p. 217° (decomp.). IR spectrum of this picrate was identical with that of the above one.

2-Benzoyl-4-(N-benzylbenzamidomethyl)-1,2,3,4-tetrahydroisoquinoline (VII)——A solution of 0.25 g. of VI in $CHCl_3$ was benzoylated with 0.9 ml. of benzoyl chloride in the presence of 5% aq. NaOH solution by Schotten-Baumann reaction.

The solvent layer was separated, washed with 10% aq. HCl and dried on K_2CO_3. Evaporation of the solvent gave a solid which was recrystallized from EtOH to give 0.35 g. (77.8%) of colorless needles, m.p. 143~146°. *Anal.* Calcd. for $C_{31}H_{28}O_2N_2$: C, 80.84; H, 6.13; N, 6.08. Found : C, 80.65; H, 6.02; N, 6.37. IR ν_{max}^{KBr} cm^{-1} : 1620 (CO).

4-Benzyl-3,4,5,6-tetrahydro-1*H*-2,6-methanobenzo[*e*][1,3]diazocine (XVIa)——A mixture of 1.0 g. of VI and 3.0 g. of paraformaldehyde in 20 ml. of benzene was refluxed for 40 min. and then the excess of 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 0.85 g. (81%) of XVIa as a colorless viscous syrup, b.p$_{1.2}$ 156~158°. UV λ_{max}^{EtOH} mμ (log ε) : 253.5 (2.96), 259.5 (2.99), 266 (3.00), 273.5 (2.87). UV $\lambda_{max}^{0.1N\ HCl}$ mμ (log ε) : 251.5 (2.64), 257 (2.69), 261.5 (2.56), 268 (2.54).

The picrate of XVIa formed yellow plates, m.p. 159~159.5° (from AcOH). *Anal.* Calcd. for $C_{18}H_{20}N_2 \cdot C_6H_3O_7N_3$: C, 58.42; H, 4.70; N, 14.19. Found : C, 58.35; H, 4.74; N, 14.14.

3-Phenyl-4-benzyl-3,4,5,6-tetrahydro-1*H*-2,6-methanobenzo[*e*][1,3]diazocine (XVIb)——After a mixture of 1.35 g. of VI and 0.57 g. of benzaldehyde in 30 ml. of MeOH had been heated at 60° for 10 min., the solvent was removed *in vacuo* and the residue was extracted with ether. The extract was washed with 10% aq. Na_2CO_3 solution and dried on K_2CO_3. Removal of the solvent gave the crude base (XVIb) as crystals, which were recrystallized from petr. ether to give 1.12 g. (1.5%) of colorless prisms, m.p. 124~126°. UV λ_{max}^{EtOH} mμ (log ε) : 253.5 (2.86), 259.5 (2.92), 266 (2.93), 274 (2.72). UV $\lambda_{max}^{0.1N\ HCl}$ mμ (log ε) : 250 (4.08), 284 (3.11). *Anal.* Calcd. for $C_{24}H_{24}N_2$: C, 84.66; H, 6.99; N, 8.23; mol. wt., 340. Found : C, 84.37; H, 6.99; N, 8.20; mol. wt. (Rast), 361.

A saturated solution of picric acid in EtOH was added to a solution of XVIb in EtOH in order to form the picrate of XVIb. Recrystallization from AcOH of the picrate separated as above gave the one of VI as yellow needles, m.p. 217° (decomp.), whose IR spectrum was superimposable on that of an authentic picrate of VI. Furthermore, IR spectrum of the free base, which was obtained by treatment of the above picrate with 10% aq. NaOH, was identical with that of VI.

Hydrolysis of XVIa with 0.1*N* Hydrochloric Acid——After a solution of 50 mg. of XVIa 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, which was identical with that of the sample (VI).

Hydrolysis of XVIb with 0.1*N* Hydrochloric Acid——After the same treatment of 50 mg. of XVIb with 20 ml. of 0.1*N* HCl, 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[16] was identical with that of an authentic sample, m.p. 237°. The above aqueous solution was basified with 10% aq. NaOH solution and extracted with ether. The solvent layer was separated and dried on K_2CO_3. Removal of the solvent afforded VI as an oil, whose IR spectrum was identical with that of the compound as above.

We thank President A. Yanagisawa, Mr. A. Takagi, and Grelan Pharmaceutical Co., Ltd. for their grateful assistance. We also thank Mrs. F. Seto and Miss N. Nanjo for microanlyses, and Miss T. Oikawa for IR spctra measurement.

Summary

In order to test the analgesic action of azabenzomorphane derivatives, 4-benzyl-3,4,5,6-tetrahydro-1*H*-2,6-methanobenzo[*e*][1,3]diazocine (XVIa) and its 2-phenyl derivative (XVIb) were synthesized by cyclization of 4-(benzylaminomethyl)-1,2,3,4-tetrahydroisoquinoline with paraformaldehyde and benzaldehyde. Both compounds were found to be extremely lavile against acid.

Methods for synthesis of VI, which was used as a key intermediate, were also examined using 4-cyanoisoquinoline (II) as a starting material according to three procedures, namely, a) catalytic hydrogenation of 4-benzylaminoisoquinoline (IV), b) reduction of 4-(benzamidomethyl)isoquinoline (X), and c) hydrogenation of the cyclization product between 4-aminomethyl-1,2,3,4-tetrahydroisoquinoline (XV) and benzaldehyde.

(Received April 28, 1965)

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[16] N. R. Campbell : Analyst, **61**, 392 (1936).