Summary

In connection with the study of the acetylation of 7-aminopyrazolo[1,5-*a*]pyrimidines, further studies on the acetylation were investigated. Mono- and diacetates were obtained from the compounds being substituted with methyl-, phenyl-, or ethoxycarbonyl group at the C-6 position and only monoacetates being unsubstituted or with a cyano group at the C-6 position. The reason for this was confirmed to be the steric effect of the substituents at the C-6 position.

Various 7-acylamino (XXXVII～XL, XLII～XLVI), 7-alkylamino (XLI, LVIII～LXVI), and 7-H pyrazolo[1,5-*a*]pyrimidines (LIII～LV) were also derived.

(Received April 26, 1965)

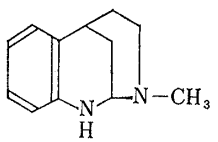
[Chem. Pharm. Bull. 13(10)1220～1224(1965)]

UDC 615.782-012 : 547.833.07

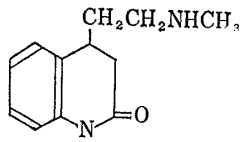
156. Tetsuji Kametani, Kazuo Kigasawa,[*1] and Mineharu Hiiragi[*2] : Azabenzomorphane and Related Compounds. VII.[*3] Synthesis of 1,2,3,4,5,6-Hexahydro-2,6-methanobenzo[*d*][1,3]diazocine Derivatives.[*4]

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

In the previous paper[*3, 1~3] four kinds of azabenzomorphane derivatives were synthesized. In this paper will be described some results of synthetical experiments of 1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*][1,3]diazocine derivatives, which appeared to have some analgesic activity.



I



II

Since the skeleton of the azabenzomorphane derivatives as above has not been synthesized yet, methods for its synthesis were examined using 1-methyl-4-carboxymethylcarbostyril (III) as a starting material.

Reductive cyclization of 4-(2-methylaminoethyl)-3,4-dihydrocarbostyril (II) gave the compound (I)[*3] in an excellent yield, whose structure was characterized by infrared, ultraviolet, nuclear magnetic resonance spectra and analytical data. Reductive cyclization of 1-methyl-4-(2-aminoethyl)-3,4-dihydrocarbostyril (Xa) and 1-methyl-4-(2-methylaminoethyl)-3,4-dihydrocarbostyril (Xb) also gave, respectively, 1-methyl- (XIa) 1,3-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*][1,3]diazocine (XIb).

---

*1 Kita-4-bancho, Sendai (亀谷哲治, 気賀沢和雄).
*2 Shinmachi-3-chome, Setagaya-ku, Tokyo (柊木峯治).
*3 Part VI : T. Kametani, K. Kigasawa, M. Hiiragi : Yakugaku Zasshi, **85**, 871 (1965).
*4 This forms part CXX of "Studies on the Syntheses of Heterocyclic Compounds" by Tetsuji Kametani.

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).

Methods for the synthesis of 4-carboxymethyl-1-methylcarbostyril (Ⅲ) were examined using citric acid as a starting material according to the procedures reported in a previous paper.[4] Cyclization of the dianilide, which was obtained by heating a mixture of diethyl acetonedicarboxylate and methylaniline, with 80% sulfuric acid gave the compound (Ⅲ).

Esterification of Ⅲ with methanol and ethanol gave, respectively, methyl ester (Ⅳa) and ethyl ester (Ⅳb), the latter of which had already been synthesized as crystals, m.p. 94~95°, by Kaslow and Cook.[5] Our sample (Ⅳb) showed m.p. 99~100°, and was characterized by its elementary analysis and infrared spectrum.

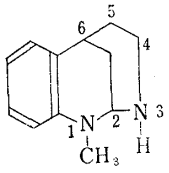
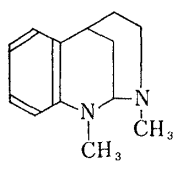
Catalytic hydrogenation of Ⅳa in methanol with platinum oxide gave 1-methyl-4-methoxycarbonylmethyl-3,4-dihydrocarbostyril (Va), which was converted into 3,4-dihydro-1-methyl-4-carboxymethylcarbostyril (Vb) by hydrolysis with concentrated hydrochloric acid.

Reduction of Va with lithium aluminum hydride in ether gave a mixture of 1-methyl-4-(2-hydroxyethyl)-3,4-dihydrocarbostyril (Ⅵ), b.$p_{0.65}$ 170°, and 1-methyl-4-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (Ⅶ), b.p_2 145°, whose infrared spectrum was identical with that of an authentic sample (Ⅶ), obtained by methylation of 4-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (Ⅷ)*3 in methanol with methyl iodide.

Chlorination of Ⅵ in chloroform with thionyl chloride gave 1-methyl-4-(2-chloroethyl)-3,4-dihydrocarbostyril (Ⅸ), which was used in the following reaction without purification. Ammonolysis of Ⅸ in ethanol at 100° in a sealed tube afforded 1-methyl-4-(2-aminomethyl)-3,4-dihydrocarbostyril (Xa) as a basic oil, b.$p_{1.2}$ 162.5°, which was characterized as the oxalate, m.p. 168~169° (decomp.). Methylamination of the above halide (Ⅸ) in ethanol with methylamine hydrochloride and potassium hydroxide at 110~120° in a sealed tube gave 1-methyl-4-(2-methylaminoethyl)-3,4-dihydrocarbostyril (Xb) as an oil, b.$p_{2.6}$ 170° (m.p. 51~53°), which was also characterized as its oxalate, m.p. 183~184° (decomp.).

Reduction of Xa and Xb in ethanol with metallic sodium gave, respectively, 1-methyl- (Ⅺa) and 1,3-dimethylazabenzomorphane derivatives (Ⅺb) in an excellent yield. This reductive cyclization removed the carbonyl band, which was recognized at 1670 cm^{-1} in case of Xa and Xb. Furthermore, Ⅺa shows a maximum at 3360 cm^{-1} (NH), and the NH band of Xb which was shown at 3350 cm^{-1} disappeared in case of Ⅺb.

Table I. Nuclear Magnetic Resonance Spectra of Ⅺa and Ⅺb.

Compound	Proton type	τ-value[a]
	N_1-CH_3	7.03 (3H)
	N_3-H	6.84 (1H)
	N-C_2-N (H)	5.76 (1H)
	aromatic	2.83~3.6 (4H)
	N_1-CH_3	6.90 (3H)
	N_3-CH_3	7.62 (3H)
	N-C_2-N (H)	5.88 (1H, triplet)
	aromatic	2.82~3.58 (4H)

a) The bands refer to 60 Mc. spectra in deuterochloroform, using tetramethylsilane as an internal standard (Varian A-60).

4) T. Kametani, M. Hiiragi, K. Kigasawa: Yakugaku Zasshi, **85**, 867 (1965).
5) C. E. Kaslow, D. J. Cook: J. Am. Chem. Soc., **67**, 1969 (1945).

The ultraviolet spectra of XIa and XIb showed hypsochromic shift in acidic media, which was characteristic feature of Ph-N-C-N.[6~8)]

Nuclear magnetic resonance spectra of XIa and XIb are shown in Table I. In case of XIb, the proton at C_2-carbon was recognized in triplet at 5.88 τ. This fact reveals that Ladenburg reduction of Xb gave the cyclized product (XIb).

Furthermore, reductive ring-closure of 1-methyl-4-carbamoylmethylcarbostyril (XII), which was obtained by amidation of IVa with 28% ammonium hydroxide solution, also gave the above compound (XIa), whose infrared spectrum was superimposable on that of the above authentic sample.

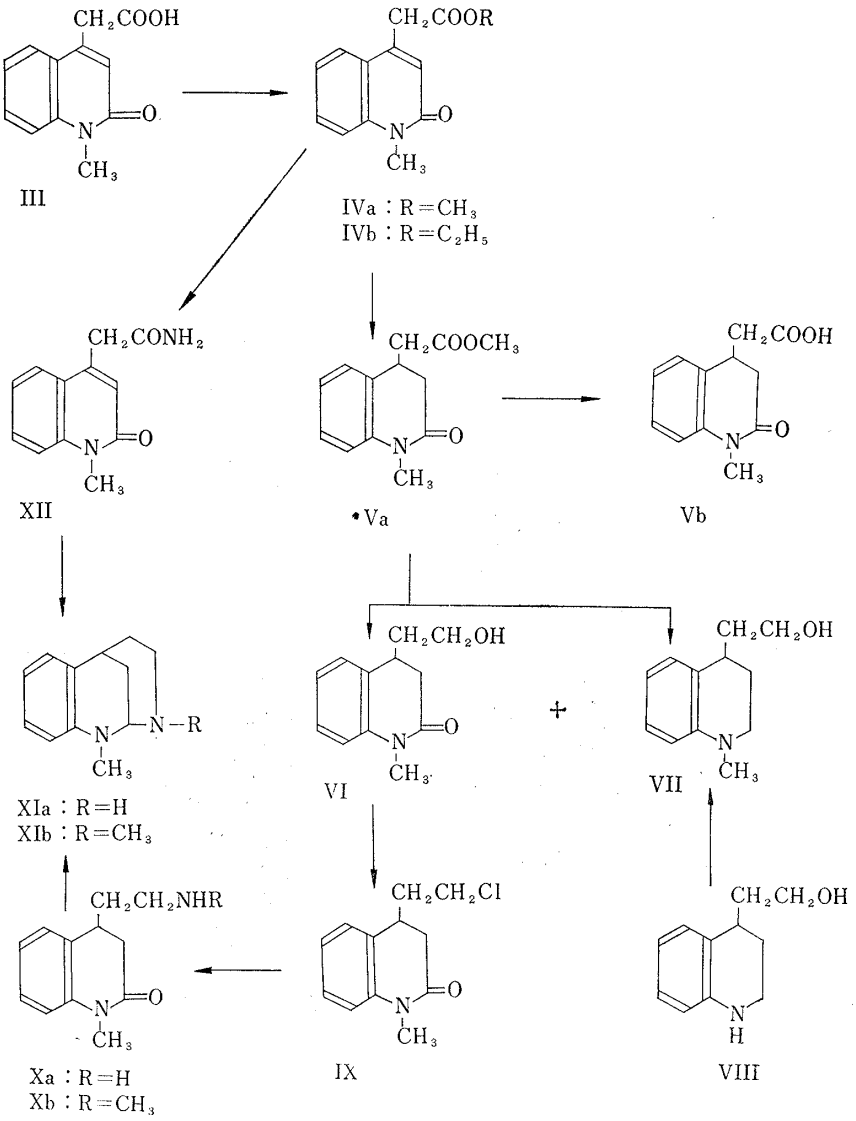


Chart 1.

Experimental[*5]

1-Methyl-4-carboxymethylcarbostyril (III)——Fourty-nine grams of N-methylaniline was dropwise added to 37 g. of diethyl acetonedicarboxylate which was heated at 150°, and a theoretical amount of

*5 Melting points are uncorrected.

6) S. Yamada, T. Hino, K. Ogawa : This Bulletin, **11**, 674 (1963).
7) H. F. Hudson, G. F. Smith : J. Chem. Soc., **1957**, 1877.
8) T. Hino : This Bulletin, **9**, 988 (1961).

EtOH distilled within ca. 2 hr. After cooling, the reaction mixture was poured on an excess of 5% aq. HCl, and an oil separated was extracted with $CHCl_3$. Removal of the $CHCl_3$ from the extract gave 53.5 g. of the dianilide as a pale yellow oil, which was so easily decomposed during distillation *in vacuo* that it was used in the following reaction without purification. IR ν_{max}^{liquid} cm^{-1} : 1730 (ketonic CO); 1660 (amide CO).

A mixture of 53.5 g. of the above crude amide and 120 ml. of 80% H_2SO_4 was heated on a water-bath for 5 hr., and, after the reaction mixture was poured on ice-water, allowed to stand at room temperature overnight. The crystals which separated and collected by filtration were dissolved in 10% aq. Na_2CO_3, and filtered. Acidification of the basic filtrate with conc. HCl gave colorless crystals, which were recrystallized from iso-PrOH to give 12.5 g. of the compound (Ⅲ) as colorless needles, m.p. 182～184° (decomp.). *Anal.* Calcd. for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.10; N, 6.45. Found : C, 66.31; H, 5.26; N, 6.38. IR ν_{max}^{KBr} cm^{-1} : 3700～3400 (OH); 1728 (CO); 1660 (amide CO).

1-Methyl-4-methoxycarbonylmethylcarbostyril (IVa)——HCl gas was introduced into a refluxed solution of 12.5 g. of Ⅲ in 200 ml. of MeOH for 5 hr. After the reaction, MeOH was removed by distillation and the residue was basified with 10% aq. Na_2CO_3, the crystals being separated. Filtration and recrystallization from benzene gave 10 g. of the methyl ester (Ⅳa) as colorless prisms, m.p. 90～92°. *Anal.* Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.67; N, 6.06. Found : C, 67.42; H, 5.84; N, 6.01.

1-Methyl-4-ethoxycarbonylmethylcarbostyril (IVb)——Esterification of 14.5 g. of Ⅲ in 200 ml. of EtOH saturated with HCl gas by the same procedure as above gave 14.5 g. of ethyl ester (Ⅳb) as colorless prisms (from benzene), m.p. 99～100° (lit.,[5] m.p. 94～95°). *Anal.* Calcd. for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16; N, 5.71. Found : C, 68.47; H, 6.20; N, 5.93. IR ν_{max}^{KBr} cm^{-1} : 1730 (ester CO); 1670 (amide CO).

1-Methyl-4-methoxycarbonylmethyl-3,4-dihydrocarbostyril (Va)——The above compound (Ⅳa) (8.4 g.) in 100 ml. of MeOH was hydrogenated with H_2 over 0.5 g. of PtO_2 on warming at 30～40°, a calculated amount of H_2 being absorbed during 20 hr. Concentration of the filtrate from the catalyst gave an oil, which was distilled *in vacuo* to give 7.25 g. (85.6%) of Va as a colorless viscous oil, $b.p_{0.7\sim1.1}$ 154～157°. This oil solidified after being allowed to stand in an ice-box. Recrystallization from ether gave Va as colorless cubes, m.p. 47～49°. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found : C, 66.93; H, 6.43; N, 6.10. IR ν_{max}^{liquid} cm^{-1} : 1740 (ester CO); 1680 (amide CO).

1-Methyl-4-carboxymethyl-3,4-dihydrocarbostyril (Vb)——A mixture of 0.5 g. of the preceding ester (Va) and 10 ml. of conc. HCl was heated on a water-bath for 1 hr. Evaportion of the reaction mixture and recrystallization from iso-PrOH gave 0.4 g. of the acid (Vb) as colorless rhombs, m.p. 141～143°. *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.93. Found : C, 65.77; H, 5.92; N, 6.54. IR ν_{max}^{KBr} cm^{-1} : 3650～3300 (OH); 1722 (acid CO); 1630 (CO).

1-Methyl-4-(2-hydroxyethyl)-3,4-dihydrocarbostyril (VI) and 1-Methyl-4-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (VII)——A solution of 3.4 g. of Va in 50 ml. of ether was dropwise added to a stirred suspension of 694 mg. (1.25 mole) of $LiAlH_4$ in 100 ml. of ether. After the addition of the above solution, the mixture was refluxed for 4 hr., then cooled, and decomposed with H_2O. The solvent layer was then separated, and an aqueous solution was extracted with $CHCl_3$. Both extracts were combined, washed with H_2O and distilled. The residue was acidified with 5% aq. HCl and again extracted with $CHCl_3$. The extract was washed with H_2O, dried on K_2CO_3, and evaporated to give 1.5 g. of a pale yellowishgreen oil. Distillation of the above residue *in vacuo* afforded 1.0 g. (30%) of Ⅵ as a pale yellow syrup, $b.p_{0.65}$ 170°. *Anal.* Calcd. for $C_{19}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.82. Found : C, 70.46; H, 7.29; N, 6.73. IR ν_{max}^{liquid} cm^{-1} : 3450 (OH); 1660 (CO).

The above acidic solution was basified with 10% aq. NaOH and extracted with ether. The extract was washed with H_2O and dried on K_2CO_3. Removal of the solvent and distillation of the residue *in vacuo* gave 1.5 g. (53.9%) of a pale yellow oil, $b.p_2$ 145°, which was found to be identical with the compound alternatively synthesized as follows. Methylation of 0.2 g. of 4-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (Ⅷ)*3 with 1 ml. of methyl iodide in 30 ml. of MeOH under reflux for 2 hr. gave 0.1 g. of the same compound (Ⅶ) as above, whose IR sprctrum was superimposable on those of the above authentic sample.

1-Methyl-4-(2-aminomethyl)-3,4-dihydrocarbostyril (Xa)——A mixture of 5 g. of Ⅵ in 50 ml. of $CHCl_3$ and 10 g. of $SOCl_2$ was refluxed for 1 hr. and the solvent was then removed. An oily residue was basified with 10% aq. Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O and dried on Na_2SO_4. Removal of the solvent gave a reddish-brown syrup (Ⅸ), which was used in the following reaction without purification. IR ν_{max}^{liquid} cm^{-1} : 1680 (C=O).

The preceding halide (Ⅸ) was dissolved in 70 ml. of EtOH which was saturated with NH_3 gas, and the mix ture was heated at 100° in a sealed tube for 6 hr. After NH_4Cl separated had been removed from the cooled reaction mixture, the filtrate was concentrated, and the residue was acidified with 20% aq. HCl and extracted with $CHCl_3$ in order to remove a neutral substance. The above acidic solution was basified with 10% aq. Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O and dried on Na_2SO_4. Removal of the solvent gave a reddish-brown oil, $b.p_{1.2}$ 162.5°. Recrystallization of the oxalate of Xa from EtOH gave colorless needles, m.p. 168～169° (decomp.). *Anal.* Calcd. for $C_{12}H_{16}ON_2 \cdot C_2H_2O_4$: C, 57.13; H, 6.17. Found : C, 56.85; H, 6.27. IR ν_{max}^{liquid} cm^{-1} : 3400 (NH_2); 1660 (CO).

1-Methyl-4-(2-methylaminoethyl)-3,4-dihydrocarbostyril (Xb)——A mixture of 4 g. of the crude halide (IX), 25 g. of $MeNH_2 \cdot HCl$, 10 g. of KOH, and 70 ml. of EtOH was heated at 110~120° in a sealed tube for 6 hr. After the reaction mixture had been concentrated, the residue was acidified with 10% aq. HCl and extracted with $CHCl_3$. The above acidic solution was basified with 10% aq. Na_2CO_3 and again extracted with $CHCl_3$. The extract was washed with H_2O and dried on K_2CO_3. Removal of the solvent gave a syrup, which was distilled *in vacuo* to give 2 g. of colorless oil, $b.p_{2.6}$ 170°. This compound (Xb) formed colorless crystals, m.p. 51~53°, on being allowed to stand. Recrystallization of its oxalate from EtOH gave colorless needles, m.p. 183~184° (decomp.). *Anal.* Calcd. for $C_{13}H_{18}ON_2 \cdot C_2H_2O_4$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.23; H, 6.64; N, 9.16. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH); 2820 (N-Me); 1670 (CO).

1-Methyl-4-carbamoylmethylcarbostyril (XII)——A mixture of 1 g. of IVa and an excess of 28% aq. NH_4OH was heated on a water-bath at 80~90° for 1 hr. The crystals separated were collected by filtration, and recrystallized from MeOH to give 0.7 g. of the amide (XII) as colorless needles, m.p. 163~164°. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.75; H, 5.66; N, 13.01. IR ν_{max}^{KBr} cm^{-1}: 3410, 3220 (NH_2); 1670, 1655 (CO).

1-Methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*][1,3]diazocine (XIa)——(a) To a stirred solution of 0.8 g. of Xa in 100 ml. of EtOH was added in small portions at room temperature 3 g. of metallic Na, and the mixture was heated at 70°, to which was furthermore added in small portions an additional 3 g. of Na. The above mixture was heated at 110~120° for 1 hr. After cooling, the mixture was decomposed with 30 ml. of H_2O, the solvent removed, and extracted with ether. The extract was washed with H_2O and dried on K_2CO_3. Removal of the solvent gave 0.6 g. of an oil (XIa) whose oxalate was recrystallized from EtOH to give colorless prisms, m.p. 177~178° (decomp.). *Anal.* Calcd. for $C_{12}H_{16}N \cdot {}_2C_2H_2O_4$: C, 60.42; H. 6.52; N, 10.07. Found: C, 60.49; H, 6.46; N, 9.86. IR ν_{max}^{liquid} cm^{-1}: 3350 (NH). UV λ_{max}^{EtOH} mμ (log ε): 255.5 (4.11), 304 (3.46). $\lambda_{max}^{EtOH\text{-}HCl}$ mμ (log ε): 245 (4.13), 292 (3.43).

(b) To a stirred solution of 1.0 g. of XII in 100 ml. of EtOH was added in small portions 6 g. of Na under the same conditions as above (a). Treatment of the reaction mixture as usual gave a reddish-brown oil, which was purified by distillation *in vacuo* to afford a pale yellow oil, $b.p_2$ 120°. Rercystallization of its oxalate from EtOH gave 50 mg. of XIa as colorless prisms, m.p. 177~178° (decomp.), whose infrared spectrum was superimposable on that of the above authentic sample.

1,3-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*][1,3]diazocine (XIb)——A solution of 0.8 g. of Xb in 80 ml. of EtOH was treated with 5.5 g. of Na according to the same procedure (method a) as above, and treatment of the reaction mixture as usual gave 0.6 g. of XIb as a colorless oil, $b.p_{1.2}$ 116°. *Anal.* Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.42; H, 8.69; N, 13.33. IR ν_{max}^{liquid} cm^{-1}: 2840 (N-Me). UV λ_{max}^{EtOH} mμ (log ε): 254 (3.55), 303 (2.88). $\lambda_{max}^{EtOH\text{-}HCl}$ mμ (log ε): 243.5 (5.49), 289.5 (2.77). Recrystallization of its picrate from EtOH gave yellow prisms, m.p. 169~170° (decomp.). *Anal.* Calcd. for $C_{13}H_{18}N_2 \cdot C_6H_3O_7N_3$: N, 16.24. Found: N, 16.27.

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

Summary

In order to test the analgesic action of 1-methyl- (XIa) and 1,3-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*][1,3]diazocine (XIb) were synthesized from 1-methyl-4-carboxymethylcarbostyril (III) as a starting material. Reductive cyclization of Xa and Xb with metallic sodium in ethanol gave, respectively, the expected azabenzomorphane derivatives, XIa and XIb. Furthermore, Ladenburg reduction of 1-methyl-4-carbamoylmethylcarbostyril (XII) also gave the above compound (XIa).

(Received April 28, 1965)