[Chem. Pharm. Bull. 24(1) 85 — 91 (1976)]

UDC 547.896'821.04 : 547.333.04

Heteroaromatic Analogs of Benzomorphan. II.[1] Synthesis of 2-Azabicyclo-[3.3.1]nonane Derivatives fused to Pyridine Ring. (2)[2]

Jun Adachi, Keiichi Nomura,[3a] and Kemmotsu Mitsuhashi[3b]

Faculty of Pharmaceutical Sciences, University of Toyama[3a] and Faculty of Pharmaceutical Sciences, Josai University[3b]

(Received May 14, 1975)

1,2,3,4,5,6-Hexahydro-1,5-methanopyrido[3,2-*c*]azocine and 1,2,3,4,5,6-hexahydro-2,6-methanopyrido[2,3-*d*]azocine derivatives were synthesized by condensation reactions of acyl derivatives of 2-azabicyclo[3.3.1]nonan-7-one (XIa) with β-aminoacrolein. The key compound (XIa) was obtained by lithium aluminum hydride reduction and the subsequent acid hydrolysis of 3-methoxy-5-oxo-3-cyclohexene-1-acetamide (IXa), which was prepared starting from 3,5-dihydroxyphenylacetic acid (IV). Mass spectra of the above pyridine derivatives were briefly described, too.

In connection with our studies on structure-activity relationship of analgesics, we attempted to synthesize benzomorphan analogs of which aromatic ring is heterocyclic. It has been investigated to synthesize 2-azabicyclo[3.3.1]nonane derivatives which fused to pyridine ring, and the synthesis of 1,2,3,4,5,6-hexahydro-1,5-methano-2-methylpyrido[2,3-*c*]-azocine (I) was reported in the previous paper.[1] In this paper, we describe the synthesis of 1,2,3,4,5,6-hexahydro-1,5-methano-2-methylpyrido[3,2-*c*]azocine (II) and 1,2,3,4,5,6-hexahydro-2,6-methano-3-methylpyrido[2,3-*d*]azocine (III).

3,5-Dimethoxyphenylacetamide (VIa) was prepared from 3,5-dihydroxyphenylacetic acid (IV)[4] by methylation with dimethyl sulfate and the subsequent conversion of the resulting carboxylic acid (V) to the amide *via* the corresponding acid chloride. Although a Birch reduction of VIa with a large excess of lithium in liquid ammonia and ethanol was incomplete, this reaction with sodium (three molar equivalents) gave the dihydro derivative (VIIa) in 56% yield. Hydrolysis of VIIa with diluted hydrochloric acid afforded 3,5-dioxocyclohexane-1-acetamide (VIIIa) quantitatively. Treatment of the β-diketone (VIIIa) with an excess of diazomethane gave the enol ether (IXa). Lithium aluminum hydride reduction of IXa afforded the amino alcohol (Xa), a precursor of α,β-unsaturated ketone. On hydrolysis of Xa with diluted sulfuric acid, an intramolecular Michael cyclization[5] occurred to yield 2-azabicyclo[3.3.1]nonan-7-one (XIa) in good yield. The compound (XIa) was apparently sensitive to acidic medium. Both of the methylations of XIa by Clarke-Eschweiler method and with methyl iodide in order to obtain XIb gave a complex material which showed many spots on thin-layer chromatography (TLC). So, XIb was prepared from 3,5-dimethoxyphenyl-N-methylacetamide (VIb) according to the similar manner as above.[6]

As a method of synthesis of pyridine derivative, an application of condensation reaction between cyclic ketone and β-aminoacrolein was successful.[1,7] The ketone (XIb) was submitted

1) Part I: J. Adachi, K. Nomura, K. Shiraki, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 658 (1974).
2) This work was presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April 1975.
3) Location: *a*) *Gofuku, Toyama*; *b*) *Sakado-cho, Saitama.*
4) W. Theilacker and W. Schmid, *Ann.*, **570**, 15 (1950).
5) W.J. Gensler, C.D. Gatsonis, and Q.A. Ahmed, *J. Org. Chem.*, 33, 2968 (1968); R. Furstoss, P. Teissier, and B. Waegell, *Chem. Commun.*, **1970**, 384.
6) In the course of this study, Mokotoff, *et al.* reported the synthesis of XIb and the corresponding N-benzyl derivative in another route: M. Mokotoff and R.C. Cavestri, *J. Org. Chem.*, **39**, 409 (1974).
7) K. Nomura, J. Adachi, M. Hanai, S. Nakayama, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 1386 (1974).

to a reaction with β-aminoacrolein in the presence of triethylamine and ammonium acetate. This reaction gave only a trace of mixture of the desired compounds (II and III) contaminated with resinous material. It was probably due to the lability of the ketone (XIb) that the above reaction was unsuccessful. The amino ketone (XIa), therefore, was acylated with acetic anhydride and with acetic formic anhydride to give the amides (XIc and XId) in 70% and 55% yield, respectively. Treatment of XIc with β-aminoacrolein under the same condition as above afforded a mixture of the pyridine derivatives (XIIa and XIIIa) in a ratio of 1:1 in 30% yield. The structures of these products were deduced by the following results. Mass and infrared (IR) spectra of them showed similar pattern, respectively. In comparison of nuclear magnetic resonance (NMR) spectra of XIIa and XIIIa, it was observed that an upfield shift of the methyl protons of the acetyl group of XIIa due to shielding effect of the aromatic ring. Furthermore, the methine proton being adjacent to the nitrogen atom of XIIa resonated at down field compared with that of XIIIa. The formamido ketone (XId) also gave a mixture of XIIb and XIIIb (1:1) in 22.5% yield on a similar treatment to that of XIc. NMR spectra revealed that all of the compounds (XIIb, XIIIa and XIIIb) consisted of a mixture of the corresponding two rotamors concerning the amido function. The acetamido derivatives (XIIa and XIIIa) were derived to XIIb and XIIIb by hydrolysis with dilute sulfuric acid and the subsequent formylation with acetic formic anhydride in 50% yield. Reduction of XIIb and XIIIb with lithium aluminum hydride yielded II and III in 66% and 64% yield, respectively. On NMR spectra the signal of the methyl protons of II also appeared at higher field than that of III. As a result, the desired compounds could be synthesized.

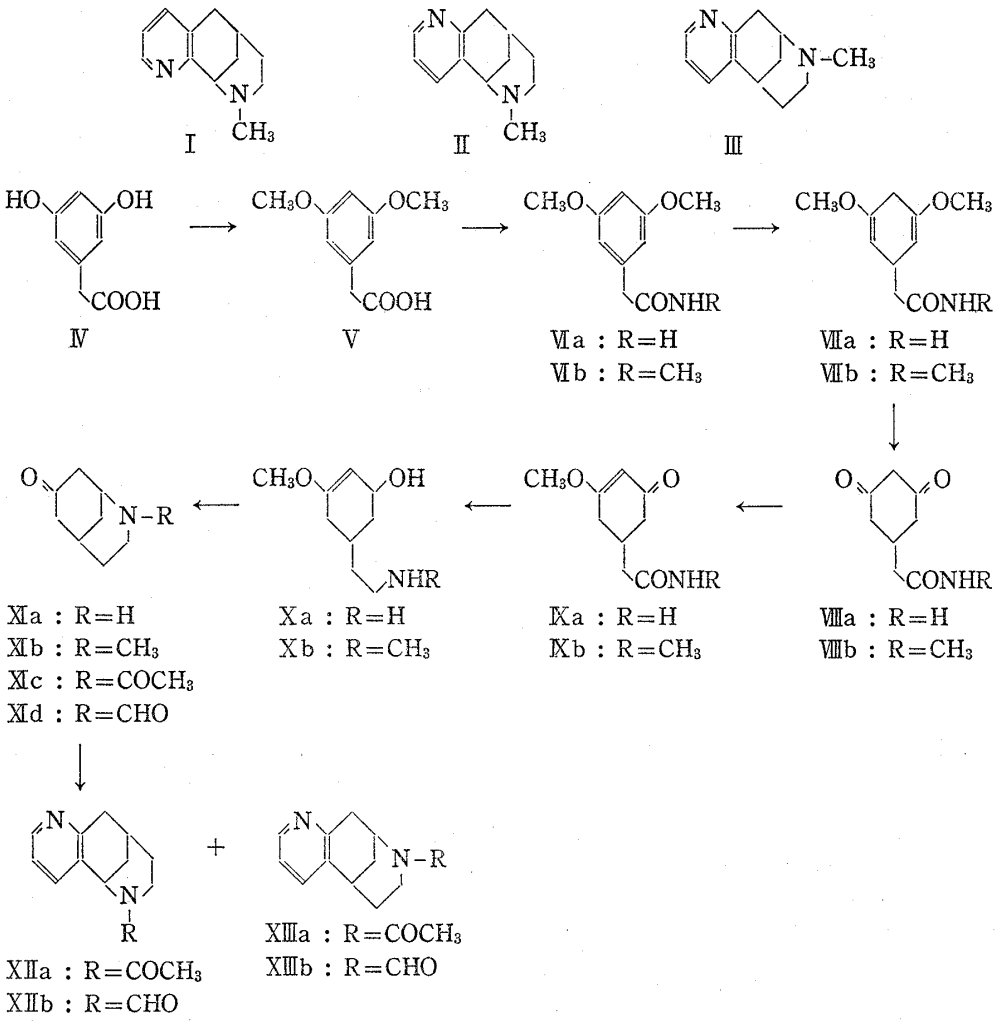

Chart 1

Finally, we comment on the mass spectra of the above pyridine derivatives (XIIa, XIIb, XIIIa, XIIIb, II and III). All of the spectra showed similar fragmentation pattern, and had common fragment ion peaks at *m/e* 173, 145, 144 and 130 (Table I). Plausible fragmenta-

Table I. Mass Spectral Data[a] of XIIa, b, XIIIa, b, II and III

Ions	*m/e* (relative intensity, %)					
	XIIa	XIIb	II[b]	XIIIa	XIIIb	III[b]
M^+	216(64)	202(92)	188(70)	216(52)	202(36)	188(76)
a	173(58)	173(44)	173(15)			
b				173(30)	173(14)	173(35)
c	124(17)	110(38)	96(100)	124(5)	110(12)	96(100)
d	82(18)	82(32)		82(20)	82(12)	
e	145(38)	145(26)	145(24)	145(24)	145(12)	145(35)
f	144(52)	144(46)	144(43)	144(30)	144(20)	144(50)
g	130(100)	130(100)	130(48)	130(100)	130(100)	130(65)

a) ionizing potential 75 eV at the lowest possible source temperature (40—120°)
b) Composition of each fragment peak was determined by high resolution mass spectrometer.

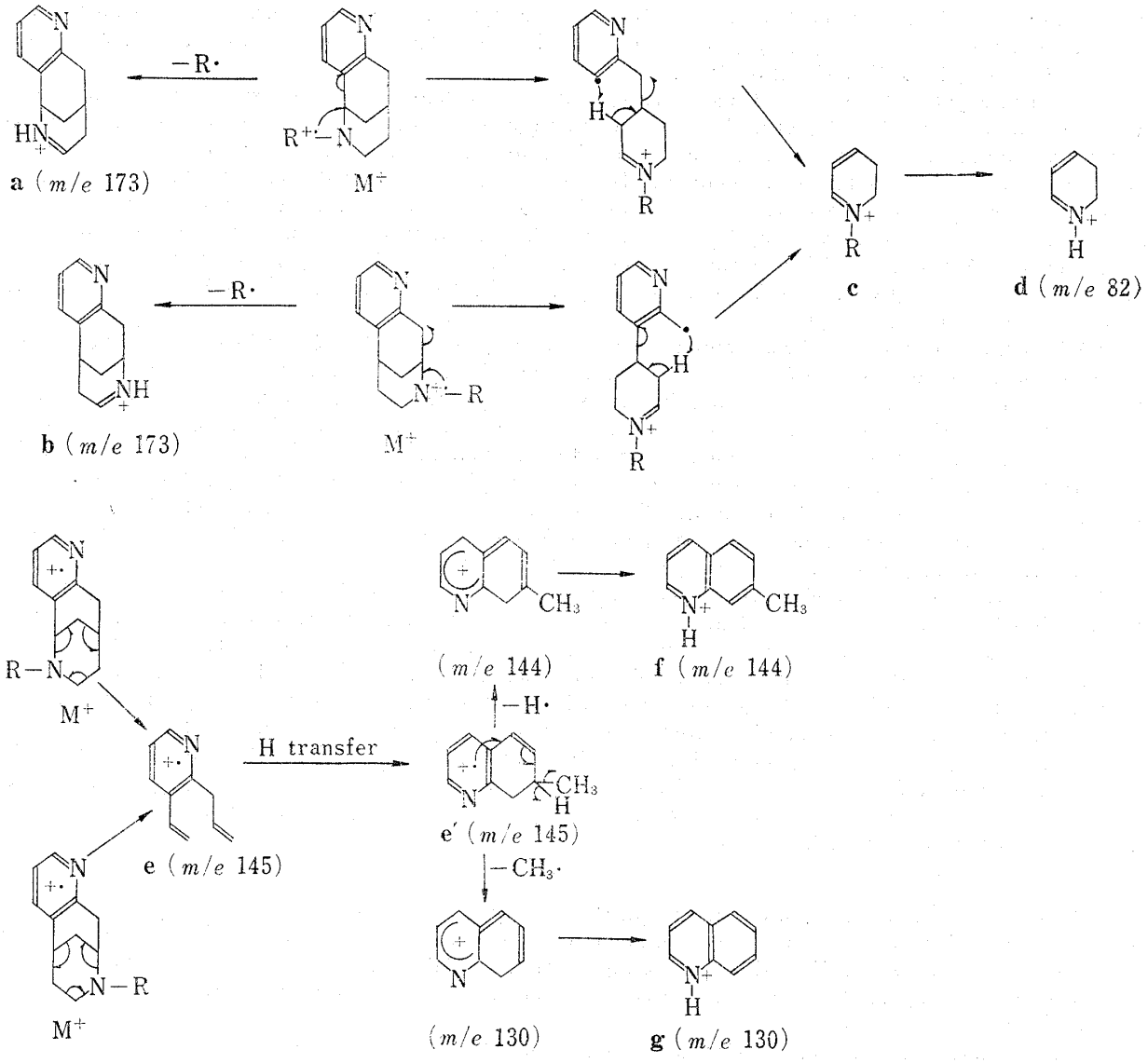

Chart 2

tion are shown in Chart 2. From the data of high resolution mass spectra of II and III, these ion peaks were assigned to the ions **a** and **b**, **e**, **f** and **g**, respectively. Dihydropyridinium type ion (**c**, base peaks of the spectra of II and III) would be formed by a cleavage at β-position to the nitrogen atom of the piperidine ring and the subsequent loss of the aromatic moiety. In the case of the amide derivatives (XIIa, b and XIIIa, b), the ion **c** losed CH_2CO or CO to form the ion **d**. On the other hand, a retro-Diels-Alder reaction of the piperidine ring of the molecular ions led to the common ion **e**, which could give successively the dihydroquinoline type ion **e'** with hydrogen transfer. Further loss of a hydrogen atom and methyl group from the ion **e'** resulted in the quinolinium ion **f** and **g** (base peaks of the spectra of XIIa, b and XIIIa, b), respectively. These fragmentation patterns resemble that of benzomorphan derivatives.[8]

The pharmacological studies of the above compounds are now under progress, and will be reported elsewhere.

Experimental[9]

3,5-Dimethoxyphenylacetic Acid (V)——To a solution of 3,5-dihydroxyphenylacetic acid[4] (IV, 27 g, mp 127—130° from CH_2Cl_2–ether) and NaOH (32 g) in water (200 ml) was added dropwise dimethyl sulfate (63 g) under refluxing over a 30-min period. The reaction mixture was refluxed for an additional 3 hr. After cooling, the mixture was made acidic with concd. HCl and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a crystalline residue which was recrystallized from *n*–hexane–ether to give 19.6 g (62%) of V, colorless needles, mp 102—105° (lit.[10] mp 101—102°). IR ν_{max}^{KBr} cm^{-1}: 3200—2500, 1710 (COOH), 1210, 1070.

3,5-Dimethoxyphenylacetamide (VIa)——To a solution of V (5.9 g) in dry benzene (100 ml) was added dropwise a solution of $SOCl_2$ (7.2 g) in dry benzene (40 ml) at room temperature. The mixture was allowed to stand overnight at the same temperature. After removal of the excess of $SOCl_2$ and the solvent *in vacuo*, the oily residue was dissolved in benzene (40 ml). To this solution was added 28% NH_4OH (60 ml) with stirring at room temperature, and the stirring was continued for 2.5 hr. The mixture was extracted with AcOEt, washed with brine and dried over Na_2SO_4. Removal of the solvent and recrystallization of the residue from benzene gave 4.45 g (75.8%) of VIa as colorless needles, mp 127—130° (lit.[11] mp 126—127°). IR ν_{max}^{KBr} cm^{-1}: 3300, 3160 (NH_2), 1640 (C=O). NMR ($CDCl_3$) δ: 3.5 (2H, s, $-CH_2CO-$), 3.8 (6H, s, $2\times-OCH_3$), 5.4—6.2 (2H, broad peak, $-CONH_2$), 6.4 (3H, s, arom.).

3,5-Dimethoxyphenyl-N-methylacetamide (VIb)——To a solution of V (15.3 g) in benzene (300 ml) was added dropwise a solution of $SOCl_2$ (18.6 g) in benzene (100 ml) at room temperature. The mixture was allowed to stand overnight. The solvent and the excess of $SOCl_2$ were removed *in vacuo*. The residue was dissolved in benzene (50 ml) and added to 40% aqueous monomethylamine (40 ml) with stirring at 5—10° over a 30-min period. The stirring was continued for an additional 30 min, the mixture was extracted with $CHCl_3$. The extract was worked up as usual to give 12.3 g (75%) of VIb, colorless needles, mp 114—116° (benzene). IR ν_{max}^{KBr} cm^{-1}: 3260, 3100 (NH), 1630 (C=O). NMR ($CDCl_3$) δ: 2.75 (3H, d, $J=5$ Hz, $-NHCH_3$), 3.5 (2H, s, $-CH_2CO-$), 3.8 (6H, s, $-OCH_3$), 5.6 (1H, broad peak, –CONH–), 6.4 (3H, s, arom.). *Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.06; H, 7.46; N, 6.98.

1,4-Dihydro-3,5-dimethoxyphenylacetamide (VIIa)——To a solution of VIa (1.95 g) in liq. NH_3 (170 ml) and abs. EtOH (30 ml) was added Na (920 mg) at −75——70° with stirring over a 15-min period. After the blue color was disappeared, to the reaction mixture was added NH_4Cl (4.3 g). The mixture was then allowed to stand at room temperature until the complete evaporation of NH_3. To the residue was added water (150 ml), and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The crystalline residue was recrystallized from benzene to give 1.1 g (55.8%) of VIIa as colorless needles, mp 138—140°. IR ν_{max}^{KBr} cm^{-1}: 3350, 3200 (NH_2), 1640 (C=O and C=C). NMR ($CDCl_3$) δ: 2.25 (2H, d, $J=7$ Hz, $-CH_2CO-$), 2.7 and 2.8 (2H, AB-type, C=C–CH_2–C=C), 3.3—3.8 (1H, m), 3.6 (6H, s, $-OCH_3$), 4.65 (2H, broad d, $J=4$ Hz, >C=CH–), 5.6—6.4 (2H, broad peak, $-CONH_2$). *Anal.* Calcd. for $C_{10}H_{15}O_3N$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.77; H, 7.69; N, 7.19.

8) S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1980 (1972).
9) All melting points were measured on a Yanagimoto Micro Melting Point Apparatus, and are uncorrected. All boiling points were indicated by bath temperatures. NMR spectra were taken on a JEOL JNM-C-60H spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken with a JEOL JMS-OlSG-2 spectrometer.
10) A. Kamal and M.A. Sandhu, *Tetrahedron Letters*, **1963**, 611.
11) S. Shibata, E. Morishita, and Y. Arima, *Chem. Pharm. Bull.* (Tokyo), **11**, 821 (1963).

1,4-Dihydro-3,5-dimethoxyphenyl-N-methylacetamide (VIIb)——To a solution of VIb (12 g) in liq. NH_3 (500 ml) and abs. EtOH (200 ml) was added Na (4 g) with stirring at −75——−70° over a 45-min period. After the blue color was faded, to the mixture was added NH_4Cl (18.6 g) and allowed to stand at room temperature to remove NH_3. The residue was worked up as above to give 10.9 g (90%) of colorless crystals of VIIb, mp 147—149°. Recrystallization from ether gave the analytical sample, colorless needles, mp 150—151°. IR ν_{max}^{KBr} cm^{-1}: 3250, 3050 (NH), 1630 (C=O). NMR ($CDCl_3$) δ: 2.2 (2H, d, J=7 Hz, $-CH_2CO-$), 2.75 (2H, AB-type, C=C–CH_2–C=C), 2.8 (3H, d, J=5 Hz, $-NHCH_3$), 3.3—3.7 (1H, m), 3.55 (6H, s, $-OCH_3$), 4.6 (2H, broad d, >C=CH–), 5.7 (1H, broad peak, –CONH–). *Anal.* Calcd. for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.42; H, 7.91; N, 6.82.

3-Methoxy-5-oxo-3-cyclohexeneacetamide (IXa)——A mixture of VIIa (8.5 g) and 2.5% HCl (20 ml) was stirred at room temperature for 30 min. The clear solution was cooled in an ice-bath, and made to pH 3.0 with K_2CO_3. The resulting colorless precipitates were collected with suction and dried to afford VIIIa in a quantitative yield, mp 80—95°. IR ν_{max}^{KBr} cm^{-1}: 1600—1500 (1,3-diketone).

The above crude VIIIa was dissolved in MeOH (50 ml), and to this solution was added a solution of CH_2N_2 in ether (prepared from 20 g of N-nitrosomethylurea, 60 ml of 50% KOH and 200 ml of ether). The mixture was allowed to stand at room temperature overnight. The excess of CH_2N_2 and the ether were removed on a water bath, the residual MeOH solution was diluted with ether (150 ml) and cooled in an ice-bath. The crystalline product was collected by filtration to obtain 5.2 g of IXa, colorless needles, mp 183—186°. The filtrate was concentrated *in vacuo*, the residue was worked up in the same manner as above to give an additional 0.5 g (total yield, 72%) of IXa. For analysis recrystallization from benzene–MeOH gave colorless needles, mp 184—186°. IR ν_{max}^{KBr} cm^{-1}: 3330, 3180 (NH_2), 1660, 1635 (C=O). NMR (CD_3OD) δ: 2.2—2.8 (7H, m), 3.75 (3H, s, $-OCH_3$), 5.4 (1H, s, >C=CH–CO–). *Anal.* Calcd. for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.87; H, 6.93; N, 7.42.

3-Methoxy-5-oxo-3-cyclohexene-N-methylacetamide (IXb)——A mixture of VIIb (1.69 g) and 2.5% HCl (5 ml) was stirred at room temperature for 20 min. To the mixture was added portionwise K_2CO_3 to make pH 4, and cooled in an ice-bath. The colorless precipitate was collected with suction to obtain 1.3 g of VIIIb, mp 170—177° (dec.) (lit.[6] mp 189—191°). IR ν_{max}^{KBr} cm^{-1}: 1620 (C=O), 1570 (1,3-diketone). The above VIIIb was dissolved in MeOH (15 ml), and to this solution was added a solution of CH_2N_2 in ether (prepared from 5 g of N-nitrosomethylurea, 15 ml of 50% KOH and 50 ml of ether). The mixture was allowed to stand at room temperature overnight. After removal of the excess of CH_2N_2 and ether at an atmospheric pressure, the residue was concentrated *in vacuo*. The crystalline residue was recrystallized from MeOH–ether to give 0.83 g (53%) of IXb as colorless needles, mp 131—133°. Recrystallization from benzene gave the analytical sample, colorless needles, mp 133—134°. IR ν_{max}^{KBr} cm^{-1}: 3300, 3050 (NH), 1640 (C=O). NMR ($CDCl_3$) δ: 1.8—2.7 (7H, m), 2.8 (3H, d, J=5 Hz, $-NHCH_3$), 3.7 (3H, s, $-OCH_3$), 5.35 (1H, s, >C=CH–CO–), 5.7—6.2 (1H, broad peak, –CONH–). *Anal.* Calcd. for $C_{10}H_{15}O_3N$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.81; H, 7.85; N, 7.00.

2-Azabicyclo[3.3.1]nonan-7-one (XIa)——To a stirred suspension of $LiAlH_4$ (304 mg) in tetrahydrofuran (30 ml) was added a suspension of IXa (366 mg) in tetrahydrofuran (40 ml) at room temperature. The mixture was then refluxed for 3 hr. After cooling, to the mixture was added saturated aqueous potassium sodium tartrate solution. The tetrahydrofuran solution was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic solutions were worked up as usual to give 318 mg of colorless oil (Xa). IR ν_{max}^{film} cm^{-1}: 3400—3160 (NH_2, OH), 1670 (C=C). The crude Xa was cooled in an ice-bath and followed by addition of 20% H_2SO_4 (3 ml). The mixture was stirred for 1 hr, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Usual working up of the $CHCl_3$ solution gave 237 mg (85%) of XIa as a colorless oil, bp 80—100° (0.3 mmHg), which crystallized on standing. IR ν_{max}^{film} cm^{-1}: 3300, 3050 (NH), 1700 (C=O). NMR ($CDCl_3$) δ: 1.4—2.1 (4H, m), 2.3 (1H, s, >NH), 2.4—3.0 (7H, m), 3.6 (1H, m). *Anal.* Calcd. for $C_8H_{13}ON$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.96; H, 9.46; N, 10.00. Picrate of XIa: yellow plates, mp 222—226° (decomp.) (acetone). *Anal.* Calcd. for $C_8H_{13}ON \cdot C_6H_3O_7N_3$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.37; H, 4.40; N, 14.97.

2-Methyl-2-azabicyclo[3.3.1]nonan-7-one (XIb)——A mixture of IXb (591 mg) and $LiAlH_4$ (456 mg) in tetrahydrofuran (80 ml) was refluxed with stirring for 3 hr. After cooling, the mixture was worked up as above to give Xb as an oil. IR ν_{max}^{film} cm^{-1}: 3300—3000 (NH, OH), 1665 (C=C). Treatment of the crude Xb with 20% H_2SO_4 (5 ml) as the same manner as in the case of Xa gave 438 mg (95%) of XIb as a colorless oil, bp 70° (0.05 mmHg). IR ν_{max}^{film} cm^{-1}: 2800 (NMe), 1700 (C=O). NMR ($CDCl_3$) δ: 1.4—2.8 (11H, m), 2.35 (3H, s, >N–CH_3), 3.0—3.4 (1H, m). Picrate of XIb: yellow cubes, mp 231—233° (decomp.). *Anal.* Calcd. for $C_9H_{15}ON \cdot C_6H_3O_7N_3$: C, 47.12; H, 4.74; N, 14.66. Found: C, 47.38; H, 4.93; N, 14.58.

2-Acetyl-2-azabicyclo[3.3.1]nonan-7-one (XIc)——To a solution of XIa (1.3 g) in pyridine (5 ml) was added a solution of Ac_2O (1.0 g) in pyridine (5 ml), and the mixture was stirred at room temperature for 1 hr. After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, 5% HCl, 5% $NaHCO_3$, and water, dried over Na_2SO_4, and concentrated. Distillation of the residue gave 910 mg (70%) of colorless oil of XIc, bp 100—110° (0.09 mmHg), which crystallized on standing, mp 123—125°. IR ν_{max}^{film} cm^{-1}: 1705, 1635 (C=O). NMR ($CDCl_3$) δ: 1.5—2.1 (4H, m), 2.1 (3H, s, $-COCH_3$), 2.3—2.8 (6H, m), 3.0—3.8 (1H, m), 4.4 (1/2H) and 5.3 (1/2H, m). *Anal.* Calcd. for $C_{10}H_{15}O_2N$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.35; H, 8.59; N, 7.93.

2-Formyl-2-azabicyclo[3.3.1]nonan-7-one (XId)——A mixture of Ac_2O (816 mg) and HCOOH (368 mg) was heated on an oil bath at 50° for 2 hr. After cooling, the mixture was diluted with benzene (10 ml), and to this solution was added a solution of XIa (216 mg) in benzene (10 ml). The reaction mixture was stirred at room temperature for 1.5 hr, and then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$, washed with saturated $NaHCO_3$ solution and dried over Na_2SO_4. Evaporation of the solvent and distillation of the residue afforded 142 mg (54.8%) of XId as a colorless oil, bp 130—150° (0.1 mmHg). IR ν_{max}^{film} cm^{-1}: 1710, 1660 (C=O). NMR ($CDCl_3$) δ: 1.5—2.1 (4H, m), 2.3—2.8 (6H, m), 3.1—3.6 (1H, m), 4.2 (1/2H) and 5.05 (1/2H, m, >N–CH<), 7.95 (1/2H) and 8.05 (1/2H, s, –CHO). Oxime of XId: colorless cubes, mp 195—197° (EtOH). *Anal.* Calcd. for $C_9H_{14}O_2N_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.33; H, 7.74; N, 15.61.

2-Acetyl-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[3,2-*c*]azocine (XIIa) and 3-Acetyl-1,2,3,4,5,6-hexahydro-2,6-methanopyrido[2,3-d]azocine (XIIIa)——A mixture of XIc (736 mg), 3-aminoacrolein[12] (570 mg), triethylamine (0.2 ml) and a catalytic amount of NH_4OAc was heated on an oil bath at 110° for 15 hr. After cooling, the mixture was dissolved in $CHCl_3$ and washed with water. The $CHCl_3$ solution was extracted with 5% HCl. From the $CHCl_3$ layer 150 mg (20%) of XIc was recovered. The aqueous layer was made alkaline with K_2CO_3, and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The brown oily residue was chromatographed on SiO_2 (2 g). Elution with $CHCl_3$ gave 265 mg (30%) of a mixture of XIIa and XIIIa (a ratio of 1: 1, determined by TLC and NMR spectrum) as a colorless oil.

The above mixture was again chromatographed on SiO_2 (4 g). The first eluate with $CHCl_3$ gave XIIa (115 mg) as a colorless oil, bp 110—120° (0.05 mmHg). IR ν_{max}^{film} cm^{-1}: 1630 (C=O). NMR ($CDCl_3$) δ: 1.5—3.7 (9H, m), 2.05 (3H, s, $-COCH_3$), 5.9 (1H, m, –CH–N<), 7.05 (1H, d.d, J=7.5, 4.5 Hz, arom.), 7.6 (1H, d.d, J=7.5, 1.5 Hz, arom.), 8.4 (1H, d.d, J=4.5, 1.5 Hz, arom.). Picrate of XIIa: yellow prisms, mp 165—167° (acetone). *Anal.* Calcd. for $C_{13}H_{16}ON_2 \cdot C_6H_3O_7N_3$: C, 51.23; H, 4.30; N, 15.73. Found: C, 51.27; H, 4.57; N, 15.46.

The second eluate with $CHCl_3$ gave XIIIa (105 mg) as a colorless oil, bp 120—130° (0.05 mmHg). IR ν_{max}^{film} cm^{-1}: 1620 (C=O). NMR ($CDCl_3$) δ: 1.5—3.6 (9H, m), 2.1 (2H) and 2.2 (1H, s, $-COCH_3$), 4.4 (2/3H) and 5.3 (1/3H, m, >CH–N<), 7.1 (1H, d.d, J=7.5, 4.5 Hz, arom.), 7.4 (1H, d.d, J=7.5, 1.5 Hz, arom.), 8.4 (1H, d.d, J=4.5, 1.5 Hz, arom.). Picrate of XIIIa: yellow prisms, mp 171—173° (acetone). *Anal.* Calcd. for $C_{13}H_{16}ON_2 \cdot C_6H_3O_7N_3$: C, 51.23; H, 4.30; N, 15.73. Found: C, 51.24; H, 4.10; N, 15.44.

2-Formyl-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[3,2-*c*]azocine (XIIb) and 3-Formyl-1,2,3,4,5,6-hexahydro-2,6-methanopyrido[2,3-*d*]azocine (XIIIb)——1) A mixture of XId (1.12 g), 3-aminoacrolein (720 mg), triethylamine (0.4 ml) and a catalytic amount of NH_4OAc was heated on an oil bath at 110° for 9 hr. After cooling, the mixture was worked up as above. From the non-basic part 420 mg (37.5%) of XId was recovered. The basic part was distilled to afford 305 mg (22.5%) of a mixture of XIIb and XIIIb (in a ratio of 1: 1), which was then chromatographed on SiO_2 (10 g). Elution with benzene–$CHCl_3$ (1: 1) gave 125 mg of XIIb, as a colorless oil, bp 110° (0.05 mmHg), which crystallized on standing, mp 110—116°. IR ν_{max}^{film} cm^{-1}: 1650 (C=O). NMR ($CDCl_3$) δ: 1.6—2.2 (5H, m), 2.4—2.8 (2H, m), 2.9—3.5 (2H, m), 4.65 (1/3H) and 5.65 (2/3H, m, >CH–N<), 7.1 (1H, d.d, J=7.5, 4.5 Hz, arom.), 7.5 (1H, d.d, J=7.5, 1.5 Hz, arom.), 7.95 (2/3H) and 8.25 (1/3H, s, –CHO), 8.4 (1H, d.d, J=4.5, 1.5 Hz, arom.). *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.47; H, 6.82; N, 13.96.

Further elution with $CHCl_3$ gave 117 mg of XIIIb as a colorless oil, bp 120° (0.05 mmHg). IR ν_{max}^{film} cm^{-1}: 1660 (C=O). NMR ($CDCl_3$) δ: 1.5—2.4 (5H, m), 2.5—3.7 (4H, m), 4.3 (1/2H) and 5.1 (1/2H, m, >CH–N<), 7.1 (1H, d.d, J=7.5, 4.5 Hz, arom.), 7.4 (1H, d.d, J=7.5, 1.5 Hz, arom.), 7.95 (1/2H) and 8.15 (1/2H, s, –CHO), 8.4 (1H, d.d, J=4.5, 1.5 Hz, arom.). *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.48; H, 7.15; N, 13.92.

2) A mixture of XIIa and XIIIa (250 mg) and 10% H_2SO_4 (5 ml) was refluxed for 9 hr. After cooling, the mixture was made alkaline with K_2CO_3, and extracted with $CHCl_3$. The extract was worked up as usual to give 190 mg of a brown oil. A mixture of Ac_2O (510 mg) and HCOOH (230 mg) was warmed on an oil bath at 50° for 2 hr, cooled and dissolved in benzene (10 ml). To this solution was added the above product dissolved in benzene (10 ml), and the mixture was stirred at room temperature for 2 hr. The mixture was then diluted with water (20 ml), and extracted with $CHCl_3$. The extract was worked up in a similar manner as above to give 120 mg (50%) of a mixture of XIIb and XIIIb, which was then chromatographed on SiO_2 as same as the procedure of 1) to give 45 mg of XIIb and 25 mg of XIIIb. These products were identical with the corresponding products obtained in 1) by the comparison of IR and NMR spectra.

1,2,3,4,5,6-Hexahydro-1,5-methano-2-methylpyrido[3,2-*c*]azocine (II)——A mixture of XIIb (110 mg) and $LiAlH_4$ (95 mg) in tetrahydrofuran (10 ml) was heated on an oil bath at 50° with stirring for 30 min. After cooling, to the mixture was added saturated potassium sodium tartrate solution, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic solutions were washed with brine, dried over Na_2SO_4, and concentrated. The residue was distilled to give 68 mg (66%) of II as a colorless oil, bp 85—95° (0.08 mmHg). IR ν_{max}^{film} cm^{-1}: 2800 (NMe). Mass Spectrum *m/e*: M^+, 188.127 (calcd. for $C_{12}H_{16}N_2$: 188.131). NMR ($CDCl_3$) δ: 1.3—3.2 (9H, m), 2.1 (3H, s, $>NCH_3$), 3.6 (1H, m, >CH–N<), 7.0 (1H,

12) E. Breitmaier and S. Gassenmann, *Chem. Ber.*, **104**, 665 (1971).

d.d, J=7.5, 4.5 Hz, arom.), 7.25 (1H, d.d, J=7.5, 1.5 Hz, arom.), 8.4 (1H, d.d, J=4.5, 1.5 Hz, arom.). Dihydrochloride of II: colorless fine needles, mp 230—233° (decomp.) (MeOH). *Anal.* Calcd. for $C_{12}H_{16}N_2 \cdot 2HCl$: C, 55.18; H, 6.95; N, 10.73. Found: C, 55.11; H, 6.67; N, 10.58.

1,2,3,4,5,6-Hexahydro-2,6-methano-3-methylpyrido[2,3-*d*]azocine (III)——A mixture of XIIIb (150 mg) and $LiAlH_4$ (152 mg) in tetrahydrofuran (15 ml) was stirred at 50° for 30 min. The mixture was worked up as similar as above to give 90 mg (64%) of III as a colorless oil, bp 90—100° (0.07 mmHg). IR ν_{max}^{film} cm^{-1}: 2800 (NMe). Mass Spectrum m/e: M^+, 188.134 (calcd. for $C_{12}H_{16}N_2$: 188.131). NMR ($CDCl_3$) δ: 1.3—3.4 (10H, m), 2.3 (3H, s, $>NCH_3$), 6.95 (1H, d.d, J=7.5, 4.5 Hz, arom.), 7.3 (1H, d.d, J=7.5, 1.5 Hz, arom.), 8.3 (1H, d.d, J=4.5, 1.5 Hz, arom.). Dihydrochloride of III: colorless fine needles, mp 239—242° (decomp.) (EtOH). *Anal.* Calcd. for $C_{12}H_{16}N_2 \cdot 2HCl$: C, 55.18; H, 6.95; N, 10.72. Found: C, 55.37; H, 7.16; N, 10.72.

Acknowledgement The authors are grateful to Mr. M. Morikoshi and Mr. H. Hori of this Faculty for NMR and mass spectral measurement and elemental analyses, respectively.