[Chem. Pharm. Bull. 21(9)2039—2047(1973)]

UDC 547.897.04

Studies on 1-Azabicyclo Compounds. XV.[1] Oxidation of 1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one Derivatives with Mercuric Acetate, and Their Conversion into 1,2,3,4,5,-6,7,8-Octahydro-2-methyl-2,5-benzodiazecine and Related Compounds[2]

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(Received March 1, 1973)

Oxidation of hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (Ia) with mercuric acetate gave the α-aminocarbinol (II), which was characterized as the quaternary ammonium bromide (III). Mercuric acetate oxidation of the diamine (VII), however, afforded the lactam (VIII). Treatment of the methiodides (XIIa, XIIb, and XIIc) with lithium in liquid ammonia yielded the piperazinones (XIIIa, XIIIb, and XIIIc), respectively. On the other hand, reduction of the methiodides (XIIa, XIIb, and XIIc) with sodium amalgam furnished selectively the ten-membered aminolactams (XVIa, XVIb, and XVIc), respectively, in fair yields, which were converted to the corresponding ten-membered diamines (XVIIa, XVIIb, and XVIIc).

In a series of our studies on 1-azabicyclo systems, we have reported a number of syntheses of nine- and ten-membered cyclic amines[4] or diamines[1] from some derivatives of indolizidine, quinolizidine or 2-azaquinolizidine by the selective cleavage of the C-N bond. This paper is concerned with the further application of this method to the conversion of hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-ones (Ia,[5] Ib, and Ic) into the ten-membered cyclic aminolactams (XVIa, XVIb, and XVIc) and the corresponding diamines (XVIIa, XVIIb and XVIIc).

Oxidation of Ia with mercuric acetate in 5% aqueous acetic acid afforded in 69% yield an amorphous product (II), which, on treatment with hydrobromic acid, formed the quaternary ammonium salt (III), $C_{12}H_{11}ON_2Br$. The infrared (IR) spectrum of III showed bands at 1685 (lactam) and 1635 cm^{-1} (iminium), and its nuclear magnetic resonance (NMR) spectrum exhibited two singlets at 0.02 (1H) and 0.85 τ (1H) besides four aromatic protons. Catalytic hydrogenation of III resulted in the uptake of 2 molar equivalents of hydrogen, giving Ia in a quantitative yield. These data deduced the structure of III as depicted.[6] On treatment with alkali, the quaternary ammonium salt (III) gave back the compound (II). Though the compound (II) could not be fully characterized, the results mentioned above would support its structure as the α-aminocarbinol (II). A quite similar result has also been noted in the

1) Part XIV: Y. Arata and Y. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 1248 (1973).
2) Reported at 35 th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, December 1972.
3) Location: *a) Tatekawa-machi, Katsuyama, 911, Japan*; *b) Takara-machi, Kanazawa, 920, Japan.*
4) *a)* Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.* (Tokyo), **17**, 1363 (1969); *b)* Y. Arata, T. Kobayashi, M. Nakamura, and T. Yasuda, *Yakugaku Zasshi*, **90**, 1424 (1970); *c)* Y. Arata, S. Yoshifuji, and T. Shioda, *ibid.*, **92**, 69 (1972); *d)* Y. Arata and T. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 325 (1972); *e)* Y. Arata and T. Shioda, *ibid.*, **20**, 783 (1972); *f)* Y. Arata and Y. Oda, *ibid.*, **21**, 752 (1973).
5) H.B. Sullivan and A.R. Day, *J. Org. Chem.*, **29**, 326 (1964).
6) Similar quaternary salts were obtained by oxidation of the derivatives of 2-alkyl-1,2,3,4-tetrahydroisoquinoline: J. Knabe and H. Roloff, *Chem. Ber.*, **97**, 3452 (1964) and references therin.

mercuric acetate oxidation of 1,1-dibenzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2,4,4-trimethyl-isoquinoline.[7]

Reduction of III with sodium borohydride in methanol afforded the enamine (IV) in 76% yield, the NMR spectrum of which showed a peak at 5.80 τ as a singlet due to the benzylic protons at C-6. The hydrochloride, IR: 2500—2800 cm^{-1} ($\geqslant N^+H$), of IV was treated with sodium borohydride in a protic solvent and with potassium cyanide,[8] recovering only the starting material in both cases. Consequently, the hydrochloride should exist as the N-protonated salt (V), but not as the iminium salt (VI). The stable conjugation between the benzene ring and the unsaturated lactam in V prevents presumably the transfer of the proton from the nitrogen to the carbon at the position of 11.[9] Catalytic hydrogenation of IV and V yielded readily Ia in quantitative yields.

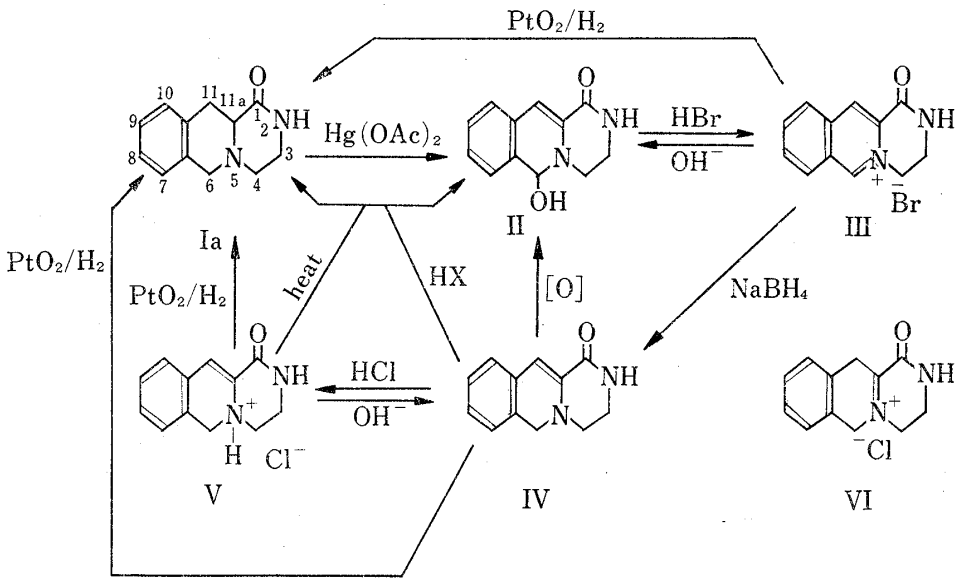


Chart 1

Heating of V in water afforded both Ia and II in 40% and 28% yield, respectively. A similar result was also obtained by heating of IV in diluted sulfuric acid or hydrobromic acid. Intermolecular reduction and oxidation would occur simultaneously in these reactions. Reaction of IV with methyl iodide in acetone did not yield the normal methiodide, but instead the compound (II) unexpectedly in 55% yield, presumably by air oxidation. Only the starting material was recovered by treatment of IV with methyl iodide in methanol or in acetone in a nitrogen atmosphere.

On the other hand, oxidation of the diamine (VII)[5] with mercuric acetate in aqueous acetic acid afforded the lactam (VIII), mp 59—60°, in 63% yield. In the NMR spectrum of VIII, the signal due to the benzylic protons at C-6 disappeared and that of the aromatic proton at C-7 appeared at a lower field (1.80—1.90 τ) than those of other aromatic protons, the paramagnetic shift of this proton being caused by the *peri*-effect of the carbonyl[10] at C-6. And the signal of the equatorial proton at C-4 appeared at 5.40—5.60 τ as a multiplet.[11] To clarify the structure VIII unambiguously, the following reactions were carried out. Eschweiler–Clarke reaction of VIII with formalin and formic aicd gave the N-methyl-lactam (IX),

7) J. Knabe and J. Kubitz, *Arch. Pharm.*, **296**, 591 (1963).
8) N.J. Leonard and A.S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).
9) *a*) E.J. Stamhuis and W. Mass, *J. Org. Chem.*, **30**, 2160 (1965); *b*) J. Elguero, R. Jacquier, and G. Tarrago, *Tetrahedron Letters*, **1965**, 4719.
10) R.H. Martin, N. Defray, and F. Greets-Evrard, *Tetrahedron*, **20**, 1505 (1964).
11) F. Bohlmann and D. Schumann, *Tetrahedron Letters*, **1965**, 2435.

which, on reduction with lithium aluminum hydride, afforded the diamine (X). The diamine thus obtained was identified with the N-methylation product derived from VII by the comparison of their IR spectra and the mixed melting point determination. In the reaction of VII, the benzylic position at C-6 adjacent to the nitrogen is probably more sensitive to the oxidizing agent than the position at C-11a, thus the lactam (VIII) was formed prior to the formation of the enamine. The mechanism of the lactam formation might be analogous to that proposed for the mercuric acetate oxidation of 2-azaquinolizidine.[1)]

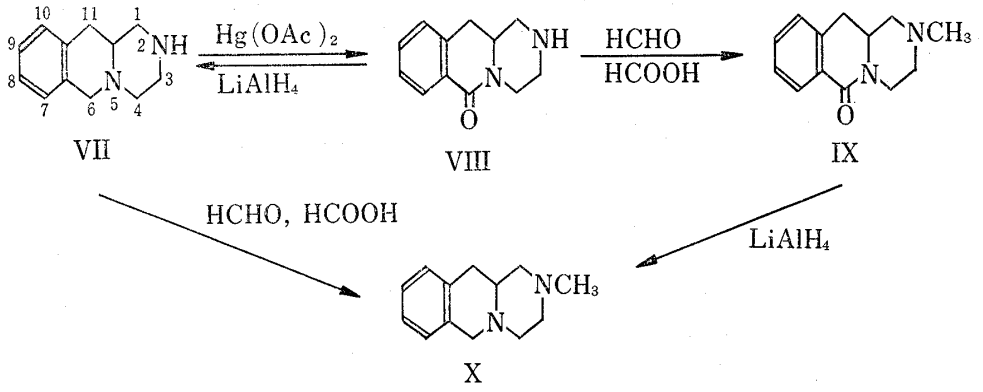
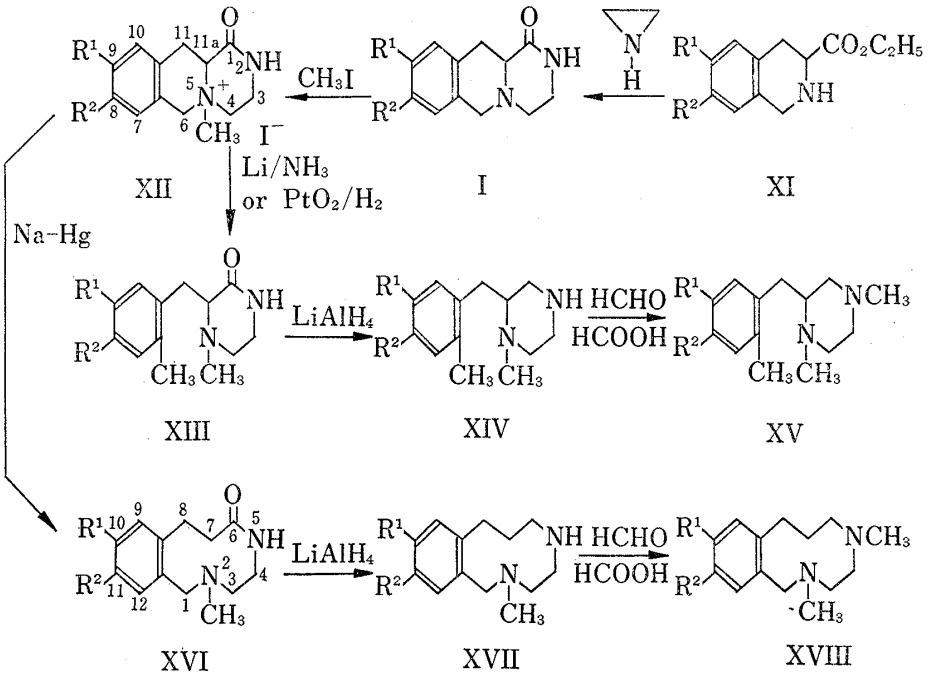


Chart 2

Next, we tried to obtain the ten-membered cyclic aminolactam and diamine derivatives from the methiodides (XIIa, XIIb, and XIIc). Hexahydro-6,7-dimethoxy- and hexahydro-6,7-methylenedioxy-2*H*-pyrido[1,2-*b*]isoquinolin-1-one (Ib and Ic) were synthesized by condensation of ethyl tetrahydro-6,7-dimethoxy- and tetrahydro-6,7-methylenedioxy-isoqui-



a : $R^1=R^2=H$
b : $R^1=R^2=OCH_3$
c : $R^1+R^2=-OCH_2O-$

Chart 3

noline-3-carboxylate (XIb[12] and XIc) with ethylenimine in 45% and 58% yield, respectively, according to the same procedure as that for Ia.[5] The latter isoquinoline (XIc) was derived from 3′,4′-methylenedioxyphenylalanine by condensation with formalin, followed by esterification.

Treatment of the methiodide (XIIa) with lithium in liquid ammonia effected hydrogenolysis of the C_6-N bond to afford 1-methyl-2-(2-methylbenzyl)piperazin-3-one (XIIIa), mp 95—96°, in 41% yield. The IR spectrum of XIIIa indicated bands at 3180 (NH) and 1660 cm^{-1} (lactam). Its NMR spectrum showed two methyl signals at 7.62 and 7.69 τ as a singlet due to an aromatic C-methyl and an N-methyl grouping, and the signal attributable to the methylene at C_6-position in XIIa disappeared. In order to obtain the further confirmation of the structure XIIIa, catalytic hydrogenation of XIIa was performed to furnish the piperazinone (XIIIa) in 23% yield, which was identical with that obtained above. On treatment with lithium in liquid ammonia, the methiodides (XIIb and XIIc) were similarly converted into the corresponding piperazinones (XIIIb and XIIIc) in 32% and 22% yield, respectively. Further reduction of the piperazinones (XIIIa, XIIIb, and XIIIc) with lithium aluminum hydride gave the piperazines (XIVa, XIVb, and XIVc) in fair yields. Eschweiler–Clarke reaction of XIVa afforded N,N-dimethylpiperazine (XVa) in 69% yield.

On the other hand, treatment of the methiodide (XIIa) with 5% sodium amalgam in 60% aqueous ethanol effected successfully the selective cleavage of the C_{11a}-N bond to give the desired ten-membered cyclic aminolactam, octahydro-2-methyl-2,5-benzodiazecin-6-one (XVIa), mp 87—89°, in 84% yield. In agreement with the structure of XVIa, the product showed bands at 3270 (NH) and 1635 cm^{-1} (lactam) in the IR spectrum, and exhibited signals at 5.90 τ (NH) as a broad singlet, at 7.53 τ (N-CH_3) as a singlet, at 6.40 τ (methylene at C-1) as a singlet and no C-methyl signals in the NMR spectrum. On similar treatment with sodium amalgam, the methiodides (XIIb and XIIc) gave selectively the benzo-octahydrodiazecinones (XVIb and XVIc) in 73% and 65% yield, respectively. The structures, XVIb and XVIc, were verified by their spectroscopic data. The benzo-octahydrodiazecinones (XVIa, XVIb, and XVIc) were further reduced with lithium aluminum hydride to afford the ten-membered cyclic diamines, octahydro-2-methyl-2,5-benzodiazecines (XVIIa, XVIIb, and XVIIc) in 89, 84, and 92% yield, respectively. The benzo-octahydrodiazecine (XVIIa) showed characteristic peaks at *m/e* 204 (M^+), 160 (base peak), 146 and 117 in the mass spectrum. Their precise empirical formulae were determined by the high-resolution mass spectrometry (see Experimental). These fragmentation peaks can be well interpreted from the structure XVIIa as shown in Chart 4. The transition from *m/e* 160 to *m/e* 117 was proved by the appearance

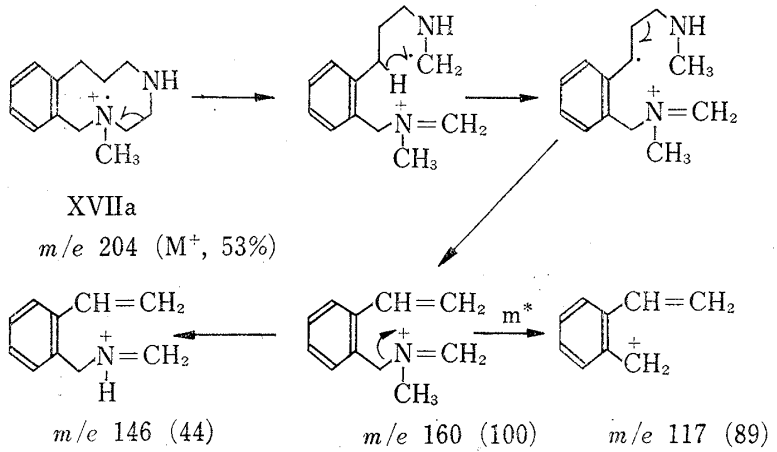


Chart 4

12) N. Sugimoto, *Yakugaku Zasshi*, **64B**, 108 (1944).

of a metastable peak at *m/e* 85.5. Eschweiler-Clarke reaction of XVIIa produced the N,N-dimethyl-octahydrodiazecine (XVIIIa) in 58% yield.

Thus, the methiodides (XIIa, XIIb, and XIIc) were treated with lithium in liquid ammonia and with sodium amalgam to give the piperazinones (XIIIa, XIIIb, and XIIIc) and the ten-membered cyclic aminolactams (XVIa, XVIb, and XVIc), respectively. The application of these reductive methods to other 1-azabicyclic systems is now in progress.

Experimental[13]

Ethyl 1,2,3,4-Tetrahydro-6,7-methylenedioxyisoquinoline-3-carboxylate (XIc)——*l*-3′,4′-Methylenedioxyphenylalanine (41.6 g) was heated at 80° for 3 hr with 37% HCHO (140 ml), 20% HCl (300 ml) and H_2O (40 ml). A precipitate was collected by filtration and washed with EtOH to give 1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline-3-carboxylic acid hydrochloride (43.5 g (84.5%)). To a refluxed suspension of the crude hydrochloride (43.5 g) in EtOH (800 ml) was added dropwise $SOCl_2$ (40.5 g), and then the reaction mixture was refluxed for 5 hr and evaporated. The residue was recrystallized from EtOH to give the hydrochloride (45.8 g (95%)) of XIc as colorless pillars, mp 223—225°. IR ν_{max}^{KBr} cm^{-1}: 1730 (ester). $[\alpha]_D^{25}$ −88° (c=0.1, EtOH). *Anal.* Calcd. for $C_{13}H_{15}O_4N \cdot HCl$: C, 54.64; H, 5.64; N, 4.90. Found: C, 54.94; H, 5.86; N, 4.89. The free base was obtained in a usual way and purified by distillation as a colorless oil, $bp_{1.5}$ 183—185°.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (Ia)——a) According to the method of Sullivan, *et al.*,[5] Ia was obtained as colorless scales, mp 189—191° (EtOH, lit.[5] 185—187°).

The methiodide (XIIa) was obtained by heating of Ia with MeI at 60° for 4 hr in 74% yield as pillars, mp 235—237° (decomp.) (H_2O). IR ν_{max}^{KBr} cm^{-1}: 1690 (lactam). NMR (in 10% D_2O) τ: 6.72 (3H, s, N-CH_3). *Anal.* Calcd. for $C_{13}H_{17}ON_2I$: C, 45.36; H, 4.98; N, 8.14. Found: C, 45.87; H, 5.08; N, 8.11.

b) Compound (III, 100 mg) was hydrogenated in EtOH (5 ml) over PtO_2 (10 mg) at atmospheric pressure and room temperature. After 2 molar equivalents of H_2 wese uptaken during 1 hr, the catalyst was filtered off and the filtrate was evaporated. The residue was made alkaline with aq. K_2CO_3 soln. and extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated. The residue (75 mg, quantitative yield) was identical with Ia in IR spectra and mixed melting point.

c) Compound (IV, 100 mg) was hydrogenated in the same procedure as that described in b) with absorption of 1 molar equivalent of H_2 during 1 hr to give the product (100 mg, quantitative yield), which was identical with Ia in IR spectra and mixed melting point. The same result was also obtained by catalytic hydrogenation of V.

1,3,4,6,11,11a-Hexahydro-8,9-dimethoxy-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (Ib)——To a refluxed solution of ethyl 1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinoline-3-carboxylate[12] (36.8 g) and its hydrochloride (4.16 g) in EtOH (200 ml) was added dropwise a solution of ethylenimine (3.0 g) in EtOH (100 ml) during 3 hr, and then the reaction mixture was refluxed for 24 hr. A solution of ethylenimine (3.0 g) in EtOH (100 ml) was again added to the reaction mixture, which was further refluxed for 48 hr. After the reaction mixture was cooled, the precipitated crystals were collected by filtration and recrystallized from EtOH to give Ib (16.4 g (45%)) as colorless needles, mp 214—216°. IR ν_{max}^{KBr} cm^{-1}: 1680 (lactam). NMR τ: 6.15 (6H, s, $OCH_3 \times 2$). *Anal.* Calcd. for $C_{14}H_{18}O_3N_2$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.82; H, 6.87; N, 10.50.

The methiodide (XIIb) was obtained in 79% yield as pale yellow needles, mp 210—212° (MeOH). IR ν_{max}^{KBr} cm^{-1}: 1670 (lactam). *Anal.* Calcd. for $C_{15}H_{21}O_3N_2I$: C, 44.56; H, 5.24; N, 6.93. Found: C, 44.73; H, 5.30; N, 6.89.

1,3,4,6,11,11a-Hexahydro-8,9-methylenedioxy-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (Ic)——The ester (XIc, 43.7 g) and its hydrochloride (5.0 g) was condensed with ethylenimine (7.5 g) in the same procedure as that for Ib to give Ic (24.8 g (58%)) as colorless scales, mp 214—216° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 1660 (lactam). NMR (in 5% d_6-$(CH_3)_2SO$) τ: 4.05 (2H, s, -OCH_2O-). $[\alpha]_D^{25}$ −268° (c=0.1, MeOH). *Anal.* Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.70; N, 11.38. Found: C, 63.43; H, 5.62; N, 11.00.

The methiodide (XIIc) was obtained in 69% yield as pale yellow fine crystals, mp 280° (MeOH). IR ν_{max}^{KBr} cm^{-1}: 1680 (lactam). $[\alpha]_D^{25}$ −87° (c=0.1, MeOH). *Anal.* Calcd. for $C_{14}H_{17}O_3N_2I$: C, 43.31; H, 4.42; N, 7.22. Found: C, 43.03; H, 4.16; N, 6.99.

Oxidation of the Aminolactam (Ia) with Mercuric Acetate——To a solution of $Hg(OAc)_2$ (57.8 g) in 5% aq. AcOH (300 ml) was added Ia (6.06 g), and the reaction mixture was heated with stirring at 100°

13) All melting points and boiling points are uncorrected. All melting points were measured with Yanagimoto Micro Melting Point Apparatus. Organic extracts were dried over anhydrous Na_2SO_4. IR spectra were measured with Spectrophotometer IRA-2, Japan Spectroscopic Co., Ltd. NMR spectra were taken on Hitachi R-20B at 60 Mc with $(CH_3)_4Si$ as an internal standard in 10% $CDCl_3$ solution unless otherwise stated. Mass spectra were taken on Hitachi RMU-7L spectrometer.

for 2.5 hr. The precipitated $Hg_2(OAc)_2$ was filtered and washed with 5% aq. AcOH. H_2S was bubbled into the combined filtrate and washings. The precipitated HgS was separated by the centrifuge. The supernatant liquid was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was dried and evaporated to give 1,3,4,6-tetrahydro-6-hydroxy-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (II, 4.5 g (69%)) as a pale yellow amorphous solid, mp 230—232° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1650 (lactam), 1605 (enamine). A solution of the α-aminocarbinol (II) in MeOH was treated with 47% HBr to give 1,2,3,4-tetrahydro-1-oxo-pyrazino[1,2-*b*]isoquinolinium bromide (III) as colorless needles, mp>300° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 1685 (lactam), 1635 (iminium). NMR (in 3% CD_3OD) τ: 0.02 (1H, s, C_6-H), 0.85 (1H, s, C_{11}-H), 1.20—1.90 (4H, m, C_7-H, C_8-H, C_9-H, C_{10}-H). *Anal.* Calcd. for $C_{12}H_{11}ON_2Br$: C, 51.63; H, 3.97; N, 10.04. Found; C, 51.48; H, 3.78; N, 9.91.

The chloride: mp>295° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 1680 (lactam), 1635 (iminium). NMR (in 3% CD_3OD) τ: 0.05 (1H, s, C_6-H), 0.89 (1H, s, C_{11}-H), 1.30—1.90 (4H, m, C_7-H, C_8-H, C_9-H, C_{10}-H). *Anal.* Calcd. for $C_{12}H_{11}ON_2Cl\cdot H_2O$: C, 57.03; H, 5.18; N, 11.09. Found: C, 56.89; H, 5.14; N, 11.14.

A solution of the bromide or the chloride in H_2O was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give an amorphous solid, mp 230—232° (decomp.), which was identical with II obtained above in IR spectra.

1,3,4,6-Tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (IV)——To a cooled solution of III (5.0 g) in MeOH (20 ml) was added $NaBH_4$ (5.0 g) in small portions, and the reaction mixture was refluxed for 3 hr and then evaporated. The residue was taken in $CHCl_3$, and $CHCl_3$ layer was washed with H_2O, dried and evaporated. The residue was recrystallized from MeOH to give IV (3.0 g (76%)) as pale yellow scales, mp 145—148°. IR ν_{max}^{KBr} cm^{-1}: 1670 (lactam), 1610 (enamine). NMR τ: 2.35 (1H, br, NH, disappeared by addition of D_2O), 3.28 (1H, s, C_{11}-H), 5.80 (2H, s, C_6-H_2). Mass Spectrum *m/e*: 200 (M^+), 199, 128, 116, 77. *Anal.* Calcd. for $C_{12}H_{12}ON_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.99; H, 6.12; N, 14.05.

The hydrochloride (V); mp 285—290° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 2500—2800 (>N^+H), 1690 (lactam), 1640 (enamine). *Anal.* Calcd. for $C_{12}H_{12}ON_2\cdot HCl$: C, 60.88; H, 5.33; N, 11.83. Found: C, 60.63; H, 5.66; N, 11.75.

Reaction of the Aminolactam (IV) and Its Hydrochloride (V) with Mineral Acids——A solution of IV (1.0 g) was heated at 100° with 10% HCl (50 ml) for 30 min. After the reaction mixture was cooled, a precipitate was collected by filtration to give the product (570 mg (48%)) as a colorless powder, mp>290°. The product was identical with the hydrochloride of Ia in IR spectra. The filtrate was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give the amorphous product (290 mg (27%)), mp 230—232° (decomp.), which was identical with II in IR spectra and mixed melting point. The same result was also obtained with 10% HBr or 10% H_2SO_4.

A solution of V (500 mg) in H_2O (50 ml) was heated at 100° for 30 min. The reaction mixture was treated in the same procedure as that described above to give the hydrochloride (200 mg (40%)) of Ia and II (130 mg (28%)).

Reaction of Aminolactam (IV) with Methyl Iodide——a) A solution of IV (100 mg) and MeI (1 ml) in acetone (50 ml) was kept overnight at room temperature. A precipitate was collected by filtration to give II (59 mg (55%)) as an amorphous powder, mp 230—232°, which was identical with authentic specimen in IR spectra and mixed melting point.

b) A solution of IV (500 mg) and MeI (5 ml) in MeOH (10 ml) was kept for 24 hr in N_2 atmosphere in a sealed tube and then evaporated to give a solid, which was identical with IV in IR spectra.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline (VII)——a) From Ia: According to the method of Sullivan, *et al.*,[5] VII was obtained as colorless scales, mp 72—75° (lit[5] mp 85—90°). IR ν_{max}^{KBr} cm^{-1}: 3280 (NH). NMR τ: 2.90 (4H, s, aromatic H), 6.11, 6.57 (2H, AB quartet, J=15 Hz, C_6-H_2), 8.17 (1H, s, NH, disappeared by addition of D_2O).

b) From VIII: To a stirred suspension of $LiAlH_4$ (500 mg) in anhyd. ether (10 ml) was added VIII (200 mg) and the reaction mixture was refluxed with stirring for 15 hr. The excess hydride was decomposed with addition of H_2O. The inorganic material was filtered off and washed with ether. The dried filtrate and washings were evaporated and the residue was recrystallized from iso-Pr_2O to give VII (140 mg (75%)), mp 72—75°, as colorless scales, which was identical with that obtained above in IR spectra and mixed melting point.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-6-one (VIII)——To a solution of $Hg(OAc)_2$ (32 g) in 5% aq. AcOH (200 ml) was added VII (1.88 g), and the reaction mixture was heated with stirring at 100° for 17 hr and treated in the same procedure as that for the oxidation of Ia. The product was isolated as the hydrochloride (1.5 g (63%)) of VIII as colorless needles, mp 280° (MeOH). *Anal.* Calcd. for $C_{12}H_{14}ON_2\cdot HCl$: C, 60.37; H, 6.33; N, 11.73. Found: C, 60.85; H, 6.53; N, 11.93.

The free base (VIII) was obtained in a usual way and recrystallized from iso-Pr_2O as colorless needles, mp 59—60°. IR ν_{max}^{KBr} cm^{-1}: 3270 (NH), 1630 (lactam). NMR τ: 1.80—1.90 (1H, m, C_7-H), 2.53—2.95 (3H, m, C_8-H, C_9-H, C_{10}-H), 5.40—5.60 (1H, m, C_4-H_{eq}), 8.13 (1H, s, NH, disappeared by addition of D_2O). *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.40; H, 6.83; N, 13.57.

1,3,4,6,11,11a-Hexahydro-2-methyl-2*H*-pyrazino[1,2-*b*]isoquinolin-6-one (IX)——A solution of VIII (1.3 g) in 37% HCHO (5 ml) and 80% HCOOH (10 ml) was stirred at 80° for 3 hr. The reaction mixture

was evaporated to dryness *in vacuo*, and the residue was made alkaline with aq. K_2CO_3 soln. and extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated. The residue was recrystallized from *n*-hexane to give IX (1.23 g (89%)) as colorless scales, mp 84—85°. IR ν_{max}^{KBr} cm^{-1}: 1630 (lactam). NMR τ: 1.79—1.94 (1H, m, C_7-H), 2.51—2.94 (3H, m, C_8-H, C_9-H, C_{10}-H), 5.45 (1H, d-m, J=13 Hz, C_4-H_{eq}), 7.63 (3H, s, N-CH_3). *Anal.* Calcd. for $C_{13}H_{16}ON_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.40; H, 7.63; N, 13.00.

1,3,4,6,11,11a-Hexahydro-2-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline (X)——a) From IX: To a stirred suspension of $LiAlH_4$ (1.0 g) in anhyd. ether (10 ml) was added IX (500 mg), and the reaction mixture was refluxed for 16 hr. The excess hydride was decomposed with H_2O, and the inorganic material was filtered and washed with ether. The filtrate and washings were combined, dried and evaporated. The residue was recrystallized from *n*-hexane to give X (330 mg (71%)) as colorless scales, mp 80—81°. NMR τ: 2.91 (4H, s, aromatic protons), 6.08, 6.60 (2H, AB-quartet, J=15 Hz, C_6-H_2), 7.65 (3H, s, N-CH_3). *Anal.* Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.25; H, 8.94; N, 14.06.

The hydrochloride: mp 234—236° (EtOH).

b) From VII: A solution of VII (5.0 g) in 37% HCHO (10 ml) and 80% HCOOH (20 ml) was stirred at 80° for 3 hr. The reaction mixture was treated in the same procedure as that for IX to give X (3.7 g (68%)) as colorless scales, mp 80—81° (*n*-hexane), which was identical with that obtained from IX in IR spectra and mixed melting point.

1-Methyl-2-(2-methylbenzyl)piperazin-3-one (XIIIa)——a) To a solution of XIIa (3.44 g) in liq. NH_3 (300 ml) was added Li (1.0 g) in small portions. The reaction mixture was stirred vigorously for 10 min and evaporated at room temperature. To the residue was added H_2O, and the mixture was extracted with ether. The extract was washed with H_2O, dried and evaporated. HCl–EtOH was added to a solution of the residue in EtOH. The precipitated crystals were collected by filtration and recrystallized from MeOH to give the hydrochloride (1.05 g (41%)) of XIIIa as colorless needles, mp 231—233°. *Anal.* Calcd. for C_{13}-$H_{18}ON_2$·HCl: C, 61.28; H, 7.52; N, 11.00. Found: C, 61.68; H, 7.58; N, 11.25.

The free base (XIIIa) was obtained in a usual way and recrystallized from iso-Pr_2O as colorless pillars, mp 95—96°. IR ν_{max}^{KBr} cm^{-1}: 3180 (NH), 1660 (lactam). NMR τ: *ca.* 2.70 (1H, br, NH, disappeared by addition of D_2O), 2.58—2.93 (4H, m, aromatic protons), 7.62 (3H, s, CH_3), 7.69 (3H, s, CH_3).

b) A suspension of XIIa (3.44 g) in MeOH (200 ml) was hydrogenated over PtO_2 (100 mg) at 150 atm. and 100° for 5 hr. The catalyst was filtered off and the filtrate was evaporated. The residue was made alkaline with aq. K_2CO_3 soln. and extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was recrystallized from iso-Pr_2O to give XIIa (506 mg (23%)) as colorless pillars, mp 95—96°, which was identical with that obtained above in IR spectra and mixed melting point.

2-(4,5-Dimethoxy-2-methylbenzyl)-1-methylpiperazin-3-one (XIIIb)——The methiodide (XIIb, 4.04 g) was treated with Li in liq. NH_3 in the same procedure as that for XIIIa to give the hydrochloride (900 mg (32%)) of XIIIb as colorless needles, mp 235—237° (EtOH). *Anal.* Calcd. for $C_{15}H_{22}O_3N_2$·HCl: C, 57.22; H, 7.36; N, 8.90. Found: C, 57.03; H, 7.55; N, 8.69.

The free base (XIIIb) was obtained in a usual way as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 3200 (NH), 1660 (lactam). NMR τ: 2.60 (1H, br, NH, disappeared by addition of D_2O), 2.93 (1H, s, aromatic proton), 3.38 (1H, s, aromatic proton), 6.18 (6H, s, OCH_3×2), 7.67 (3H, s, CH_3), 7.70 (3H, s, CH_3).

1-Methyl-2-(2-methyl-4,5-methylenedioxybenzyl)piperazin-3-one (XIIIc)——The methiodide (XIIc, 3.88 g) was treated with Li in liq. NH_3 in the same procedure as that for XIIIa to give XIIIc (580 mg (22%)) as colorless needles, mp 186—187° (iso-PrOH). IR ν_{max}^{KBr} cm^{-1}: 3190 (NH), 1670 (lactam). NMR τ: 3.14 (1H, s, aromatic proton), 3.15 (1H, br, NH, disappeared by addition of D_2O), 3.41 (1H, s, aromatic proton), 4.16 (2H, s, -OCH_2O-), 7.66 (3H, s, CH_3), 7.72 (3H, s, CH_3). $[\alpha]_D^{25}$ −15° (c=0.1, MeOH). *Anal.* Calcd. for $C_{14}H_{18}O_3N_2$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.50; H, 6.77; N, 10.75.

1-Methyl-2-(2-methylbenzyl)piperazine (XIVa)——To a suspension of $LiAlH_4$ (1.0 g) in anhyd. ether (10 ml) was added XIIIa (500 mg), and the reaction mixture was refluxed for 16 hr. The excess hydride was decomposed with H_2O, and the inorganic material was filtered and washed with ether. The filtrate and washings were combined, dried and evaporated to give XIVa (350 mg (75%)) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 3250 (NH). NMR τ: 2.87 (4H, s, aromatic protons), 7.53 (3H, s, CH_3), 7.65 (3H, s, CH_3), 8.27 (1H, s, NH, disappeared by addition of D_2O).

2-(4,5-Dimethoxy-2-methylbenzyl)-1-methylpiperazine (XIVb)——Compound (XIIIb, 700 mg) was reduced with $LiAlH_4$ (300 mg) in anhyd. Ether (7 ml) in the same procedure as that for XIVa to give XIVb (560 mg (84%)) as a pale yellow oil. IR ν_{max}^{liq} cm^{-1}: 3250 (NH). NMR τ: 3.38 (2H, br, aromatic protons), 6.16 (6H, s, OCH_3×2), 7.44 (1H, s, NH, disappeared by addition of D_2O), 7.54 (3H, s, CH_3), 7.74 (3H, s, CH_3).

The hydrochloride, mp 198—199° (EtOH–acetone). *Anal.* Calcd. for $C_{15}H_{24}O_2N_2$·2HCl: C, 53.41; H, 7.77; N, 8.31. Found: C, 53.38; H, 7.60; N, 8.47.

1-Methyl-2-(2-methyl-4,5-methylenedioxybenzyl)piperazine (XIVc)——Compound (XIIIc, 300 mg) was reduced with $LiAlH_4$ (150 mg) in anhyd. ether (5 ml) in the same procedure as that for XIVa to give XIVc (193 mg (68%)) as colorless fine crystals, mp 115—117° (iso-Pr_2O). IR ν_{max}^{KBr} cm^{-1}: 3220 (NH). NMR τ: 3.45 (2H, s, aromatic protons), 4.15 (2H, s, -OCH_2O-), 7.56 (3H, s, CH_3), 7.76 (3H, s, CH_3), 7.90 (1H, s, NH,

disappeared by addition of D_2O). $[\alpha]_D^{25}$ +68° (c=0.1, MeOH). *Anal.* Calcd. for $C_{14}H_{20}O_2N_2$: C, 67.71; H, 8.21; N, 11.28. Found: C, 67.50; H, 8.33; N, 11.01.

1,4-Dimethyl-2-(2-methylbenzyl)piperazine (XVa)——A solution of XIVa (500 mg) in 37% HCHO (1 ml) and 80% HCOOH (2 ml) was stirred at 80° for 3 hr and treated in the same procedure as that for IX to give the product, which was converted to the hydrochloride (490 mg (69%)) of XVa as colorless leaflets, mp 227—229° (EtOH–ether (1: 1)). *Anal.* Calcd. for $C_{14}H_{22}N_2 \cdot 2HCl$: C, 57.73; H, 8.31; N, 9.62. Found: C, 57.70; H, 8.54; N, 9.30.

The free base (XVa) was obtained in a usual way as a colorless oil. NMR τ: 2.90 (4H, s, aromatic protons), 7.53 (3H, s, CH_3), 7.67 (3H, s, CH_3), 7.83 (3H, s, CH_3).

1,2,3,4,5,6,7,8-Octahydro-2-methyl-2,5-benzodiazecin-6-one (XVIa)——To a solution of XIIa (5.0 g) in 60% aq. EtOH (100 ml) was added powdered 5% Na-Hg (25 g), and the reaction mixture was stirred at room temperature for 15 hr. The precipitated Hg was filtered off and the filtrate was evaporated. The residue was dissolved in $CHCl_3$ and the $CHCl_3$ layer was washed with H_2O, dried and evaporated. The residue was recrystallized from iso-Pr_2O to give XVIa (2.65 g (84%)) as colorless pillars, mp 87—89°. IR ν_{max}^{KBr} cm^{-1}: 3270 (NH), 1635 (lactam). NMR τ: 2.79 (4H, m, aromatic protons), 5.90 (1H, br, NH, disappeared by addition of D_2O), 6.40 (2H, s, C_1-H_2), 7.53 (3H, s, N-CH_3). *Anal.* Calcd. for $C_{13}H_{18}ON_2$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.75; H, 8.35; N, 12.86.

1,2,3,4,5,6,7,8-Octahydro-10,11-dimethoxy-2-methyl-2,5-benzodiazecin-6-one (XVIb)——The methiodide (XIIb, 2.0 g) was treated with 5% Na-Hg (10 g) in the same procedure as that for XVIa to give XVIb (1.0 g (73%)) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 3280 (NH), 1640 (lactam). NMR τ: 3.22 (1H, s, C_9-H, or C_{12}-H), 3.32 (1H, s, C_9-H or C_{12}-H), 5.55 (1H, br, NH, disappeared by addition of D_2O), 6.15 (6H, s, $OCH_3 \times 2$), 6.46 (2H, s, C_1-H_2), 7.51 (3H, s, N-CH_3).

The Hydrochloride: mp 125—127° (iso-PrOH). *Anal.* Calcd. for $C_{15}H_{22}O_3N_2 \cdot HCl$: C, 57.22; H, 7.36; N, 8.90. Found: C, 57.01; H, 7.25; N, 8.74.

1,2,3,4,5,6,7,8-Octahydro-2-methyl-10,11-methylenedioxy-2,5-benzodiazecin-6-one (XVIc)——The methiodide (XIIc, 3.0 g) was treated with 5% Na-Hg (15 g) in the same procedure as that for XVIa to give XVIc (1.31 g (65%)) as colorless scales, mp 203—205° (iso-PrOH). IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1640 (lactam). NMR τ: 3.30 (1H, s, C_9-H or C_{12}-H), 3.36 (1H, s, C_9-H or C_{12}-H), 4.10 (2H, s, -OCH_2O-), 5.72 (1H, br, NH, disappeared by addition of D_2O), 6.50 (2H, s, C_1-H_2), 7.55 (3H, s, N-CH_3). *Anal.* Calcd. for $C_{14}H_{18}O_3N_2$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.17; H, 7.08; N, 10.40.

1,2,3,4,5,6,7,8-Octahydro-2-methyl-2,5-benzodiazecine (XVIIa)——To a solution of $LiAlH_4$ (4.0 g) in anhyd. ether (30 ml) was added XVIa (3.0 g) and the reaction mixture was refluxed with stirring for 16 hr. The excess hydride was decomposed with H_2O, and the inorganic material was filtered and washed with ether. The filtrate and washings were combined, dried and evaporated to give XVIIa (2.5 g (89%)) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 3300 (NH). NMR τ: 2.72—2.95 (4H, m, aromatic protons), 6.25 (2H, s, C_1-H_2), 7.11 (1H, s, NH, disappeared by addition of D_2O), 7.64 (3H, s, N-CH_3).

The Hydrochloride: mp 204—206° (EtOH). *Anal.* Calcd. for $C_{13}H_{20}N_2 \cdot 2HCl$: C, 56.32; H, 7.27; N, 10.11. Found: C, 56.24; H, 7.11; N, 10.40. Mass Spectrum: Principal peaks were shown in Table I.

Table I. Exact Masses and Compositions of Peaks in Mass Spectrum of XVIIa

m/e observed	m/e calculated	Composition
204.1622	204.1626	$C_{13}H_{20}N_2$
160.1141	160.1126	$C_{11}H_{14}N$
159.1069	159.1048	$C_{11}H_{13}N$
146.0960	146.0969	$C_{10}H_{12}N$
131.0811	131.0860	$C_{10}H_{11}$
117.0704	117.0704	C_9H_9

1,2,3,4,5,6,7,8-Octahydro-10,11-dimethoxy-2-methyl-2,5-benzodiazecine (XVIIb)——Compound (XVIb, 750 mg) was treated with $LiAlH_4$ (400 mg) in anhyd. THF (10 ml) in the same procedure as that for XVIIa to give XVIIb (600 mg (84%)) as a colorless oil. NMR τ: 3.37 (2H, s, C_9-H and C_{12}-H), 6.18 (6H, s, $OCH_3 \times 2$), 6.28 (2H, s, C_1-H_2), 7.32 (1H, s, NH, disappeared by addition of D_2O), 7.62 (3H, s, N-CH_3).

The Hydrochloride: mp 182—184° (iso-PrOH). *Anal.* Calcd. for $C_{15}H_{24}O_2N_2 \cdot 2HCl$: C, 53.41; H, 7.77; N, 8.31. Found: C, 53.62; H, 7.69; N, 8.48.

1,2,3,4,5,6,7,8-Octahydro-2-methyl-10,11-methylenedioxy-2,5-benzodiazecine (XVIIc)——Compound (XVIc, 400 mg) was treated with $LiAlH_4$ (250 mg) in anhyd. THF (5 ml) in the same procedure as that for XVIIa to give XVIIc (350 mg (92%)) as a colorless oil. NMR τ: 3.40 (2H, s, C_9-H and C_{12}-H), 4.16 (2H, s, -OCH_2O-), 6.32 (2H, s, C_1-H_2), 7.64 (3H, s, N-CH_3), 7.75 (1H, s, NH, disappeared by addition of D_2O).

The Hydrochloride: mp 194—196° (MeOH). *Anal.* Calcd. for $C_{14}H_{20}O_2N_2 \cdot 2HCl$: C, 52.34; H, 6.90; N, 8.72. Found: C, 52.27; H, 6.91; N, 8.68.

1,2,3,4,5,6,7,8-Octahydro-2,5-dimethyl-2,5-benzodiazecine (XVIIIa)——A solution of XVIIa (600 mg) in 37% HCHO (1.5 ml) and 80% HCOOH (3 ml) was stirred at 80° for 3 hr and treated in the same procedure as that for IX to give XVIIIa (370 mg (58%)) as a colorless oil. NMR τ: 2.50—2.92 (4H, m, aromatic protons), 6.00 (2H, s, C_1-H_2), 7.44 (3H, s, N-CH_3), 7.56 (4H, s, N-CH_2CH_2-N), 7.80 (3H, s, N-CH_3).

The Hydrochloride: mp 240—242° (EtOH). *Anal.* Calcd. for $C_{14}H_{22}N_2 \cdot 2HCl$: C, 57.73; H, 8.31; N, 9.62. Found: C, 57.87; H, 8.34; N, 9.51.

Acknowledgement The authors are grateful to Hitachi Ltd. for mass spectral measurement.