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Studies on Fused Hydrazines. IV.[1] Some Rearrangement Reactions of 4-Methyl-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazinium Iodide and Related Compounds to N-Aminoalkyl-isoindole or N-Aminoalkyl-pyrrole[2]

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When heated with potassium *t*-butoxide (*t*-BuOK), 4-methyl-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazinium iodide (I) gave 2-(3-methylaminopropyl)isoindole (IV), while 5-methyl-1,4,6,11-tetrahydropyridazino[1,2-*b*]phthalazinium iodide (VII) gave 1-(2-methylaminomethylbenzyl) pyrrole (X) on heating with *t*-BuOK and also with sodium methoxide (CH_3ONa). Analogously, 13-methyl-5-oxo-5,7,12,14-tetrahydrophthalazino-[2,3-*b*]phthalazinium iodide (XII) reacted with CH_3ONa to give 13-methyl-5,7,12,13a-tetrahydro-13H-isoindolo[2,3-*b*][2,4]benzodiazepin-5-one (XIII) and -7-one (XIV). These reactions were interpreted to proceed by the initial abstraction of α-benzyl or α-allyl proton.

Though the alkaline decomposition of quaternary ammonium salts is well known in the field of nitrogen-containing heterocyclic chemistry, there had been no reports on that of quaternary fused hydrazinium salts until 1969. Thereafter, Sandoz group and the present authors have reported the alkaline decomposition of quaternary fused hydrazinium salts including four types of reactions.[4,5] Those consist of the Hofmann-type elimination leading to medium-sized diazaheterocycles,[1,4] the Stevens-type rearrangement leading to the ring contraction from 6/6/*n* fused ring system to 6/5/*n*+1 fused ring system,[5] the rearrangement to new quaternary salts,[1] and of the N–CH_2–N bridging.[6]

We now report the fifth type of reaction leading to an N-aminoalkylisoindole or -pyrrole.

The fused hydrazinium salts used in this experiment, 4-methyl-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazinium iodide (I), 5-methyl-1,4,6,11-tetrahydropyridazino[1,2-*b*]-phthalazinium iodide (VII) and 13-methyl-5-oxo-5,7,12,14-tetrahydrophthalazino[2,3-*b*]-phthalazinium iodide (XII) were prepared by lithium aluminum hydride or sodium borohydride reduction of the corresponding diones followed by quaternization.

When I reacted with potassium *t*-butoxide in *t*-butanol at the boiling temperature for 3 hours,[7] 2-(3-methylaminopropyl)isoindole (IV) was obtained as an unstable syrup in 84% yield. The structure of this compound was elucidated by means of ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR) spectroscopy, and also of synthesis. Namely, its IR spectrum shows NH stretching band at 3290 cm^{-1}, and its UV spectrum (λ_{max}^{EtOH} nm: 223, 266, 270, 277, 289, 315s, 326, 339s) shows the presence of an isoindole moiety.[8] The NMR spectrum in deuterochloroform ($CDCl_3$) shows a 1H singlet due to the NH at 1.25 ppm which vanishes on deuteration, a 2H quintet due to the C–CH_2–C at 1.83 ppm (J=6.8 Hz), a 2H

1) Part III: A. Nakamura and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 1445 (1972).
2) Presented at the 6th Congress of Heterocyclic Chemistry, Nagoya, Nov. 2, 1973.
3) Location: *Kamiyoga 1-18-1, Setagaya, Tokyo.*
4) P. Aeberli and W.J. Houlihan, *J. Org. Chem.*, **34**, 2715 (1969).
5) A. Nakamura and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 69 (1972).
6) P. Aeberli and W.J. Houlihan, *J. Org. Chem.*, **34**, 2720 (1969).
7) When reacted with sodium methoxide, I gave 5-methyl-1,2,3,4,6,10b-hexahydropyrimido[2,1-*a*]isoindolium iodide and 6-methyl-4,5,6,7-tetrahydro-3H-2,6-benzodiazonine.[1]
8) R. Bonnett and R.F.C. Brown, *Chem. Commun.*, **1972**, 393.

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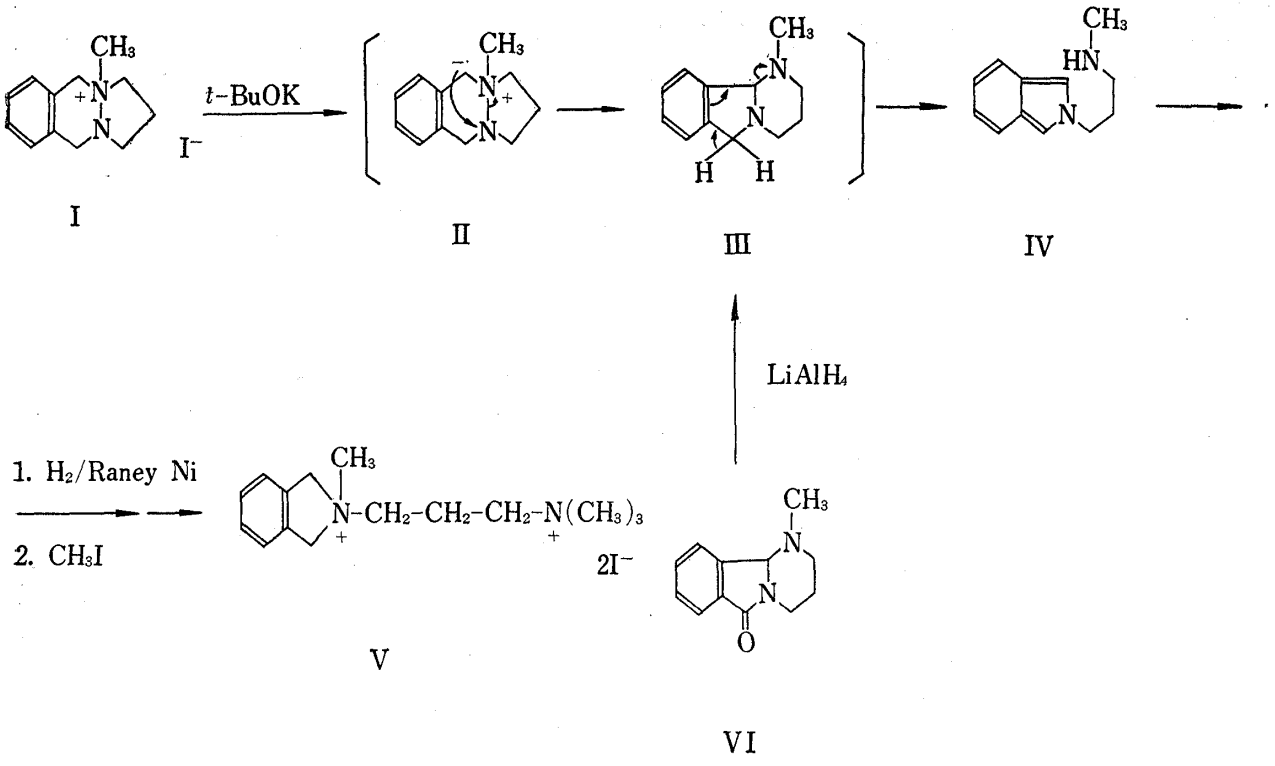

Chart 1

triplet due to the N-CH_2- at 2.35 ppm (J=6.8 Hz), a 2H triplet due to the CH_2-isoindole at 4.01 ppm (J=6.8 Hz), and a 2H singlet due to the protons at 1 and 3 positions of the isoindole moiety at 6.90 ppm.[8,9] Actually, on catalytic hydrogenation with Raney nickel followed by quaternization, IV gave a bisquaternary salt V, mp 238—239° (decomp.), which was identical with a specimen prepared according to the literature.[10]

The mechanism of this rearrangement should involve the initial abstraction of the α-benzyl proton to yield an ylide II which rearranges to III. Compound (III) must be an unseparable intermediate which easily converts to IV by aromatization, and, as a matter of fact, its intermediacy could be confirmed by the fact that reduction of 1-methyl-1,3,4,10b-tetrahydro-2H-pyrimido[2,1-*a*]isoindol-6-one (VI) with lithium aluminum hydride gave IV in such a high yield of 80%.

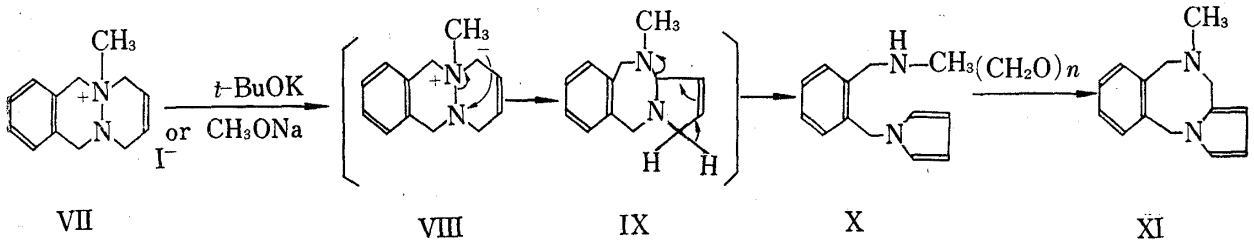

Chart 2

Analogously, as shown in Chart 2, VII reacted not only with potassium *t*-butoxide but also with sodium methoxide to give the rearranged product, 1-(2-methylaminomethylbenzyl)-pyrrole (X) as an unstable syrup in 50—70% yield. Compound (X) gave a magenta color with Ehrlich's reagent, and its IR and NMR spectra were reasonable for the proposed structure as noted in the experimental part. In addition, when X was heated with paraformaldehyde

9) P. Aeberli and W.J. Houlihan, *J. Org. Chem.*, **34**, 1720 (1969).
10) L.M. Rice, C.H. Grogan and E.E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

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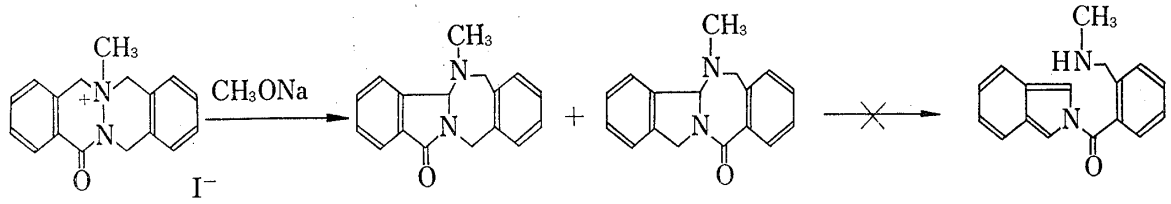
in absolute ethanol at 100° for 2 hours, 5-methyl-4,5,6,11-tetrahydropyrrolo[1,2-*b*][2,5]benzodiazocine (XI) was obtained in 46% yield. This compound also showed a magenta color with Ehrlich's reagent, no NH absorption band in the IR spectrum, and reasonable NMR spectrum.



XII XIII XIV XV

Chart 3

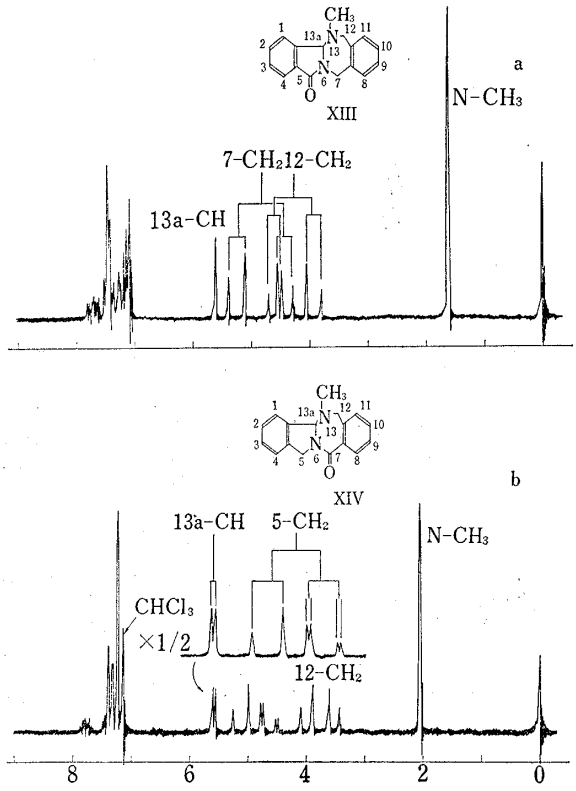


Fig. 1. The NMR Spectra of 13-Methyl-5,7,12,13a-tetrahydro-13H-isoindolo[2,3-*b*][2,4]-benzodiazepin-5-one (XIII) and -7-one (XIV)

Finally, the third fused hydrazinium iodide XII reacted with sodium methoxide to give two products A, mp 206—207°, and B, mp 119—121°, in 79 and 8% yields, respectively. Compound (A) and (B) had the same empirical formula, $C_{17}H_{16}ON_2$, and their structures were elucidated to be 13-methyl-5,7,12,13a-tetrahydro-13H-isoindolo-[2,3-*b*][2,4]benzodiazepin-5-one (XIII) for A and 13-methyl-5,7,12,13a-tetrahydro-13H-isoindolo[2,3-*b*][2,4]benzodiazepin-7-one(XIV) for B, by means of IR and NMR spectroscopy. Namely, the IR spectrum of XIII in nujol shows the presence of a five-membered lactam-CO[5,11] at 1689 cm^{-1}, while that of XIV does ν_{CO} band at 1639 cm^{-1}. As shown in Fig. 1-a, the NMR spectrum of XIII shows a 1H singlet due to the 13a angular methine proton at 5.59 ppm, and two sets of AB quartet centered at 4.26 and 4.83 ppm. On the other hand, as shown in Fig. 1-b, the signal of the angular methine proton of XIV at 5.58 ppm couples with one of the methylene protons of the isoindoline moiety to split into doublet (J=1.95 Hz). Analogous long-range coupling in the N-acyl isoindoles were observed by Gerig.[12]

This reaction is also considered as the Stevens-type rearrangement initiated by abstraction of the α-benzyl protons at 12 and 14 position of XII, but the resulting compound (XIV) did not change to an isoindole XV. This fact was in contrast to the case of III.

In general, the alkaline decomposition of quaternary ammonium salts having β-benzyl protons gives β-elimination products, and certain quaternary fused hydrazinium salts also behave analogously.[1,4] However, in the cases of compounds described above, the reactions proceeded by initial abstraction of the α-benzyl or α-allyl proton, though they had β-benzyl

11) W. Theilacker and W. Schmidt, *Ann.*, **567**, 95 (1956); A.E. Kellie, D.G. O'Sullivan and P.W. Sadler, *J. Chem. Soc.*, **1956**, 3809.
12) J.T. Gerig, *Tetrahedron Letters*, **1967**, 4625.

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or β-allyl protons. In this stage we hardly interpret these facts reasonably. Further extension of this reaction to various kinds of fused hydrazinium salts is desired in order to understand these results better.

Experimental[13]

4-Methyl-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazinium Iodide (I)——Compound (I), colorless plates (from methanol), mp 180—182°, was synthesized by the method reported previously.[14]

5-Methyl-1,4,6,11-tetrahydropyridazino[1,2-*b*]phthalazinium Iodide (VII)——To a mixture of 4.30 g (0.113 mole) of lithium aluminum hydride in 200 ml of dehyd. tetrahydrofuran was added 9.7 g (0.0453 mole) of 1,4,6,11-tetrahydropyridazino[1,2-*b*]phthalazine-6,11-dione[15] with stirring, and the mixture was refluxed for 5 hr. Then, 9 ml of 2N sodium hydroxide aqueous solution and then 14 ml of water were carefully added to the reaction mixture cooled with ice-water, and the precipitates separated were filtered. The precipitates on the filter paper were washed with tetrahydrofuran. The filtrate and washings were combined, the solution was dried over anhyd. sodium sulfate, and the solvent was removed under reduced pressure. The residue was distilled under reduced pressure to give colorless syrup, bp 145—147° (6 mmHg). Yield, 5.3 g (63%). IR (CCl_4) cm^{-1}: 2840 (90), 2805 (128), 2670 (18). NMR (CS_2) ppm at 30°: 3.21 (broad s, 4H, N–CH_2–C=), 3.79 (broad s, 4H, Ar–CH_2–N), 5.59 (t, 2H, –CH=CH–, J=1.2 Hz), 6.88 (m, 4H, aromatic H). The syrup was dissolved in 100 ml of acetone, and a large excess of methyl iodide was added to the solution, and the mixture was allowed to stand overnight at room temperature. The crystals separated were filtered, washed with acetone, and dried. Colorless granules, mp 183—185° (decomp.). Yield, 8.3 g (56% from the starting dione). Recrystallization twice from methanol gave colorless needles, mp 184—187° (decomp.). *Anal.* Calcd. for $C_{13}H_{17}N_2I$: C, 47.58; H, 5.22; N, 8.53. Found: C, 47.71; H, 5.35; N, 8.21.

13-Methyl-5-oxo-5,7,12,14-tetrahydrophthalazino[2,3-*b*]phthalazinium Iodide (XII)——A mixture of 4.6 g (0.0174 mole) of 5,7,12,14-tetrahydrophthalazino[2,3-*b*]phthalazine-5,14-dione[16a] and 1.32 g (0.0348 mole) of sodium borohydride in 50 ml of ethanol was stirred at room temperature. After two days the mixture became clear, and after additional two days, the crystals were separated. These were filtered, washed with ethanol and dried. Yield, 3.52 g (81%). Recrystallization from ethanol gave 2.38 g (55%) of colorless leaflets, mp 194—196°. The melting point was identical with that of 5,7,12,14-tetrahydrophthalazino[2,3-*b*]-phthalazin-5-one reported by Hatt and Stephenson.[16b] *Anal.* Calcd. for $C_{16}H_{14}ON_2$: C, 76.78; H, 5.62; N, 11.19. Found: C, 77.18; H, 5.85; N, 11.19. IR (Nujol) cm^{-1}: 1658 (CO). NMR ($CDCl_3$) ppm: 3.91 (s, 2H, –CH_2– at 12 position), 4.41 (s, 2H, –CH_2– at 14 position), 5.02 (s, 2H, –CH_2– at 7 position), 6.8—8.2 (m, 8H, aromatic H). Then, 1.10 g (0.0044 mole) of the crystals and 0.7 g (0.0056 mole) of dimethyl sulfate were dissolved in 20 ml of chloroform and the solution was heated in a sealed tube at 100° for 4 hr. The chloroform was evaporated under reduced pressure, and the residue was dissolved in 15 ml of ethanol. To the solution was added 0.8 g of sodium iodide and the solution was allowed to stand at room temperature overnight. Yellow short needles were separated, filtered, washed with ethanol, and dried. Recrystallization twice from ethanol gave colorless needles, mp 194—196°. Yield, 0.89 g (52%). *Anal.* Calcd. for $C_{17}H_{17}ON_2I$: C, 52.06; H, 4.37; N, 7.14. Found: C, 53.03; H, 4.83; N, 8.01. IR (Nujol) cm^{-1}: 1680 (CO). NMR (DMSO-d_6) ppm: 3.45 (s, 3H, $\overset{+}{N}$–CH_3), 5.18 (AB quartet, 2H, δ_{AB}=15 Hz, J_{AB}=15 Hz, –CH_2– at 7 position), 5.32 (s, 2H, –CH_2– at 12 position), 5.54 (s, 2H, –CH_2– at 14 position), 7.25—8.1 (m, 8H, aromatic H).

2-(3-Methylaminopropyl)isoindole (IV)——a) From I: To a freshly prepared solution of 0.78 g (0.02 gram atom) of metallic potassium in 30 ml of *t*-butanol was added 2.44 g (0.008 mole) of I, and the mixture was refluxed under nitrogen atmosphere for 3 hr. The solvent was removed under reduced pressure. Water was added to the residue and the mixture was extracted with dichloromethane. The extract was washed with water, dried over anhyd. sodium sulfate, and the dichloromethane was evaporated to dryness. Orange red syrup. Yield, 1.27 g (84%).

b) From 1-Methyl-1,3,4,10b-tetrahydro-2H-pyrimido[2,1-*a*]isoindol-6-one (VI): According to the synthetic procedure of VII, 2.02 g (0.01 mole) of VI was reduced by 0.83 g (0.022 mole) of lithium aluminum hydride in 70 ml of tetrahydrofuran to give 1.5 g (80%) of pale green yellow syrup. Its IR and NMR spectra were identical with those of IV synthesized according to the procedure a).

13) All melting points are uncorrected. IR spectra were measured on a JASCO Model IR-S spectrophotometer. NMR spectra were measured on a JEOL C-60HL (at 60 MHz) spectrometer and tetramethylsilane was used as an internal standard. UV spectrum was measured on a Shimadzu Double-40R spectrophotometer. Mass spectrum was measured on a JEOL JMS-01SG-2 spectrometer.

14) A. Nakamura and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **18**, 1526 (1970).

15) R.A. Clement, *J. Org. Chem.*, **25**, 1724 (1960).

16) *a*) H.H. Hatt and E.F.M. Stephenson, *J. Chem. Soc.*, **1943**, 658; *b*) *Idem, ibid.*, **1952**, 199.

17) The α- and β-protons of pyrrole resonate at 6.22 and 6.88 ppm, respectively (Varian High Resolution NMR Spectra Catalog, Spectral No. 55, Varian Associates, Palo Alto, 1962).

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N-(3-Dimethylaminopropyl)isoindoline Dimethiodide (V)——The syrup (IV) prepared from 2.02 g (0.01 mole) of VI was dissolved in 100 ml of methanol and the solution was shaken with 5 g of Raney nickel under hydrogen atmosphere for 12 hr. The reaction mixture was immediately filtered into the flask which contained the solution of a large excess of methyl iodide in acetone. The resulting solution was refluxed for 30 min and the solvent was removed under reduced pressure. The residue was treated with a small amount of ethanol and the crystals separated were filtered, washed with ethanol, and dried. Recrystallization three times from ethanol gave colorless needles, mp 238—239° (decomp.). (lit. mp 237—238°).[10] Yield, 1.38 g (38% from IV). *Anal.* Calcd. for $C_{15}H_{26}N_2I_2$: C, 36.90; H, 5.36; N, 5.73. Found: C, 36.83; H, 5.26; N, 5.90.

1-(2-Methylaminomethylbenzyl)pyrrole (X)——Compound (VII) (0.6 g, 0.00183 mole) was refluxed with sodium methoxide (0.21 g of metallic sodium in 7 ml of methanol) for 15 hr to give a red oil. The oil was dissolved in a small amount of benzene and the solution was layed on the silica gel column, and eluted with benzene–methanol (200: 3). A red syrup, which showed a single spot on thin-layer chromatography, was obtained as a main product. Yield, 0.174 g (48%). IR (liquid film) cm^{-1}: 3370 (NH). NMR ($CDCl_3$) ppm: 1.70 (s, 1H, NH), 2.37 (s, 3H, N–CH_3), 3.61 (s, 2H, Ar–CH_2–N), 5.11 (s, 2H, Ar–CH_2–pyrrole), 6.05 (t, 2H, J=2.1 Hz, β-H of pyrrole), 6.53 (t, 2H, J=2.1 Hz, α-H of pyrrole[17]), 7.15 (m, 4H, aromatic H).

5-Methyl-4,5,6,11-tetrahydropyrrolo[1,2-*b*][2,5]benzodiazocine (XI)——The compound (X) prepared from VII (3.28 g, 0.01 mole) with potassium *t*-butoxide in the analogous manner mentioned about IV was dissolved in 30 ml of abs. ethanol. To the solution was added 0.3 g (0.01 mole) of paraformaldehyde and the mixture was heated in a sealed tube at 100° for 2 hr. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel using chloroform as eluent. After the elution of a small amount of the unknown oil, the fraction which showed a red violet spot on thin-layer chromatography (Wakogel B5-UA, $CHCl_3$: EtOH=6 ml: 5 drops) under UV light were collected. The solvent was removed and the solidified residue (0.64 g) was recrystallized twice from isopropyl ether to give 0.49 g (23% from VII) of colorless pillars, mp 104—105°. *Anal.* Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.08; H, 7.66; N, 13.34. NMR (DMSO-d_6) ppm: 1.83 (s, 3H, N–CH_3), 3.99 (AB-quartet, 2H, δ_{AB}=33.3 Hz, J_{AB}=13.8 Hz, –CH_2– at 4 or 6 position), 4.08 (AB quartet, 2H, δ_{AB}=49.0 Hz, J_{AB}=14.3 Hz, –CH_2– at 4 or 6 position), 4.98 (AB quartet, 2H, δ_{AB}=33.8 Hz, J_{AB}=13.5 Hz, –CH_2– at 11 position), 5.63 (d, 2H, J=1.8 Hz, protons at 2 and 3 positions), 6.67 (t, 1H, J=1.8 Hz, proton at 1 position), 6.9—7.5 (m, 4H, aromatic H).[18]

13-Methyl-5,7,12,13a-tetrahydro-13H-isoindolo[2,3-*b*][2,4]benzodiazepin-5-one (XIII) and 13-Methyl-5,7,12,13a-tetrahydro-13H-isoindolo[2,3-*b*][2,4]benzodiazepin-7-one (XIV)——To a solution of 0.28 g of metallic sodium in 10 ml of methanol was added 0.78 g (0.002 mole) of XII, and the mixture was refluxed for 26 hr and allowed to stand overnight at room temperature. Compound (XIII) separated from the reaction mixture as colorless granules was filtered, washed with methanol, and dried (0.39 g). The filtrate and washings were combined, and the solvent was removed under reduced pressure. Water was added to the residue and the mixture was extracted with dichloromethane. The extract was washed with water, dried over anhyd. sodium sulfate and the dichloromethane was evaporated to dryness. The residue was chromatographed on silica gel using benzene–acetone (5: 1) as eluent to give 0.025 g of XIII and 0.042 g of XIV. 13-Methyl-5,7,12,13a-tetrahydro-13H-isoindolo[2,3-*b*][2,4]benzodiazepin-5-one (XIII). Yield, 0.415 g (79%). Recrystallization twice from ethanol gave colorless pillars, mp 206—207°. *Anal.* Calcd. for $C_{17}H_{16}ON_2$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.29; H, 6.11; N, 10.50. Picrate of XIII: Yellow needles (from EtOH), mp 216—218°. *Anal.* Calcd. for $C_{17}H_{16}ON_2 \cdot C_6H_3O_7N_3$: C, 55.98; H, 3.88; N, 14.19. Found: C, 56.38; H, 3.60; N, 14.08. 13-Methyl-5,7,12,13a-tetrahydro-13H-isoindolo[2,3-*b*][2,4]benzodiazepin-7-one (XIV). Yield, 0.042 g (8%). Colorless granules (from EtOH–ether), mp 119—121°. Mass Spectrum *m/e*: Calcd. for $C_{17}H_{16}ON_2$: 264.126. Found: 264.125.

18) The three sets of AB quartet coalesced at 75° and changed to three sharp singlets at 129°. This temperature-dependent NMR spectral change can be explained by a slow ring-inversion of eight-membered ring of XI. In contrast to the case of XI, it is of interest that the NMR spectrum of the N-desmethyl analog of XI, 4,5,6,11-tetrahydropyrrolo[1,2-*b*][2,5]benzodiazocine, shows three singlets due to the methylenes even at 30° (G. De Martino, S. Massa, M. Scalzo and R. Giuliano, *J. Chem. Soc., Perkin I*, 1972, 2504).

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