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Studies on 1-Azabicyclo Compounds. XVI.[1] Synthesis of 1'-Methylindan-2-spiro-2'-piperazine and Related Compounds

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A new synthesis of the spirodiamines (IIIa—c) from the methiodides (Ia—c) *via* the spiroaminolactams (VIIa—c) by Stevens rearrangement is described.

In the previous paper,[1] we reported the synthesis of the ten-membered cyclic diamines (II) from 1,3,4,6,11,11*a*-hexahydro-5-methyl-1-oxo-2*H*-pyrazino[1,2-*b*]isoquinolinium iodides (I) by the selective cleavage of the central C–N bond. This paper describes a new synthesis of the spirodiamines (III) from the methiodides (I).

Stevens rearrangement[3] is one of the most common reactions for the quaternary ammonium ylides. The methiodides[1] (I) have sufficient functionality, properly situated, for Stevens rearrangement to be effected. In the previous experiment,[1] treatment of I with lithium in liquid ammonia only produced hydrogenolysis to afford the piperazinones (IV). Now we found that lithium aluminum hydride effected Stevens rearrangement successfully to convert I to the spirodiamines (III).

The methiodide (Ia) was heated for 17 hr with 10 molar equivalents of lithium aluminum hydride in tetrahydrofuran to give the spirodiamine (IIIa) in 64% yield accompanied with the piperazine (Va), which, on being heated with formaldehyde solution in the presence of formic acid, yielded the N-methylpiperazine (VIa), identified with the authentic specimen.[1] The molecular formula of the major product was expressed as $C_{13}H_{18}N_2$ (M^+ 202) by the elemental analysis and mass spectrum. Its infrared (IR) spectrum showed the amino band at 3250 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum exhibited the characteristic signals as shown in Table I. The structure of this product as 1'-methylindan-2-spiro-2'-piperazine was verified by the observation that the signal due to the methylene at C-3' appeared as a singlet and the AB-quartet (4H) due to both the benzylic methylenes at C-1 and C-3 appeared at the same chemical shift. Further confirmation of the assigned structure (IIIa) was obtained from the analysis of its mass spectrum shown in Chart 2 and Table II. The exact empirical formulae of the peaks were determined by the high-resolution mass spectrometry (see Experimental). The transition from M^+ (*m/e*: 202) to b (*m/e* 146) was proved by the appearance of a metastable peak at *m/e*: 105.5.

The transformation of the methiodide (Ia) to the spirodiamine (IIIa) seems to proceed *via* the spiroaminolactam (VIIa). Namelyl the ylide (I'a), formed from the methiodide (Ia) with lithium aluminum hydride as the base, was transformed by the Stevens rearrangement to the spiroaminolactam (VIIa), which was then reduced with excess lithium aluminum hydride to yield the spirodiamine (IIIa). In order to prove directly the above assumption, the methiodide (Ia) was heated for 2 hr with 0.5 molar equivalent of lithium aluminum hy-

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[1] Part XV: H. Kato, E. Koshinaka, Y. Arata and M. Hanaoka, *Chem. Pharm. Bull.* (*Tokyo*), 21, 2039 (1973).

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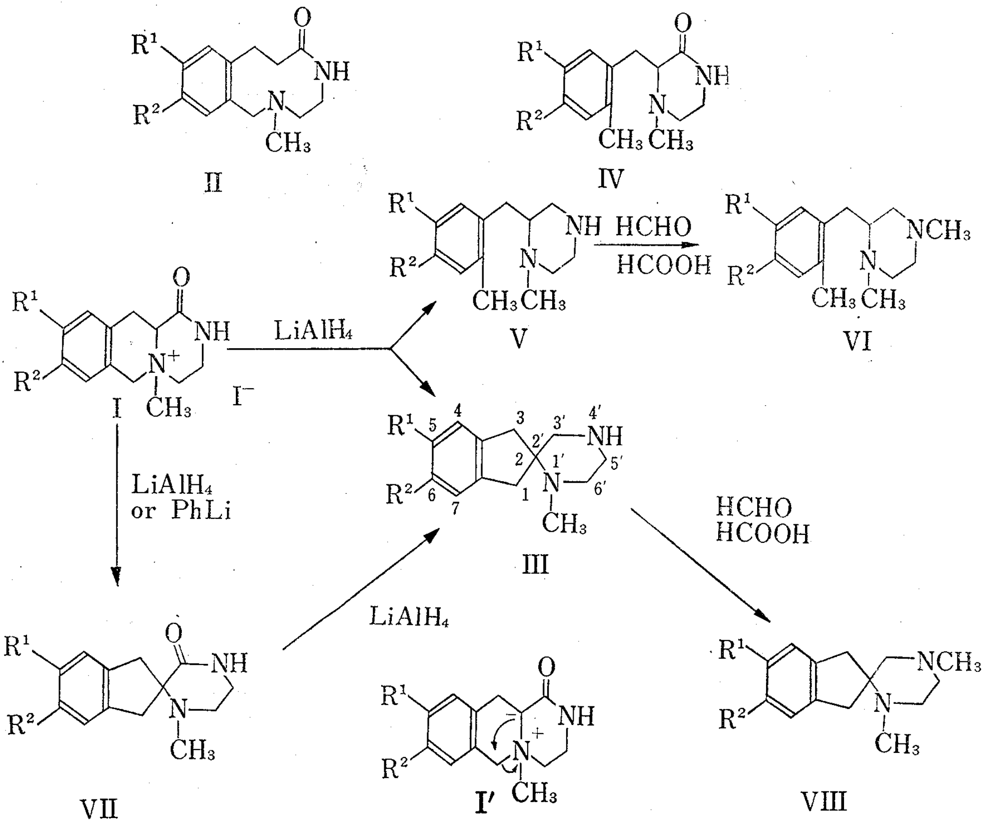
[3] S.H. Pine, "Organic Reactions," Vol. 18, John Wiley & Sons, Inc., New York, 1970, p. 403.



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

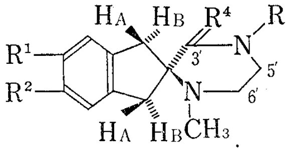
Chart 1

dride in tetrahydrofuran to produce the key intermediate, the spiroaminolactam (VIIa), mp 86—87°, though in a poor yield. In agreement with the structure of VIIa, the product showed bands at 3200 (NH) and 1650 cm^{-1} (lactam) in its IR spectrum and exhibited almost the same signals as those of IIIa except for the disappearance of the singlet due to the methylene at C-3′ in IIIa in the NMR spectrum. The spiroaminolactam (VIIa) was also obtained in 8% yield by treatment of Ia with phenyllithium and identified with that obtained as above. Further reduction of VIIa with lithium aluminum hydride gave the spirodiamine (IIIa), which was identical in all respects with that obtained directly from Ia.

Similarly, on treatment with excess lithium aluminum hydride, the methiodides (Ib and Ic) were converted to the spirodiamines (IIIb and IIIc) in 59% and 61% yield, respectively. In these reactions, the corresponding piperazines (Vb and Vc) were not obtained. And treatment of the methiodides (Ib and Ic) with phenyllithium afforded the spiroaminolactams (VIIb and VIIc) in 22% and 12% yield, respectively, which were reduced with lithium aluminum hydride to furnish the corresponding spirodiamines (IIIb and IIIc). The structures of IIIb, IIIc, VIIb, and VIIc were fully verified by their elemental and spectral analyses. The spirodiamines (IIIa, IIIb, and IIIc) were heated with formaldehyde solution and formic acid to afford the N-methyl derivatives (VIIIa, VIIIb, and VIIIc) in 84, 74, and 87% yield, respectively.

Table I shows NMR spectral data of all the spiro compounds obtained here. Both the methylenes at C-1 and C-3 appeared as AB-quartet at the same chemical shift with the geminal coupling of $J=16.5$ Hz and the two protons (H_A), located *cis* to the nitrogen at 1′, resonated at a lower field (6.78—6.93 τ) because of the deshielding effect of the nitrogen. In the amino-

TABLE I. NMR Spectral Data of Spiro Compounds (IIIa—c, VIIa—c, and VIIIa—c) (τ, in $CDCl_3$)[a]



Compd.	R^1	R^2	R^3	R^4	Ar-H	H_A AB-q (J=16.5 Hz)	H_B AB-q (J=16.5 Hz)	H-5'	H-6'	H-3'	$N-CH_3$	NH[b]	OCH_3	OCH_2O
IIIa	H	H	H	H_2	2.88 s	6.81	7.23	6.90—7.15m	7.35—7.60m	7.19 s	7.90 s	8.05 s		
IIIb	OCH_3	OCH_3	H	H_2	3.31 s	6.85	7.32	6.95—7.20m	7.35—7.60m	7.16 s	7.90 s	7.81 s	6.18 s	
IIIc	OCH_2O		H	H_2	3.39 s	6.89	7.37	6.95—7.20m	7.35—7.60m	7.18 s	7.87 s	8.11 s		4.13 s
VIIIa	H	H	CH_3	H_2	2.89 s	6.78	7.23	7.30—7.50m		7.62 s	7.76 s 7.90 s			
VIIIb	OCH_3	OCH_3	CH_3	H_2	3.35 s	6.87	7.30	7.44 br-s		7.62 s	7.76 s 7.90 s		6.18 s	
VIIIc	OCH_2O		CH_3	H_2	3.40 s	6.93	7.36	7.48 br-s		7.62 s	7.76 s 7.89 s			4.15 s
VIIa	H	H	H	O	2.86 s	6.82	6.39	6.50—6.75m	7.20 t (J=5.5 Hz)		7.90 s	3.10 br		
VIIb	OCH_3	OCH_3	H	O	3.32 s	6.90	6.46	6.55—6.80m	7.21 t (J=5.5 Hz)		7.87 s	2.93 br	6.17 s	
VIIc	OCH_2O		H	O	3.35 s	6.93	6.49	6.50—6.75m	7.20 t (J=5.5 Hz)		7.85 s	3.60 br		4.09 s

[a] s: singlet; t: triplet; q: quartet; m: multiplet; br: broad

[b] The signal of this proton disappeared by addition of D_2O.

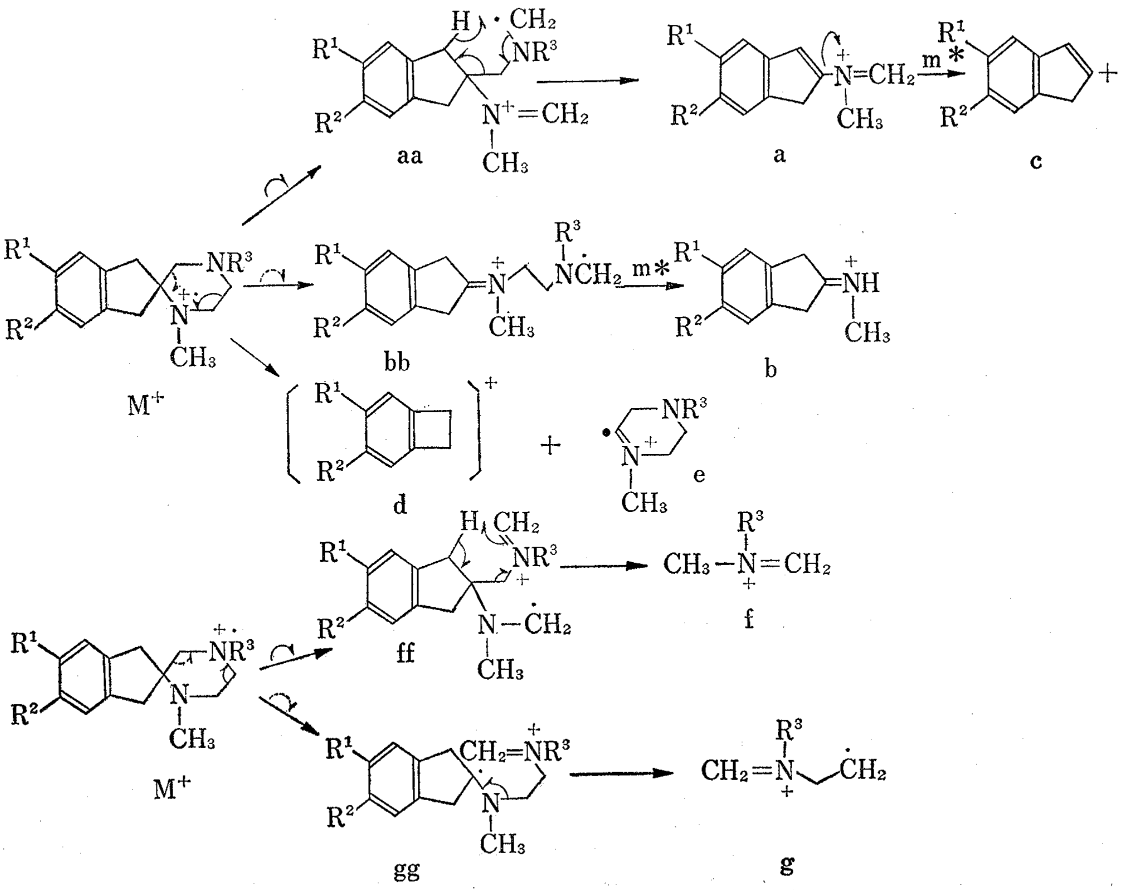
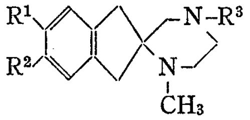


Chart 2

lactam (VII), however, H_B resonated at a lower field than H_A. As the carbonyl group lay in the same plane with the proton H_B at C-1 in one conformer of VII and with that at C-3 in another conformer having a half-chair conformation of the piperazinone ring, the signal of H_B in VII was shifted to a very lower field. The methylene at C-6′ adjacent to N-methyl resonated at a higher field than that at C-5′ adjacent to NH, as reported for N-methylpiperazine.[4] Consequently, the singlet at 7.16—7.19 τ due to the methylene at C-3′ in the diamines (IIIa—c) was shifted to the higher field at 7.62 τ in the N-methyl derivatives (VIIIa—c).

TABLE II. Mass Spectrometric Data of Spirodiamines (IIIa—c and VIIIa—c) (*m/e* (%))



Compound	R^1	R^2	R^3	Ion[a)							
				M^+	a	b	c	d	e	f	g
IIIa	H	H	H	202 (100)	158 (100)	146 (53)	115 (78)	104 (56)	98 (23)		
IIIb	OCH_3	OCH_3	H	262 (95)	218 (100)	206 (9)	175 (18)	164 (14)	98 (27)		
IIIc	OCH_2O		H	246 (84)	202 (100)	190 (11)	159 (34)	148 (20)	98 (19)		
VIIIa	H	H	CH_3	216 (42)	158 (45)		115 (17)	104 (13)	112 (9)	58 (100)	71 (17)
VIIIb	OCH_3	OCH_3	CH_3	276 (54)	218 (59)		175 (11)	164 (7)	112 (19)	58 (100)	71 (5)
VIIIc	OCH_2O		CH_3	260 (50)	202 (61)		159 (22)	148 (14)	112 (21)	58 (100)	71 (16)

a) see Chart 2

The mass spectrometric data of the spirodiamines (IIIa—c and VIIIa—c) are summarized in Chart 2 and Table II. α-Cleavage of M^+ involving the 5′—6′ bond, followed by the McLafferty rearrangement of a resulting ion aa furnished an ion a (base peak), which decomposed further by shedding the elements of N-methylimine to give an ion c. The latter transition was proved by a metastable peak at *m/e*: 125.1 in IIIc. The alternative mode of α-cleavage led to an ion b *via* an ion bb, but the ion b appeared as a trivial peak in VIIIa—c. Third cleavage without fission of a piperazine ring resulted in ions d and e. Though there are no significant ions produced from the molecular ion M^+ having a charge at N-4′ in the spirodiamines (IIIa—c), in the N-methyl derivatives (VIIIa—c), M^+ decomposed prominently *via* ions ff and gg to afford ions f (base peak) and g, respectively.

Thus, it was found that the Stevens rearrangement provides a new synthesis of the spiroamine derivatives.

Experimental[5]

1′-Methylindan-2-spiro-2′-piperazine (IIIa)——a) From Ia: To a stirred suspension of $LiAlH_4$ (3.8 g) in anhyd. THF (100 ml) was added Ia (3.44 g) in small portions, and the reaction mixture was refluxed

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4) N.S. Bhacca, L.F. Johnson and J.N. Shoolery, "NMR Spectra Catalog", Vol. I, No. 119, Varian Associates, California (1962).

5) All melting points were measured with Yanagimoto Micro Melting Point Apparatus and are uncorrected. Organic extracts were dried over anhyd. Na_2SO_4. IR spectra were measured with Spectrophotometer IRA-2, Japan Spectroscpic 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 and shown in Table I. Mass spectra were taken on Hitachi RMU-7L spectrometer and shown in Table II.

with stirring for 17 hr. The excess hydride was decomposed with H_2O, and the inorganic material was filtered and washed with THF. The filtrate and washings were combined, dried and evaporated. The residue was dissolved in 10% HCl and washed with ether. The aqueous layer was made alkaline with K_2CO_3 and extracted with ether. The extract was dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel with $CHCl_3$ and MeOH as eluent. The first fraction eluted with MeOH was treated with HCl–EtOH and the precipitate was recrystallized from MeOH–iso-Pr_2O to give the hydrochloride (1.75 g (64%)) of IIIa as colorless needles, mp 235—240°. *Anal.* Calcd. for $C_{13}H_{18}N_2 \cdot 2HCl$: C, 56.73; H, 7.33; N, 10.18. Found: C, 56.50; H, 7.24; N, 9.79. Mass Spectrum: Principal peaks were shown in Table III. The free base (IIIa) was obtained in a usual way as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3250 (NH).

TABLE III. Exact Masses and Compositions of Peaks in Mass Spectrum of IIIa

m/e observed	*m/e* calculated	Composition
202.1474	202.1470	$C_{13}H_{18}N_2$
158.0979	158.0969	$C_{11}H_{12}N$
146.0950	146.0969	$C_{10}H_{12}N$
115.0554	115.0547	C_9H_7
104.0617	104.0625	C_8H_8
98.0849	98.0843	$C_5H_{10}N_2$

The second fraction eluted with MeOH was heated with stirring at 80° for 3 hr with 37% HCHO (5 ml) and 80% HCO_2H (10 ml) and the reaction mixture 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 chromatographed on silica gel with $CHCl_3$ and MeOH. The fraction eluted with MeOH was treated with HCl–EtOH and the precipitated crystals were recrystallized from EtOH–ether (1:1) to give the hydrochloride (140 mg (5%)) of 1,4-dimethyl-2-(2-methylbenzyl)piperazine (VI) as colorless leaflets, mp 227—229°. This compound was identical with the authentic specimen[1] in IR spectra and mixed mp.

b) From VIIa: Compound (VIIa, 40 mg) was reduced with $LiAlH_4$ (100 mg) in anhyd. ether (50 ml) in a usual way with refluxing for 16 hr and the product was treated with HCl–EtOH to give the hydrochloride (40 mg (78%)) as colorless needles, mp 235—240° (MeOH–iso-Pr_2O), which was identical with the hydrochloride of IIIa obtained above in IR spectra and mixed mp.

5,6-Dimethoxy-1′-methylindan-2-spiro-2′-piperazine (IIIb)——a) From Ib: Compound (Ib, 4.04 g) was treated with $LiAlH_4$ (3.8 g) in THF (100 ml) in the same procedure as that for IIIa from Ia to give the hydrochloride (1.96 g (59%)) of IIIb as colorless scales, mp 277—280° (MeOH–iso-Pr_2O). *Anal.* Calcd. for $C_{15}H_{22}O_2N_2 \cdot 2HCl$: C, 53.73; H, 7.21; N, 8.36. Found: C, 53.80; H, 7.15; N, 8.22. The free base (IIIb) was obtained in a usual way as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3300 (NH).

b) From VIIb: Compound (VIIb, 100 mg) was reduced with $LiAlH_4$ (400 mg) in anhyd. THF (50 ml) in the same procedure as that for IIIa from VIIa to give the hydrochloride (60 mg (50%)) as colorless scales, mp 277—280° (MeOH–iso-Pr_2O), which was identical with the hydrochloride of IIIb obtained above in IR spectra and mixed mp.

1′-Methyl-5,6-methylenedioxyindan-2-spiro-2′-piperazine (IIIc)——a) From Ic: Compound (Ic, 3.88 g) was treated with $LiAlH_4$ (3.8 g) in THF (100 ml) in the same procedure as that for IIIa from Ia to give the hydrochloride (1.93 g (61%)) of IIIc as colorless fine crystals, mp 275—278° (MeOH). *Anal.* Calcd. for $C_{14}H_{18}O_2N_2 \cdot 2HCl$: C, 52.67; H, 6.32; N, 8.78. Found: C, 52.49; H, 6.27; N, 8.48. The free base (IIIc) was obtained in a usual way as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3250 (NH).

b) From VIIc: Compound (VIIc, 150 mg) was reduced with $LiAlH_4$ (500 mg) in anhyd. THF (50 ml) in the same procedure as that for IIIa from VIIa to give the hydrochloride (100 mg (54%)) as colorless fine crystals, mp 275—278° (MeOH), which was identical with the hydrochloride of IIIc obtained above in IR spectra and mixed mp.

1′-Methylindan-2-spiro-2′-piperazin-3′-one (VIIa)——a) With $LiAlH_4$: To a stirred suspension of $LiAlH_4$ (190 mg) in anhyd. THF (100 ml) was added Ia (3.44 g) and the reaction mixture was refluxed for 2 hr. The excess hydride was decomposed with H_2O, and the inorganic material was filtered and washed with MeOH. The filtrate and washings were combined and evaporated. The residue was dissolved in 10% HCl and washed with ether. The aqueous layer was made alkaline with K_2CO_3 and extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was recrystallized from EtOH to give IIa (30 mg (1.4%)) as colorless scales, mp 86—87°. *Anal.* Calcd. for $C_{13}H_{16}ON_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.30; H, 7.21; N, 12.85. IR ν_{max}^{KBr} cm^{-1}: 1650 (lactam).

b) With PhLi: To a solution of PhLi in ether (100 ml) (prepared from Li (0.28 g) and PhBr (3.77 g)) was added a suspension of Ia (3.44 g) in THF (100 ml), and the reaction mixture was stirred at room temperature overnight and evaporated. The residue was dissolved in 10% HCl, and the aqueous layer was washed with ether, made alkaline with K_2CO_3 and extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was triturated with EtOH and the resulting crystals were recrystallized from EtOH to give VIIa (165 mg (8%)) as colorless scales, mp 86—87°, which was identical with that obtained in a) in IR spectra and mixed mp.

5,6-Dimethoxy-1′-methylindan-2-spiro-2′-piperazin-3′-one (VIIb)——To a solution of PhLi in ether (prepared from Li (0.28 g) and PhBr (3.77 g)) was added a suspension of Ib (3.0 g) in THF (100 ml), and the reaction mixture was treated in the same procedure as that for VIIa to give VIIb (450 mg (22%)) as colorless scales, mp 216—217° (EtOH). *Anal.* Calcd. for $C_{15}H_{20}O_3N_2$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.04: H, 7.50; N, 9.81. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1660 (lactam).

1′-Methyl-5,6-methylenedioxyindan-2-spiro-2′-piperazin-3′-one (VIIc)——To a solution of PhLi in ether (100 ml) (prepared from Li (0.28 g) and PhBr (3.77 g)) was added a suspension of Ic (3.88 g) in THF (100 ml), and reaction mixture was treated in the same procedure as that for VIIa to give VIIc (300 mg (12%)) as colorless scales, mp 263—265° (EtOH). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.52; H, 6.45; N, 10.56. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1650 (lactam).

1′,4′-Dimethylindan-2-spiro-2′-piperazine (VIIIa)——A solution of IIIa (500 mg), 37% HCHO (1 ml) and 80% HCO_2H (2 ml) was stirred at 80° for 3 hr and then 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 to give VIIIa (450 mg (84%)) as a colorless oil.

The hydrochloride was obtained as colorless scales, mp 255—258° (MeOH–iso-Pr_2O). *Anal.* Calcd. for $C_{14}H_{20}N_2 \cdot 2HCl$: C, 58.13; H, 7.67; N, 9.69. Found: C, 58.39; H, 7.70; N, 10.00.

5,6-Dimethoxy-1′,4′-dimethylindan-2-spiro-2′-piperazine (VIIIb)——Compound (IIIb, 200 mg) was methylated with 37% HCHO (1 ml) and 80% HCO_2H (2 ml) in the same procedure as that for VIIIa to give VIIIb (155 mg (74%)) as colorless plates, mp 103—105° (*n*-hexane). *Anal.* Calcd. for $C_{16}H_{24}O_2N_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.41; H, 8.85; N, 9.90.

1′,4′-Dimethyl-5,6-methylenedioxyindan-2-spiro-2′-piperazine (VIIIc)——Compound (IIIc, 200 mg) was methylated with 37% HCHO (1 ml) and 80% HCO_2H (2 ml) in the same procedure as that for VIIIa to give VIIIc (184 mg (87%)) as colorless pillars, mp 94—96° (petro. ether). *Anal.* Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.03; H, 7.76; N, 10.55.

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