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Studies on Psychotropic Agents. VI.[1] Synthesis of 1′-Methylspiro[6-fluoroindan-1,3′-pyrrolidine]-3-one and Related Compounds

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The title compounds (**19**) were synthesized by rearrangement of the 1-ethoxycarbonyl-4-aryl-3,4-epoxypiperidines (**7**) to give the 3-aryl-3-formylpyrrolidine derivatives (**12**) for pharmacological testing. Compound (**19b**) exhibited moderate central nervous system depressing activity. The mechanism of the rearrangement of 1-substituted 4-aryl-3,4-epoxypiperidine with boron trifluoride etherate is discussed.

Keywords——spiro[indan-1,3′-pyrrolidine]-3-one; 4-aryl-3,4-epoxypiperidine; rearrangement; 4-amino-4′-fluorobutyrophenone; central nervous system depressing activity

A number of butyrophenone derivatives, which have the 4-aminobutyrophenone moiety as a common structural unit, have been used for the treatment of schizophrenia. Recently, we reported that 1-substituted 3-(*p*-fluorophenacyl)pyrrolidine or piperidine derivatives (I), which contain the above moiety, possessed central nervous system (CNS) depressing activities.[3] On the other hand, haloperidol (II), the prototype of the neuroleptic butyrophenone derivatives, has a *p*-chlorophenyl group in the 4-position of the piperidine ring. In order to determine some of the structural requirements for neuroleptic activity, therefore, we attempted to synthesize the 3-phenacylpyrrolidine homologs III and IV, which have the aryl group in the 3-position.

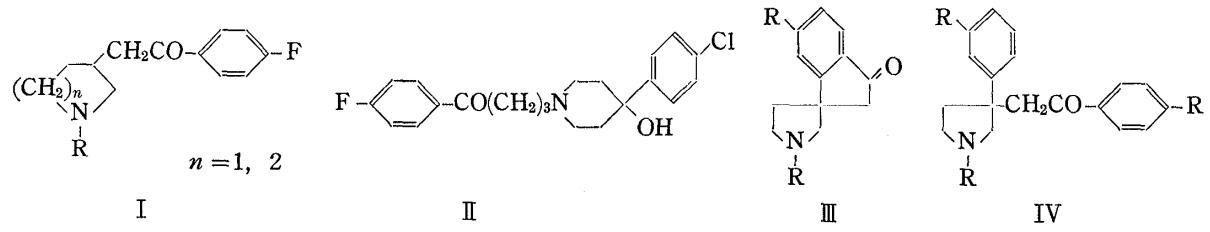

Chart 1

The Grignard reaction of 1-substituted 4-piperidone (**1**) with the appropriate arylmagnesium halide followed by dehydration with hydrochloric acid gave the 1,2,5,6-tetrahydropyridines (**3**). It was reported[4] that the reaction of **3a** with bromine-sodium bromide in water afforded 1-methyl-3-bromo-4-phenyl-4-piperidinol (**4**), which, on treatment with base, was converted to 1-methyl-4-phenyl-3,4-epoxypiperidine (**6**). Similar treatment of **3b** and **3c**, however, gave the 3,4-dibromopiperidines (**5**). The reaction of the epoxide (**6**) with ethyl chloroformate gave the epoxy-carbamate (**7a**) in high yield. As an alternative route to the epoxy-carbamates (**7**), the 1,2,5,6-tetrahydropyridines (**3c** and **3d**) were treated with ethyl chloroformate, and subsequent epoxidation with *m*-chloroperbenzoic acid afforded the epoxides (**7**).

1) Part V: Y. Nagai and H. Uno, *Chem. Pharm. Bull.*, **27**, 2056 (1979).
2) Location: *33-94, Enokicho, Suita, Osaka.*
3) Y. Nagai, H. Uno, and S. Umemoto, *Chem. Pharm. Bull.*, **25**, 1911 (1977).
4) R.E. Lyle and W.E. Krueger, *J. Org. Chem.*, **30**, 394 (1965).

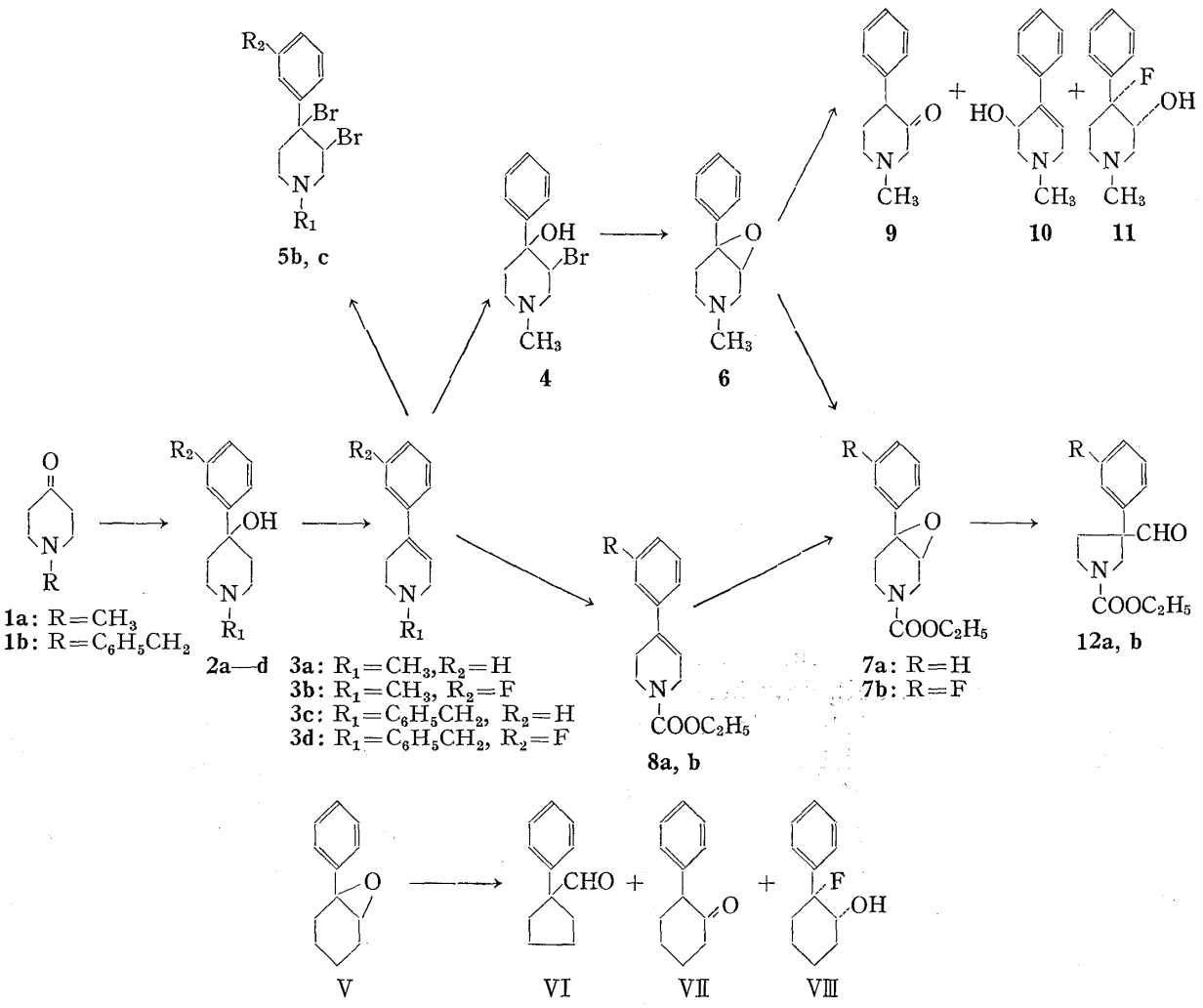

Chart 2

Lyle *et al.*[4] reported that the heating of 1-methyl-4-phenyl-3,4-epoxypiperidine (**6**) with a large excess of boron trifluoride etherate in ether for 8 hours gave 1-methyl-4-phenyl-3-piperidone (**9**) in 65% yield, and in our reexamination, similar treatment of **6** gave **9** in 72% yield and 4-phenyl-1,2,5,6-tetrahydro-5-pyridinol (**10**)[4] in 16% yield. On the other hand, it was reported[5] that similar treatment of 1-phenyl-1,2-epoxycyclohexane (V) in ether afforded a mixture of the cyclopentanecarboaldehyde (VI), cyclohexanone (VII) and an unidentified product.

Interestingly, the same treatment of the epoxy-carbamates (**7**) afforded the aldehydes (**12**) quantitatively, and this rearrangement went to completion within 2 minutes. The reaction of **7a** with 2 moles of boron trifluoride etherate in ether at room temperature for 1 minute also gave the aldehyde (**12a**) in 86.5% yield.

There is a difference in reactivity between V and **7** since it was reported[6] that the treatment of V with 2 moles of boron trifluoride etherate in ether for 5 minutes afforded the fluorohydrin (VIII) in high yield.

It has been shown[6–8] that the 1-aryl-1,2-epoxycyclohexane rearranges through an open carbonium ion, or in a more concerted manner. In the nuclear magnetic resonance

5) I.I. Schiketanz, I. Necsiou, M. Rentea, and C.D. Nenitzescu, *Rev. Roumaine Chim.*, **13**, 1385 (1968).
6) G. Berti, B. Macchia, F. Macchia, and I. Monti, *J. Chem. Soc.* (*C*), **1971**, 3371.
7) P.L. Barili, B. Berti, B. Macchia, F. Macchia, and L. Monti, *J. Chem. Soc.* (*C*), **1970**, 1168.
8) P.L. Barili, G. Bellucci, G. Berti, B. Macchia, and F. Macchia, *J. Chem. Soc. Perkin I*, **1974**, 477.

(NMR) spectra of **7** in pyridine-d_5 the J values between the oxiran proton (C_3-H) and adjacent methylene protons (C_2-H) were 2.8—2.9 and 1.0—1.1 Hz. This suggests that **7** exist as a mixture of two conformers (**7A** and **7B**).[9] Since the epoxy-carbamates (**7**) rearranged rapidly to **12** under the mild condition, the rearrangement of **7** might proceed through an at least partly concerted mechanism, involving axial cleavage of the C-O bond in the half-chair conformation (**7C**) followed by *trans* migration, which is the favored process[10] leading to the ring-contracted product, resembling the rearrangement[6] of V in benzene to give the aldehyde (VI) as the main product.

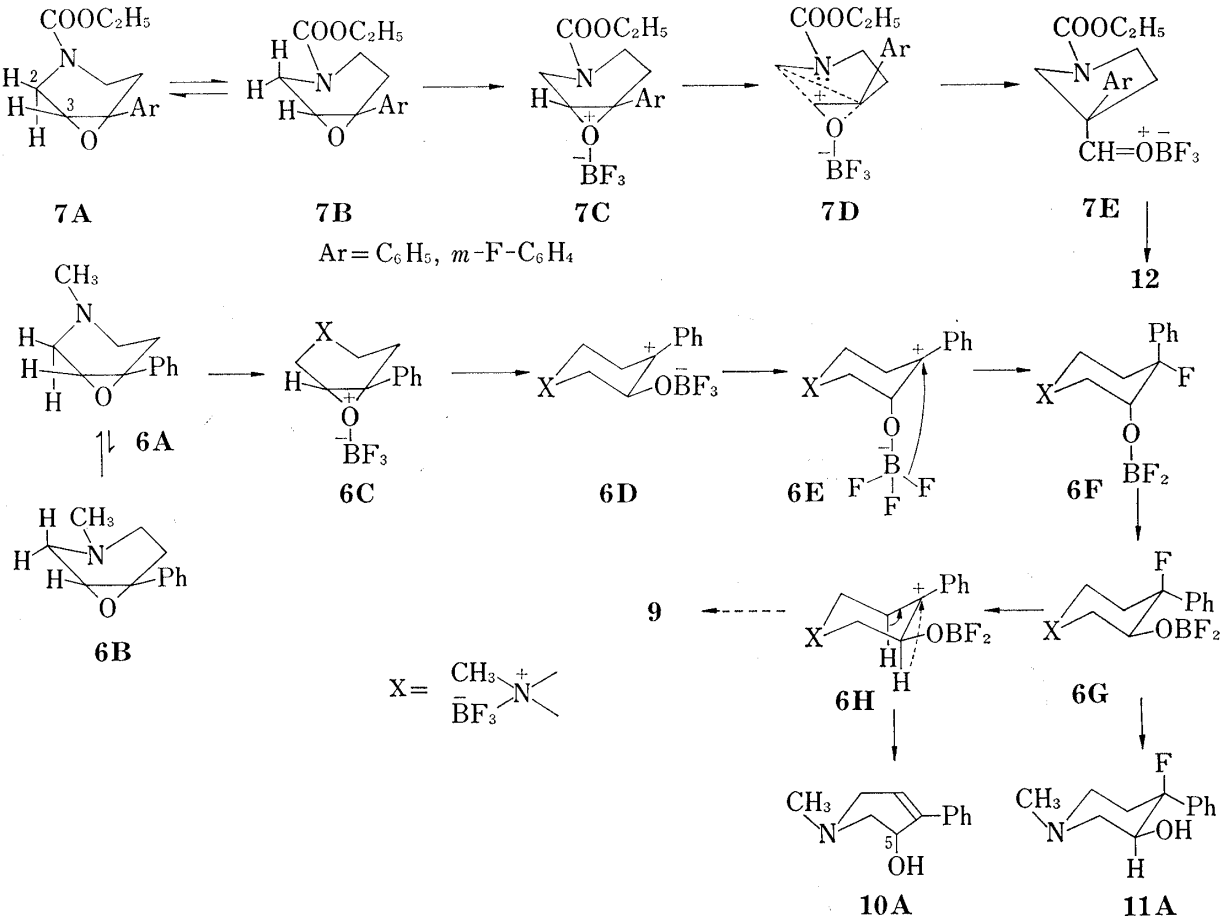

Chart 3

The mechanism of the rearrangement of the epoxide (**6**) into **9** was also studied. In the NMR spectrum of **6** the J values between the oxiran proton (C_3-H) and adjacent methylene protons (C_2-H) were 4.3 and 0.5 Hz. Therefore, **6** should exist predominantly as **6A**.[9] The reaction of **6** with a large excess of boron trifluoride etherate in ether for 2 minutes afforded

9) Tori *et al.* have deduced for the 1,2-epoxycyclohexane ring system a simple form of Karplus equation: $J=5.1\cos^2\theta$—(I) correlating the J value with an oxiran proton and an adjacent cyclohexyl proton with the corresponding dihedral angle [K. Tori, T. Komeno and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1974)]. From a Dreiding model of the stable half-chair conformation (**7A**) of **7**, the dihedral angles between the C_2 proton and C_3 proton are approximately 20° and 100°. Application of Eq. (I) gave $J_{2eq,3}=4.5$ Hz and $J_{2ax,3}=0$ Hz. On the other hand, in the stable half-chair conformation (**7B**) of **7** the two dihedral angles are about 60°, which would correspond to $J_{2,3}=1.3$ Hz according to Eq. (I). The observed J values of **7** were approximately half the sums of the above J values of **7A** and **7B**. In the case of **6A** and **6B**, the J values would be similar to those of **7A** and **7B** on the basis of Dreiding model examination.

10) M.P. Hartshorn and D.N. Kirk, *Tetrahedron*, **21**, 1547 (1965).

the *cis*-fluorohydrin (**11**) as the main product. In the NMR spectrum of the maleate of **11**, a proton (C_3-H) in the α position to the hydroxyl group appeared as two double-doublets (J=11.1 and 5 Hz) centered at δ 4.28 and 4.54, separated by 25.8 Hz ($^3J_{HF}$). This suggests the conformation (**11A**), in which an axial proton is anticoplanar to the fluorine atom,[11] and thus **11** would be formed chiefly through equatorial cleavage of the epoxide ring followed by inversion of the piperidine ring and subsequent intramolecular transfer of the fluorine.[6] Therefore, the *cis*-adduct (**6G**), which would afford the *cis*-fluorohydrin (**11**) on hydrolysis, should be the intermediate of this rearrangement, giving **9** *via* the carbonium ion (**6H**), as shown in Chart 3. Compound (**10**) may also be formed *via* this ion (**6H**) and should exist in the conformation (**10A**), since the J values between an allylic proton (C_5-H) in the α position to the hydroxyl group and adjacent methylene protons (C_6-H) were 2.7 and 2.7 Hz.

The substituent on the nitrogen atom in the 4-aryl-3,4-epoxypiperidine determined the rearrangement course. The lone pair of the nitrogen atom might stabilize the nonclassical carbonium ion in **7D**, and consequently **7** would give larger amounts of ring-contracted products than V. In the case of **6**, the decreased carbocationic character in the 4-position of the transition state owing to the -I effect of the boron trifluoride-coordinated amino group (CH_3–$\overset{+}{N}$–$\bar{B}F_3$) would result in the formation of **11**.[8,12]

The reduction of **12** with lithium aluminum hydride gave the carbinols (**13**), which were treated with thionyl chloride followed by reaction with sodium cyanide to give the nitriles (**15**). We reported that the Grignard reaction of 1-benzyl-3-cyanomethylpyrrolidine with *p*-fluorophenylmagnesium bromide followed by hydrolysis afforded the 3-(*p*-fluorophenacyl)pyrrolidine derivative,[3] but attempts to convert the nitriles (**15**) into the *p*-fluorophenacyl derivatives (**16**) resulted in recovery of the starting materials even under the conditions of the above Grignard reaction. The hydrolysis of **15** gave the acetic acids (**17**) quantitatively and Friedel-Crafts reaction of the acetyl chlorides (**18**) derived from **17** with fluorobenzene afforded the desired spiro compounds (**19**).

The above compounds (**19**) were evaluated pharmacologically by the usual methods as potential neuroleptics. Compound (**19b**) showed moderate CNS depressing activities, which were weak in comparison with those of haloperidol (II).

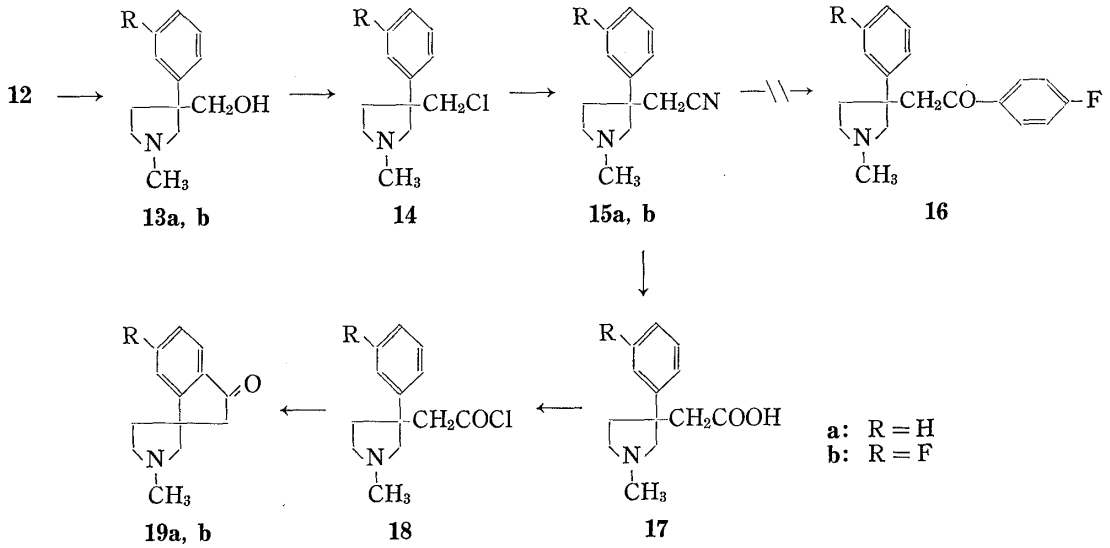

Chart 4

11) L.D. Hall and J.F. Manville, *Chem. Ind.* (London), **1965**, 991.
12) I.G. Guest and B.A. Marples, *J. Chem. Soc. Perkin I*, **1973**, 900.

Experimental[13]

1-Methyl(or benzyl)-4-(*m*-fluorophenyl)-4-piperidinol (2b and 2d)——To a suspention of Mg (0.03 mol) in tetrahydrofuran (THF) (30 ml), *m*-bromofluorobenzene (0.03 mol) was added dropwise with stirring at a rate sufficient to maintain the reflux, and then the reaction mixture was heated under reflux for 1 hr. After further addition of THF (50 ml) to the mixture, a solution of **1a** (or **1b**) (0.025 mol) in THF (30 ml) was added and then the mixture was heated under reflux for 20 hr. The mixture was concentrated and dil. HCl was added to the residue with cooling. The mixture was stirred for a while and the dil. HCl layer was separated, made alkaline with NaOH and extracted with ether. The extract was dried over K_2CO_3 and concentrated. The residue was recrystallized from ether to give **2b** (or **2d**) (35—42%). **2b**: mp 93—94°. *Anal.* Calcd for $C_{12}H_{16}FNO$: C, 68.87; H, 7.71; F, 9.08; N, 6.69. Found: C, 69.00; H, 7.91; F, 9.10; N, 6.79. **2d**: mp 120—122°. *Anal.* Calcd for $C_{18}H_{20}FNO$: C, 75.76; H, 7.07; F, 6.66; N, 4.91. Found: C, 75.64; H, 7.15; F, 6.42; N, 4.75.

1-Methyl(or benzyl)-4-(*m*-fluorophenyl)-1,2,5,6-tetrahydropyridine (3b and 3d)——A solution of **2b** (or **2d**) (0.02 mol) in a mixture of conc. HCl (7 ml), EtOH (12 ml) and H_2O (14 ml) was heated under reflux for 50 hr. After removing EtOH *in vacuo*, the residue was made alkaline with NaOH and extracted with $CHCl_3$. The extract was dried over K_2CO_3 and concentrated. The residue was converted into the hydrochloride or hydrobromide and recrystallized from EtOH–ether. **3b**·HBr: mp 154—155°. Yield, 54%. *Anal.* Calcd for $C_{12}H_{14}FN\cdot HBr$: C, 52.95; H, 5.56; Br, 29.36; F, 6.98; N, 5.15. Found: C, 52.69; H, 5.65; Br, 29.14; F, 7.21; N, 5.15. **3d**·HCl: mp 214—216°. Yield, 62%. *Anal.* Calcd for $C_{18}H_{18}FN\cdot HCl$: C, 71.16; H, 6.30; Cl, 11.67; F, 6.25; N, 4.61. Found: C, 71.01; H, 6.11; Cl, 11.69; F, 6.22; N, 4.82.

1-Methyl(or benzyl)-3,4-dibromo-4-phenylpiperidine (5)——A solution of bromine (0.011 mol) and sodium bromide (0.03 mol) in H_2O (30 ml) was added to a solution of **3b**·HBr (or **3c**·HBr) (0.01 mol) in H_2O (30 ml) during 20 min, and the mixture was stirred for 2 hr at room temperature. The crude hydrobromide of the product, if it separated as a solid, was collected and recrystallized from EtOH–MeOH to give **5c**·HBr (quantitative yield); if it remained dissolved in the reaction mixture, the mixture was made alkaline with NaOH and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated. The residue was recrystallized from ether to give 1.5 g (44%) of **5b**. **5b**: mp 80—82°. *Anal.* Calcd for $C_{12}H_{14}Br_2FN$: C, 41.05; H, 4.02; Br, 45.53; F, 5.41; N, 4.00. Found: C, 41.45; H, 4.26: Br, 45.09; F, 5.85; N, 4.20. **5c**·HBr: mp 142—144°. *Anal.* Calcd for $C_{18}H_{19}Br_2N\cdot HBr$: C, 44.11; H, 4.11; Br, 48.92; N, 2.86. Found: C, 44.28; H, 4.00; Br, 48.57; N, 2.95.

1-Methyl-4-phenyl-3,4-epoxypiperidine (6)[4]——NMR (δ in pyridine-d_5): 3.20 (d-d, J=4.3 and 0.5 Hz, 1H, –CH(O)—C<).

1-Ethoxycarbonyl-4-phenyl(or *m*-fluorophenyl)-1,2,5,6-tetrahydropyridine (8)——A mixture of **3c** (or **3d**) (0.01 mol) and ethyl chloroformate (0.015 mol) in benzene (40 ml) was heated under reflux for 3 hr. The mixture was washed with dil. HCl and H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel and the fraction eluted with hexane–$CHCl_3$ (2: 1) gave **8** (82—85%) as an oily product. **8a**. *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.10; H, 7.13; N, 6.13. Found: C, 71.67; H, 7.41; N, 6.06. MS *m/e*: 231 (M^+). **8b**. *Anal.* Calcd for $C_{14}H_{16}FNO_2$: C, 67.45; H, 6.47; F, 7.62; N, 5.62. Found: C, 67.10; H, 6.67; F, 5.58; N, 7.71. MS *m/e*: 249 (M^+).

1-Ethoxycarbonyl-4-phenyl(or *m*-fluorophenyl)-3,4-epoxypiperidine (7)——a) A solution of ethyl chloroformate (23.2 g) in benzene (150 ml) was added under reflux to a solution of **6** (27 g) in benzene (50 ml) during 10 min, and the resulting solution was refluxed for a further 10 min. The solution was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel and the fraction eluted with ether gave 31 g (91%) of **7a** as an oily product. **7a**. *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.67. Found: C, 67.62; H, 6.83; N, 5.78. MS *m/e*: 247 (M^+). NMR (δ in pyridine-d_5): 3.23 (d-d-d, J=2.8, 1.0 and 0.8 Hz, 1H, –CH(O)—C<), this signal collapsed to d-d (J=2.8 and 1.0 Hz) on irradiation at 2.13 (>CH–C(O)—CH–).

b) A solution of 8 (0.01 mol) in $CHCl_3$ (35 ml) was treated with *m*-chloroperbenzoic acid (85% pure, 0.013 mol) in $CHCl_3$ (30 ml) under cooling, and the resulting mixture was stirred at room temperature overnight. Next, 20% Na_2SO_3 (58 ml) was added and the mixture was stirred vigorously for 1 hr. The $CHCl_3$ layer was washed with dil. HCl and H_2O, dried over Na_2SO_4 and concentrated to give **7** (quantitative yield) as an oily product. **7b**. *Anal.* Calcd for $C_{14}H_{16}FNO_3$: C, 63.38; H, 6.08; F, 7.16; N, 5.28. Found: C, 63.07;

13) All melting points are uncorrected. NMR spectra were taken with a Varian A-60 or a Varian HA-100 spectrometer using TMS as an internal standard; s, singlet; d, doublet; m, multiplet. MS spectra were taken with a Hitachi RMU-6L mass spectrometer, and IR spectra with a EPI-S2 spectrometer. Gas chromatography (GLC) was carried out with a Yanagimoto G-180 gas chromatograph equipped with a flame ionization detecter.

H, 6.18; F, 7.02; N, 5.17. MS *m/e*: 265 (M^+). NMR (δ in pyridine-d_5): 3.22 (d-d-d, J=2.9, 1.1 and 0.8 Hz, 1H, CH(O)—C—), this signal collapsed to d-d (J=2.9 and 1.1 Hz) on irradiation at 2.10 (>CH–C(O)—CH–).

Treatment of 6 with Boron Trifluoride Etherate——Boron trifluoride etherate (150 ml) was added over a period of 7 min to a solution of **6** (12.5 g) in ether (125 ml). The mixture was heated under reflux for 5 hr, neutralized with 5 N NaOH (350 ml) under cooling and stirred for 30 min. The ether layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, dried over K_2CO_3 and concentrated. The residual oil was chromatographed on silica gel and the earlier fraction eluted with $CHCl_3$ gave 9.0 g (72%) of **9**.[4] The later fraction eluted with $CHCl_3$ gave a crude solid, which was recrystallized from ether–hexane to give 2.5 g (16%) of **10**.[4] **9**·HCl (from EtOH–ether–acetone): mp 162—164°. *Anal.* Calcd for $C_{12}H_{15}NO \cdot HCl$: C, 63.85; H, 7.15; Cl, 15.21; N, 6.21. Found: C, 63.45; H, 7.15; Cl, 16.00; N, 6.40. **10**: mp 102—103°. *Anal.* Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.09; H, 7.76; N, 7.24. MS *m/e*: 189 (M^+). NMR (δ in $CDCl_3$): 2.98 (d-d-d, J=11.8, 2.7 and 1.1 Hz, 1H, –CH(OH)–CH(H)–N), 2.45 (d-d-d, J=11.8, 2.7 and 0.7 Hz, 1H, –CH(OH)–CH(H)–N), 4.49 (m, 1H, –CH(OH)–), 6.15 (d-d, J=4.6 and 2.5 Hz, –CH=C).

1-Ethoxycarbonyl-3-formyl-3-phenyl(or *m*-fluorophenyl)pyrrolidine (12)——a) Boron trifluoride etherate (85 ml) was added over a period of 5 min to a solution of **7** (0.02 mol) in ether (50 ml). The mixture was heated under reflux for 5 hr, neutralized with 5 N NaOH under cooling and stirred for 1 hr. The ether layer was separated, washed with H_2O, dried over Na_2SO_4 and concentrated to give **12** (quantitative yield). **12a**: An oily product which was gas-chromatographically pure. *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.67. Found: C, 67.59; H, 6.82; N, 5.67. MS *m/e*: 247 (M^+). NMR (δ in $CDCl_3$): 9.46 (s, 1H, CHO). **12b**: mp 56—59°. *Anal.* Calcd for $C_{14}H_{16}FNO_3$: C, 63.38; H, 6.08; F, 7.16; N, 5.28. Found: C, 63.32; H, 6.27; F, 7.35; N, 5.36. MS *m/e*: 265 (M^+). NMR (δ in $CDCl_3$): 9.55 (s, 1H, CHO).

b) A solution of **7a** (0.4 g) in ether (4 ml) was treated with boron trifluoride etherate (6.5 ml), and after 2 min at room temperature, the mixture was neutralized with 5 N NaOH under cooling. The reaction mixture was extracted with ether, then the extract was washed with H_2O, dried oerv Na_2SO_4 and concentrated to give **12a** (quantitative yield), which was gas-chromatographically pure.

c) A solution of **7a** (0.22 g) in ether (28 ml) was treated with boron trifluoride etherate (0.26 g), and after 1 min at room temperature, the mixture was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residual oily product (quantitative yield) was analyzed gas-chromatographically; it contained 86.5% of **12a**.

***cis*-1-Methyl-4-fluoro-4-phenyl-3-piperidinol (11)**——Compound **6** (0.3 g) in ether (6 ml) was treated with boron trifluoride etherate (8 ml) using the procedure described for the preparation of **12a** (procedure b). The oily product was converted into the maleate and recrystallized from acetone–ether to give 0.35 g (68%) of **11**·maleate, mp 164—166°. *Anal.* Calcd for $C_{12}H_{16}FNO \cdot C_4H_4O_4$: C, 59.07; H, 6.20; F, 4.31. Found: C, 59.25; H, 6.29; F, 5.83; N, 4.14. NMR (δ in D_2O): 4.41 (d-d-d, J=25.8, 11.1 and 5.0 Hz, 1H, –CH(OH)–C(F)<).

1-Methyl-3-hydroxymethyl-3-phenyl(or *m*-fluorophenyl)pyrrolidine (13)——A solution of **12** (0.02 mol) in dry ether (60 ml) was added to a suspension of lithium aluminum hydride (0.08 mol) in dry ether (100 ml) at a rate sufficient to maintain gentle reflux. The mixture was heated under reflux for 3 hr, then cooled and treated with H_2O. The mixture was filtered, and the filtrate was dried over Na_2SO_4 and concentrated. The crude product, if solid, was purified by recrystallization from hexane in **13a**; if an oil, it was converted into the picrate and recrystallized from acetone–ether in **13b**. **13a**: mp 53—55°. Yield, 96%. *Anal.* Calcd for $C_{12}H_{17}NO$: C, 75.22; H, 9.03; N, 7.32. Found: C, 75.21; H, 9.03; N, 7.18. **13b**·picrate: mp 89—93°. Yield, 94%. *Anal.* Calcd for $C_{12}H_{16}FNO \cdot C_6H_3N_3O_7 \cdot 1/2(C_2H_5)_2O$: C, 50.52; H, 5.09; N, 11.78. Found: C, 50.91; H, 5.32; N, 11.78. Free base, MS *m/e*: 209 (M^+).

1-Methyl-3-chloromethyl-3-phenyl(or *m*-fluorophenyl)pyrrolidine (14)——A solution of **13** (0.01 mol) in $CHCl_3$ (40 ml) was saturated with dry HCl and then thionyl chloride (0.015 mol) was added. The mixture was refluxed for 5 hr and concentrated *in vacuo*. Dil. NH_4OH was added to the residue and the mixture was extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel and the fraction eluted with $CHCl_3$–MeOH (100: 1) gave **14** (68—74%) as an oily product. **14a**. *Anal.* Calcd for $C_{12}H_{16}ClN$: C, 68.72; H, 7.69; Cl, 16.91; N, 6.68. Found: C, 68.61; H, 7.51; Cl, 16.58; N, 6.82. MS *m/e*: 209 (M^+). **14b**. *Anal.* Calcd for $C_{12}H_{15}ClFN$: C, 63.29; H, 6.64; Cl, 15.57; F, 8.34; N, 6.15. Found: C, 63.07; H, 6.73; Cl, 15.29; F, 8.14; N, 6.32. MS *m/e*: 227 (M^+).

1-Methyl-3-cyanomethyl-3-phenyl(or *m*-fluorophenyl)pyrrolidine (15)——A mixture of **14** (0.01 mol) and sodium cyanide (0.03 mol) in dimethylsulfoxide (40 ml) was heated at 130—140° for 10 hr with stirring. Ice–H_2O was added and the resulting mixture was extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel and the fraction eluted with $CHCl_3$–MeOH (200: 1) gave **15** (55—63%) as an oily product. **15a**. *Anal.* Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.72; H, 8.32; N, 13.66. IR ν_{max}^{film} cm^{-1}: 2250 (C≡N). MS *m/e*: 200. **15b**. *Anal.* Calcd for $C_{13}H_{15}FN_2$: C, 71.53; H, 6.92; F, 8.70; N, 12.84. Found: C, 71.32; H, 6.81; F,

8.44; N, 12.76. IR ν_{max}^{film} cm^{-1}: 2250 (C≡N).

The Grignard Reaction of 15 with *p*-Fluorophenylmagnesium Bromide——*p*-Bromofluorobenzene (3.84 g) in dry ether (10 ml) was added with stirring to a suspension of magnesium (0.54 g) in dry ether (10 ml) at a rate sufficient to maintain reflux, and then the reaction mixture was heated under reflux for 1.5 hr. After adding dry ether (15 ml) to the mixture, a solution of **15a** (2.2 g) in dry ether (5 ml) was added and the mixture was refluxed for 8 hr. Dil. HCl was added to the reaction mixture and the mixture was stirred for a while. The dil. HCl layer was separated, heated at 70° for 30 min, made alkaline with NaOH and extracted with ether. The extract was dried over Na_2SO_4 and concentrated to give 1.8 g of **15a**.

The Grignard reaction of **15** with *p*-fluorophenylmagnesium bromide in THF followed by hydrolysis gave no product with a carbonyl band in the IR spectrum.

1′-Methylspiro[indan(or 6-fluoroindan)-1,3′-pyrrolidine]-3-one (19)——A solution of **15** (0.01 mol) in conc. HCl (40 ml) was heated under reflux for 10 hr, and then concentrated *in vacuo*. Acetone was added to the residue, and after stirring, the solution was concentrated to dryness *in vacuo*. The residual powder (**17**) was used for the next reaction without further purification. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). The crude **17** was treated $CHCl_3$ (40 ml) and thionyl chloride (2.4 g) was added to the resulting suspension under ice-cooling. The mixture was stirred for 3 hr at 35° and then concentrated *in vacuo* at room temperature. The syrupy residue (**18**) was used for the next reaction without further purification. IR ν_{max}^{film} cm^{-1}: 1790 (C=O). Fluorobenzene (15 ml) and pulverized anhydrous aluminum chloride (2.6 g) were added to the crude **18** under ice-cooling, the mixture was stirred under ice-cooling for 30 min and then heated on a water-bath for 30 min. The reaction mixture was poured into dil. HCl and the aqueous layer was separated, made alkaline with dil. NH_4OH and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was converted into the maleate or fumarate and recrystallized from EtOH. **19a**·maleate: mp 175—178°. Yield, 38%. *Anal.* Calcd for $C_{13}H_{15}NO \cdot C_4H_4O_4$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.34; H, 6.37; N, 4.28. NMR (δ in D_2O): 3.11, 3.71 (s, each 2H, –Ç–CH_2CO or –Ç–CH_2–N<). Free base, IR ν_{max}^{film} cm^{-1}: 1710 (C=O). **19b**·semifumarate: mp 232—235°. Yield, 34%. *Anal.* Calcd for $C_{13}H_{14}FNO \cdot 1/2C_4H_4O_4$: C, 64.96; H, 5.81; F, 6.85; N, 5.05. Found: C, 64.59; H, 5.89; F, 6.89; N, 5.10. MS *m/e*: 219 (M^+). NMR (δ in D_2O): 3.06, 3.79 (s, each 2H, –Ç–CH_2–CO or –Ç–CH_2–N<). Free base, IR ν_{max}^{film} cm^{-1}: 1713 (C=O).

GLC Analysis——A glass column (100×0.2 cm) was filled with 3% OV-25. The column temperature was 160° while the injector and detector were maintained at 250°. Helium was used as a carrier gas at a flow rate of 30 ml/min. Retention time: **12a**, 23.4 min.

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