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Studies on Psychotropic Agents. II.[1] Synthesis of 1-Substituted-3-(*p*-fluorophenacyl)piperidines and the Related Compounds

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A series of 1-substituted-3-phenacylpiperidine derivatives (VI) and 1-substituted-3-(*p*-fluorophenacyl)pyrrolidine derivatives (XI) were synthesized for pharmacological testing. The conversion of 3-phenacyl-4-piperidone derivatives (XXII) into 4,5,6,7-tetrahydrofuro(or -1H-pyrrolo)[3,2-*c*]pyridine derivatives (XX, XXV), the rearrangement of the quaternary salts of these products (XXa, XXVb) with phenyllithium and the dimerization of the dehydration product of 1-benzyl-3-hydroxymethyl-4-piperidone (K) were also described.

Among the compounds synthesized, 1-(*p*-fluorobenzoyl)propyl-3-(*p*-fluorophenacyl)-pyrrolidine (XId) showed remarkable central nervous system depressing activities.

Keywords——new major tranquilizer; *p*-fluorobenzoyl group; piperidine derivative; pyrrolidine derivative; furo[3,2-*c*]pyridine derivative; pyrrolo[3,2-*c*]pyridine derivative; Sommelet rearrangement; dimerization of α,β-unsaturated ketone; structure–activity relationship

A number of phenothiazine and butyrophenone derivatives have been practically used as major tranquilizers. Between these derivatives, there is a similar structural feature, that is, they consist of a phenothiazin-10-yl or a *p*-fluorobenzoyl moiety, a three-carbon chain and a basic amino group, as shown in chlorpromazine (A) and haloperidol (B). Therefore, it might be possible to say that the phenothiazin-10-yl and the *p*-fluorobenzoyl moieties are bioisosteric-like, and replacement of the former with the latter may be expected to bring about similar pharmacological activities. Thus we intended to synthesize the compounds (D), which have the *p*-fluorobenzoyl or its analogous moiety in place of the phenothiazin-10-yl moiety in mepazine (C), and the related compounds (D). In addition, this paper deals

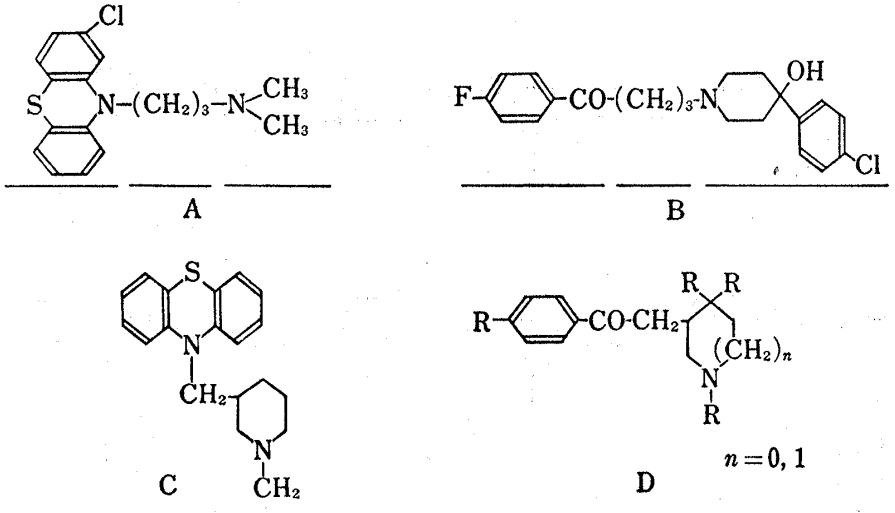


Chart 1

1) Part I: Y. Nagai, A. Maki, H. Kanda, K. Natsuka, and S. Umemoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 1179 (1976).

2) Location: *33–94, Enokicho, Suita, Osaka.*

with some interesting findings concerning the reactions of the compounds (D) and their intermediates.

The synthesis of 1-substituted-3-phenacylpiperidine derivatives (VI) was accomplished by the procedures, shown in Chart 2. Treatment of ethyl 3-piperidineacetate (I)[3] with benzyl chloride followed by hydrolysis gave 1-benzyl-3-piperidineacetic acid (III). The Friedel-Craft reaction of 1-benzyl-3-piperidineacetyl chloride (IV) derived from III with fluorobenzene afforded the 3-(*p*-fluorophenacyl) derivative (VIe), but the hydrochloride of IV was considerably unstable in the chloroform solution at the temperature higher than 40°. So the Grignard reaction of 1-substituted-3-piperidineacetonitrile (V)[4] with the corresponding arylmagnesium halide followed by hydrolysis was carried out to afford VIa—f. 3-(*p*-Fluorophenacyl)piperidine (VIII) was obtained by the treatment[5] of VIe with ethyl chlorofor-

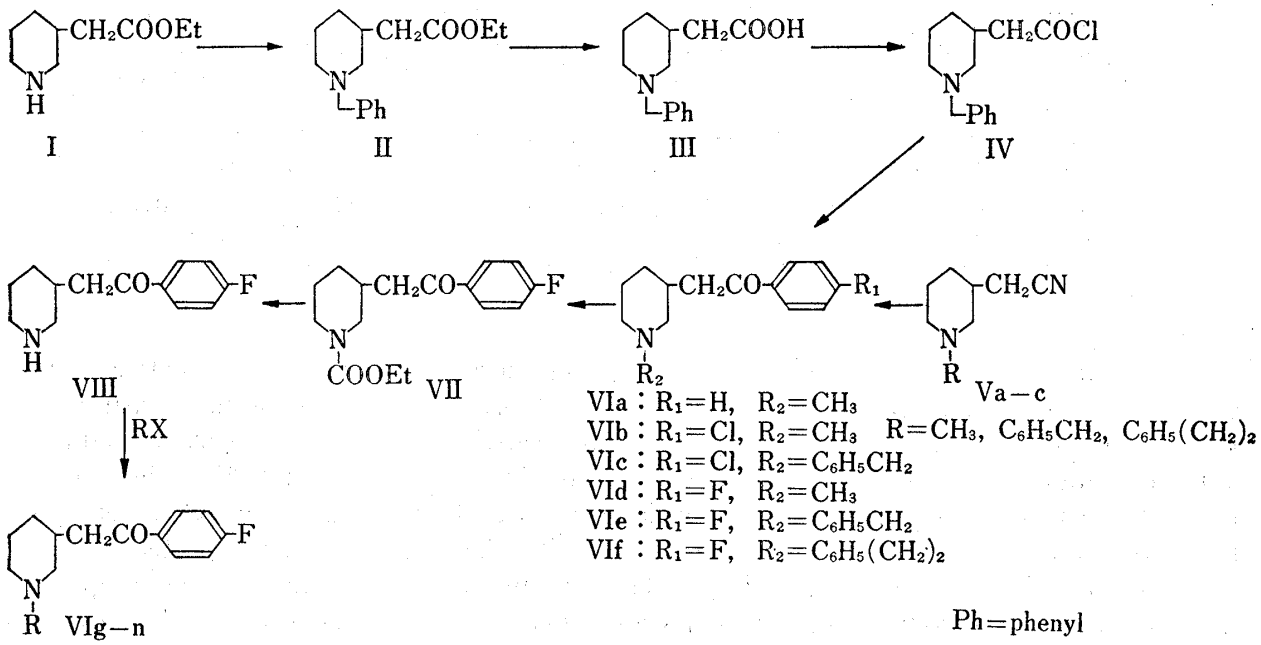


Chart 2

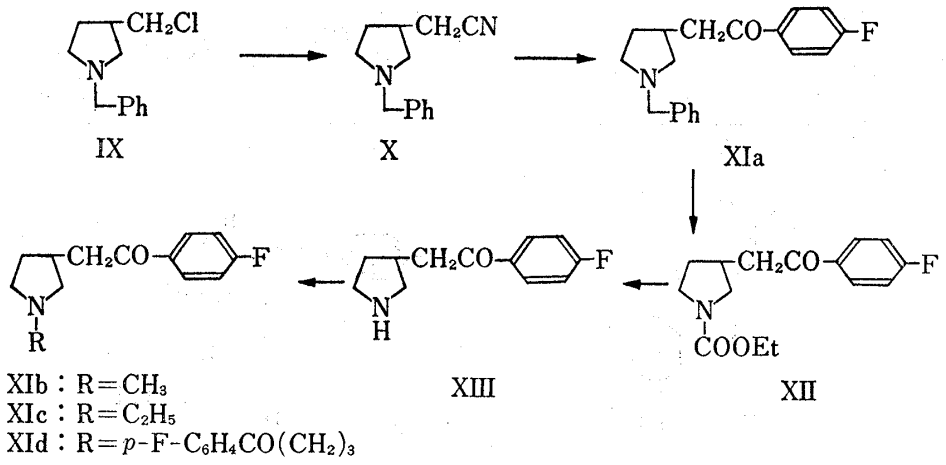


Chart 3

3) H. Najer, R. Giudicelli, J. Loisean, and J. Menin, *Bull. Soc. Chim. France*, **1963**, 2831.
4) M. Freifelder, *J. Pharm. Soc.*, **55**, 535 (1966).
5) M. Nakanishi and K. Arimura, *Yakugaku Zasshi*, **90**, 1324 (1970).

mate in benzene followed by hydrolysis. The 1-substituted derivatives (VIg—n) of VIII listed in Table II were prepared by alkylation of VIII with appropriate halides.

The 3-(*p*-fluorophenacyl)pyrrolidine derivatives (XI) were prepared from 1-benzyl-3-chloromethylpyrrolidine (IX) *via* the 3-cyanomethyl derivative (X) by the similar procedure mentioned above, as shown in Chart 3.

It has been reported[6] that some 4'-fluoro-4-piperidinobutyrophenone derivatives having a spiro ring at the 4-position of the piperidine ring possess the central nervous system (CNS) depressing activities. The synthesis of the 3-(*p*-fluorophenacyl)piperidine derivative

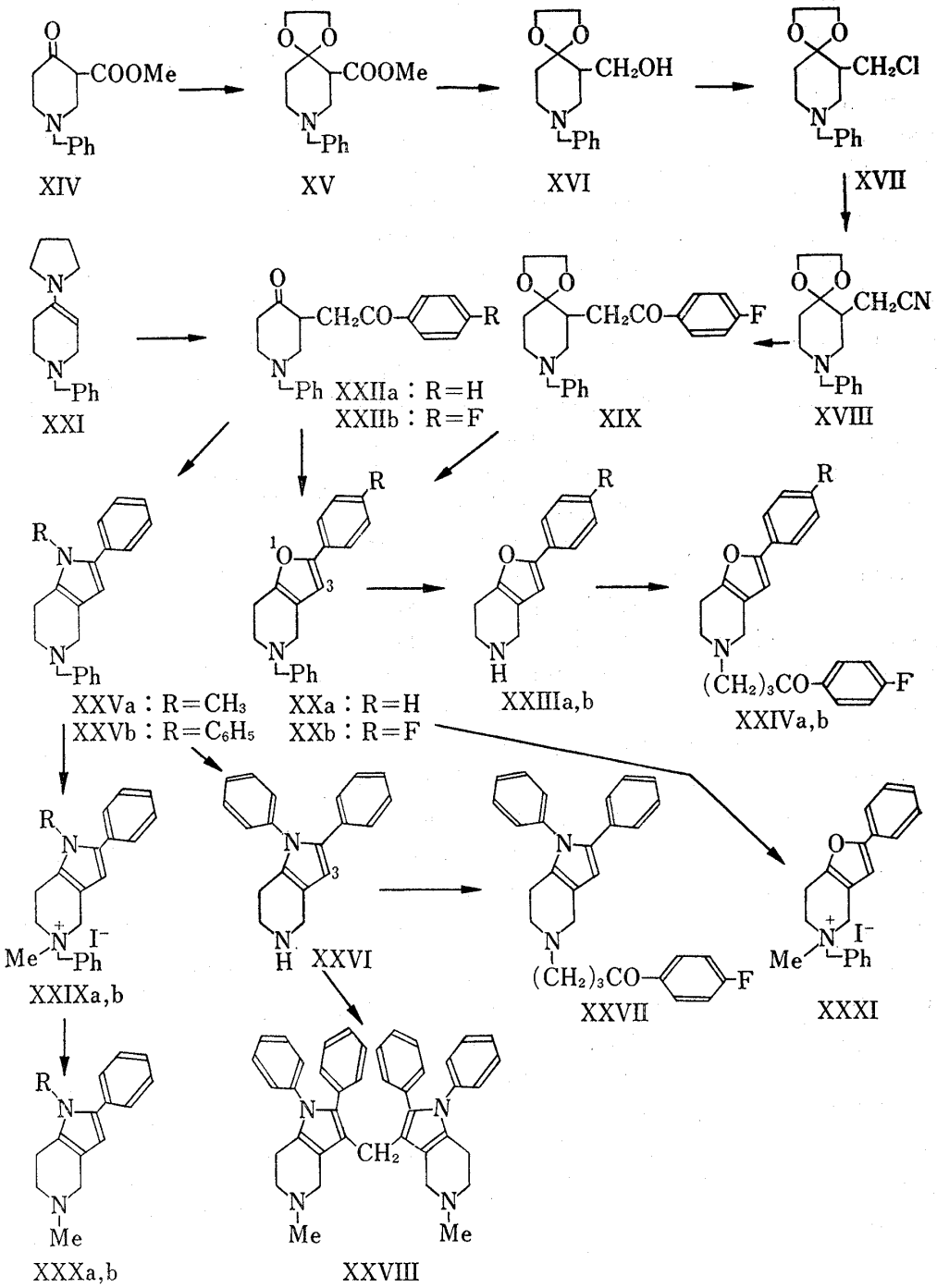


Chart 4

6) P.A.J. Janssen, U.S. Patent 3161644 (1962) [*C.A.*, **63**, 9952 (1965)]; K. Yamatsu, T. Ohgo, and K. Otsu, *Nippon Yakurigaku Zasshi*, **63**, 16 (1967); Sandoz Ltd., Belg. Patent 609766 [*C.A.*, **58**, 3403 (1963)].

(XIX) having a 1,3-dioxolane moiety as a spiro ring at the 4-position was carried out as follows. The ketal (XV) of methyl 1-benzyl-4-oxonipecotate (XIV) was reduced with lithium aluminum hydride to give a 3-hydroxymethyl derivative (XVI). On chlorination followed by reaction with potassium cyanide, XVI gave a 3-cyanomethyl derivative (XVIII). The Grignard reaction of XVIII with *p*-fluorophenylmagnesium bromide followed by hydrolysis with 5% hydrochloric acid at 70° for 1 hour afforded the target (XIX).

It is generally known that the ring closure of 1,4-dicarbonyl compounds with the intramolecular dehydration gives furan derivatives[7] and the reaction of those compounds with amines gives pyrrole derivatives.[8] On hydrolysis with 20% hydrochloric acid, XIX gave 2-(*p*-fluorophenyl)-5-benzyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (XXb) which resulted in the ring closure of the expected 1-benzyl-3-(*p*-fluorophenacyl)-4-piperidone (XXIIb). The infrared (IR) spectrum of XXb showed no carbonyl band and its nuclear magnetic resonance (NMR) spectrum showed a proton (C_3–H) in the furan ring at δ 6.44 as a singlet. The compounds (XXII), however, were prepared by the reaction of 1-benzyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine (XXI)[9] with phenacyl bromide or *p*-fluorophenacyl bromide followed by hydrolysis. As expected, the treatment of XXII with concentrated hydrochloric acid gave XX in good yields. The catalytic hydrogenation of XX on palladium-carbon gave N-debenzylated compounds (XXIII), which were treated with (*p*-fluorobenzoyl)propyl chloride to yield N-substituted compounds (XXIV). The condensation of XXIIa with appropriate primary amines in acetic acid gave 1-substituted-2-phenyl-5-benzyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine of new skeleton (XXV), whose structures were confirmed by IR and NMR spectrum measurements. The catalytic hydrogenation of XXVb on palladium-carbon afforded the N-debenzylated compound (XXVI), which was allowed to react with (*p*-fluorobenzoyl)-propyl chloride to afford the N-substituted compound (XXVII). The reaction of XXVI with formic acid–formalin did not give the desired N-methylated compound (XXXb) but a dipyrrylmethane derivative (XXVIII). The NMR spectrum of XXVIII showed a methylene signal at δ 3.80 as a singlet and was lacking in a proton (C_3–H) in the pyrrole ring of XXVI. The mass spectrum of XXVIII exhibited a molecular ion peak at *m/e* 588. Then XXV were converted into the quaternary ammonium salts (XXIX), which were catalytically hydrogenated in the presence of platinum dioxide to give the N-methylated compounds (XXX). On quaternization, XXa also gave the compound (XXXI).

These synthetic methods for 2-aryl-4,5,6,7-tetrahydrofuro(or-1H-pyrrolo)[3,2-*c*]pyridine derivatives (XX, XXV) *via* 3-phenacyl-4-piperidone derivatives (XXII) are convenient ones.

Grethe, *et al.*[10] reported that rearrangement of 2-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinolinium salt derivatives (E) with phenyllithium gave 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline derivatives (F) as a major product and 1-(*o*-tolyl)-2-methyl derivatives (G) as a minor product. The former resulted in the Stevens rearrangement and the latter the Sommelet rearrangement. So the rearrangement of the quaternary ammonium salts (XXXI, XXIXb) with phenyllithium in ether was studied. Treatment of XXXI with phenyllithium gave two products (XXXII and XXXIII) in 14.2 and 0.7% yields, respectively. The NMR spectrum of XXXII showed a benzylic proton (C_4–H) in the α position to the nitrogen atom at δ 4.39 as a singlet, and two methyl signals at δ 2.28 and 2.41. The IR spectrum of XXXII showed a strong band at 755 cm^{-1} indicating the presence of the *ortho*-disubstituted phenyl group. Accordingly, XXXII must be 2-phenyl-4-(*o*-tolyl)-5-methyl-4,5,6,7-tetrahydrofuro[3,2-

7) C. Paal, *Chem. Ber.*, **17**, 2756 (1884); C. Paal, *Chem. Ber.*, **18**, 58 (1885).
8) C. Paal, *Chem. Ber.*, **18**, 367 (1885); L. Knorr, *Ann.*, **236**, 290 (1886); M. A. Volodina, V. G. Mishina, E. A. Pronina, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **33**, 3295 (1963) [*C.A.*, **60**, 5437 (1964)].
9) S. Danishefsky and R. Cavanaugh, *J. Org. Chem.*, **33**, 2959 (1968).
10) G. Grethe, H. L. Lee, and M. R. Uskokovic, *Tetrahedron Lett.*, **1969**, 1937.

c]pyridine. On the other hand, the NMR spectrum of XXXIII exhibited the signal of a proton (C_4–H), attached to the carbon atom bearing a benzyl group, at δ 3.76 as a quartet. Therefore, XXXIII was considered to be 2-phenyl-4-benzyl-5-methyl-4,5,6,7-tetrahydrofuro-[3,2-*c*]pyridine. The same treatment of XXIXb gave a product (XXXIV) presumed to be 1,2-diphenyl-4-(*o*-tolyl)-5-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine. The NMR spectrum of XXXIV showed a benzylic proton (C_4–H) in the α position to the nitrogen atom, at δ 4.46 as a singlet and two methyl signals at δ 2.25 and 2.45. In both cases the main products were the Sommelet rearrangement ones, contrary to Grethe's findings.[10]

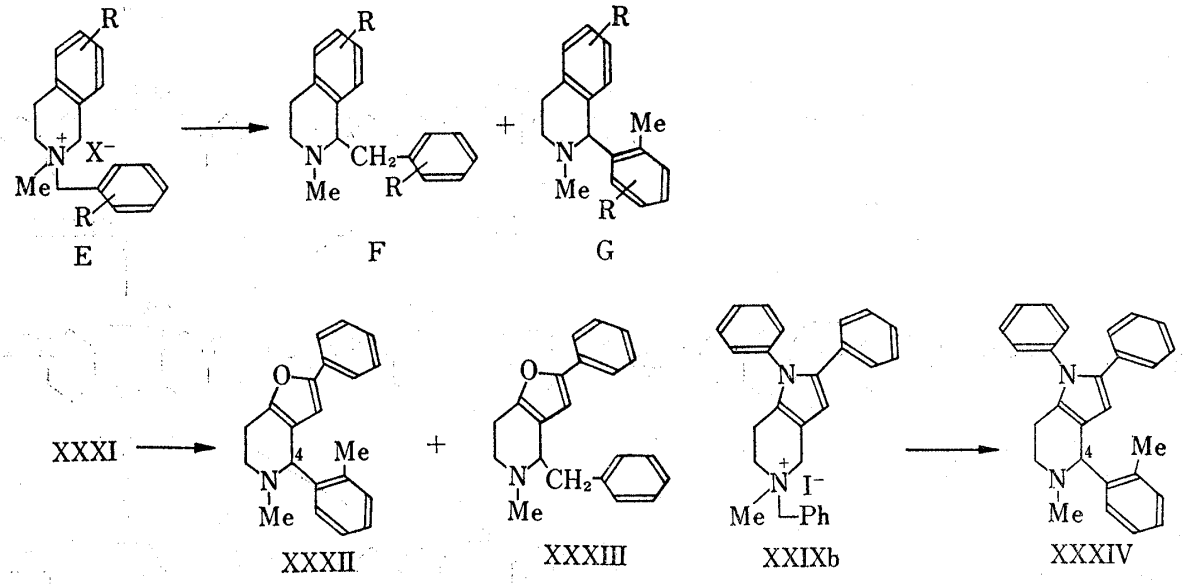


Chart 5

Colonge, *et al.*[11] reported that heating 2-hydroxymethylcyclohexanone (H) with aqueous oxalic acid afforded decahydro-2H,5aH-4a,9a-epoxydibenz[*b*,*f*]oxepin-5a-ol (I),[12] which was formed by the Diels-Alder type reaction between two molecules of an intermediate, 2-methylenecyclohexanone. In order to examine whether the same dimerization occurs in the case of the piperidine analogus of H, 1-benzyl-3-hydroxymethyl-4-piperidone (K), when heated with 20% hydrochloric acid for 8 hours, XVI gave colorless needles (XXXV) of mp 161—163° in 14% yield and XVII also afforded XXXV in 25% yield. The mass spectral and the elemental analytical data on XXXV established the molecular formula, $C_{26}H_{32}N_2O_3$. The IR spectrum of XXXV showed a faint carbonyl band at 1708 cm^{-1} and a hydroxyl band at 3395 cm^{-1} in chloroform solution, and showed a weak hydroxyl band at 3390 cm^{-1} and no carbonyl band in potassium bromide disk. Compound (XXXV) gave a dioxime (XXXVI) suggesting the presence of two carbonyl groups. The NMR spectrum of XXXVI taken in d_6-dimethyl sulfoxide (DMSO-d_6) solution exhibited the signal of a tertiary hydroxyl proton at δ 4.30 along with the signals of two hydroxyl protons of oxime groups. Reduction of XXXV with sodium borohydride afforded a triol (XXXVII), whose NMR spectrum in DMSO-d_6 showed the signals of two secondary hydroxyl protons. Treatment of XXXV with hydrazine hydrate gave a compound (XXXVIII) which was deduced to be a diaza-octadiene derivative from results of the elemental analysis and of the mass spectrum (M^+, *m*/*e* 416). These chemical properties of XXXV were similar to those of I,[12] but attempts to convert XXXV into the isomer (L) resulted in the recovery of XXXV in spite of applying the condition[13]

11) J. Colonge, J. Dreux, and H. Delplace, *Bull. Soc. Chim. France*, **1956**, 1635.
12) C. Mannich, *Chem. Ber.*, **74**, 557; H.J. Roth and G. Dvorak, *Arch. Pharm.*, **296**, 510 (1963).
13) C. Mannich, *Chem. Ber.*, **74**, 565 (1941).

of the rearrangement of I to J. Thus a tentative structure for XXXV which satisfies the experimental results described above is 2,8-dibenzyldecahydro-2H,5aH-4a,9a-epoxydipyrido-[4,3-*b*: 3′,4′-*f*]oxepin-5a-ol of new skeleton (XXXVa) which preferably exists and it might be interconverted into the tautomers, XXXVb or XXXVc, in a solvent.

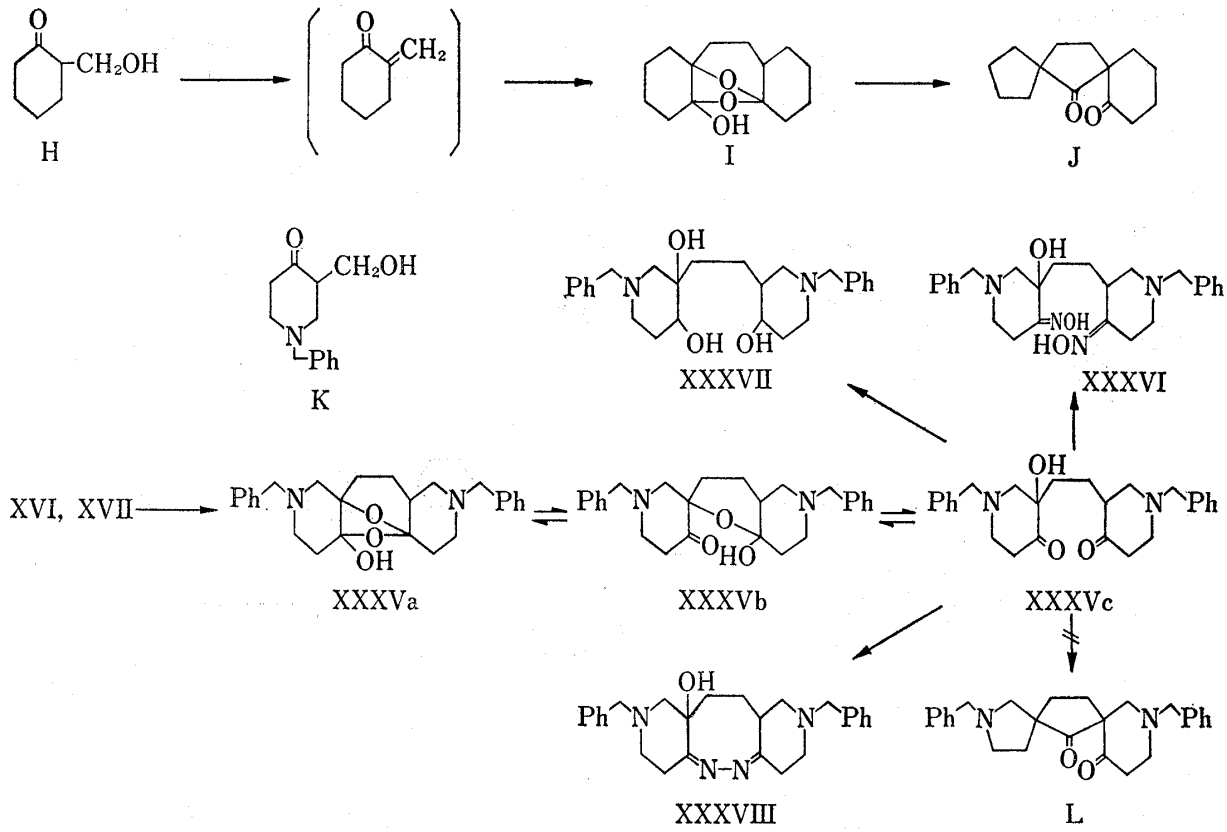


Chart 6

Table I. Comparative CNS Effects of VIg, XId and Reference Compounds

	ED_{50}, mg/kg *p.o.*		
	Anti-apomorphine effect (rat)	Inhibition of locomotor activity (mouse)	Anti-writhing effect (acetic acid) (mouse)
VIg	18.0(12.7 —20.6)[a]	6.98(3.78—12.9)	4.12(2.17—10.2)
XId	0.84(0.65— 1.10)	1.50(0.77— 2.91)	1.02(0.54— 1.93)
Chlorpromazine	2.50(1.70— 3.10)	6.54(3.70—11.6)	1.43(0.53— 3.89)
Haloperidol	0.11(0.07— 0.14)	0.50(0.33— 0.77)	1.59(1.41— 1.79)

a) 95% confidence limits.

Pharmacology

All compounds prepared in this study were evaluated pharmacologically. Most of VI and XI showed CNS depressing activities. Among them, XId exhibited the most potent activities which were comparable to those of A or B, and VId showed relatively moderate activities. Some of activities of the typical compounds, VIg and XId, are shown in Table I. On the other hand, XXXb showed marked antidepressant activities. However, XIX did not exhibit any activity. Further pharmacological studies with XId and XXXb would be reported elsewhere in near future.

Experimental[14]

Ethyl 1-Benzyl-3-piperidineacetate (II)——To a mixture of 14 g of I[3] and 20 g of triethylamine in 70 ml of benzene was added 10.4 g of benzyl chloride under ice-cooling. After being allowed to stand overnight at room temperature, the precipitates were removed by filtration and the filtrate was concentrated. The residue was converted into the hydrochloride by ethanolic HCl and recrystallized from EtOH to give 16 g (66%) of II·HCl, mp 144—145. *Anal.* Calcd. for $C_{16}H_{23}NO_2 \cdot HCl$: C, 64.52; H, 8.12; Cl, 11.91; N, 4.70. Found: C, 64.19; H, 8.33; Cl, 12.25; N, 4.51.

1-Benzyl-3-(*p*-fluorophenacyl)piperidine (VIe)——A solution of 6.0 g of II in 40 ml of 20% HCl was heated under reflux for 4 hr, and then concentrated under reduced pressure. To the residue was added 40 ml of acetone. After being stirred, the solution was concentrated to dryness under reduced pressure. The residual powder (III) was used for the next step without any purification. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O). To the crude III was added 40 ml of $CHCl_3$ and to the resulting suspension was added 21 ml of thionyl chloride under ice-cooling. The mixture was stirred at 38—40° for 3 hr and then concentrated under reduced pressure at room temperature. The syrupy residue (IV) was used for the next step without any purification. IR ν_{max}^{film} cm^{-1}: 1795 (C=O). To the crude IV was added 25 ml of fluorobenzene and then 5.5 g of pulverized anhydrous aluminum chloride under ice-cooling. The mixture was stirred under ice-cooling for 30 min and then heated on a water-bath for 30 min. After being cooled, the reaction mixture was poured into dil. HCl. The aqueous layer was washed with ether, made alkaline with NH_4OH and extracted with $CHCl_3$. The extract was dried over K_2CO_3 and concentrated. The residue was recrystallized from acetone to give 3.5 g (49%) of VIe, mp 113—114. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O).

1-Substituted-3-phenacylpiperidine Derivatives (VIa—f)——To a suspension of magnesium (0.1 mol) in 40 ml of dry ether was added dropwise aryl bromide (0.1 mol) at a rate to maintain the reflux under stirring, and then the reaction mixture was heated under reflux for 1 hr. After the additional addition of 80 ml of dry ether to the mixture, a solution of 1-substituted-3-piperidineacetonitrile[4] (V) (0.07 mol) in 30 ml of dry ether was added and then the mixture was heated under reflux for 20 hr. A dil. HCl was added to the reaction mixture under cooling and the mixture was stirred for a while. The dil. HCl layer was separated, heated at 70° for 1 hr, made alkaline with NaOH and extracted with ether. The extract was dried over K_2CO_3 and concentrated. The crude product, if an oil, was purified by chromatography on silica gel with $CHCl_3$–MeOH (60: 1), or converted into appropriate salt; if solid, it was refined by recrystallization. Results are summarized in Table II.

1-Ethoxycarbonyl-3-(*p*-fluorophenacyl)piperidine (VII)——To a solution of 11g of VIe in 100 ml of benzene was added 6.3 g of ethyl chloroformate at 60—70° under stirring and then the mixture was heated under reflux for 3 hr. After being cooled, the benzene solution was washed with dil. HCl and water, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (80 g). Elution with $CHCl_3$ gave 8 g (77%) of a colorless oil. *Anal.* Calcd. for $C_{16}H_{20}FNO_3$: C, 65.51; H, 6.87; F, 6.48; N, 4.78. Found: C, 65.49; H, 6.76; F, 6.16; N, 4.71. IR ν_{max}^{film} cm^{-1}: 1690 (C=O).

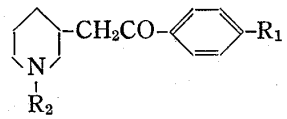
3-(*p*-Fluorophenacyl)piperidine (VIII)——A suspension of 12 g of VII in 70 ml of 20% HCl was heated under reflux for 20 hr. After being cooled, the solution was made alkaline with NaOH and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (80 g). Elution with $CHCl_3$–MeOH (7: 1) gave 6 g (66%) of a colorless oil. Picrate: mp 184—186° (from EtOH). *Anal.* Calcd. for $C_{13}H_{16}FNO \cdot C_6H_3N_3O_7$: C, 50.67; H, 4.25; N, 12.44. Found: C, 50.99; H, 4.00; N, 12.26.

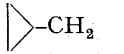
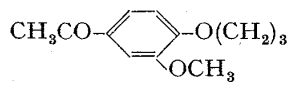
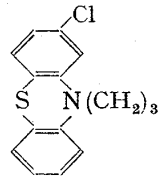
1-Substituted-3-(*p*-fluorophenacyl)piperidines (VIg—n)——A mixture of VIII (0.01 mol), an appropriate halide (0.012 mol) and triethylamine (0.012 mol) in 50 ml of xylene was heated under reflux for 3—20 hr. After being cooled, the reaction mixture was washed with water, dried over K_2CO_3 and concentrated under reduced pressure. The crude product, if an oil, was purified by chromatography on silica gel with $CHCl_3$–MeOH (50: 1) in VIj, k and with $CHCl_3$ in VIn, or converted into salt; if solid, it was purified by recrystallization. Results are shown in Table II.

1-Benzyl-3-pyrrolidineacetonitrile (X)——A mixture of 6.4 g of 1-benzyl-3-chloromethylpyrrolidine[15] (IX) and 4.2 g of potassium cyanide in 40 ml of dimethyl sulfoxide was heated at 130—140° for 10 hr. After being concentrated, to the residue was added 5% NaOH and the resulting mixture was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and concentrated. The residue was distilled under reduced pressure to give 5.1 g (83%) of a colorless oil (X), bp 160—164° (4 mmHg). *Anal.* Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.75; H, 7.85; N, 14.11. IR ν_{max}^{film} cm^{-1}: 2250 (C≡N).

14) All melting points are uncorrected. NMR spectra were taken in $CDCl_3$ or DMSO-d_6 solution with Varian A-60 or Varian HA-100 spectrometer using TMS as an internal standard and IR spectra with a Hitachi EPI-S2 spectrometer. Mass spectra were taken with a Hitachi RMU-6L spectrometer with a heated direct inlet system.

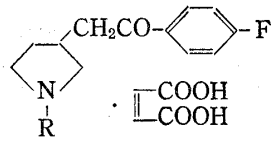
15) YAO-HUA WU and R.F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).

TABLE II. 1-Substituted-3-phenacylpiperidines 

Compd. No.	R_1	R_2	mp (°C)	Yield (%)	Recryst. solvent	Formula (salt)	Analysis (%) Calcd. (Found) C	H	Cl	F	N
VIa	H	CH_3	130—132	29	Acetone +EtOH	$C_{14}H_{19}NO \cdot C_6H_3N_3O_7$ [a]	53.81 (53.48)	4.97 (4.85)			12.55 (12 44)
VIb	Cl	CH_3	175—176	58	Acetone +EtOH	$C_{14}H_{18}ClNO \cdot HCl$	58.34 (58.36)	6.65 (6.34)	24.86 (24.31)		4.86 (4.59)
VIc	Cl	$C_6H_5CH_2$	81— 82	66	Ether+ petr. ether	$C_{20}H_{22}ClNO$	73.27 (73.31)	6.75 (6.69)	10.82 (10.90)		4.27 (4.22)
VId	F	CH_3	133—135	32	Acetone +EtOH	$C_{14}H_{18}FNO \cdot C_6H_3N_3O_7$ [a]	51.73 (51.41)	4.56 (4.61)			12.06 (12.01)
VIe	F	$C_6H_5CH_2$	113—114	77	Ether+ petr. ether	$C_{20}H_{22}FNO$	77.14 (77.06)	7.12 (7.01)		6.10 (5.88)	4.50 (4.53)
VIf	F	$C_6H_5(CH_2)_2$		44		$C_{21}H_{24}FNO$	77.51 (77.51)	7.43 (7.12)		5.84 (5.47)	4.30 (4.75)
VIg	F	C_2H_5	104	72	Acetone	$C_{15}H_{20}FNO \cdot C_4H_4O_4$ [b]	62.45 (62.53)	6.62 (6.48)		5.20 (5.16)	3.83 (3.69)
VIh	F	$CH_2=CHCH_2$	132—133	68	Acetone +EtOH	$C_{16}H_{20}FNO \cdot C_6H_3N_3O_7$ [a]	53.88 (53.93)	4.73 (4.62)			11.42 (11.17)
VIi	F	$HO(CH_2)_2$	120—122	38	Acetone +EtOH	$C_{15}H_{20}FNO_2 \cdot C_6H_3N_3O_7$ [a]	51.01 (51.22)	4.69 (4.61)			11.33 (11.36)
VIj	F			45		$C_{17}H_{22}FNO$	74.15 (73.85)	8.05 (8.37)			5.09 (4.97)
VIk	F	$CH_3(CH_2)_3$		64		$C_{17}H_{24}FNO$	73.61 (73.36)	8.72 (8.92)		6.85 (6.53)	5.05 (5.62)
VIl	F	p-F-$C_6H_4CO(CH_2)_3$	128—130	44	iso-PrOH +ether	$C_{23}H_{25}F_2NO_2 \cdot HCl$	65.48 (65.12)	6.21 (5.92)	8.40 (8.21)	9.01 (8.91)	3.32 (3.27)
VIm	F		154—155	47	Acetone +EtOH	$C_{25}H_{30}FNO_4 \cdot C_6H_3N_3O_7$ [a]	56.71 (56.45)	5.07 (5.01)			8.53 (8.36)
VIn	F			49		$C_{28}H_{28}ClFN_2OS$	67.93 (67.99)	5.70 (5.99)	7.16 (7.45)	3.84 (3.85)	5.66 (5.36)

a) Picric acid. b) Maleic acid.

Table III. 1-Substituted-3-(*p*-fluorophenacyl)pyrrolidines



Compd. No.	R	mp (°C)	Yield (%)	Recryst solvent.	Formula (salt)	Analysis (%) Calcd. (Found) C	H	F	N
XIa	$C_6H_5CH_2$	137—138	69	Ether +EtOH	$C_{19}H_{20}FNO \cdot C_4H_4O_4$	66.81 (66.93)	5.85 (5.98)	4.60 (4.42)	3.39 (3.40)
XIb	CH_3	138—139	45	Benzene +ether	$C_{13}H_{16}FNO \cdot C_4H_4O_4$	60.52 (60.37)	5.98 (6.13)	5.63 (5.43)	4.15 (4.18)
XIc	C_2H_5	133—134	58	AcOEt	$C_{14}H_{18}FNO \cdot C_4H_4O_4$	61.52 (61.82)	6.31 (6.39)	5.41 (5.16)	3.99 (4.02)
XId	p-F-$C_6H_4CO(CH_2)_3$	120—123	34	AcOEt	$C_{22}H_{23}F_2NO_2 \cdot C_4H_4O_4$	64.05 (64.08)	5.58 (5.28)	7.80 (7.52)	2.87 (2.98)

1-Benzyl-3-(*p*-fluorophenacyl)pyrrolidine (XIa)——XIa was prepared from X and *p*-fluorophenacylmagnesium bromide by the same procedure as described for the preparation of VIa—f.

1-Ethoxycarbonyl-3-(*p*-fluorophenacyl)pyrrolidine (XII)——XII was prepared from XIa and ethyl chloroformate by the same procedure as described for the preparation of VII. The crude product was purified by chromatography on silica gel with benzene–ether (7: 3). XII was a colorless oil. Yield, 60%. *Anal.* Calcd. for $C_{15}H_{18}FNO_3$: C, 64.50; H, 6.50; F, 6.80; N, 5.02. Found: C, 64.62; H, 6.35; F, 6.61; N, 4.88. IR ν_{max}^{film} cm^{-1}: 1695 (C=O).

1-Substituted-3-(*p*-fluorophenacyl)pyrrolidines (XIb—d)——A mixture of XII (0.02 mol) in 40 ml of 20% HCl was refluxed for 15 hr under stirring. After being cooled, the solution was washed with ether, made alkaline with NaOH and extracted with $CHCl_3$. The extract was dried over K_2CO_3 and concentrated to give 4.2 g of crude XIII as an oily product, which was used for the next step without purification. A mixture of (*p*-fluorobenzoyl)propyl chloride (methyl benzenesulfonate or ethyl iodide, 0.02 mol), XIII (0.015 mol) and triethylamine (0.02 mol) in 70 ml of xylene was heated at 40—140° for 4—8 hr. After being cooled, the reaction mixture was washed with water, dried over K_2CO_3 and concentrated. The residue was converted into the maleate and recrystallized from a suitable solvent. Results are summarized in Table III.

8-Benzyl-1,4-dioxa-8-azaspiro[4,5]decane-6-carboxylic Acid Methyl Ester (XV)——A solution of 26 g of XIV in 52 ml of ethyleneglycol was saturated with dry HCl under ice-cooling. The solution was warmed at 70° for 2 hr and then allowed to stand at room temperature overnight. The mixture was poured into ice-water, made alkaline with Na_2CO_3 and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was distilled under reduced pressure to give 20 g (65%) of a colorless oil (XV), bp 175—181 (1 mmHg). *Anal.* Calcd. for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.66; H, 7.01; N, 5.08. IR ν_{max}^{film} cm^{-1}: 1730 (C=O).

6-Chloromethyl-8-benzyl-1,4-dioxa-8-azaspiro[4,5]decane (XVII)——A solution of 20 g of XV in 50 ml of dry ether was added to a suspension of 4 g of lithium aluminum hydride in 350 ml of dry ether at such a rate as to maintain gentle reflux. After the addition, the solution was heated under reflux for 3 hr, cooled and treated with ethyl acetate followed by 10% H_2SO_4. The acid layer was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. The extract was dried over K_2CO_3 and concentrated to give 15 g (83%) of crude XVI as a colorless oil (which was used for the next step without further purification). IR ν_{max}^{film} cm^{-1}: 3400 (OH). MS *m/e*: 263 (M^+). A solution of 15 g of XVI in 50 ml of $CHCl_3$ was saturated with dry HCl under ice-cooling and then to the solution was added dropwise 9 g of thionyl chloride. The mixture was heated under reflux for 1 hr. After evaporation of $CHCl_3$ and an excess of thionyl chloride, the residue was dissolved in water, made alkaline with Na_2CO_3 and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was distilled under reduced pressure to give 11 g (69%) of a colorless oil (XVII), bp 185° (2 mmHg). *Anal.* Calcd. for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; Cl, 12.58; N, 4.97. Found: C, 64.29; H, 7.41; Cl, 12.01; N, 5.01.

8-Benzyl-1,4-dioxa-8-azaspiro[4,5]decane-6-acetonitrile (XVIII)——A solution of 10 g of XVII and 5.3 g of sodium cyanide in 130 ml of dry dimethyl sulfoxide was heated at 130° for 10 hr under stirring and concentrated. The residue was dissolved in dil. HCl. The acidic solution was washed with ether, made alkaline with Na_2CO_3 and extracted with ether. The extract was dried over K_2CO_3 and concentrated. The residue was distilled under reduced pressure to give 6.8 g (71%) of a colorless oil, bp 169° (1.5 mmHg).

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.81; H, 7.66; N, 10.13. IR ν_{max}^{film} cm^{-1}: 2250 (C≡N).

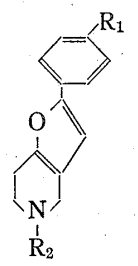
6-(*p*-Fluorophenacyl)-8-benzyl-1,4-dioxa-8-azaspiro[4,5]decane (XIX)——XIX was prepared from XVIII and *p*-fluorophenylmagnesium bromide by the same procedure as described for the preparation of VIa—f. The crude oily product was converted into the picrate and recrystallized from acetone+EtOH. XIX picrate: mp 158—160°. Yield, 38%. *Anal.* Calcd. for $C_{22}H_{24}FNO_3 \cdot C_6H_3N_3O_7$: C, 56.19; H, 4.55; N, 9.36. Found: C, 55.94; H, 4.53; N, 9.18. Free base, IR ν_{max}^{film} cm^{-1}: 1680 (C=O).

Treatment of XIX with 20% HCl——A solution of 1 g of XIX in 20 ml of 20% HCl was heated under reflux for 3 hr. After being cooled, the solution was 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 0.35 g (42%) of XXb. NMR (δ in $CDCl_3$): 6.44 (s, 1H, C_3–H).

1-Benzyl-3-phenacyl(or *p*-fluorophenacyl)-4-piperidone (XXII)——To a stirred, ice-cooled solution of 26 g of 1-benzyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine (XXI)[9] in 130 ml of benzene was added dropwise a solution of 21 g of phenacyl bromide in 70 ml of benzene during 1 hr and the reaction mixture was stirred at room temperature overnight. To the mixture was added water and then stirring was continued for 1 hr. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The residual solid was recrystallized from ether to give 18 g (55%) of XXIIa, mp 109—111°. *Anal.* Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.01; H, 6.63; N, 4.72. IR ν_{max}^{KBr} cm^{-1}: 1727, 1685 (C=O). XXIIb was prepared by the similar procedure. XXIIb maleate: mp 171—172° (dec.). Yield, 32%. *Anal.* Calcd. for $C_{20}H_{20}FNO_2 \cdot C_4H_4O_4$: C, 65.30; H, 5.48; F, 4.30; N, 3.17. Found: C, 65.07; H, 5.35; F, 4.11; N, 3.16. IR ν_{max}^{KBr} cm^{-1}: 1730, 1680 (C=O).

Preparation of XX from XXII——A suspension of XXII in conc. HCl was heated under reflux for 3 hr. After being cooled, the solution was made alkaline with NaOH and extracted with ether. The extract was dried over K_2CO_3 and concentrated. The residue was recrystallized from a suitable solvent. Results are summarized in Table IV.

TABLE IV.



Compd. No.	R_1	R_2	mp (°C)	Yield (%)	Recryst. solvent	Formula (salt)	Analysis (%) Calcd. (Found) C	H	Cl	F	N
XXa	H	$C_6H_5CH_2$	98— 99	85	Ether+ petr. ether	$C_{20}H_{19}NO$	83.01 (82.96)	6.62 (6.81)			4.84 (4.54)
XXb	F	$C_6H_5CH_2$	107—108	73	Ether	$C_{20}H_{18}FNO$	78.15 (78.40)	5.90 (6.07)		6.18 (5.91)	4.56 (4.49)
XXIIIa	H	H	79— 81	70	Ether+ petr. ether	$C_{13}H_{13}NO$	78.36 (78.64)	6.58 (6.72)			7.03 (7.02)
XXIIIb	F	H	75— 76	57	Acetone+ petr. ether	$C_{13}H_{12}FNO$	71.84 (71.62)	5.57 (5.36)		8.75 (8.50)	6.45 (6.60)
XXIVa	H	*p*-F-$C_6H_4CO(CH_2)_3$	253—254	36	dil. EtOH	$C_{23}H_{22}FNO_2 \cdot HCl$	69.26 (69.10)	5.56 (5.82)	8.89 (8.92)	4.76 (4.59)	3.51 (3.51)
XXIVb	F	*p*-F-$C_6H_4CO(CH_2)_3$	243—245	40	MeOH	$C_{23}H_{21}F_2NO_2 \cdot HCl$	66.11 (66.14)	5.31 (5.26)	8.48 (8.62)	9.09 (9.28)	3.35 (3.36)

2-Phenyl(or *p*-Fluorophenyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (XXIII)——Into 150 ml of EtOH were added XX (0.04 mol) and 2 g of 5% palladium-carbon, and the mixture was submitted to catalytic hydrogenation at ordinary temperature and pressure. After the theoretical amount of H_2 was absorbed, the catalyst and the solvent were removed. The residue was recrystallized from a suitable solvent.

2-Phenyl(or *p*-Fluorophenyl)-5-(*p*-fluorobenzoyl)propyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (XXIV)——A mixture of XXIII (0.01 mol), (*p*-fluorobenzoyl)propyl chloride (0.012 mol) and triethylamine (0.012 mol) in 40 ml of xylene was heated under reflux for 20 hr. After being cooled, to the reaction mixture was added dil. HCl, the resulting precipitates were collected and recrystallized from a suitable solvent. Results are shown in Table IV.

1-Substituted-2-phenyl-5-benzyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine (XXV)——A solution of XXIIa (0.02 mol) and an appropriate amine (0.026 mol) in 60 ml of AcOH was heated under reflux for 40 min. After being allowed to stand at room temperature overnight, the mixture was poured into water. The precipitated crystals were collected and recrystallized from a suitable solvent. Results are shown in Table V. XXVa, NMR (δ in $CDCl_3$): 6.21 (s, 1H, C_3–H). XXVb, NMR (δ in $CDCl_3$): 6.26 (s, 1H, C_3–H).

1,2-Diphenyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine (XXVI)——XXVI was prepared from XXVb by the same procedure as described for the preparation of XXIII.

1,2-Diphenyl-5-(*p*-fluorobenzoyl)propyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine (XXVII)——A mixture of 2 g of (*p*-fluorobenzoyl)propyl chloride, 2.8 g of XXVI and 2 g of triethylamine in 70 ml of xylene was heated uder reflux for 8 hr. After being cooled, the reaction mixture was extracted with dil. HCl, the dil. HCl layer was made alkaline with NH_4OH and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from ether+hexane.

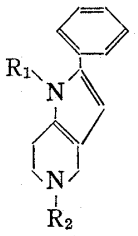
The Reaction of XXVI with Formic Acid–Formalin——A solution of 1.3 g of XXVI in a mixture of 10 ml of 85% formic acid and 10 ml of formalin was heated under reflux for 30 min. After being cooled, the mixture was made alkaline with NH_4OH and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was triturated with ether, and the solid was recrystallized from EtOH to give 0.4 g (29%) of XXVIII, mp 250—255°. *Anal.* Calcd. for $C_{41}H_{40}N_4$: C, 83.64; H, 6.85; N, 9.52. Found: C, 83.43; H, 6.88; N, 9.63. NMR (δ in $CDCl_3$): 3.81 (s, 2H, >–CH_2–⟨), 2.93 (s, 4H, >N–CH_2–⟨), 2.30 (s, 6H, >N–CH_3). MS *m/e*: 588 (M^+).

1-Methyl(or Phenyl)-2-phenyl-5-benzyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine Methiodide (XXIX)——A mixture of XXV and an excess of methyl iodide in acetone was heated under reflux for 4 hr. After being cooled, resulting precipitates were colleted and recrystallized from acetone. Yields were quantitative. XXIXa, mp 222—224°. *Anal.* Calcd. for $C_{21}H_{22}N_2 \cdot CH_3I$: C, 59.46; H, 5.67; I, 28.56; N, 6.30. Found: C, 59.18; H, 5.59; I, 28.69; N, 6.05. XXIXb, mp 226—228°. *Anal.* Calcd. for $C_{26}H_{24}N_2 \cdot CH_3I$: C, 64.04; H, 5.37; I, 25.06; N, 5.53. Found: C, 63.97; H, 5.28; I, 25.35; N, 5.64.

1-Methyl(or Phenyl)-2-phenyl-5-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine (XXX)——A mixture of XXIX (0.01 mol) and 0.1 g of PtO_2 in 50 ml of EtOH was submitted to catalytic hydrogenation at 70° under ordinary pressure. After the theoretical amount of H_2 was adsorbed, the catalyst and the solvent were removed. To the residue was added dil. NH_4OH and the solution was extracted with $CHCl_3$. The extract was dried over K_2CO_3 and concentrated. The residue was recrystallized from acetone.

2-Phenyl-5-benzyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine Methiodide (XXXI)——A solution of 3 g of XXa and an excess of methyl iodide in 30 ml of AcOEt was heated under reflux for 3 hr, the separated quaternary ammonium salt was collected and recrystallized from EtOH to give 3.6 g (80%) of XXXI, mp 205—206°. *Anal.* Calcd. for $C_{20}H_{19}NO \cdot CH_3I$: C, 58.48; H, 5.14; I, 29.42; N, 3.25. Found: C, 58.50; H, 5.15; I, 29.32: N, 3.21.

Table V.



Compd. No.	R_1	R_2	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	F	N
XXVa	CH_3	$C_6H_5CH_2$	122—123	47	Acetone	$C_{15}H_{18}N_2$	79.60 (79.37)	8.02 (7.97)		12.38 (12.36)
XXVb	C_6H_5	$C_6H_5CH_2$	160—162	71	Acetone	$C_{26}H_{24}N_2$	85.68 (85.64)	6.64 (6.35)		7.69 (7.63)
XXVI	C_6H_5	H	142—143.5	71	Acetone	$C_{19}H_{18}N_2$	83.18 (83.30)	6.61 (6.40)		10.21 (10.19)
XXVII	C_6H_5	*p*-F-$C_6H_4CO(CH_2)_3$	101—102	35	Ether+ *n*-hexane	$C_{29}H_{27}FN_2O$	79.43 (79.47)	6.21 (6.37)	4.32 (4.52)	6.39 (6.29)
XXXa	CH_3	CH_3	122—123	43	Acetone	$C_{15}H_{18}N_2$	79.60 (79.37)	8.02 (8.01)		12.38 (12.36)
XXXb	C_6H_5	CH_3	96—97	75	Acetone	$C_{20}H_{20}N_2$	83.29 (83.14)	6.99 (6.97)		9.71 (9.55)

The Rearrangement of 2-Phenyl-5-benzyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine Methiodide (XXXI) with Phenyllithium——The phenyllithium reagent was prepared from 5.5 g of bromobenzene and 0.51 g of metallic lithium in 70 ml of dry ether. To the ethereal phenyllithium was added 5.6 g of XXXI rapidly under vigorous stirring. The mixture was heated under nitrogen for 1.5 hr after the exothermic reaction had ceased. After being cooled, ice-water was added to the reaction mixture to decompose the excess of reagent, and the basic compound was extracted with dil. HCl. The acidic solution was made alkaline with NH_4OH and extracted with ether. The extract was dried over K_2CO_3 and concentrated. The residue was chromatographed on silica gel (70 g) and eluted with ether. The product obtained from the earlier fractions was converted to the maleate, which was recrystallized from acetone to give 0.77 g (14%) of XXXII maleate, mp 178—179°. The product from the later fractions was also converted to the maleate, which was recrystallized from AcOEt to give 40 mg (0.74%) of XXXIII maleate, mp 155—156°. XXXII maleate. *Anal.* Calcd. for $C_{21}H_{21}NO \cdot C_4H_4O_4$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.71; H, 6.12; N, 3.29. Free base, NMR (δ in $CDCl_3$): 4.39 (s, 1H, C_4–H), 2.28, 2.41 (s, each 3H, CH_3). XXXIII maleate. *Anal.* Calcd. for $C_{21}H_{21}NO \cdot C_4H_4O_4$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.46; H, 5.93; N, 3.41. Free base, NMR (δ in $CDCl_3$): 3.76 (d–d, J=5 and 7 Hz, C_4–H).

The Rearrangement of 1,2-Diphenyl-5-benzyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine Methiodide (XXIXb) with Phenyllithium——To a stirred solution of phenyllithium prepared from 5.5 g of bromobenzene and 0.51 g of metallic lithium in 80 ml of dry ether, 6.5 g of XXIXb was added rapidly under nitrogen. The mixture was worked up as described for the rearrangement of XXXI to yield 4.5 g of a crude oily base, which was chromatographed on basic alumina (80 g) and eluted with hexane. The product obtained from earlier fractions was converted to the picrate, which was recrystallized from acetone+EtOH to give 2.89 g (37%) of XXXIV picrate, mp 163—165°. *Anal.* Calcd. for $C_{27}H_{26}N_2 \cdot C_6H_3N_3O_7$: C, 65.23; H, 4.81; N, 11.53. Found: C, 65.06; H, 4.58; N, 11.20. Free base, NMR (δ in $CDCl_3$): 4.46 (s, 1H, C_4–H), 2.25, 2.45 (s, each 3H, CH_3).

Treatment of XVI with 20% HCl——A solution of 3 g of XVI in 30 ml of 20% HCl was heated under reflux for 8 hr. After being cooled, the solution was made alkaline with NH_4OH and extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated. To the residue was added ether, the precipitates were collected and recrystallized from acetone to give 0.34 g (14%) of XXXV, mp 161—163°. *Anal.* Calcd. for $C_{26}H_{32}N_2O_3$: C, 74.25; H, 7.67; N, 6.66. Found: C, 74.44; H, 7.84; N, 6.45. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1708 (C=O), 3395 (OH). IR ν_{max}^{KBr} cm^{-1}: 3390 (OH). MS *m/e*: 420 (M^+).

Treatment of XVII with 20% HCl——The same treatment of XVII with 20% HCl gave XXXV in 25% yield.

Reaction of XXXV with Hydroxylamine——A solution of 0.5 g of XXXV, 0.33 g of hydroxylamine hydrochloride and 0.19 g of NaOH in a mixture of 10 ml of EtOH and 4 ml of water was heated on a water-bath for 3 hr. After the reaction mixture was concentrated, the residue was made alkaline with NH_4OH and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from acetone+EtOH to give 0.16 g (30%) of dioxime (XXXVI), mp 193—196°. *Anal.* Calcd. for $C_{26}H_{34}N_4O_3$: C, 69.31; H, 7.61; N, 12.43. Found: C, 69.50; H, 7.53; N, 12.24. IR ν_{max}^{KBr} cm^{-1}: 3490, 3220 (OH). NMR (δ in DMSO-d_6): 4.30 (s, 1H, –C–OH, disappeared by treatment with D_2O), 10.25, 10.58 (s, each 1H, >C=NOH, disappeared by treatment with D_2O), 3.28 (s, 4H, >N–CH_2–Ar), 7.28 (s, 10H, arom. H). MS *m/e*: 450 (M^+).

Reduction of XXXV with Sodium Borohydride——To a solution of 0.5 g of XXXV in a mixture of 40 ml of EtOH and 30 ml of water was added 0.25 g of sodium borohydride, the resulting mixture was heated under reflux for 1 hr and then allowed to stand at room temperature overnight. The mixture was concentrated and the residue was extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from AcOEt+hexane to give 0.13 g (26%) of the triol (XXXVII), mp 134—135°. *Anal.* Calcd. for $C_{26}H_{36}N_2O_3$: C, 73.55; H, 8.55; N, 6.60. Found: C, 73.30; H, 8.36; N, 6.62. IR ν_{max}^{KBr} cm^{-1}: 3330, 3400 (OH). NMR (δ in DMSO-d_6): 3.77 (d, J=2 Hz, 1H, >CH–OH, disappeared by treatment with D_2O), 4.37 (d, J=2 Hz, 1H, >CH–OH, disappeared by treatment with D_2O). MS *m/e*: 424 (M^+).

Reaction of XXXV with Hydrazine Hydrate——A solution of 2 g of XXXV and 6 ml of hydrazine hydrate in a mixture of 20 ml of AcOH and 30 ml of EtOH was heated under reflux for 20 min. The mixture was poured into water. The aqueous solution was made alkaline with NH_4OH and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (30 g). Elution with ether gave crystalline mass which was recrystallized from ether to give 0.18 g (9%) of XXXVIII, mp 134—134.5°. *Anal.* Calcd. for $C_{26}H_{32}N_4O$: C, 74.96; H, 7.74; N, 13.45. Found: C, 74.79; H, 7.74; N, 13.44. MS *m/e*: 416 (M^+).

Treatment of XXXV with 20% H_2SO_4[13]——A solution of 1 g of XXXV in 30 ml of 20% H_2SO_4 was heated under reflux for 5 or 15 hr. After being cooled, the solution was made alkaline with NH_4OH and extracted with ether. The extract was dried over Na_2SO_4 and concentrated to give 0.95 g of XXXV.

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