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Studies on Psychotropic Agents. III.[1] Synthesis of 1-Substituted 2-[2-(*p*-Fluorobenzoyl)ethyl]piperidines and Related Compounds

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A series of 1-substituted piperidine and 1,2,3,6-tetrahydropyridine derivatives bearing an aroylethyl group in the 2-position or a *p*-fluorobenzoyl group in the 4-position were synthesized for pharmacological testing. 1-Ethyl-2-[2-(*p*-fluorobenzoyl)ethyl]piperidine (**6e**) exhibited the most potent neuroleptic activity and its pharmacological profile is similar to that of thioridazine (I).

Among the butyrophenone derivatives containing their side chain in the piperidine ring, 1-ethyl-3-(*p*-fluorophenacyl)piperidine (III) showed the most potent activity.

Keywords——new neuroleptic; structure–activity relationship; *p*-fluorobenzoyl group; piperidine derivative; 1,2,3,6-tetrahydropyridine derivative

A number of neuroleptics have been used practically in the treatment of schizophrenia. However, almost all of them except thioridazine (I) have serious side effects, such as extrapyramidal syndrome (EPS). Many attempts have been made to prepare better neuroleptics with little or no EPS side effect.

In the previous paper,[1] the synthesis and central nervous system (CNS) depressing activities were reported of 1-substituted 3-(*p*-fluorophenacyl)piperidine derivatives, which were derived from mepazine (II), a moderate neuroleptic, by replacing the phenothiazin-10-yl moiety with a *p*-fluorobenzoyl group. The effects of related compounds were also described. Among the compounds synthesized, 1-ethyl-3-(*p*-fluorophenacyl)piperidine (III) and 1-[3-(*p*-fluorobenzoyl)propyl]-3-(*p*-fluorophenacyl)pyrrolidine (IV) exhibited marked CNS depressing activities.

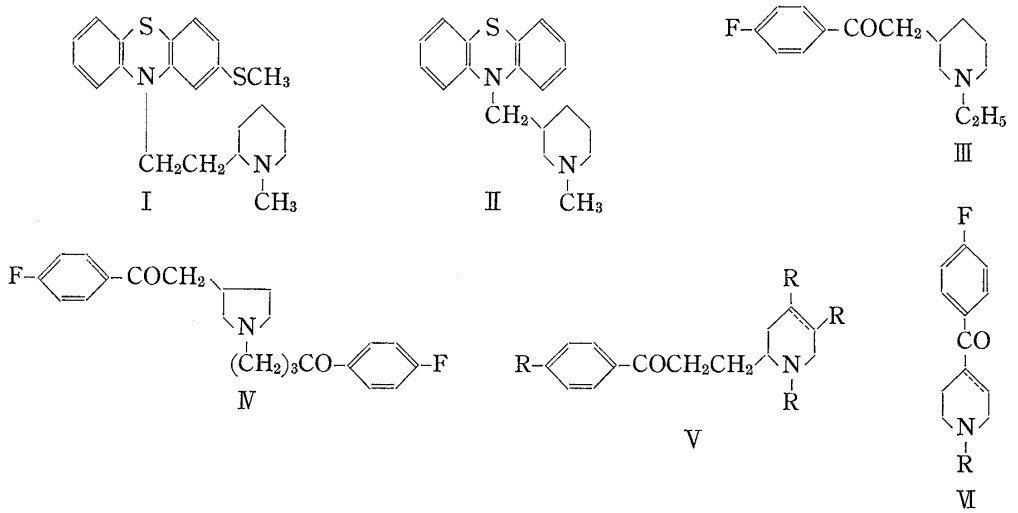


Chart 1

1) Part II: Y. Nagai, H. Uno, and S. Umemoto, *Chem. Pharm. Bull.* (Tokyo), **25**, 1911 (1977).
2) Location: *33-94, Enokicho, Suita, Osaka.*

In a further pharmacological study of III, it was found that III possessed relatively weak cataleptic activitiy, which is regarded as a measure of EPS,[3] in comparison with other CNS depressing activities as shown in Table II. Therefore, in a search for a new neuroleptic with reduced EPS, we attempted to synthesize 1-substituted 2-[2-(*p*-fluorobenzoyl)ethyl]-piperidine derivatives and related compounds (V), which are derived from thioridazine (I) similarly by replacing the 2-methylthiophenothiazin-10-yl moiety with a *p*-fluorobenzoyl group. This paper describes the synthesis and structure–activity relationships of these compounds (V) and 1-substituted 4-(*p*-fluorobenzoyl)piperidines (VI), which can be viewed as butyrophenone derivatives containing their side chain [$-CH_2CH_2CH_2-$] in the piperidine ring.

The synthesis of 2-benzoylethylpiperidine derivatives (**6**) was accomplished by the procedures shown in Chart 2, starting with 2-pyridinealdehyde (**2**). The Claisen-Schmidt condensation of acetophenones (**1**) with **2** gave 2-benzoylvinylpyridines (**3**), which were catalytically hydrogenated in the presence of palladium-carbon and then converted to the quaternary ammonium salts (**5**). The catalytic hydrogenation of **5** on platinum dioxide gave the desired 2-benzoylethylpiperidine derivatives (**6**).[4] The catalytic hydrogenation of the hydrochloride of **4b** on platinum dioxide as an alternative route to **6** gave a mixture of 3-(*p*-fluorophenyl)indolizidine (**8**) and the desired 2-(*p*-fluorobenzoylethyl)piperidine (**7**) in 30

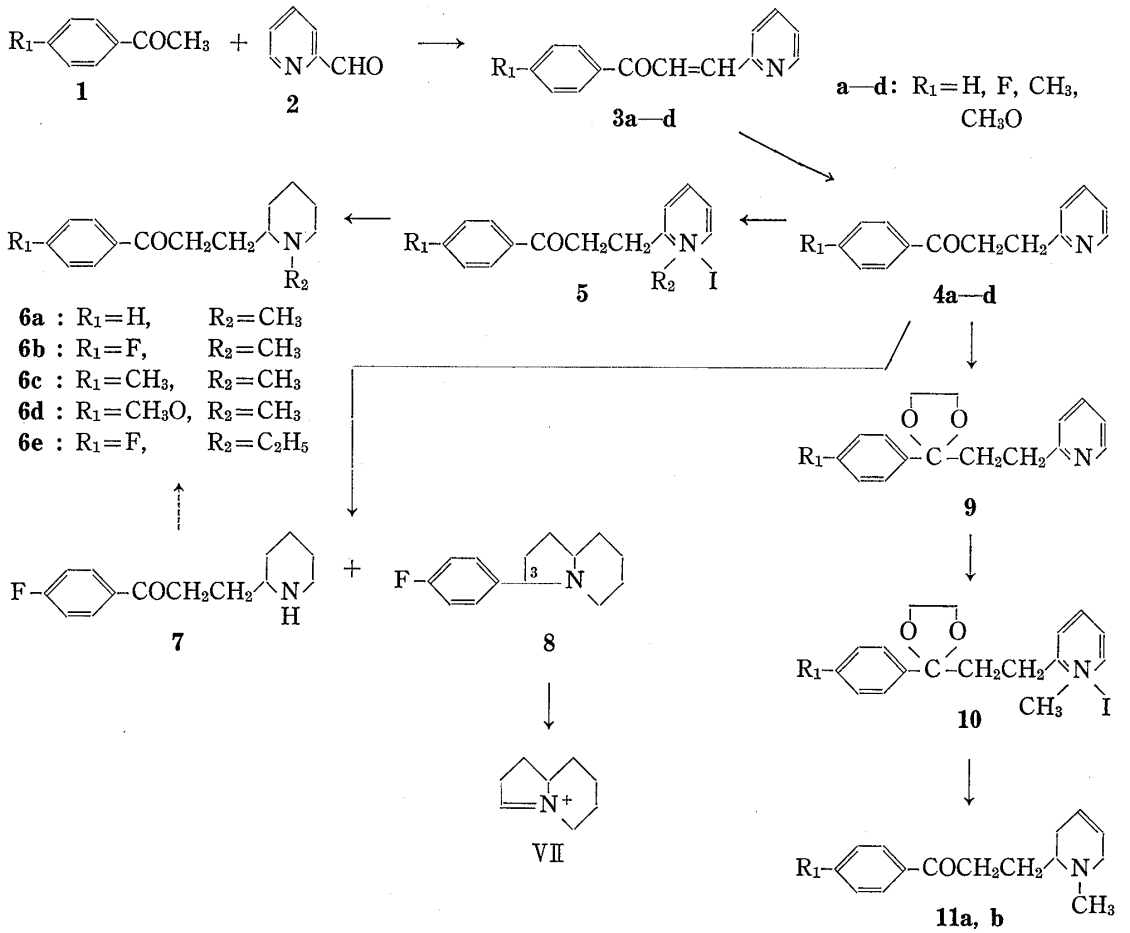


Chart 2

3) O. Hornykieucz, C.H. Markham, W.G. Clark, and R.M. Fleming, "Principles of Psychopharmacology," ed. by W.G. Clark, Academic Press, New York, N.Y., 1970, p. 585.

4) In U.S. Patent 3637712 (1972) [*C.A.*, **75**, 113085], R.A. Partyka and his coworker prepared **6b** as an intermediate for the synthesis of 1-(*p*-fluorophenyl)-3-(1-methyl-2-piperidinyl)-1-propanol by the catalytic reduction of the methiodide of 2-(*p*-fluorobenzoylvinyl)pyridine, but the pharmacolcgical properties of **6b** were not described.

and 9.8% yields, respectively. The structure of **8** was confirmed by the observations that the nuclear magnetic resonance (NMR) spectrum of **8** shows a benzylic proton (C_3–H) in the α position to the nitrogen atom at δ 3.15 as a triplet, and the mass spectrum exhibited a molecular ion peak at *m/e* 219 and a base peak at *m/e* 124 which was assumed to be the ion (VII) (Chart 2).

It has been reported that a 1-[3-(*p*-fluorobenzoyl)propyl]-1,2,3,6-tetrahydropyridine derivative[5] also possesses neuroleptic activity. The synthesis of 2-benzoylethyl-1,2,3,6-tetrahydropyridine derivatives (**11**) was carried out as follows. The ketals of **4a** and **4b** were quaternized and reduced with sodium borohydride followed by acid hydrolysis to give the desired compounds (**11**).

Compounds (**17** and **21**) having a methyl group at the **4** or **5** position of the piperidine ring were also prepared. Bromination of 2-pyridineethanol derivatives (**12**) followed by treatment with sodium cyanide gave 2-cyanoethylpyridine derivatives (**14**). By the Grignard reaction of **14** with *p*-fluorophenylmagnesium bromide, 2-(*p*-fluorobenzoylethyl)pyridine derivatives (**15**) were obtained. Similarly, the methiodides of **15** were catalytically hydrogenated to give piperidine derivatives (**17**).

On quaternization, **14** gave the methiodides (**18**). In general, it is known that the reduction of a 1,2,4-trisubstituted pyridinium ion with sodium borohydride yields a 1,2,3,6-tetrahydropyridine.[6] The same reduction of **18a**, however, gave a 2-cyanoethyl-1,2,3,6-

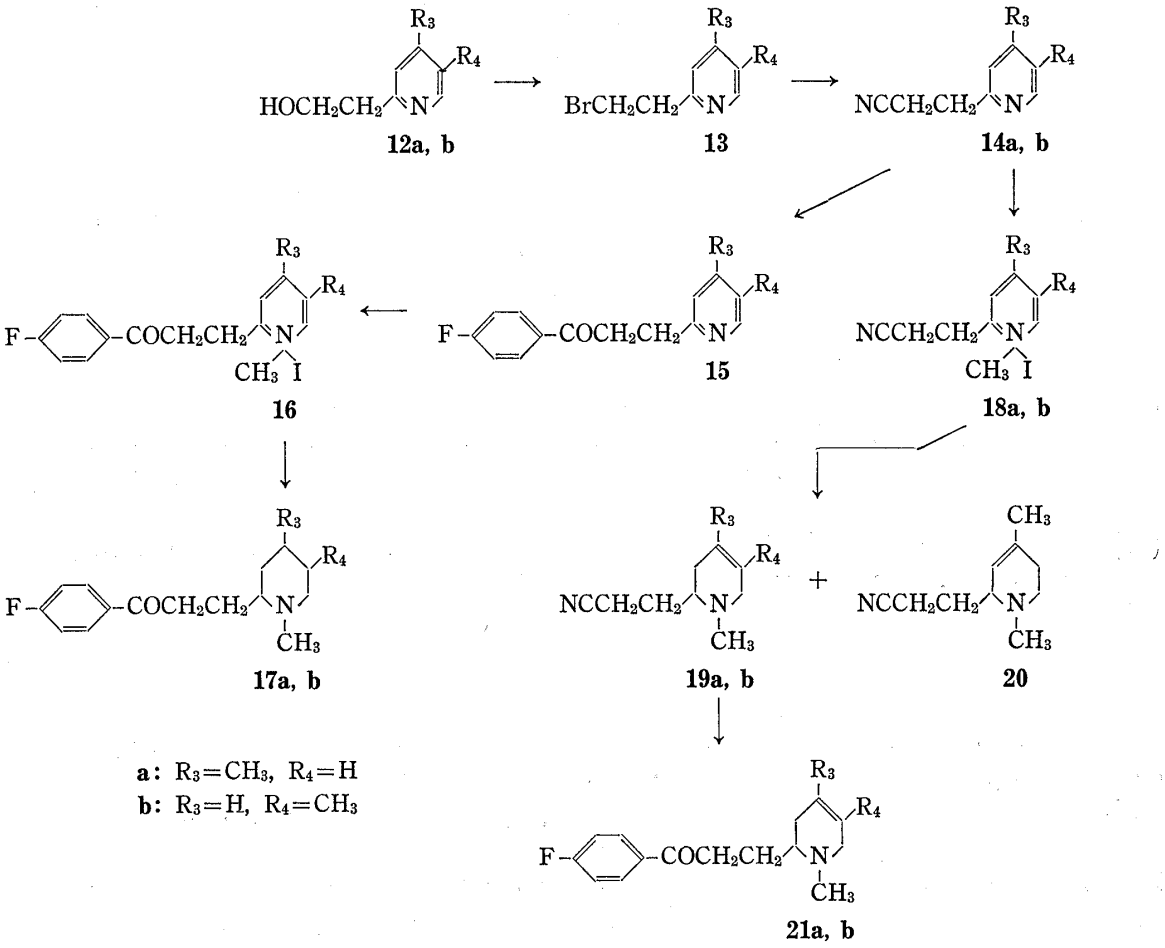


Chart 3

5) 1-[1-[3-(*p*-fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl]-2-benzimidazolinone (droperidol).
6) R.E. Lyle and P.S. Anderson, "Advances in Heterocyclic Chemistry," Vol. 6, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, New York and London, 1966, pp. 45—62; G. Thyagarajan and E.L. May, *J. Heterocycl. Chem.*, **8**, 465 (1971).

tetrahydropyridine derivative (**19a**) and 1,2,5,6-tetrahydropyridine derivative (**20**) in 21 and 16% yields, respectively.

The NMR spectrum of the picrate of **19a** taken in acetone-d_6 showed two allylic protons in the α position to the nitrogen atom at δ 3.95 as a multiplet. On the other hand, the NMR spectrum of the picrate of **20** showed an allylic proton in the same position relative to the nitrogen atom at δ 4.00 as a multiplet. The reduction of **18b** gave 2-cyanoethyl-1,2,3,6-tetrahydropyridine (**19b**) in 71% yield. By the Grignard reaction of **19** with *p*-fluorophenylmagnesium bromide, compounds (**21**) were obtained.

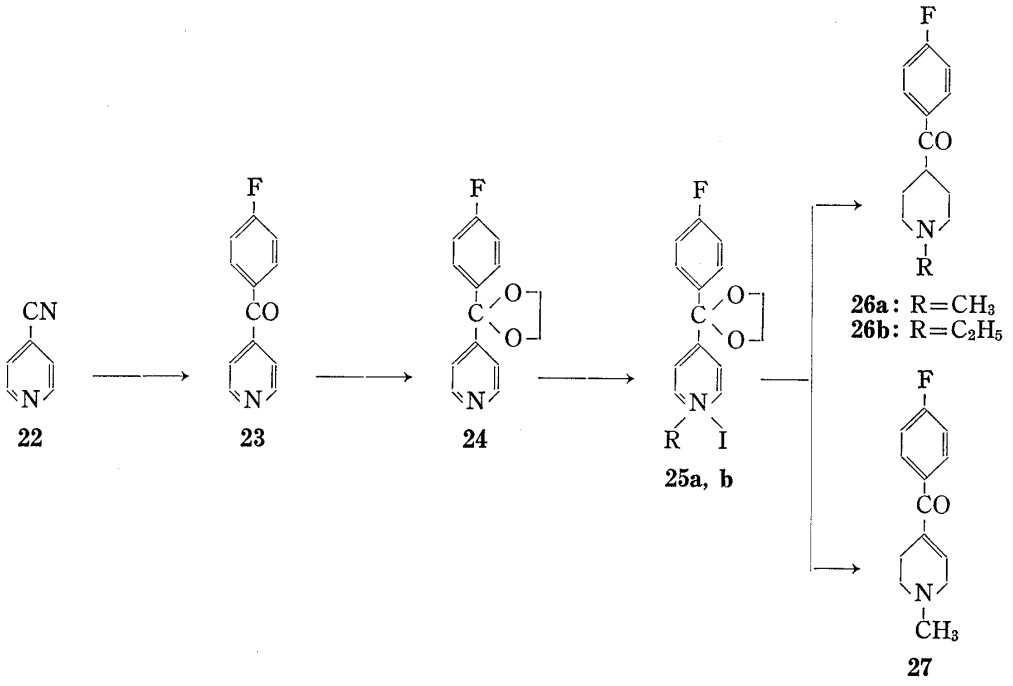


Chart 4

Duncan *et al.*[7] prepared 1-substituted 4-benzoylpiperidine derivatives, which have a bulky substituent at the 1 position. We also synthesized 1-substituted 4-(*p*-fluorobenzoyl)-piperidine derivatives (**26**) as an extention of the butyrophenone derivative study. 4-(*p*-Fluorobenzoyl)pyridine (**23**) was obtained by the Grignard reaction of 4-cyanopyridine (**22**) with *p*-fluorophenylmagnesium bromide. Quaternization of the ketal of **23** gave the compounds (**25**), which were catalytically hydrogenated and then hydrolyzed to give 1-alkylated compounds (**26**). The reduction of **25a** with sodium borohydride followed by hydrolysis afforded the 1,2,3,6-tetrahydropyridine derivative (**27**).

Pharmacology

All the compounds (**6, 11, 17, 21 26** and **27**) prepared in this study were examined at 100 mg/kg *p.o.* as a primary screening test, and the results are summarized in Table I. The compounds (**6b** and **6e**) with a *p*-fluoro substituent on the benzene ring showed more potent activity than the unsubstituted compound (**6a**) or the compounds (**6c** and **6d**) with a methoxy or a methyl substituent. The 1,2,3,6-tetrahydropyridine derivatives (**11a** and **11b**) with no substituent at the 4 or 5 position showed high toxicity. The introduction of a methyl group into the 4 or 5 position in the piperidine ring (**17a** and **17b**) did not affect the activities.

4-(*p*-Fluorobenzoyl)piperidine or 4-(*p*-fluorobenzoyl)-1,2,3,6-tetrahydropyridine derivatives (**26** and **27**) showed no or only mild CNS depressing activities.

7) R.L. Duncan, Jr., G.C. Helsley, W.J. Westead, Jr., J.P. Da Vanzo, W.H. Funderburk, and C.D. Lunsford, *J. Med. Chem.*, **13**, 1 (1970).

Compound (**6e**), which showed the most potent activities, was studied in more detail as shown in Table II. The CNS depressing potency of **6e** is almost equal to that of thioridazine (I) and its pharmacological profile is similar to that of I; namely, relatively mild cataleptic activity and very weak anti-apomorphine activity.

As for the butyrophenone derivatives containing their side chain in the piperidine ring, *i.e.*, 2-[2-(*p*-fluorobenzoyl)ethyl]piperidine, 3-(*p*-fluorophenacyl)piperidine and 4-(*p*-fluorobenzoyl)piperidine derivatives, the neuroleptic activities of the most active members (III, **6e** and **26a**) in each series decreased in the following order, III>**6e**>**26a**, as shown in Table II.

Table I. Results of First Screening Tests at 100 mg/kg, *p.o.* in Mice

No. of compound	Anti-MAMP[a]	Neurotoxicity	Catalepsy
6a	29.5	0/5[b]	0/5[b]
6b	81.0	1/5	1/5
6c	−81.5	0/5	0/5
6d	20.6	0/5	0/5
6e	93.0	5/5	3/5
11a[c]	45.6	0/5	0/5
11b[d]	65.0	5/5	1/5
17a	82.9	3/5	0/5
17b	71.8	0/5	0/5
21a	41.5	0/5	0/5
21b	29.9	0/5	0/5
26a	9.4	0/5	1/5
26b	5.5	0/5	1/5
27	4.5	0/5	0/5
Chlorpromazine	97.5	5/5	5/5

a) Inhibition of methamphetamine-induced hyperactivity (%).
b) No. of positive effects/no. tested.
c) Data at 10 mg/kg, *p.o.* In the these tests, four-fifths of the mice died at 100 mg/kg, *p.o.*
d) Data at 50 mg/kg, *p.o.* In neurotoxicity tests, all the mice died.

Table II. Comparative CNS Effects

Compounds	ED_{50}, mg/kg		
	Suppression of locomotor activity mice (*p.o.*)	Anti-Apomorphine effect rats (*s.c.*)	Catalepsy mice (*p.o.*)
6e	14.7 (5.20— 41.5)[a]	>100	28.7 (13.1—62.7)
26a[b]	58.6 (28.0 —122.4)	>100	>100
III[c]	6.98(3.78— 12.9)	18.0 (12.7—20.6)	33.8 (16.8—67.8)
Thioridazine	12.2 (7.46— 19.7)	>100	34.0 (14.4—80.1)
Chlorpromazine	6.54(3.70— 11.6)	2.50(1.70—3.10)	9.97(6.20—16.0)

a) 95% confidence limits.
b) Hydrochloride.
c) Maleate.

Experimental[8]

3-(2-Pyridyl)acrylophenones (3a—d)——To a mixture of 10% NaOH (20 ml) and MeOH (10 ml) was added 2-pyridinealdehyde (10 g) at 0—10°. To this solution **1** (0.06 mol) was added dropwise at 10° with stirring

8) All melting points are uncollected. NMR spectra were taken with a Varian HA-100 spectrometer using TMS as an internal standard; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. MS spectra were taken with a Hitachi RMU-6L mass spectrometer, and IR spectra with a 215 Hitachi grating infrared spectrometer.

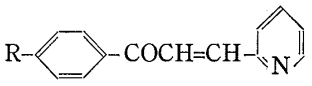
during 1 hr. The reaction mixture was stirred at 10° for 1.5 hr. The resulting crystals were collected and recrystallized from a suitable solvent. The results are shown in Table III.

2-(2-Aroylethyl)pyridines (4a—d)——A mixture of **3** (0.05 mol) and 5% palladium–carbon (1 g) in EtOH (150 ml) was subjected to catalytic hydrogenation at normal temperature and pressure.[9] After the theoretical amount of H_2 had been absorbed, the catalyst and the solvent were removed. The residue was converted into the hydrochloride with ethanolic HCl and recrystallized from a suitable solvent. The results are shown in Table IV.

2-(2-Aroylethyl)pyridine Alkyliodides (5)——A solution of **4** and an excess of alkyliodide in AcOEt or toluene was heated under reflux for 10 hr. Solid products (**5a—d**) were collected and recrystallized from EtOH, and the oily product (**5e**) was used directly in the next step.

1-Substituted 2-(2-Aroylethyl)piperidines (6)——Using PtO_2 (0.1 g), **5** (0.01 mol) was hydrogenated in EtOH (50 ml). After the theoretical amount of H_2 (0.03 mol) had been absorbed, the catalyst and the solvent were removed. To the residue was added dil. NH_4OH, and the solution was extracted with ether. The

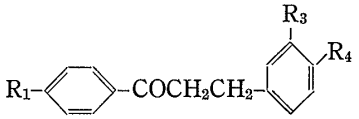
Table III. 3-(2-Pyridyl)acrylophenones



Compd. No.	R	mp (C°)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
3a[a]	H	59—61	60	EtOH				
3b[b]	F	81—82	56	EtOH	$C_{14}H_{10}FNO$	73.99 (74.33	4.44 4.54	6.17 6.10)
3c	CH_3	67—68	74	EtOH+*n*-hexane	$C_{15}H_{13}NO$	80.69 (80.92	5.87 6.28	6.21 5.91)
3d	CH_3O	71—72	45		$C_{15}H_{13}NO_2$	75.30 (75.26	5.48 5.61	5.85 5.81)

a) C.S. Marvel, L.E. Coleman, Jr., and G.P. Scott, *J. Org. Chem.*, **20**, 1785 (1955).
b) See reference 4.

Table IV. 2-(2-Aroylethyl)pyridines



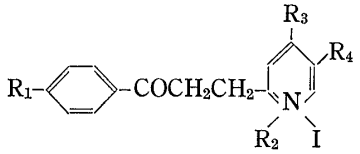
Compd. No.	R_1	R_3	R_4	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	Cl	F	N
4a[a]	H	H	H	122—123	88	EtOH						
4b	F	H	H	166—167	73	EtOH	$C_{14}H_{12}FNO\cdot HCl$	63.28 (63.20	4.93 4.83	13.34 13.62	7.15 7.36	5.27 5.05)
4c	CH_3	H	H	149—150	74	iso-PrOH	$C_{15}H_{15}NO\cdot HCl$	68.83 (68.65	6.16 6.20	13.54 13.59		5.35 5.08)
4d	CH_3O	H	H	151—152	84	EtOH+ether	$C_{15}H_{15}NO_2\cdot HCl$	64.86 (64.73	5.81 5.72	12.77 12.48		5.04 4.83)
15a	F	CH_3	H		42		$C_{15}H_{14}FNO$	74.05 (74.32	5.80 5.62		7.81 7.61	5.76 5.44)
15b	F	H	CH_3	198—200	51	EtOH+acetone	$C_{15}H_{14}FNO\cdot C_6H_3N_3O_7$	53.39 (53.37	3.63 3.92			11.86 11.58)

a) J. Krapcho, *J. Med. Chem.*, **6**, 814 (1963).

9) All catalytic hydrogenation were carried out under these conditions unless otherwise stated.

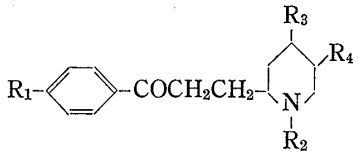
extract was dried over K_2CO_3 and concentrated. The residue was converted into the hydrochloride with ethanolic HCl and recrystallized from a suitable solvent. The results are shown in Table VI.

TABLE V.



Compd. No.	R_1	R_2	R_3	R_4	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	F	I	N
5a	H	CH_3	H	H	170—171	96	EtOH	$C_{14}H_{13}NO\cdot CH_3I$	51.01	4.57		35.93	3.97
									(50.88	4.44		35.60	3.68)
5b	F	CH_3	H	H	186—187	91	EtOH	$C_{14}H_{12}FNO\cdot CH_3I$	48.53	4.07	5.12	34.19	3.77
									(48.64	4.28	5.57	34.07	3.59)
5c	CH_3	CH_3	H	H	184—185	92	EtOH	$C_{15}H_{15}NO\cdot CH_3I$	52.33	4.94		34.56	3.81
									(52.47	5.13		34.78	3.66)
5d	CH_3O	CH_3	H	H	162—163	95	EtOH	$C_{15}H_{15}NO_2\cdot CH_3I$	50.14	4.73		33.12	3.66
									(50.23	4.68		33.22	3.81)
5e	F	C_2H_5	H	H		98		$C_{14}H_{12}FNO\cdot C_2H_5I$	49.88	4.45	4.93	32.95	3.64
									(49.40	4.14	4.58	32.51	3.31)
16a	F	CH_3	CH_3	H	166—168	95	EtOH	$C_{15}H_{14}FNO\cdot CH_3I$	49.88	4.45	4.93	32.95	3.64
									(49.57	5.02	4.41	32.67	3.32)
16b	F	CH_3	H	CH_3	198—200	92	EtOH	$C_{15}H_{14}FNO\cdot CH_3I$	49.88	4.45		32.95	3.64
									(49.51	4.56		33.01	3.62)

TABLE VI. 1-Substituted 2-(2-Aroylethyl)piperidines

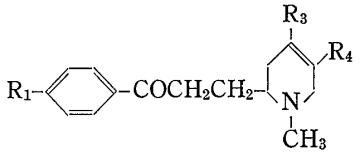


Compd. No.	R_1	R_2	R_3	R_4	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	Cl	F	N
6a	H	CH_3	H	H	166—167	84	EtOH	$C_{15}H_{21}NO\cdot HCl$	67.28	8.28	13.24		5.23
									(67.20	8.20	13.19		5.03)
6b[a]	F	CH_3	H	H	164—165	58	EtOH+ ether	$C_{15}H_{20}FNO\cdot HCl$	63.04	7.41	12.41	6.65	4.90
									(62.78	7.50	12.38	6.65	4.95)
6c	CH_3	CH_3	H	H	129—130	58	EtOH+ ether	$C_{16}H_{23}NO\cdot HCl$	68.19	8.57	12.58		4.97
									(67.87	8.71	12.64		4.75)
6d	CH_3O	CH_3	H	H	170—171	66	EtOH+ ether	$C_{16}H_{23}NO_2\cdot HCl$	64.52	8.12	11.91		4.70
									(64.24	7.97	11.79		4.43)
6e	F	C_2H_5	H	H	153—155	54	EtOH+ acetone	$C_{18}H_{22}FNO\cdot C_6H_3N_3O_7$	53.66	5.12			11.38
									(53.57	5.12			11.21)
17a	F	CH_3	CH_3	H	186—187	53	Acetone	$C_{16}H_{22}FNO\cdot C_6H_3N_3O_7$	53.66	5.12		3.86	11.38
									(53.72	5.53		3.58	11.27)
17b	F	CH_3	H	CH_3	152—154	59	Acetone	$C_{16}H_{22}FNO\cdot C_6H_3N_3O_7$	53.66	5.12		3.86	11.38
									(53.41	5.36		3.51	11.06)

a) See reference 4

Catalytic Hydrogenation of 4b·HCl——Using PtO_2 (0.1 g), **4b**·HCl (2.66 g) was hydrogenated in EtOH, at 60°. After the catalyst and the solvent had been removed, the residue was recrystallized from EtOH and ether to give 200 mg (9.8%) of **7**·HCl. The mother liquor was concentrated, then the residue was made

TABLE VII. 1-Methyl-2-(2-aroylethyl)-1,2,3,6-tetrahydropyridines



Compd. No.	R_1	R_3	R_4	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	Cl	F	N
11a	H	H	H	169—170	65	EtOH+ether	$C_{15}H_{10}NO\cdot HCl$	67.79 (67.51	7.58 7.60	13.34 13.25		5.27 5.30)
11b	F	H	H	175—176	57	EtOH+ether	$C_{15}H_{18}FNO\cdot HCl$	63.49 (63.48	6.75 6.86	12.50 12.32	6.70 7.01	4.94 5.06)
21a	F	CH_3	H	141—143	50	Acetone+ether	$C_{16}H_{20}FNO\cdot C_6H_3N_3O_7$	53.88 (54.13	4.73 5.03			11.42 11.34)
21b	F	H	CH_3	133—134	52	Acetone+ether	$C_{16}H_{20}FNO\cdot C_6H_3N_3O_7$	53.88 (53.68	4.73 4.88			11.42 11.44)

alkaline with NH_4OH and extracted with ether. The extract was dried over $MgSO_4$ and concentrated. The residue was converted into picrate, which was recrystallized from acetone to give 1 g (30%) of **8**·picrate.

7·HCl: mp 155—158°. *Anal.* Calcd. for $C_{14}H_{18}FNO\cdot HCl$: C, 61.87; H, 7.05; Cl, 13.05; F, 6.99; N, 5.16. Found: C, 61.65; H, 7.13; Cl, 13.40; F, 6.84; N, 5.06.

8: mp 106—107° (picrate). *Anal.* Calcd. for $C_{14}H_{13}FN$: C, 76.68; H, 8.27; F, 8.66; N, 6.39. Found: C, 76.87; H, 8.47; F, 8.97; N, 6.11. NMR (δ in $CDCl_3$): 3.15 (t, 1H, C_3–H). MS *m/e*: 219 (M^+, 63%), 124 (100%).

2-(2-Aroylethyl)pyridine Ketal Methiodides (10)——A solution of **4** (**a** and **b**) (0.02 mol) and *p*-toluene sulfonic acid (0.025 mol) in ethyleneglycol (25 ml) and toluene (50 ml) was refluxed for 7 hr with stirring, while separating the isolated H_2O. The aqueous layer was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated to give crude **9** as a colorless oil (which was used in the next step without further purification). The IR spectrum of **9** showed no carbonyl band.

A mixture of crude **9** and an excess of methyliodide in AcOEt was refluxed for 7 hr. The separated quaternary salt was collected and recrystallized from EtOH.

10a: mp 139—140°. Yield, 68%. *Anal.* Calcd. for $C_{16}H_{17}NO_2\cdot CH_3I$: C, 51.40; H, 5.07; I, 31.94; N, 3.53. Found: C, 51.77; H, 5.10; I, 32.33; N, 4.01.

10b: mp 142—143°. Yield, 58%. *Anal.* Calcd. for $C_{16}H_{16}FNO_2\cdot CH_3I$: C, 49.17; H, 4.61; F, 4.69; I, 30.84; N, 3.37. Found: C, 49.57; H, 4.41; F, 4.69; I, 30.84; N, 3.38.

1-Methyl-2-(2-aroylethyl)-1,2,3,6-tetrahydropyridines (11)——To a solution of NaOH (0.02 mol) and **10** (0.01 mol) in a mixture of MeOH (10 ml) and H_2O (30 ml), $NaBH_4$ (0.015 mol) was added dropwise at room temperature. The mixture was warmed at 50—60° for 3 hr and then allowed to stand at room temperature overnight. The mixture was extracted with ether and the extract was concentrated. To the oily residue was added 5% HCl (20 ml), and the solution was warmed at 70° for 30 min. The mixture was made alkaline with Na_2CO_3 and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was converted into the hydrochloride with ethanolic HCl and recrystallized from a suitable solvent. The reeults are shown in Table VII.

11a: NMR (δ in CF_3COOH): 5.81, 6.14 (m, each 1H, H–C=C–H), 4.26 (d, $J=8$ Hz, 1H, $>N-\dot{C}\underline{H}-C=$); this signal collapsed to br. singlet on irradiation at 3.75 ($>N-\underline{H}C-C=$). **11b**: NMR (δ in CF_3COOH): 5.83, 6.11 (m, each 1H, H–C=C–H), 4.21 (d, $J=8$ Hz, 1H, $>N-\dot{C}\underline{H}-C=$); this signal collapsed to br. singlet on irradiation at 3.72 ($>N-\underline{H}C-C=$).

4-(or 5-)Methyl-2-(2-aroylethyl)pyridine (14)——A mixture of **12** (50 g), 47% HBr (120 ml) and conc. H_2SO_4 (40 ml) was refluxed for 8 hr. The reaction mixture was added dropwise to aqueous K_2CO_3 solution with cooling, then the mixture was extracted with ether. The extract was dried over Na_2SO_4 and concentrated to give crude **13** as an oily product, which was used in the next step without further purification. Compound **13** showed no hydroxyl band in the IR spectrum. A solution of **13** and KCN (15 g) in a mixture of

EtOH (60 ml) and H_2O (20 ml) was refluxed for 8 hr with stirring. The mixture was concentrated *in vacuo* and ether was added to the residue. The solution was extracted with dil. HCl. The HCl layer was made alkaline with K_2CO_3 and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was distilled under reduced pressure.

14a: bp 130—134°/6—7 mmHg. Yield 51%.

14b: bp 114°/5 mmHg. Yield, 65.5%.

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. **14a**, Found: C, 73.78; H, 6.98; N, 18.70. **14b**, Found: C, 73.76; H, 6.90; N, 18.22.

2-[2-(*p*-Fluorobenzoyl)ethyl]-4-(or 5-)methylpyridine (15)——To a suspension of magnesium (0.05 mol) in dry ether (40 ml), *p*-fluorobromobenzene (0.05 mol) was added with stirring at a rate sufficient to maintain the reflux, and then the reaction mixture was heated under reflux for 1.5 hr. Dry ether (80 ml) was added to the mixture, then a solution of **14** (0.04 mol) in dry ether (30 ml) was added. The mixture was refluxed for 8 hr. Dil. HCl was added to the mixture with cooling, 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 K_2CO_3 and concentrated.

The crude **15a** was chromatographed on alumina. Elution with ether gave **15a** as a colorless oil.

The crude **15b** was converted into the picrate and recrystallized from a suitable solvent. The results are shown in Table IV.

2-[2-(*p*-Fluorobenzoyl)ethyl]-4-(or 5-)methylpyridine Methiodide (16)——A solution of **15** (1.9 g) and an excess of methyliodide in AcOEt (30 ml) was heated under reflux for 5 hr. The resulting quaternary ammonium salt was collected and recrystallized from a suitable solvent. The results are shown in Table V.

2-[2-(*p*-Fluorobenzoyl)ethyl]-1,4-(or 1,5-)dimethylpiperidine (17)——By the procedure described for the preparation of **6**, compounds **17** were prepared from **16**. The oily product was converted into the picrate and recrystallized from a suitable solvent. The results are shown in Table VII.

2-(2-Cyanoethyl)-4-(or 5-)methylpyridine Methiodide (18)——By the procedure described for the preparation of **16**, compounds **18** were obtained from **14**, then recrystallized from EtOH.

18a: mp 156—160°. Yield, 51%. *Anal.* Calcd. for $C_9H_{10}N_2 \cdot CH_3I$: C, 41.69; H, 4.55; I, 44.04; N, 9.72. Found: C, 41.59; H, 4.64; I, 44.09; N, 9.39.

18b: mp 165—167.5°. Yield, 70%. *Anal.* Found: C, 41.87; H, 4.70; I, 44.38; N, 9.78.

Reduction of 18 with Sodium Borohydride——To a solution of **18** (20 g) and NaOH (5.5 g) in a mixture of MeOH (20 ml) and H_2O (200 ml), $NaBH_4$ (3.4 g) was added at room temperature and the reaction mixture was warmed at 50—60° for 2 hr. After being cooled, the mixture was saturated with K_2CO_3 and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The oily residue was chromatographed on basic alumina (100 g). Elution with petr. ether gave 1.8 g (16%) of **20** and elution with ether gave 2.4 g (21%) of **19a**. Compounds **19a** and **20** were converted into the picrates and recrystallized from acetone and ether.

19a·picrate: mp 136—138°. *Anal.* Calcd. for $C_{10}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 48.85; H, 4.87; N, 17.81. Found: C, 49.16; H, 5.00; N, 17.93. NMR (δ in acetone-d_6): 3.95 (m, 2H, >N–CH_2–C=).

20·picrate: mp 104—106°. *Anal.* Found: C, 49.01; H, 4.94; N, 18.02. NMR (δ in acetone-d_6): 4.00 (m, 1H, >N–CH–C=).

Compound **18b** was also reduced by the procedure described for the reduction of **18a**. The oily product was chromatographed on basic alumina. Elution with petr. ether–ether (2: 1) gave a colorless oil in 71% yield. Compound **19b** was converted into the picrate and recrystallized from acetone and EtOH, mp 98—100°. *Anal.* Calcd. for $C_{10}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 48.85; H, 4.87; N, 17.81. Found: C, 48.87; H, 5.01; N, 17.91. NMR (δ in acetone-d_6): 3.93 (m, 2H, >N–CH_2–C=).

2-[2-(*p*-Fluorobenzoyl)ethyl]-1,4-(or 5-)dimethyl-1,2,3,6-tetrahydropyridine (21)——Using the procedure described for the preparation of **15**, compounds **21** were prepared from **19** and *p*-fluorophenylmagnesium bromide. The crude oily product was chromatographed on basic alumina. Elution with petr. ether–ether (1: 1) gave **21** as a colorless oil. Compounds **21** were converted into the picrate and recrystallized from a suitable solvent. The results are shown in Table VII.

4-(*p*-Fluorobenzoyl)pyridine (23)——Compound **23** was prepared from 4-cyanopyridine (**22**) and *p*-fluorophenylmagnesium bromide, by the procedure described for the preparation of **15**. The crude product was converted into the hydrochloride with ethanolic HCl and recrystallized from EtOH. mp 180—182°, Yield, 62%. *Anal.* Calcd. for $C_{12}H_8FNO \cdot HCl$: C, 60.65; H, 3.82; Cl, 14.92; F, 7.99; N, 5.89. Found: C, 60.94; H, 4.11; Cl, 14.92; F, 7.87; N, 5.78.

1-Alkyl-4-(*p*-fluorobenzoyl)piperidines (26)——From **23**, **24** was prepared by the procedure described for the preparation of **9**. Compound **24** was obtained as a colorless oil in 88% yield. The IR spectrum of **24** showed no carbonyl band.

A mixture of **24** and an excess of alkyl iodide in AcOEt was refluxed for 3 hr. The resulting oily product (**25**) was separated by decantation in quantitative yield and used in the next step without any purification.

A mixture of **25** (0.01 mol) and PtO_2 (0.1 g) in EtOH (50 ml) was subjected to catalytic hydrogenation at 70°. After the catalyst and the solvent had been removed, dil. HCl was added to the residue. The

solution was heated at 70° for 30 min, made alkaline with NaOH and extracted with benzene. The extract was dried over Na_2SO_4 and concentrated. The residue was converted into the salt.

26a·HCl: mp 217—219° (from EtOH and ether). Yield, 72%. *Anal.* Calcd. for $C_{13}H_{16}FNO$·HCl: C, 60.58; H, 6.65; Cl, 13.76; F, 7.37; N, 5.44. Found: C, 60.39; H, 6.65; Cl, 13.52; F, 7.27; N, 5.21.

26b·maleate: mp 141—142° (from acetone). Yield, 65%. *Anal.* Calcd. for $C_{14}H_{18}FNO \cdot C_4H_4O_4$: C, 61.53; H, 6.31; F, 5.41; N, 3.99. Found: C, 61.83; H, 6.20; F, 5.51; N, 3.73.

1-Methyl-4-(*p*-fluorobenzoyl)-1,2,3,6-tetrahydropyridine (27)——Using $NaBH_4$, **25a** was reduced by the procedure described for the preparation of **11**. Dil. HCl was added to the product of the reduction, and the solution was heated at 70° for 30 min. The solution was made alkaline and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was converted into the picrate and recrystallized from EtOH and acetone.

27·picrate: mp 146—148°. Yield, 68%. *Anal.* Calcd. for $C_{13}H_{14}FNO \cdot C_6H_3N_3O_7$: C, 50.90; H, 3.82; N, 12.50. Found: C, 50.90; H, 3.77; N, 12.40.

Pharmacological Methods

Anti-methamphetamine Effect——The suppression of methamphetamine-induced hyperactivity was examined according to a modification of the method of Ueki *et al.*[10] At 100 min after the administration of test drugs, mice were injected with methamphetamine (5 mg/kg, *i.p.*) and 10 min thereafter, the locomotor activity was measured with a photo cell activity meter for 20 min.

Neurotoxicity——Neurotoxicity was examined according to a modification of the method of Young and Lewis.[11] Mice were put into a rotating cylinder (2 cycle/min) and a fall from the cylinder within 2 min was considered as a positive effect.

Catalepsy——Groups of 5 mice were tested for catalepsy according to a modification of the method of Courvoisier *et al.*[12] Each mouse was forced to put its fore paws on a rubber cap 2.8 cm in height. Mice which failed to remove their paw from the cap within 30 sec were considered to be cataleptic.

Suppression of Locomotor Activity——The suppressive effect on locomotor activity was examined using a Animex activity meter (Svensson and Thieme).[13] At an appropriate time after the administration of test drugs, each mouse was put into the cage on the Animex and the locomotor activity was measured for 3 min.

Anti-apomorphine Effect——The anti-apomorphine effect was examined according to the method of Janssen *et al.*[14] At an appropriate time after the administration of test drugs, rats were injected with apomorphine HCl (1 mg/kg, *i.v.*) and 5, 10 and 20 min thereafter, the animals were observed for 1 min. Absence of the typical gnawing movement at least once in three measurements was regarded as a positive effect.

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10) S. Ueki, H. Sugino, N. Sato, J. Iwaki, H. Yonemura, T. Funada, H. Yamada, S. Nurimoto, G. Hayashi, and Y. Kowa, *Folia Pharmacol. Japan.*, **61**, 421 (1965).
11) D.M. Young and A.H. Lewis, *Science*, **105**, 368 (1947).
12) S. Courvoisier, R. Ducrot, and L. Julou, "Psychotropic Drugs," ed. by S. Garattini and V. Ghetti, Amsterdam, 1957, p. 373.
13) T.H. Svensson and G. Thieme, *Psychopharmacologia*, **14**, 157 (1969).
14) P.A.J. Janssen, C.J.E. Miemegeers, and K.H.L. Schellekens, *Arzneim.-Forsch.*, **15**, 104 (1965).