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Synthetic Studies on Psychotropic Agents. I. A New Synthesis of 2′-Amino-4′-fluorobutyrophenone Derivatives using a Serective *ortho*-Amination of 2′,4′-Difluorobutyrophenone Derivatives

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A new synthesis of 2′-amino-4′-fluoro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)piperidino]butyrophenone using a selective *ortho*-amination as a key step was described.

The solvents and temperature effects on the selectivity for this ortho-amination of 2′,4′-difluoro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)piperidino]butyrophenone were investigated.

Keywords——psychotropic agent; *ortho*-amino butyrophenone; nucleophilic substitution; selective benzylamination; solvent and temperature effects

Introduction

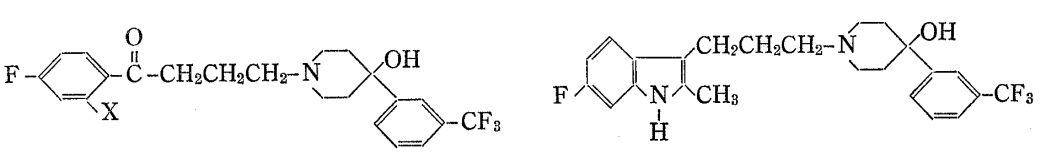
2′-Amino-4′-fluoro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)piperidino]butyrophenone [ID-4708 (Ia)] synthesized by the present authors has been shown to be a new potent neuroleptic butyrophenone derivative.[2]

The structure of Ia is characterized by its amino moiety (X=NH_2) introduced onto the *ortho*-position of the known neuroleptic butyrophenone [triperidol (Ib)].

The synthesis of Ia, therefore, had to be oriented how to introduce such amino moiety into the proper position of the butyrophenone skeleton.

Previously we reported the synthesis of Ia *via* 6-fluoro-2-methyl-3-piperidinopropyl indole derivative (II), in which the formation of the *ortho*-amino butyrophenone skeleton was achieved by the oxidative ring cleavage of the indole ring.[2a] However, this synthesis suffered from some hardships of too many steps or relatively low yields.

Here we wish to report a novel synthetic approach for Ia using a selective *ortho*-amination on *ortho*, *para*-difluoro-butyrophenone as a key step for formation of the objective skeleton and further to discuss the effects of solvents and reaction temperature in this *ortho*-amination.



Ia: ID-4708 (X=NH_2)
Ib: triperidol (X=H)

II

Chart 1

1) Location: *2-1, Takatsukasa 4-chome, Takarazuka-shi, Hyogo, Japan*; *a*) To whom correspondences should be addressed.

2) *a*) T. Honma, K. Sasajima, K. Ono, S. Kitagawa, Sh. Inaba, and H. Yamamoto, *Arzneim-Forsch* (*Drug Res.*), **24**, 1248 (1974); *b*) T. Honma and H. Fukushima, *Neuropharmacology*, **15**, 601 (1976).

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Results and Discussion

Synthesis of 2′-Amino-4′-fluoro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)piperidino]butyrophenone (ID-4708)

ID-4708 (Ia) was synthesized from *m*-difluorobenzene in six-steps. By the Friedel Crafts reaction between *m*-difluorobenzene and 4-chlorobutyryl chloride, 4-chloro-2′,4′-difluorobutyrophenone (III) was obtained in about 90% yield. A long-range hydrogen-fluorine spin–spin coupling between the *ortho*-fluorine and the α-methylene proton (J=3.2 Hz) was observed in the PMR spectrum of III. III was easily converted to the ethylene ketal (IV) by heating with an excess of ethylene glycol and ethyl orthoformate in the presence of *p*-toluensulfonic acid. The condensation of IV with 4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)-piperidine and the subsequent hydrolysis gave the 2′,4′-difluorobutyrophenone (VI) as a white crystal in high purity (yield=75%). The preferential 2′-fluorine displacement of VI with benzylamine was achieved by refluxing in a nonpolar solvent such as *n*-hexane, benzene or the like. Detailed studies of this selective nucleophilic aromatic substitution are described later. Debenzylation of 2′-benzylamino-4′-fluoro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)-piperidino]butyrophenone (VII) proceeded quantatively at room temperature to give the objective compound (Ia).

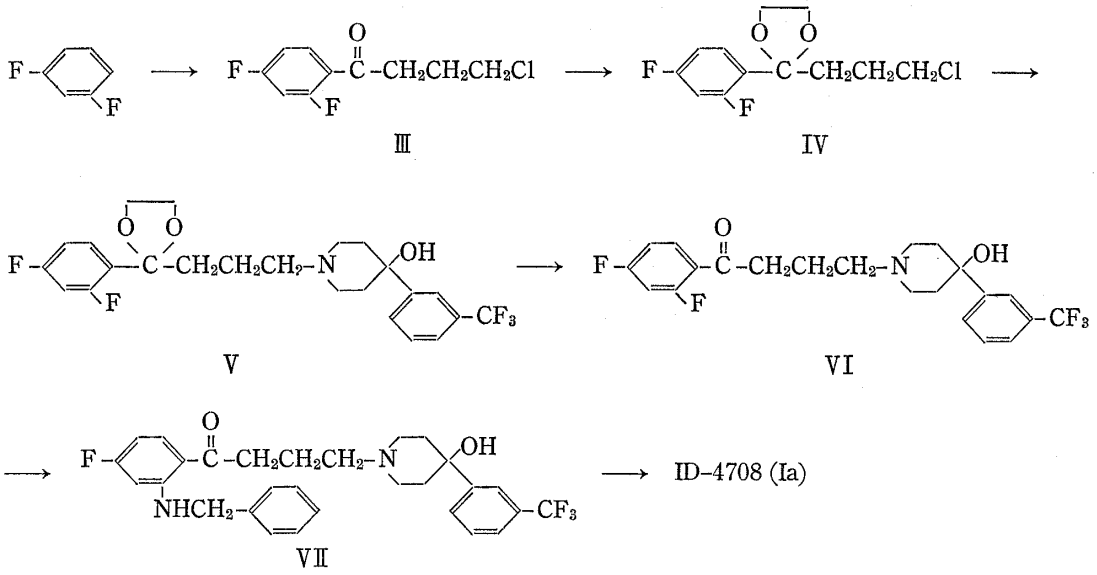

Chart 2

This synthetic method was fairly simple and each stage proceeded with fairly good yields. Accordingly this method may be useful for the synthesis of the other *ortho*-substituted derivatives.

The *ortho*:*para* Ratio in the Nucleophilic Substitution of VI with Benzylamine

The nucleophilic aromatic displacement of fluorine activated by electron-withdrawal groups is well known[3] but there is a few study about the selectivity of displacement of fluorine atoms in *o*,*p*-difluorophenyl ketone systems. Thus the present authors have started to study the selectivity of the benzylamination of VI in some detail and also the effects of the sort of solvent and the reaction temperature on its selectivity.

3) Examples in the field of the fluorine chemistry; *a*) P. Tarrant (ed), "Fluorine Chemistry Review," Vol. 7, Marcel Dekker, Inc., New York, 1974, pp. 1—114; *b*) Y. Kobayashi and I. Kumadaki, *Yuki Gosei Kagaku Kyokai Shi*, **29**, 126 (1971).

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Effect of Solvents

The results of the reaction in different solvents at 27° are shown in Table I. Although *ortho*-substitution occurred preferentially in most solvents used, the (*o*/*p*) ratio increased with decreasing polarity of the solvents, in roughly speaking.

Thus the (*o*/*p*) ratio was about 5—8 in a nonpolar solvent such as *n*-hexane, benzene, toluene and dioxane (the dielectric constants (ε) of them are approximately the same), whereas it decreased below 1 in an aprotic dipolar solvent such as dimethyl sulfoxide, N,N-dimethylacetamide and N,N-dimethylformamide (DMF). Moreover in case of the solvents with a moderate dielectric constant, such as ethyl acetate or tetrahydrofuran, moderate selectivity was observed.

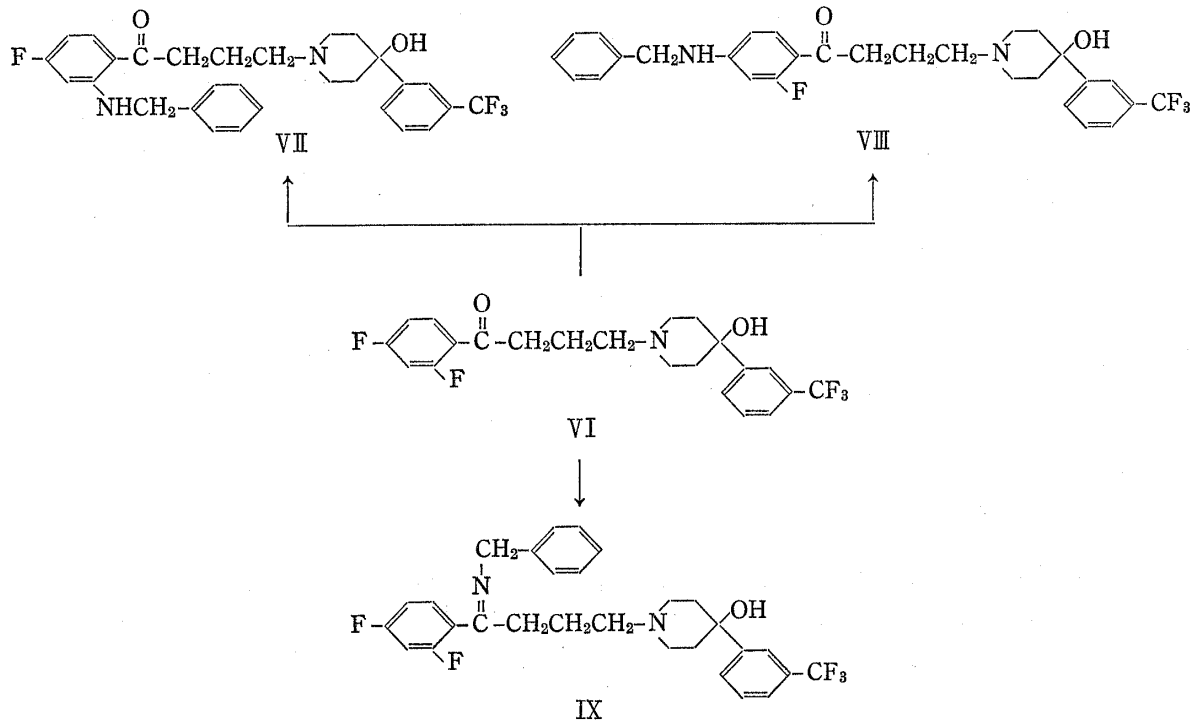

Chart 3

Table I. Effect of Solvents in the Reaction of VI with Benzylamine

Solvent	ε	Reaction time(days)	VII	VIII	VI	*o*/*p*
n-Hexane	1.9	14	58.9	11.0	13.3	5.35
Dioxane	2.2	14	62.8	10.1	15.6	6.22
Benzene	2.27	14	56.5	7.0	27.0	8.07
Toluene	2.38	14	60.9	7.4	26.1	8.23
Ethyl acetate	6.03	14	49.2	11.8	18.6	4.17
Tetrahydrofurane	7.4	14	61.4	18.0	10.9	3.41
Methanol	32.6	14	16.4	9.3	61.3	1.76
Acetonitrile	37.4	14	52.2	20.4	18.6	2.56
Nitromethane	35.8	14	43.3	11.8	24.9	3.67
Benzyl amine		14	55.7	23.4	1.9	2.38
DMF	36.7	3	29.8	36.7	12.3	0.81
DMA_c	37.8	3	28.4	40.1	7.9	0.71
Sulforane	44.0	2	26.9	13.3	30.0	2.02
DMSO	48.5	2	32.4	56.9	4.6	0.57

Reaction mixture composition(%) after the reaction of VI (1 g) and benzylamine (5 g) in 10 ml of solvent at 27±0.3°.

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The correlation obtained here between the (*o*/*p*) ratio and the dielectric constant of the solvent was roughly compatible with those observed in the similar systems such as the reaction of pentafluoronitrobenzene, pentafluorobenzoic acid ethyl ester[4] or 1,2,3,4-tetrafluoroanthraquinone[5] with nucleophiles and it may be explained as suggested by the earlier workers[6]; in nonpolar solvents, the formation of hydrogen bonding resulted in *ortho*-orientation, whereas, in polar solvents, the stabilization by sterically unhindered solvation in the largely ionic para transition state resulted in *para*-orientation. On the other hand, in the case of polar solvents such as methanol, acetonitrile, nitromethane and sulfolan which have approximately the same dielectric constants as DMF *etc.*, the effects of solvents upon orientation are very interesting. That is, the (*o*/*p*) ratios of them were anormalously high in comparison with the results reported in the literature.[4,7] Furthermore, in these solvents the percentage of the starting material (VI) was relatively high. From these results, it was suggested that some other factors than the polarity of the solvent might also influence the site-selectivity of the displacement of this reaction.

It can be presumed that the acidic nature of these solvents decelerates the displacement reaction of VI owing to decreasing nucleophilicity of benzylamine, but the correlation between this acidic nature and the preferential *ortho*-orientation in these solvents is not still evident. It seems necessary to be further investigated.

Effect of Reaction Temperature

In all solvents used, the (*o*/*p*) ratio significantly increased at elevated temperature. Although the highest (*o*/*p*) ratio was observed under refluxing in nitromethane, unknown tarry by-products were predominantly formed in this conditions. The effect of the elevating temperature on the (*o*/*p*) ratio is great in a nonpolar solvent such as *n*-hexane or benzene than in a polar one. These results suggest that the entropy effect ascribed to the hydrogen bonding formation was more significant in the *ortho* transition state.

Table II. Effect of Reaction Temperature of the Reaction of VI with Benzylamine

Solvent	Temperature (°C)	Reaction time	VII	VIII	VI	*o*/*p*
n-Hexane	Refluxing	30 hr	82.0	4.1	4.1	20.0
	27	14 days	58.9	11.0	13.3	5.4
	1.5	30 days	32.7	13.5	38.4	2.4
Benzene	Refluxing	30 hr	72.1	2.5	7.6	28.8
	27	14 days	56.5	7.0	27.0	8.1
Methanol	Refluxing	30 hr	30.0	12.9	39.6	2.3
	27	14 days	16.4	9.3	61.3	1.8
Nitromethane	Refluxing	30 hr	38.2	0.4	1.3	95.5
	27	14 days	43.3	11.8	24.9	3.7
DMF	70	9 hr	23.6	18.0	5.2	1.3
	27	3 days	29.8	36.7	12.3	0.8
	1.5	30 days	25.4	45.5	15.6	0.5
DMSO	70	9 hr	30.7	30.9	5.1	0.9
	27	2 days	32.4	56.9	4.6	0.5

4) L.S. Kobrina, G.G. Furin, and G.G. Yakobson, *Zh. Obshchei. Khim.*, **38** (**No. 3**), 514 (1967).
5) V.A. Loskutov, L.N. Nekrasova, and E.P. Fokin, Izv. Sibersk, *Otd. Akad. Nauk SSSR*, **2** (**N4**), 119 (1970); E.P. Fokin, V.A. Loskutov and A.V. Konstantinova, *ibid.*, **3** (**N11**), 110 (1966).
6) *a*) R.R. Bishop, E.A.S. Cavell, and N.B. Chapman, *J. Chem. Soc.*, 437 (**1952**); *b*) J.G. Allen, J. Burdon, and J.C. Taylow, *J. Chem. Soc.*, 1045 (**1965**); *c*) S.D. Ross, "Progress in Physical Organic Chemistry," Vol. 1, John Wiley and Sons, Inc., New York, 1963, p. 31.
7) L.S. Kobrina, G.G. Furin, and G.G. Yakobson, *Zh. Org. Khim.*, **6**, 512 (1970).

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Effect of Solvents for Schiff Base Formation in the Reaction of 2,4-Difluoroacetophenone with Benzylamine

Our results described above were obtained after the reaction mixture had been treated with a diluted hydrochloric acid solution in order to remove the excess of benzylamine, and hence it was not possible to detect the Schiff base (IX) formed. In order to take account of the formation of the Schiff base, we examined it in the reaction between 2,4-difluoroacetophenone and benzylamine, a more simple reaction system similar to the reaction of VI. The results obtained in different solvents are shown in Table III. The (*o*/*p*) ratio in this reaction system was relatively similar to that of the reaction of VI.

The ratio of the formation of the Schiff base to the mono-benzylamination varied in wide range according to a solvent used, and methanol remarkably accelerated the Schiff base formation. In nitromethane, similar acceleration of Schiff base formation was observed and the para-substitution was decelerated than in DMF. As suggested by these results, the Schiff base (IX) may be more formed in methanol or nitromethane than in DMF, benzene or *n*-hexane. The preferential *ortho*-orientation in these acidic solvents might be correlated to their acceleration of the Schiff base formation, but the reason for this is not still evident.

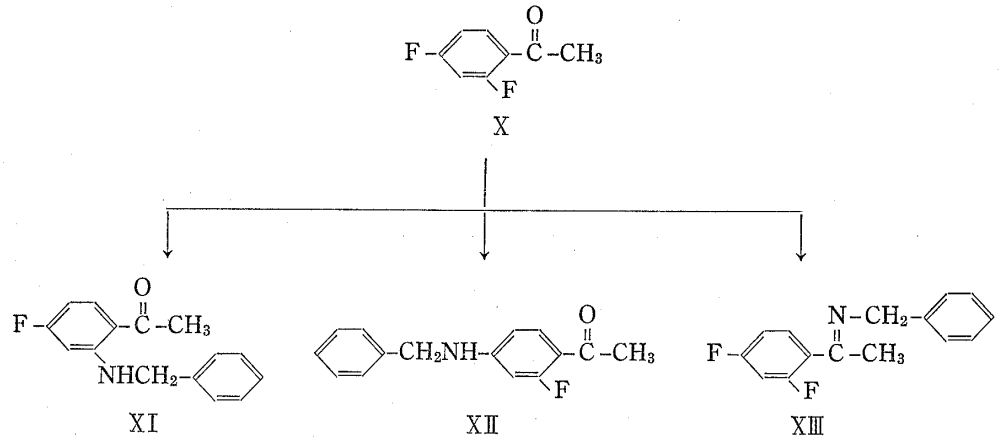

Chart 4

TABLE III. Effect of Solvent on the Formation of Schiff Base (XIII)

Solvent	XI	XII	XIII	X	XIII/XI+XII
n-Hexane	9.0	1.0	6.1	84.0	0.61
Benzene	10.6	1.0	5.6	82.8	0.48
Nitromethane	13.7	1.9	13.9	70.5	0.89
Methanol	5.2	3.6	32.0	59.3	3.63
DMF	23.4	20.2	9.1	47.4	0.21

Reaction mixture composition (%) after the reaction of X (1 g) with benzylamine (5 g) in a solvent (5 g) indicated for 1 hr at 60°.

Experimental

All melting points were determined with Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi model EPI-G3 IR spectro-photometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 spectrometer using TMS as an internal standard. GLC was carried out by the use of a Shimadzu model GL-5A gas chromatograph equipped with hydrogen flame ionization detector.

4-Chloro-2′,4′-difluorobutyrophenone (III)——To a cooled mixture of *m*-difluorobenzene (700 g) and anhydrous aluminum chloride (550 g) was added 4-chlorobutyryl chloride (433 g) at 5—10°. After the stirring for additional 3.5 hr at room temperature, the resulting mixture was poured into water containing

NII-Electronic Library Service

crashed ice. The organic layer separated was washed with saturated NaCl aq., dried over Na_2SO_4 and evaporated *in vacuo*. By vacuum distillation of the residual oil, 603.7 g (89.9%) of the product (III) was obtained, bp 103.5—110.0° (0.7—0.85 mmHg). IR ν_{max}^{film} cm^{-1}: 1685, NMR δ^{CCl_4}: 3.11 (m, 2H, α-methylene), 2.19 (quintet J=6.8 Hz, β-methylene), 3.67 (t, J=6.8 Hz, γ-methylene).

Ethylene Ketal of III——While a mixture of III (570 g), ethylene glycol (809 g), ethyl orthoformate (580 g) and *p*-toluenesulfonic acid (44.8 g) was heated at 90—95° for 45 minutes, 340 ml of the distillate was removed from the reaction mixture. After cooling, the mixture was diluted with toluene, washed with saturated NaCl aq., dried over Na_2SO_4 and evaporated *in vacuo*. By vacuum distillation of the residual oil, 645.2 g (94.2%) of the ketal (IV) was obtained, bp 122—129° (1.3—1.4 mmHg), NMR δ^{CCl_4}: 3.52 (t, J= 6.81 Hz, γ-methylene), 6.81 (m, 2H, aromatic), 7.45 (m, 1H, aromatic).

2′,4′-Difluoro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)piperidino]butyrophenone (VI)——A mixture of IV (51.4 g), 4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)piperidine (41.6 g), K_2CO_3 (22.9 g), KI (1.2 g) and DMF (400 ml) was stirred for 4 hr at 90—100°. After the evaporation of DMF *in vacuo*, the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4 and evaporated *in vacuo* to leave the ethylene ketal of VI as a solid, which was immediately dissolved into a solution of methanol (350 ml), water (120 ml) and 35% HCl aq. (60 ml). This mixture was refluxed for 1 hr and then concentrated until the crystals became to precipitate. After cooling, the precipitate was collected and dried to give the hydrochloride of VI (75%), mp 237.5—239.5°. The free base from ethanol–water as colorless crystals, mp 86—92°. IR ν_{max}^{Nujol} cm^{-1}: 1675, 1615, 1335, 1130. NMR δ^{CDCl_3}: 1.5—3.5 (m, 15H), 6.75—7.15 (m, 2H), 7.3—8.2 (m, 5H). *Anal.* Calcd. for $C_{22}H_{22}F_5NO_2$: C, 61.82; H, 5.19; N, 3.28. Found: C, 61.51; H, 5.40; N, 3.30.

2′-Benzylamino-4′-fluoro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)piperidino]butyrophenone (VII)——A solution of VI (40 g) and benzylamine (400 g) in *n*-hexane (1000 g) was stirred for 52 hr under refluxing. After the filtration, the filtrate was evaporated *in vacuo* and the residue was taken up in chloroform. The chloroform solution was washed successively with 5% HCl aq., saturated NaCl aq., 5% NH_3 aq. and saturated NaCl aq., dried over Na_2SO_4 and evaporated to leave a oil (48.25 g). The composition of this crude oil was determined by GLC analysis and was as follows: VII=82.7%; VIII=0.3%; VI=6.2%.

For the preparation of the authentic sample of VII, the crude oil was chromatographed on silica gel. Elution with *n*-hexane–ethyl acetate–methanol–28% NH_3aq. (50: 45: 20: 0.3) and the crystallization of the eluate from diisopropyl ether afforded pure VII, mp 80.5°, IR ν_{max}^{Nujol} cm^{-1}: 3340, 1650, 1620, 1200, 1120, NMR δ^{CDCl_3}: 4.37 (d, J=5.8 Hz, benzyl proton), 6.07—6.43 (m, 2H, aromatic), 7.30—7.97 (m, 10H, aromatic), 9.63 (1H, –NH). *Anal.* Calcd. for $C_{29}H_{30}F_4N_2O_2$: C, 67.69; H, 5.88; N, 5.44. Found: C, 67.62; H, 5.82; N, 5.39.

2′-Amino-4′-fluoro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)piperidino]butyrophenone (ID-4708)——A mixture of the crude VII (48.25 g), 35% HClaq. (98 g), 10% palladium on charcoal (9.6 g suspended 10 g of water) and ethanol (760 ml) was vigorously stirred in hydrogen atmosphere at room temperature until the consumption of hydrogen ceased. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to leave the crude solids.

The procedure of the purification is as following: The ethyl acetate solution of the free base was treated with small portion of silica gel and extracted with 12% HClaq. The aqueous layer was made alkaline and extracted with ethyl acetate. The ethyl acetate layer was evaporated *in vacuo* and the residue was dissolved in a solution of isopropyl alcohol (80 ml) and 35% HClaq. (16 g) under heating. After cooling, the hydrochloride of Ia was collected by filtration. Recrystallization from ethanol to give colorless crystals of ID-4708 (18.2 g, 51% based on VI), mp 205—206°. IR ν_{max}^{Nujol} cm^{-1}: 3440, 3330, 2660, 2580, 2560, 1655, 1625, 1590, 1560. *Anal.* Calcd. for $C_{22}H_{25}ClF_4N_2O_2$: C, 57.32; H, 5.48; N, 6.08; Cl, 7.69. Found: C, 56.96; H, 5.50; N, 6.17; Cl, 7.72.

Reaction of VI with Benzylamine——A solution of VI (1 g) in benzylamine (5 g) and an appropriate solvent (10.0 ml) was placed in a flask equipped with a soda-lime drying tube. The flask had been placed in a controlled water bath which was set a temperature at 27°, 70° or the biling point of solvent used respectively, for a period represented in Table I or II.

Reaction of 2′,4′-Difluoroacetophenone with Benzylamine——A solution of 2′,4′-difluoroacetophenone 1 g in benzylamine 5 g and appropriate solvent (10.0 ml) was placed in a flask equipped with a soda-lime drying tube.

GLC-Analysis for the Reaction of VI with Benzylamine——The glass column (100×0.3 cm) was filled with 2% SE-30. The column temperature was 245° while injector and detector temperature were maintained at 300°. Nitrogen was used as carrier gas at a flow-rate of 30 ml/min.

GLC Analysis for the Reaction of X with Benzylamine——The glass column (100×0.3 cm) was filled with 20% SE-30 and the column temperature was varied from 100° to 240° over a period of about 16 min. The injector and detector temperature were respectively 250° and 270°. Helium was used as carrier gas at a flow-rate of 35 ml/min.

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