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Psychotropic Agents. V.¹⁾ Synthesis of 1,3-Diphenyl-4-(4-substituted piperidinyl)-1-butanones and Related Compounds

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A series of 1,3-diphenyl-1-butanone derivatives (11—14) was synthesized as part of a search for new psychotropic agents.

In the reaction of 4-chloro-1,3-diphenyl-1-butanones (8a,d) with piperidine derivatives (10,15), rearranged products (16—18) were obtained together with 1,3-diphenyl-1-butanone derivatives (11,14,20). A reaction mechanism involving the cyclization of 8a,d to cyclopropane derivatives (22a,d) and subsequent addition reaction with piperidine derivatives (10,15) to 22a,d is proposed.

Keywords—butyrophenone; neuroleptic activity; 1,3-diphenyl-1-butanone derivatives; 1,4-diphenyl-1-butanone derivatives; rearrangement

Although much work has been done²⁾ in recent years on syntheses of butyrophenones having neuroleptic activity, no synthetic study on butyrophenones substituted with a phenyl group on the butanone chain has been reported. In the present paper, we describe the synthesis of 1,3-diphenyl-4-(4-substituted piperidinyl)-1-butanone derivatives (A), which have a phenethylamine moiety in the molecule, as part of our search for new psychotropic agents. A rearrangement reaction, which was found during this work, is also reported.

In the preceding paper¹⁾ we reported the synthesis of β -phenyl- γ -butyrolactone derivatives (1—4). These compounds were thought to be suitable starting materials for conversion to 4-chloro-1,3-diphenyl-1-butanones (8a—d,f) which are key intermediates for the synthesis of the target butanone derivatives (A).

The synthesis of 4-chloro-1,3-diphenyl-1-butanones (8a—d,f) was carried out by the procedure described in the previous paper.³⁾ Thus, the Claisen condensation of β -phenyl- γ -butyrolactone (1) with ethyl benzoate (5) in the presence of sodium methylate gave α -benzoyl- β -phenyl- γ -butyrolactone (7a), whose structure was supported by its elemental analysis and infrared (IR) spectrum [1775, 1680 cm⁻¹ (C=O)]. Heating of 7a with conc. HCl gave 4-chloro-1,3-diphenyl-1-butanone (8a). The structure of 8a was confirmed by its elemental analysis and mass spectrum (MS) [m/e 259, 261 (M⁺)]. The nuclear magnetic resonance (NMR) spectrum of 8a exhibits complex multiplets at 3.5 (2H) and 3.8 ppm (3H) assignable to the five protons of the butanone chain. As the isolation of 7b—d,f was troublesome, it was more practical to use the crude condensation products (7b—d,f) for the next step without further purification. That is, the butanone derivatives (8b—d,f) were obtained by reaction of the crude condensation products (7b—d,f) with conc. HCl.

The butanone derivatives (8a—d,f) were converted to 1,3-dioxolane derivatives (9a—d,f)

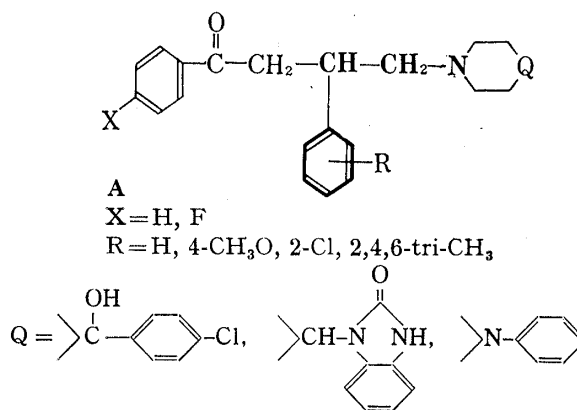
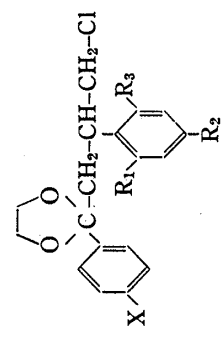
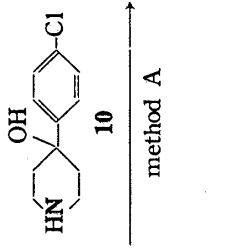
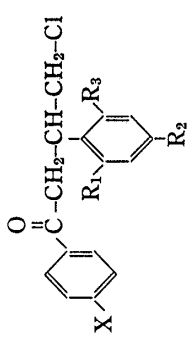
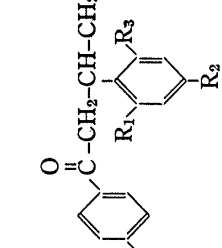
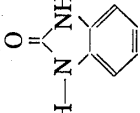


Chart 1

TABLE I. Physical Properties of 1,3-Diphenyl-4-(4-substituted piperidinyl)-1-butanones

 9a-d, f  10  8a, d																
 11-14, 20, 21 method A method B																
3-phenyl isomer																
Compd. No.	X	R ₁	R ₂	R ₃	Q	Method ^{a)}	Yield %	mp (°C)	Recrystn solvent ^{b)}	Formula	Analysis (%)			NMR spectral data (in CDCl ₃) (δ ppm)		
											Calcd (Found)	C	H	N	C ₂ -protons	C ₃ -protons
11	H	H	H	H	OH	A	63.0	132-133	Et ₂ O-Pt·E	C ₂₇ H ₂₈ ClNO ₂	74.72 (74.72)	6.50 (6.36)	3.20 (3.50)		2.74 (dd, J=4, 15 Hz)	3.75 (m)
12	F	H	H	H	OH	A	35.6	122.5-123	Et ₂ O-Pt·E	C ₂₇ H ₂₇ ClFNO ₂	71.75 (72.14)	6.02 (6.17)	3.10 (3.30)		2.85 (dd, J=7, 15 Hz)	3.7 (m)
13	F	Cl	H	H	OH	A	22.3	132.5-133.5	C ₆ H ₆ -Hx	C ₂₇ H ₂₆ Cl ₂ FNO ₂	66.67 (66.83)	5.38 (5.69)	2.88 (3.10)		2.91 (dd, J=4, 15 Hz)	4.26 (m)
14	F	H	CH ₃	H	OH	A	36.6	149-151	CCl ₄	C ₂₈ H ₂₉ ClFNO ₃	69.77 (69.66)	6.06 (6.01)	2.91 (2.97)		2.81 (dd, J=7, 15 Hz)	3.7 ^{c)}
20	H	H	H	H		B	5.4	216-219	Ac-Et ₂ O	C ₂₈ H ₂₈ N ₃ O ₂	76.51 (76.33)	6.65 (6.75)	9.56 (9.43)		2.88 (dd, J=4, 15 Hz)	3.83 (m)
21	F	CH ₃	CH ₃	CH ₃	OH	B	—	—	—	—	—	—	—	—	3.67 (dd, J=7, 15 Hz)	—

a) See Chart 2.

b) Et₂O: diethyl ether, Pt·E: petroleum ether, C₆H₆: benzene, CCl₄: carbon tetrachloride, Hx: hexane, Ac: acetone.

c) Overlapped with the signal of the methoxy protons.

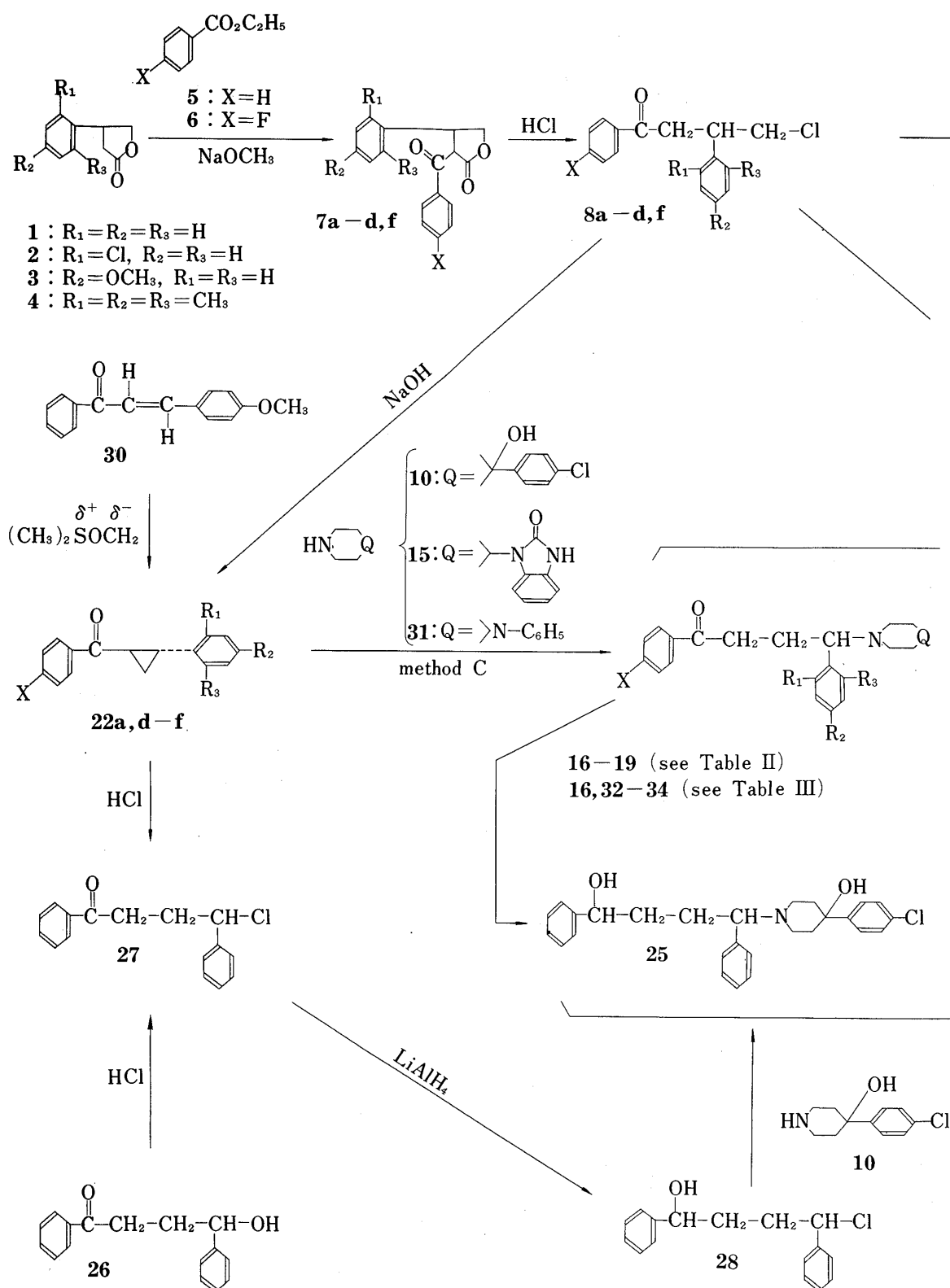
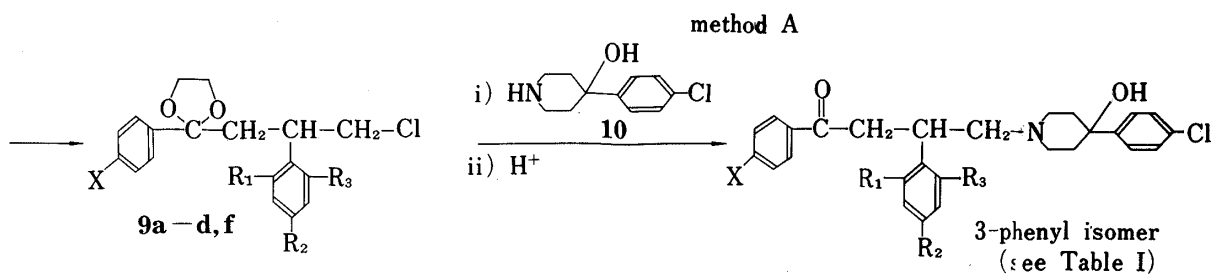
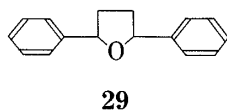
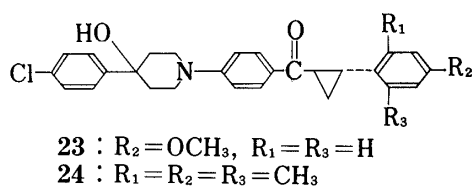
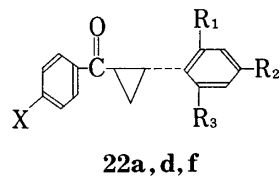
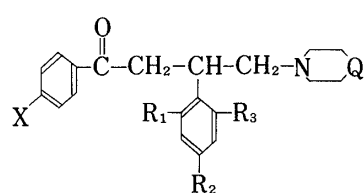
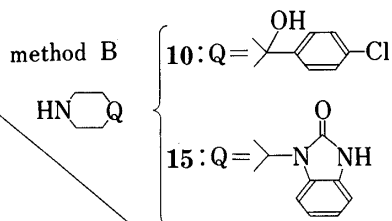


Chart 2



- 11 : X=R₁=R₂=R₃=H
 12 : X=F, R₁=R₂=R₃=H
 13 : X=F, R₁=Cl, R₂=R₃=H
 14 : X=F, R₂=OCH₃, R₁=R₃=H



- a : X=H, R₁=R₂=R₃=H
 b : X=F, R₁=R₂=R₃=H
 c : X=F, R₁=Cl, R₂=R₃=H
 d : X=F, R₂=OCH₃, R₁=R₃=H
 e : X=H, R₂=OCH₃, R₁=R₃=H
 f : X=F, R₁=R₂=R₃=CH₃

TABLE II. Physical Properties of 1,4-Diphenyl-4-(4-substituted piperidinyl)-1-butanones and Related Compounds (Method B)

10, 15

method B^{a)}

16-19

4-phenyl isomer

11, 14, 20, 21

3-phenyl isomer (see Table I)

Compd. No.	X	R ₁	R ₂	R ₃	Q	Yield %	mp (°C)	Recrystn solvent ^{b)}	Formula	Analysis (%)			NMR signal of C _{4'} -proton isomer ^{c)} (CDCl ₃ , δ ppm)	Yield of 3-phenyl Compd. (%)		Compd. No.	Yield of 3-phenyl Compd. (%)	
										Calcd (Found)	C	H		N	Compd. No.			Yield (%)
16	H	H	H	H		21.0	148.5-150	Et ₂ O	C ₂₇ H ₂₈ -ClNO ₂	74.72 6.50 3.20 (74.66 6.50 3.19)	3.20	3.53	(t, J = 7 Hz)	11	(5.2)	22a	(58.2)	—
17	H	H	H	H		18.8	201.5-203.5	Ac-Et ₂ O	C ₂₈ H ₂₉ -N ₃ O ₂	76.51 6.65 9.56 (76.72 6.48 9.82)	3.60	3.60	(t, J = 7 Hz)	20	(5.4)	22a	(62.6)	—
18	F	H	OCH ₃	H		13.7	149-150	Ac-Et ₂ O Pt-E	C ₂₈ H ₂₉ -ClFNO ₃	69.77 6.06 2.91 (69.48 6.00 3.13)	3.47	3.47	(t, J = 7 Hz)	14	(3.2)	22d	(24.7)	23 (29.6) R ₂ =OCH ₃ R ₁ =R ₃ =H
19	F	CH ₃	CH ₃	CH ₃		—	—	—	—	—	—	—	—	21 (—)	22f	(28.7)	24 (50.4) R ₁ =R ₂ =R ₃ =CH ₃	

a) See Chart 2.

b) Et₂O: diethyl ether, Ac: acetone, Pt E: petroleum ether.

c) Physical properties of 3-phenyl isomers (**11**, **14** and **20**) are shown in Table I.

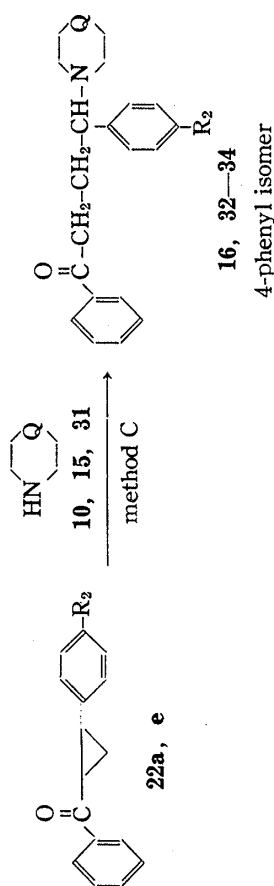
d) See Chart 2.

in order to prevent the formation of by-products, which are described below, in the condensation reaction of **8a,d,f** with piperidine derivatives (**10**, **15**). The reactions of **9a—d** with **10** followed by hydrolysis of the resulting condensation products gave 1,3-diphenyl-4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-butanone derivatives (**11—14**) (Method A). In the case of the reaction of the mesityl derivative (**9f**) with **10**, no condensation product was detected and the starting materials were recovered. The physical properties of (**11—14**) are listed in Table I. The structures of (**11—14**) were supported by their IR spectra, in which the C=O bands of the butanones appeared near 1665 cm^{-1} . The NMR spectra of (**11—14**) showed signals due to the C₂-methylene of the butanone chain at around 3.5 and 2.8 ppm (ABX type). In the case of the 3-(2-chlorophenyl)-1-butanone derivative (**13**), the presence of ABX-type proton signals of the butanone chain was confirmed by a spin decoupling experiment. Irradiation of the methine proton at 4.26 ppm changed the two double doublets at 3.49 and 2.91 ppm into a pair of doublets ($J=15\text{ Hz}$). In addition, the two double doublets at 3.18 and 3.03 ppm due to the C₂-methylene of the butanone chain of **13** in the NMR spectrum (in C₅D₅N) disappeared on treatment with 40% NaOD at 70°C. On the basis of the above data, the structures of **11—14** were confirmed.

On the other hand, the reaction mode of the butanone derivative (**8a**) with **10** was very different from that of the ketal compound (**9a**) with **10**, *i.e.*, three reaction products (**11**, **16**, **22a**) were separated by column chromatography, followed by preparative thin layer chromatography. The least mobile fraction gave the butanone derivative (**16**) in 21% yield. The structure of **16** was confirmed by the spectral data [MS: m/e 433, 435 (M^+); NMR: 3.53 ppm 1H, t, $J=7\text{ Hz}$, $-\text{CH}(\text{Ph})\text{N}\langle\rangle$] and by the chemical transformation of **16** to the 1-butanol derivative (**25**), which was identical with a sample prepared from a known compound (**27**)⁴ via the butanol derivative (**28**). In the reaction of **28** with the piperidine derivative (**10**), the yield of **25** was poor because of the formation of 2,5-diphenyltetrahydrofuran (**29**). The more mobile fraction afforded the 3-phenyl isomer (**11**) (5.2%), which was identified by comparison of its IR spectrum with that of an authentic sample synthesized by method A. A neutral compound (**22a**) was obtained in 58.2% yield from the most mobile fraction. The structure of **22a** was confirmed by comparison of its IR and NMR spectra with those of an authentic sample prepared from **8a** by a modified method reported by Cannon *et al.*⁵ Rearranged compounds (**16—18**) were similarly obtained in the reactions of butanone derivatives (**8a, d**) with secondary amines (**10**, **15**), and the results are summarized in Table II (Method B). In the reaction of 4-chloro-1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1-butanone (**8d**) with **10**, a more complicated result was found. That is, another cyclopropane derivative (**23**) was isolated together with the 3-(4-methoxyphenyl) isomer (**14**), the 4-(4-methoxyphenyl) isomer (**18**) and the cyclopropane derivative (**22d**). The elemental analysis and mass spectrum of **23** established the molecular formula C₂₈H₂₈ClNO₃. On the basis of the above data and a similar example reported by Welstead *et al.*,⁶ the structure of **23** was elucidated to be 4-(4-chlorophenyl)-4-hydroxy-1-[4-[2-(4-methoxyphenyl)cyclopropan-1-ylcarbonyl]phenyl]piperidine. On the other hand, the reaction of **8f** with the piperidine derivative (**10**) afforded cyclopropane derivatives (**22f**, **24**) as the main products instead of butanone derivatives (**19**, **21**). The steric hindrance of the mesityl group of **8f** seems to prevent the formation of butanone derivatives (**19**, **21**).

The cyclopropane derivative (**22a**) was prepared in good yield by treatment of **8a** with 10% sodium hydroxide aqueous solution.⁵ Accordingly, the formation of **22a,d,f** in the reaction of **8a,d,f** with piperidine derivatives (**10**, **15**) occurred by an intramolecular condensation reaction catalyzed by the secondary amines (**10**, **15**). Furthermore, the rearranged products (**16**, **32—34**) were also obtained in fairly good yields without any detectable formation of the 3-phenyl isomers by heating of the cyclopropane derivatives (**22a, e**) with secondary amines (**10**, **15**, **31**) at 110—160°C, and the results are listed in Table III (Method C). On the basis of the above results, it appears that the formation of 4-phenyl isomers (**16—18**) in the

TABLE III. Physical Properties of 1,4-Diphenyl-4-(4-substituted Piperidiny)-1-Butanones and Related Compound (Method C)



Compd. No.	R ₂	Q	Yield (%)	Reaction conditions	mp (°C)	Recrystn. solvent ^{a)}	Formula	Analysis (%)				NMR signal of C ₄ -proton (CDCl ₃ , δ ppm)
								Calcd (Found)	C	H	N	
16	H		13.9 17.7	110°C, 18 h 110°C, 48 h	150—152.5	Et ₂ O	C ₂₇ H ₂₈ ClNO ₂	—	—	—	—	^{b)}
32	OCH ₃		26.4 48.5	160°C, 30 h 160°C, 40 h	169—170	Ac-Et ₂ O	C ₂₈ H ₃₀ ClNO ₃	72.47 (72.28)	6.52 6.33	3.02 3.16	3.50 (t, J = 7 Hz)	
33	OCH ₃		41.1	160°C, 20 h	195.5—197.5	Ac	C ₂₉ H ₃₁ N ₃ O ₃	74.47 (73.99)	6.65 6.53	8.95 8.84	3.56 (t, J = 7 Hz)	
34	OCH ₃		41.7	160°C, 50 h	196—198	EtOH-Ac	C ₂₇ H ₃₀ N ₂ O ₃ HCl	71.90 (71.62)	6.93 6.73	6.21 6.12	3.45 (dd, J = 6, 8 Hz) ^{c)}	

a) Et₂O: diethyl ether, Ac: acetone, EtOH: ethanol.

b) See Table II.

c) Measured with free base of **34**.

reaction of **8a,d** with piperidine derivatives (**10, 15**) can be interpreted in terms of an addition reaction of the secondary amines (**10, 15**) to the cyclopropane derivatives (**22a, d**) as shown in Chart 3. A similar addition reaction was also found in the reaction of **22a** with hydrogen chloride in ether at room temperature, and the structure of the product (**27**) was confirmed by comparison with an authentic sample synthesized from 1,4-diphenyl-4-hydroxy-1-butanone (**26**) by the method of Lutz *et al.*⁴⁾ This result shows that the ring opening reaction is favored under acidic rather than basic conditions.

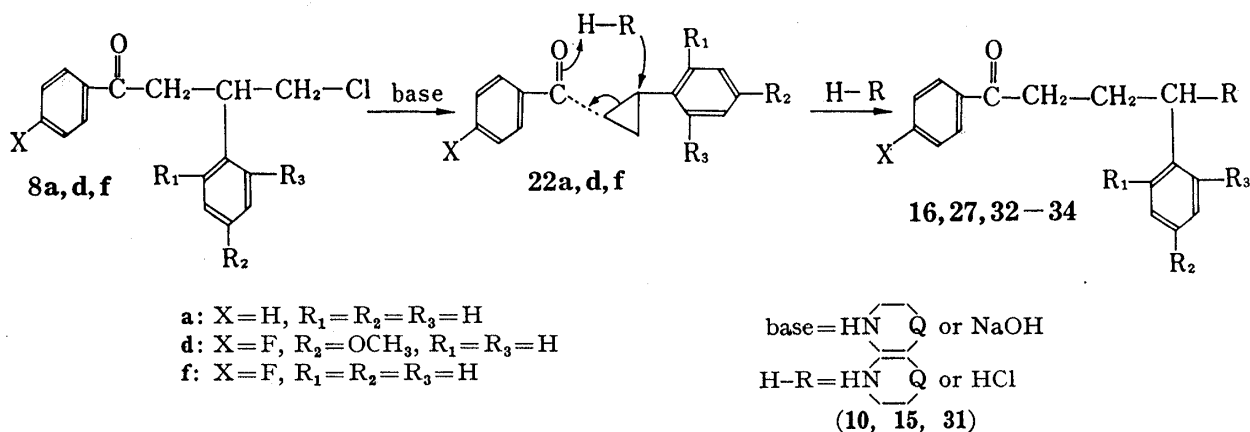


Chart 3

The inhibitory effects of the present compounds on spontaneous motor activity³⁾ were far less than that of haloperidol. The details will be published elsewhere.

Experimental

The following instruments were used. IR spectra, a Hitachi EPI-G 2 type infrared spectrometer; NMR (tetramethylsilane as an internal standard), a JEOL JNM-4H-100 spectrometer (100 MHz) and a Varian XL-200 NMR spectrometer (200 MHz); mass spectra, a Hitachi RMS-4 mass spectrometer (electron impact ionization, direct inlet, 70 eV) and a JEOL JMS-01SG-2 spectrometer [field desorption (FD)]; melting points, a Yanagimoto melting point apparatus (Type MP-1). All melting points are uncorrected.

α -Benzoyl- β -phenyl- γ -butyrolactone (7a)—A mixture of β -phenyl- γ -butyrolactone (**1**) (1.62 g, 0.01 mol), ethyl benzoate (7.51 g, 0.05 mol) and sodium methylate (1.35 g, 0.025 mol) was heated at 100°C for 30 min. After cooling, the reaction mixture was poured into ice-water and washed with chloroform. The chloroform layer was extracted with 4N NaOH. The combined aqueous layer was acidified with 7% HCl and extracted with benzene. The organic layer was successively washed with 5% NaHCO₃ and water, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was crystallized from acetone-petroleum ether to give colorless crystals (1.19 g, 44.5%) of **7a**, mp 140–141.5°C. *Anal.* Calcd for C₁₇H₁₄O₃: C, 76.67; H, 5.30. Found: C, 76.30; H, 5.29. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1775, 1680 (C=O).

4-Chloro-1,3-diphenyl-1-butanone (8a)—A mixture of **7a** (533 mg, 2 mmol) and conc. HCl (50 ml) was heated under reflux for 5 h. The reaction mixture was extracted with benzene. The extract was washed with H₂O, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was crystallized from Et₂O to afford colorless needles of **8a** (382 mg, 73.7%), mp 76–77°C. *Anal.* Calcd for C₁₆H₁₅ClO: C, 74.27; H, 5.84; Cl, 13.32. Found: C, 73.99; H, 5.81; Cl, 13.08. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1675 (C=O). MS *m/e*: 259, 261 (M⁺). NMR (δ in CDCl₃): 3.4–3.6 (m, 2H, COCH₂–), 3.7–3.9 (3H, m, –CH–CH₂Cl), 7.2–7.6 (8H, m, –C₆H₅ and *meta* protons of *para*-fluorophenyl group), 7.92 (2H, dd, *J*=2.5, 8 Hz).

4-Chloro-1-(4-fluorophenyl)-3-phenyl-1-butanone (8b)—A mixture of β -phenyl- γ -butyrolactone (**1**), (5.03 g, 0.031 mol), ethyl 4-fluorobenzoate (26 g, 0.154 mol) and sodium methylate (4.16 g, 0.077 mol) was heated at 100°C for 30 min with stirring. The reaction mixture was worked up as described for **7a** to provide **7b** as a pale brown oil (2.63 g). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1765, 1675 (C=O). The crude product was used for the next step without further purification. A mixture of **7b** (2.63 g) and conc. HCl (300 ml) was refluxed for 6 h. The reaction mixture was extracted with benzene. The benzene layer was washed with water, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) using benzene-petroleum ether (2:3), and the eluate was concentrated to afford **8b** as a pale yellow oil (1.87 g, 21.9%), IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1675 (C=O).

4-Chloro-3-(2-chlorophenyl)-1-(4-fluorophenyl)-1-butanone (8c)—Prepared from **2** (4.92 g, 0.025 mol) as described for **8b**. Yield 1.47 g (19%), a pale yellow oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1680 (C=O).

4-Chloro-1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1-butanone (8d)—Prepared from **3** (11.72 g, 0.061 mol) as described for **8b**. Yield 3.65 g (19.5%), a pale yellow oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1685.

4-Chloro-1-(4-fluorophenyl)-3-(2,4,6-trimethylphenyl)-1-butanone (8f)—Prepared from **4** (8.50 g, 0.042 mol) as described for **8b**. Yield 2.67 g (28%), a pale yellow oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1685.

2-(3-Chloro-2-phenylpropyl)-2-phenyl-1,3-dioxolane (9a)—A mixture of 4-chloro-3-phenyl-1-butanone (**8a**) (638 mg, 2.3 mmol), *p*-toluenesulfonic acid monohydrate (100 mg), ethylene glycol (10 ml) and dry benzene (100 ml) was stirred under reflux for 60 h. The H_2O formed during the reaction was separated by means of a Dean-Stark apparatus. After cooling, the reaction mixture was extracted with benzene and the organic layer was washed with H_2O , dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on Al_2O_3 with benzene-petroleum (3 : 7). The eluate was concentrated to give **9a** as a pale yellow oil (486 mg, 65.2%). NMR (δ in CDCl_3): 2.2—2.6 (2H, m, $-\text{C}-\text{CH}_2-\text{CH}(\text{C}_6\text{H}_5)-$), 3.1—3.3 (1H, m, $-\text{CH}-\text{C}_6\text{H}_5-$), 3.5—4.0 (6H, m, CH_2Cl , 1,3-dioxolane ring protons), 7.0—7.6 (10H, m, 2 $\times$ phenyl).

2-[3-Chloro-2-(4-fluorophenyl)propyl]-2-phenyl-1,3-dioxolane (9b)—Prepared from **8b** (1.67 g, 6 mmol) as described for **9a**. Yield 1.63 g (84.8%), a pale yellow oil.

2-[3-Chloro-2-(4-fluorophenyl)propyl]-2-(2-chlorophenyl)-1,3-dioxolane (9c)—Prepared from **8c** (2.59 g, 8.3 mmol) as described for **9a**. Yield 1.95 g (66%), a pale yellow oil.

2-[3-Chloro-2-(4-fluorophenyl)propyl]-2-(4-methoxyphenyl)-1,3-dioxolane (9d)—Prepared from **8d** (3.91 g, 12.7 mmol) as described for **9a**. Yield 1.0 g (22.4%), a pale yellow oil.

2-[3-Chloro-2-(4-fluorophenyl)propyl]-2-(2,4,6-trimethylphenyl)-1,3-dioxolane (9f)—Prepared from **8f** (2.51 g, 7.8 mmol) as described for **9a**. Yield 1.88 g (66.3%), a pale yellow oil.

General Procedure for the Synthesis of Butanone derivatives (11—14) (Method A)—A mixture of the dioxolane derivative (**9**) (1 mmol), 4-(4-chlorophenyl)-4-hydroxypiperidine (**10**) (424 mg, 2 mmol) and KI (50 mg, 0.3 mmol) was heated at 110°C for 20 h in a sealed tube. The reaction mixture was dissolved in CH_3OH (5 ml) and conc. HCl (0.3 ml), and the solution was concentrated under reduced pressure after standing at room temperature for 1 h. To the residue was added 10% NaOH and the mixture was stirred and extracted with CHCl_3 . The CHCl_3 layer was washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on Al_2O_3 (30 g) using benzene-ether (3 : 2), (1 : 1) and (2 : 3). The eluate with benzene-ether (2 : 3) was concentrated *in vacuo*, and recrystallized from a suitable solvent. The physical data of **11—14** are listed in Table I.

Reaction of 4-Chloro-1,3-diphenyl-1-butanone (8a) with 4-(4-Chlorophenyl)-4-hydroxypiperidine (10) (Method B)—A mixture of 4-chloro-1,3-diphenyl-1-butanone (**8a**) (440 mg, 1.7 mmol) and 4-(4-chlorophenyl)-4-hydroxypiperidine (**10**) (790 mg, 3.73 mmol) was heated at 110°C for 16 h in a sealed tube. The reaction mixture was purified by chromatography on silica gel (30 g) with benzene, CHCl_3 and CHCl_3 - EtOH (19 : 1). The benzene eluate was concentrated to give **22a** as a colorless oil (220 mg, 58.2%). Crystallization from Et_2O -petroleum ether afforded colorless plates, mp $45\text{--}46^\circ\text{C}$,⁷ which were identified by comparison of the IR spectrum with that of an authentic sample synthesized from **8a** by the method of Cannon *et al.*⁵

The eluates with CHCl_3 and CHCl_3 - EtOH (19 : 1) were combined and concentrated. The residue was separated into the following two fractions (a and b) by preparative continuous-development TLC (SiO_2 , CHCl_3 : EtOH = 49 : 1).

a) The less polar fraction was crystallized from Et_2O -hexane to give **11** as colorless needles (38 mg, 5.2%), mp $131\text{--}132^\circ\text{C}$. The structure was confirmed by direct comparison with an authentic sample prepared by Method A.

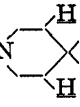
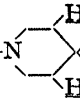
b) The more polar fraction was crystallized from Et_2O to give **16** as colorless plates (155 mg, 21%), mp $148.5\text{--}150^\circ\text{C}$. The physical data of **16** are listed in Table II. FD MS m/e : 433, 435 (M^+).

Reaction of 4-Chloro-1,3-diphenyl-1-butanone (8a) with Piperidine Derivative (15)—A mixture of **8a** (1.55 g, 6 mmol), **15** (2.6 g, 12 mmol) and KI (300 mg, 1.8 mmol) was heated at 110°C for 18 h in a sealed tube. The reaction mixture was worked up as described above (see Method B). The physical data of the reaction products (**17**, **20**, **22a**) are listed in Tables I and II. Compound (**20**) was identified by comparison with an authentic sample prepared by Method A. The structure of **22a** was confirmed by comparison of its IR spectrum with that of a sample prepared by cyclization⁵ of **8a** with NaOH .

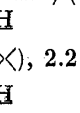
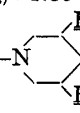
Reaction of 4-Chloro-1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1-butanone (8d) with the Piperidine Derivative (10)—A mixture of **8d** (1.01 g, 3.3 mmol), **10** (1.61 g, 7.6 mmol) and KI (200 mg, 1.2 mmol) was heated at 110°C for 18 h in a sealed tube, and the reaction mixture was worked up as described above. The physical data of the reaction products (**14**, **18**, **22d**) are listed in Tables I and II. 4-(4-Chlorophenyl)-4-hydroxy-1-[4-[2-(4-methoxyphenyl)cyclopropan-1-ylcarbonyl]phenyl]piperidine (**23**) was isolated from the CHCl_3 fraction on silica gel (100 g) chromatography as pale yellow needles, mp $182\text{--}185.5^\circ\text{C}$. Yield 453 mg (29.6%). *Anal.* Calcd for $\text{C}_{28}\text{H}_{28}\text{ClNO}_3$: C, 72.79; H, 6.11; N, 3.03. Found: C, 72.52; H, 5.97; N, 3.31.

$$\begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{CO} \quad \text{ph} \end{array}$$

MS m/e : 461, 463 M^+ (MW = 462.00). NMR (200-MHz) (δ in CDCl_3): 1.44 (1H, m, $-\text{CO}-$), 1.7 (1H,

broad, OH), 1.84 (3H, m, -ph and , 2.18 (2H, m, , 2.63 and 2.78 (2H, m, -ph), 3.42 (2H, m, , 3.80 (3H, s, OCH₃), 3.85 (2H, m, , 6.87 and 7.14 (4H, AB q, *J* = 9 Hz, -C₆H₄OCH₃), 6.96 and 7.98 (4H, AB q, *J* = 9 Hz, -CO-C₆H₄-), 7.41 (4H, AB q, *J* = 9 Hz, Cl-C₆H₄-).

Reaction of 4-Chloro-1-(4-fluorophenyl)-3-(2,4,6-trimethylphenyl)-1-butanone (8f) with the Piperidine Derivative (10)—A mixture of **8f** (1.28 g, 4 mmol), **10** (1.91 g, 9 mmol) and KI (250 mg, 1.5 mmol) was heated at 110°C for 20 h in a sealed tube. The reaction mixture was worked up as described in Method B, and 1-(4-fluorobenzoyl)-2-(2,4,6-trimethylphenyl)cyclopropane (**22f**) was obtained from the fraction eluted with benzene-petroleum ether (1:2) on silica gel (80 g) as colorless oil. Yield 324 mg (28.7%). The structure of **22f** was confirmed by cyclization⁵ of **8f** with NaOH. 4-(4-Chlorobenzoyl)phenylpiperidine (**24**) was obtained from the fraction eluted with benzene-petroleum ether (1:2) on silica gel (80 g) as pale yellow crystals, mp 102–103°C. *Anal.* Calcd for C₃₀H₃₂ClNO₂: C, 76.01; H, 6.80; N, 2.96. Found: C, 76.01; H, 6.80; N, 2.96.

NMR (200-MHz) (δ in CDCl₃): 1.35 (1H, m, -ph and , 2.2 (2H, m, , 2.27

88 (3H, m, -ph), 2.32 (6H, s, *o*-methyl

protons of mesityl), 2.63 and 2.75 (2H, m, -ph), 3.45 (2H, m, , 3.86 (2H, m, , 6.86 (2H, s, mesityl), 6.99 and 8.04 (4H, AB q, *J* = 9 Hz, -CO-C₆H₄-), 7.43 (4H, AB q, *J* = 8 Hz, Cl-C₆H₄-).

trans-1-Benzoyl-2-phenylcyclopropane (22a)—A mixture of 4-chloro-1,3-diphenyl-1-butanone (**8a**) (1.04 g, 4 mmol), NaOH (400 mg, 10 mmol) and H₂O (0.72 ml) was heated at 100 °C for 6 h.⁵ The reaction mixture was extracted with ether and the organic layer was washed with water, dried over Na₂SO₄ and concentrated. The residue was purified by chromatography on silica gel (30 g). The fraction eluted with benzene-petroleum ether (1:1) was concentrated *in vacuo* and the residue was crystallized from ether-petroleum ether to afford colorless plates (**22a**), mp 45–46°C.⁷ Yield 726 mg (81.5%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1670. NMR (δ in CDCl₃): 1.54 and 1.90 (2H, m, methine protons of cyclopropane), 2.79 (2H, m, methylene protons of cyclopropane), 7.0–7.5 (8H, m, phenyl, and *meta* and *para* protons of benzoyl), 7.96 (2H, ABX type q, *J* = 8, 2 Hz).

trans-1-(4-Fluorobenzoyl)-2-(4-methoxyphenyl)cyclopropane (22d)—Prepared from **8d** (613 mg, 2 mmol) as described for **22a**. Yield 420 mg (77.6%), colorless prisms, mp 74–75°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1665. NMR (δ in CDCl₃): 1.52, 1.88 (2H, each m, methylene protons of cyclopropane), 2.68 (2H, m, methine protons of cyclopropane), 3.79 (3H, s, OCH₃), 6.8–7.3 (6H, m, aromatic ring protons of 4-methoxyphenyl and *meta* protons of *para* fluorobenzoyl), 8.02 (2H, ABX type q, *ortho* protons of *para* fluorobenzoyl).

trans-1-(4-Fluorobenzoyl)-2-(2,4,6-trimethylphenyl)cyclopropane (22f)—Prepared from **8f** (860 mg, 2.7 mmol) as described for **22a**. Yield 659 mg (86.5%), a pale yellow oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1660. NMR (δ in CDCl₃): 1.42, 1.84 (2H, each m, methylene protons of cyclopropane), 2.24 (3H, s, *para* methyl), 2.29 (6H, s, *ortho* methyls), 2.67 (2H, m, methine protons of cyclopropane), 6.82 (2H, s, mesityl ring protons), 7.14 (2H, t, *meta* protons of *para* fluorobenzoyl), 8.08 (2H, ABX type q, *ortho* protons of *para* fluorobenzoyl).

1-Benzoyl-2-(4-methoxyphenyl)cyclopropane (22e)—Prepared from 2-(4-methoxyphenyl)vinyl phenyl ketone (**30**) (20.49 g, 0.086 mol) by the method reported by Corey *et al.*⁸ Yield 12.25 g (56.5%), a pale yellow oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1665. NMR (δ in CDCl₃): 1.49, 1.86 (2H, each m, methylene protons of cyclopropane), 2.75 (2H, m, methine protons of cyclopropane), 3.73 (3H, s, OCH₃), 7.4 (4H, AB q, *J* = 8 Hz, methoxy phenyl ring protons), 7.38 (3H, m, *meta* and *para* protons of benzoyl), 7.90 (2H, ABX type q, *J* = 2, 8 Hz, *ortho* protons of benzoyl).

4-Chloro-1,4-diphenyl-1-butanone (27)—Dry HCl gas was bubbled through a solution of **22a** (50 mg, 0.23 mmol) in Et₂O (10 ml) for 20 min, and the reaction mixture was allowed to stand at room temperature for 1 h. The reaction mixture was washed with cold water, dried over Na₂SO₄ and concentrated to dryness, and the residue was crystallized from Et₂O-petroleum ether to yield colorless needles (51 mg, 87%), mp 87.5–88.5°C. The structure was confirmed by comparison of the IR spectrum with that of an authentic sample synthesized from **26** by the method reported by Lutz *et al.*⁴

4-Chloro-1,4-diphenyl-1-hydroxybutane (28)—LiAlH₄ (380 mg, 10 mmol) was added to a cold (0–5°C) solution of **27** (518 mg, 2 mmol) in dry ether (60 ml), and the mixture was stirred for 4 h in an ice-bath, treated with AcOEt (10 ml) and then with H₂O (10 ml) and diluted with Et₂O. The organic layer was

separated, washed with H₂O, dried over Na₂SO₄ and concentrated. The residue was crystallized from Et₂O–petroleum ether. The crystals were filtered off and the filtrate was concentrated to give a colorless oil (318 mg, 60.9%). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 3590, 3380 (OH). NMR (δ in CDCl₃): 1.7–2.5 (5H, m, methylene protons and OH), 4.55–5.2 (2H, m, methine protons), 7.1–7.5 (10H, m, phenyl).

1,4-Diphenyl-4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxybutane (25)—ex. i) NaBH₄ (95 mg, 2.5 mmol) was added to a solution of (16) (109 mg, 0.25 mmol) in CH₃OH (10 ml) at room temperature with stirring, and the reaction mixture was heated under reflux for 30 min. The solvent was removed *in vacuo* and the residue was extracted with CHCl₃ (50 ml $\times$ 2). The extract was washed with water, dried over Na₂SO₄ and concentrated. The residue was crystallized from acetone–petroleum ether to afford colorless needles (98 mg, 90%) of **25**, mp 75–77°. Anal. Calcd for C₂₇H₃₀ClNO₂: C, 74.37; H, 6.94; N, 3.21. Found: C, 74.28; H, 6.82; N, 3.18. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3680 (sh.), 3420 (OH).

ex. ii) A mixture of 4-chloro-1,4-diphenyl-1-butanol (**28**) (172 mg, 0.65 mmol), 4-(4-chlorophenyl)-4-hydroxypiperidine (**10**) (340 mg, 1.6 mmol) and KI (30 mg, 0.18 mmol) was heated in a sealed tube for 5 h. The reaction mixture was taken up in 10% NaOH (20 ml) and benzene (50 ml), and the organic layer was separated, washed with H₂O, dried over Na₂SO₄ and concentrated. The residue was chromatographed on silica gel (15 g) with benzene, CHCl₃ and CHCl₃–EtOH (20:1). The fraction eluted with benzene was concentrated to give 2,5-diphenyltetrahydrofuran (**29**) (110 mg, 75.3%) as a colorless oil. NMR (δ in CDCl₃): 1.49, 2.38 (each 2H, each m, methylene protons), 5.00, 5.22 (each 1H, each t, *J* = 7 Hz, methine protons), 7.1–7.5 (10H, m, phenyl). MS *m/e*: 224 (M⁺).

The fraction eluted with CHCl₃–EtOH (20:1) was concentrated to afford a 4-piperidinyl-1-butanol derivative (**25**) as a colorless oil (60 mg, 21%). The oily product was crystallized from acetone–petroleum ether to give colorless needles (5 mg, 1.8%) of **25**, mp 74–77°C; this product was identified by comparison of its IR spectrum with that of the sample obtained in ex. i), and by mixed melting point determination.

Preparation of 1,4-Diphenyl-1-butanone Derivatives (16, 32–34) (Method C): 1,4-Diphenyl-4-[4-(4-chlorophenyl)-4-hydroxy]-1-piperidinyl-1-butanone (16)—A mixture of *trans*-1-benzoyl-2-phenylcyclopropane (**22a**) (333 mg, 1.5 mmol) and 4-(4-chlorophenyl)-4-hydroxypiperidine (**10**) (423 mg, 2 mmol) was heated in a sealed tube at 110°C for 18 h. The reaction mixture was chromatographed on silica gel (40 g) with benzene, CHCl₃ and CHCl₃–EtOH (19:1). The fractions eluted with benzene and CHCl₃ were combined and concentrated to recover the starting material (**22a**) (257 mg, 77%) as an oil. The fraction eluted with CHCl₃–EtOH (19:1) was concentrated to afford an oil (113 mg), which was crystallized from Et₂O to give colorless crystals of (16) (90 mg, 13.9%), mp 150–152.5°C. The physical data of **16** are listed in Table III. The structure of **16** was confirmed by comparing its IR spectrum with that of a sample prepared by method B as described above. The following compounds were similarly synthesized.

4-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]-4-(4-methoxyphenyl)-1-phenyl-1-butanone (32)—Prepared from **22e** as described for **16**. The physical data of **32** are listed in Table III.

4-[4-(2,3-Dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]-4-(4-methoxyphenyl)-1-phenyl-1-butanone (33)—Prepared from **22e** as described for **16**. The physical data of **33** are listed in Table III.

4-(4-Methoxyphenyl)-1-phenyl-4-(4-phenyl-1-piperazinyl)-1-butanone Hydrochloride (34)—Prepared from **22e** as described for **16**. The physical data of **34** are listed in Table III.

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