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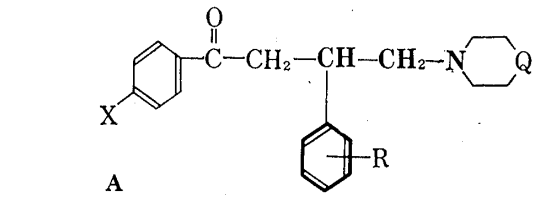
A series of 1,3-diphenyl-1-butanone derivatives (**11**—**14**) was synthesized as part of a search for new psychotropic agents.

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 done[2] 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 paper[1] 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**).



A
X=H, F
R=H, 4-CH_3O, 2-Cl, 2,4,6-tri-CH_3

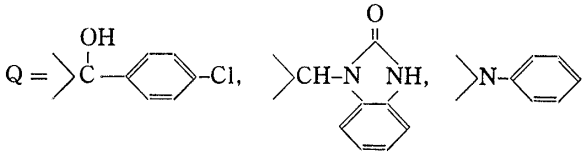
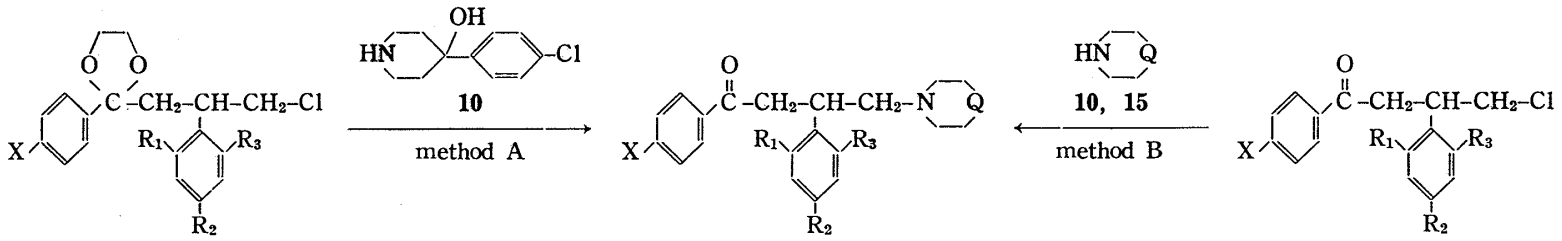


Chart 1

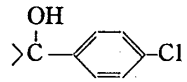
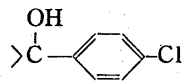
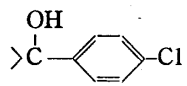
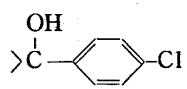
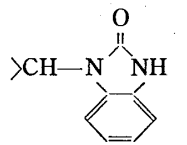
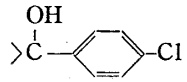
The synthesis of 4-chloro-1,3-diphenyl-1-butanones (**8a—d,f**) was carried out by the procedure described in the previous paper.[3] Thus, the Claisen condensation of β-phenyl-γ-butyrolactone (**1**) with ethyl benzoate (**5**) in the presence of sodium methylate gave α-benzoyl-β-phenyl-γ-butyrolactone (**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**)

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



9a—d, f **11—14, 20, 21** 3-phenyl isomer **8a, d**

Compd. No.	X	R_1	R_2	R_3	Q	Method[a]	Yield %	mp (°C)	Recrystn solvent[b]	Formula	Analysis (%) Calcd (Found) C	H	N	NMR spectral data (in $CDCl_3$) (δ ppm) C_2-protons	C_3-proton
11	H	H	H	H		A	63.0	132—133	Et_2O–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) 3.59 (dd, J=7, 15 Hz)	3.75 (m)
						B	5.2	131—132	Et_2O–Pt·E						
12	F	H	H	H		A	35.6	122.5—123	Et_2O–Pt·E	$C_{27}H_{27}ClFNO_2$	71.75 (72.14	6.02 6.17	3.10 3.30)	2.85 (dd, J=4, 14 Hz) 3.53 (dd, J=7, 14 Hz)	3.7 (m)
13	F	Cl	H	H		A	22.3	132.5—133.5	C_6H_6–Hx	$C_{27}H_{26}Cl_2FNO_2$	66.67 (66.83	5.38 5.69	2.88 3.10)	2.91 (dd, J=4, 15 Hz) 3.49 (dd, J=7, 15 Hz)	4.26 (m)
14	F	H	OCH_3	H		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=4, 15 Hz) 3.49 (dd, J=7, 15 Hz)	3.7[c]
						B	3.2	150—151	Et_2O–Pt·E						
20	H	H	H	H		B	5.4	216—219	Ac–Et_2O	$C_{28}H_{29}N_3O_2$	76.51 (76.33	6.65 6.75	9.56 9.43)	2.88 (dd, J=4, 15 Hz) 3.67 (dd, J=7, 15 Hz)	3.83 (m)
21	F	CH_3	CH_3	CH_3		B	—	—	—						

a) See Chart 2.
b) Et_2O: diethyl ether, Pt·E: petroleum ether, C_6H_6; benzene, CCl_4: carbon tetrachloride, Hx: hexane, Ac: acetone.
c) Overlapped with the signal of the methoxy protons.

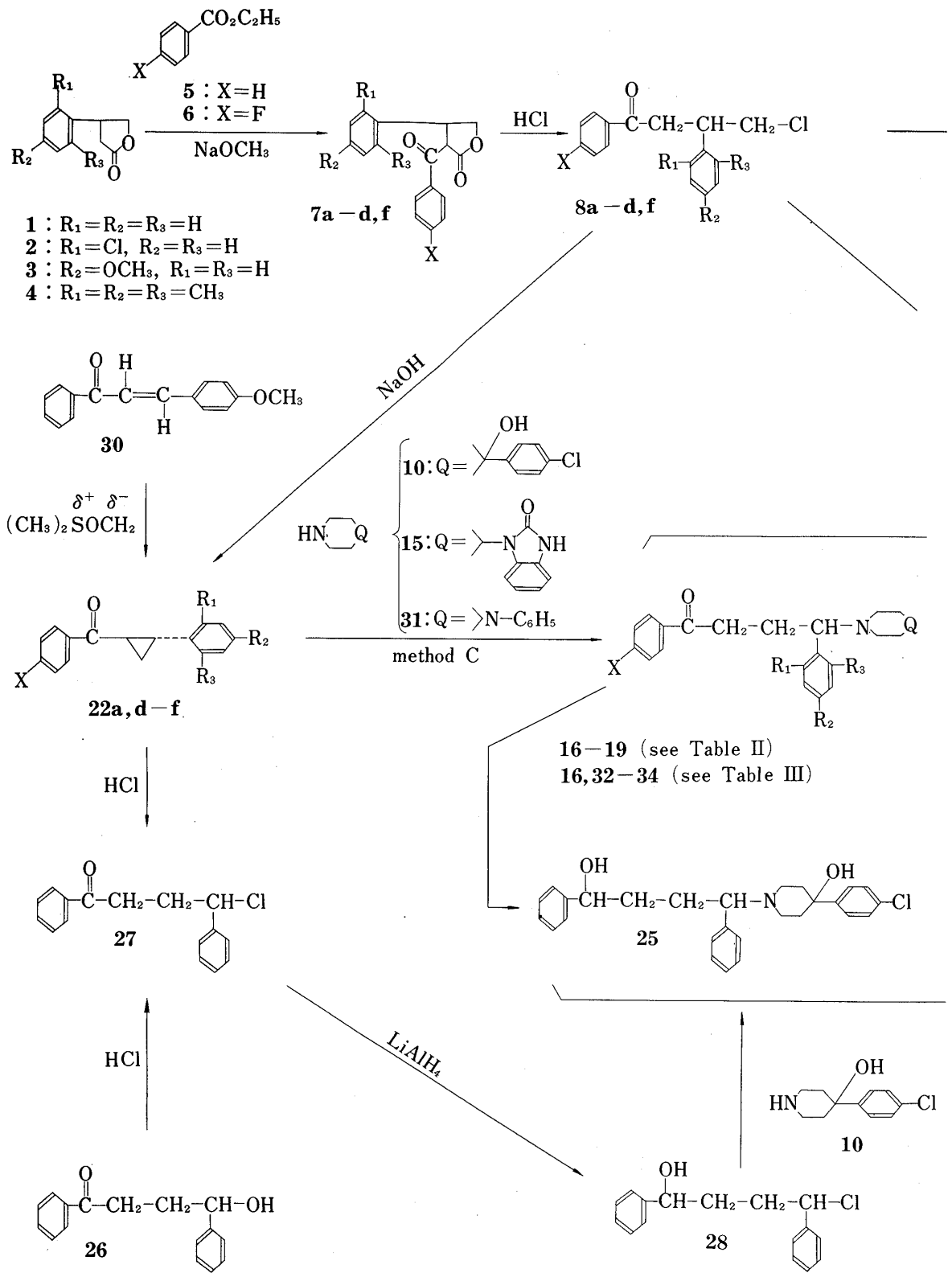
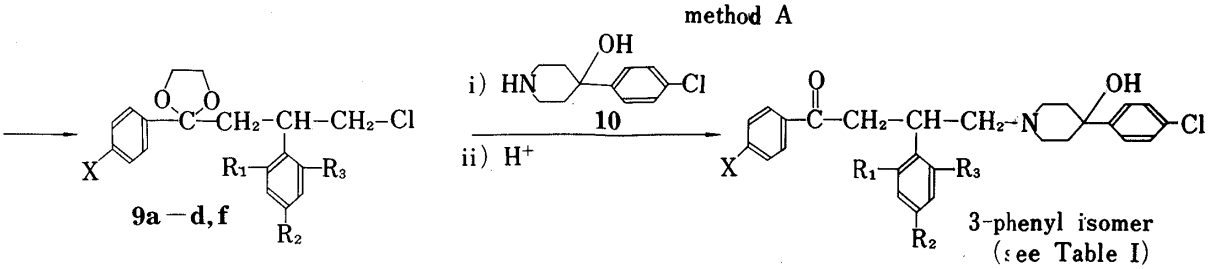
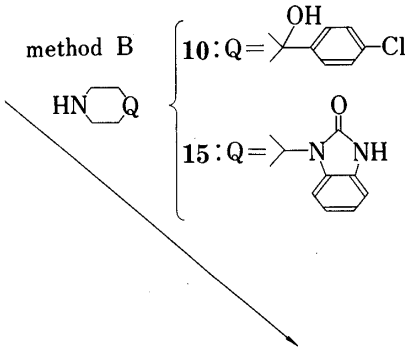
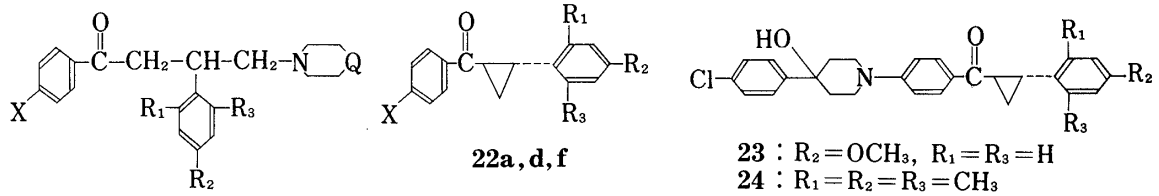


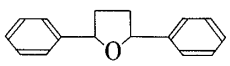
Chart 2



11 : X=R_1=R_2=R_3=H
12 : X=F, R_1=R_2=R_3=H
13 : X=F, R_1=Cl, R_2=R_3=H
14 : X=F, R_2=OCH_3, R_1=R_3=H







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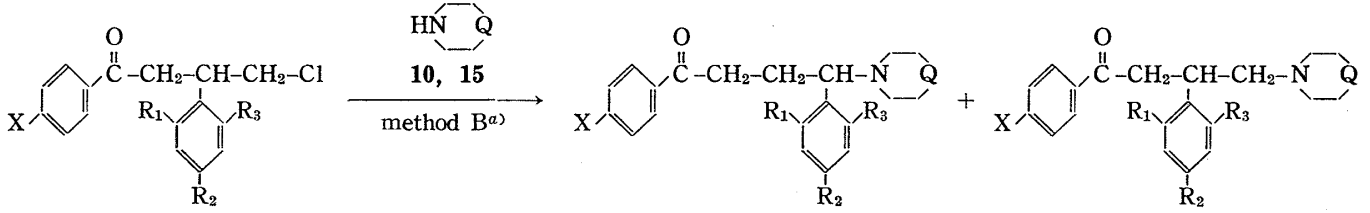
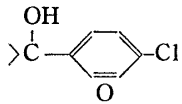
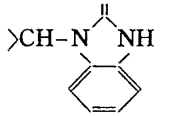
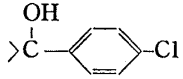
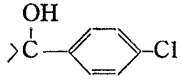
a : X=H, R_1=R_2=R_3=H
b : X=F, R_1=R_2=R_3=H
c : X=F, R_1=Cl, R_2=R_3=H
d : X=F, R_2=OCH_3, R_1=R_3=H
e : X=H, R_2=OCH_3, R_1=R_3=H
f : X=F, R_1=R_2=R_3=CH_3

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



8a, d, f → **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 (%) Calcd (Found) C	H	N	NMR signal of C_4-proton ($CDCl_3$, δ ppm)	Yield of 3-phenyl isomer[c)] Compd. No.	(%)	Yield of by-products[d)] Compd. No.	(%)	Compd. No.	(%)
16	H	H	H	H		21.0	148.5—150	Et_2O	$C_{27}H_{28}ClNO_2$	74.72 (74.66	6.50 6.50	3.20 3.19)	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_2O	$C_{28}H_{29}N_3O_2$	76.51 (76.72	6.65 6.48	9.56 9.82)	3.60 (t, J=7 Hz)	**20**	(5.4)	**22a**	(62.6)	—	
18	F	H	OCH_3	H		13.7	149—150	Ac–Et_2O–Pt·E	$C_{28}H_{29}ClFNO_3$	69.77 (69.48	6.06 6.00	2.91 3.13)	3.47 (t, J=7 Hz)	**14**	(3.2)	**22d**	(24.7)	**23** $R_2=OCH_3$, $R_1=R_3=H$	(29.6)
19	F	CH_3	CH_3	CH_3		—	—	—	—	—	—	—	—	**21**	(—)	**22f**	(28.7)	**24** $R_1=R_2=R_3=CH_3$	(50.4)

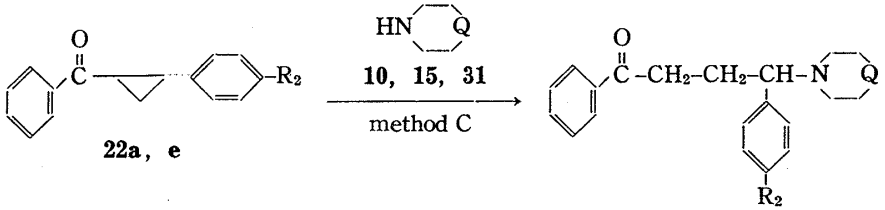
a) See Chart 2.
b) Et_2O: diethyl ether, Ac: acetone, Pt E: petroleum ether.
c) Physical properties of 3-phenyl isomers (**11**, **14** and **20**) are shown in Table I.
d) See Chart 2.

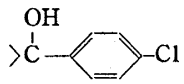
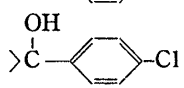
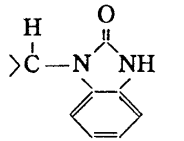
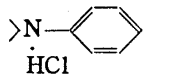
in order to prevent the formation of by-products, which are described below, in the condensation reaction of **8a,d,f** with piperidine derivatives (**10**, **15**). The reactions of **9a—d** with **10** followed by hydrolysis of the resulting condensation products gave 1,3-diphenyl-4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-butanone 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 C_2-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 Hz). In addition, the two double doublets at 3.18 and 3.03 ppm due to the C_2-methylene of the butanone chain of **13** in the NMR spectrum (in C_5D_5N) 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 Hz, $-C\underline{H}(Ph)N\langle$)] 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 $C_{28}H_{28}ClNO_3$. 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 derivaves (**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 Piperidinyl)-1-Butanones and Related Compound (Method C)



Compd. No.	R_2	Q	Yield (%)	Reaction conditions	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	N	NMR signal of C_4-proton ($CDCl_3$, δ ppm)
16	H		13.9 17.7	110°C, 18 h 110°C, 48 h	150—152.5	Et_2O	$C_{27}H_{28}ClNO_2$	—	—	—	[b]
32	OCH_3		26.4 48.5	160°C, 30 h 160°C, 40 h	169—170	Ac–Et_2O	$C_{28}H_{30}ClNO_3$	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	$C_{29}H_{31}N_3O_3$	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	$C_{27}H_{30}N_2O_3HCl$	71.90 (71.62	6.93 6.73	6.21 6.12)	3.45 (dd, J=6, 8 Hz)[c]

a) Et_2O: 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.

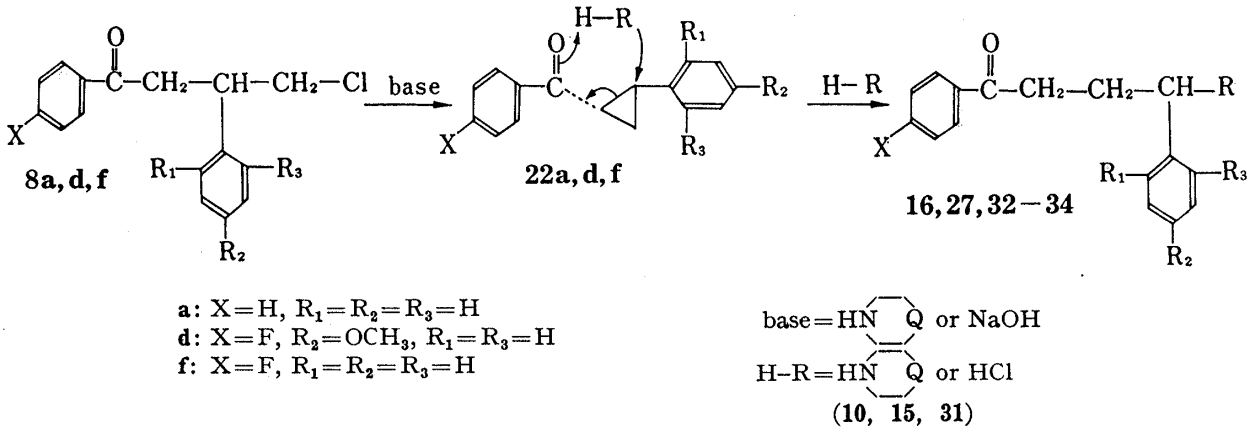


Chart 3

The inhibitory effects of the present compounds on spontaneous motor activity[3] 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 4 N NaOH. The combined aqueous layer was acidified with 7% HCl and extracted with benzene. The organic layer was successively washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4 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 $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.30; H, 5.29. IR ν_{max}^{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 H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was crystallized from Et_2O to afford colorless needles of **8a** (382 mg, 73.7%), mp 76—77°C. *Anal.* Calcd for $C_{16}H_{15}ClO$: C, 74.27; H, 5.84; Cl, 13.32. Found: C, 73.99; H, 5.81; Cl, 13.08. IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O). MS *m/e*: 259, 261 (M^+). NMR (δ in $CDCl_3$): 3.4—3.6 (m, 2H, $COCH_2$–), 3.7—3.9 (3H, m, –CH–CH_2Cl), 7.2—7.6 (8H, m, $-C_6H_5$ 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 ν_{max}^{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 Na_2SO_4 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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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, $-\underset{\diagdown\,\diagup}{C}-CH_2-CH(C_6H_5)-$), 3.1—3.3 (1H, m, $-CH-C_6H_5-$), 3.5—4.0 (6H, m, CH_2Cl, 1,3-dioxolane ring protons), 7.0—7.6 (10H, m, 2×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—46°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).

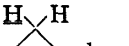
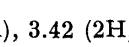
a) The less polar fraction was crystallized from Et_2O–hexane to give **11** as colorless needles (38 mg, 5.2%), mp 131—132°C. The structure was confirmed by direct comparison with an authentic sample prepared by Method A.

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

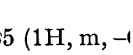
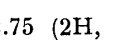
Reaction of 4-Chloro-1,3-diphenyl-1-butanone (8a) with Piperidine Derivative (15)——A mixture of **8a** (1.55 g, 6 mmol), **15** (2.6 g, 12 mmol) and KI (300 mg, 1.8 mmol) was heated at 110°C for 18 h in a sealed tube. The reaction mixture was worked up as described above (see Method B). The physical 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 cyclization[5] 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—185.5°C. Yield 453 mg (29.6%). *Anal.* Calcd for $C_{28}H_{28}ClNO_3$: C, 72.79; H, 6.11; N, 3.03. Found: C, 72.52; H, 5.97; N, 3.31.

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

broad, OH), 1.84 (3H,m, –CO–  –ph and –N ), 2.18 (2H, m, –N ), 2.63 and 2.78 (2H, m, –CO–  –ph), 3.42 (2H, m, –N(CH_2)$_2$), 3.80 (3H, s, OCH_3), 3.85 (2H, m, –N(CH_2)$_2$), 6.87 and 7.14 (4H, AB q, J=9 Hz, –C_6H_4OCH$_3$), 6.96 and 7.98 (4H, AB q, J=9 Hz, –CO–C_6H_4–), 7.41 (4H, AB q, J=9 Hz, Cl–C_6H_4–).

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-trimethylph from the fraction eluted with benzene–petroleum ether (1: 2) on sili orless oil. Yield 324 mg (28.7%). The structure of **22f** was confirmed that of a sample prepared by cyclization[5] of **8f** with NaOH. 4-(4-Chlo ethylphenyl)cyclopropan- 1-ylcarbonyl]phenyl]piperidine (**24**) was obt $CHCl_3$ on silica gel (80 g) chromatography as pale yellow crystals, mp *Anal.* Calcd for $C_{30}H_{32}$- $ClNO_2$: C, 76.01; H, 6.80; N, 2.96. Found: C 3, 475 M^+ (MW=474.05).

NMR (200-MHz) (δ in $CDCl_3$): 1.35 (1H, m, –C 88 (3H, m, –CO–  –ph and –N ), 2.2 (2H, m, –N ), 2.27), 2.32 (6H, s, *o*-methyl protons of mesityl), 2.63 and 2.75 (2H, m, –CO–  –ph), 3.45 (2H, m, –N(CH_2)$_2$–), 3.86 (2H, m, –N(CH_2)$_2$–), 6.86 (2H, s, mesityl), 6.99 and 8.04 (4H, AB q, J=9 Hz, –CO–C_6H_4–), 7.43 (4H, AB q, J=8 Hz, Cl–C_6H_4–).

***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 H_2O (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 Na_2SO_4 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 ν_{max}^{KBr} cm^{-1}: 1670. NMR (δ in $CDCl_3$): 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 ν_{max}^{KBr} cm^{-1}: 1665. NMR (δ in $CDCl_3$): 1.52, 1.88 (2H, each m, methylene protons of cyclopropane), 2.68 (2H, m, methine protons of cyclopropane), 3.79 (3H, s, OCH_3), 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 ν_{max}^{neat} cm^{-1}: 1660. NMR (δ in $CDCl_3$): 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 ν_{max}^{neat} cm^{-1}: 1665. NMR (δ in $CDCl_3$): 1.49, 1.86 (2H, each m, methylene protons of cyclopropane), 2.75 (2H, m, methine protons of cyclopropane), 3.73 (3H, s, OCH_3), 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 Et_2O (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 Na_2SO_4 and concentrated to dryness, and the residue was crystallized from Et_2O–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)——$LiAlH_4$ (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 H_2O (10 ml) and diluted with Et_2O. The organic layer was

separated, washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was crystallized from Et_2O–petroleum ether. The crystals were filtered off and the filtrate was concentrated to give a colorless oil (318 mg, 60.9%). IR ν_{max}^{neat} cm^{-1}: 3590, 3380 (OH). NMR (δ in $CDCl_3$): 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) $NaBH_4$ (95 mg, 2.5 mmol) was added to a solution of (**16**) (109 mg, 0.25 mmol) in CH_3OH (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 $CHCl_3$ (50 ml × 2). The extract was washed with water, dried over Na_2SO_4 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 $C_{27}H_{30}ClNO_2$: C, 74.37; H, 6.94; N, 3.21. Found: C, 74.28; H, 6.82; N, 3.18. IR ν_{max}^{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 H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (15 g) with benzene, $CHCl_3$ and $CHCl_3$–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 $CDCl_3$): 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 $CHCl_3$–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, $CHCl_3$ and $CHCl_3$–EtOH (19: 1). The fractions eluted with benzene and $CHCl_3$ were combined and concentrated to recover the starting material (**22a**) (257 mg, 77%) as an oil. The fraction eluted with $CHCl_3$–EtOH (19: 1) was concentrated to afford an oil (113 mg), which was crystallized from Et_2O 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-1*H*-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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