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Psychotropic Agents. I. Synthesis of 1-Pyridinyl-1-butanones, 1-Indolyl-1-butanones and the Related Compounds

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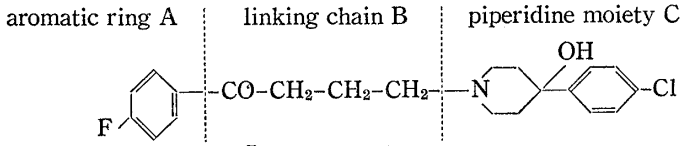
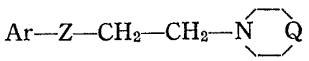
In order to search for new psychotropic agents, several 1-butanone derivatives (VIII) substituted by pyridine, indole or quinoline were synthesized. And the carbonyl group of VIII was modified to methylene (XII), secondary alcohol (XIII) and vinyl (XIV). The effects of the compounds on spontaneous motor activity and rotarod test in mice were determined. The structure-activity relationships of these derivatives are discussed.

Keywords——psychotropic agents; 1-pyridinyl-1-butanones; butene derivatives; phenylpiperazine derivatives; rotarod test; spontaneous motor activity; 1-indolyl-1-butanones

Haloperidol[2] (I), the prototype of butyrophenones, is one of the most widely prescribed agents in the therapy of psychic disorders, especially of schizophrenia. From a viewpoint of structure-activity relationships, the structure of I can be divided into three portions, aromatic ring A, linking chain B and piperidine moiety C. To determine the effects on the pharmacological activity of each portion, the modifications as shown in Chart 1 were designed. Pyridine, quinoline and indole derivatives were used as ring A, phenylpiperazines and piperidine derivatives as moiety C and chain B was modified from ketone to methylene, alcohol or vinyl group. The present paper deals with the syntheses and activities of these butanone derivatives (II).



I Haloperidol



II

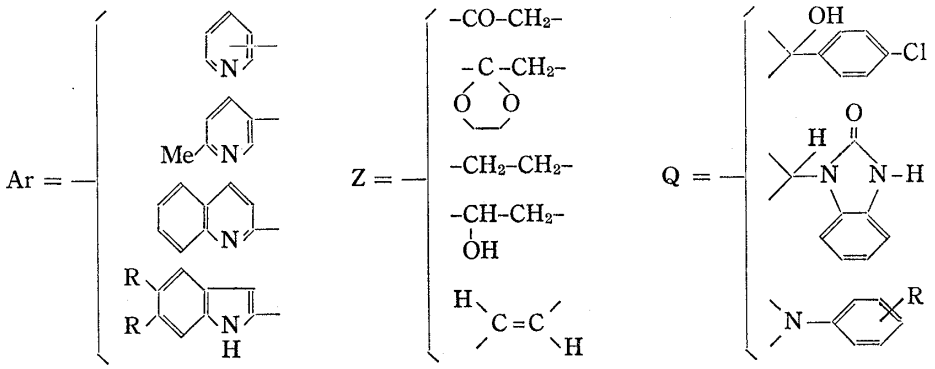


Chart 1

1) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
2) P.A.J. Janssen, C.J.E. Niemegeers, and K.H.L. Schellekens, *Arzneim.-Forsch.*, **15**, 104 (1965).

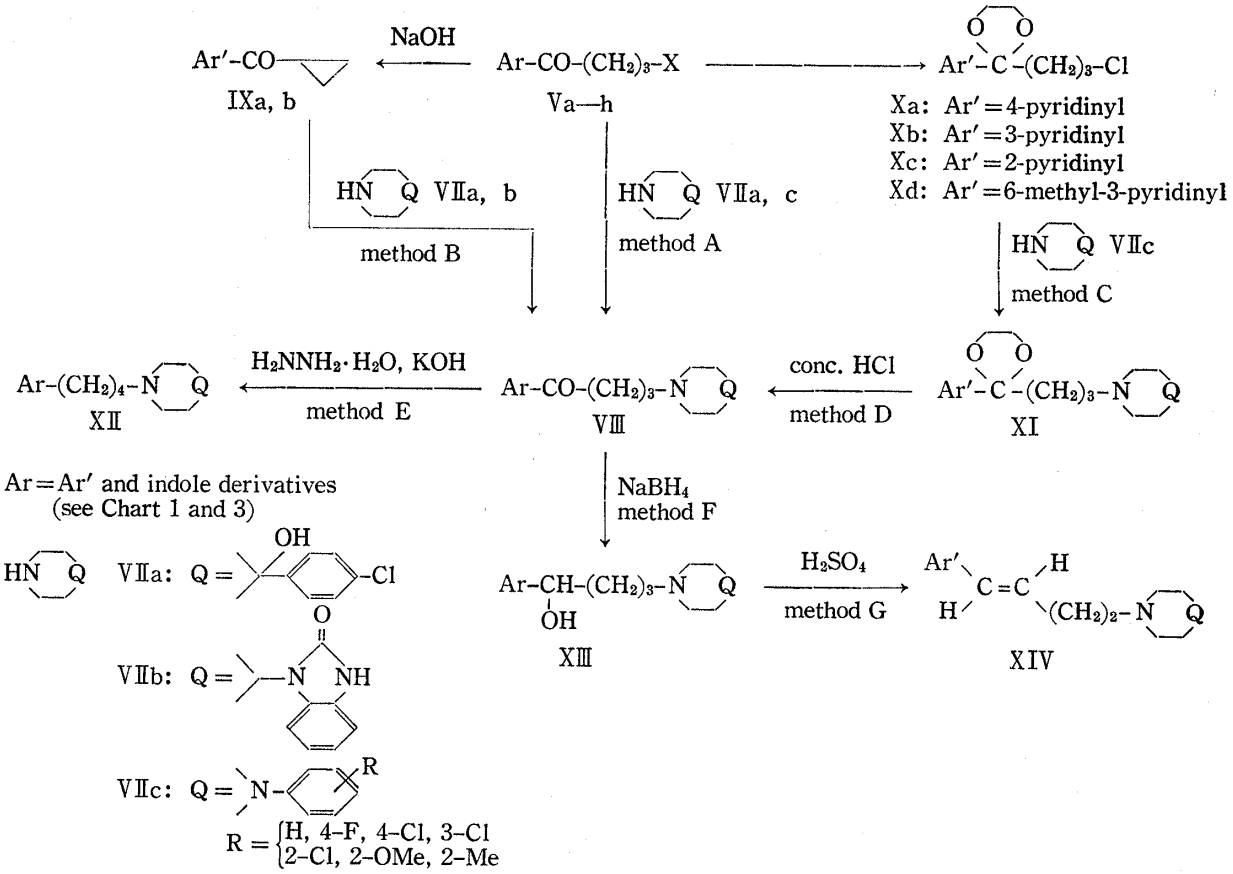


Chart 2

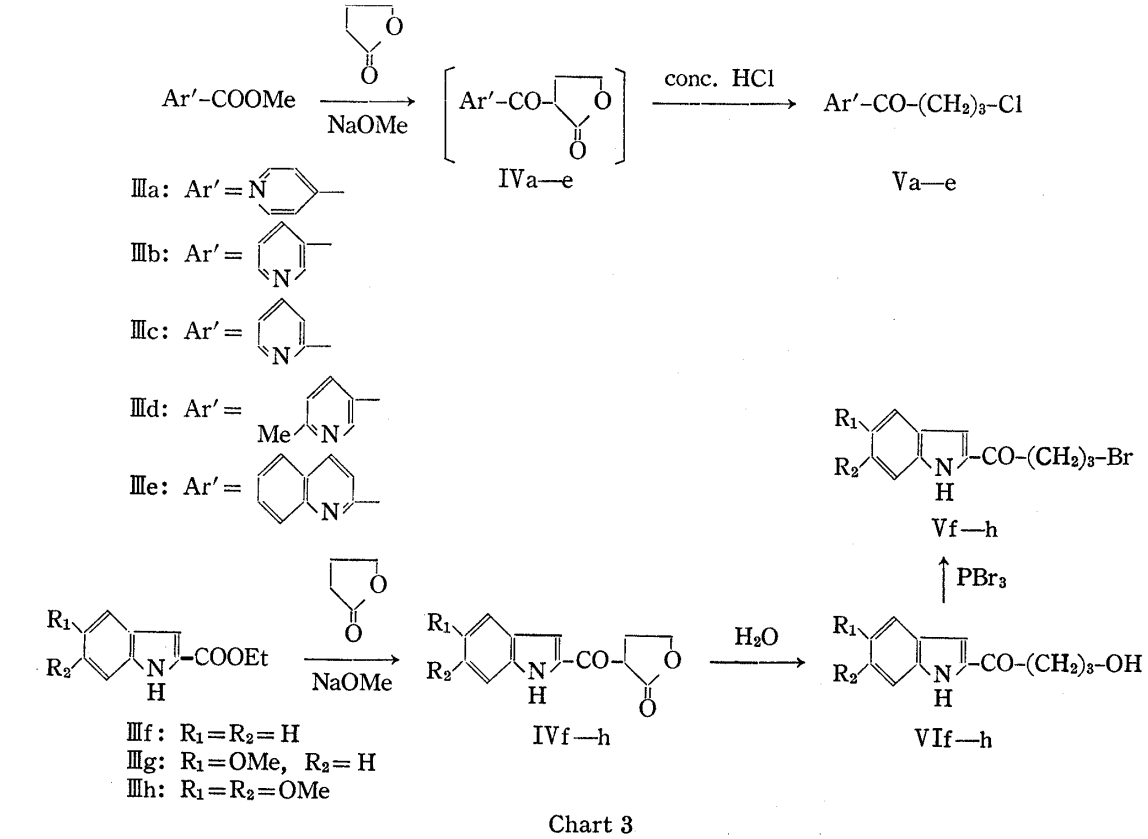


Chart 3

Various butanones (VIII) and their derivatives (XII), (XIII) and (XIV) substituted with a heteroaromatic ring such as pyridine, indole or quinoline at the 1 position were prepared by the general routes outlined in Chart 2 and listed in Table I. Key intermediates, 4-chloro-1-butanone derivatives (Va—e) were obtained from esters (IIIa—e) respectively as described in Chart 3 by one batch synthesis which was a modified method of the synthesis of 4-hydroxy-1-(2-pyridinyl)-1-butanone by Winterfeld *et al.*[3] Claisen condensation of esters (IIIa—e) with γ-butyrolactone in the presence of NaOMe gave intermediates (IVa—e), which were heated in conc. HCl without isolation to afford 4-chloro-1-butanone derivatives (Va—e). The structure of Va—e was confirmed by their infrared (IR) spectra in which the C=O bands of butanones appeared in 1690 cm^{-1} regions. The nuclear magnetic resonance (NMR) spectra of (Va—e) revealed the signals due to the methylene protons at C_2 and C_4 positions of the butanone at 3.2 and 3.7 ppm as triplets with $J=7$ Hz, respectively. The yield of 4-chloro-1-(2-pyridinyl)-1-butanone (Vc) was very low because of a formation of quinolizinium salt reported by Miyadera *et al.*[4] Since indole derivatives were labile to acid, the Claisen condensation products (IVf—h) were heated in water in a sealed tube to give 4-hydroxy-1-indolyl-1-butanone (VIf—h), and the butanols were treated with PBr_3 to give 4-bromo-1-indolyl-1-butanones (Vf—h).

Various 4-piperidinyl-1-butanones and 4-phenylpiperazinyl-1-butanone derivative (VIII) were synthesized by condensation of V with piperidine derivatives or phenylpiperazines (VII), (method A).

The other synthetic routes to VIII from cyclopropane derivative (IXa) and from 1,3-dioxolane derivatives (XI) were also successful. The cyclopropylketones (IXa, b) were prepared by cyclization of 4-chloro-1-pyridinyl-1-butanones (Va, b) with caustic alkali, and then a mixture of IXa and 4-(4-chlorophenyl)-4-hydroxypiperidine (VIIa) in xylene was heated in a sealed tube at 160° to give 4-(4-chlorophenyl-4-hydroxyl-1-piperidinyl)-1-(3-pyridinyl)-1-butanone (VIII), (method B), which was identified with the sample synthesized by method A. The following mechanism appears to account for the formation of VIII (Chart 4).

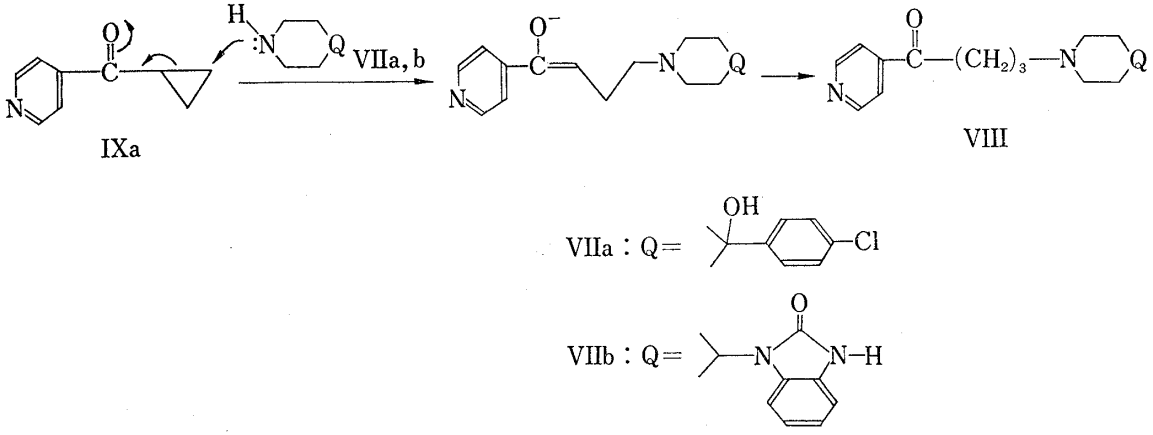


Chart 4

On the other hand, 1,3-dioxolane derivatives (XI) were obtained by condensation of the chlorides (Xa—d) with VIIc, (method C). As the 1,3-dioxolane ring of XI was rather stabilized, its removal to give butanones (VIII) required such a condition as to reflux with conc. HCl for ten hours, (method D). VIII were converted to butane derivatives (XII) by Wolff-Kischner's reduction (method E), and were reduced to the secondary alcohols (XIII) with

3) K. Winterfeld and F.W. Holschneider, *Arch. Pharm.*, **273**, 305 (1935).
4) T. Miyadera and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1338 (1964).

sodium borohydride (method F). Then, XIII were heated in conc. H_2SO_4 for 30 min at 160° to give butenes (XIV) (method G).

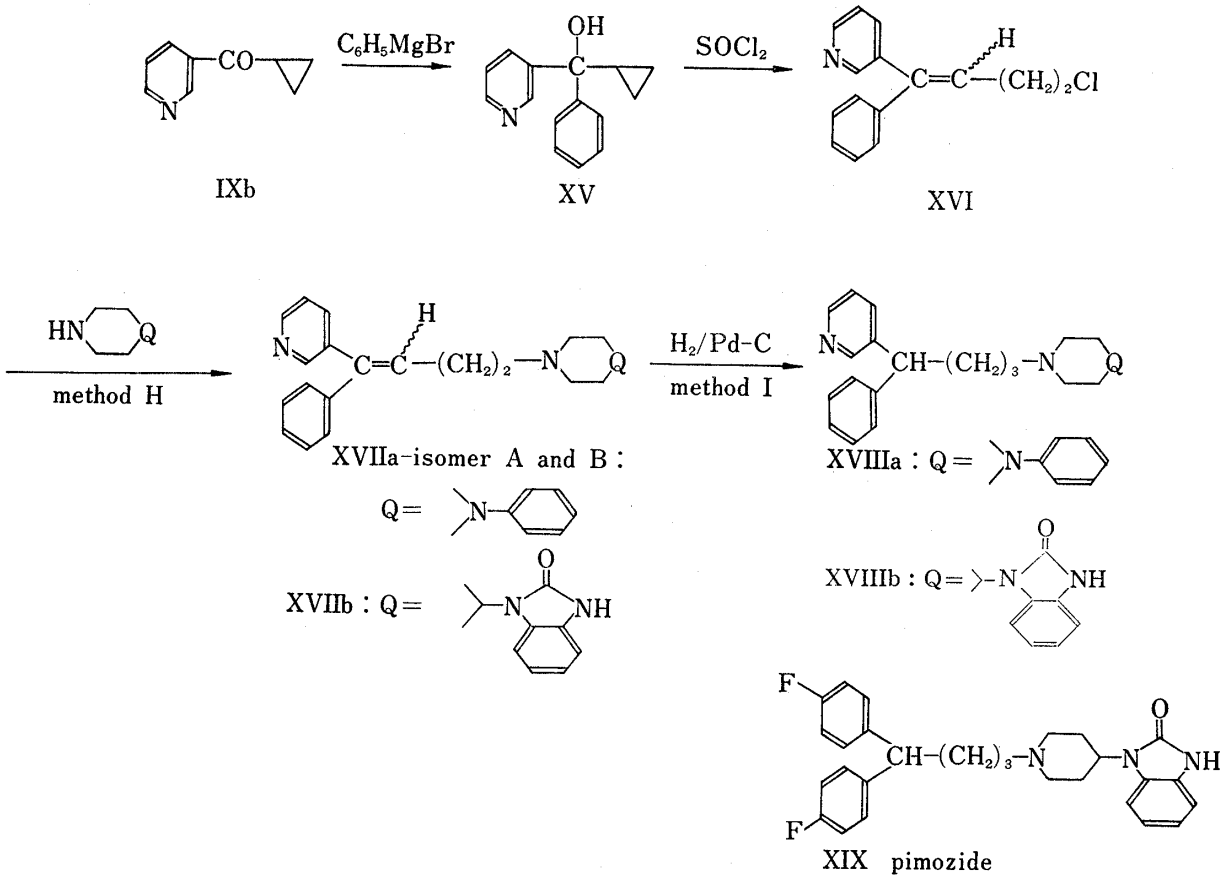


Chart 5

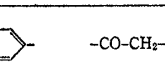
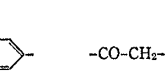
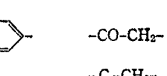
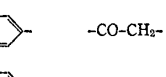
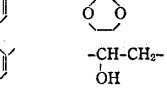
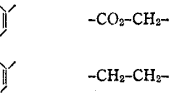
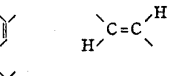
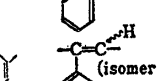
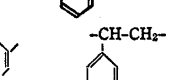
Furthermore 1-phenyl-1-(3-pyridinyl)butane derivatives (XVIII), which are analogs of pimozide (XIX), were synthesized as follows. According to Janssen's procedure,[5] cyclopropyl 3-pyridinyl ketone (IXb) was treated with the Grignard reagent (C_6H_5-MgBr) to give tertiary alcohol (XV), which was converted to 4-chloro-1-butene derivative (XVI). Condensation of XVI with phenylpiperazine gave two isomeric products (XVIIa-A, B), which were separated by means of preparative thin-layer chromatography (TLC), (method H). The configurations of the isomers remained unclear. The catalytic hydrogenation of XVII over palladium-carbon afforded 1-phenyl-1-(3-pyridinyl)butane derivative, (XVIII) (method I).

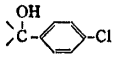
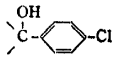
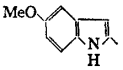
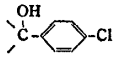
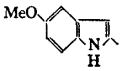
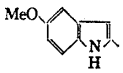
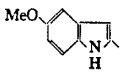
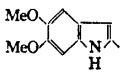
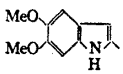
The compounds synthesized in the present work were first subjected to the rotarod test in mice and the results obtained were shown in Table I. Some structure-activity relationships of the compounds are as follows: (1) Replacement of FC_6H_4 moiety of haloperidol or benperidol by pyridine, quinoline or indole derivatives results in a considerable loss of activity (**1**, **2**, **31**, **34**, **36**). (2) In a series of phenylpiperazine derivatives *trans*-1-pyridinyl-1-butenes (**7**, **15**) and 1-pyridinyl-1-butanes (**14**, **24**) are more active than haloperidol or chlorpromazine, and moderate activity is observed in 1-pyridinyl-1-butanols (**5**, **12**), 1-pyridinylbutanes (**6**, **26**) and 1-pyrdinyl-1-butanone derivatives (**13**, **23**). (3) Substitution at the 2 position of pyridine (**27**—**30**) lowers the activity. (4) Only weak or no activity is observed in quinoline (**31**—**33**) and indole derivatives (**34**—**41**) except 1-indolyl-1-butanol derivative (**39**).

5) P.A.J. Janssen, Fr. Patent M3059 (1965) [*C.A.*, **63**, 9955*g* (1965)].

TABLE I. 4-Substituted-1-pyridinyl-1-butanones, 4-Substituted-1-indolyl-1-butanones and Their Derivatives

Ar–Z–CH_2–CH_2–N Q

Compd. No.	Ar	Z	Q	Method[a]	Yield (%)	mp (°C)	Appearance[b]	Recryst. solvent[c]	Formula	Analysis (%) Calcd. (Found) C	H	N	Rotarod test[d] ED_{50} mg/kg [hr][e]	SMA test[d] ID_{50} mg/kg
1		-CO-CH_2-		A	42.3	124.5—125.5	ne	$CHCl_3$–$(C_2H_5)_2O$	$C_{20}H_{23}ClN_2O_2$	66.93 (67.16	6.46 6.48	7.80 7.89)	>40	NT[f]
				B	36.3	124.5—125.5	ne	C_6H_6–$(C_2H_5)_2O$						
2		-CO-CH_2-		B	57.1	186.5—188	pr	Ac–$(C_2H_5)_2O$	$C_{21}H_{24}N_4O_2$	69.21 (69.20	6.64 6.44	15.38 15.08)	>40	NT
3		-CO-CH_2-		D	63.3	111—112	ne	$(C_2H_5)_2O$–Pt·E	$C_{19}H_{23}N_3O$	73.75 (73.42	7.49 7.28	13.58 13.70)	29.3 (18.9—45.4) [2][e]	NT
4				C	61.1	125.5—127	pr	$(C_2H_5)_2O$–Pt·E	$C_{21}H_{27}N_3O_2$	71.36 (71.34	7.70 7.47	11.89 11.71)	16.0 (10.7—24.0) [0.5]	NT
5				F	79.1	92—94	ne	C_6H_6	$C_{19}H_{25}N_3O$	73.28 (73.10	8.09 8.05	13.49 13.25)	9.6 (6.6—13.9) [1]	NT
6		-CH_2-CH_2-		E	77.1	265—269 (dec.)	ne	EtOH	$C_{19}H_{25}N_3$·3HCl	56.37 (56.41	6.97 6.84	10.38 10.27)	6.8 (4.1—15.3) [0.5]	8.8 (7.1—10.9)
7				G	45.0	116—118	ne	AcOEt	$C_{19}H_{23}N_3$	77.77 (77.80	7.90 8.03	14.32 14.36)	3.5 (2.0—6.1) [0.5]	4.5 (3.1—6.7)
8		-CO-CH_2-		D	90.0	117.5—118.5	ne	$(C_2H_5)_2O$–Pt·E	$C_{19}H_{22}FN_3O$	69.69 (69.59	6.77 6.99	12.83 12.98)	40.7 (25.8—64.3) [0.5]	NT
9		-CO-CH_2-		D	90.6	93.5—95	pr	Ac	$C_{19}H_{22}ClN_3O$	66.36 (66.59	6.45 6.19	12.23 11.93)	31.0 (22.6—42.5) [2]	NT
10		-CO-CH_2-		D	47.6	63.5—65	pr	$(C_2H_5)_2O$–Pt·E	$C_{19}H_{22}ClN_3O$	66.36 (66.22	6.45 6.34	12.23 12.11)	27.0 (18.2—40.0) [0.5]	NT
11				C	55.5	99—103	ne	AcOEt	$C_{21}H_{27}N_3O_2$	71.36 (71.20	7.70 7.63	11.89 11.92)	25.4 (21.5—30.0) [0.5]	NT
12				F	86.1	220—225 (dec.)	ne	EtOH	$C_{19}H_{25}N_3O$·3HCl	54.23 (54.19	6.71 6.71	9.99 9.98)	9.7 (5.9—16.0) [0.5]	10.2 (6.8—15.3)
13		-CO_2-CH_2-		D	66.6	78—79	ne	$(C_2H_5)_2O$	$C_{19}H_{23}N_3O$	73.75 (73.95	7.49 7.50	13.58 13.48)	8.7 (6.1—12.4) [0.5]	20.3 (14.4—28.7)
14		-CH_2-CH_2-		E	72.5	226—232 (dec.)	ne	EtOH	$C_{19}H_{25}N_3$·3HCl	56.37 (56.07	6.97 6.87	10.38 10.24)	4.4 (2.3—8.5) [0.5]	NT
15				G	59.6	244—246 (dec.)	ne	EtOH	$C_{19}H_{23}N_3$·3HCl	56.65 (56.60	6.51 6.34	10.43 10.49)	1.4 (0.52—3.78) [0.5]	NT
16		-CO-CH_2-		D	46.1	206—207 (dec.)	ne	EtOH	$C_{19}H_{25}N_3O$·3HCl·H_2O	51.45 (51.92	6.47 6.49	9.00 8.86)	40.3 (30.8—52.8) [0.5]	NT
17		-CO-CH_2-		D	56.8	68—70	pr	$(C_2H_5)_2O$–Pt·E	$C_{19}H_{22}ClN_3O$	66.36 (66.23	6.45 6.41	12.23 12.31)	27.6 (17.8—42.8) [1]	NT
18		-CO-CH_2-		A	17.7	230—233 (dec.)	pow	MeOH–Ac	$C_{20}H_{25}N_3O$·3HCl	55.50 (55.40	6.52 6.48	9.71 9.57)	25.1 (14.8—42.7) [1]	NT
19		(isomer A)		H	17.4	94.5—96.5	pr	$(C_2H_5)_2O$	$C_{25}H_{27}N_3$	81.26 (81.36	7.37 7.24	11.37 11.63)	>40	NT
20		(isomer B)		H	11.9	68—69	pr	c-Hx-Hx	$C_{25}H_{27}N_3$	81.26 (80.95	7.37 7.42	11.37 11.34)	28.2 (16.6—47.9) [0.5]	NT
21				I	74.3	102.5—104	pr	$(C_2H_5)_2O$	$C_{25}H_{29}N_3$	80.82 (80.52	7.87 7.90	11.31 11.30)	31.6 (20.4—49.0) [0.5]	NT
22				I	46.4	194—197	pr	$CHCl_3$–$(C_2H_5)_2O$	$C_{22}H_{30}N_4O$·1/2H_2O	74.45 (74.17	7.17 7.08	12.86 12.53)	>40	25.1 (17.6—35.9)

Compd. No.	Ar	Z	Q	Method[a]	Yield (%)	mp (°C)	Appearance[b]	Recryst. solvent[c]	Formula	Analysis (%) Calcd. (Found) C	H	N	Rotarod test[d] ED_{50} mg/kg [hr][e]	SMA test[d] ID_{50} mg/kg
23		-CO-CH_2-		D	76.4	111—112.5	ne	C_6H_6–$(C_2H_5)_2O$	$C_{20}H_{25}N_3O$	74.27 (74.31)	7.79 (7.75)	12.99 (12.76)	8.5 (5.9—12.2) [0.5]	14.9 (9.8—22.6)
24		-CH_2-CH_2-		E	93.2	215—217 (dec.)	pow	MeOH	$C_{20}H_{27}N_3 \cdot 3HCl$	57.35 (57.56)	7.22 (7.24)	10.03 (10.39)	4.6 (2.8—7.5) [1]	NT
25		-CO-CH_2-		D	83.2	78—79.5	ne	$(C_2H_5)_2O$	$C_{20}H_{24}ClN_3O$	67.11 (67.18)	6.76 (6.69)	11.75 (11.57)	18.8 (11.9—29.7) [0.5]	NT
26		-CH_2-CH_2-		E	79.8	213—215 (dec.)	pow	Ac–$(C_2H_5)_2O$	$C_{20}H_{26}ClN_3 \cdot 2HCl \cdot 1/2H_2O$	56.40 (56.41)	6.86 (6.79)	9.86 (9.81)	8.3 (5.8—12.0) [1]	NT
27		-CH(OH)-CH_2-		F	89.3	80—81.5	pow	$(C_2H_5)_2O$–Pt·E	$C_{19}H_{25}N_3O$	73.28 (73.52)	8.09 (8.07)	13.49 (13.63)	>40	NT
28		-CO-CH_2-		A	49.5	73.5—75	ne	$(C_2H_5)_2O$–Pt·E	$C_{19}H_{23}N_3O$	73.75 (74.06)	7.49 (7.41)	13.58 (13.35)	>40	NT
29				C	10.0	91.5—93	pr	$(C_2H_5)_2O$–Pt·E	$C_{21}H_{27}N_3O_2$	71.36 (71.30)	7.70 (7.57)	11.89 (12.02)	36.6 (21.5—62.2) [0.5]	NT
30				G	44.3	81—82	ne	$(C_2H_5)_2O$–Pt·E	$C_{19}H_{23}N_3$	77.77 (78.30)	7.90 (7.78)	14.32 (13.98)	32.7 (22.9—46.8) [0.5]	NT
31		-CO-CH_2-		A	33.1	125.5—127	pr	$(C_2H_5)_2O$–Pt·E	$C_{24}H_{25}ClN_2O_2$	70.48 (70.36)	6.16 (6.08)	6.85 (6.72)	>40	NT
32		-CO-CH_2-		A	40.6	142—143	pl	$CHCl_3$–Ac	$C_{23}H_{25}N_3O$	76.85 (77.03)	7.01 (6.88)	11.69 (11.43)	25.4 (16.6—38.9) [0.5]	NT
33				G	46.1	149.5—150.5	ne	MeOH	$C_{23}H_{25}N_3$	80.43 (80.57)	7.34 (7.31)	12.24 (11.95)	15.5 (10.3—23.3) [1]	20.0 (12.0—34.0)
34		-CO-CH_2-		A	70.8	170.5—172.5 (dec.)	ne	MeOH	$C_{25}H_{25}ClN_2O_2$	69.60 (69.36)	6.35 (6.22)	7.06 (6.91)	>40	NT
35		-CO-CH_2-		A	62.2	165—168	ne	C_6H_6	$C_{22}H_{25}N_3O$	76.05 (76.17)	7.25 (7.13)	12.05 (11.95)	>40	NT
36		-CO-CH_2-		A	63.8	200—202	ne	MeOH	$C_{24}H_{27}ClN_2O_2$	67.52 (67.30)	6.37 (6.14)	6.56 (6.40)	>40	NT
37		-CO-CH_2-		E	72.9	150—152	ne	MeOH	$C_{23}H_{29}N_3O$	75.99 (76.25)	8.04 (8.06)	11.56 (11.58)	>40	NT
38		-CO-CH_2-		A	72.8	176—177.5	ne	C_6H_6	$C_{23}H_{27}N_3O_2$	73.18 (73.41)	7.21 (7.26)	11.13 (11.29)	38.1 (19.1—76.2) [1]	NT
39		-CH(OH)-CH_2-		F	95.4	160—163	ne	C_6H_6	$C_{22}H_{29}N_3O_2$	72.79 (73.03)	7.70 (7.71)	11.07 (11.01)	10.0 (6.25—16.0) [1]	6.7 (3.7—12.0)
40		-CH(OH)-CH_2-		F	80.5	166—169	ne	MeOH	$C_{24}H_{31}N_3O$	70.39 (70.30)	7.63 (7.52)	10.26 (10.27)	>40	NT
41		-CO-CH_2-		A	75.1	192—195	ne	C_6H_6	$C_{24}H_{29}N_3O_3$	70.73 (70.49)	7.17 (7.18)	10.31 (10.09)	>40	NT
Chlorpromazine													7.9 (5.26—11.9) [4]	6.0 (4.5—8.0)
Oxypertine													7.1 (4.4—11.4) [0.5]	4.5 (3.0—6.9)
Haloperidol													6.5 (3.1—13.7) [1]	0.8 (0.4—1.8)

a) See Chart 3, 4.
b) ne: colorless needles, pr: colorless prisms, pow: colorless crystalline powder, pl: colorless plates.
c) $CHCl_3$: chloroform, $(C_2H_5)_2O$: diethyl ether, C_6H_6: benzene, Pt·E: petroleum ether, Ac: acetone, EtOH: ethanol, MeOH: methanol, AcOEt: ethyl acetate, c-Hx: cyclohexane, Hx: hexane.
d) See pharmacological method.
e) Figures in brackets indicate time at which ED_{50} values were obtained.
f) NT: not tested.

In consideration of the chemical structure and efficacy in the rotarod test, inhibitory effects of some compounds (**6**, **7**, **12**, **13**, **22**, **23**, **33**, **39**) on spontaneous motor activity were examined in male STD-ddY mice, and the results were listed in Table I. These compounds were far less active than haloperidol.

Experimental

The following instruments were used. IR spectra: a Hitachi EPI-G2 type Infrared Spectrophotometer; NMR (tetramethylsilane as an internal standard): a JNM-4H-100 spectrometer (100 MHz) (Japan Electron Optics Lab. Tokyo, Japan); a Hitachi Mass spectrometer RMS-4 (direct inlet, at 70 eV); Melting points: a Yanagimoto melting point apparatus (Type MP-1). All melting points are uncorrected. For column chromatography, silica gel (Merck, 70—230 mesh) and Al_2O_3 (Merck, Active 1, neutral) were used. For preparative thin-layer chromatography, silica gel (Merck, GF_{254}) was used.

Method of Rotarod Test——Ten male mice of ddY strain weighing 19—26 g were used in each group. The animals stayed for at least 1 min on a wooden rod (30 mm in diameter) rotating at 13 rpm were selected and subjected to testing 0.5, 1, 2, 4 and 6 hr after *p.o.* administration of test drugs as a suspension or a solution in 0.5% carboxymethyl cellulose (CMC). The animals fell down from the rod within 1 min were taken as being affected. ED_{50} values were calculated according to the method of Litchfield-Wilcoxon[6] from affected % at the time when maximal effect was observed.

Method of SMA Test——Ten male mice of ddY strain weighing 20—30 g were used in each group. Wheel cages (210 mm in diameter, 40 mm in width, Kishimoto Ika Co. Ltd.) were used for the measurement of spontaneous motor activity. The number of revolution of the cage which the mouse rotated for 5 min was taken as index for spontaneous motor activity. Test compounds were administered orally 1 hr before testing. ED_{50} values were obtained by comparing the number of rotation of the cage between vehicle and treated groups.

General Procedure for the Synthesis of 1-Substituted-4-chloro-1-butanone (V)——To a mixture of ester (III) (0.3 mol) and γ-butyrolactone (38.7 g, 0.45 mol) in dioxane (100 ml), NaOMe (48.6 g, 0.9 mol) was added and the mixture was heated at 110° for 30 min with stirring. After addition of conc. HCl (500 ml) under chilling, the mixture was refluxed for 16 hr, and was made alkaline with Na_2CO_3 on cooling. The resulting mixture was extracted with benzene. The benzene extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (100 g) using C_6H_6–petroleum ether (1: 1) to give a pale yellow oil (V) in 40—60% yield, which was used for the next step without further purification. The following compounds were synthesized.

4-Chloro-1-(4-pyridinyl)-1-butanone (Va)——Yield 48.6%, a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 1695 (C=O). NMR (δ in $CDCl_3$): 3.19 (2H, t, J=7 Hz, –CO–CH_2–), 2.23 (2H, quintet, –C<u>H</u>$_2$–CH_2–Cl), 3.68 (2H, t, J=7 Hz, –CH_2–Cl).

4-Chloro-1-(3-pyridinyl)-1-butanone (Vb)——Yield 59.3%, a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 1685 (C=O). NMR (δ in $CDCl_3$): 3.25 (2H, t, J=7 Hz, –CO–CH_2–), 2.28 (2H, m, –C<u>H</u>$_2$–CH_2–Cl), 3.73 (2H, t, J=7 Hz, –CH_2–Cl).

4-Chloro-1-(2-pyridinyl)-1-butanone (Vc)——Yield 39.1%, a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 1695 (C=O). NMR (δ in $CDCl_3$): 3.43 (2H, t, J=7 Hz, –CO–CH_2–), 3.23 (2H, m, –C<u>H</u>$_2$–CH_2–Cl), 3.69 (2H, t, J=7 Hz, –CH_2Cl).

4-Chloro-1-(6-methyl-3-pyridinyl)-1-butanone (Vd)——Yield 59.6%, colorless prisms (from $(C_2H_5)_2O$–petroleum ether), mp 43.5—44.5°. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). NMR (δ in $CDCl_3$): 3.13 (2H, t, J=7 Hz, –CO–CH_2–), 2.19 (2H, quintet, –C<u>H</u>$_2$–CH_2–Cl), 3.64 (2H, t, J=7 Hz, –CH_2–Cl).

4-Chloro-1-(2-quinolinyl)-1-butanone (Ve)——Yield 48.2%, a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 1695 (C=O). NMR (δ in $CDCl_3$): 3.55 (2H, t, J=7 Hz, –CO–CH_2–), 2.28 (2H, m, –C<u>H</u>$_2$–CH_2–Cl), 3.71 (2H, t, J=7 Hz, –CH_2–Cl).

α-[(Indol-2-yl)carbonyl]-γ-butyrolactone (IVf)——A mixture of ethyl indole-2-carboxylate (IIIf) (47.3 g, 0.25 mol), γ-butyrolactone (86.1 g, 1 mol), NaOMe (108 g, 2 mol) and dioxane (25 ml) was heated at 110° for 4.5 hr with stirring. To the reaction mixture were added ice-water (1000 ml) and conc. HCl under chilling and the mixture was adjusted to pH 4—6, and extracted with $CHCl_3$. The chloroform extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography on silica gel with $CHCl_3$ and recrystallization from $CHCl_3$ gave 23.1 g (40.4%) of pale yellow needles, mp 170—173°. *Anal.* Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.23; H, 4.77; N, 6.05. IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1750, 1645, 1630 (C=O).

α-[(5-Methoxyindol-2-yl)carbonyl]-γ-butyrolactone (IVg)——Prepared from ethyl 5-methoxyindole-2-carboxylate (IIIg) (54.8 g, 0.25 mol) as described for IVf. Recrystallization from $CHCl_3$ gave 37.2 g (57.4%) of pale yellow needles, mp 163—165°. *Anal.* Calcd. for $C_{14}H_{13}NO_4$: C, 64.81; H, 5.05; N, 5.40. Found: C,

6) J.T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

64.74; H, 5.02; N, 5.54. IR ν_{max}^{KBr} cm^{-1}: 3340 (NH), 1750, 1650 (C=O).

α-[(5,6-Dimethoxyindol-2-yl)carbonyl]-γ-butyrolactone (IVh)——With the aid of heat, a mixture of ethyl 5,6-dimethoxyindole-2-carboxylate (IIIh) (26.4 g, 0.11 mol) and γ-butyrolactone (72.9 g, 0.85 mol) was dissolved in tetraline (85 ml). At about 50°, NaOMe (91.5 g, 1.69 mol) and tetraline (100 ml) were added to the mixture. After heating (130—140°) and continuous stirring (1.5 hr), the reaction mixture was cooled and IVh was obtained by the above procedure. Yield 7.12 g (23.2%), pale yellow needles (from $CHCl_3$), mp 197—201°. *Anal.* Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.08; H, 5.23; N, 4.94. IR ν_{max}^{KBr} cm^{-1}: 3330 (NH), 1740, 1645 (C=O).

4-Hydroxy-1-(indol-2-yl)-1-butanone (VIf)——A suspension of IVf (20.0 g, 0.09 mol) in H_2O (400 ml) was heated at 190—200° for 6 hr in an autoclave. After being cooled, the precipitate was filtered, washed with H_2O and dried. The crude product was purified by chromatography on silica gel (150 g) with $CHCl_3$–MeOH (40: 1) and recrystallized from $CHCl_3$ to give 13.0 g (73.3%) of yellow needles, mp 130—133°. *Anal.* Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.98; H, 6.37; N, 6.90. IR ν_{max}^{KBr} cm^{-1}: 3310 (NH, OH), 1645 (C=O). NMR (δ in DMSO-d_6): 1.85 (2H, m, $-CH_2-CH_2-OH$), 3.03 (2H, t, J=7 Hz, $-CO-CH_2-$), 3.52 (2H, m, $-CH_2-OH$), 4.57 (1H, t, J=4 Hz, OH), 6.91—7.78 (5H, m, indole), 11.70 (1H, broad, NH).

4-Hydroxy-1-(5-methoxyindol-2-yl)-1-butanone (VIg)——Prepared from IVg (2.8 g, 0.011 mol) as described for VIf. Recrystallization from $CHCl_3$ gave 2.09 g (83.1%) of pale yellow needles, mp 139—141°. *Anal.* Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.83; H, 6.52; N, 6.26. IR ν_{max}^{KBr} cm^{-1}: 3310, 3280 (NH, OH), 1635 (C=O). MS *m/e*: 233 (M^+). NMR (δ in DMSO-d_6): 1.85 (2H, quintet, $-CH_2-CH_2-OH$), 2.99 (2H, t, J=7 Hz, $-CO-CH_2-$), 3.51 (2H, m, $-CH_2-OH$), 3.78 (3H, s, OCH_3), 4.54 (1H, t, J=5 Hz, OH), 6.8—7.5 (4H, m, indole), 11.58 (1H, broad, NH).

4-Hydroxy-1-(5,6-dimethoxyindol-2-yl)-1-butanone (VIh)——Prepared from IVh (500 mg, 1.73 mmol) as described for VIf. Recrystallization from MeOH gave 320 mg (70.3%) of yellow needles, mp 188—192°. *Anal.* Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.88; H, 6.52; N, 5.26. IR ν_{max}^{KBr} cm^{-1}: 3560 (OH), 3320 (NH), 1640 (C=O).

4-Bromo-1-(indol-2-yl)-1-butanone (Vf)——To a solution of VIf (8.13 g, 0.04 mol) in anhydrous THF (300 ml), which was chilled at −5°, PBr_3 (3.60 g, 0.01 mol) in anhydrous THF (40 ml) was added dropwise with stirring and the mixture was stirred for 2 days at −5°. The reaction mixture was concentrated at about 30° *in vacuo* after the addition of $NaHCO_3$ (300 mg) and the residue was diluted with H_2O (100 ml), neutralized with 0.1 N Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography on silica gel (200 g) with C_6H_6 to afford 3.20 g (30.1%) of pale yellow crystals, which were recrystallized from ether to give pale yellow needles, mp 148—149° (dec.). *Anal.* Calcd. for $C_{12}H_{12}BrNO$: C, 54.15; H, 4.55; N, 5.26. Found: C, 54.30; H, 4.56; N, 5.25. IR ν_{max}^{KBr} cm^{-1}: 3330 (NH), 1640 (C=O).

4-Bromo-1-(5-methoxyindol-2-yl)-1-butanone (Vg)——Prepared from VIg (100 mg, 0.43 mmol) as described for Vf. Recrystallization from $CHCl_3$–$(C_2H_5)_2O$ gave 40 mg (31.5%) of colorless needles, mp 153—155° (dec.). *Anal.* Calcd. for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.77; N, 4.73. Found: C, 52.53; H, 4.66; N, 4.51. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1640 (C=O). NMR (δ in $CDCl_3$): 2.34 (2H, quintet, $-CH_2-CH_2-Br$), 3.15 (2H, t, J=7 Hz, $-CO-CH_2$), 3.54 (2H, t, J=7 Hz, $-CH_2-Br$), 3.85 (3H, s, OMe), 6.9—7.4 (4H, m, indole), 9.20 (1H, broad, NH).

4-Bromo-1-(5,6-dimethoxyindol-2-yl)-1-butanone (Vh)——Prepared from VIh (2.11 g, 8 mmol) as described for Vf. Yield 1.07 g (41.0%), pale red needles. The crude product was used for the next step without further purification. IR ν_{max}^{KBr} cm^{-1}: 3290 (NH), 1620 (C=O).

Reaction of 1-Substituted-4-chloro(or 4-bromo)-1-butanone (Va—h) with Amine (VIIa—c), Method A——A mixture of Va—h (0.01 mol), amine (VIIa—c) (0.02 mol) and KI (0.002 mol) was heated at 110° for 18 hr in a sealed tube. To the reaction mixture, 10% NaOH (10 ml) was added and the mixture was extracted with $CHCl_3$, washed with H_2O, dried over Na_2SO_4. Evaporation of the solvent gave a brown oil. The crude product was purified by chromatography on silica gel, eluting with $CHCl_3$, $CHCl_3$–EtOH (49: 1) and $CHCl_3$–EtOH (19: 1). Eluate with $CHCl_3$–EtOH (19: 1) was concentrated *in vacuo*, and recrystallized from a suitable solvent. When the product was an oil, it was dissolved in ether, passed through Al_2O_3 and acidified with HCl or HCl–MeOH. The resulting precipitate was collected by filtration and recrystallized from a suitable solvent and the details were summarized in Table I.

Cyclopropyl 4-Pyridinyl Ketone (IXa)——A mixture of Va (1.85 g, 0.01 mol), NaOH (1.2 g, 0.03 mol) and H_2O (1 ml) was heated at 100—110° for 4 hr with stirring. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (40 g) using $CHCl_3$ as an eluent. Removal of the solvent afforded 1.22 g (88.8%) of a colorless oil (IXa), which was purified by distillation, bp 86—90° (3 mmHg). [lit. bp 65° (0.03 mmHg)[7]]. IR ν_{max}^{neat} cm^{-1}: 1675 (C=O). NMR (δ in $CDCl_3$): 1.0—1.4 (4H, m, $-CH_2-CH_2-$), 2.5—2.8 (1H, m, $-CH<$), 7.77 (2H, diffused d, J=7 Hz, α-protons of pyridine-ring), 8.82 (2H, diffused d, J=7 Hz, β-protons of pyridine-ring)

7) W.B. Edwards III, *J. Heterocycl. Chem.*, **12**, 413 (1975).

Cyclopropyl 3-Pyridinyl Ketone (IXb)——Prepared from Vb (43.5 g, 0.24 mol) as described for IXa. Yield 25.9 g (74.5%), a colorless oil, bp 99—100° (5 mmHg). [Lit. bp 80—81° (0.79 mmHg)[7]]. IR ν_{max}^{neat} cm^{-1}: 1675 (C=O). NMR (δ in $CDCl_3$): 0.9—1.4 (4H, m, $-CH_2-CH_2-$), 2.4—2.9 (1H, m, $-CH\langle$).

Reaction of Cyclopropyl 4-Pyridinyl Ketone (IXa) with Amine (VIIa) or (VIIb), Method B——A mixture of IXa (296 mg, 2 mmol) and VIIa (423 mg, 2 mmol) and xylene (2 ml) was heated at 160° for 40 hr in a sealed tube. And the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 10 g), eluting with $CHCl_3$ and $CHCl_3$–EtOH (20: 1). The fraction eluted with $CHCl_3$–EtOH (20: 1) was concentrated *in vacuo* and the residue was recrystallized from C_6H_6–$(C_2H_5)_2O$ to give 261 mg (36.3%) of colorless needles, mp 124.5—125.5°, which were identified by mixed melting point test and comparison of IR spectra with the authentic sample synthesized by Method A, (see Compd. No. 1 in Table I). IR ν_{max}^{KBr} cm^{-1}: 3420, 3360, 3130 (OH), 1690 (C=O). The compound No. 2 in Table I was prepared in a similar manner. Details were summarized in Table I. IR ν_{max}^{KBr} cm^{-1}: 3170, 3125 (NH), 1690 (C=O).

2-(3-Chloropropyl)-2-(4-pyridinyl)-1,3-dioxolane (Xa)——A mixture of Va (27.5 g, 0.15 mol), ethyleneglycol (300 ml), *p*-toluene sulfonic acid monohydrate (38.0 g, 0.2 mol) and dry C_6H_6 (600 ml) was refluxed with stirring for 15 hr. The H_2O formed during the reaction was separated by Dean-Stark apparatus. After cooling, the reaction mixture was made alkaline with 10% NaOH solution and the C_6H_6 layer was separated, washed with H_2O and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g). Elution with C_6H_6 and $CHCl_3$ gave 24.9 g (74.9%) of a pale yellow oil, which was used for the next step without further purification. NMR (δ in $CDCl_3$): 1.96 (4H, m, $-CH_2-CH_2-CH_2-Cl$), 3.53 (2H, t, $J=6$ Hz, $-CH_2-Cl$), 3.7—4.1 (4H, m, $-O-CH_2-CH_2-O-$), 7.36 (2H, diffused d, $J=7$ Hz, β-protons of pyridine ring), 8.60 (2H, d, $J=7$ Hz, α-protons of pyridine ring).

2-(3-Chloropropyl)-2-(3-pyridinyl)-1,3-dioxolane (Xb)——Prepared from Vb (54.6 g, 0.296 mol) as described for Xa. Yield 60.7 g (90.1%), a pale yellow oil.

2-(3-Chloropropyl)-2-(2-pyridinyl)-1,3-dioxolane (Xc)——Prepared from Vc (12.9 g, 0.07 mol) as described for Xa. Yield 12.9 g (81.2%), a pale yellow oil.

2-(3-Chloropropyl)-2-(6-methyl-3-pyridinyl)-1,3-dioxolane (Xd)——Prepared from Vd (11.9 g, 0.06 mol) as described for Xa. Yield 14.2 g (97.5%), a pale yellow oil.

General Procedure for the Synthesis of XI, Method C——A mixture of X (0.01 mol), amine (VII) (0.025 mol) and KI (400 mg, 2.4 mmol) was heated at 110° for 18 hr in a sealed tube and the reaction mixture was worked up as in Method A. The physical data of XI are listed in Table I.

General Procedure for the Synthesis of Butanone Derivatives (VIII), Method D——A solution of XI (4 mmol) in conc. HCl (50 ml) was refluxed for 10 hr, and concentrated *in vacuo*. To the residue 10% NaOH solution (20 ml) was added and the mixture was stirred and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. And the residue was purified by chromatography (Al_2O_3, 30 g), eluting with C_6H_6 and C_6H_6–$CHCl_3$ (9: 1). The fraction eluted with C_6H_6–$CHCl_3$ (9: 1) was concentrated *in vacuo* and the residue was recrystallized from a suitable solvent. The physical data of VIII are listed in Table I.

General Procedure for the Synthesis of Butane Derivatives (XII)——A mixture of the butanone (VIII) (3 mmol), NaOH (600 mg, 15 mmol), 80% NH_2NH_2-hydrate (0.55 ml, 9 mmol) and diethyleneglycol (5 ml) was heated at 150° for 10 min and at 190—195° for 4.5 hr. The H_2O formed during the reaction was separated by Dean-Stark apparatus. After being cooled, the reaction mixture was extracted with C_6H_6. The C_6H_6 solution was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo* to give a colorless oil, which was dissolved in EtOH and filtered. The filtrate was made acidic with HCl–EtOH to give colorless crystals, which were recrystallized from a suitable solvent. The physical data of XII are listed in Table I.

General Procedure for the Synthesis of 1-Butanol Derivatives (XIII)——To a solution of VIII (0.016 mol) in MeOH (300 ml), $NaBH_4$ (6.05 g, 0.16 mol) was added at room temperature with stirring and the reaction mixture was refluxed for 40 min. The solvent was removed *in vacuo* and the residue was extracted with $CHCl_3$ and worked up as usual. The crude product was chromatographed on Al_2O_3. The $CHCl_3$ eluate was distilled under reduced pressure and the residue was dissolved in EtOH. The solution was made acidic with HCl–EtOH to give colorless crystals, which were recrystallized from a suitable solvent. The physical data of XIII are listed in Table I.

General Procedure for the Synthesis of Butene Derivatives (XIV), Method G——Butanol (XIII) (0.02 mol) was dissolved in conc. H_2SO_4 (15 ml) and heated at 160° for 30 min. The reaction mixture was poured into ice-water and made alkaline with Na_2CO_3, extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g) with $CHCl_3$–EtOH (30: 1). The eluate was concentrated and was made acidic with HCl–EtOH. The resulting precipitate was collected by filtration and recrystallized from a suitable solvent. The physical data of XIV are listed in Table I.

1-Cyclopropyl-1-(3-pyridinyl)benzylalcohol (XV)——To a Grignard reagent (C_6H_5-MgBr) prepared from Mg (876 mg, 0.036 atom), C_6H_5Br (6.28 g, 0.04 mol) and dry $(C_2H_5)_2O$ (30 ml), IXb (2.94 g, 0.02 mol) in dry $(C_2H_5)_2O$ (25 ml) was added at room temperature and reflux for 2 hr. Ice-water and diluted HCl were

added to the mixture under chilling and the aqueous layer was separated, made alkaline with 10% NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography on silica gel (40 g) with C_6H_6–$CHCl_3$ (1: 1) and recrystallization from $(C_2H_5)_2O$–hexane gave 1.91 g (42.4%) of XV, mp 105.5—107.5°. *Anal.* Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.02; H, 6.57; N, 6.15. IR ν_{max}^{KBr} cm^{-1}: 3150 (OH).

4-Chloro-1-phenyl-1-(3-pyridinyl)-1-butene (XVI)——To XV (1.53 g, 6.7 mmol), $SOCl_2$ (830 mg, 0.07 mol) was added dropwise and allowed to react for 3 min and the solution was heated at 95° for 5 min. After chilling, the reaction mixture was made alkaline with 5% Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was passed through an Al_2O_3 (3 g) using $(C_2H_5)_2O$. Removal of the solvent afforded 1.51 g (92.4%) of a pale yellow oil (XVI), which was used for the next step without further purification. NMR (δ in $CDCl_3$): 2.63 (2H, m, =CH–CH_2–), 3.57 (2H, t, J=7 Hz, –CH_2–Cl), 6.13 (*ca.* 0.4H, t, J=8 Hz, =CH–), 6.18 (*ca.* 0.6H, t, J=8 Hz, =CH–), 7.22 (7H, m, –C_6H_5 and β,γ-protons of pyridine ring), 8.49 (2H, m, α-protons of pyridine ring).

1-Phenyl-4-(4-phenyl-1-piperazinyl)-1-(3-pyridinyl)-1-butene (XVIIa-isomer A, B), Method H——A mixture of XVI (1.46 g, 6 mmol), phenylpiperazine (2.43 g, 15 mmol), KI (100 mg) and toluene (20 ml) was heated at 120° for 38 hr in a sealed tube. After cooling, the resulting precipitate was filtered off and the filtrate was concentrated. The residue was purified by chromatography (silica gel 30 g), eluting successively with C_6H_6, C_6H_6–$CHCl_3$ (1: 1), $CHCl_3$ and $CHCl_3$–EtOH (50: 1). After the fraction eluted with C_6H_6 was discarded, the combined eluates were submitted to preparative TLC using $CHCl_3$–$(CH_3)_2CO$ (9: 1) as developing solvent. The more mobile fraction was extracted with $(CH_3)_2CO$ and recrystallized from $(C_2H_5)_2O$ to give colorless prisms (385 mg, 17.4%) of XVIIa-isomer A. mp 94.5—96.5°. *Anal.* Calcd. for $C_{25}H_{27}N_3$: C, 81.26; H, 7.37; N, 11.37. Found: C, 81.36; H, 7.24; N, 11.63. NMR (δ in $CDCl_3$): 2.47 (8H, m, methylene protons), 3.10 (4H, m, $(CH_2)_2N$–C_6H_5), 6.18 (1H, t, J=7 Hz, =CH–). The less mobile fraction was recrystallized from cyclohexane–hexane to give colorless prisms (264 mg, 11.9%) of XVIIa-isomer B, mp 68—69°. *Anal.* Calcd. for $C_{25}H_{27}N_3$: C, 81.26; H, 7.37; N, 11.37. Found: C, 80.95; H, 7.42; N, 11.34. NMR (δ in $CDCl_3$): 2.49 (8H, m, methylene protons), 3.18 (4H, m, $(CH_2)_2N$–C_6H_5), 6.22 (1H, t, J=7 Hz, =CH–).

4-[4-(2,3-Dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]-1-phenyl-1-(3-pyridinyl)-1-butene (XVIIb)——Prepared from XVI (1.95 g, 8 mmol) and VIIb (3.04 g, 0.014 mol) as described for XVIIa. Yield 1.04 g (30.6%), colorless crystalline solid, mp 179—181°. The product was used for the next step as the mixture of two isomers.

General Procedure for the Synthesis of XVIII, Method I——A mixture of XVII (2 mmol) and 10% palladium-carbon (500 mg) in MeOH (40 ml) was submitted to catalytic hydrogenation at ordinary temperature and pressure. After the theoretical amount of H_2 was absorbed, the catalyst and the solvent were removed. The residue was passed through an Al_2O_3 (4 g) column using $(C_2H_5)_2O$ to give colorless crystals, which were recrystallized from a suitable solvent. The physical data of XVIII are listed in Table I.

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