Chem. Pharm. Bull. 27(1) 119—128 (1979)

UDC 547.822.3.04.09 : 615.214.2.011.5.015.11

Psychotropic Agents. II.[1] Synthesis and Psychotropic Activity of conformationally Restricted Butyrophenone Analogs

Makoto Sato, Masayuki Kitagawa, Fumihiko Uchimaru, Katsujiro Ueno, Hiroshi Kojima, and Terukiyo Yamasaki

Research Institute, Daiichi Seiyaku Co., Ltd.[2]

(Received July 20, 1978)

In order to search for new psychotropic agents, several conformationally restricted analogs (see Chart 1D) of haloperidol or benperidol were synthesized. *cis*- and *trans*-1-[2-(2-Phenylcyclopropyl)ethyl]piperidine derivatives (Xa, Xb, and XXIV) were prepared in several steps from the corresponding *cis*- and *trans*-1-phenyl-1-butene derivatives (III and XX). The effect of the compounds on spontaneous motor activity in mice was determined. *trans*-Isomer (Xb), which was the most active compound, was about 11 times more active than *cis*-isomer (XXIV). But the activity of Xb was about one-fifth as potent as benperidol. Structure-activity relationships of these compounds are discussed.

Keywords——psychotropic agents; neuroleptics; *cis*-phenylcyclopropane; *trans*-phenylcyclopropane; Simmons-Smith reaction; *cis*-1-butene derivatives; *trans*-1-butene derivatives; 1-butyne derivatives

A previous article[1] from our laboratory reported the synthesis of several butanone derivatives substituted at the 1-position with heteromatic rings such as pyridine, indole or quinoline in order to search for new psychotropic agents. The butanone side-chain was

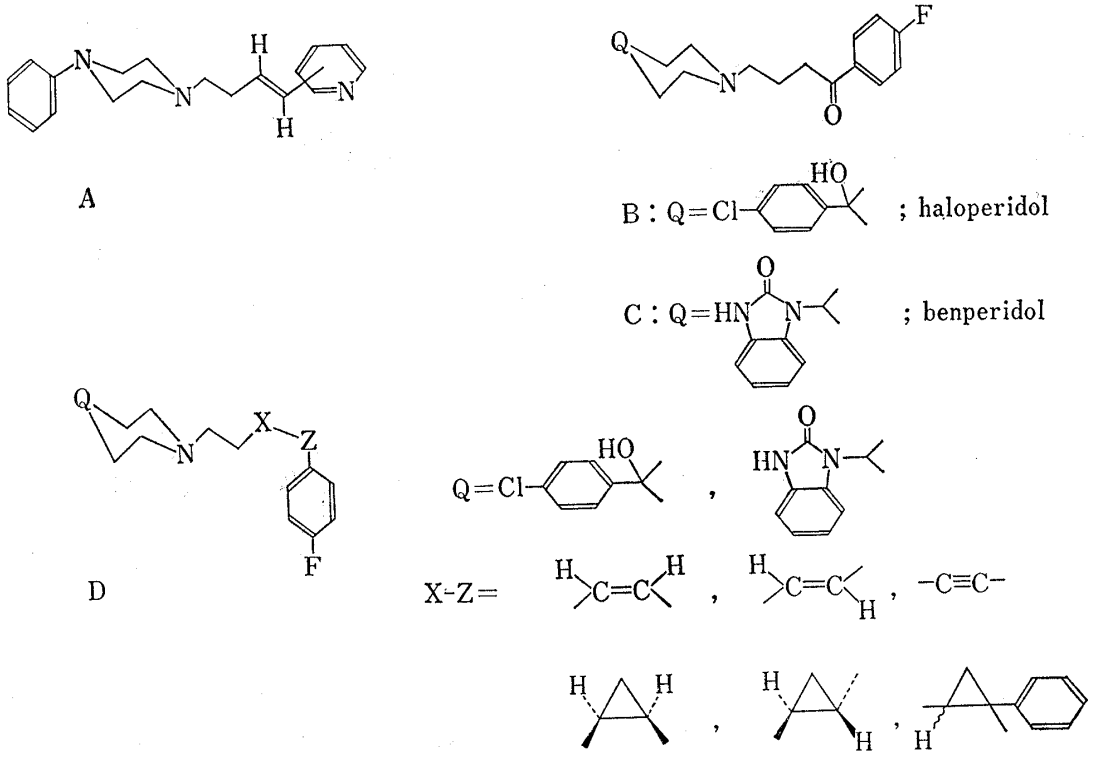


Chart 1

1) Part I: M. Sato, H. Tagawa, A. Kosasayama, F. Uchimaru, H. Kojima, T. Yamasaki, and T. Sakurai, *Chem. Pharm. Bull.* (Tokyo), **26**, 3296 (1978).
2) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*

also modified to butane, butanol and butene. It was very interesting that the *trans*-butene (A) was the most active among the compounds examined, suggesting that the conformational restriction of the molecule would be significant for the psychotropic activity.

These previous observations prompted us to prepare the analogs of butyrophenones (B, C)[3] and evaluate their biological activities which were conformationally restricted by introduction of acetylenic and olefinic bonds, and cyclopropane ring to the molecule (see Chart 1 D).

In this paper, we describe the preparation of pairs of geometric isomers in these analogs and the relationships between stereochemistry and neuroleptic activity. The present results may provide an interesting example which demonstrates importance of geometry of molecules on the psychotropic activity.

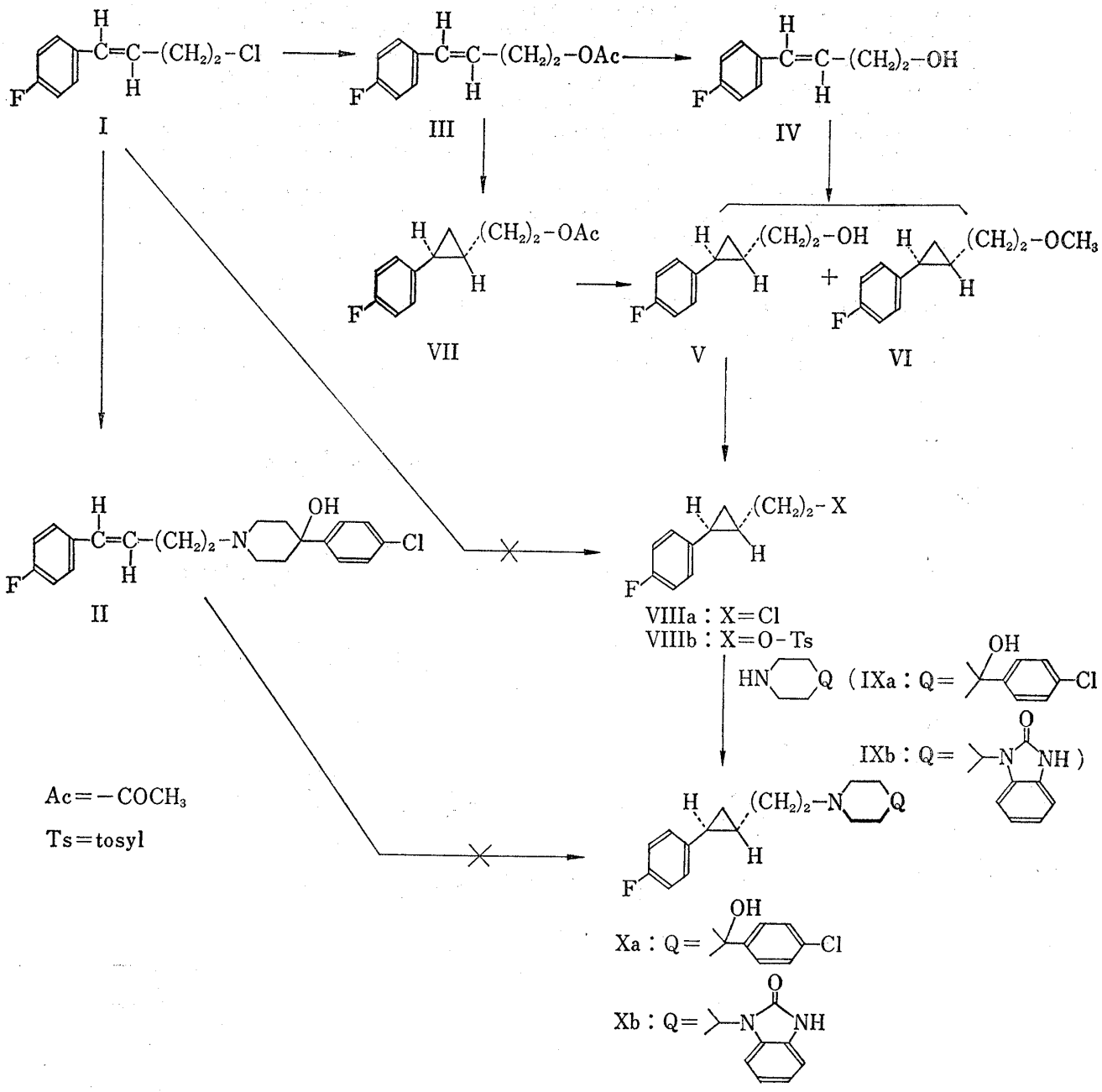


Chart 2

3) P.A.J. Janssen, C.J.E. Niemegeers, and K.H.L. Schellekens, *Arzneim.-Forsch.*, **15**, 104 (1965).

Chemistry

As for the synthesis of cyclopropane derivatives of the butyrophenone analogs, Baboulene *et al.*[4] have reported a stereospecific preparation of *trans*-1-aminomethyl-2-benzoylcyclopropane derivatives. The synthesis of a pair of *cis*- and *trans*-1-[2-(1-piperidinyl)ethyl]-2-phenylcyclopropane derivatives (D), however, is hitherto unknown. Among the several methods for preparing cyclopropanes, the Simmons–Smith[5] type carbenoid insertion reaction to olefinic bond was chosen for our purpose because of its high stereospecificity[6] and convenience.

A direct synthesis of *trans*-cyclopropane derivatives (Xa) from the known *trans*-butene derivative (II)[7] according to a modified procedure of Shank *et al.*[8] was unsuccessful. The transformation of *trans*-4-chloro-1-butene derivative (I) into chloroethylcyclopropane derivative (VIIIa) was also unsatisfactory because the purification of the products was troublesome. Therefore, the Simmons–Smith reaction of *trans*-3-buten-1-ol derivative (IV) was finally tried. The *trans*-butene derivative (IV) was prepared with ease from I by acetylation with potassium acetate followed by hydrolysis with caustic alkali.[9] The carbenoid insertion reaction of IV according to Shank's method afforded two major cyclopropane derivatives (V and VI), which were purified by column chromatography and distillation. The nuclear magnetic resonance (NMR) spectrum of a more volatile product showed a signal at δ 3.34 as a singlet assignable to a methyl group. The mass spectral and the elemental analytical data established the molecular formula, $C_{12}H_{15}FO$. The infrared (IR) spectrum did not show a stretching band of hydroxy group. Thus, the structure of the more volatile product was confirmed to be *trans*-1-(4-fluorophenyl)-2-(methoxyethyl)cyclopropane (VI). The formation of VI can be explained in terms of the carbenoid insertion to the hydroxy group. The structural proof of a less volatile product (V) mainly rests upon its IR and NMR spectra. The NMR spectrum of V exhibits complex multiplets assignable to the four protons of the cyclopropane ring. On addition of tris-(dipivalomethanato)europium [Eu(DPM)$_3$] (0.3 mol) to V in carbon tetrachloride, the spectrum became more readily analysable. The NMR spectrum showed two methine protons of the cyclopropane ring at δ 3.45 and δ 4.3 as multiplet and methylene protons of the cyclopropane ring at δ 2.0—2.7 as complex multiplet. The IR spectrum of V showed a hydroxy streching band at 3370 cm^{-1}. When 4-acetoxy-1-butene derivative (III) was employed as a starting material, the cyclopropane derivative (V) was obtained after hydrolysis of the resulting acetate (VII) without the formation of the by-product (VI). As the reaction of 2-chloroethylcyclopropane derivative (VIIIa) with piperidine derivatives (IXa) required rather drastic conditions, an alternative procedure was applied for the synthesis of the desired compounds (Xa and Xb). The compound (V) was converted to *p*-toluenesulfonate (VIIIb) and subsequent treatment with piperidine derivative (IXa and IXb) gave *trans*-1-[2-[2-(4-fluorophenyl)cyclopropyl]ethyl]piperidine derivative (Xa and Xb) in good yields.

1-(4-Fluorophenyl)-1-phenylcyclopropane derivative (XVI) was also prepared by the method described above from butene (XI), which had been prepared by Janssen[7] (see Chart 3). The starting material (XI) was found to be a mixture of *cis* and *trans* isomers (*ca.* 1:1) by NMR spectral analysis. Accordingly, the product (XVI) must be a mixture of two geometric isomers. Although this aspect was confirmed on the basis of the NMR spectrum, attempts to separate both the isomers were in failure.

cis-Cyclopropane derivative (XXIV) was synthesized as follows (see Chart 4). Butyne derivative (XVIII), which was synthesized according to a modified method reported by Corey

4) M. Baboulene and G. Sturtz, *Bull. Soc. Chim. Fr.* II, **1974**, 2929.
5) H.E. Simmons and R.D. Smith, *J. Am. Chem. Soc.*, **81**, 4256 (1959).
6) H. Nozaki and R. Noyori, *Yuki Gosei Kagaku Kyokai Shi*, **24**, 519 (1966).
7) P.A.J. Janssen, U.S. Patent 3238216 (1966) [*C.A.*, **65**, 8925*b* (1966)].
8) R.S. Shank and H. Shechter, *J. Org. Chem.*, **24**, 1825 (1959).
9) M. Hanack, S. Kang, J. Häffner, and K. Görler, *Ann. Chem.*, **690**, 98 (1965).

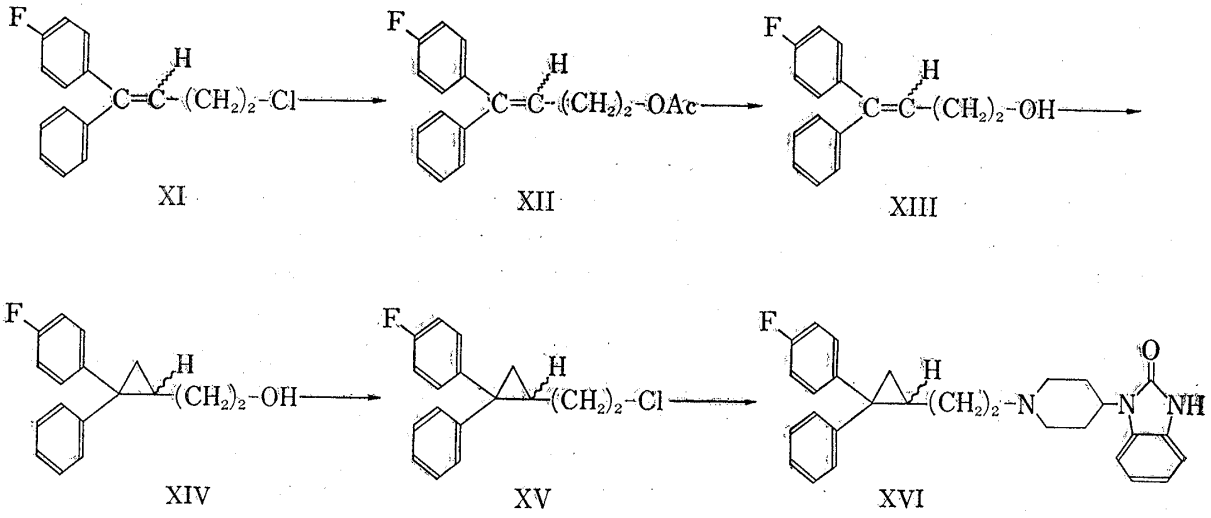


Chart 3

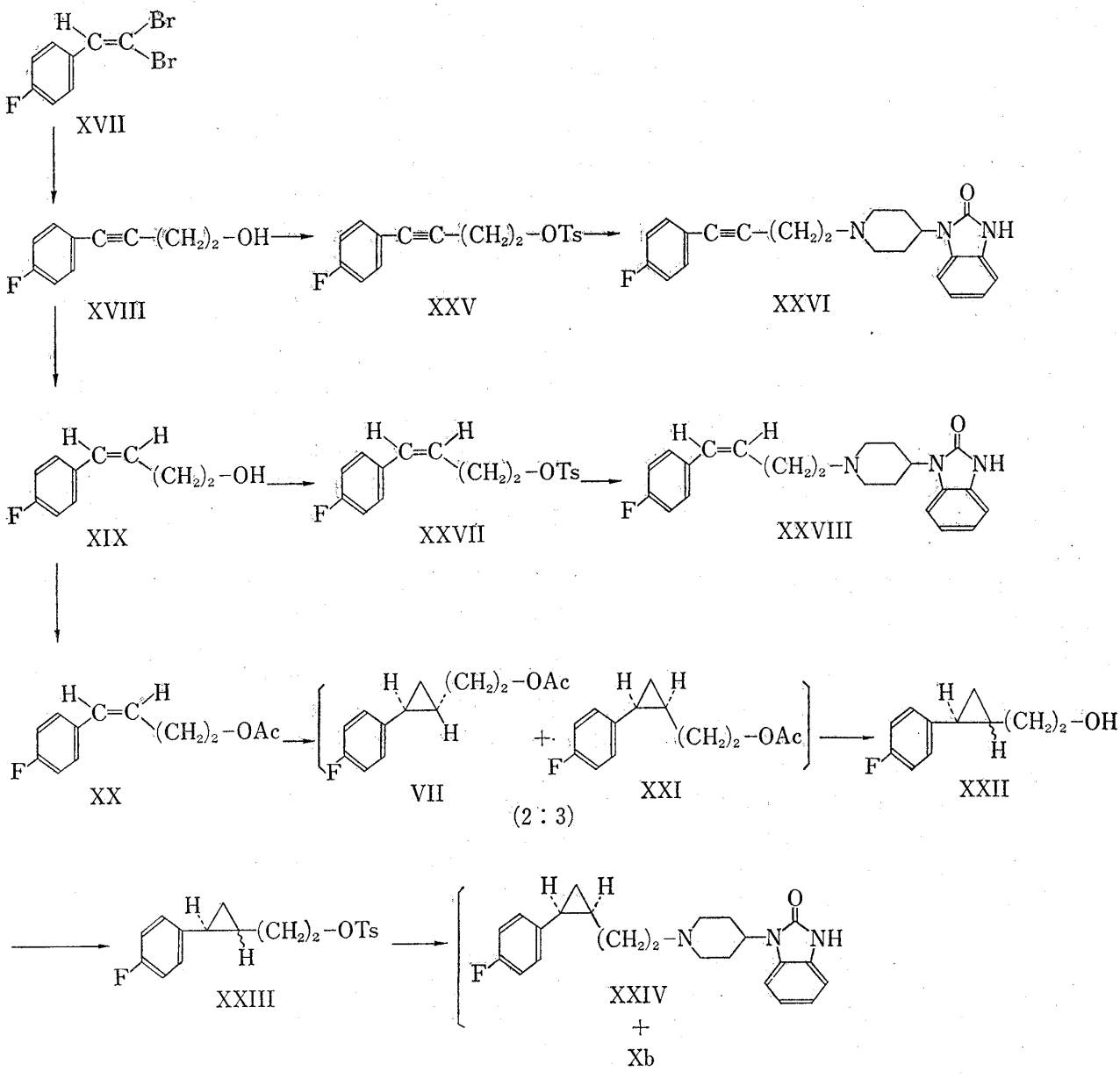
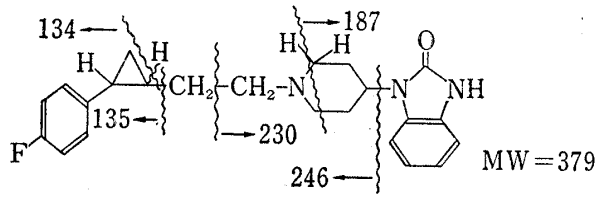


Chart 4

et al.,[10] was hydrogenated over Lindlar catalyst[11] to give *cis*-butene derivative (XIX). No contamination of *trans*-isomer (IV) was observed by means of gas–liquid chromatography. The small coupling constant (J=11.5 Hz) of the vinyl protons in the NMR spectrum confirmed the *cis*-configuration of XIX in comparison with the coupling constant (J=15.5 Hz) of the vinyl protons of the *trans* isomer (IV). Acetylation of XIX with acetic anhydride in pyridine gave an acetate (XX) in high yield. Unexpectedly, the reaction of XX with methylene iodide and zinc–copper couple gave two isomeric cyclopropane derivatives (VII and XXI). The ratio of the isomers (*ca.* 2:3) was estimated on the basis of the gas chromatographic and NMR spectral data. The retention time of the minor product in the gas chromatography was consistent with that of *trans*-isomer (VII) previously mentioned. The separation of the isomers was difficult. Thus, the mixture was used for the next step without further purification. Toluenesulfonates (XXIII) were obtained by hydrolysis of two isomeric acetate (VII and XXI) followed by treatment with *p*-toluenesulfonyl chloride. Condensation of XXIII with 4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine(IXb) gave also two isomeric products. A more mobile product in the thin-layer chromatography was identified as the *trans*-isomer (Xb) on the basis of the *Rf* value. The less mobile isomer (XXIV) was iso-

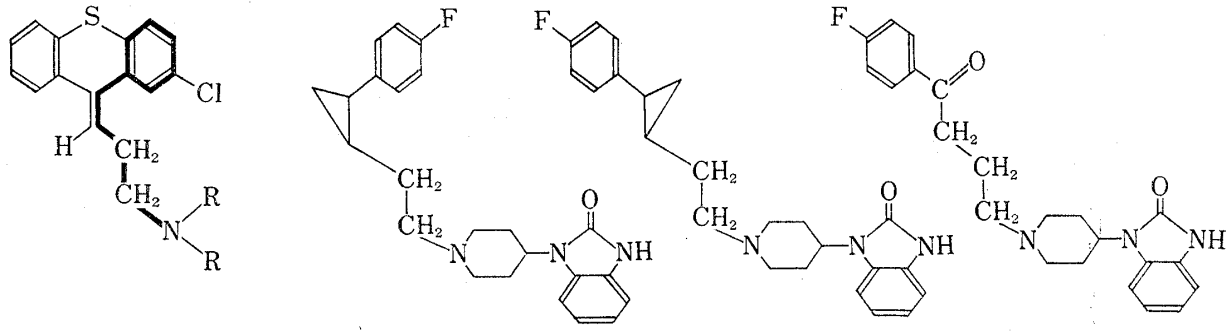


Xb or XXIV

Chart 5

Table I. High MS of the Two Isomeric Cyclopropane Derivatives (Xb and XXIV)

Measured mass of *trans*-isomer (Xb)	Error (mmu)	Measured mass of *cis*-isomer (XXIV)	Error (mmu)	Calculated mass	Element
134.0483	4.7	134.0499	3.2	134.0531	C_9H_7F
135.0584	2.5	135.0569	4.0	135.0610	C_9H_8F
187.0877	0.6	187.0825	4.7	187.0871	$C_{11}H_{11}N_2O$
230.1266 (base ion)	2.7	230.1330 (base ion)	3.7	230.1293	$C_{13}H_{16}N_3O$
246.1649	0.8	Not observed	—	246.1658	$C_{16}H_{21}FN$
379.2021(M^+)	3.8	Not observed	—	379.2059	$C_{23}H_{26}FN_3O$

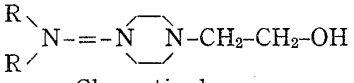


chlorprotixene: R=CH_3

XXIV

Xb

benperidol

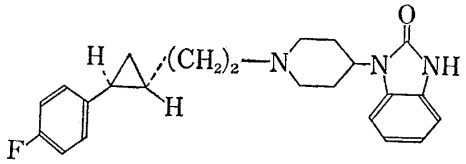
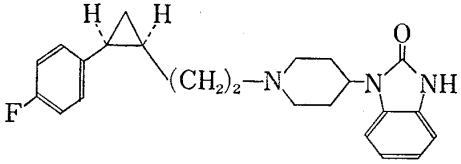
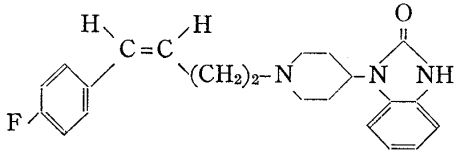
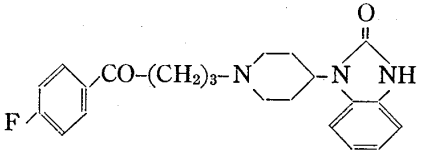
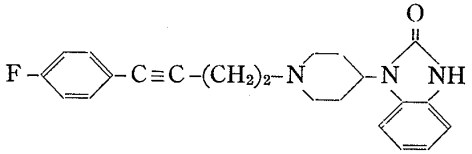
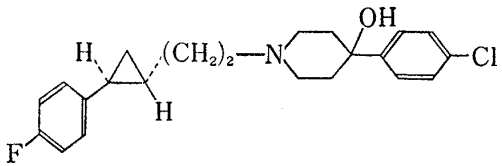
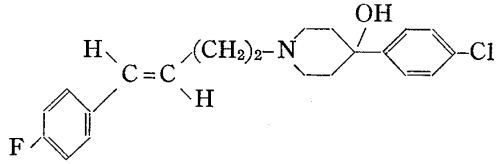
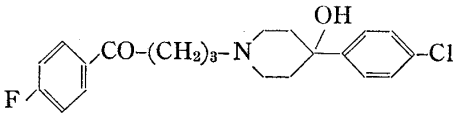
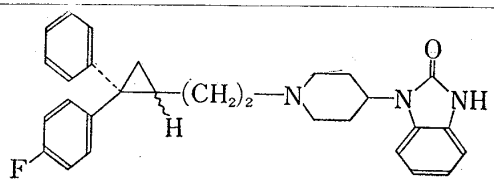
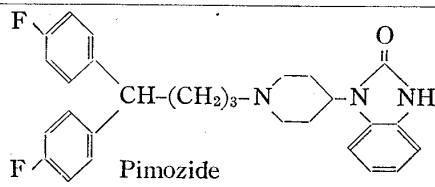


Clopentixol

Chart 6

10) E.J. Corey and P.L. Fuchs, *Tetrahedron Lett.*, **1972**, 3769.
11) H. Lindlar and R. Dubuis, "Organic Syntheses," Coll. Vol. V, ed. by H.E. Baumgarten, John Wiley, and Sons. Inc., New York, 1973, p. 880.

TABLE II. Suppression of Spontaneous Motor Activity (SMA) (Wheel Cage Method) of Mice by the Present Compounds and Other Neuroleptics, 1 hr after *p.o.* Administration[a)]

No.	Structure	SMA ED_{50} mg/kg	Relative potency	Structure	SMA ED_{50} mg/kg	Relative potency
Xb		2.7(1.4—5.4)	[0.207]			
XXIV		30.0(22—40)	[0.019]			
XXVIII		*ca.* 40	[0.014]	 Benperidol	0.56(0.35—0.91)	[1]
XXVI		42.7(29.3—62.3)	[0.013]			
Xa		5.5(2.8—11)	[0.145]			
II		9.2(6.3—13)	[0.087]	 Haloperidol	0.80(0.43—1.5)	[1]
XVI		*ca.* 40	[0.19]	 Pimozide	7.4(4—14)	[1]

a) Test method has been described in a prior publication.[1)]

lated by preparative thin-layer chromatography. The structure was supported by the elemental analysis and spectral data, *i. e.*, the ultraviolet (UV) spectrum and the fragmentation pattern in its mass spectrum were quite similar to those of *trans*-isomer (Xb), respectively. The composition of the main fragment ions was elucidated by high-resolution mass spectrometry (Table I and Chart 5).

The intermediates, 3-butyn-1-ol (XVIII) and *cis*-3-buten-1-ol (XIX), were converted to XXVI and XXVIII by the analogous method described above, respectively.

Structure–Activity Relationships

The effect of the compounds on spontaneous motor activity (wheel cage method) in mice was determined using the proceure described earlier.[1] The results listed in Table II and the relative potencies of the present compounds in comparison with the corresponding butyrophenones[3] are shown in brackets. The data in Table II indicate that the *cis*-cyclopropane derivative (XXIV) was about one-eleventh as active as *trans*-isomer (Xb), and that the *cis* butene derivative (XXVIII) also showed weaker activity than *trans*-analogue (II). Fieldings *et al.*[12] have reported a conformational similarity linking with butyrophenones and thioxanthenes such as chlorprotixene which are known to have pharmacologically similar properties.[3] In thioxanthenes, the *cis*-isomers are known to be far more active neuroleptics than the *trans*-isomers.[13,14] It is notable that our results are not in parallel with those obtained in the thioxanthenes (see Chart 6). Although there is no clear explanation for this inconsistency,[14] the present observation provides a further example demonstrating importance of the geometry in the side-chain of butyrophenone analogue.

The most active derivative (Xb) among the present compounds was about one–fifth as active as benperidol. Whether the lower potency of Xb in comparison with benperidol is due to the steric hindrance of the cyclopropane ring or the lack of carbonyl group remains unanswered. And butyne derivative (XXVI) was as active as *cis* butene derivative (XXVIII). Diphenylcyclopropane derivative (XVI) was about one-fifth as active as pimozide. Further pharmacological studies of these compounds are in progress and the details will be published elsewhere.

Experimental

The following instruments were used. UV spectra: a Hitachi 323 Spectrometer; IR spectra: a Hitachi EPI-G 2 type Infrared Spectrometer; NMR (tetramethylsilane as an internal standard): a Hitachi R-20B spectrometer (60 MHz); a Hitachi Mass spectrometer RMS-4 (direct inlet, at 70 eV); high-resolution mass spectra: JEOL JMS-01SG-2 Mass spectrometer; gas-liquid chromatography: a Hitachi Gas Chromatograph (K-53) attached with a hydrogen flame detector; melting points: a Yanagimoto melting point apparatus (Type MP-1). All melting points are uncorrected.

***trans*-4-Acetoxy-1-(4-fluorophenyl)-1-butene (III)**——Prepared from I (3.0 g, 0.016 mol) according to the procedure of Hanack.[9] Yield 2.66 g (78.7%), bp 104—106° (2 mmHg).

***trans*-4-(4-Fluorophenyl)-3-buten-1-ol (IV)**——Prepared from III (9.0 g, 0.043 mol) by the procedure of Hanack.[9] Yield 5.65 g (78.6%), bp 124—128° (7 mmHg). NMR (δ in $CDCl_3$): 2.07 (1H, s, OH), 2.50 (2H, m, =CH–C$\underline{H}_2$–), 3.73 (2H, t, J=7 Hz, –C$\underline{H}_2$–OH), 5.8—6.25 (1H, m, =C$\underline{H}$–CH_2–), 6.46 (1H, d, J=15.5 Hz, FC_6H_4–C$\underline{H}$=CH–), 6.8—7.4 (4H, m, FC_6H_4–).

***trans*-2-[2-(4-Fluorophenyl)cyclopropyl]ethanol (V) and *trans*-1-(4-Fluorophenyl)-2-(2-methoxyethyl)-cyclopropane (VI)**——(i) CH_2I_2 (42.0 g, 0.157 mol) and I_2 (119 mg, 0.47 mmol) were added to a mixture of zinc–copper couple[8] (11.6 g) and anhydrous ether (80 ml), and the mixture was refluxed for 30 min with stirring and external heating was discontinued. IV (13.0 g, 0.078 mol) in anhydrous ether (20 ml) was added

12) S. Fieldings and H. Lal "Neuroleptics. Futura," New York, 1974 (For a review, see A. Pletscher, *Chimia*, 32, 113 (1978)).

13) The *cis*- and *trans*-geometries correspond the relation between chlorobenzene ring and side-chain in thioxanthenes.

14) *a*) J.D. Dunitz, H. Eser, and P. Strickler, *Helv. Chim. Acta*, **47**, 1897 (1964); *b*) K. Pelz and M. Protiva, *Collect. Czech. Chem. Commun.*, 32, 2161 (1967); *c*) J.F. Muren and B.M. Bloom, *J. Med. Chem.*, 13, 17 (1970).

dropwise to the reaction mixture, and refluxed for 4 hr. And then CH_2I_2 (14.7 g, 0.055 mol) and zinc–copper couple (4.2 g) were added to the reaction mixture and refluxed for 2.5 hr. The reaction mixture was cooled and filtered. The precipitate was washed with 5% HCl and ether. The combined filtrates were extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on Al_2O_3 (250 g) eluted with ether to be separated into two components.

The first eluted product was 2.40 g (15.8%) of a colorless oil (VI), which was purified by distillation, bp 104—106° (5 mmHg). *Anal.* Calcd. for $C_{12}H_{15}FO$: C, 74.20; H, 7.78. Found: C, 74.11; H, 7.53. MS *m/e*: 194 (M^+). NMR (δ in $CDCl_3$): 0.5—1.3 (3H, m, methylene protons of cyclopropane and $>C\underline{H}-CH_2-$), 1.3—1.9 (3H, m, $FC_6H_4-C\underline{H}<$ and $-C\underline{H}_2-CH_2-OCH_3$), 3.34 (3H, s, –OMe), 3.48 (2H, t, $J=7$ Hz, $-C\underline{H}_2-OMe$), 6.8—7.05 (4H, m, FC_6H_4-).

The second eluted product was 6.15 g (43.6%) of a pale yellow oil (V), which was purified by distillation, bp 107—108° (3 mmHg). *Anal.* Calcd. for $C_{11}H_{13}FO$: C, 73.31; H, 7.27. Found: C, 73.19; H, 7.17. IR ν_{max}^{neat} cm^{-1}: 3370 (OH). MS *m/e*: 180 (M^+). NMR (δ in $CDCl_3$): 0.5—1.4 (3H, m, methylene protons of cyclopropane and $>C\underline{H}-CH_2-$), 1.4—1.9 (3H, m, $FC_6H_4-C\underline{H}<$ and $-C\underline{H}_2-CH_2-OH$), 1.85 (1H, s, OH), 3.75 (2H, t, $J=7$ Hz, $-C\underline{H}_2-OH$), 6.8—7.2 (4H, m, C_6H_4-). NMR (δ in CCl_4 containing tris-(dipivalomethanato)-europium (0.3 mol)): 2.0—2.7 (2H, m, methylene protons of cyclopropane), 3.45 (1H, m, $FC_6H_4-C\underline{H}<$), 4.3 (1H, m, $>C\underline{H}-CH_2-$), 5.90 (2H, m, $-C\underline{H}_2-CH_2-OH$), 7.08 (2H, ABX type t, FC_6H_4-), 7.81 (2H, ABX type q, FC_6H_4-), 11.18 (2H, t, $J=7$ Hz, $-C\underline{H}_2-OH$).

(ii) A mixture of acetate (VII) (10.3 g, 0.046 mol), 1 N NaOH (116 ml) in MeOH (680 ml) was allowed to stand overnight at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, evaporated *in vacuo* and passed through an Al_2O_3 using $CHCl_3$ to give 8.17 g (98.2%) of a colorless oil (V), which was identified by comparison of IR spectra with the authentic sample synthesized in experimental (i).

***trans*-2-(2-Acetoxyethyl)-1-(4-fluorophenyl)cyclopropane (VII)**——Prepared from III (14.6 g, 0.07 mol) as described for V. Distillation of the crude product gave 10.4 g (66.7%) of a colorless oil (VII), bp 103—107° (2 mmHg). IR ν_{max}^{neat} cm^{-1}: 1740 (C=O). NMR (δ in $CDCl_3$): 0.5—1.4 (3H, m, methylene protons of cyclopropane and $>C\underline{H}-CH_2-$), 1.4—1.9 (3H, m, $FC_6H_4-C\underline{H}<$ and $-C\underline{H}_2-CH_2-OCOMe$), 2.05 (3H, s, –OCOMe), 4.19 (2H, t, $J=7$ Hz, $-CH_2-O-CO-$), 6.8—7.1 (4H, m, FC_6H_4-). Gas–liquid chromatography: column, 10% XE 60 on Anakrom ABS; column length, 1 m; column temperature, 170°; carrier gas, N_2, 0.6 kg/cm², t_R, 5.0 min.

***trans*-2-(2-Chloroethyl)-1-(4-fluorophenyl)cyclopropane (VIIIa)**——A mixture of V (1.70 g, 9 mmol) and $SOCl_2$ (3.4 ml) in pyridine (1.7 ml) was heated at 95° for 10 min. To the reaction mixture was added ice–water under chilling. The mixture was extracted with ether, and the extracts were washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on Al_2O_3 with ether to give 1.52 g (81.6%) of a pale yellow oil (VIIIa). *Anal.* Calcd. for $C_{11}H_{12}ClF$: C, 66.50; H, 6.09. Found: C, 66.77; H, 6.10. MS *m/e*: 198, 200 (M^+) (MW=198.66). NMR (δ in $CDCl_3$): 0.6—1.2 (3H, m, methylene protons of cyclopropane and $>C\underline{H}-CH_2-$), 1.2—1.9 (3H, m, $FC_6H_4-C\underline{H}<$ and $-C\underline{H}_2-CH_2Cl$), 3.63 (2H, t, $J=7$ Hz, $-CH_2-Cl$), 6.7—7.2 (4H, m, FC_6H_4-).

***trans*-2-[2-(4-Fluorophenyl)cyclopropyl]ethyl *p*-Toluenesulfonate (VIIIb)**——To a solution of V (8.14 g, 0.045 mol) in pyridine (55 ml) was added *p*-toluenesulfonylchloride (17.2 g, 0.09 mol) under chilling, and allowed to stand overnight in a refrigerator. To the reaction mixture was added ice–water, and the mixture was extracted with $CHCl_3$, washed successively with cold 17% HCl and H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel (25 g) eluted with $CHCl_3$ to afford 13.1 g (86.4%) of a pale yellow oil (VIIIb), which was used for the next step without further purification. NMR (δ in $CDCl_3$): 0.84 (3H, m, methylene protons of cyclopropane and $>C\underline{H}-CH_2-$), 1.68 (3H, m, $FC_6H_4-C\underline{H}<$ and $-C\underline{H}_2-CH_2-O-$), 2.43 (3H, s, $-CH_3$), 4.13 (2H, t, $J=7$ Hz, $-CH_2-O-SO_2-$), 6.8—7.1 (4H, m, FC_6H_4-), 7.27 (2H, d, $J=9$ Hz, *meta* protons of *p*-toluenesulfonyl), 7.47 (2H, d, $J=9$ Hz, *ortho* protons of *p*-toluenesulfonyl).

***trans*-4-(4-Chlorophenyl)-1-[2-[2-(4-fluorophenyl)cyclopropyl]ethyl]-4-piperidinol (Xa)**——A mixture of VIIIa (2.98 g, 0.015 mol), 4-(4-chlorophenyl)-4-piperidinol (IXa) (8.44 g, 0.04 mol) and KI (100 mg) in xylene (120 ml) was heated at 120—125° for 120 hr in an autoclave. After cooling, the resulting precipitate was filtered off, washed with $CHCl_3$. The filtrate was concentrated *in vacuo*, and a solution of the residue in $CHCl_3$ was washed successively with diluted NaOH solution and H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (150 g). The fraction eluted with $CHCl_3$–EtOH (49: 1) was concentrated *in vacuo* and the residue was recrystallized from $CHCl_3$–ether to give 3.90 g (69.5%) of colorless needles (Xa), mp 132.5—134.5°. *Anal.* Calcd. for $C_{22}H_{25}ClFNO$: C, 70.67; H, 6.74; N, 3.75. Found: C, 71.00; H, 6.74; N, 3.87. IR ν_{max}^{KBr} cm^{-1}: 3170 (OH). NMR (δ in $CDCl_3$): 0.4—1.1 (3H, broad m, $-CH_2-$ of cyclopropane, $>C\underline{H}-(CH_2)_2-N<$), 6.8—7.1 (4H, m, FC_6H_4-), 7.36 (4H, AB type q, $J=9$ Hz, $Cl-C_6H_4$).

***trans*-1-[1-[2-[2-(4-Fluorophenyl)cyclopropyl]ethyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (Xb)**——A mixture of VIIIb (11.7 g, 0.035 mol) and 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one (IXb) (15.2 g, 0.07 mol) in xylene (210 ml) was refluxed for 5 hr. The reaction mixture was treated as described for Xa and recrystallization from $CHCl_3$–ether gave 10.9 g (81.7%) of colorless crystals (Xb), mp 152.5—156°. *Anal.* Calcd. for $C_{23}H_{26}FN_3O$: C, 72.80; H, 6.91; N, 11.07. Found: C, 72.92; H, 7.08; N, 11.11. IR ν_{max}^{KBr}

cm^{-1}: 3180, 3150 (NH), 1695 (C=O). NMR (δ in $CDCl_3$): 0.4—1.1 (3H, broad m, $-CH_2-$ of cyclopropane, $>C\underline{H}-(CH_2)_2-N<$), 4.40 (1H, broad m, methine proton of piperidine), 6.7—7.5 (8H, m, protons of aromatic rings). UV $\lambda_{max}^{ethanol}$ nm: 274 (sh.), 282.5, 289 (sh.).

***cis*- and *trans*-4-Acetoxy-1-(4-fluorophenyl)-1-phenyl-1-butene (XII)**——Prepared from XI[7] (33.9 g, 0.13 mol) as described for III. Yield 36.8 g (99.5%), a yellow oil, which was used for the next step without further purification. IR ν_{max}^{neat} cm^{-1}: 1740 (C=O). NMR (δ in $CDCl_3$): 2.5 (3H, s, $-COCH_3$), 2.2—2.45 (2H, m, $-C\underline{H}_2-CH_2-OAc$), 4.14 (2H, t, $J=7$ Hz, $-CH_2OAc$), 5.9—6.2 (1H, m, $-CH-$), 6.7—7.5 (9H, m, aromatic ring protons).

***cis*- and *trans*-4-(4-Fluorophenyl)-4-phenyl-3-buten-1-ol (XIII)**——Prepared from XII (33.6 g, 0.129 mol) as described for IV. Yield 28.98 g (92.9%), bp 145—154° (1 mmHg). IR ν_{max}^{neat} cm^{-1}: 3330 (OH). NMR (δ in $CDCl_3$): 1.70 (1H, s, OH), 2.2—2.6 (2H, m, $-C\underline{H}_2-CH_2-OH$), 3.69 (2H, t, $J=7$ Hz, $-CH_2OH$), 5.9—6.2 (1H, m, $=CH-$), 6.7—7.5 (9H, m, aromatic ring protons).

***cis*- and *trans*-2-[2-(4-Fluorophenyl)-2-phenylcyclopropyl]ethanol (XIV)**——Prepared from XIII (7.27 g, 0.03 mol) as described for V. Yield 4.63 g (60.2%), a pale yellow oil. NMR (δ in $CDCl_3$): 0.8—1.4 (3H, m, cyclopropane ring protons), 1.65 (1H, s, OH), 1.4—2.1 (2H, m, $-C\underline{H}_2-CH_2-OH$), 3.69 (2H, t, $J=7$ Hz, $-C\underline{H}_2-OH$), 6.7—7.5 (9H, m, aromatic ring protons).

***cis*- and *trans*-2-(2-Chloroethyl)-1-(4-fluorophenyl)-1-phenylcyclopropane (XV)**——Prepared from XIV (2.2 g, 8.6 mmol) as described for VIIIa. Yield 1.24 g (52.5%), a pale yellow oil. NMR (δ in $CDCl_3$): 1.0—1.5 (3H, m, protons of cyclopropane), 1.5—2.2 (2H, m, $-C\underline{H}_2-CH_2-Cl$), 3.57 (2H, t, $J=7$ Hz, $-CH_2-Cl$), 6.7—7.6 (9H, m, protons of benzene rings).

***cis*- and *trans*-1-[1-[2-[2-(4-Fluorophenyl)-2-phenylcyclopropyl]ethyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (XVI)**——Prepared from XV (962 mg, 3.5 mmol) and 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one (IXb) (2.17 g, 0.01 mol) as described for Xa, and recrystallization from $CHCl_3$–ether gave 981 mg (61.5%) of colorless prisms (XVI), mp 200—204°. *Anal.* Calcd. for $C_{29}H_{30}FN_3O$: C, 76.45; H, 6.64; N, 9.22. Found: C, 76.26; H, 6.71; N, 9.11. IR ν_{max}^{KBr} cm^{-1}: 3175, 3140 (NH), 1690 (C=O). NMR (δ in $CDCl_3$): 0.4—3.3 (15H, m, methylene protons, and methine proton of cyclopropane ring), 4.0—4.7 (1H, m, methine proton of piperidine), 6.8—7.5 (13H, m, protons of aromatic rings).

4-(4-Fluorophenyl)-3-butyn-1-ol (XVIII)——To a tetrahydrofuran (THF) solution of lithium 4-fluorophenylacetylide, which was prepared from β,β-dibromo-4-fluorostyrene (8.19 g, 0.03 mol) by the method of Corey,[10] 1.7 equivalent amounts of ethylene oxide in dry THF (23 ml) were added during 30 min. And the reaction mixture was stirred for 5 hr at room temperature. Addition of H_2O, extraction with ether, and distillation afforded crude product, which was purified by chromatography on silica gel (60 g). The fraction eluted with $CHCl_3$–MeOH (30: 1) was concentrated *in vacuo* to give 2.15 g (43.7%) of a colorless oil. NMR (δ in $CDCl_3$): 2.38 (1H, s, OH), 2.66 (2H, t, $J=7$ Hz, $-C\underline{H}_2-CH_2-OH$), 3.80 (2H, t, $J=7$ Hz, $-C\underline{H}_2-OH$), 6.8—7.5 (4H, m, FC_6H_4-).

***cis*-4-(4-Fluorophenyl)-3-buten-1-ol (XIX)**——Butyne derivative (XVIII) (980 mg, 6 mmol) in C_6H_6 (30 ml) was hydrogenated over Lindlar catalyst[11] (200 mg). After the absorption of theoretical amount of hydrogen, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel (30 g). The fraction eluted with $CHCl_3$–EtOH (24: 1) was evaporated *in vacuo* to afford 773 mg (78.1%) of a pale yellow oil (XIX). NMR (δ in $CDCl_3$): 2.07 (1H, s, OH), 2.60 (2H, m, $-C\underline{H}_2-CH_2OH$), 3.73 (2H, t, $J=7$ Hz, $-C\underline{H}_2OH$), 5.41—5.9 (1H, m, $=C\underline{H}-CH_2-$), 6.51 (1H, d, $J=11.5$ Hz, $-C\underline{H}=CHCH_2-$), 6.8—7.6 (4H, m, FC_6H_4). IR ν_{max}^{neat} cm^{-1}: 3350 (OH). Gas–liquid chromatography: column, 5% PEG succinate on Anakrom ABS: column length, 2 m; column temperature, 160°; carrier gas, N_2, 0.6 kg/cm^2; t_R, 3.6 min.

cis-4-Acetoxy-1-(4-fluorophenyl)-1-butene (XX)——A mixture of XIX (1.89 g, 11.4 mmol) and Ac_2O (1.74 g, 17 mmol) in pyridine (3 ml) was allowed to stand at room temperature for 24 hr. To the reaction mixture was added ice–water. The mixture was extracted with ether, washed successively with cold 17% HCl and H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (10 g), eluting with C_6H_6. Removal of the solvent gave 2.13 g (90%) of a pale yellow oil. NMR (δ in $CDCl_3$): 2.0 (3H, s, $-COCH_3$), 2.6 (2H, m, $-C\underline{H}_2-CH_2-O-Ac$), 4.14 (2H, t, $J=7$ Hz, $-CH_2C\underline{H}_2-OAc$), 5.6 (1H, m, $=C\underline{H}-CH_2-$), 6.5 (1H, d, $J=12$ Hz, $-C\underline{H}=CH-CH_2-$), 6.8—7.4 (4H, m, FC_6H_4). Gas–liquid chromatography: column, 10% XE 60 on Anakrom ABS; column length, 1 m; column temperature, 170°; carrier gas, N_2, 0.6 kg/cm^2, t_R, 3.1 min.

***cis*- and *trans*-2-(2-Acetoxyethyl)-1-(4-fluorophenyl)cyclopropane (XXI), (VII)**——Prepared from XX (2.3 g, 0.011 mol) as described for V. The crude product was purified by chromatography on silica gel (15 g), eluting with C_6H_6 and C_6H_6–$CHCl_3$ (1: 1). Removal of the solvent gave 1.59 g (64.9%) of a pale yellow oil, which was used for the next step without further purification. NMR (δ in $CDCl_3$): 2.02 (*ca.* 0.6×3H), s, $-OCOCH_3$ of *cis*-isomer), 2.05 (*ca.* 0.4×3H, s, $-OCOCH_3$ of *trans*-isomer), 4.02 (*ca.* 0.6×2H, t, $J=7$ Hz, $-C\underline{H}_2-OAc$ of *cis*-isomer), 4.18 (*ca.* 0.4×2H, t, $J=7$ Hz, $-C\underline{H}_2-OAc$ of *trans*-isomer), 6.8—7.3 (4H, m, FC_6H_4). Gas–liquid chromatography: column, 10% XE 60 on Anakrom ABS; column length, 1 m; column temperature, 170°; carrier gas, N_2; 0.6 kg/cm^2; t_R, 4.6 min (*cis*-isomer), 5.0 min (*trans*-isomer). *cis*/*trans* Ratio = 1.6: 1.

***cis*- and *trans*-2-[2-(4-Fluorophenyl)cyclopropyl]ethanol (XXII)**——Prepared from a mixture of XXI and VII (3:2) (482 mg, 2.17 mmol) as described for V. Yield 377 mg (96.4%), a pale yellow oil. NMR (δ in $CDCl_3$): 0.5—2.8 (6H, m, protons of cyclopropane ring and $-C\underline{H}_2-CH_2-OH$), 2.2 (1H, s, OH), 3.52 (*ca.* 0.6×2H, t, $J=7$ Hz, $-C\underline{H}_2-OH$ of *cis*-isomer), 3.68 (*ca.* 0.4×2H, t, $J=7$ Hz, $-C\underline{H}_2OH$ of *trans*-isomer), 6.7—7.3 (4H, m, $FC_6\underline{H}_4$).

***cis*- and *trans*-2-[2-(4-Fluorophenyl)cyclopropyl]ethyl *p*-Toluenesulfonate (XXIII)**——Prepared from XXII (377 mg, 2.1 mmol) as described for VIIIb. Yield 612 mg (87.6%), a pale yellow oil. NMR (δ in $CDCl_3$): 0.5—2.3 (6H, m, protons of cyclopropane ring and $-C\underline{H}_2-CH_2-OTs$), 2.44 (3H, s, CH_3), 3.90 (*ca.* 0.7×2H, t, $J=7$ Hz, $-C\underline{H}_2-OTs$ of *cis*-isomer), 4.12 (*ca.* 0.3×2H, t, $J=7$ Hz, $-C\underline{H}_2-OTs$ of *trans*-isomer), 6.7—7.4 (6H, m, FC_6H_4 and *meta* protons of *p*-toluenesulfonyl), 7.72 (2H, d, $J=9$H, *ortho* protons of *p*-toluenesulfonyl).

***cis*-1-[1-[2-[2-(4-Fluorophenyl)cyclopropyl] ethyl] - 4-piperidinyl] - 1, 3 - dihydro - 2*H* - benzimidazol - 2 - one (XXIV)**——Prepared from XXIII (563 mg, 1.7 mmol) as described for Xb. The crude product was fractionated with preparative TLC using $CHCl_3$–MeOH–H_2O (85:15:1) as developing solvent.

The less mobile fraction afforded a pale yellow solid (249 mg), which was recrystallized from ether to give 86 mg (13.5%) of colorless crystals (XXIV), mp 119—121°. *Anal.* Calcd. for $C_{23}H_{26}FN_3O$: C, 72.80; H, 6.91; N, 11.07. Found: C, 72.73; H, 7.09; N, 11.06. IR ν_{max}^{KBr} cm^{-1}: 3150 (NH), 1700 (C=O). NMR (δ in $CDCl_3$): 4.0—4.6 (1H, m, methine proton of piperidine), 6.8—7.4 (8H, m, protons of aromatic rings), 10.65 (1H, s, NH). UV λ_{max}^{EtOH} nm: 274 (sh.), 282.5, 289 (sh.).

1-(4-Fluorophenyl)-4-(*p*-toluenesulfonyloxy)-1-butyne (XXV)——Prepared from XVIII (450 mg, 2.74 mmol) as described for VIIIb. Yield 539 mg (61.8%), a pale yellow oil. NMR (δ in $CDCl_3$): 2.38 (3H, s, $-CH_3$), 2.72 (2H, t, $J=7$ Hz, $-C\equiv C-C\underline{H}_2-$), 4.16 (2H, t, $J=7$ Hz, $-CH_2-OTs$), 6.8—7.8 (8H, m, $FC_6\underline{H}_4-$ and $CH_3-C_6\underline{H}_4-SO_2-$).

1-[1-[4-(4-Fluorophenyl)-3-butyn-1-yl]-4-piperidinyl] - 1, 3-dihydro - 2*H* - benzimidazol-2-one (XXVI)——Prepared from XXV (79 mg, 0.25 mmol) as described for Xb. The crude product (73 mg, 81%) was recrystallized from ether to give 27 mg (29.7%) of colorless crystals, mp 179—182°. *Anal.* Calcd. for $C_{22}H_{22}FN_3O$: C, 72.70; H, 6.10; N, 11.56. Found: C, 72.81; H, 6.32; N, 11.52. IR ν_{max}^{KBr} cm^{-1}: 1695 (C=O). NMR (δ in $CDCl_3$): 1.5—3.3 (12H, m, methylene protons), 4.1—4.6 (1H, m, methine proton of piperidine), 6.8—7.6 (8H, m, protons of aromatic rings), 11.3 (1H, broad s, NH).

***cis*-1-(4-Fluorophenyl)-4-(*p*-toluenesulfonyloxy)-1-butene (XXVII)**——Prepared from XIX (332 mg, 2 mmol) as described for VIIIb. Yield 380 mg (60.9%), a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 1360, 1180, 1190 (SO_2). NMR (δ in $CDCl_3$): 2.44 (3H, s, $-C_6H_4-C\underline{H}_3$), 2.62 (2H, m, $-C\underline{H}_2-CH_2-OTs$), 4.10 (2H, t, $J=6.5$ Hz, $-CH_2-OTs$), 5.50 (1H, m, $=C\underline{H}-CH_2-$), 6.48 (1H, d, $J=12$ Hz, $FC_6H_4-C\underline{H}=$), 6.8—7.5 (6H, m, FC_6H_4- and *meta* protons of toluenesulfonyl), 7.78 (2H, d, $J=8$ Hz, *ortho* protons of toluenesulfonyl).

***cis*-1-[1-[4-(4-Fluorophenyl)-3-buten-1-yl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (XXVIII)**——Prepared from XXVII (298 mg, 0.93 mmol) as described for Xb. The crude product (201 mg, 59.1%) was recrystallized from ether–hexane to give 146 mg (43%) of colorless crystals (XXVIII), mp 138—142°. *Anal.* Calcd. for $C_{22}H_{24}FN_3O$: C, 72.30; H, 6.62; N, 11.50. Found: C, 72.39; H, 6.78; N, 11.41. IR ν_{max}^{KBr} cm^{-1}: 1695 (C=O). NMR (δ in $CDCl_3$): 1.6—3.3 (12H, m, methylene protons), 4.1—4.6 (1H, m, methine proton of piperidine), 5.4—6.0 (1H, m, $=C\underline{H}-CH_2-$), 6.46 (1H, d, $J=11.5$ Hz, $FC_6H_4-C\underline{H}=$), 6.8—7.5 (4H, m, FC_6H_4-).

Acknowledgement The authors are indebted to Dr. G. Ohta, director of this institute, for his support and encouragement, and Dr. A. Kasahara for his valuable advice. Thanks are also due to the members of the analytical section of this institute for the elemental analyses and the mass spectra.