form is smaller than that to the azo form (Fig. 1); *i.e.*, the number of the binding sites of the former is 0.7, although that of the latter is 3.2. Moreover, as was shown previously (18), the circular dichroism spectra of the azo form induced by bovine serum albumin was larger than that of the hydrazone form. Taking into consideration this result and the theory of Takenaka *et al.* (19) that the contact ion pair formation between unchiral benzoic acid derivatives and chiral amines introduces the larger circular dichroism, the azo form may be present as the contact ion pairs in the 2-(4′-hydroxyphenylazo)benzoic acid–bovine serum albumin interaction.

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Polymorphism of Butyrophenones Related to Haloperidol

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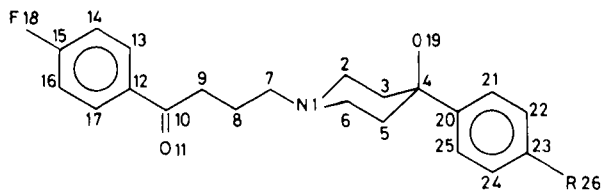
Abstract □ A comparison of X-ray powder diffraction patterns, IR spectra, and crystal structures of structurally related compounds belonging to the butyrophenone family has been undertaken to obtain information about the elements of chemical structure which predispose a substance to exhibit polymorphism. Five butyrophenones, differing by the nature of only one substituent, were selected. After crystallization from 15 solvents, it appears that two compounds of the group exhibit more than one crystalline form. An explanation of the absence of polymorphism in the other compounds of the group is proposed and discussed.

Keyphrases □ Polymorphism—disubstituted butyrophenones, comparison of IR spectra, X-ray diffraction patterns, and crystal structures □ Haloperidol—polymorphism, comparison of IR spectra, X-ray diffraction patterns, and crystal structures □ Moperone—polymorphism, comparison of IR spectra, X-ray diffraction patterns, and crystal structures □ Bromperidol—polymorphism, comparison of IR spectra, X-ray diffraction patterns, and crystal structures

Many papers have been published in the past 10 years about drug polymorphism, generally describing the way of obtaining the polymorphs of a given substance (1–3); their IR spectra (2, 4, 5), thermal behaviors (6–8), and X-ray diffraction patterns (3, 8, 9); their dissolution and solubility profiles (2, 8, 10, 11); and more rarely their *in vivo* rates of release (12–15). Studies of polymorphism are thus often empirical. Few studies attempted to determine what structural characteristics predispose an organic compound to exhibit polymorphism; in a paper concerning the polymorphism of sulfamides, Yang and Guillory (16) investigated that problem.

This work was undertaken to study the polymorphism of closely related compounds belonging to the butyrophenone family; to compare their IR spectra, X-ray diffraction patterns, and crystal structures; and to correlate, if possible, the frequency of polymorphism occurrence and chemical structure. The substances were chosen because of their therapeutic importance, structural simplicity, and crystalline nature (17–21).



HALOPERIDOL: R = Cl
BROMPERIDOL: R = Br
I: R = F
II: R = H
MOPERONE: R = CH_3

EXPERIMENTAL

Materials—Five butyrophenones were selected for study: haloperidol[1], bromperidol[2], 4-[4-hydroxy-4-(4-fluorophenyl)-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone[3] (I), moperone[4], and 4-(hydroxy-4-phenyl-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone[5] (II). The difference between these substances lies only in the nature of the substituent at the 26 position.

[1] Haloperidol: 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone.

[2] Bromperidol: 4-[4-(4-bromophenyl)-4-hydroxy-1-piperidinyl]-1-(-4-fluorophenyl)-1-butanone.

[3] I: 4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone (no generic name).

[4] Moperone: 4′-fluoro-4(4-hydroxy-4-*p*-tolylpiperidino)butyrophenone.

[5] II: 4-(4-hydroxy-4-phenyl-1-piperidinyl)-1-(4-fluorophenyl)-1-butanone (no generic name).

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Table I—X-ray Powder Diffraction Data of Moperone

Form I		Form II		Hydrated	
d, Å	I/I_1	d, Å	I/I_1	d, Å	I/I_1
8.75	22	8.98	24	9.78	14
5.33	90	6.67	11	6.78	13
5.08	14	5.30	66	5.79	39
4.80	34	5.04	14	5.34	53
4.70	46	4.75	25	5.14	48
4.51	14	4.63	22	4.98	41
4.32	21	4.38	22	4.88	78
4.20	20	4.32	20	4.74	40
4.05	27	4.00	100	4.66	45
3.98	100	3.49	18	4.55	21
3.66	12			4.34	26
3.60	10			4.12	100
3.46	16			4.04	18
3.12	11			3.66	14
3.08	10			3.60	35
				3.42	11
				3.37	11
				3.25	30

Thermal Analysis—Thermal behavior was studied on a differential scanning calorimeter[6] (DSC) at a heating rate of 4°C/min. Temperatures of fusion were measured at the onset point of each peak. A thermogravimetric analyzer[7] (TGA) was used for distinguishing between polymorphs and solvates and for determining the stoichiometry of the solvates.

Infrared Spectrometry[8]—IR spectra were recorded in potassium bromide[9] pellets (0.5 % w/w) and in *n*-hexane or carbon tetrachloride solution[10] (1 mg/mL).

X-ray Diffraction[11]—X-ray powder diffraction patterns were recorded using a powder camera. The incident beam was CuKα with λ = 1.5406 Å. The interplanar spacing (d values) were obtained by direct measurement on the films, and the corresponding intensities were estimated using a densitometer[12].

Crystallizations—Crystallizations of the five selected compounds were performed in analytical-grade[13] acetone, benzene, 1-butanol, carbon tetrachloride, chloroform, cyclohexane, dichloromethane, ether, dimethyl sulfoxide, ethanol, *n*-heptane, *n*-hexane, isopropyl alcohol, methanol, and petroleum ether either by slow evaporation at room temperature or by slow cooling of hot saturated solutions.

RESULTS AND DISCUSSION

Three polymorphic forms of moperone, including a monohydrated form, were observed and characterized. At ~70°C, the hydrated form undergoes dehydration, which generates polymorph III. This form melts at 96°C; it is very unstable and cannot be isolated. Forms I and II are stable. Form II undergoes a solid–solid transition to form I at 110°C; form I melts at 124°C. X-ray powder diffraction patterns (Table I) and IR spectra in potassium bromide pellets (Table II) exhibit significative differences between the three forms. In the spectrum of form II, only one —OH stretching vibration band appears at 3180 cm^{-1}. The IR spectrum of form I presents two —OH stretching vibration bands: a large one at 3100 cm^{-1} and a narrow and very strong one at 3560 cm^{-1}. Comparison with spectra obtained in carbon tetrachloride solution allows assignment of the 3560 cm^{-1} band to the vibration of weakly bonded —OH group; the 3180 and 31,000 cm^{-1} bands correspond to hydrogen-bonded hydroxyl groups (22).

Two polymorphs of II were obtained by recrystallization. They are easily identified by DSC (Fig. 1): form II melts at 112°C (ΔH_{fusion} = 35 kJ/mol) and form I melts at 140°C (ΔH_{fusion} = 43 kJ/mol). The data from X-ray diffraction patterns show great differences between the two forms (Table III). The IR spectra in potassium bromide pellets also have obvious differences, especially in the region of the —OH, —CH, and CO stretching vibrations (Table IV). The band of the —OH stretching appears as at 3180 cm^{-1} in the two spectra, but it is broader for form II. As the —OH stretching frequency of II in carbon tetrachloride solution is observed at 3620 cm^{-1}, it can be concluded that the two polymorphs are hydrogen bonded. The stability of form II is poor.

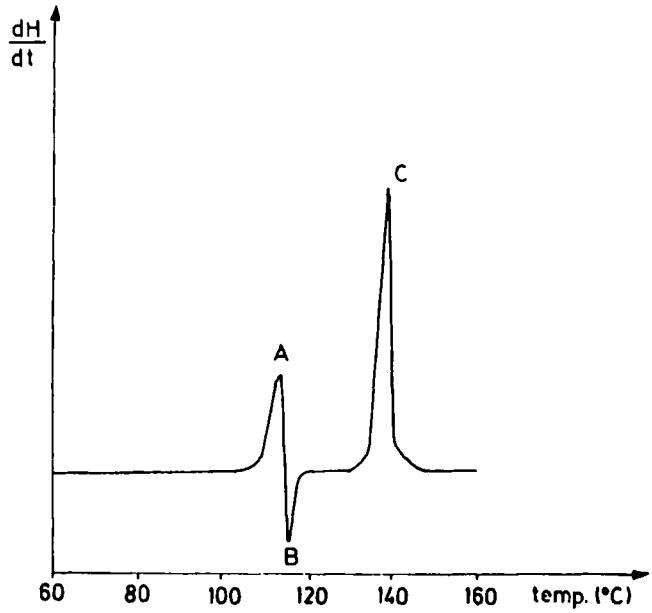

Figure 1—*Thermogram of a mixture of two polymorphs of II. Key: (A) melting of form II; (B) recrystallization of form I from the melt; (C) melting of form I.*

Despite repeated crystallizations from 15 solvents at room temperature and in a water bath, we find no evidence of polymorphism in haloperidol, bromperidol, and I. All crystallization batchs give the same X-ray powder diffraction patterns, the same DSC thermograms, and the same spectra (Table V). Temperatures and heats of fusion of haloperidol, bromperidol, and I are, respectively, 150°C and 48 kJ/mol, 158°C and 51 kJ/mol, 123°C and 34 kJ/mol. Thus, it appears that the three dihalosubstituted compounds do not exhibit polymorphism, whereas moperone and II occur as two or more polymorphs or pseudopolymorphs.

To obtain a better understanding of the phenomenon of polymorphism and to confirm the influence of the substituent on the occurrence of polymorphism in this family, the crystal structure of each polymorph must be investigated. Instability of moperone form II and II form II produces poor quality monocrystals and did not allow determination of their crystal structures. Nevertheless, considering the crystal structure of polymorph I and using the data of the IR spectra of form II of both compounds, the solid structures of moperone form II and II form II can be approached.

The main differences between the crystal structures of haloperidol, bromperidol, I, and moperone forms I and II lie in the nature and strength of the intermolecular hydrogen bonds and in intermolecular van der Waals contacts. Crystal structures show that haloperidol, bromperidol, and I are isomorphs (2-4). Their molecules are bonded together by a strong intermolecular O(19)—N(1) hydrogen bond. The length of that bond is, respectively, 2.84, 2.86, and 2.84 Å (Table VI). The energy of the hydroxyl group stretching vibrations in the IR spectra is in good agreement with these data. The intermolecular van der Waals contacts are the same in the three substances. Dipole–dipole F(18)—C(15) interactions and R(26)—R(26) contacts hold the molecules end to end (Table VII).

Molecules of II form I are also held together by a O(19)—N(1) bond, but in this case the bond is longer (2.94 Å) (Table VI). The position of the —OH stretching vibration band at 3180 cm^{-1} indicates a bond weaker than in the first group of substances. An F(18)—C(19) van der Waals contact stabilizes the crystal lattice (Table VII).

The crystal structure of II form II was not resolved. Meanwhile, considering the crystallographic data of form I, the enlargement of the νOH band and the lowering (15 cm^{-1}) of the νCO band in form II (Table IV) can be attributed to the existence of a O(19)—O(11) bond. Hydrogen bonding is thus different between the two forms.

Moperone form I presents a very peculiar crystal structure: its asymmetric unit is made up by two independent molecules, A and B (Table VI). Molecules of type A are held together by a short O(10)—N(1) hydrogen bond. The two absorption bands at 3100 and 3560 cm^{-1} can now be explained (Table II): the first arises from the strong O(19)—N(1) hydrogen bond, and the second can be attributed to the stretching of a hydroxyl group included in a cyclic dimeric structure. The narrowness of the band at 3560 cm^{-1} supports this interpretation. The van der Waals contacts between molecules A and B con-

[6] DSC model 1B; Perkin-Elmer.
[7] TGA model 951; Du Pont.
[8] Model 580 IR spectrophotometer; Perkin-Elmer.
[9] IR quality potassium bromide; Merck, Darmstadt, West Germany.
[10] Spectroscopic quality solvents; Merck, Darmstadt, West Germany.
[11] Philips PW 1720 diffraction equipment with a model XDC 700 Guinier-Hägg camera.
[12] Home-made densitometer.
[13] Merck, Darmstadt, West Germany.

Table II—IR Spectra of Moperone: Observed Frequencies (cm^{-1}) and Their Assignments

Form I	Form II	Hydrated	Assignments
3560 (strong, narrow)			ν OH
			ν OH (water)
3350	3350	3350	2ν CO
		3230	ν OH (moperone)
	3180		ν OH
3100			ν OH
3080, 3060, 3030	3080, 3060, 3030	3080, 3060, 3030	ν CH (aromatic)
2960, 2930, 2980	2960, 2930, 2980	2970, 2950, 2930, 2900	ν CH (nonnitrogen-bonded methylenic CH)
2820(sh), 2790	2840, 2790	2830, 2790	ν CH (Bohlman's bands)[a]
1685	1685	1685	ν CO
1600, 1510, 1472	1600, 1510, 1475	1600, 1510, 1475	aromatic ring
1370, 1345, 1315, 1300, 1275	1370, 1345, 1320, 1300, 1275	1370, 1350, 1320, 1300	δ CH (methylenic CH bending)
1235 (sh)	1235	1235 (sh)	ν CF
1155 (sh)	1155	1160	δ CH (in-plane aromatic CH bending)
840	835	835	γ CH (out-of-plane fluorophenyl CH bending)
820	845	825	γ CH (out-of-plane benzyl CH bending)

[a] See Ref. 23.

tribute to the building of the crystal lattice. The main intermolecular contacts are F(18)—C(2) and F(18A—C26)B. Knowing the crystal structure of moperone form I and the IR spectra of moperone form II, it is possible to infer the existence of only one type of hydrogen bond, O(19)—N(1), in moperone form II (Tables II and VI).

Table III—X-ray Powder Diffraction Data of II

Form I		Form II	
d, Å	I/I_1	d, Å	I/I_1
7.70	22	6.26	11
7.45	18	5.06	16
7.17	35	4.82	19
6.78	23	4.76	22
5.85	16	4.66	49
5.74	18	4.49	59
5.45	100	4.31	100
4.74	23	4.25	65
4.63	44	4.17	38
4.56	42	4.04	54
4.25	40	3.34	14
4.14	63	2.96	19
4.01	11	2.18	21
3.94	11		
3.88	48		
3.85	45		
3.79	11		
3.59	10		
3.42	55		
3.14	32		
2.92	18		

Table IV—IR Spectra of II: Observed Frequencies (cm^{-1}) and Their Assignments

Form I	Form II	Assignments
3350	3330	2ν CO
3180	3180 (larger)	ν OH
3080, 3050, 3020	3080, 3060, 3030	ν CH (aromatic CH)
2980, 2960, 2950, 2930, 2920, 2900	2960, 2950, 2920	ν CH (nonnitrogen-bonded methylenic CH)
2920, 2800, 2770	2890, 2870, 2850	ν CH (Bohlman's bands)[a]
1685	1670	ν CO
1600, 1505, 1490, 1470, 1460, 1445, 1410	1600, 1505, 1445, 1410	aromatic ring
1365, 1340, 1310	1375, 1340	δ CH (methylenic CH bending)
1230 (sh)	1230	ν CF
1155	1155	δ CH (in-plane aromatic CH bending)
830	830	γ CH (out-of-plane fluorophenyl CH bending)
765	760, 705	γ CH (out-of-plane phenyl CH bending)

[a] See Ref. 23.

Comparison of the crystallographic data of haloperidol, bromperidol, I, moperone form I, and II form I shows differences of molecular conformation in the crystal lattices (17–21). The side chain of the three dihalosubstituted compounds is in a TTGT conformation, while it is in a TTTT conformation in moperone form I and II form I. The latter is the most frequent among the five isoenergetic confirmations showed by PCILO calculations (25). The piperidine ring is in the usual chair form encountered in the butyrophenones, the hydroxyl group is axial, and the phenyl ring equatorial. The torsion angle along the C(4)—C(20) bond takes a relatively constant value, except in molecule B of moperone form I (17–21).

The three dihalosubstituted substances (haloperidol, bromperidol, and I) are thus isomorphs. Their crystals are monoclinic, with a $P2_1/C$ spatial grouping and four molecules per unit cell. The molecules are packed into parallel layers, which are built up by the intermolecular van der Waals contacts between the R-26 substituents of two molecules put end to end and by dipole–dipole F(18)—C(15) contacts. The layers are linked together by the strong O(19)—N(1) hydrogen bond, and they generate areas of high halogen concentration. From these observations, it is apparent that electrostatic forces, caused by the presence of the halogens and acting at the extremities of each molecule, play a significant role in the building of the crystal structure. In the process of crystal growth, a molecule reaching the surface of a crystal is influenced predominantly by the halogens of the molecule extremities located on the faces of the growing crystal. Bernstein *et al.* (26–28), working on dihalosubstituted substances, have made the same observations. The van der Waals contacts and the hydrogen bonds give a great stability to the crystal building. The observed crystal packing therefore depicts the highest probabilities of occurrence, which elucidate the absence of polymorphism of haloperidol, bromperidol, and I.

Moperone and II exhibit polymorphism. Moreover, they present a very different crystalline structure from the other three substances. In II form II and molecule B of moperone form I, peculiar hydrogen bonds appear: O(19)—O(11) and O(19)—C(22). The absence of halogen in the R-26 position leads to more disordered crystal structures, and the linear packing of haloperidol, bromperidol, and I disappears. During the crystallization, the

Table V—IR Spectra of Haloperidol, Bromperidol, and I: Observed Frequencies (cm^{-1}) and Their Assignments

Haloperidol	Bromperidol	I	Assignments
3350	3350	3350	2ν CO
3130	3130	3120	ν OH
2960, 2930	2970, 2960	2960, 2950	ν CH (nonnitrogen-bonded methylenic CH)
2850, 2830	2850, 2830	2840, 2820	ν CH (Bohlman's bands)[a]
1685	1685	1685	ν CO
1600, 1510, 1470, 1410	1600, 1510, 1480, 1410	1600, 1510, 1480, 1410	aromatic ring
1375, 1365, 1300	1365, 1365, 1300	1365, 1300	δ CH (methylenic CH bending)
1225	1225	1240	ν CF
1160	1160	1160	δ CH (in-plane aromatic CH bending)
	1070		ν CBr
1090			ν CCl
830	830	830 (sh)	γ CH (out-of-plane aromatic bending)

[a] See Ref. 23.

Table VI—Nature and Strength of the Hydrogen Bonds [a]

	Bromperidol	Haloperidol	I	II		Moperone		
				Form I	Form II[b]	Form I		Form II[b]
						Molecule A	Molecule B	
Type	O(19)—N(1)	O(19)—N(1)	O(19)—N(1)	O(19)—N(1)	O(10)—O(11)	O(19)—N(1)	O(19)—C(22)	O(10)—N(1)
Length, Å[c]	2.86	2.84	2.84	2.94	—	2.85	3.37	—
νO-H, cm^{-1}	3130	3130	3120	3180	3180	3100	3560	3180
δH[d], kcal/mol	7.40	7.40	7.55	6.64	8.56	7.85	0.91	6.64

[a] SD on bond lengths: 0.01 Å. [b] Crystal structure not resolved. [c] From Refs. 17-21. [d] Values calculated from Ref. 24.

Table VII—van der Waals Contacts Observed in the Crystal Structures [a]

	Bromperidol	Haloperidol	I	II, Form I	Moperone, Form I
Type	F(18)—C(15)	F(18)—C(15)	F(18)—C(15)	—	—
Length, Å	3.11	3.07	3.10		
Sum of van der Waals radii, Å	3.20	3.20	3.20		
Type	Br(26)—Br(26)	Cl(26)—Cl(26)	F(26)—F(26)[b]	—	—
Length, Å	3.60	3.52	4.24		
Sum of van der Waals radii, Å	3.90	3.60	2.70		
Type	—	—	—	F(18)—C(19)	F(18)A—C(2)B
Length, Å				3.28	3.38
Sum of van der Waals radii, Å				3.35	3.35
Type	—	—	—	—	F(18)A—C(26)B
Length, Å					3.17
Sum of van der Waals radii, Å					3.35

[a] From Refs. 17-21. SD on bond lengths: 0.01 Å. [b] Reported in this table for information and comparison, although the distance between fluorine atoms is longer than the sum of their van der Waals radii.

molecules have a greater freedom and several crystal structures are possible; this explains why moperone and II exhibit more than one crystalline form. In this limited group of butyrophenones, it can be concluded that the substituent at the 26 position predominantly influences the occurrence or absence of polymorphism.

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