Figure 7—*Insulin adsorbed onto the segmental poly(urethane ether) copolymer under high shear with 2.0 mg/ml urea, 2100 ×.*

for urea concentrations ranging from 1.0 to 3.0 mg/ml. At higher urea concentration, aggregation times were ~4 days.

Scanning microscopy revealed that insulin adsorption onto various polymer surfaces was substantially greater under high shear as compared with static conditions. The morphology of the adsorbed insulin was found also to be dependent on shear conditions. Scanning electron micrographs of insulin adsorbed under high shear onto poly(dimethylsiloxane), poly(urethane ether), and cellulose are presented in Figs. 4–6, respectively. Under high shear, insulin adsorbs onto all of the polymers evaluated as disk-like structures. Without high shear rates, such disk-like insulin adsorbates were not observed over the time frame evaluated. Under high shear, the morphology of the adsorbed insulin appears independent of the polymer nature, disk-like adsorbates were observed on all types of polymer surfaces. However, under static conditions the morphology may be dependent upon the polymer substrate.

Concentrations of urea that prolonged insulin macromolecular aggregation times were found also to inhibit insulin adsorption onto polymer surfaces. Disk-like insulin adsorbates were not observed on the various polymer surfaces with the addition of 2.0 mg/ml urea under high shear, as shown for poly(urethane ether) in Fig. 7 as a representative case.

The self-association of insulin molecules in solution and the adsorption of insulin onto container surfaces pose complications in the administration of insulin. These problems are of particular importance with long-term insulin infusion devices where insulin crystals on the various surfaces of such devices have been observed by several investigators (9, 10). With such systems, insulin can be subjected to shear rates that can greatly effect and potentiate this process.

The addition of urea in a limited concentration range (*i.e.*, 1–3 mg/ml of urea) inhibits both insulin self-association and surface adsorption. It has been suggested that the initial step in insulin self-association is the hydrophobic association of the B23–28 regions on insulin monomers to form insulin dimers which further associate into larger oligomers. Urea, a water structure-breaking solute, was found to greatly inhibit insulin self-association and surface adsorption presumably by decreasing interactions between dimers to prevent further self-association. Higher urea concentrations were found to denature insulin, leading to rapid macromolecular aggregation times. The concentration range of urea that inhibits these processes poses little to no toxicity risks and can stabilize insulin preparations for extended periods, both for conventional administration preparations and for the development of long-term insulin delivery systems.

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Conformational Study of Two Polymorphs of Spiperone: Possible Consequences on the Interpretation of Pharmacological Activity

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Received December 18, 1981, from the **Laboratoire d'Analyse des Médicaments, Institut de Pharmacie UCL 7340, 1200, Bruxelles, Belgium*, and the ‡*Laboratoire de Chimie physique et de Cristallographie, Université de Louvain, Place Louis Pasteur, 1348, Louvain-la-Neuve, Belgium.* Accepted for publication April 15, 1982.

Abstract □ A second polymorph of spiperone, 8-[3-(*p*-fluorobenzoyl)-propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, has been isolated and characterized by thermal analysis and IR spectrometry. Its structure was solved by X-ray diffraction analysis. The results are compared with those previously obtained on spiperone, the main difference being in the conformation of the side chain and in the nature of the hydrogen bonding.

Keyphrases □ Spiperone—polymorphs, conformational study, possible consequences on interpretation of pharmacological activity □ Pharmacological activity—conformational study of two polymorphs of spiperone, possible consequences of interpretation □ Polymorphs—spiperone, conformational study, possible consequences on interpretation of pharmacological activity

Complete data about the crystal structure and solid-state molecular conformation of different polymorphs of the same drug are rarely available. The main reason lies in the difficulty in obtaining single crystals of good quality from the different polymorphs. Studies of drug polymorphism are generally restricted to determination of IR

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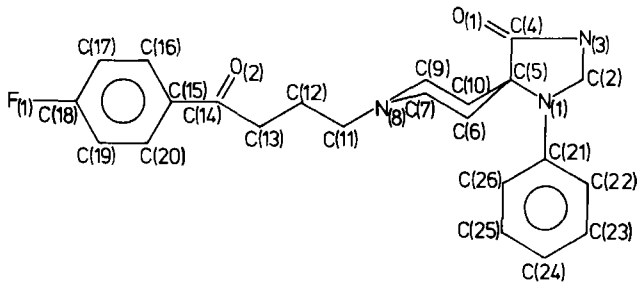

Figure 1—*Chemical structure and atom numbering of spiperone.*

Table I—Crystal Data of Spiperone I and II

	Form I	Form II[a]
Molecular formula	$C_{23}H_{26}FN_3O_2$	$C_{23}H_{26}FN_3O_2$
Molecular weight	395.46	395.46
Space group	$P2_1/a$	$P2_1/c$
System	Monoclinic	Monoclinic
Unit cell dimensions, Å or degrees		
a	12.722	18.571
b	7.510	6.072
c	21.910	20.681
β	95.08	118.69
Unit cell volume, Å^3	2085.1	2045.7
Number of formula Unit per cell = Z	4	4

[a] Data from ref. 5.

spectra and thermal properties, determination of dissolution characteristics, and recording of X-ray powder diffraction spectra (1–3).

Many crystal and molecular structures of neuroleptics belonging to the family of butyrophenones have been published, without reference to possible polymorphism (4–13). Among those was the crystal structure of spiperone[1] (Fig. 1), one of the most potent neuroleptic drugs (5). The structure of spiperone is mainly characterized by its unique conformation of the side chain and is often used as reference in studies of the structure–activity relationship for testing the conformational resemblance of neuroleptics to dopamine (14, 15).

This paper characterizes the crystal structure of a second polymorph of spiperone, compares this polymorph with the known structure, and discusses the possible consequences on the interpretation of the pharmacological activity.

EXPERIMENTAL

IR Spectrometry[2]—IR spectra were recorded in potassium bromide pellets (0.5%, w/w).

X-Ray Diffraction[3]—The intensities of 2551 reflections were measured on a four-circle diffractometer by the ω-scan technique up to $2\theta = 44°$. Incident radiation was graphite-monochromatized Mo$K\alpha$: $\lambda = 0.7107$ Å. Only 921 reflections with $I > 2.5\sigma(I)$ were considered as observed and retained for the resolution and refinement of the structure. The structure was solved by direct methods using the MULTAN 80 computer system[4]. The refinement was carried out by the SHELX 76[5] program with anisotropic thermal parameters. The positions of the hydrogen atoms were calculated by SHELX. The final conventional R index was 0.079. For crystal data see Table I.

[1] Janssen Pharmaceutica, Beerse, Belgium, U.S. Patent no. 3,155,669 (1964 J. Ph.).

[2] Perkin-Elmer model 580 IR spectrophotometer.

[3] Enraf Nonius CAD-4 four-circle diffractometer.

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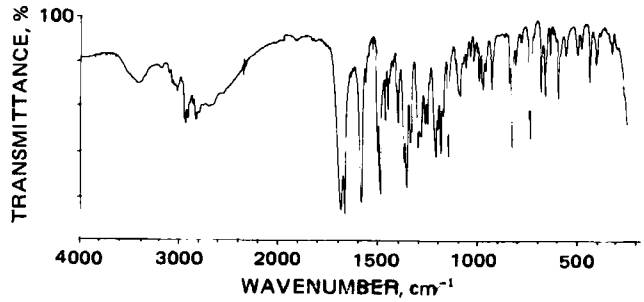

Figure 2—*IR spectrum of polymorph I.*

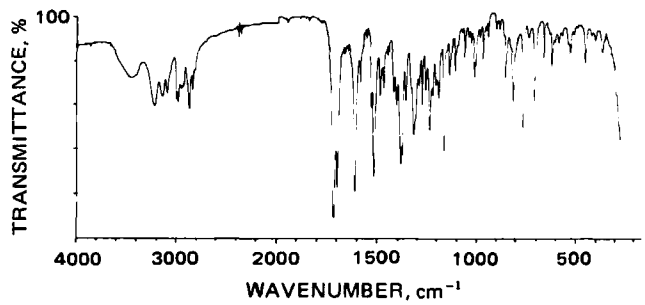

Figure 3—*IR spectrum of polymorph II.*

Table II—Atomic Coordinates ($\times 10^4$) and B_{eq} Values (Å^2)

	X/A	Y/B	Z/C	B_{eq}
N(1)	8679 (8)	515 (15)	6455 (5)	4.26
C(2)	9766 (8)	−79 (18)	6412 (7)	4.38
N(3)	10380 (8)	1076 (15)	6820 (6)	4.98
C(4)	9800 (11)	2318 (21)	7086 (7)	4.10
O(1)	10176 (7)	3445 (14)	7424 (5)	6.16
C(5)	8643 (9)	2087 (15)	6871 (6)	3.11
C(6)	8258 (9)	3742 (16)	6496 (6)	4.16
C(7)	8090 (11)	5339 (17)	6920 (6)	4.36
N(8)	7382 (7)	4909 (14)	7365 (5)	4.08
C(9)	7830 (9)	3462 (17)	7769 (6)	3.88
C(10)	8001 (10)	1773 (16)	7397 (6)	4.02
C(11)	7172 (11)	6560 (19)	7725 (7)	5.75
C(12)	6326 (14)	6434 (22)	8133 (8)	7.22
C(13)	6078 (13)	8242 (19)	8416 (8)	6.68
C(14)	5101 (14)	8185 (28)	8722 (9)	7.13
O(2)	4559 (13)	6812 (18)	8718 (8)	11.62
C(15)	4732 (14)	9765 (25)	9016 (7)	5.50
C(16)	3831 (14)	9648 (29)	9370 (8)	7.22
C(17)	3469 (18)	11124 (36)	9628 (9)	7.17
C(18)	3970 (18)	12651 (37)	9586 (9)	8.22
F(1)	3546 (11)	14138 (18)	9826 (7)	14.73
C(19)	4817 (14)	12836 (22)	9232 (9)	8.14
C(20)	5229 (12)	11402 (21)	8973 (6)	5.14
C(21)	7875 (10)	−278 (18)	6066 (6)	3.94
C(22)	8103 (11)	−1620 (18)	5677 (6)	3.87
C(23)	7321 (14)	−2400 (19)	5321 (6)	5.59
C(24)	6266 (13)	−1925 (22)	5343 (7)	5.76
C(25)	6012 (11)	−655 (22)	5731 (7)	5.67
C(26)	6788 (10)	172 (18)	6091 (6)	4.58

Thermal Analysis[6]—Thermal behavior was studied on a differential scanning calorimeter at a heating rate of 5°/min. Temperatures of fusion were measured at the onset point of each peak.

Preparation of Crystals[7]—Good quality crystals were obtained by slow evaporation at 60° of n-heptane (form I) and by slow evaporation at 60° of 2-propanol (form II).

RESULTS AND DISCUSSION

Two polymorphs of the title compound were isolated and characterized by differential scanning calorimetry. Form I[8] melted at 209.8° (heat of fusion: 52.3 kJ/mole), whereas form II melted at 207.0° (heat of fusion 51.8 kJ/mole). These two forms showed an equivalent stability at room

[6] Perkin-Elmer DSC-model 2.

[7] Spiperone, Janssen Pharmaceutica, Beerse, Belgium.

[8] Polymorphs are numbered I and II in decreasing order of their melting points.

Table III—Interatomic Distances, Å

C(2) —N(1)	1.464 (13)
C(5) —N(1)	1.494 (14)
C(21)—N(1)	1.404 (14)
N(3) —C(2)	1.426 (14)
C(4) —N(3)	1.353 (15)
O(1) —C(4)	1.197 (14)
C(5) —C(4)	1.515 (16)
C(6) —C(5)	1.545 (14)
C(10)—C(5)	1.490 (14)
C(7) —C(6)	1.543 (15)
N(8) —C(7)	1.421 (13)
C(9) —N(8)	1.484 (13)
C(11)—N(8)	1.505 (15)
C(10)—C(9)	1.533 (15)
C(12)—C(11)	1.462 (18)
C(13)—C(12)	1.536 (18)
C(14)—C(13)	1.465 (21)
O(2) —C(14)	1.240 (17)
C(15)—C(14)	1.448 (20)
C(16)—C(15)	1.441 (20)
C(20)—C(15)	1.389 (18)
C(17)—C(16)	1.345 (22)
C(18)—C(17)	1.319 (24)
F(1) —C(18)	1.366 (21)
C(19)—C(18)	1.390 (23)
C(20)—C(19)	1.344 (17)
C(22)—C(21)	1.367 (15)
C(26)—C(21)	1.430 (16)
C(23)—C(22)	1.343 (16)
C(24)—C(23)	1.394 (18)
C(25)—C(24)	1.337 (18)
C(26)—C(25)	1.357 (16)

Table IV—Bond Angles, Degrees

C(5) —N(1) —C(2)	111.0 (1.0)	C(14)—C(13)—C(12)	111.8 (1.5)
C(21)—N(1) —C(2)	118.3 (1.1)	O(2) —C(14)—C(13)	121.0 (1.9)
C(21)—N(1) —C(5)	130.2 (1.1)	C(15)—C(14)—C(13)	120.1 (1.8)
N(3) —C(2) —N(1)	104.1 (1.0)	C(15)—C(14)—O(2)	118.9 (1.8)
C(4) —N(3) —C(2)	113.6 (1.1)	C(16)—C(15)—C(14)	119.6 (2.0)
O(1) —C(4) —N(3)	123.5 (1.3)	C(20)—C(15)—C(14)	121.8 (1.8)
C(5) —C(4) —N(3)	109.8 (1.2)	C(20)—C(15)—C(16)	118.6 (1.6)
C(5) —C(4) —O(1)	126.7 (1.4)	C(17)—C(16)—C(15)	119.7 (1.9)
C(4) —C(5) —N(1)	101.5 (1.0)	C(18)—C(17)—C(16)	120.0 (2.3)
C(6) —C(5) —N(1)	109.7 (1.0)	F(1) —C(18)—C(17)	118.3 (2.0)
C(6) —C(5) —C(4)	109.1 (1.0)	C(19)—C(18)—C(17)	122.0 (2.1)
C(10)—C(5) —N(1)	113.3 (0.9)	C(19)—C(18)—F(1)	119.0 (2.4)
C(10)—C(5) —C(4)	111.2 (1.0)	C(20)—C(19)—C(18)	120.4 (1.8)
C(10)—C(5) —C(6)	111.6 (1.1)	C(19)—C(20)—C(15)	118.9 (1.5)
C(7) —C(6) —C(5)	111.1 (1.1)	C(22)—C(21)—N(1)	120.5 (1.3)
N(8) —C(7) —C(6)	111.5 (1.0)	C(26)—C(21)—N(1)	122.1 (1.3)
C(9) —N(8) —C(7)	110.0 (1.0)	C(26)—C(21)—C(22)	117.2 (1.2)
C(11)—N(8) —C(7)	108.9 (1.0)	C(23)—C(22)—C(21)	119.8 (1.3)
C(11)—N(8) —C(9)	111.5 (1.0)	C(24)—C(23)—C(22)	122.3 (1.5)
C(10)—C(9) —N(8)	110.7 (1.0)	C(25)—C(24)—C(23)	119.5 (1.5)
C(9) —C(10)—C(5)	113.2 (1.0)	C(26)—C(25)—C(24)	119.5 (1.5)
C(12)—C(11)—N(8)	116.2 (1.2)	C(25)—C(26)—C(21)	121.7 (1.4)
C(13)—C(12)—C(11)	112.2 (1.4)		

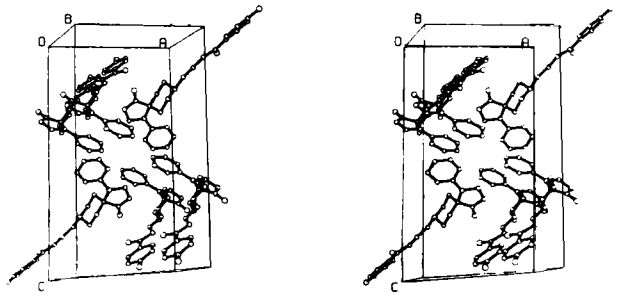

Figure 4—*Stereoscopic view of crystal packing of spiperone I*[10].

temperature, in the presence of water, and under high pressure required for preparation of potassium bromide pellets.

The IR spectrum in the solid state of form I corresponded to that obtained from the commercial product[9] (Figs. 2 and 3) and was different from that of form II.

[9] Janssen Pharmaceutica specification report number 598 (760317).

Table V—Selected Torsion Angles, Degrees

C(9)	—N(8)	—C(11)	—C(12)	−68
C(7)	—N(8)	—C(11)	—C(12)	170
N(8)	—C(11)	—C(12)	—C(13)	−173
C(11)	—C(12)	—C(13)	—C(14)	169
C(12)	—C(13)	—C(14)	—C(15)	180
C(12)	—C(13)	—C(14)	—O(2)	−2
C(4)	—C(5)	—C(6)	—C(7)	−76
C(10)	—C(5)	—C(6)	—C(7)	47
C(6)	—C(5)	—C(10)	—C(9)	−47
C(5)	—C(6)	—C(7)	—N(8)	−56
C(6)	—C(7)	—N(8)	—C(9)	63
C(6)	—C(7)	—N(8)	—C(11)	−175
C(7)	—N(8)	—C(9)	—C(10)	−61
N(8)	—C(9)	—C(10)	—C(5)	54
C(2)	—N(1)	—C(21)	—C(22)	3
C(2)	—N(1)	—C(21)	—C(26)	178
C(5)	—N(1)	—C(21)	—C(22)	174
C(5)	—N(1)	—C(21)	—C(26)	−11

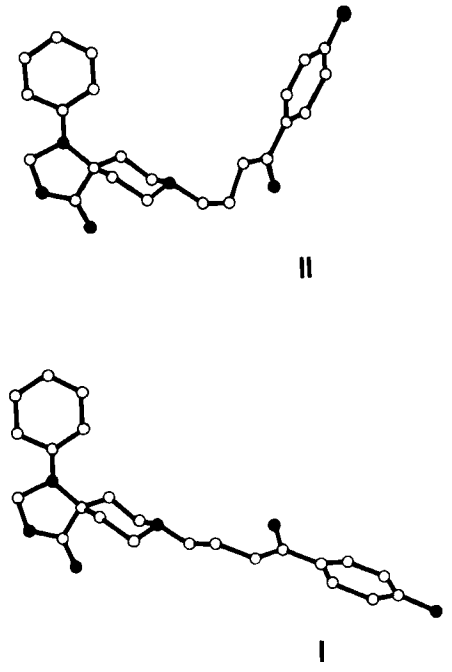

Figure 5—*Molecular conformation of spiperone I and II.*

Unit cell parameters of form II corresponded to those published earlier (5), while the crystal lattice of form I was different (Table I). Complete crystal structure of form I was thus determined and compared with that of form II (Tables II–V, Fig. 4).

The main difference between the molecular conformation of the polymorphs was found to be in the conformation of the side chain. Form I was shown to have the same side-chain conformation as aceperone[11], azaperone[12] I, benperidol[13] I, moperone[14] I, III (R1838)[15,19]-I, pipamperone[16], IV (R1616 hydrochloride)[17,19], haloperidol hydrobromide[18],

[10] S. Motherwell and W. Clegg, PLUTO, University of Cambridge, England, 1978.

[11] Aceperone—4 - [4-(acetamidomethyl) -4- phenylpiperidino]-4′-fluorobutyrophenone. Belgian Patent no. 606,849 (1961), Janssen Pharmaceutica.

[12] Azaperone—1-(4-fluorophenyl)-4-[4-(2-pyridinyl)-1-piperazinyl]-1-butanone. U.S. Patent no. 2,979,508 (1961), Janssen Pharmaceutica.

[13] Benperidol—1-{1-[3 - (*p*-fluorobenzoyl)propyl] -4- piperidol}-2-benzimidazolinone. Belgian Patent no. 626,307 (1963), Janssen Pharmaceutica.

[14] Moperone—4′ - fluoro -4- (4 - hydroxy-4-*p*-tolylpiperidino)butyrophenone, British Patent no. 881,893 (1961), Janssen Pharmaceutica.

[15] R 1838—4-(4 - hydroxy -4- phenyl -1- piperidinyl)-1-(4-fluorophenyl)-1-butanone.

[16] Pipamperone—1′-[4-(4 - fluorophenyl) -4- oxobutyl]-[1,4′ - bipiperidine]-4′-carboxamide. Belgian Patent no. 610,830 (1962), Janssen Pharmaceutica.

[17] R 1616 hydrochloride—4 - [4 - (4-fluorophenyl) -4- hydroxy-1-piperidinyl] -1- (4-fluorophenyl)-1-butanone hydrochloride.

[18] Haloperidol hydrobromide—4-[4 - (4 - chlorophenyl)-4-hydroxy -1- piperidinyl] -1- (4-fluorophenyl)-1-butanone hydrobromide.

[19] Names to be published.

Table VI—Intermolecular Bond Characteristics [a] of Spiperone I and II

	Hydrogen Bonding			Other Short Intermolecular Contacts		
	Contact	Position	Distance, Å	Contact	Position	Distance, Å
Spiperone I	N(8)—N(3)	−2(0,1,0)	2.81	C(20)-O(1)	−2(0,2,0)	3.39
	N(3)—N(8)	−2(1,1,0)	2.81	F—C(17)	2(0,0,2)	3.28
Spiperone II [b]	O(1)—N(3)	−1(1,1,0)	2.87	C(23)—C(2)	2(1,1,0)	3.36
	N(3)—O(1)	−1(1,1,0)	2.87	O(2)—C(13)	2(0,0,1)	3.30
				O(1)—C(23)	−2(0,1,0)	3.33
				F—C(26)	−1(0,1,0)	3.26

[a] Hydrogens are not positioned. [b] Calculated from ref. 5 data.

moperone hydrobromide (4, 6, 7, 9, 11, 12, 14, 15) (Fig. 5). The side-chain conformation of form II was found to be different from the compounds described above.

This modification of the conformation between the two polymorphs of spiperone is not surprising since PCILO (16) calculations have showed the possible existence of five isoenergetic minima for the propyl chain of butyrophenones (5, 14–17). The piperidine ring of form I is in the usual chair form encountered in most butyrophenones.

The angle between the mean plane of the piperidine and phenyl rings, and the corresponding torsion angles, are nearly identical in the two polymorphs (Table V). This fact may be explained by the coplanarity of the phenyl and five-membered rings that are attached by a $C(sp_2)$-$N(sp_3)$ single bond with lengths of 1.404 Å (I) and 1.394 Å (II), respectively (18). As a result the rotation of the phenyl ring is not allowed. The PCILO potential energy curve of the phenyl ring-containing moiety of spiperone leads to an identical interpretation (15, 17). Experimental values of torsion angles of spiperone I fall in the same minimum of the PCILO curve as those of spiperone II, thus confirming the existence of a potential barrier.

The two polymorphs differ entirely from one another in the nature and the force of hydrogen bonding. Indeed, in form II, each molecule is bonded to another by two hydrogen bonds, [N(3) to O(1)], and the crystal is made up of dimers which are held together by packing forces only (5). On the other hand, in form I only one type of hydrogen bond, [N(3) to N(8)] contributes to the building of a polymeric lattice (Table VI). Differences between intermolecular bonding of the two forms are visible in IR spectra. In form I, the stretching of the NH—N polymeric bond appears in the 3000–3100 cm^{-1} region as a broad peak, whereas the narrow bands observed at 3190 and 3110 cm^{-1} in form II indicate that the NH vibrator included has a more localized bond, such as a dimeric structure. Nevertheless, the shift of the C=O(1) vibration frequency (1705 cm^{-1}) is not visible because the N(3)H to O(1)C hydrogen bond taken individually is not very strong; intensity of the corresponding absorption band is only increased.

The two polymorphs of spiperone exhibit different crystal structures. Their molecular conformation and intermolecular bonds in solid state differ entirely.

The study of molecular conformation of the two polymorphs confirms the flexibility of the side chain of butyrophenone derivatives claimed previously by PCILO calculations (15, 17). Moreover, existence of two conformations of the side chain for the same compound proves definitively that this conformation is not influenced by the nature of the phenyl ring-containing moiety and by the substituents on that ring.

Several authors have attempted to explain the high level of activity of spiperone by relatively high local concentrations in brain regions, caused by dimerization *in vivo*, considering that spiperone preferentially forms dimers (14). The structure of form I proves that a stable nondimerized form of spiperone can exist with a high probability of occurrence.

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