Reaction of Haloperidol with 5-(Hydroxymethyl)-2-furfuraldehyde, an Impurity in Anhydrous Lactose

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Abstract □ In the investigation of haloperidol direct compression tablets, using anhydrous lactose as one excipient, a 5–8% loss was encountered on initial assays. Analysis of the lactose by UV, GLC, and mass spectrometry confirmed the presence of 5-(hydroxymethyl)-2-furfuraldehyde. Haloperidol was reacted with 5-(hydroxymethyl)-2-furfuraldehyde and furfural, and conversion to addition compounds resulted. Although both addition compounds were characterized, they could not be isolated from the direct compression tablets.

Keyphrases □ Haloperidol—reaction with 5-(hydroxymethyl)-2-furfuraldehyde impurity in anhydrous lactose □ 5-(Hydroxymethyl)-2-furfuraldehyde as impurity in anhydrous lactose—reactions with haloperidol □ Lactose, anhydrous, containing 5-(hydroxymethyl)-2-furfuraldehyde as contaminant—reaction with haloperidol

Direct compression as a method of tablet manufacture continues to receive attention in the industry because it offers distinct economic advantages over conventional methods. Interest is also high because the tablets produced usually have significantly faster dissolution rates since there are no collodial binders to envelop the granules. The use of lactose (beadlets) and dextrose[1] as excipients in this method of manufacture was recently proposed (1). Spray-dried lactose, anhydrous lactose, and microcrystalline cellulose have also been used as excipients in the direct compression technique.

During an investigation of haloperidol[2] direct compression tablets, using anhydrous lactose as one excipient, a 5–8% drug loss was encountered in initial assays. This problem was unexpected since it had been demonstrated (2) that anhydrous lactose could be used successfully in the manufacture of tablets of the related butyrophenone trifluperidol hydrochloride {4′-fluoro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl)piperidino]butyrophenone} and no evidence of a reaction between trifluperidol hydrochloride and anhydrous lactose was observed.

The anhydrous lactose was then tested for the presence of 5-(hydroxymethyl)-2-furfuraldehyde (I), since other workers (3, 4) had reported problems caused by the aldehyde in spray-dried lactose forming Schiff bases with drugs containing a primary amine. In a related study, Brownley and Lachman (5) demonstrated a relationship between the presence of I and the discoloration of spray-dried lactose. UV absorption spectra of the various lots of anhydrous lactose used in this study indicated the presence of I even though the lactose used was white in color.

Haloperidol, being a tertiary amine, could not form a Schiff base with I. However, when haloperidol was reacted with I, a Claissen–Schmidt condensation compound resulted. A similar compound resulted when haloperidol was similarly reacted with 2-furfural. The condensation compounds were characterized.

EXPERIMENTAL[3]

The haloperidol tablets and capsules were assayed for intact drug by the official method (6). The assay is stability indicating for haloperidol. Haloperidol tablets were manufactured using formulas similar to those given previously (2). They contained about 85% anhydrous lactose, 15% starch, and 0.7% calcium stearate.

Nonspecific Assay for Haloperidol—Weigh accurately a portion of tablet powder, equivalent to about 1 mg of haloperidol, and transfer it to a 120-ml (4-oz) bottle. Add exactly 50 ml of chloroform and 30 ml of methyl orange solution (a saturated solution in pH 5 buffer, 0.2 *M* sodium phosphate adjusted to pH with 1 *M* sodium hydroxide). Shake on a mechanical shaker for 15 min, centrifuge, aspirate, and discard the aqueous layer. Transfer exactly 5 ml of the chloroform layer to exactly 10 ml of acidified methanol (5% v/v hydrochloric acid in methanol), and mix. Concomitantly determine the absorbance of the solution and of a solution of haloperidol standard, taken through the assay, in 1-cm cells at the maximum at about 522 nm.

Assay and Identification of I—Anhydrous lactose was assayed for I by a published UV method (7). Further identification and confirmation of the UV data were obtained by the GLC method as follows.

Ten percent aqueous solutions of lactose were used. Aqueous solutions of I were used as standards. The analyses were performed using a dual-column chromatograph[4] equipped with dual flame-ionization detectors. Injector port and detector temperatures were 280 and 300°, respectively. Helium flow was 60 ml/min. The glass column was 1.82 m (6 ft) × 2 mm i.d., containing 3% cyclohexanedimethanol succinate on 100–120-mesh silanized, acid-washed, flux-calcined diatomite[5]. The column temperature was programmed from 90 to 250° at 20°/min, holding at 250° until all components were eluted.

The column has to be conditioned as follows prior to use. Maintain the column at 250° overnight with a helium flow of about 5 ml/min. Connect the column outlet to the detector and inject 10-μl samples of water with the column at 250° and normal helium flow until a reproducible peak is obtained.

Reaction of Haloperidol with 5-(Hydroxymethyl)-2-furfuraldehyde—Haloperidol (2 g, 0.0053 mole), I (3 g, 0.0229 mole), and methanol (3 g) were added to a 120-ml (4-oz) screw-capped bot-

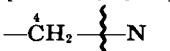
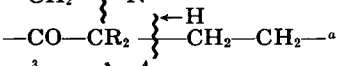
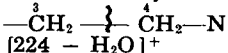
[1] PAF 2011.
[2] Marketed as Haldol.

[3] 5-(Hydroxymethyl)-2-furfuraldehyde was obtained from Aldrich Chemical Co., Milwaukee, Wis., and the anhydrous lactose was obtained from Sheffield Chemical Co. Melting points were determined in a Thomas–Hoover melting-point apparatus and are uncorrected. IR spectra were determined as potassium bromide dispersions in a Perkin-Elmer 521 grating IR spectrophotometer. NMR spectra were determined with a Varian A-60 spectrometer, using tetramethylsilane as the internal standard. All spectra were obtained in $CDCl_3$ in about 10% concentration. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 mass spectrometer. The samples were introduced by the direct inlet technique. UV spectra were obtained on a Beckman DK-2A or Cary 14 recording spectrophotometer. Microanalyses were performed by Cilag-Chemie, Schaffhausen, Switzerland.

[4] Perkin-Elmer 900.

[5] Hi-EFF-8BP on Gas Chrom Q, Applied Science Laboratories, State College, Pa.

Table I—Partial Mass Spectra of Haloperidol and Its Furfural Adducts

Fragment	*m/e* (% of base peak) Adduct II	Adduct III	Haloperidol
M^+	453 (0.3)	483 (0.9)	375 (2.3)
$[M - H_2O]^+$	435 (0.9)	465 (0.5)	357 (1.3)
$[M—FC_6H_4CO]^+$	330 (0.4)	360 (0.3)	252 (0.3)
	243 (5)	273 (2)	165 (15)
 [a]	237 (1.5)	237 (22)	237 (71)
	224 (100)	224 (100)	224 (100)
$[224 - H_2O]^+$	206 (46)	206 (27)	206 (19)
$[224 - Cl]^+$	189 (5)	189 (9)	189 (3)
$Cl—C_6H_4—CO^+$	139 (13)	139 (11)	139 (9)
$F—C_6H_4—CO^+$	123 (37)	123 (32)	123 (34)
$F—C_6H_4^+$	95 (20)	95 (13)	95 (16)
$C_5H_{10}N^+$	84 (10)	84 (8)	84 (12)
$C_3H_6N^+$	56 (24)	56 (16)	56 (26)
$C_2H_4N^+$	42 (64)	42 (60)	42 (87)

[a] McLafferty rearrangement (8).

tle. Water (5 ml) was added, and the mixture was stored in an 80° oven for about 60 hr. The cooled solution was transferred to a separator, made alkaline with sodium hydroxide solution (10%), and extracted with chloroform. The chloroform solution was evaporated to about 5 ml, diluted with 200 ml of ether, and then filtered. Ethereal hydrogen chloride was added, and a tan solid was obtained. Isolation of the free base resulted in an oil which would not recrystallize. Regeneration of the salt from the free base resulted in 1.9 g (68% of theory) of a white solid, mp 219–222°.

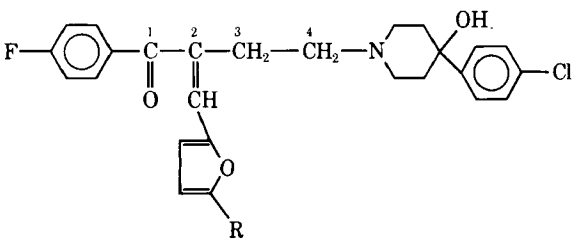
Anal.—Calc. for $C_{27}H_{27}ClFNO_4 \cdot HCl$: C, 62.31; H, 5.42; N, 2.69. Found: C, 61.49; H, 5.45; N, 2.59.

Reaction of Haloperidol with Furfural—Haloperidol (2 g, 0.0053 mole), furfural (5 g, 0.038 mole), and methanol (3 g) were mixed in a 120-ml (4 oz) screw-capped bottle. Water (5 ml) was added, and the mixture was stored in an 80° oven for about 60 hr. The cooled solution was transferred to a separator, made acidic with hydrochloric acid (10%), and extracted with chloroform. The remainder of the procedure was the same as described previously. Regeneration of the salt from the free base resulted in 2.1 g (81% of theory), mp 231–233°.

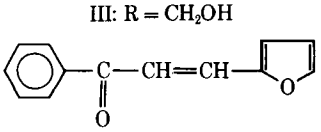
Anal.—Calc. for $C_{26}H_{25}ClFNO_3 \cdot HCl$: C, 63.68; H, 5.34; N, 2.86. Found: C, 63.30; H, 5.37; N, 2.85.

STRUCTURE DETERMINATION

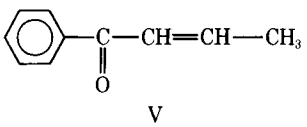
The mass spectra of the adducts of haloperidol with furfural (II) and hydroxymethylfurfural (III) are presented in Table I along with that of haloperidol. In addition to confirming the molecular weights and exhibiting many fragmentations seen in haloperidol, the base peak at *m/e* 224 and the strong *m/e* 123 peak are of particular interest. These fragments localize the point of attachment of the furfural moiety to either C-2 or C-3 of the butyrophenone.



II: R = H
III: R = CH_2OH



IV



V

The NMR spectra are in general agreement with these structures, showing one vinyl proton at δ 5.7 as well as the expected ratio of aliphatic to aromatic protons.

The IR spectra show a shift of the carbonyl stretch absorption to lower frequencies relative to haloperidol. This implies an extension of the conjugation of the aryl ketone.

The UV spectra of the adducts corroborate this extended conjugation. Comparisons with spectra of 3-(2-furyl)acrylophenone (IV), crotonophenone (V), and haloperidol show (Table II) the close resemblance of the adduct spectra with that of the furylacrylophenone (IV). Therefore, the furfural moiety must be attached to C-2 of the butyrophenone, confirming the assigned structures of II and III.

RESULTS AND CONCLUSIONS

Determination of I in Lactose—The UV spectra of 1% aqueous solutions of the various lots of anhydrous lactose used in the manufacture of the tablets were similar to the hydroxymethylfurfural spectra previously reported (7). GLC *analysis of the* aqueous solutions of the lactose resulted in a peak whose retention time, about 6.5 min, was identical to that of I. Furthermore, when the mass spectrum of that peak was compared to a spectrum of I, they were identical, proving that the lactose did indeed contain 5-(hydroxymethyl)-5-furfuraldehyde.

Tablet Assays—The initial batch of direct compression haloperidol tablets assayed satisfactorily. This batch was manufactured with a lot of anhydrous lactose containing less than 2 mg I/kg. These tablets possessed excellent physical characteristics, such as small tablet weight variation, uniform drug distribution, fast disintegration times, and rapid dissolution rates. In addition, high temperature and high humidity had no adverse effects on either the physical or chemical properties of the tablets. Subsequent batches of tablets were manufactured with lots of anhydrous lactose with higher amounts of I (10 times or more).

A comparison of the assay results for the initial batch of direct

Table II—Comparison of UV Absorption Spectral Data

Compound	λ_{max} (ϵ)	
Furfural adduct, II	258 (11,200), 332 (17,200)	
Hydroxymethylfurfural adduct, III	258 (8000), 336 (24,400)	
3-(2-Furyl)acrylophenone, IV	260 (8500), 344 (26,800)	(9)
Crotonophenone, V	256 (17,400)	(10)
Haloperidol	247 (11,900)	

Table III—Effect of Aging on Haloperidol Direct Compression Tablets

Batch	Label Amount, mg Haloperidol/ Tablet	Hydroxymethyl Furfural Content of Lactose, mg/kg	Percent Label Amount			
			Nonspecific Assay	Initial Assay	3 Months at 40°	3 Months at 60°
A	0.5	<2	100	102	101	101
B	0.5	29	98	92	93	93
C	1	29	97	93	92	91
D	2	29	97	93	94	94

compression tablets, which assayed satisfactorily, with three other batches of tablets, which assayed low, is given in Table III. Also included are results obtained by the nonspecific assay for haloperidol. The nonspecific colorimetric assay demonstrates that the tertiary nitrogen of haloperidol is still present in the dosage form. Without this assay, a question of whether the correct amount of drug had been added could have been raised. The stability of the dosage forms is also shown in Table III. The data show that haloperidol is lost initially and that the degradation does not proceed further with aging at elevated temperatures.

Haloperidol capsules were manufactured with a lot of anhydrous lactose containing 240 mg I/kg lactose. The nonspecific assay demonstrated that the drug was present as shown in Table IV, while the stability-indicating assay showed that the haloperidol content was low. The low assays were verified by repeated assays and remained essentially constant even after aging for 1 year. Capsules were then manufactured with the identical manufacturing directions but using hydrous lactose. They assayed satisfactorily (Table IV). The only other ingredient in the capsule besides the haloperidol and lactose was a small amount of the lubricant calcium stearate.

Extensive TLC work did not demonstrate the presence of the haloperidol–I condensation products in the tablets or capsules. But the fact that haloperidol could react easily with either I or furfural indicates that hydroxymethylfurfural in anhydrous lactose can be responsible for the low assay for direct compression haloperidol tablets. The nonspecific colorimetric assay demonstrates that the basic nitrogen of haloperidol remains in the dosage form, while the stability-indicating assay for haloperidol clearly indicates that there is a definite loss of haloperidol in the dosage forms.

Reactions—It was previously demonstrated (2) that anhydrous lactose could be used successfully in the manufacture of trifluperidol hydrochloride tablets. No evidence of a reaction between trifluperidol hydrochloride and anhydrous lactose was observed. Haloperidol is chemically related to trifluperidol hydrochloride, both drugs belonging to the class of compounds known as the butyrophenones.

When it became apparent that haloperidol could easily react with I and furfural, it was decided to see if the same reaction could occur with trifluperidol hydrochloride. When trifluperidol hydrochloride was reacted with either I or furfural, no condensation products were obtained. Instead, trifluperidol was recovered intact from the reaction mixtures. The postulated Claissen–Schmidt condensation between haloperidol and I or furfural is a base-catalyzed reaction. Therefore, the free base of trifluperidol and furfural were reacted. A condensation compound of the same type obtained for haloperidol resulted.

Furthermore, compounds that resemble haloperidol structurally but do not contain the carbonyl group adjacent to the *p*-fluorophenyl group do not react with either I or furfural. For example, pimozide, 1-[1-[4,4-bis(*p*-fluorophenyl)butyl]-4-piperidyl]-2-benzimidazolinone, does not react with either furfural or hydroxymethylfurfural.

Table IV—Assay of Haloperidol Capsules

Batch	Label Amount, mg Haloperidol/ Capsule	Hydroxymethylfurfural Content of Lactose, mg/kg	Percent Label Amount	
			Nonspecific Assay	Stability Assay
E	1	240	—	92
F	2	240	96	90
G	1	0	—	100
H	2	0	102	102

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