Thermal Decomposition of Ibuproxam

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Received July 5, 1979, from the *Instituto Medicina del Lavoro, University of Florence, Largo Palagi 1, Florence, Italy, and the ‡Società Italo-Britannica L. Manetti-H. Roberts, Florence, Italy. Accepted for publication November 26, 1979.

Abstract □ The thermal behavior of ibuproxam was studied at several temperatures, and the degradation products were separated by column chromatography and ethereal extractions. The resulting products were ibuprofen [2-(4-isobutylphenyl)propionic acid], 1-(4-isobutylphenyl)-ethylamine, 4-isobutylacetophenone, and 4-isobutylacetophenone oxime. The compounds were identified by IR, UV, and NMR spectroscopy and elemental analyses. 4-Isobutylacetophenone was treated with hydroxylamine to give 4-isobutylacetophenone oxime.

Keyphrases □ Thermal decomposition—ibuproxam, analysis of degradation products □ Ibuproxam—thermal decomposition, identification of thermal degradation products □ Anti-inflammatory agents—ibuproxam, identification of thermal degradation products

Ibuproxam [(*RS*)-2-(4-isobutylphenyl)propiohydroxamic acid, I] is a potent oral nonsteroidal anti-inflammatory agent (1, 2). The pharmacology of ibuproxam was described previously (3), and absorption, metabolism, and extraction patterns in animals (4) and humans (5–7) were reported. Ibuproxam is safe and effective in the treatment of rheumatic diseases. Preclinical pharmacology has indicated the utility of oral dosage forms; this paper identifies the compounds arising from thermal decomposition of ibuproxam.

RESULTS AND DISCUSSION

The stability studies showed that I was thermally unstable (Table I). This instability initially was ascribed to the impurities of the technical grade product, but further testing of the analytical grade substance led to the conclusion that the observed trend was characteristic of the compound (Fig. 1). Ibuproxam, heated over 70°, decomposed to give four products; during these preliminary tests, the presence of water and metals (particularly iron) due to the manufacturing process did not substantially alter the decomposition (Table II).

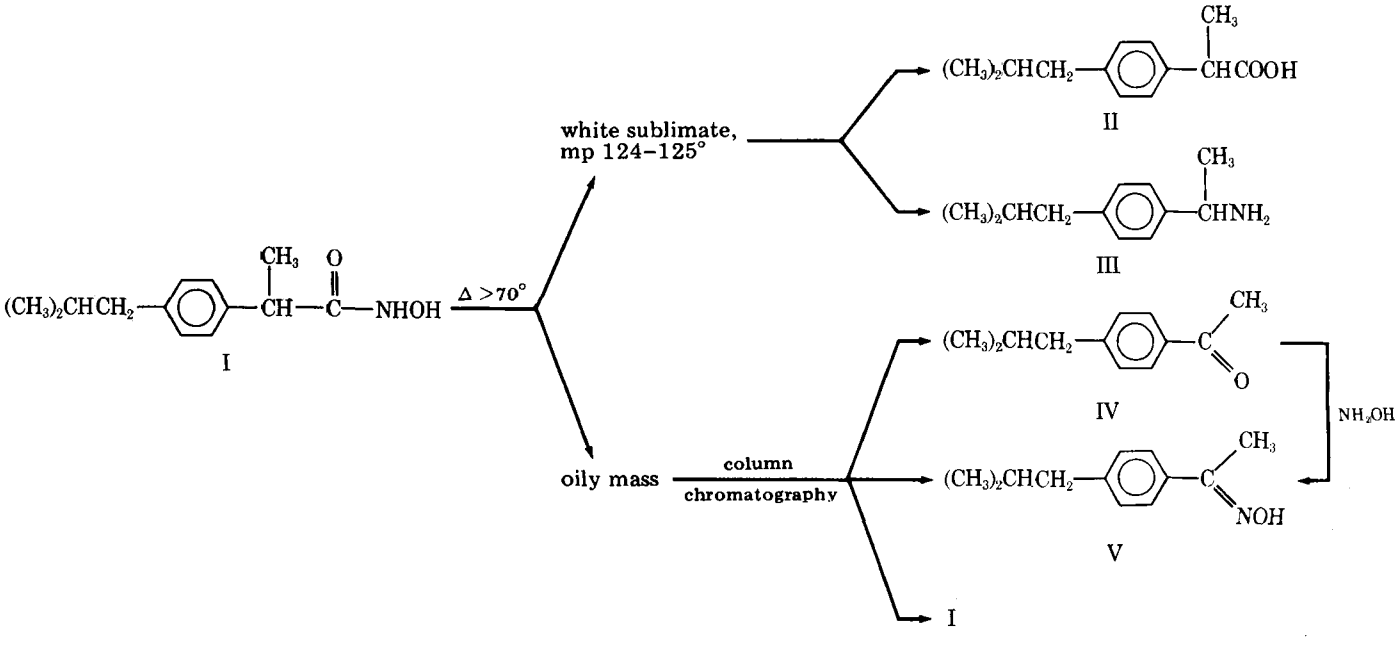
Table I—GLC Analysis of Thermal Decompostion of I at Different Temperatures [a]

Time	Degradation Products, %			
	40°	60°	80°	105°
10 min	0	0	0	2.4
20 min	0	0	2.7	49.5
40 min	0	0	30.0	67.0
1 hr	0	0	57.5	81.0
2 hr	0	1.2	76.0	87.5
4 hr	0	3.8	90.3	97.0
8 hr	0	7.4	96.7	—
12 hr	0	12.3	—	—
24 hr	0	48.2	—	—
2 days	0	81.3	—	—
4 days	0	91.3	—	—
8 days	0	98.5	—	—
16 days	0	—	—	—
1 month	1.7	—	—	—
2 months	1.9	—	—	—
4 months	4.8	—	—	—
8 months	7.9	—	—	—

[a] Samples were analyzed with a Perkin-Elmer 990 gas–liquid chromatograph on a 2-m × 6.35-mm 3% Dexil on Anachrom AB column at 180° with nitrogen as the carrier gas at 30 ml/min.

From a preliminary examination of the crude decomposition product, it was possible to separate two main products: a white sublimate (insoluble in most organic solvents but soluble in water) and a sticky yellow mass that still contained the nondecomposed product (TLC controls) (Fig. 2). Chemical and spectroscopic properties of the sublimate gave evidence of its saline structure, which was confirmed by isolation of II and III; further evidence (melting point and IR spectrum) was obtained by treatment of a commercial sample of II with III.

By column chromatography of the oily mass, IV and V were obtained together with a small amount of I. The structure of V was confirmed chemically by reaction of ketone IV with hydroxylamine (Scheme I).



Scheme I

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Table II—^{1}H-NMR Spectra of Ibuproxam and Degradation Products [a]

Compound	Proton Resonance, ppm	Assignment
I	0.78 (d, J = 7 Hz)	6H, $(CH_3)_2CH$
	1.4 (d, J = 7 Hz)	3H, $CH_3CHCONHOH$
	1.65–2.05 (m)	1H, $CHCH_2$
	2.42 (d, J = 7 Hz)	2H, CH_2
	3.45 (q, J = 7 Hz)	1H, $COCHCH_3$
	6.9–7.3 (m)	4H, aromatic H_4
	8.8[b] (broad s)	1H, NH
III	0.88 (d, J = 7 Hz)	6H, $(CH_3)_2CH$
	1.33 (d, J = 7 Hz)	3H, CH_3CHNH_2
	1.47[b] (s)	2H, NH_2
	1.5–2.1 (m)	1H, $CHCH_2$
	2.42 (d, J = 7 Hz)	2H, CH_2
	4.03 (q, J = 7 Hz)	1H, CH_3CHNH_2
	7.0–7.3[c] (m)	4H, aromatic H_4
IV	0.88 (d, J = 7 Hz)	6H, $(CH_3)_2CH$
	1.5–2.1 (m)	1H, CH
	2.52 (s)	3H, CH_3CO
	7.2[c] (d)	2H, H-2, H-6
	7.87[c] (d)	2H, H-3, H-5
V	0.89 (d, J = 7 Hz)	6H, $(CH_3)_2$-CH
	1.5–2.1 (m)	1H, CH
	2.27 (s)	3H, CH_3CNOH
	2.47 (d, J = 7 Hz)	2H, CH_2
	7.14[c] (d)	2H, H-2, H-6
	7.54[c] (d)	2H, H-3, H-5
	9.52[b] (s)	1H, OH

[a] Obtained at 90 MHz; δ values are expressed in parts per million; tetramethylsilane was the internal reference, and deuterated chloroform was the solvent. [b] Signal disappears on deuteration. [c] For these signals, a progressive change was noted from a pattern type of *AA'BB'* to *AA'XX'*.

EXPERIMENTAL[1]

Thermal Degradation—Ibuproxam (I) (4 g) was sublimed at 110° and 760 mm Hg for 24 hr to yield a white product (1.5 g) and a pale-yellow residue. This residue was extracted with ether (50 ml), and evaporation of the extracts gave an oil (2.3 g).

Ibuprofen [2-(4-Isobutylphenyl)propionic Acid, II]—The sublimate (1 g), purified by several washings with ether (mp 124–125°), was dissolved in water (25 ml). Acidification with concentrated hydrochloric acid (pH 1–2) precipitated a white solid (0.48 g, 90% yield), mp 76–77° (after crystallization from ethyl acetate).

Anal.—Calc. for $C_{13}H_{18}O_2$: C, 75.73; H, 8.73. Found: C, 75.81; H, 8.75.

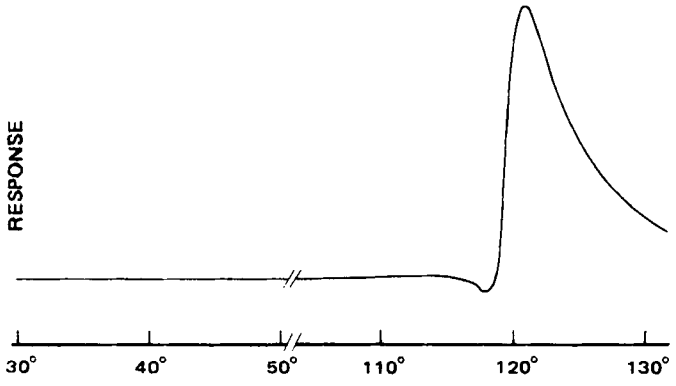

Figure 1—*Thermal decomposition of I. The scan speed was 4°/min, R = 500 μv, and the nitrogen gas flow rate was 20 ml/min.*

[1] Unless otherwise stated, IR spectra were measured for dispersions in Nujol with a Perkin-Elmer 457 spectrometer, and UV spectra were measured for solutions in ethanol with a Perkin-Elmer 124 recording spectrophotometer. ^{1}H-NMR spectra were recorded with a Perkin-Elmer R 32 instrument; chemical shifts are reported in parts per million downfield from the internal standard, tetramethylsilane. Thermal analysis was taken with a TA 2000 Mettler apparatus. Silica gel plates (Merck F_{254}) were used for analytical TLC, and the spots were detected by their UV absorption. Column chromatography was carried out with silica gel (Merck kieselgel 60, 70–230 mesh, ASTM). The extracts were dried over sodium sulfate, and the solvents were removed under reduced pressure. Melting points (uncorrected) were determined by the capillary method.

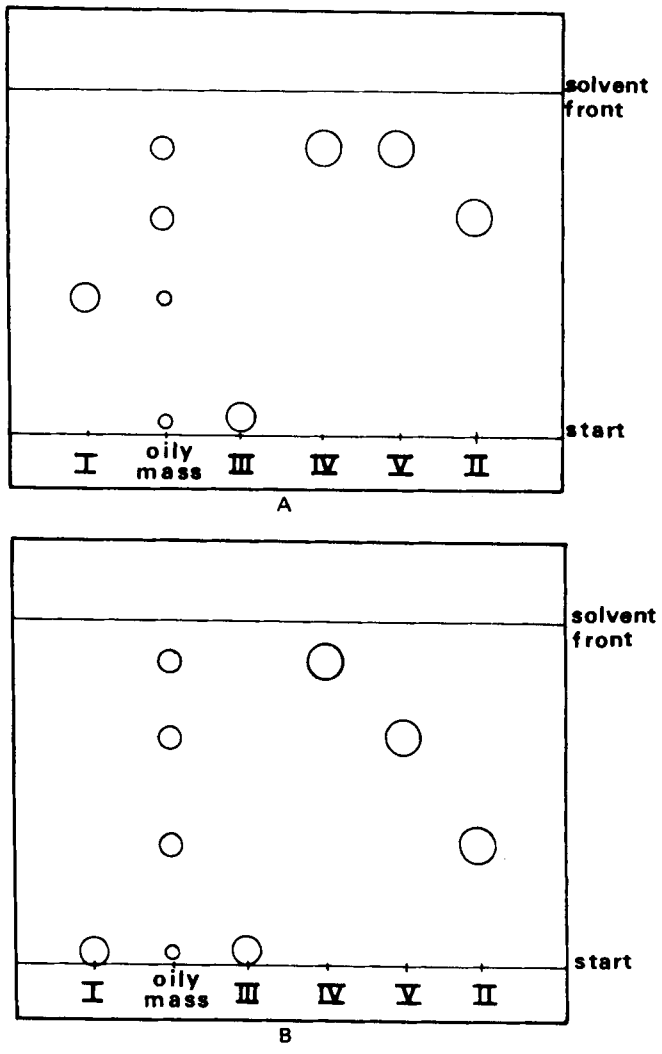

Figure 2—*TLC of the decomposition products of I. Key: A, eluent of benzene–ethyl acetate (1:1 v/v); and B, eluent of benzene–cyclohexane–ethyl acetate (5:5:1 v/v). The spot for I was detected best by spraying with sodium sulfate solution in methanol to give a characteristic green color.*

The product was identical to a commercial sample on the basis of mixed melting-point, IR, UV, and NMR analyses.

1-(4-Isobutylphenyl)ethylamine (III)—The sublimate (1 g), purified as described, was dissolved in water (25 ml); the solution was made alkaline with 10% NaOH and extracted with ether (3 × 30 ml). Removal of the solvent left an oil, which was purified by column chromatography with methanol as the eluent. Compound III (0.35 g, 75% yield) is a colorless liquid whose hydrochloride melts at 178–180°; IR: ν_{max} 3370, 3280, 2955, and 2860 cm^{-1}; UV: λ_{max} 263 (log ϵ 2.20), 272 sh (2.09), 252 (1.97), and 258 (2.12) nm.

Anal.—Calc. for $C_{12}H_{19}N$: C, 81.35; H, 10.73; N, 7.90. Found: C, 81.50; H, 10.95; N, 8.05.

4-Isobutylacetophenone (IV)—The oily residue (2 g) from thermal degradation was resolved into two products by column chromatography with benzene as the eluent. The first fractions gave IV (0.44 g, 50% yield) as a yellow liquid, bp 248°; IR: ν_{max} 2955, 2920, 2860, 1680, and 1608 cm^{-1}; UV: λ_{max} 254 nm (log ϵ 3.94).

Anal.—Calc. for $C_{12}H_{16}O$: C, 81.81; H, 9.09. Found: C, 82.05; H, 9.28.

4-Isobutylacetophenone Oxime (V)—*Method A*—The second product of the oily residue, treated as described, gave V as a white solid (0.57 g, 60% yield), mp 64–65° (after crystallization from *n*-hexane); IR: ν_{max} 3500–2800 br, 2955, 2920, and 2860 cm^{-1}; UV: λ_{max} 250 nm (log ϵ 3.86).

Anal.—Calc. for $C_{12}H_{17}NO$: C, 75.39; H, 11.80; N, 7.32. Found: C, 75.32; H, 11.60; N, 7.46.

Method B—A solution of IV (0.2 g) in methanol (20 ml) was treated with hydroxylamine (0.1 g) and refluxed gently for 6 hr. Removal of the solvent left a white solid (0.2 g, 90% yield), which was identical (melting point, IR, and NMR analyses) with the material obtained by Method A.

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High-Performance Liquid Chromatographic Analysis of Griseofulvin in Drug Substance and Solid Dosage Forms: Separation of Impurities and Metabolites

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Received July 30, 1979, from the *Physical and Analytical Chemical Research and Development Department, Schering-Plough Corporation, Bloomfield, NJ 07003.* Accepted for publication December 5, 1979.

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Abstract □ A high-performance liquid chromatographic (HPLC) system, consisting of a methanol–water (3:2 v/v) mobile phase and a Zorbax CN column with *m*-phenylphenol as the internal standard, was utilized to determine the purity of griseofulvin bulk drug substance, to assay griseofulvin in powders, tablets, capsules, and boluses, and to separate griseofulvin from its metabolites. The method was tested on commercial griseofulvin samples, griseofulvin tablets, and a mixture of griseofulvin and its metabolites. The HPLC method is compared to a GLC method.

Keyphrases □ Griseofulvin—high-performance liquid chromatographic analysis, purity and stability of drug substance, powders, tablets, capsules, and boluses, metabolites □ High-performance liquid chromatography—analysis, griseofulvin, purity and stability of griseofulvin dosage forms, metabolites □ Antifungal agents—griseofulvin, high-performance liquid chromatographic analysis of powders, tablets, capsules, and boluses

Griseofulvin has well-established fungistatic activity against various species of *Microsporum, Epidermophyton,* and *Trichophyton.* Usual dosage forms are powders, capsules, tablets, and boluses. Liquid–solid extraction methods for the preparation of griseofulvin for subsequent analysis include extraction of griseofulvin from tablets with boiling alcohol (1) and extraction from tablets with warm chloroform (2, 3).

The drug substance has been determined by several methods, the most common of which is a simple UV analysis (1, 4, 5). Other methods include polarography (6), GLC (2, 3), spectrofluorometry (7, 8), colorimetry (9–11), iodimetry (12), paper chromatography (13), and TLC (14–17). Liquid chromatography has been useful for the analysis of griseofulvin in crude mycelium (18) and in plasma (19).

This report describes a specific, simple, and robust high-performance liquid chromatographic (HPLC) procedure. It is applicable to the drug substance and solid dosage forms and to the separation of griseofulvin from its metabolites. The procedure is offered as an alternative to the GLC method (2), which suffers from the difficulty of drug analysis at high temperatures.

EXPERIMENTAL

Materials—*m*-Phenylphenol[1], reagent grade dichloromethane[2], sodium chloride[3], and anhydrous sodium sulfate[4] were obtained from commercial sources.

Apparatus—The modular high-pressure liquid chromatograph was equipped with a constant-flow pump[5], a valve-type injector[6], a fixed-wavelength (254-nm) UV detector[7], and a strip-chart recorder[8]. Stainless steel columns (4.6 mm × 30 cm) were packed with fully porous 10-μm silica particles to which a monomolecular layer of cyanopropylsilane[9] was chemically bonded. A rotating mixing wheel[10] and centrifuge tubes[11] were used to extract the samples. A data acquisition system[12] was used for both peak height and area measurements.

Chromatographic Conditions—The mobile phase was methanol–water (3:2). This solution was passed through a 0.45-μm filter[13], degassed, and then pumped through the HPLC system at a rate of 1 or 2 ml/min.

Table I—Analysis for Purity and Dechlorogriseofulvin Content in Griseofulvin Batches from Worldwide Sources

Batch	Purity[a], %	Dechlorogriseofulvin Content, %
0672-F2	100[b]	0.6
UGFP-1961	99.4	1.1
UGRB-505	96.6	2.0
GU-4830S	97.0	3.2
GU-4910S	97.0	2.8
26	99.7	0.9
5209	98.9	1.6
15 (805/7)	97.9	1.5

[a] Determined using USP XIX, p. 584. [b] USP reference standard.

[1] Eastman Organic Chemicals, Rochester, N.Y.
[2] Matheson, Coleman and Bell, Norwood, Ohio.
[3] NF grade, J. T. Baker Chemical Co., Phillipsburg, N.J.
[4] NF grade, Fisher Scientific Co., Fair Lawn, N.J.
[5] Model M-6000 A chromatography pump, Waters Associates, Milford, Mass.
[6] Universal injector model U6K, Waters Associates, Milford, Mass.
[7] Model 440 absorbance detector, Waters Associates, Milford, Mass.
[8] Class 19, No. 196711-008-000-506-01, Honeywell, Fort Washington, Pa.
[9] Zorbax CN column, E.I. duPont de Nemours & Co., Wilmington, Del.
[10] Rugged Rotator, Craft Apparatus, New York, N.Y.
[11] Bellco Glass Co., Vineland, N.J.
[12] PDP 11/34 minicomputer, Peak 11 Software Digital Electronics Corp., Maynard, Mass.
[13] Metricel membrane filter DM-450, Gelman Instrument Co., Andover, Mich.

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