Impurities in Drugs V: Meprobamate

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Abstract □ One lot of meprobamate raw material and 28 lots of tablets were examined for impurities by TLC. All lots contained di-(2-methyl-2-propyl-3-carbamoyloxypropyl) carbonate (V) at levels that ranged between 0.1 and 1.0% of the total drug content. Nine lots also contained low levels of a second impurity (~0.1%), and one of these lots contained a third impurity (~0.1%), neither of which was identified. Estimates of the unidentified impurities were based on the assumption of a TLC response with furfural–hydrochloric acid spray equivalent to that of meprobamate. Compound V was identified by mass spectrometry and PMR and IR spectroscopy and by comparison of the TLC R_f value to that of a synthesized sample of V.

Keyphrases □ Meprobamate—identification of impurities in tablets □ Drug impurities—meprobamate, identification in tablets

The origins of organic impurities in drugs and some consequences of their presence were outlined previously (1). The present paper reports the occurrence of impurities in 28 lots of meprobamate tablets.

Meprobamate (I) can be synthesized (2, 3) by reduction of methylpropylpropanedioic acid diethyl ester (II) with lithium aluminum hydride to the corresponding 2-methyl-2-propyl-1,3-propanediol (III). Reaction of III with phosgene affords the dichlorocarbonate (IV), which, upon treatment with ammonia, yields I.

USP XX (4) and BP 1973 (5) contain specifications for meprobamate raw material and tablets. The BP includes a specification of 1% for related substances (not specified), with the test to be done by TLC. There are no USP specifications for impurities in meprobamate.

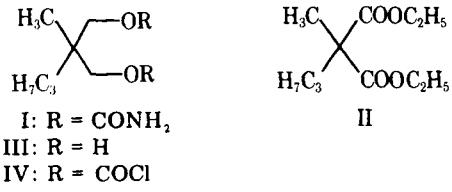
EXPERIMENTAL

Materials—All drugs and formulations were obtained directly from the manufacturer. Ammonia[1], 2-methyl-2-propyl-1,3-propanediol[2], ethyl chlorocarbonate[3], diethyl carbonate[3], furfural[4], pyridine[4], sodium methoxide[4], hydrochloric acid[5], and anhydrous sodium sulfate[5] were obtained commercially. All solvents[6] were analytical grade. Precoated silica gel GF-60 (20-cm × 20-cm × 0.25-mm) TLC plates[7] and silica gel powder[5] (60–200 mesh) were used. All PMR spectra were obtained in deuterochloroform[8] on an 80-MHz instrument[9] with tetramethylsilane as the internal standard. Mass spectral[10] samples were introduced *via* the direct probe and were recorded at an ionizing potential of 70 ev.

Standard Solutions—The standard solutions consisted of 100 mg of I/ml and 1.0 mg of V/ml in acetone.

TLC System—The chloroform–ethanol (90:10) developing solution was allowed to equilibrate in filter paper-lined chromatographic tanks for 20 min prior to use. Spots were visualized by spraying the plates sequentially with furfural and concentrated hydrochloric acid. The R_f values and the lower limits of detection of I and related compounds were established by the serial dilution of stock solutions.

Sample Preparation—To prepare the raw material samples, ~400 mg of I, accurately weighed, was dissolved in 4 ml of acetone. To prepare the tablet samples, an amount of powdered tablet equivalent to 400 mg of I was weighed into a 10-ml screw-capped tube, extracted by shaking for 15 min with 4 ml of acetone, centrifuged, and filtered.



I: R = $CONH_2$
III: R = H
IV: R = COCl

II

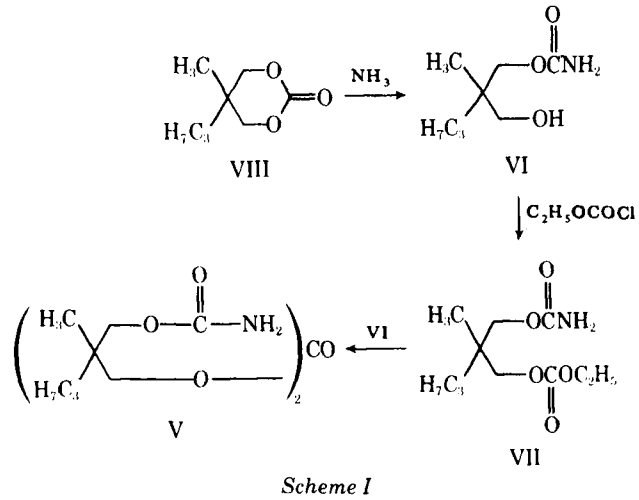
Screening for Impurities—Aliquots (10 μl) of the tablet extracts in acetone were applied to the TLC plates. Decomposition on the plate was checked for by two-dimensional TLC but was not found. The concentration of impurities was estimated by comparison of the spot diameters and intensities with the corresponding spots from the standard solutions, with the assumption that the response of the unidentified impurities to the spray was the same as that of I.

Isolation of Impurities—An amount of formulation equivalent to 2 g of I was shaken with two 40-ml portions of acetone for 15 min and filtered. The combined fractions were evaporated to dryness, and the residue was dissolved in 200 ml of ether. The ether solution was partitioned three times with 0.05 *N* NaOH to remove any fatty acids present as excipients, evaporated to dryness, redissolved in ~10 ml of the TLC solvent system, and poured onto the top of a slurry-packed silica gel[5] glass column prepared from 50 g of silica gel and 200 ml of the TLC solvent. After ~70 ml of the TLC solvent system had flowed through the column, 45 fractions of 3 ml each were collected.

The location of the various compounds was established by spotting a 15-μl aliquot of every other fraction on a TLC plate. The plate was developed and the spots were visualized with the furfural–hydrochloric acid spray. The fractions containing the impurity to be identified were combined, evaporated to dryness, and subjected to mass spectral, NMR, and IR[11] analyses.

Syntheses—The syntheses are illustrated in Scheme I.

2-Methyl-2-propyl-3-hydroxypropylcarbamate (VI)—Compound VI was prepared in a 40% yield from the dioxanone (VIII) using the method described by Ludwig and coworkers (2, 3), mp 51–52°; IR (KBr): 3380 (OH), 3240, 3200 (NH), 1690 (C=O), 1620 (C–N), 1075, and 1040



Scheme I

[1] Matheson, Toronto, Ontario, Canada.
[2] Chemicals Procurement Laboratories, College Point, N.Y.
[3] Pfaltz & Bauer, Stamford, Conn.
[4] British Drug Houses, Poole, England.
[5] J. T. Baker Chemical Co., Phillipsburg, N.J.
[6] Caledon Laboratories Ltd., Georgetown, Ontario, Canada.
[7] Brinkmann Instruments, Toronto, Ontario, Canada.
[8] Stohler Isotope Chemicals, Waltham, Mass.
[9] Bruker WP-80 spectrometer.
[10] Varian MAT model 311 A mass spectrometer.
[11] Pye Unicam SP 1000 IR spectrophotometer.

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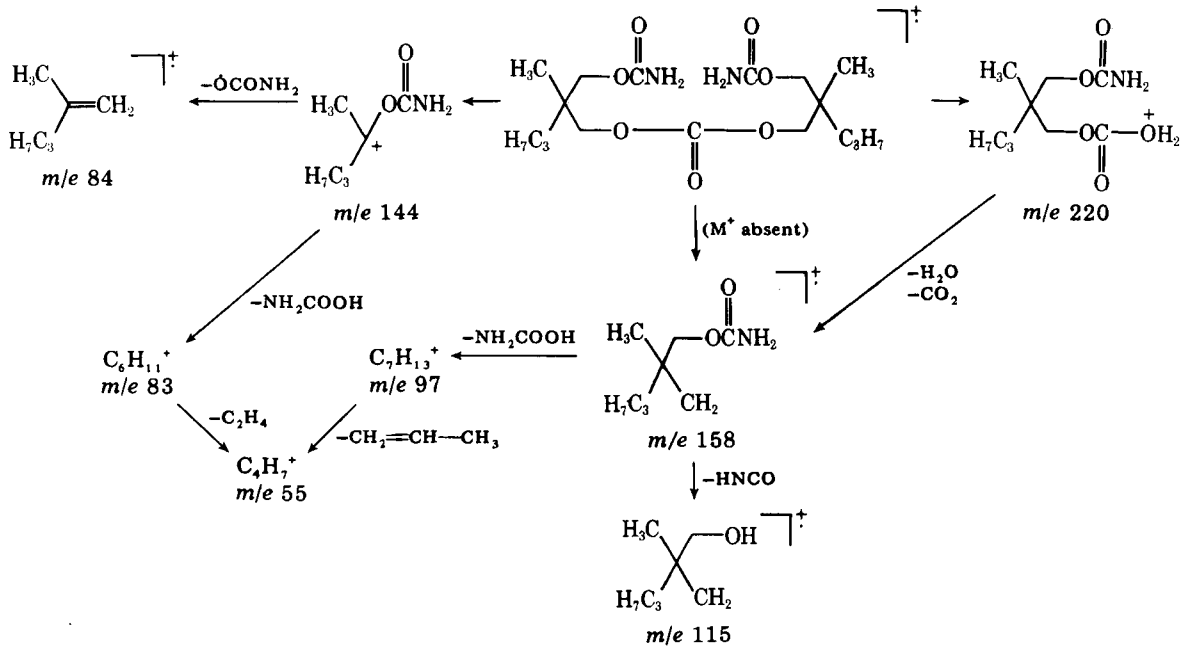

Scheme II

(C–O) cm^{-1}; PMR ($CDCl_3$): δ 5.16 (broad, 2H, NH_2), 3.90 (s, 2H, CH_2O), 3.28 [s, 2H, CH_2OH (disappears with D_2O exchange)], 3.03 (broad, 1H, OH), 1.22, and 0.90 (m, 10H, alkyl protons) ppm; mass spectrum (70 ev, 45°): M^+ absent, *m/e* 101 (31.0%), 96 (18), 84 (100), 83 (95), 75 (88), 62 (87), and 55 (96).

(2-Methyl-2-propyl-3-carbamoyloxypropyl)ethyl Carbonate (VII) (*2, 3*)—To 4 ml of chloroform in which 118 mg (1.5 mmoles) of pyridine had been dissolved were added 52 mg (0.3 mmole) of VI and 33 mg (0.3 mmole) of ethyl chlorocarbonate dissolved in ~2 ml of chloroform. The reaction mixture was refluxed for 1 hr and then poured into cold water. The chloroform layer was washed with 10% hydrochloric acid, washed again with water, dried over anhydrous sodium sulfate, and filtered. Evaporation of the filtrate yielded 69 mg (95%) of oily VII; IR (film): 3470, 3360 (NH), 1730 (C=O), 1600 (C–N), 1060, and 1005 (C–O) cm^{-1}; PMR ($CDCl_3$): δ 4.62 (broad, 2H, NH_2), 4.20 (q, 2H, OCH_2CH_3), 3.94 (s, 2H, CH_2O), 3.90 (s, 2H, CH_2O), 1.28, and 0.90 (m, 13H, alkyl protons) ppm; mass spectrum (70 ev, 25°): M^+ absent, *m/e* 173 (28%), 144 (26), 114 (50), 101 (42), 96 (95), 84 (96), 83 (100), 75 (55), 62 (88), and 55 (96).

Di-(2-methyl-2-propyl-3-carbamoyloxypropyl) Carbonate (V) (*2, 3*)—Compound VI, 18 mg, and 25 mg of VII were dissolved in 5 ml of chloroform and refluxed in the presence of ~1 mg of sodium methoxide for 3 hr. The mixture was cooled, diluted with chloroform, washed with water, and dried over anhydrous sodium sulfate. Evaporation to dryness yielded V (45%), mp 88–90°; IR (film): 3490, 3380 (NH), 1730 (C=O), 1610 (C–N), 1260, and 1070 (C–O) cm^{-1}; PMR ($CDCl_3$): δ 4.70 (broad, 4H, NH_2), 3.97 (s, 4H, OCH_2), 3.93 (s, 4H, OCH_2), 1.26, and 0.93 (m, 20H, alkyl protons) ppm; mass spectrum (70 ev, 115°): M^+ absent, *m/e* 220 (33%), 158 (90), 144 (16), 115 (24), 97 (100), 84 (45), 83 (57), and 55 (63).

RESULTS AND DISCUSSION

The TLC R_f values and the limits of detection of I, VI, VII, and the impurities in tablet formulations are given in Table I.

Twenty-eight lots of meprobamate tablets and one lot of drug raw material were screened for impurities by TLC. All lots contained V at levels ranging from 0.1 to 1.0%. Nine lots also contained a second impurity, designated as IX, and one of these lots contained a third impurity, X. The levels of IX and X were estimated by TLC to be ~0.1%, with the assumption of a response identical to that of meprobamate. They were not investigated further. The identity of V was established by IR, PMR, and mass spectral analyses and by comparison of the TLC R_f value with that of a synthesized specimen.

Table I—TLC Characteristics of Meprobamate and Related Compounds

Compound	R_f Absolute	R_f Relative	Limit of Detection, μg
I	0.26	1.00	1
VI	0.27	1.04	2
VII	0.56	2.15	2
V	0.42	1.61	1
IX	0.35	1.35	—
X	0.65	2.50	—

The structure postulated for V is supported by the mass spectral and PMR data. The molecular ion is absent from the electron-impact mass spectrum, but the chemical-ionization spectrum obtained with methane shows a weak peak at *m/e* 377 (3%), attributable to MH^+, and a strong fragment at *m/e* 158 (100%), also present in the electron-impact spectrum, corresponding to breakage of the carbonate bond. The ion at *m/e* 115 is formed by the loss of isocyanic acid from the *m/e* 158 fragment, and the base peak, *m/e* 97, is attributable to a loss of water from *m/e* 115. Mechanisms for the formation of fragments in the mass spectrum of V are proposed in Scheme II (6, 7). The PMR spectrum shows the NH_2 protons at 4.70 ppm and two singlets for the two sets of $-CH_2-$, with each singlet integrating for four protons. The aliphatic part of the spectrum is similar to that of meprobamate because of the symmetry of the molecule.

Compound V may form during the synthesis of meprobamate by the reaction of IV with the semichlorinated derivative of III, which, upon treatment with ammonia, would yield V. It is unlikely that V is a degradation product of meprobamate.

REFERENCES

(1) K. M. McErlane, N. M. Curran, and E. G. Lovering *J. Pharm. Sci.*, **66**, 1015 (1977).

(2) B. J. Ludwig, L. S. Powell, and F. M. Berger, *J. Med. Chem.*, **12**, 462 (1969).

(3) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5779 (1951).

(4) "The United States Pharmacopeia," 20th rev., Mack Publishing Co., Easton, Pa., 1980.

(5) "British Pharmacopoeia 1973," Her Majesty's Stationery Office, London, England, 1973.

(6) R. T. Coutts, *J. Pharm Sci.*, **62**, 769 (1973).

(7) I. J. Rouse and D. A. Brent, *Biomed. Mass Spectrom.*, **1**, 256 (1974).

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