measurements provides an objective and rapid method of optimizing dosage regimens of procainamide for individual patients.

(1) J. Koch-Weser, *N. Engl. J. Med.*, **287**, 227(1972).
(2) J. Koch-Weser and S. W. Klein, *J. Amer. Med. Ass.*, **215**, 1454(1971).
(3) J. Koch-Weser, *Ann. N.Y. Acad. Sci.*, **179**, 370(1971).
(4) E. V. Giardina, R. H. Heissenbuttel, and J. T. Bigger, *Ann. Intern. Med.*, **78**, 183(1973).
(5) G. O. Gey, R. H. Levy, L. Fisher, G. Pettet, and R. A. Bruce, *ibid.*, **80**, 718(1974).
(6) R. A. Bruce, F. Kusumi, and D. Hosmer, *Amer. Heart J.*, **84**, 546(1973).

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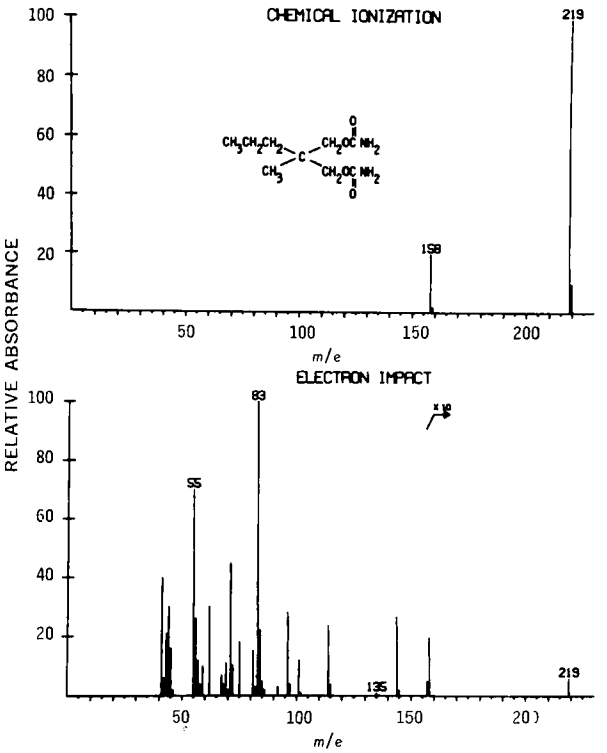


Figure 1—*Comparison of the normalized electron-impact and chemical ionization mass spectra of Compound Ia. All other dicarbamates listed in Table I gave similar spectra.*

Combined Application of High-Resolution Chemical Ionization and Electron-Impact Mass Spectrometry to Medicinal Dicarbamates

Keyphrases □ Mass spectrometry, electron impact and high-resolution chemical ionization—application to medicinal dicarbamates □ Dicarbamates, medicinal—combined application of high-resolution chemical ionization and electron-impact mass spectrometry

To the Editor:

A recent report on the application of field desorption mass spectrometry to a series of medicinal dicarbamates to determine the molecular weight (1) prompts us to communicate earlier results on the application of chemical ionization mass spectrometry to a series of structurally similar dicarbamates (2).

Several electron-impact mass spectral studies of monocarbamates have appeared (3–7). It has been pointed out that, in addition to having relatively predictable spectra, the volatility of carbamates, the small amounts of sample required for analysis, and the wealth of structural information contained in the spectra make mass spectrometry an excellent tool for structural elucidation (3). In addition, it was noted that relatively obvious molecular ions were obtained and that no recombination peaks were detected (3).

When a series of 10 dicarbamates having the general structure, I (Scheme I), were examined by high-resolution electron-impact mass spectrometry, spectra rich in readily interpretable fragment ions were obtained but molecular ions were conspicuously absent. Instead, peaks of less than 1% relative abundance were observed at *m/e* (M + 1) in all instances. Due to the difficulty in obtaining high-resolution data on the very weak M + 1 ions along with the desirability of directly determining the molecular formula[1], an investigation of the chemical ionization mass spectrometry was undertaken.

In an effort to minimize fragmentation, the combination of a low inlet temperature of 100°[2] and a mild chemical ionization reagent, isobutane, was used. In all chemical ionization (C.I.) spectra, the MH^+ ion was the most intense ion, with the only significant fragment ion arising from the direct loss of carbamic acid from the MH^+ ion[3]. Fast-scan high-resolution data were readily obtained.

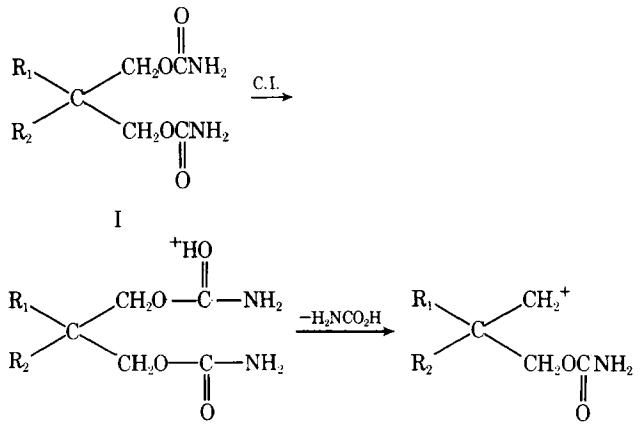
A comparison of the spectra obtained in the chemical ionization and electron-impact modes for Ia [R_1 = CH_3, R_2 = $CH_2CH_2CH_3$ (meprobamate)] is given in Fig. 1 and is typical of all dicarbamates investigated.

[1] With only low-resolution data, the recombination M + 1 ion could be misinterpreted as the molecular ion.
[2] Dicarbamates are susceptible to thermal decomposition at higher inlet temperatures.
[3] The direct loss was established from metastable ions.

Table I—High-Resolution Chemical Ionization[a,b] Mass Spectral Data for MH^+ Ions

R_1	R_2	Elemental Composition	Theoretical	Found	Relative Intensity: Chemical Ionization	Relative Intensity: Electron Impact[c]
CH_3	$CH_3CH_2CH_2$	$C_9H_{19}N_2O_4$	219.1344	219.1361	100%	0%
CH_3	$ClCH_2CH_2CH_2$	$C_9H_{18}ClN_2O_4$	253.0954	253.0925	100%	0%
$CH_3CH_2CH_2$	$ClCH_2$	$C_9H_{18}ClN_2O_4$	253.0954	253.0970	100%	0%
CH_3CH_2	$ClCH_2$	$C_8H_{16}ClN_2O_4$	239.0815	239.0798	100%	0%
$CH_2=CHCH_2$	H	$C_8H_{15}N_2O_4$	203.0998	203.1031	100%	0%
$CH_3CH_2OCH_2$	$CH_2=CHCH_2$	$C_{11}H_{21}N_2O_5$	261.1445	261.1440	100%	0%
$CH_3OCH_2CH_2$	CH_3	$C_9H_{19}N_2O_5$	235.1293	235.1276	100%	0%
CH_3OCH_2	CH_3OCH_2	$C_9H_{19}N_2O_6$	251.1238	251.1229	100%	0%
$CH_3CH_2OCH_2$	CH_3	$C_9H_{19}N_2O_5$	235.1293	235.1301	100%	0%
$CH_3OCH(CH_3)$	CH_3	$C_9H_{19}N_2O_5$	235.1293	235.1287	100%	0%

[a] 500 ev. [b] Perfluorokerosene-H was used as an internal standard for exact mass measurements. [c] Molecular ion, M^+.



I

Scheme I

High-resolution data were obtained in both modes, so the combined use of the two modes provides a very potent method for structural elucidation of dicarbamates. The electron-impact spectra are rich in readily interpretable fragment ions from which much detailed structural information can be derived, while the high-resolution chemical ionization mode allows an unequivocal determination of the molecular formula. In Table I, the exact measured mass of all MH^+ ions is listed and compared with the theoretical mass.

Although the application of field desportion mass spectrometry to dicarbamates allows the determination of an unequivocal molecular weight (1), chemical ionization mass spectrometry offers a distinct advantage in the precise determination of molecular formula and ease of application[4].

(1) D. J. Rouse and D. A. Brent, Abstracts, American Society for Mass Spectrometry, 22nd Annual Conference on Mass Spectrometry and Allied Topics, Philadelphia, Pa., May 1974.

(2) Presented in part: G. L. Nelson and C. F. Kuhlman, Abstracts, Seventh Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb. 1972.

(3) C. P. Lewis, *Anal. Chem.*, **36**, 1582(1964).

(4) *Ibid.*, **36**, 176(1964).

(5) W. E. Pereira, *Org. Mass Spectrom.*, **5**, 157(1971).

(6) J. B. Thompson, P. Brown, and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 4049(1966).

(7) W. R. Benson and J. N. Damico, *J. Ass. Offic. Anal. Chem.*, **51**, 347(1968).

[4] High-resolution data were not obtained by Rouse and Brent (1). At present, considerable effort and time are required to obtain field desorption mass spectra.

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Powder Mixing by Frictional Pressure: Specific Example of Use of Ordered Mixing

Keyphrases □ Powder mixing—frictional pressure, example of use of ordered mixing □ Mixing, powder—frictional pressure, example of use of ordered mixing □ Dissolution rate—effect of ordered mixing

To the Editor:

A recent study (1) reported the effect of different methods of preparing triturations of either digoxin or hydrocortisone with lactose on the dissolution rates of these drugs. It was demonstrated that frictionally deposited drug, *i.e.*, where the drugs were spread over the surface of the diluent by frictional pressure in a mortar and pestle, gave the highest dissolution rate. The other trituration methods investigated were simple blending by bottle tumbling, simple blending with ground drug, and solvent deposition.