work is analogous to the work of Piccolo and Tawashi (5), who found that at low concentrations of some dyes, inhibition occurred to single crystal dissolution of a number of drugs.

SUMMARY AND CONCLUSIONS

In the presence of benzoic acid, both the dissolution rate and equilibrium solubility of sulfamethazine were suppressed. The phenomenon was attributed to the adsorption of benzoic acid on the sulfonamide particles. The inhibition of sulfamethazine dissolution was only shown when the sulfonamide particles were saturated by benzoic acid. Due to the protective effect of polyvinylpyrrolidone, as low as 5 mg.% of the polymer prevented the adsorption of benzoic acid and, consequently, its suppressive effect on sulfamethazine dissolution.

REFERENCES

(1) H. S. Bean and G. Dempsey, *J. Pharm. Pharmacol., Suppl.*, **19**, 197S(1967).

(2) R. B. Tinker and A. J. McBay, *J. Amer. Pharm. Ass., Sci. Ed.*, **43**, 315(1954).

(3) A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *J. Pharm. Sci.*, **59**, 633(1970).

(4) I. Moriguchi and N. Kaneniwa, *Chem. Pharm. Bull.*, **5**, 961 (1969).

(5) J. Piccolo and R. Tawashi, *J. Pharm. Sci.*, **60**, 1818(1971).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 12, 1972, from the *Department of Pharmaceutics, Faculty of Pharmacy, The University of Ife, Ibadan Branch, Ibadan, Nigeria.*

Accepted for publication September 21, 1972.

The authors thank Professor I. Ello for his valuable discussions.

▲ To whom inquiries should be directed. Present address: Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt.

Identification of a Rearranged Degradation Product from Carbamazepine-10,11-epoxide

K. M. BAKER, A. FRIGERIO▲, P. L. MORSELLI, and G. PIFFERI*

Abstract □ Carbamazepine-10,11-epoxide, a metabolite of carbamazepine found in human urine, undergoes a rearrangement and degradation to 9-acridinecarboxaldehyde during GLC.

Keyphrases □ Carbamazepine-10,11-epoxide—identification of GLC degradation product as 9-acridinecarboxaldehyde □ 9-Acridinecarboxaldehyde—identified as carbamazepine-10,11-epoxide GLC rearrangement product, synthesis, physical-chemical properties

In previous papers (1, 2), it was reported that carbamazepine-10,11-epoxide was found in human urine as a metabolite of carbamazepine. The epoxide was isolated and identified; however, at the same time it was mentioned that subjection of this compound to GLC resulted in a degradation to another material. This paper reports the isolation, identification, and alternative preparation of the degradation product.

EXPERIMENTAL[1]

Carbamazepine-10,11-epoxide—The synthesis described previously (1) was altered to give better, consistent yields for pharmaceutical requirements.

A solution of carbamazepine (50 g., 0.21 mole) and *m*-chloroperbenzoic acid (47.4 g., 0.27 mole) in 2 l. of ethylene chloride was heated under reflux with irradiation by a sun lamp (200 w.) for 3 hr. After cooling and washing with dilute aqueous sodium sulfite solution and with 5% aqueous sodium bicarbonate, the organic phase was dried and evaporated. The residue was taken up in boiling benzene and cooled, and the precipitate collected. The crude product was recrystallized from ethanol to give carbamazepine-10,11-epoxide as pale-yellow needles (16 g., 30%), m.p. 205–207° dec. [lit. (1) m.p. 190–195°]; IR (mineral oil mull): 3500–3100 (NH_2), 1675 (C=O, urea), 865 (C—O, epoxide), 752 (CH out-of-plane bending) $cm.^{-1}$; NMR (acetone–dimethyl sulfoxide, 2:1): 4.38 (s, 2H, —HCO— epoxide), 5.34 (broad s, 2H, $CONH_2$), and 7.7–7.1 (m, 8H, ArH).

9-Methylacridine—Diphenylamine, acetic anhydride, and anhydrous zinc chloride were heated together at 190° for 5 hr. according to Porai-Koshits and Khaskhazov (3). Separation and crystallization from hexane gave pure 9-methylacridine, m.p. 116–118° [lit. (4) m.p. 117–118°]; IR (mineral oil mull): 1150 (CH in-plane bending) and 755 (CH out-of-plane bending) $cm.^{-1}$.

9-Acridinecarboxaldehyde—This was prepared according to Tsuge *et al.* (5). 9-Methylacridine (0.40 g., 2.07 mmoles), *p*-nitroso-*N*,*N*-diethylaniline (0.55 g., 3.72 mmoles), and concentrated hydrochloric acid (0.1 ml.) were heated together under reflux for 2 hr. The resulting red-brown material, m.p. 235–237° dec., was hydrolyzed with 10% aqueous hydrochloric acid to yield 9-acridinecarboxaldehyde as yellow needles (0.1 g., 21%), m.p. 145–146° (ethanol), [lit. (6) m.p. 147°]; IR (mineral oil mull): 1680 (C=O, aldehyde), 1150 and 1040 (CH in-plane bending), and 870 and 745 (CH out-of-plane bending) $cm.^{-1}$; NMR ($CDCl_3$): 8.8–7.2 (m, 8H, ArH) and 11.38 (s, 1H, CHO).

RESULTS AND DISCUSSION

A clean, single-component gas chromatogram resulted from an ethanol solution of carbamazepine-10,11-epoxide. The mass spectrum (Fig. 1) obtained by hookup to the GLC showed a molecular ion at *m/e* 207 (100%) and a fragmentation to give *m/e* 179 (90%) corresponding to a loss of 28 atomic mass units (CO). This transition was confirmed by the presence of a metastable ion. Also present were ions at *m/e* 152 (15%) and 151 (17%) corresponding

[1] Melting points were determined with a Büchi capillary apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 157 spectrophotometer as mineral oil mulls or as liquid films. NMR spectra were determined with a Varian A60 or XL100/15 spectrometer using tetramethylsilane as an internal reference. Mass spectra were obtained on an LKB 9000 instrument operating under the previously described conditions (1). GLC was carried out on a Carlo Erba Fractovap G1 chromatograph using a 2-m. OV-17 column operating at 220° and an injection port temperature of 250°.

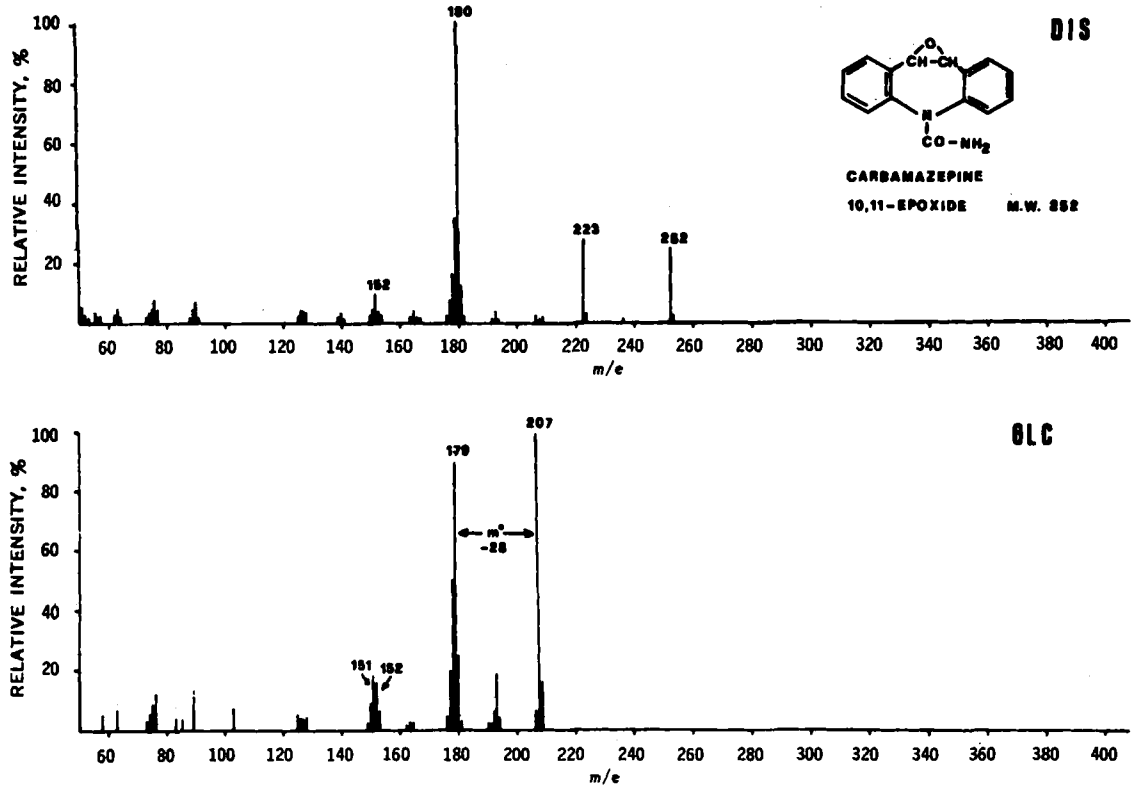


Figure 1—*Mass spectra of carbamazepine-10,11-epoxide. Key: upper panel, direct in the system (DIS); and lower panel, GLC.*

to dibenzocyclobutane (loss of HCN from *m/e* 179, the acridinium ion).

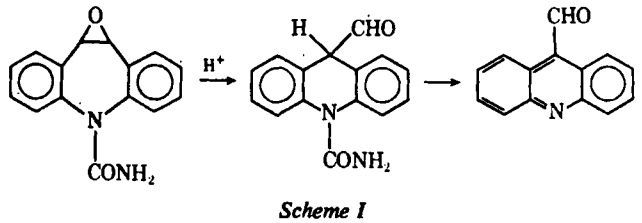
9-Acridinecarboxaldehyde was proposed for this material. For confirmation, the compound was isolated from the GLC column *via* a splitter. Yellow needles, m.p. 138–139°, were obtained [lit. (6) m.p. 147°].

The authentic material prepared was yellow needles, m.p. 145–146° (see *Experimental*). Comparison with the rearranged material proved that they were identical. Both showed the same retention time on GLC, the same UV maximum (264 nm. in methanol), and identical mass spectra.

A mechanism rationalizing the rearrangement is shown in Scheme I. The process is probably catalyzed by the slightly acidic column at high temperature, and then the intermediate imide decomposes to give the much more stable, completely aromatic system, 9-acridinecarboxaldehyde.

It is possible that the rearrangement could take place in a biological system and, therefore, 9-acridinecarboxaldehyde would be found as a metabolite of carbamazepine. Steps are in progress at the moment to determine if this is indeed so.

The result indicates the care that must be taken in identifying drug metabolites. In many cases the quantities available for identification may be very small and GLC–mass spectrometry must be used, but alternative methods should be employed in conjunction wherever possible to check that no rearrangements or degradations take place during one of the physical measurements.



Scheme I

REFERENCES

(1) A. Frigerio, R. Fanelli, P. Biandrate, G. Passerini, P. L. Morselli, and S. Garattini, *J. Pharm. Sci.*, **61**, 1144(1972).

(2) P. L. Morselli, P. Biandrate, A. Frigerio, M. Gerna, and G. Tognoni, "Proceedings Workshop on the Determination of Antiepileptic Drugs in Body Fluids," Noordwijkerhout, The Netherlands, 1972.

(3) A. E. Porai-Koshits and A. A. Khaskhazov, *Bull. Acad. Sci. USSR*, **1944**, 243; through *Chem. Abstr.*, **39**, 16318(1945).

(4) W. Schindler and H. Blattner, *Helv. Chim. Acta*, **44**, 753 (1961).

(5) O. Tsuge, M. Nishinohara, and M. Tashiro, *Bull. Chem. Soc. Jap.*, **36**, 1477(1963).

(6) O. Tsuge, M. Nishinohara, and K. Sadano, *ibid.*, **38**, 2037 (1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 26, 1972, from *Istituto di Ricerche Farmacologiche "Mario Negri," via Eritrea 62, 20157 Milan, Italy.*

Accepted for publication September 21, 1972.

The authors thank Dr. M. Pinza and Mr. F. Parravicini for their assistance in the experimental work. This work was supported by grants from the Wellcome Foundation to K. M. Baker and from the National Institutes of Health, Grant 1PO1-GMI8376 01 PTR.

• Present address: ISF–Italseber S.p.A.–Research Laboratories, 20090 Trezzano S/N, via Leonardo da Vinci 1, Milan, Italy.

▲ To whom Inquiries should be directed.