Journal of Chromatography, 150 (1978) 257–258

CHROM. 10,465

Note

Limitations of pentafluorobenzyl chloroformate as a derivatizing reagent for the gas–liquid chromatographic analysis of tertiary amines

LARRY A. STERNSON*

Department of Pharmaceutical Chemistry, McCollum Laboratories, University of Kansas, Lawrence, Kan. 66044 (U.S.A.)

and

AARON D. COOPER

Analytical Chemistry Department, Vick Divisions Research & Development, 1 Bradford Road, Mount Vernon, N.Y. 10553 (U.S.A.)

(Received August 2nd, 1977)

The conversion of tertiary methylamines to pentafluorobenzyl carbamates by their reaction with pentafluorobenzyl chloroformate has proven to be a useful derivatization process for low-level gas chromatographic analysis of these amines[1–4]. Picogram levels of the amines can be quantitated by electron capture detection of the acylated substrate. The method has been applied to the analysis of medicinal agents containing a tertiary methylamine ($R_2N–CH_3$) moiety, such as the tricyclic antidepressants imipramine and trimipramine[4] and the antihistaminics, diphenhydramine and Recipavrin®[2]. Most antihistamines are either ethanolamine derivatives, ethylenediamine derivatives or propylamine derivatives in which the terminal N atom is a tertiary dimethylamine function and should thus be amenable to low-level analysis by this method.

In the process of adapting the derivatization procedure to structurally similar compounds, we found that the reaction fails with dimethylaminoalkanes which also contain a pyridine nucleus. Many of the effective antihistaminics incorporate both of these structural features in the molecule and, therefore, failure of the reaction to proceed with such compounds imposes a significant limitation on the method.

EXPERIMENTAL

The derivatization reaction was carried out as described by Hartvig *et al.*[4] and the reaction mixture chromatographed on a Hewlett-Packard 5710 gas chromatograph. The glass column (6 ft. × 1/4 in.) was packed with 10% OV-17 on Gas-Chrom Q (80–100 mesh). Nitrogen, used as carrier gas, flowed at a rate of 40 ml/min. Mixtures were separated with the aid of a temperature program: 208° for 3 min, then heated at 10°/min to 260° where the temperature was maintained for 7 min. The injector and detector temperatures were 240° and 280°, respectively.

* To whom correspondence should be addressed.

RESULTS AND DISCUSSION

Diphenhydramine, dimenhydrinate and bromdiphenhydramine contain tertiary dimethylamine groupings but no pyridine substituent. These compounds reacted with the chloroformate reagent to yield an electron capture active derivative which was shown by gas–liquid chromatography–mass spectrometry (GLC–MS) to correspond to the corresponding carbamate. Reaction was almost quantitative and was complete within 50 min.

Chlorpheniramine contains a tertiary dimethylaminoalkane moiety similar to that present in the three compounds cited above. However, a phenyl group in a part of the molecule remote from the amine function has been replaced by a pyridine substituent. When subjected to the conditions of the derivatization reaction, the parent compound rapidly disappeared as a function of time, as shown by GLC (with flame ionization detection of the column effluent). However, only a small fraction ($<10\%$) of the parent compound was converted to the carbamate and the reaction was not reproducible. Both GLC and thin-layer chromatographic analysis of the reaction mixture indicated that the reaction proceeds with the formation of a large number of products. Similar results were obtained when doxylamine, carbinoxamine, brompheniramine or pyrilamine were subjected to the carbamylation reaction. All of these compounds have both an α-pyridyl substituent and dimethylaminoalkyl group, and fail to yield analytically useful products after reaction with the chloroformate reagent. Reaction of pyridine or α-picoline with pentafluorobenzyl chloroformate yielded a brown tarry mass. Monitoring this reaction by proton NMR shows perturbation of the pyridine absorption bands. These results suggest that the pyridine ring may also react with the reagent in a ring opening reaction, making the derivatization procedure not applicable to analysis of tertiary methylamines which also contain a pyridine nucleus in the structure.

REFERENCES

1 J. Vessman, P. Hartvig and M. Molander, *Anal. Lett.*, 6 (1973) 699.
2 P. Hartvig and J. Vessman, *Anal. Lett.*, 7 (1974) 223.
3 P. Hartvig and J. Vessman, *Acta Pharm. Suecica*, 11 (1974) 115.
4 P. Hartvig, W. Handl, J. Vessman and C. M. Svahn, *Anal. Chem.*, 48 (1976) 390.