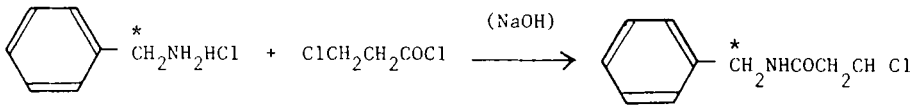
FACILE SYNTHESIS OF N-(Methylene-^{14}C)BENZYL-3-CHLOROPROPIONAMIDE (BECLAMIDE)

N-Benzyl-3-chloropropionamide (beclamide) is an anticonvulsant (1) used in the treatment of grand mal and psychomotor epilepsy (2,3). It is also employed in the treatment of behavioural disorders found in association with epilepsy or latent epilepsy (4). Although the drug has been in use for at least 20 years, there have been no reports on its metabolism. This may, in part, be related to the lack of sensitive and specific assay methods available for this compound. More recently, a gas-liquid chromatographic method has been developed for the determination of the unchanged drug in plasma and urine (5) but application of this procedure has not provided adequate information on the metabolic handling of beclamide in animals and man. The compound labelled with carbon-14 was prepared in order to facilitate a detailed study of its absorption, elimination and metabolism.

N-(Methylene-^{14}C)Benzyl-3-chloropropionamide (beclamide) (III) is readily obtained on the microscale by condensing (I) with 3-chloropropionyl chloride (II) using a slightly modified procedure described by Pichat and Audinot (6). This synthesis has the obvious advantage of incorporating the ^{14}C in the final step and at a position in the molecule that is likely to be relatively metabolically stable. As judged by the radiochromatographic behaviour on TLC, (I) did not undergo spontaneous decomposition when kept under conditions approximating to physiological temperature and pH.



(I) (II) (III)

+ (NaCl + H_2O)

*denotes position of ^{14}C.

0362-4803/79/0216-0369$01.00

Received May 4, 1978
Revised July 3, 1978

EXPERIMENTAL

(Methylene-^{14}C)Benzylamine hydrochloride (I) was purchased from ICN, Isotope & Nuclear Division, Irvine, California. Its chemical purity was checked by electrophoresis in formic acid/acetic acid/water 15:46:240 (>99%). The specific activity was 4.0mCi/mmol measured by beta liquid scintillation using a Tracerlab Corumatic-200 instrument.

3-Chloropropionyl chloride (II) was purchased from Koch-Light Laboratories Ltd., Colnbrook, Bucks, and was used as supplied.

N-(Methylene-^{14}C)Benzyl-3-chloropropionamide (beclamide) (III)

(Methylene-^{14}C)Benzylamine hydrochloride (53.85mg), dissolved in distilled water (1.5ml), was mixed with 1.0M sodium hydroxide (0.415 ml), the mixture being cooled in an ice bath. To this solution, 3-chloropropionyl chloride (97.8mg) and sodium hydroxide (30.8mg dissolved in water 0.8ml) were added dropwise and alternately during 1.5hr. Vigorous mixing was maintained throughout this period by the use of a vibromixer and the mixing continued for a further 0.5hr on completion of the addition. The precipitate formed was filtered off, dried at 50°C, and was then recrystallized from aqueous ethanol, filtered and vacuum dried ($CaCl_2$) (41mg, 55.4% yield). This material was mixed with pure non-labelled beclamide (159mg) and the mixture recrystallized twice from 40% (v/v) ethanol in water to yield the crystalline labelled material (180mg, 90% yield) m.pt. 92-94°C (mixed m.pt. with authentic beclamide 91.5-93.5°C). The radioactivity in this sample co-chromatographed with authentic non-labelled beclamide on Merck silica gel 60 F254 thin layer plates (0.25mm thick) in four solvent systems (R_f values of beclamide:- 0.61 in chloroform: ethanol: acetic acid, 95/5/0.5, v/v; 0.66 in benzene: 1,4-dioxan: formic acid, 75/20/5, v/v; 0.70 in chloroform: acetone, 75/25, v/v; 0.83 in diethylether: methanol: formic acid: water, 95/1/3.6/0.4, v/v). In each case, only one radioactive spot was detectable by scanning with a Tracerlab 4π radiochromatogram scanner or by autoradiography using Kodirex

X-ray film. The non-labelled beclamide was located either as a quenching spot under light at 254nm or as a blue-coloured spot after spraying the plates with a solution of ammonium thiocyanate (3g) and cobaltous chloride (1g) in distilled water (20ml). These results were taken to indicate a purity of the final prepared product of >99%. The specific activity, determined against a standard (^{14}C) hexadecane sample, was 4.2μCi/mg (= 50.7% recovery of radioactivity), a value suitable for the planned biological investigations. The (^{14}C) beclamide was dissolved in 0.1M phosphate buffer pH 7.4 to give a solution of 30μg/ml which was then placed in an incubator at 37°C. Samples of the solution were taken at 0,1,4,12 and 24 hr for thin layer chromatography in the above four solvent systems. Autoradiography of the chromatograms revealed the presence, in all the samples, of a single radioactive spot with a mobility identical to that of beclamide. This demonstrates that the labelled material does not undergo any detectable decomposition under conditions of physiological temperature and pH.

ACKNOWLEDGMENT

We wish to thank Rona Laboratories Ltd., Hitchin, Herts., for purchasing the (^{14}C) benzylamine hydrochloride used and for a generous sample of pure beclamide. We also thank Mr. P. Martin for his technical assistance.

P.J. Nicholls and D.K. Luscombe

Welsh School of Pharmacy, UWIST, Cardiff CF1 3NU, U.K.

REFERENCES

1. Harned, B.K., Cunningham, R.W., Clark, M.C., Hine, C.H., Kane, M.M., Smith, F.H., Vessey, R.E., Yuda, N.N. and Zabransky, F.W. - J.Pharmac. exp. Ther., 107 : 403 (1953).

2. Wilson, J., Walton, J.N. and Newell, D.J. - Br. med. J., 1 : 1275 (1959).

3. Puech, J., Robin, Ch., Richet, L. and Tetart, A. - Presse Med., 70 : 1015 (1962).

4. Sharpe, D.S., Dutton, G. and Mirrey, J.R. - Br. med. J., 1 : 1044 (1959)

5. Jones, O.P., Leach, H., Luscombe, D.K. and Nicholls, P.J. - Br. J. clin. Pharmac., 2 : 364 (1975).

6. Pichat, L. and Audinot, M. - Bull. Soc. chim. (France), 1641 (1956).