SYNTHESIS OF 10-[^{3}H]-5H-DIBENZ[b,f]AZEPINE-5-CARBOXAMIDE ([^{3}H]-CARBAMAZEPINE)

D.E. BRUNDISH

Ciba-Geigy Pharmaceuticals Division,
Research Centre, Horsham,
West Sussex, RH12 4AB, England

SUMMARY

The title compound has been prepared from a bromo derivative at a specific activity of 27 Ci mmol^{-1} with radiochemical purity of 98.4% by a selective catalytic reduction with tritium gas. Bromine was replaced without reduction of the stilbene double bond using a poisoned, deactivated catalyst.

Key words: Carbamazepine, tritiation, selective reduction

INTRODUCTION

Carbamazepine, 5-H-dibenz[b,f]azepine-5-carboxamide (the active substance of Tegretol®, trade name of CIBA-GEIGY AG) has been used successfully in the treatment of epilepsy and trigeminal neuralgia since its introduction in the early 1960's, and has been recommended in the treatment of temporal lobe epilepsy and of secondary tonic-clonic seizures in children and adolescents (1).

Although several hundred papers have appeared related to the metabolic and pharmacokinetic behaviour of the drug (for a review, see reference 2), in some of which studies the ^{14}C-labelled molecule was used, it has not been possible to date to study the interaction of the drug at the level of the receptor. To this end, carbamazepine labelled to a high specific activity with tritium was required.

0362-4803/85/010037-05$01.00

Received June 11, 1984
Revised July 19, 1984

A readily available potential substrate, which would avoid the necessity to consider either a 'hot' synthesis or the generation of a suitably protected substrate for labelling, was identified as the 10-bromo analogue (3). It was stated recently (4) in a publication on the exchange labelling of tricyclic antidepressants with tritium, that during exchange it was not possible to avoid catalytic reduction of the double bond in a stilbene-like structure, thus necessitating 'hot' synthesis as their only available approach to these compounds. A literature report (5) of a successful and rapid selective debromination of a bromo-olefin to an olefin for an angelic acid derivative suggested that carbamazepine might nevertheless be preparable from its 10-bromo analogue.

RESULTS AND DISCUSSION

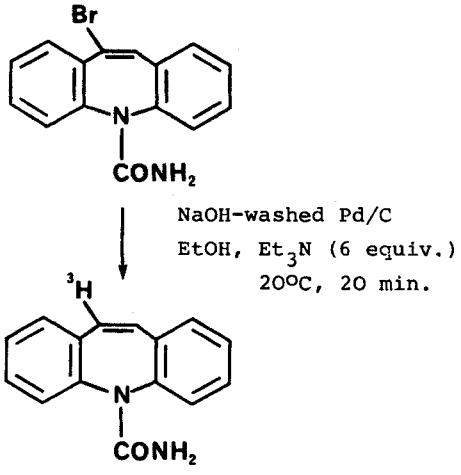
Alkali-washed palladium on charcoal catalyst was prepared as described by Kupchan and Afonso (5). Using this deactivated catalyst in the presence of a large excess of triethylamine as poison under the exact conditions of stoichiometry used for the angelic acid esters (5), 10-bromo carbamazepine was rapidly reduced to carbamazepine by hydrogen. After 15 minutes hydrogenation, no bromo compound remained and the extent of reduction of the 10-11 double bond was estimated by high pressure liquid chromatographic (h.p.l.c.) analysis as less than 6%. If triethylamine was omitted from the reduction mixture, the proportion of 10,11-dihydrocarbamazepine generated in this time rose to 30%, whereas use of unwashed catalyst in the presence of excess of triethylamine resulted in multiple reduction products of which the desired carbamazepine was a minor component.

Repetition of the successful reduction using tritium gas proceeded without additional complication. The reduction product was chromatographed on a column of ODS-silica which allowed isolation of the product in good radiochemical purity at high specific radioactivity. The UV spectrum of the product corresponded to that of the reference material and was not distinguishable from it in four thin layer chromatography (t.l.c.) systems or by h.p.l.c.

Thus, using specialised catalysts it can be possible to perform highly selective reductions in the presence of other reducible functional groups. Addition of base as catalyst poison in this instance further increases the selectivity, although further investigation would be needed before it could be clear whether this present observation is of a general nature.

SCHEME

Synthesis of [^{3}H]-Carbamazepine



Yield: 52%
(26.7 Ci mmol^{-1})

EXPERIMENTAL

10-Bromo-5H-dibenz[b,f] azepine-5-carboxamide (5.4 mg, 17 µmoles) was dissolved in ethanol (0.5 ml) containing triethylamine (15 µl, 108 µmoles) and the mixture was stirred under $^3H_2$ gas (3.2 ml, 8 Ci) in the presence of NaOH-washed 10% Pd/C catalyst (0.5 mg) (5) for 20 minutes at room temperature. The catalyst was removed by filtration through a pad of cellulose powder and the filtrate was evaporated to dryness. The residue was dissolved in methanol (0.28 ml), water (0.22 ml) was added and the solution was applied using a Rheodyne injection valve to a column (50 x 0.7 cm) of Nucleosil 10C$_{18}$ ODS-silica and eluted at a flow rate of 4.0 ml min^{-1} with methanol:water:acetic

acid (500:500:1, by volume). The eluate was examined at 254 nm (Cecil CE212) and fractions (1 minute) were collected automatically. Portions (20 µl) of relevant fractions were examined by analytical h.p.l.c. using the conditions described for preparative h.p.l.c. to determine the elution position of the 10,11-dihydro contaminant, which was present in fraction 21. Fractions 18-20 were combined and evaporated to dryness and the residue was dissolved in 50% aqueous ethanol (40 ml). For quantitation at 284 nm, a portion (0.5 ml) of this solution was diluted 20-fold. For determination of tritium a portion (100 µl) of the dilute solution was diluted to 25 ml and portions (10 µl) were counted in BBOT scintillant using [^{3}H]-hexadecane as internal standard.

The product (9.92 µmoles, 58%) had a specific activity of 26.7 $\pm$ 0.6 Ci mmol^{-1}. The radiochemical purity of the preparation was estimated as 98.4 $\pm$ 1.0% after t.l.c. on thin layers of silica gel which were examined after development with a Panax E.0111/XPD-05 radiochromatogram scanner system. The results are given in the Table.

The compound was stored in solution in 50% aqueous ethanol at a concentration of 6.6 mCi ml^{-1} at the temperature of liquid nitrogen (-196°C).

TABLE

Radiochemical purity of [^{3}H]-carbamazepine as judged by t.l.c. Details are given in the text.

Solvent System	% Radiochemical Purity	
	Without Carrier	With Carrier (1 mg ml^{-1})
$CHCl_3$:Me_2CO (85:15)	96.4 $\pm$ 0.1	99.3 $\pm$ 0.1
EtOAc:Me_2CO (50:50)	98.0 $\pm$ 0.2	97.9 $\pm$ 0.3
EtOAc:C_6H_6:CH_3OH (5:4:1)	98.1 $\pm$ 0.2	99.3 $\pm$ 0.1
$CHCl_3$:i-PrOH (9:1)	98.2 $\pm$ 0.1	97.2 $\pm$ 0.2

ACKNOWLEDGEMENT

The author is indebted to Dr. H. Allgeier, CIBA-GEIGY AG, Basle, Switzerland for the supply of 10-bromo-5H-dibenz[b,f] azepine-5-carboxamide, 5H-dibenz[b,f]azepine-5-carboxamide (carbamazepine) and 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide.

REFERENCES

1. Davidson D.L.W. - Brit. Med. J. 286: 2043 (1983)

2. Faigle J.W., Brechbühler S., Feldmann K.F. and Richter W.J. - Epileptic Seizures – Behaviour - Pain, Birkmayer, W. (ed.), H. Huber, publ., Bern/Stuttgart/Vienna, 127-140 (1976)

3. Allgeier H. and Schmid E. - Ger. Offen. 2,542,335. Chem. Abs. 85: 32888s (1976)

4. Buchman O., Azran J. and Shimoni M. - J. Labelled Compounds Radiopharm. 20: 887 (1983)

5. Kupchan S.M. and Afonso A. - J. Org. Chem. 25: 2217 (1960)