A CONVENIENT PREPARATION OF ^{14}C-LABELLED 5H-2,3-BENZODIAZEPINES

G. Zólyomi, T. Láng, J. Körösi and T. Hámori

Institute for Drug Research,
H-1325 Budapest, P.O.B. 82, Hungary

SUMMARY

A convenient method for preparing 5H-2,3-benzodiazepines labelled with ^{14}C was developed in which the corresponding phenylacetone derivatives were acylated by labelled aromatic carboxylic acid. In spite of the low yield, this method is advantageous in comparison the known ones because of the obtainable specific activity, which is a consequence of the few stages and simplicity of the synthesis.

Key words: Tofizopam, 5H-2,3-benzodiazepine, Isobenzopyrylium salts, Carbon-14, Acylation

INTRODUCTION

In 1974 we reported (1) the labelling of Tofizopam [1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (1a)] with ^{14}C for pharmacokinetic and metabolism studies. The label was located either in the methoxy groups or in the ethyl substituent of the benzodiazepine ring. In the first case the labelled sites of the molecule were affected by metabolism (2), in the second case a fairly complicated synthesis, involving too many steps, enabled us to obtain a limited specific activity.

DISCUSSION

Recently ^{13}C-labelling in the C-1 position of the benzodiazepine skeleton for spectroscopic investigations was required.

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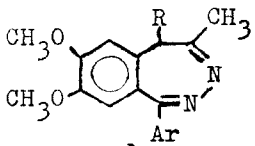
For this purpose a still more circuitous synthesis route was elaborated (3), which started with the Friedel-Crafts acylation of 4-propylveratrole by ^{13}C-veratric acid. Studying this type of the reactions, we found out that Dorofeenko and coworkers (4) published the acylation of 3,4-dimethoxyphenylacetone (2b) in polyphosphoric acid (PPA) resulting in isobenzopyrylium salts*, which are the precursors of 5H-2,3-benzodiazepines, with reasonable yield. This finding encouraged us to make an attempt for the acylation of α-ethyl-α-(3,4-dimethoxyphenyl)-acetone (2a) by veratric acid in the same way. Since ^{14}C-veratric acid is readily producible (6), we should have an excellent method for preparation of labelled Tofizopam. Moreover, since an intense research work is in progress on this field in our institute, a general possibility for labelling further derivatives is of interest to us.



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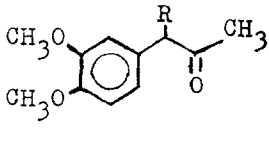

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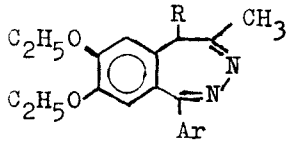

3

a, R = ethyl, Ar = 3,4-dimethoxyphenyl
b, R = H Ar = 3,4-dimethoxyphenyl
c, R = H Ar = 3-chlorophenyl

Essentially we succeeded in performing this reaction, there were, however, some problems to overcome. The mixture of PPA and phenylacetone derivative is a thick honey-like material, which is hardly miscible with veratric acid. An attempt to use the low

* An attempt at the Friedel-Crafts acylation of phenylacetone derivatives in order to obtain isobenzopyrylium salts was first made by Balaban et al. (5) in 1961.

melting ethyl ester instead of the crystalline acid was unsuccessful. We could achive a sufficient stirring by attaching the reaction vessel, which contained the reactants and was immersed in an oil bath, to a rotatory evaporator. When this method was used for labelling other 5H-2,3-benzodiazepine derivatives, e.g. 1-(3--chlorophenyl)-4-methyl-7,8-diethoxy-5H-2,3-benzodiazepine (GYKI-51 666; 3c) (7), another advantage of this set-up came out, because 3-chlorobenzoic acid sublimed from the reaction mixture, but the rotation caused the crystals to fall back. In practice the importance of this device is considerable. Because of the sublimation of the acid, the yield may be very poor; therefore, on acylating 2b, where the methoxy groups are less affected by the Friedel--Crafts catalyst, 3-chlorobenzoyl chloride in the presence of $AlCl_3$ was used for labelling 1-(3-chlorophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine (GYKI-51 189; 1c) (8).

In the preparation of 1a about 5-10% of an extraneous product with lower R_f value was detected by TLC. In a "cold" run it was isolated by chromatography, and identified as 1b, (M.p. 158-160°C, lit. (9) 158-159°C, mixed m.p. 158-160°C) so we supposed that the starting material (2a), which was prepared by the method of Müller and coworkers (10), was not pure enough. Starting from 2a which had fractionated twice, still 3-5% of 1b was detectable in the product. This result can be explained partly by the fact that the last trace of 2b is inseparable by distillation, partly by the relatively higher yield of the acylation of 2b, in consequence of which the amount of 1b increased significantly in the product, and it had to be chromatographed to obtain radiochemically pure 1a.

In the experimental part three variations of the preparation of different ^{14}C-labelled 5H-2,3-benzodiazepines are described. The yield after all was rather low (in case of 1a, 1c and 3c it was 18.5, 18.4 and 16.5% based on $Ba^{14}CO_3$ respectively) but the accomplishment of labelling is much simpler than that of known methods

(1,3) and the specific activity is limited by that of the starting $BaCO_3$ only.

EXPERIMENTAL

The melting points were determined on a Boëtius hot stage and are uncorrected. TLC was carried out on silica gel HF_{254} (Merck) using benzene-cyclohexane-ethanol = 5:4:1 solvent system, and a Berthold TLC scanner Model LB-2723 was used for evaluation. Radioactivity was measured by liquid scintillation technique using a Packard TRI-CARB Model 2660 spectrometer. All evaporations were carried out under reduced pressure.

1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-(1-^{14}C)-2,3-benzodiazepine (Tofizopam-^{14}C; 1a-^{14}C)

Carboxy-^{14}C-veratric acid (586.6 mg, 3.22 mmol; 2.38 GBq) prepared from 4 mmoles of $Ba^{14}CO_3$ (2.96 GBq) in a yield of 80.5% as described (6), compound 2a (1080 mg, 4.86 mmol) and PPA (6.5 ml) were placed in a round-bottom flask attached to a rotatory evaporator, then stirred and heated at 100°C for 90 min. The heating was discontinued and a mixture of 70% perchloric acid (0.65 ml) and acetic acid (1.0 ml) was added. After being stirred additionally for 30 min., the cooled mixture was diluted with water (20 ml) and left to stand overnight. Next day the liquid was drained off, and the solid was crystallized from a mixture of ether-ethanol = 2:1 (20 ml), filtered and washed with ether. The yellow crystals of the isobenzopyrylium perchlorate were suspended in hot methanol (10 ml), hydrazine hydrate (0.4 ml) was added, and the solution after refluxing for 10 min. was evaporated. To the residue water (10 ml) was added and on standing 1a-^{14}C was precipitated. It was filtered off, washed with water, dried, and chromatographed on silica gel using ethyl acetate-conc.NH_4OH = 200:1 solvent system. The fractions containing 1a were evaporated, and the residue was

heated in water (10 ml) for 40 min. After cooling the precipitated 1a-^{14}C was filtered off, washed with water and dried. Yield: 282.0 mg (0.74 mmol), 23.0%. M.p. 154-155°C. Activity: 0.55 GBq (0.74 GBq/mmol, 1.95 GBq/g). Radiochemical purity checked by TLC was higher than 99%.

1-(3-Chlorophenyl)-4-methyl-7,8-diethoxy-5H-(1-^{14}C)-2,3-benzodiazepine (GYKI-51 666-^{14}C; 3c-^{14}C)

Carboxy-^{14}C-3-chlorobenzoic acid (1311 mg, 8.32 mmol; 6.16 GBq) was prepared from 10 mmoles of $Ba^{14}CO_3$ (7.40 GBq) similarly to ^{14}C-labelled 4-chlorobenzoic acid (11). A mixture of this acid, 3,4-diethoxyphenylacetone (2220 mg, 10 mmol) and PPA (17 ml) was heated at 110°C for 30 min. as described above. Then it was cooled, diluted with water (100 ml) and extracted with chloroform (3x30 ml). The combined extract was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was treated with 700 mg of $NaHCO_3$ in water (30 ml) at 50°C, after cooling extracted again with chloroform (3x30 ml), and the combined extract was dried over anhydrous $MgSO_4$. (By acidifying the aqueous solution 3.9 mmoles, 2.88 GBq of carboxy-^{14}C-3-chlorobenzoic acid was recovered.) The oily product remained after evaporating the chloroform was dissolved in acetic acid (5 ml), and heated on a water bath with 70% perchloric acid (1.2 ml) for 5 min. The mixture was cooled, and crystallization from ethyl acetate yielded yellow crystals, which were filtered off and refluxed with hydrazine hydrate (0.8 ml) in 10 ml of 2-propanol. The clear solution was evaporated, the residue was mixed with water, heated on a water bath for 2 hours and after cooling the precipitated solid was filtered off. Recrystallization from 2-propanol (5 ml) gave 317.4 mg (0.89 mmol) of radiochemically pure 3c-^{14}C. M.p. 117-118°C. Activity: 0.65 GBq (0.73 GBq/mmol, 2.05 GBq/g). Yield: 10.5% based on 3-chlorobenzoic acid, conversion: 19.8%. Radiochemical yield: 16.5% based on $Ba^{14}CO_3$ consider-

ing the conversion.

1-(3-Chlorophenyl)-4-methyl-7,8-dimethoxy-5H-(1-^{14}C)-2,3-benzodiazepine (GYKI-51 189-^{14}C; 1c-^{14}C)

Carboxy-^{14}C-3-chlorobenzoic acid (633.4 mg, 4.05 mmol; 2.99 GBq) prepared from $Ba^{14}CO_3$ (5.0 mmol, 3.7 GBq) was refluxed with thionyl chloride (1 ml) for 2 hours, and evaporated. The residue was dissolved in nitrobenzene (2 ml) and to the cooled solution anhydrous aluminium chloride (1200 mg, 9.0 mmol) and 3,4-dimethoxyphenylacetone (796.0 mg, 4.1 mmol) were added successively. After 3 hours' stirring at 40°C, ethyl acetate (15 ml) was added to the mixture, followed by water (4 ml) and conc.HCl (0.2 ml), then it was heated on a water bath for 30 min. After cooling the organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. To the solution conc.H_2SO_4 (0.2 ml) was added. Yellow crystals were precipitated on standing overnight, which were filtered off, washed with ethyl acetate and suspended in 2-propanol (10 ml). To the hot suspension hydrazine hydrate (0.5 ml) was added, the clear solution obtained was evaporated and the residue was heated in 20 ml of water at 90°C for 2 hours. On cooling almost colourless crystals were precipitated, which were filtered off, dried and recrystallized from a mixture of benzene-cyclohexane-ethanol to give 302.5 mg (0.92 mmol) of radiochemically pure 1c-^{14}C. Yield: 22.7%. M.p. 167-168°C. Activity: 0.68 GBq (0.74 GBq/mmol, 2.26 GBq/g).

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