SYNTHESIS OF 1,3-DIHYDRO-1-METHYL-7-NITRO-5-PHENYL-2H-1,4-BENZODIAZEPIN-2-ONE-5-^{14}C (NIMETAZEPAM-5-^{14}C).

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SUMMARY

The synthesis from carbon-^{14}C dioxide of 1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one-5-^{14}C (I) for use in metabolic studies has been described. The synthesis was achieved by the sequence shown in figure 1 . The overall yield of labelled nimetazepam (I) was nearly 36%.

INTRODUCTION.

Nimetazepam (I), a new benzodiazepine derivative,[1] has anticonvulsant, muscle relaxant and taming properties qualitatively similar to those of diazepam and nitrazepam.[2] Preliminary studies on the metabolic fate in animals[3] were carried out with nimetazepam-^{14}C labelled at C-2 position of benzodiazepinone ring. Nimetazepam-2-^{14}C was synthesized[4] from bromoacetyl-1-^{14}C bromide according to the well known procedure.[5] In order to detail metabolic studies, especially on the moiety of benzophenone, a labelling at C-5 position was investigated.

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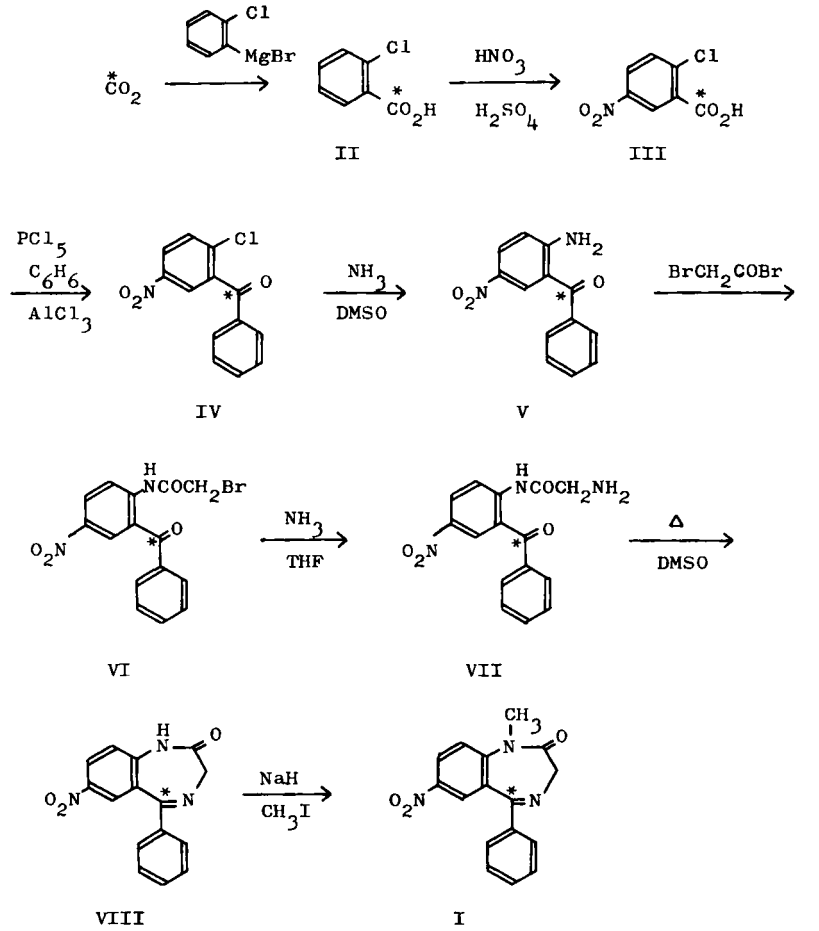

Fig. 1. Reaction Sequence of Synthesis of Nimetazepam-5-^{14}C

DISCUSSION.

The synthetic route used to prepare I is shown in Figure 1. Grignard reaction of carbon-^{14}C dioxide with o-chlorophenyl magnesium bromide yielded o-chlorobenzoic acid-(carboxyl-^{14}C) (II). This substance was treated with a mixture of conc. nitric acid and conc. sulfuric acid at room temperature to afford 2-chloro-5-nitrobenzoic acid-(carboxyl-^{14}C) (III). The structure of III, prepared previously by Blanksma[6], was confirmed by its nmr spectrum which showed a typical pattern of aromatic protons of 1,2,5-trisubstituted benzene. By modifying Middleton's method[7] the acid chloride of III, prepared with phosphorus pentachloride, was allowed to react with an excess of benzene using anhydrous aluminum chloride as a catalyst to give 2-chloro-5-nitrobenzophenone-(carbonyl-^{14}C) (IV) in a quantitative yield. The conversion of IV to 2-amino-5-nitrobenzophenone-(carbonyl-^{14}C) (V) was effected by ammonia gas in dimethylsulfoxide at 130° in a yield of 95%.

2-Amino-5-nitrobenzophenone-(carbonyl-^{14}C) (V) was converted to nimetazepam-5-^{14}C (I) essentially by the procedure of Sternbach and coworkers[5,8] by which they synthesized a variety of benzodiazepinone derivatives from benzophenones. In the present work, however, we made some modifications and improvements as discussed below. Acylation of V with bromoacetyl bromide in refluxing benzene afforded 2-bromoacetamido-5-nitrobenzophenone-(carbonyl-^{14}C) (VI) in 90%. Ammonolysis of VI with liquid or gaseous ammonia in a solvent such as ethanol, benzene or methylene chloride was tried using various conditions described previously[5,8], but gave only poor yields of VII or the cyclized derivative (VIII) with a large amount of undesired by-products. However, when VI in tetrahydrofuran was treated with gaseous ammonia at room temperature for 3 hours, it was possible to obtain 4:1 mixture of 2-aminoacetamido-5-nitrobenzophenone-(carbonyl-^{14}C) (VII) and the corresponding benzodiazepinone-5-^{14}C (VIII). Heating the mixture with dimethylsulfoxide on steam bath for a short time gave VIII in 83% overall yield from VI. The reaction of VIII in methanol with sodium methoxide followed by N-methylation with methyl iodide gave nimetazepam-5-^{14}C (I) in 75%. The overall radiochemical yield from carbon-^{14}C dioxide to nimetazepam-5-^{14}C (I) was 35.6%.

EXPERIMENTAL.

Material

Barium carbonate-^{14}C was purchased from The Radiochemical Center, Amersham, England and had a specific activity of 58.6 mCi/mmole, 294 μCi/mg.

o-Chlorobenzoic acid-(carboxyl-^{14}C) (II)

A solution of o-bromochlorobenzene (3.8 g) in absolute ether (10 ml) was added dropwise to magnesium turnings (0.48 g) covered with absolute ether (10 ml). The reaction was maintained at gentle reflux by the addition of the halide, which required about 30 min. Further refluxing with stirring for 30 min. consumed most of the remaining magnesium and produced a brown solution of o-chlorophenylmagnesium bromide. The carbon-^{14}C dioxide liberated from barium carbonate-^{14}C (0.966 g, 5.0 mmoles), by addition of conc. H_2SO_4, was carried into the stirred Grignard solution (15 ml, 7.3 mmoles) at -15 to -20°. After stirring at the same temperature for 1 hr., the complex was hydrolyzed with 5% HCl and extracted with ethyl acetate. The ethyl acetate solution was then extracted with 5% Na_2CO_3 solution. The separated aqueous layer was acidified with conc. HCl and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to give a crystalline crude product. To the crude product nonradioactive o-chlorobenzoic acid (0.63 g) was added and the mixture was recrystallized from benzene to afford o-chlorobenzoic acid-(carboxyl-^{14}C) (II) (1.01 g, 83% of radiochemical yield), mp 141-142°, specific activity 17.5 mCi/mmole.

2-Chloro-5-nitrobenzoic acid-(carboxyl-^{14}C) (III)

To a solution of o-chlorobenzoic acid-(carboxyl-^{14}C) (II) (1.01 g) in conc. H_2SO_4 (10 ml) was added dropwise a mixture (3 ml) of conc. HNO_3 and conc. H_2SO_4 (1:2 v/v) at 0 to -5°. After stirring at room temperature for 2.5 hr., the mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to dryness to afford a

crystalline product. Recrystallization from hot water gave 2-chloro-5-nitrobenzoic acid-(carboxyl-^{14}C) (III) (1.21 g, 82%), mp 166-167° (lit.[6] mp 165°); ir cm^{-1}(nujol): 2500-3500(OH), 1700(CO) and 1530(NO_2); nmr δ (acetone): 7.80(1H, doublet, J=8 Hz), 8.37 (1H, doublet-doublet, J=8 Hz, 3 Hz) and 8.65(1H, doublet, J=3 Hz).

2-Chloro-5-nitrobenzophenone-(carbonyl-^{14}C) (IV)

A mixture of 2-chloro-5-nitrobenzoic acid-(carboxyl-^{14}C)(III) (1.21 g) and PCl_5 (1.5 g) in dry benzene (30 ml) was heated under reflux for 2 hr. After removal of excess PCl_5 with benzene the residue was dissolved in dry benzene (30 ml). To the solution $AlCl_3$ (1.5 g) was added and the mixture was stirred at room temperature for 10 hr, and at 60-65° for 7 hr. The reaction mixture was added to conc. HCl-ice water and extracted with ethyl acetate. The extract, after washing with 5% aqueous Na_2CO_3 solution and then water, was evaporated to dryness to yield 2-chloro-5-nitrobenzophenone-(carbonyl-^{14}C) (IV) (1.57 g, 98%), mp 84-85°, identical in all respects with authentic unlabelled material.

2-Amino-5-nitrobenzophenone-(carbonyl-^{14}C) (V)

A solution of 2-chloro-5-nitrobenzophenone-(carbonyl-^{14}C)(IV) (1.57 g) in dimethylsulfoxide (40 ml) was heated in an oil bath at 125-135° and a slow stream of dry NH_3 gas was passed through the solution for 7 hr. After cooling the reaction mixture was added to water and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to afford a crystalline crude product. Recrystallization from ethanol gave 2-amino-5-nitrobenzophenone-(carbonyl-^{14}C) (V) (0.89 g). The mother liquid was chromatographed over silica gel to recover additional V (0.47 g, total yield 95%). Pure 2-amino-5-nitrobenzophenone-(carbonyl-^{14}C) (V) had a melting point of 166-168° and a specific activity of 1.56 mCi/mmole, and showed its ir spectrum identical with that of authentic unlabelled material.

2-Bromoacetamido-5-nitrobenzophenone-(carbonyl-^{14}C) (VI)

A mixture of 2-amino-5-nitrobenzophenone-(carbonyl-^{14}C) (V)

(0.85 g) and bromoacetyl bromide (0.90 g) in dry benzene (40 ml) was heated under reflux for 40 min. After cooling, the mixture was poured into 5% aqueous Na_2CO_3 solution and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to dryness. The crystalline residue was washed with ethanol to afford 2-bromoacetamido-5-nitrobenzophenone-(carbonyl-^{14}C) (VI) (1.17 g, 90%), mp 156-158°, specific activity 11.5 mCi/mmole.

1,3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one-5-^{14}C (VIII)

2-Bromoacetamido-5-nitrobenzophenone-(carbonyl-^{14}C)(VI)(1.17 g) was dissolved in anhydrous tetrahydrofuran (40 ml) and dry NH_3 gas was passed through the solution at room temperature for 3 hr. After removal of the solvent under reduced pressure, the residue was taken up in ethyl acetate and the solution was washed with water and dried. Evaporation of the solvent gave a 4:1 oily mixture (98% of radiochemical yield) of 2-aminoacetamido-5-nitrobenzophenone-(carbonyl-^{14}C) (VII) and 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one-5-^{14}C (VIII). Without any purification the mixture was dissolved in dimethylsulfoxide (5 ml) and heated on steam bath for 1 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried. Evaporation gave a crude crystalline product to which authentic unlabelled material (VIII) (0.37 g) was added. Chromatography over silica gel and recrystallization from isopropyl alcohol gave pure 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one-5-^{14}C (VIII) (1.12 g, radiochemical yield 85%). It had a melting point and a mixed melting point of 226-227°, a specific activity of 8.03 mCi/mmole, and was identical in every respect with authentic sample.

1,3-Dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one-5-^{14}C (I)

A mixture of 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one-5-^{14}C (VIII) (0.78 g) and sodium methoxide (1.53 g,

12% methanol solution) in methanol (10 ml) was stirred at room temperature for 30 min. After removal of the solvent under reduced pressure, the residue was dissolved in anhydrous dimethyl formamide (20 ml). The solution was allowed to react with methyl iodide (2 g) at room temperature with stirring for 1 hr. The mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to give a crystalline residue. The residue was chromatographed over silica gel and eluted with chloroform. Evaporation of the eluent gave nimetazepam-5-^{14}C (I) (0.47 g, 75%), mp 157-158° (recrystallization from ethyl ether), specific activity 8.03 mCi/mmole. It was identical in every respect with authentic unlabelled nimetazepam.

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REFERENCES

1. Inaba,S., Ishizumi,K., Mori,K. and Yamamoto,H. - Chem. Pharm. Bull. (Tokyo), 19: 722 (1971).
2. Sakai,S., Kitagawa,S. and Yamamoto,H. - Arzneimittel Forschung, in press.
3. Endo,M., Yanagi,Y., Miyake,K., Haga,F. and Kitagawa,S. - Proceeding of the Third Symposium on Drug Metabolism and Action (Pharmaceutical Society of Japan, Tokyo), in press.
4. Endo,M. and Miyake,K. - Research Report, unpublished.
5. Sternbach,L.H., Fryer,R.I., Keller,O., Metlesics,W., Sach,G. and Steiger,N. - J. Medicinal Chem., 6: 261 (1963).
6. Blanksma,J. - Rec. trav. chim., 65: 207 (1946).
7. Middleton,S. - Australian J. Chem., 27: 218 (1959).
8. Sternbach,L.H., Fryer,R.I., Metlesics,W., Reeder,E., Sach,G., Saucy,G. and Stempel,A. - J. Org. Chem., 27: 3788 (1962).