THE SYNTHESIS OF DIMETHOXYMETHYL PHENOBARBITAL LABELED WITH ^{14}C

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SUMMARY

Dimethoxymethyl phenobarbital (DMMP), labeled with ^{14}C on the ring and side chains was prepared for drug metabolism studies. The synthesis of DMMP-ethyl-1-^{14}C (4a) in four steps provided a 43% yield from ethyl-1-^{14}C iodide. The yields of DMMP-2-^{14}C (4b) and DMMP-dimethylene-^{14}C (4c) were 87.5% and 30% respectively.

Key Words: Dimethoxymethyl phenobarbital-^{14}C, Thiophenobarbital-^{14}C, Phenobarbital-^{14}C, Alkylation, Condensation, Oxidation.

INTRODUCTION

Dimethoxymethyl phenobarbital (DMMP) has been reported to possess a wide range of anticonvulsant activity in experimental animals.[1] The metabolism and distribution of DMMP in rate was studied using DMMP-ethyl-1-^{14}C (4a), and DMMP-2-^{14}C[2](4b). The clinical evaluation of DMMP was the subject of several publications.[3,4,5]

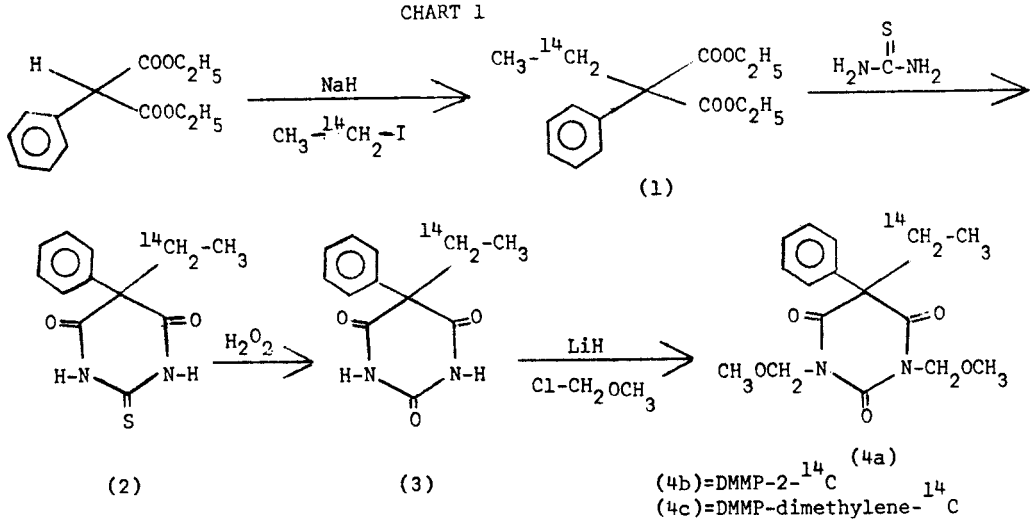
In order to determine the metabolic pathways involved and the mode of DMMP metabolism, appropriately labeled compounds were required. DMMP-ethyl-1-^{14}C (4a), DMMP-2-^{14}C (4b), and DMMP-diemthylene-^{14}C (4c) were synthesized as outlined in chart 1.

The synthesis of DMMP-ethyl-1-^{14}C (4a) consists first of ethylation of diethyl phenylmalonate by ethyl-1-^{14}C iodide to form diethyl ethyl-1-^{14}C-phenylmalonate (1), which in turn is condensed with thiourea to yield 2-thiophenobarbital-ethyl-1-^{14}C (2). Compound 2 is then oxidized with peracetic acid to form phenobarbital-ethyl-1-^{14}C (3). Finally, methoxymethylation of the dilithium salt of compound 3, using chloromethyl methyl ether in DMF, produces DMMP-ethyl-1-^{14}C (4a).

The synthesis of DMMP-2-^{14}C (4b) and DMMP-dimethylene-^{14}C (4c) was accomplished from phenobarbital-2-^{14}C and chloromethyl methyl ether or phenobarbital and chloro-

methyl methyl ether-methylene-^{14}C respectively, in the same fashion as outlined for the synthesis of 4a.

CHART 1



(1) (2) (3) (4a)

(4b)=DMMP-2-^{14}C

(4c)=DMMP-dimethylene-^{14}C

EXPERIMENTAL (6)

Diethyl ethyl-1-^{14}C-phenylmalonate (1). A 50% oily suspension of 480mg of sodium hydride(240 mg of NaH, 10 mmole) in 5 ml of dimethylformamide was added dropwise to 2.36g (10 mmole) of diethyl phenylmalonate. The slurry was well stirred throughout the addition. Hydrogen evolution was complete in 30 minutes. A solution of 1.56g (10 mmole, 9.0 mCi) of ethyl-1-^{14}C iodide(7) in 5 ml of dimethylformamide was added at a moderate rate to the reaction mixture with good stirring, and the mixture was stirred for an hour longer at room temperature. The mixture was poured into 25 ml of ice water. The aqueous suspension was extracted three times with ether. The combined ether extract was dried over sodium sulfate, filtered and the ether was evaporated. A crude yellowish oil was obtained. The weight of the crude product was 2.746g (10.4 mmole, ostensibly, containing 9.0 mCi).

2-Thiophenobarbital-ethyl-1-^{14}C (2). Cut pieces of clean sodium, 0.50g (22.0 mmole), were added intermittently to 10 ml of absolute methanol. After the metal was completely dissolved, 1.52g (20 mmole) of thiourea was added to the warm solution. The reaction mixture was stirred at 50°C until all the solid was dissolved. A solution of 2.746g (10 mmole, ostensibly, 9.0 mCi) of crude 1, in 5 ml of absolute

methanol was added into the reaction mixture. The mixture was stirred and kept at 55-60°C for 24 hours. Then the mixture was cooled in an ice bath and then was added to 15 ml of ice water. The pH of the mixture was adjusted to pH 2 by the addition of 10% hydrochloric acid. A precipitate was obtained which was filtered and crystallized from methanol. Obtained was 1.613g compound, mp 214-217°C (literature 215-217°C).[8]

The product was greater than 98% pure radiochemically by tlc analysis on a silica gel plate using acetone-chloroform (1:9) solvent system for development. The radioassay yielded 5.85 mCi (65% for two steps).

Phenobarbital-ethyl-1-^{14}C (3). Into a suspension of 1.551g (6.25 mmole, 5.63 mCi) of compound 2 in 15 ml of glacial acetic acid, 9 ml of 30% aqueous solution of hydrogen peroxide was added dropwise at ice water temperature. The reaction mixture was stirred at room temperature for one hour then poured into ice. The precipitate was collected by filtration and crystallized from 75% ethanol. The compound was identified by comparing the mp, infrared spectrum and tlc data with those of an authentic sample. The compound possessed greater than 98% radiochemical purity on the basis of tlc analysis using silica gel plate in acetone-chloroform (1:9) solvent system for development. The yield was 1.626g, 4.90 mCi (87%).

DMMP-ethyl-1-^{14}C (4a). Into a stirred solution of 931 mg (4.0 mmole, 3.61 mCi) of compound 3 in 10 ml of dimethylformamide, 80 mg (10 mmole) of lithium hydride was added at room temperature. Hydrogen evolution was complete in 30 minutes. A solution of freshly distilled chloromethyl methyl ether (804 mg, 10 mmole), in 2 ml of dimethylformamide was added slowly to the reaction mixture at ice water bath temperature. The mixture was stirred in ice water bath for one hour and then 50 ml of water was added. A precipitate was formed, which was collected and crystallized from methanol. Obtained was compound 4a, mp 116-118°C. The mp, ir specta and tlc data were identical with those of an authentic sample of DMMP.[1]

The radiochemical purity was found to be greater then 98% pure by tlc analysis on silica gel plates, using benzene-ethyl acetate (9:1) and chloroform-ethyl acetate (30:1) solvent systems for development. The yield was 974 mg (76%, 2.74 mCi) at 0.900 mCi/mmole. The overall yield of the four steps was 43%.

DMMP-2-^{14}C (4b). Compound 4b was prepared from phenobarbital-2-^{14}C[7](116.1

mg, 0.5 mmole, 0.50 mCi) and chloromethyl methyl ether (120 mg, 1.50 mmole) in the same way as described for the preparation of compound 4a. The yield was 141 mg (87.5%, 0.440 mCi), at 1.01 mCi/mmole.

DMMP-dimethylene-^{14}C (4c). Compound 4c was prepared from phenobarbital (464.4 mg, 2.0 mmole) and chloromethyl methyl ether-methylene-^{14}C[7] (322 mg, 4.0 mmole, 4.0 mCi) in the same way as described for the preparation of compound 4a. The yield was 202.7 mg (30%, 1.21 mCi) at 1.90 mCi/mmole.

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6. Microanalysis are within ±0.3% of the theoretical values as performed by Galbraith Laboratories, Knoxville, Tenn. Melting points are obtained on a Fisher-Johns hot stage and are corrected. Ir spectra are recorded on a Perkin-Elmer 337 grating ir spectrophotometer. Type QIF silica gel plates from Quantum Industries are used for tlc development. UV spectra are recorded on a Bausch & Lomb Spectronic 505 spectrophotometer. Ir, uv, spectra and tlc are all appropriate. Radiochromatograms are recorded on a 4TT Tracer-Lab Scanner using tlc plates. Radioassays are performed using a Packard Tri-Carb Liquid Scintillation Spectrometer, Model 3320.

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