SYNTHESIS OF 6-CHLORO-9-[(4-(ETHYLETHYL-1-^{14}C-AMINO)-1-METHYL-BUTYL)AMINO]-2-METHOXYACRIDINE

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SUMMARY

The carbon of the N-ethyl group of the side-chain of atabrine (I) has been labelled with carbon-14 as part of a metabolic study of this compound. The overall radiochemical yield was 38% based on ethyl-1-^{14}C iodide.

Key Words: 6-Chloro-9-[(4-(ethylethyl-1-^{14}C-amino)-1-methylbutyl)amino] -2-methoxy-acridine, Atabrine, Carbon-14, Antimalarial agent

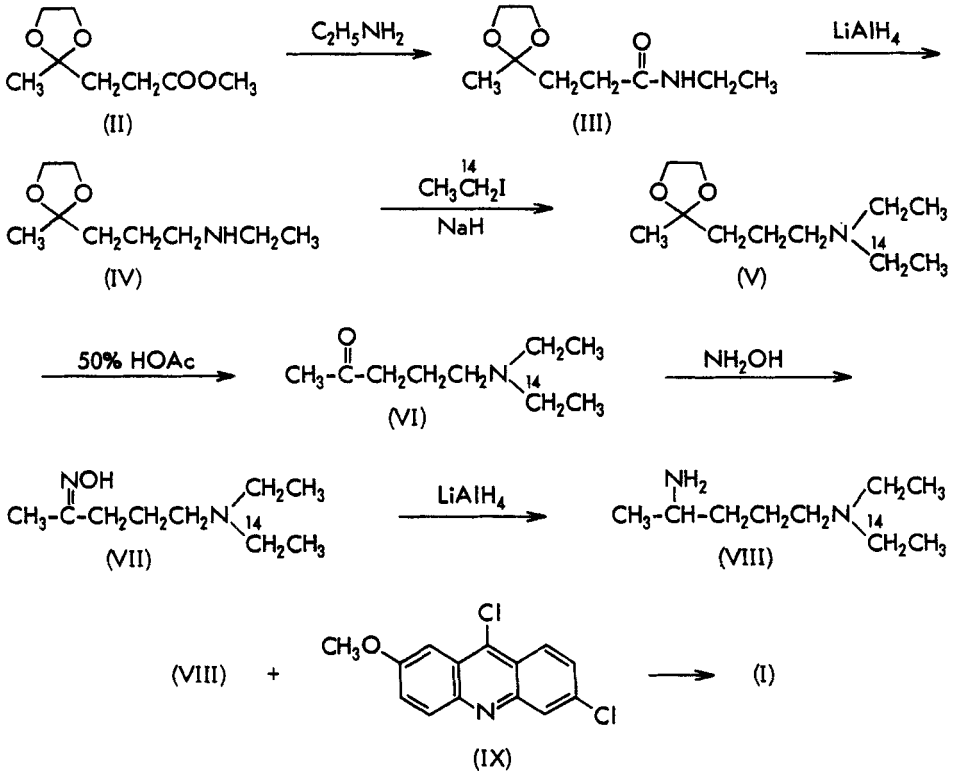
INTRODUCTION

Atabrine (quinacrine) (I) is an effective antimalarial agent and the most promising of more than 300 acridine derivatives. A number of papers[1] have reported studies of syntheses, structure-activity relationships, mode of action, metabolic disposition, toxicity and side effects, and clinical uses. We were requested to label the carbon of the N-ethyl group of the side-chain as part of a metabolic study of this compound.

In order to synthesize the labelled compound (I) by the procedure of Mietzsh and Mauss[2],

(I)

we labelled the carbon of the N-ethyl group of N^1-diethyl-1,4-pentanediamine (VIII) with carbon-14 by the route shown in the synthetic scheme.



2-(2-(Methoxycarbonyl)ethyl)-2-methyl-1,3-dioxolane (II) was dissolved in ethylamine and heated at 65° in an autoclave to give an acid amide (III), which was reduced with lithium aluminium hydride, leaving 2-(3-(ethylamino)propyl)-2-methyl-1,3-dioxolane (IV). When the sodium salt of the amine (IV) was heated with ethyl-1-^{14}C iodide, a diethylamino-^{14}C derivative (V) was obtained in 73% radiochemical yield. The labelled compound (V) was converted into an oxime-^{14}C (VII) by deketalization of V, followed by treatment with hydroxylamine, in 96% radiochemical yield. Reduction of the oxime (VII) was performed by lithium aluminium hydride to give N^1-ethyl-N^1-ethyl-1-^{14}C-1,4-pentanediamine (VIII) in good yield. When the diamine (VIII) was heated with 6,9-dichloro-2-methoxy-acridine (IX) in phenol[2], 6-chloro-9-[(4-(ethylethyl-1-^{14}C-amino)-1-methylbutyl)amino]-2-methoxyacridine dihydrochloride (I) was obtained in 38% overall radiochemical yield based on ethyl-1-^{14}C iodide.

EXPERIMENTAL

Radioactivity determination was carried out with a Packard "Tri-Carb" Liquid Scintillation Spectrometer 3390.

2-(2-(N-Ethylcarbamoyl)ethyl)-2-methyl-1,3-dioxolane (III)--2-(2-(Methoxycarbonyl)-ethyl)-2-methyl-1,3-dioxolane (II) (8 g, 46 mmol) was dissolved in 10 ml of ethylamine. This solution was allowed to stand for 80 hr at room temperature and then heated at 65° for 9 hr in an autoclave. This was evaporated to remove an excess of ethylamine, leaving a residue (8.7 g). The residue was dissolved in benzene and chromatographed on silica gel to give 2-(2-(N-ethylcarbamoyl)ethyl)-2-methyl-1,3-dioxolane (III) as a colorless oil (6.34 g), b.p. 180-181°/0.1 mmHg, in 73.5% yield (Found: C, 57.59; H, 9.05; N, 7.75. $C_9H_{17}NO_3$ requires C, 57.73; H, 9.15; N, 7.48%).

2-(3-(Ethylamino)propyl)-2-methyl-1,3-dioxolane (IV)--A solution of 6.34 g (33.9 mmol) of 2-(2-(N-ethylcarbamoyl)ethyl-2-methyl-1,3-dioxolane (III) in 25 ml of tetrahydrofuran was added dropwise to a mixture of 3 g of lithium aluminium hydride in 25 ml of tetrahydrofuran with stirring for 30 min at room temperature and then heated under reflux for 5.5 hr. This mixture was decomposed by addition of water and extracted with ether. The extract was dried (K_2CO_3) and evaporated to leave an oily residue (5.4 g). The residue was dissolved in light petroleum and chromatographed on alumina (200 g) to give 2-(3-(ethylamino)propyl)-2-methyl-1,3-dioxolane (IV) as a colorless oil (3.03 g), b.p. 100-101°/14 mmHg, in 51.6% yield (Found: C, 62.27; H, 10.92; N, 8.03. $C_9H_{19}NO_2$ requires C, 62.39; H, 11.05; N, 8.08%).

2-(3-(Ethylethyl-1-^{14}C-amino)propyl)-2-methyl-1,3-dioxolane (V)--A solution of 300 mg (1.7 mmol) of 2-(3-(ethylamino)propyl)-2-methyl-1,3-dioxolane (IV) in 0.7 ml of anhydrous benzene was added dropwise to a suspension of 84 mg (1.65 mmol) of 50% sodium hydride in 1 ml of anhydrous benzene with stirring, then stirred for 10 min at room temperature. A solution of 2.7 mCi (52 mg, 0.3 mmol) of ethyl-1-^{14}C iodide and 191 mg (1.23 mmol) of carrier ethyl iodide in 0.7 ml of anhydrous benzene was added dropwise to this mixture with stirring. This was heated under reflux for 4 hr and allowed to stand overnight at room

temperature. Ice water was added to the reaction mixture, and the mixture was salted out with K_2CO_3 and extracted with ether (3 ml x 2). The extract was dried (K_2CO_3) and evaporated to leave an oily residue (450 mg). The residue was dissolved in light petroleum and chromatographed on alumina (15 g) to give 2-(3-(ethylethyl-1-^{14}C-amino)propyl)-2-methyl-1,3-dioxolane (V) as a colorless oil (226 mg, 1.97 mCi) in 73% radiochemical yield. Elemental analysis: Found C, 65.60; H, 11.41; N, 6.89. $C_{11}H_{23}NO_2$ requires C, 65.63; H, 11.52; N, 6.96%.

5-(Ethylethyl-1-^{14}C-amino)-2-pentanone oxime (VII)--2-(3-(Ethylethyl-1-^{14}C-amino)-propyl-2-methyl-1,3-dioxolane (V) (1.97 mCi, 226 mg, 1.12 mmol) was dissolved in 2 ml of 50% acetic acid and heated at 85-90° (bath temperature) with stirring for 4.5 hr. The solution was made alkaline with K_2CO_3 and extracted with ether (4 ml x 3). The extract was dried (K_2CO_3) and evaporated to leave an oily residue (VI, 195 mg). The residue and hydroxylamine hydrochloride (104 mg, 1.5 mmol) were dissolved in 2 ml of ethanol and heated under reflux for 4 hr. The solvent was evaporated to leave a residue, to which water (4 ml) was added. The mixture was salted out with K_2CO_3 and extracted with ether (4 ml x 3). The extract was dried (K_2CO_3) and evaporated to leave 5-(ethylethyl-1-^{14}C-amino)-2-pentane oxime (VII) as a colorless oil (184 mg, 1.89 mCi) in 96% radiochemical yield. Elemental analysis: Found C, 62.51; H, 11.59. $C_9H_{20}N_2O$ requires C, 62.75; H, 11.70%.

N^1-Ethyl-N^1-ethyl-1-^{14}C-1,4-pentanediamine (VIII)--A solution of the oxime (VII) (1.89 mCi, 184 mg, 1.07 mmol) in 6 ml of anhydrous ether was added dropwise to a suspension of 157 mg of lithium aluminium hydride in 5 ml of anhydrous ether with stirring at room temperature and heated under reflux with stirring for 8.5 hr. The mixture was decomposed by addition of water, salted out with K_2CO_3, and extracted with ether (15 ml x 2). The extract was dried (K_2CO_3) and evaporated, leaving N^1-ethyl-N^1-ethyl-1-^{14}C-1,4-pentanediamine (VIII) as an oil (143 mg, 1.6 mCi) in 84.5% radiochemical yield. Dipicrate: yellow prisms, m.p. 138°. Elemental analysis (dipicrate): Found C, 40.97; H, 4.58; N, 17.94. $C_{21}H_{28}N_8O_{14}$ requires C, 40.91; H, 4.58; N, 18.18%.

6-Chloro-9-[(4-(ethylethyl-1-^{14}C-amino)-1-methylbutyl)amino]-2-methoxyacridine--A solution of the diamine (VIII) (1.6 mCi, 143 mg, 0.905 mmol) and 6,9-dichloro-2-methoxyacridine (IX) (300 mg, 1.1 mmol) in phenol (1 ml) was heated with stirring at 100° (bath temperature) for 4 hr. The reaction solution was made alkaline with 10% NaOH (10 ml), and the mixture was extracted with ether (5 ml x 3). The extract was washed with 10% NaOH, dried (Na_2SO_4), and evaporated, leaving a residue (440 mg). The residue was dissolved in benzene-hexane (1 : 1) and chromatographed on alumina (12 g) to give crude 6-chloro-9-[(4-(ethylethyl-1-^{14}C-amino)-1-methylbutyl)amino]-2-methoxyacridine (298 mg). The crude product was dissolved in 5% HCl (15 ml) and extracted with ether-dichloromethane (4 : 1) (25 ml x 2). The aqueous layer was made alkaline with 10% NaOH and extracted with ether (20 ml x 2). The ether extract was washed with water, dried (Na_2SO_4), and evaporated, leaving 6-chloro-9-[(4-(ethylethyl-1-^{14}C-amino)-1-methylbutyl)amino]-2-methoxyacridine as a viscous oil (275 mg, 1.214 mCi, 1.76 mCi/mmol) in 75.6% radiochemical yield.

6-Chloro-9-[(4-(ethylethyl-1-^{14}C-amino)-1-methylbutyl)amino]-2-methoxyacridine dihydrochloride (I)--Three ml of a solution of hydrochloric acid in ethanol (25 mg/ml) was added to a solution of 6-chloro-9-[(4-(ethylethyl-1-^{14}C-amino)-1-methylbutyl)amino]-2-methoxyacridine (1.214 mCi, 275 mg) in ethanol (2 ml). The solution was concentrated to separate crystals, which were recrystallized from ethanol-methanol (5 : 3) to give 6-chloro-9-[(4-ethylethyl-1-^{14}C-amino)-1-methylbutyl)amino]-2-methoxyacridine dihydrochloride (I) as bright yellow prisms, m.p. 246-248° (294 mg, 1.026 mCi, 1.76 mCi/mmol), in 84.4% radiochemical yield and in 38% overall radiochemical yield based on ethyl-1-^{14}C iodide. Elemental analysis: Found C, 55.98; H, 7.01; N, 8.37; Cl, 21.46. $C_{23}H_{30}ClN_3O \cdot 2HCl \cdot H_2O$ requires C, 56.27; H, 6.98; N, 8.56; Cl, 21.67%. The product was confirmed to be pure by t.l.c.-autoradiogram and t.l.c.-radioactinogram [X-ray film, Al_2O_3 plate, solvent system = chloroform-methanol (30 : 1)].

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