SYNTHESIS OF SITE SPECIFICALLY DEUTERATED PRIMAQUINES II. N-ALKYL DEUTERATED PRIMAQUINES.

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SUMMARY

Two site specifically deuterated primaquines were prepared. 4',4'-Dideutero primaquine 3 was obtained from the corresponding dideutero alcohol which was prepared by the low temperature reduction of the ester compound 4 with lithium aluminium deuteride. 1'-Deutero primaquine 5 was prepared by the reductive alkylation of 6-methoxy-8-aminoquinoline with N-(2-oxopentyl)-phthalimide in the presence of sodium cyanoborodeuteride followed by removal of protective phthalimide group.

Key Words: Primaquine, deuterium

INTRODUCTION

Synthesis of five quinoline ring deuterated derivatives of the antimalarial drug, primaquine 1, was reported recently by us. (1) The study of metabolism of primaquine in microorganisms (2) and in laboratory animals (3) led to the identification of 8-(3-carboxy-1-methylpropylamino)-6-methoxyquinoline 2 as the major metabolite of the drug. This prompted us to synthesize primaquine labelled with deuterium at the carbon atom adjacent to the primary amino group (4' position) of the N-alkyl chain. It would be of interest to know whether the introduction of deuterium at the site of metabolism caused a shift in the amount of drug distributed in competing metabolic pathways. Also described is the deuteration of the methine proton (position 1') in the N-alkyl group as this position may represent another potential site of metabolism.

RESULTS AND DISCUSSION

Ester 4, the synthesis of which we recently reported (4), was a convenient starting compound for the preparation of the 4',4'-dideutero primaquine, 3.

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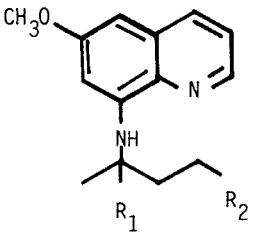
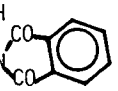
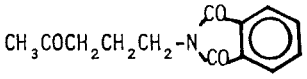


1. R_1 = H R_2 = $-CH_2NH_2$
2. R_1 = H R_2 = $-COOH$
3. R_1 = H R_2 = $-CD_2NH_2$
4. R_1 = H R_2 = $-COOC_2H_5$
5. R_1 = H R_2 = $-CONH_2$
6. R_1 = H R_2 = $-CONHCH_2$- 
7. R_1 = H R_2 = $-CD_2OH$
8. R_1 = H R_2 = $-CD_2-N$ 
9. R_1 = D R_2 = $-CH_2NH_2$



10.

The yield of ester 4 formed by reductive alkylation of 6-methoxy-8-aminoquinoline with ethyl levulinate could be improved to 85% by increasing the duration of the reaction period from seven days to about twenty days. The initial plan was to convert 4 into the amide 5 which could then be reduced to the required deuterated primaquine 3 with lithium aluminium deuteride. However the difficulty encountered in the attempted preparation of the amide (5) from the ester forces us to think in terms of an alternate route. Attempted preparation of the N-benzylamide 6 from either 2 or 4 using several reaction conditions was not successful. We had planned to reduce the N-benzylamide to the N-benzylamine and to debenzylate the secondary amine by hydrogenolysis to produce 3.

An alternative approach was to reduce ester 4 to the dideutero alcohol 7 and then convert the alcohol to an amino compound by one of several methods reported in the literature. Some interesting observations were made during the reduction of the ester group to the corresponding primary alcohol group with lithium aluminium deuteride. No reduction took place in ether at room temperature and there was very little conversion even at reflux in ether. The reaction was nearly instantaneous even at room temperature when terahydrofuran was used as the solvent. The color of the reaction solution changed from yellow to red as soon as a solution of ester 4 in terahydrofuran was added to a suspension of lithium aluminium deuteride in tetrahydrofuran. Work-up of the reaction and purification by column chromatography gave a homogeneous product. The ^{1}H-nmr of the purified product showed clearly that deuteration had occurred at position C-2 of the quinoline ring as well as there being reduction of the ester group. The C-3 and C-4 protons appeared as a pair of doublets with J = 10 Hz, while the C-2 proton was absent. The reduction was repeated at low temperatures. There was no reaction when acetone-Dry Ice® bath was used to lower the reaction temperature. The reduction appeared to take place at about -35 degrees C when the temperature of the reaction was allowed to warm slowly. ^{1}H-nmr analysis of the product obtained by low temperature reduction in the presence of a slight excess of the reducing agent showed that there was no deuterium incorporation at position C-2 of the quinoline ring.

Alcohol 7 could not be converted into the corresponding iodo compound in satisfactory yield. However it could be converted into N-phthalimide derivative 8 by the method of Mitsunobo. (6) It was found that the use of benzene in place of terahydrofuran and reflux of the reaction gave better results. The major product of the reaction was purified by column chromatography and then subjected to hydrazinolysis to remove the phthalimide protecting group to produce the required 4',4-dideutero primaquine in yields ranging from 30 to 40%. The ^{1}H-nmr and mass spectral data were in complete agreement with the expected structure.

The synthesis of 9 was achieved as follows. Potassium phthalimide was alkylated with 5-bromo-2-pentanone (7) in refluxing acetone to give N-(2-oxopentyl)-phthalimide 10 in 74% yield. Reductive alkylation of 6-methoxy-8-aminoquinoline with 10 in the presence of sodium cyanoborodeuteride (prepared according to the method of Borch (8) from sodium cyanoborohydride) gave the N-phthalimide derivative of 9. Hydrazinolysis of the phthalimide compound gave the required 9, the ^{1}H-nmr of which showed a three-proton singlet at 1.3 δ , C-5' methyl. The two deuterated derivatives of primaquine are being examined in metabolic studies to discover any changes in the transformation pathways.

EXPERIMENTAL[1]

Preparation of 8-(4-hydroxy-4,4-d_2-1-methylbutylamino)-6-methoxyquinoline, 7: To a suspension of lithium aluminium deuteride (0.045 g, 1 mmole) in tetrahydrofuran (15 ml), cooled in acetone-Dry Ice® bath, was added dropwise with stirring a solution of 4 (0.302 g, 1 mmole) in terahydrofuran (10 ml). After the addition was complete, the temperature of the solution was slowly raised to -35 degrees C where the color of the solution changed from pale yellow to deep red. The reaction was kept stirring at that temperature for fifteen minutes and then deuterium oxide (8 ml) was added and the resulting mixture stirred well. Tetrahydrofuran was removed under reduced pressure at room temperature and the residue was extracted with methylene chloride (25 ml). The organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated to give a yellow oil which was purified by column chromatography using neutral alumina as the absorbent and

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[1]TLC was done on Sil G-25 UV_{254} (Brinkmann Instruments, Inc.) plates using A) methanol:chloroform (15:85) and B) ethanol:benzene (8:92) as solvents. HPLC was done with a Waters Associates M6000A pump, U6-K injector and UV detector (254 nm) using a uBondapak C_{18} column. A mobile phase of 1.2 L distilled water:2.8 L methanol containing 2.2 g potassium dihydrogen phosphate and 3.3 g potassium hydrogen phosphate was used at a flow rate of 2 ml/min. Column chromatography was performed with E. Merck alumina, neutral, activity grade I, 70-230 mesh. GC was performed on a Beckman GC65 instrument using a 6 ft. x ¼ OD glass column of 3% OV-17 with deactivated support. NMR was recorded on a Varian E-390 instrument using tetramethylsilane as internal standard. MS was recorded on a Finnigan 3200 GC/MS/DS (INCOS) System.

hexane-chloroform (1:1) as the eluant. The eluted pale yellow oil was homogenous by TLC (Solvent A) and HPLC. Yield 0.205 g (78%).

^{1}H NMR ($CDCl_3$): 8.57 δ (1H, dd, J = 5,2 Hz, C-2H), 7.87 (1H, dd, J = 8,2 Hz, C-4H), 7.20 (1H, dd, J = 5,8 Hz, C-3H), 6.3(2H, s, C-5H and C-7H), 6.0 (1H, b, exchangeable with D_2O), 3.84 (3H, s, OCH_3), 3.57 (1H, m), 2.5 (1H, exchangeable with D_2O), 1.63 (4H, m) and 1.27 (3H, d, J = 7 Hz). ^{13}C NMR(PND)($CDCl_3$): 159.6 (C-6), 145.2 (C-8), 144.4 (C-2), 135.5 (C-8a), 134.8 (C-4), 130.0 (C-4a), 121.7 (C-3), 96.9 (C-7), 91.8 (C-5), 55.1 (OCH_3) 48.1 (C-2'), 33.8 (C-1'), 29.9 (C-3') and 20.5 (C-5'). MS (m/z): 262 (M^+, 21.4%), 201 (100.0%), 186 (21.5), 174 (28.7) and 159 (23.0).

Preparation of 8(4-amino-4,4-d_2-1-methylbutylamino)-6-methoxyquinoline, 3:

A mixture of alcohol 7 (0.786 g, 3 mmole), triphenylphosphine (0.780 g, 2 mmole), ehtyl azidodicarboxylate (0.525 g, 2 mmole) and phthalimide (0.900, 6 mmole) in benzene (30 ml) was refluxed under nitrogen atmosphere for three hours. No starting alcohol compound remained (TLC, Solvent A). Benzene was removed at reduced pressure and the residue was chromatographed on a column of neutral alumina and eluted with chloroform. The purified material 8, was refluxed in alcohol (25 ml) containing hydrazine hydrate (1.0 ml) for one hour. Alcohol and excess hydrazine were removed under reduced pressure and the residue was chromatographed on neutral alumina. Chloroform: methanol (19:1) eluted the desired compound 3 as a yellow oil. Yield, 0.248 g (33.0% based on 8). Diphosphate, light orange crystals, m.p. 200-02 degrees C.

^{1}H NMR ($CDCl_3$): 8.57 δ (1H,dd,J=5,2 Hz, C-2H), 7.87(1H, dd, J = 8,2 Hz, C-4H), 7.2 (1H, dd, J = 5,8 Hz, C-3H), 6.3(2H, s, C-5H and C-7-H), 3.84(3H, s, OCH_3), 3.57 (1H, m), 1.63(4H, m) and 1.27(3H, d, J = 7 Hz). MS (m/z): 261 (M^+, 11.3%), 244 (M^+- NH_3, 5.9), 201(100.0%), 186(22.2) and 174(31.4).

Preparation of N-(2-oxopentyl)-phthalimide, 10:

A mixture of potassium phthalimide (18.6 g, 0.1 mole) and 5-bromo-2-pentanone (16.5 g, 0.1 mole) in anhydrous acetone (100 ml) was refluxed for sixteen hours until gas chromatographic analysis of an aliquot of the mixture showed that the reaction was complete. The solid was filtered and the clear filtrate was concentrated to yield a solid residue. The residue obtained was crystallized

from chloroform-methanol mixture as colorless needles, m.p. 72-74 degrees C. Yield, 16.6 g, (74.0%).

^{1}H NMR($CDCl_3$): 7.8 δ (4H, aromatic), 3.73(2H, m, $-CH_2\underline{CH_2}-N=$), 2.53(2H, m, $-\underline{CH_2}CH_2CH_2N=$), 2.13 (3H, s, $\underline{CH_3}CO$) and 2.0(2H, m, $-CH_2\underline{CH_2}CH_2N=$).

Preparation of 8-(4-amino-1'-d -1-methylbutylamino)-6-methoxyquinoline 9:

To a mixture of 6-methoxy-8-aminoquinoline (0.35 g, 2 mmole) and 10 (0.25 g, 1.1 mmole) in methanol-d_1(20 ml) were added 4A moleculer sieves (5 g) and p-toluene-sulfonic acid (0.15 g). The reaction mixture was stirred at room temperature for two hours. Sodium cyanoborodeuteride (0.135 g, 2 mmole) was added with stirring and the reaction was kept stirring for five days at room temperature, additional quantities (0.66 g each) of sodium cyanoborodeuteride were added every twenty-four hours. The solution was diluted with chloroform (25 ml) and filtered. The filterate was concentrated and the residue was refluxed in alcohol (20 ml) containing hydrazine hydrate (0.8 ml) for one hour. Alcohol and excess hydrazine were removed at reduced pressure and the residue was purified by column chromatography on neutral alumina. Elution with chloform:methanol (19:1) gave the desired compound 9 as a yellow oil, yield, 0.120 g (46% based on 10).

^{1}H NMR ($CDCl_3$): methine proton at 3.57 δ was absent and a singlet (three protons) at 1.3 δ ($\underline{CH_3}CDCH_2$) was present. MS (m/z): 260 (M^+, 13.7%), 243($M^+ - NH_3$,8.5), 202 (100.0%), 187 (26.3) and 174(32.0).

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