THE PREPARATION OF ^{14}C-LABELLED 6-^{n}BUTYL-2,8-DICARBOXY-4,10-DIHYDROXY-1,7-PHENANTHROLINE (ICI 74,917)

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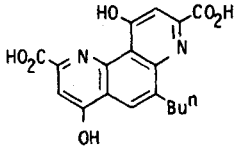
SUMMARY

The preparation of 6-^{n}butyl-2,8-dicarboxy-4,10-dihydroxy(3,9-^{14}C)-1,7-phenanthroline (ICI 74,917) from ethyl acetate -2-^{14}C is described. The overall radiochemical yield was 12%, at a specific activity of 29.7 μCi/mg.

As part of a programme of work on anti-asthmatic compounds[1] we required a ^{14}C-labelled sample of 6-^{n}butyl-2,8-dicarboxy-4,10-dihydroxy-1,7-phenanthroline (I), a potent inhibitor of allergic reactions[2], for metabolic studies.



ICI 74,917

(1)

The route chosen for the synthesis of (I), hereinafter referred to as ICI 74,917, via the Conrad-Limpach reaction, is essentially that described by Waring[3], and is shown in Figure I.

The Claisen condensation of diethyl oxalate and ethyl acetate -2-^{14}C, carried out similarly to the procedure reported for ethyl acetate -1-^{14}C(4), proved unexpectedly sluggish. In cold runs the reaction was essentially complete after 18 hours, whereas with labelled material no reaction was apparent (by g.l.c.) even after 24 hours. A satisfactory yield of keto-ester (II) was obtained only after 72 hours.

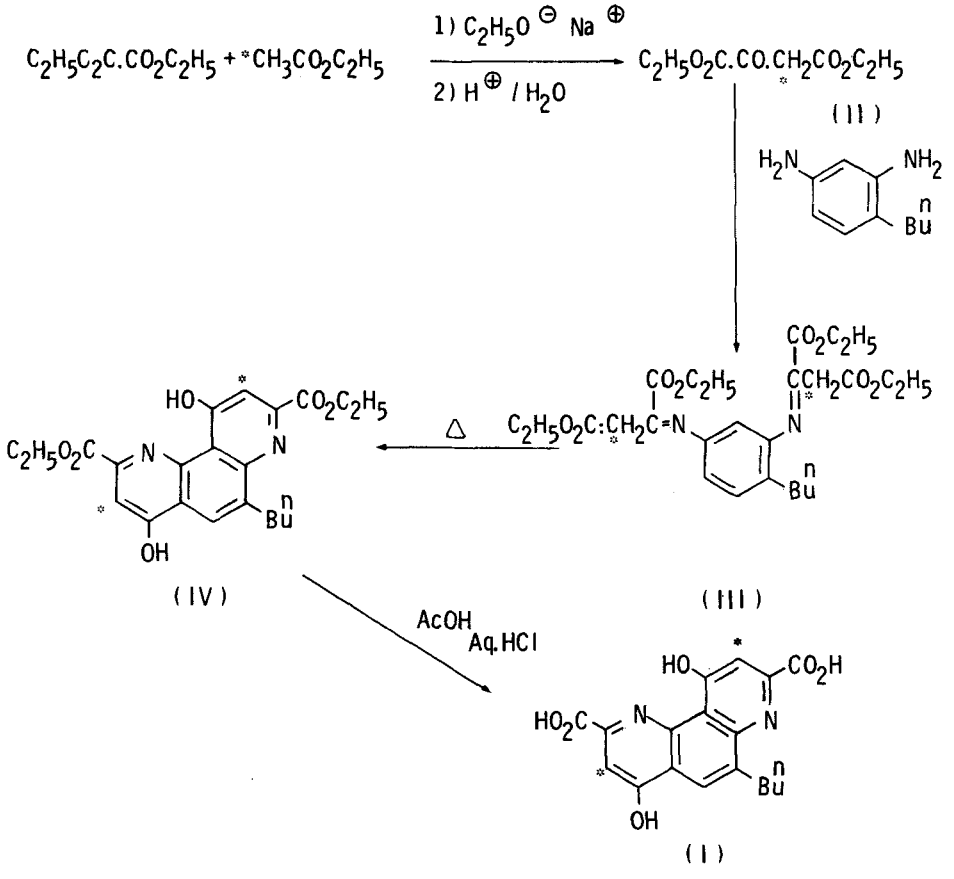


Figure 1

Condensation of ethyl oxaloacetate with 2,4-diamino-1-^{n}butylbenzene proceeded smoothly to the bis-anil (III), a viscous red oil, which was used without further purification. The anil was converted to the phenanthroline (IV), albeit in low yield, by heating at 250-255°C in dibutyl phthalate. Alternative methods of cyclisation of (III) were examined, including those listed below,

but none gave significantly better yields than the thermally-induced cyclisation.

(a) Refluxing glacial acetic acid.

(b) Treatment with phosphoryl chloride at 130°C.

(c) Reaction with polyphosphoric ester in chloroform at reflux.

(d) Heating in neat polyphosphoric ester at 130°C.

The ester (IV) was purified by preparative-scale thin-layer chromatography (PTLC) using two different solvent systems, followed by two recrystallisations. Purification at this stage is particularly important since acidic impurities in the hydrolysis product are difficult to separate from ICI 74,917.

Acid-catalysed hydrolysis of the ester (IV), purified by the method described, smoothly gave the very insoluble di-acid ICI 74,917 (I) in a high degree of purity ($\lesssim$98%).

EXPERIMENTAL

Sulphur-free toluene (May and Baker Ltd.) and absolute alcohol (B.P. Ltd.) were used without further purification. All reaction solvents were of analytical grade. Merck silica gel GF was obtained from Andermanns Ltd., and 2-(4′-^{t}butylphenyl)-5-(4″-biphenylyl)-1,3,4-oxadiazole (butyl-PBD) from Koch-Light Laboratories Ltd. Ethyl acetate -2-^{14}C was purchased from the Radiochemical Centre, Amersham.

Samples were counted on a Packard Tricarb Liquid Scintillator Spectrometer Model 3320 in standard 20 ml glass screw-cap vials of low potassium content (Packard Instruments Ltd.). Kodak "Kodirex" X-ray film was used for autoradiography.

Ethyl oxaloacetate-3-^{14}C (II)

Diethyl oxalate (730 mg; 5 mmole) and ethyl acetate -2-^{14}C (172 mg at 14.3 mCi/mmole[28 mCi]) isotopically diluted to 440 mg (5 mmole), in ether (5 ml), was added to a cooled, stirred, solution of sodium ethoxide prepared from ethanol (0.45 ml) and sodium hydride (220 mg of 60% dispersion in oil; 5.5 mmole). Cooling was maintained for a further 2 hours. After 72 hours at room temperature the slurry was treated with dilute sulphuric acid (11 ml of 2N) and

the ether layer separated. The aqueous solution was extracted with methylene chloride (5 x 5 ml), and the organic extracts combined and dried over magnesium sulphate. Filtration and removal of the solvent under reduced pressure gave (II) as a yellow oil (750 mg; 80%).

6-^{n}Butyl-2,8-dicarbethoxy-4,10-dihydroxy[3,9-^{14}C]-1,7-phenanthroline (IV)

Ethyl oxaloacetate-3-^{14}C (750 mg; 4 mmole) and 2,4-diamino-1-^{n}butyl-benzene (327 mg; 2 mmole) in benzene (15 ml) were heated overnight under Dean and Stark conditions. Evaporation of the solvent left the bis-anil (III) as a dark-red oil. This was dissolved in dibutyl phthalate (2 ml) and added dropwise to dibutyl phthalate (12 ml) at 250-255°C under nitrogen. The temperature was maintained at 250-5° for a further 30 mins. The cooled reaction mixture was poured into light petroleum (b.p. 60-80°) (400 ml) and the product which separated on standing overnight was purified by PTLC on 8 silica plates (20 x 40 x 0.1 cm) using tetrahydrofuran/l. petroleum b.p. 60-80° (1/1) as eluent. A second purification by PTLC using benzene/acetone (1/1), followed by 2 recrystallisations from ethanol/l. petroleum (b.p. 60-80°) gave pure (IV) (160 mg; 19%).

6-^{n}Butyl-2,8-dicarboxy-4,10-dihydroxy[3,9-^{14}C]-1,7-phenanthroline (I)

The ester (IV) (160 mg) was heated for 24 hours in acetic acid (2.7 ml) containing hydrochloric acid (2.7 ml of 3N). The grey precipitate formed was separated by centrifugation and, after washing successively with 2 portions of acetic acid, water, acetone, benzene, chloroform, and ether, dried in vacuo to give (I) (110 mg; 80%) (Anal. Calc. for $C_{18}H_{16}N_2O_6$: C, 60.7; H, 4.5; N, 7.9%. Found: C, 60.7; H, 4.5; N, 7.6%).

TLC on silica gel using ethanol/chloroform/ammonia (0.88)/water (55/30/15/10) and isopropanol/ammonia (0.88)/water (7/3/1) showed a single radioactive and ultraviolet-absorbing zone corresponding to authentic (I). Segmentation of the TLC plates and liquid scintillation counting in a toluene/Butyl-PBD (6%) phosphor indicated a minimum radiochemical purity of 98%. The specific activity was 29.7 μCi/mg, representing an overall radiochemical yield of 12

REFERENCES

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4) M. Rothstein, J. Org. Chem., 22: 324 (1957).