LABELLED PSORALENS. SYNTHESIS OF 4'-AMINOMETHYLTRIOXSALEN-3-t

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SUMMARY

Bromination of 4'-phthalimidomethyltrioxsalen (3) provided the 3-monobromo derivative (4) which on hydrogenolysis with either deuterium or tritium provided the corresponding labelled derivatives 5 and 6. Removal of the phthalimide moiety from 6 produced the title compound (9) having specific activity of 7.46 Ci/mmole.

Key words: Bromination of psoralens, hydrogenolysis, 4'-aminomethyltrioxsalen-3-t

INTRODUCTION AND DISCUSSION

Certain psoralen derivatives, particularly 3-aminomethyl-2,5,9-trimethyl-7H-furo [3,2g] [1] benzopyran-7-one, commonly referred to as 4'-aminomethyl-4,5'-8-trimethylpsoralen or 4'-aminomethyltrioxsalen (AMT) 7 (1), have shown biological activity due to their ability to photoreact readily with viral DNA and RNA (2,3). The utilization of this property is considerably enhanced when psoralens are used in labelled form. Their preparation with a tritium label has been accomplished using an exchange technique (2). This process provides material with modest levels of specific activity, and we now wish to report the synthesis of AMT specifically labelled with

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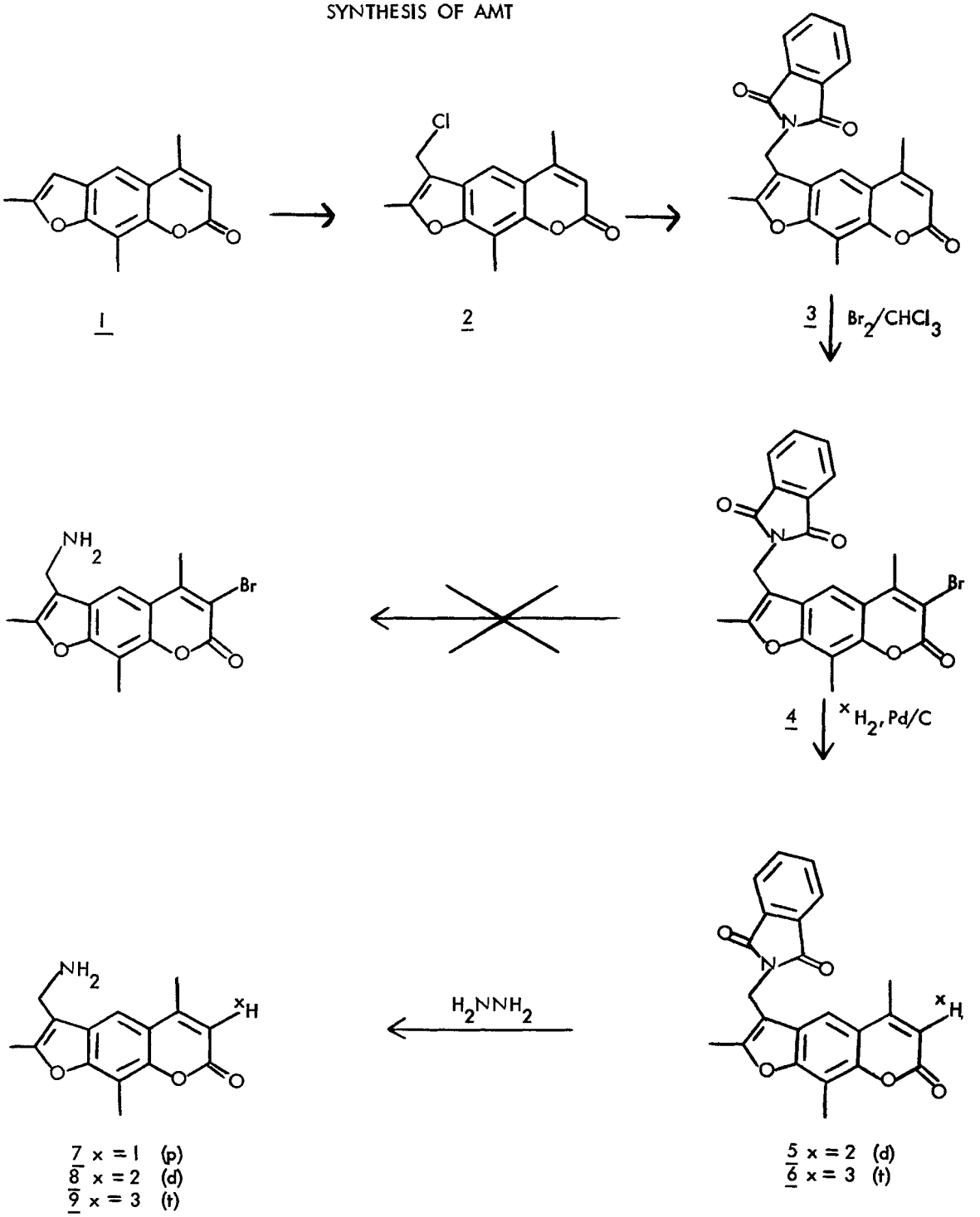
SCHEME

SYNTHESIS OF AMT



7 x = 1 (p)
8 x = 2 (d)
9 x = 3 (t)

5 x = 2 (d)
6 x = 3 (t)

tritium having a specific activity of 7.46 Ci/mmole.

From commercially available trioxsalen (1, Scheme), the phthalimide 3 was prepared via the chloromethyl derivative 2 as described (2). The 4'-substituted furanocoumarin was found to brominate readily at C-3 to provide the bromide 4. We attempted to limit the number of subsequent radiochemical steps by converting the phthalimide group to the aminomethyl derivative prior to hydrogenolysis, but the conversion (hydrazinolysis) was not straightforward. Accordingly, isotopic hydrogenolysis was effected at this point after which conversion to the desired products proceeded as described(2). Using deuterium gas, AMT-3-d (8) was obtained after hydrazinolysis of 5. No dilution of deuterium enrichment occurred during hydrazinolysis. The use of tritium gas provided AMT-3-5 (9) with specific activity of 7.46 Ci/mmole.

EXPERIMENTAL

Melting points are uncorrected. All solvents were distilled prior to use. Radiochemical purity was determined on thin layer chromatograms with a Packard Model 7201 radiochromatogram scanner system. Nuclear magnetic resonance spectra were taken on a Jeolco-C-60H or Varian HA-100 or Varian XL-100 spectrometer. The mass spectra were recorded on either a Varian-CH-5 or CEC-100 instrument at an ionizing voltage of 70eV.

3-[(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)methyl]-2,5,9-trimethyl-7H-furo[3,2-g] [1] benzopyran-7-one (3). This compound was prepared starting with 3 mmoles of 4,5',8-trimethylpsoralen (1) as described (2) with the modification of chromatographing the product over silica gel as a means of final purification. The yield of 4'-chloromethyl-4,5',8-trimethylpsoralen (2) was 35% on this scale and 76% from 2 to the product 3. The m.p. of 2 was 221-222°C, lit. (2) 215-217°C and for 3, 272-274°C, lit. (2) 267-274°C.

6-Bromo-3-[(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)methyl[-2,5,9-trimethyl-7H-furo[3,2-g] [1] benzopyran-7-one (4). A 0.37 mmole sample of phthalimide 3 (144 mg) dissolved in 3 mL of chloroform was treated with 0.74 mL of 1M bromine in chloroform solution. After stirring for 1 h at room termperature, an additional 0.75 mL of the bromine solution was added, and stirring was maintained for a second hour. The mixture was then concentrated in vacuo to a residue which was chromatographed over silica gel (EM Lobar #4219) using chloroform-cyclohexane (4:1) for elution. Concentration of the appropriate fractions yielded 122 mg (70%) of 4, mp. > 315°C. NMR ($CDCl_3$) δ 2.54, 2.70, (3s $3CH_3$-); 4.90, (s,-NCH_2-); 7.70 and 7.82 (AA'BB' pattern, phthalimide 4H); 8.03, (s,-CH=); m/e 465, 467 (calcd. for $C_{23}H_{16}BrNO_5$,465, 467).

3-[2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)methyl-2,5,9-trimethyl-7H-furo[3,2-g] [1] benzopyran-7-one 6-t (6). A mixture of 46.9 mg (0.1 mmole) of 4, 32.4 mg of 10% Pd/C, 0.3 mL of triethylamine and 3.5 ml of tetrahydrofuran (THF) was degassed at < 1μ and then treated with 10 Ci of carrier free T_2 gas. The resulting mixture was vigorously stirred at room temperature for 6 h. Unreacted tritium gas was removed prior to filtering the mixture through Celite. The filter cake was washed with 10 mL of THF,

and the combined filtrates were concentrated in vacuo to a residue which was chromatographed over a silica gel column (EM Lobar #4219) with chloroform-cyclohexane (4:1). The fractions containing the product were combined and concentrated to a constant weight of 27.6 mg of solid which was identical by tlc (SiO_2, $CHCl_3$ elution) to a nonlabelled sample of 3.

3-(Aminomethyl)-2,5,9-trimethyl-7H-furo[3,2-g] [1] benzopyran-7-one 6-t hydrochloride (9). All of the phthalimide derivative, 27.6 mg. (6) obtained above was mixed with 20 µL of hydrazine hydrate and 4.5 mL of 95% ethanol. The resulting mixture was heated at 90°C for 5 h. A sample probe of the mixture showed by tlc that some 6 remained; therefore, an additional 20 µL of hydrazine hydrate was added and heating maintained for another 5 hours. The mixture was cooled and concentrated in vacuo to a residue which was treated with 7 mL of 0.1N sodium hydroxide solution then extracted with four 5 mL portions of chloroform. The extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was treated with 4.5 mL of 1NHCl, and the mixture was evaporated under nitrogen to a solid residue. This was dissolved in 13 mL of absolute ethanol, and then 13 mL of dry ether was added. The mixture was stored at 4°C overnight, and the resulting precipitate was isolated by centrifugation and washed several times with ether to yield 9 mg of product (9) after drying. Specific activity was determined to be 7.46 Ci/mmole, and the radiochemical purity exceeded 99% (SiO_2, methanol-NH_4OH, 99:1). The deuterated analog (8) was obtained via 5 in similar fashion beginning with 50 mg of 4, 40 mg of 10% Pd/C, and 0.4 mL of triethylamine in 5 mL of THF which was hydrogenolyzed with deuterium gas at 1 atm. The intermediate deuterated phthalimido derivative (5), 69% d_1, on hydrazinolysis, provided 8 in similar yield; m/e 258 (calcd. for $C_{15}H_{14}DNO_3$, 258), 68% d_1.

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REFERENCES

1. The ambiguity in numbering these molecules is due to their consideration as furanocoumarins or as furobenzopyrans. Numbering according to the latter is consistent with the Ring Index and has been used in naming these compounds in the Experimental section. Since the furanocoumarin designation is used exclusively in the application of these materials, it has been retained in our discussion.

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