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A new and improved synthesis of methoxsalen (**3**) has been developed for the preparation of specifically carbon-14 labelled **3**. Introduction of the label by a Gattermann reaction on 6-hydroxy-7-methoxycoumaran (**1**) followed by dehydrogenation provides an intermediate **6** which, on reaction with carbethoxymethylenetriphenylphosphorane (**8**) and heat inversion, provides the title compound in overall yields of up to 50%. By these procedures, **3** has been prepared ^{14}C labelled at C-5. Alternatively, **3** may be prepared from **6** and ethyl cyanoacetate in lower overall chemical yield but in potentially higher radiochemical yield if labelling at C-6 or C-7 is required since the Wittig process utilizes an excess of phosphorane.

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Methoxsalen [**3**, also called 8-methoxypsoralen or 9-methoxypsoralen (**1**)] was first described (2) as a component, zanthotoxin, of an alcoholic extract of *fagara zanthoxyloides Lam.* Over the years, the purified compound, now called xanthotoxin (3), was shown to possess substantial biological activity which stimulated considerable synthetic effort, extensive chemical investigation (4) and structure modification (5). An increasing interest in the use of **3** as a photochemotherapeutic agent in the systemic treatment of psoriasis has prompted our investigation of its preparation, specifically carbon-14 labelled and suitable for metabolic study.

The initial synthesis of methoxsalen (6) utilized 6,7-dihydroxycoumaran which was condensed with malic acid and then converted to **3** in quite low yield. This approach has been studied (7) in some detail and improved, but not to the point where we believed that either malic-^{14}C acid (8) or the coumaran-^{14}C were attractive as ^{14}C carriers. A second route (9) to the synthesis of **3**, which begins with the reaction of 2,4-dihydroxy-3-methoxybenzaldehyde and ethyl cyanoacetate, again provides the desired compound unambiguously but in low yield. This approach is also disadvantageous in that it would represent a multistep radiochemical synthesis. A significantly improved synthesis (10) of **3** utilizes 7-allyloxy-8-hydroxycoumarin as a key intermediate and introduction of the ^{14}C label *via* allyl bromide would lead, in reasonable yield, to methoxsalen labelled in the furano protion. However, the difficulty of preparing specifically labelled allyl bromide led us to consider alternate routes.

The unsubstituted furocoumarin, psoralen, has been prepared ^{14}C labelled (11) *via* a Gattermann reaction (for introducing the label) on 6-hydroxycoumaran. Condensation of the intermediate aldehyde with malonic acid followed by decarboxylation and dehydrogenation provided the product. We consequently considered the preparation of the analogous 6-hydroxy-7-methoxycoumaran (**1**) by a similar series of reactions which would lead to methoxsalen-5-^{14}C *via* the aldehyde **2** (12).

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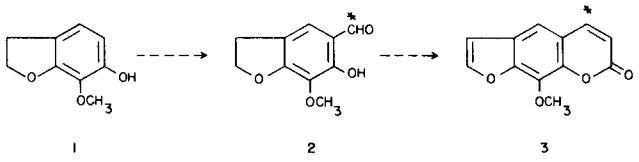

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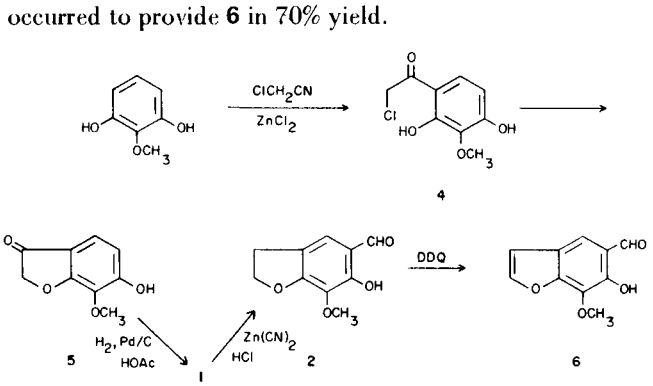
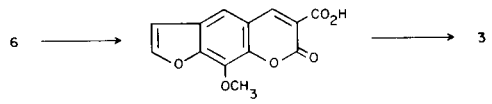
The benzofuranone **5** was prepared from 2,6-dihydroxyanisole along lines described in the literature (**13**). We found that isolation of the intermediate chloroketone **4** improved the overall yield of **5** which was then smoothly converted to **1** by hydrogenation in acetic acid by a modification of the described (6) procedure. The Gattermann reaction of **1** with zinc cyanide and hydrochloric acid gave yields of over 90% of the aldehyde **2** thereby providing a good point of entry for the carbon-14. The literature syntheses of psoralen and derivatives utilizing a coumaran as starting material involve aromatization at the final stages, generally in poor yield. Therefore, dehydrogenation to **6** at this stage would be advantageous. Our attempts to prepare **6** by catalytic dehydrogenation of **2** resulted in simultaneous decarbonylation but with dichlorodicyanoquinone (DDQ), only dehydrogenation occurred to provide **6** in 70% yield.



Our approach to methoxsalen initially involved condensation of **6** with ethyl cyanoacetate [based on the Rodighiero and Antonello synthesis (9)] to provide, after workup, the acid **7** which was decarboxylated as its calcium salt to give **3** in about 30% yield. Since the label



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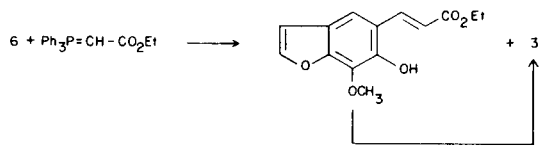
could be introduced at this stage *via* the cyanoacetate, we examined the sequence **6→7→3** in detail in an effort to improve the yield (13). We concluded that the final decarboxylation was the weak step which we attempted to eliminate by treating 6 with the phosphorane **8** derived from ethyl bormoacetate. This reaction yielded the *trans* ester **9** and methoxsalen (**3**). When the reaction was carried out in benzene solution, the ratio 9:3 was 95:5 and in more polar solvents, such as methanol, the ratio was 85.15. However, the *trans* ester is readily converted to methoxsalen by simple heating and by this process, overall yields of **3** from aldehyde **2**, are approximately 50%, a substantial improvement over the existing procedures.

The Wittig reaction requires two equivalents of phosphorane for complete reaction and therefore is not an economical process for labelling at C-6 or C-7. These positions may be labelled in reasonable radiochemical yield using ethyl cyanoacetate-1-^{14}C or 2-^{14}C as discussed. For the present work, labelling at the metabolically stable C-5 position was effected by the Gattermann reaction followed by Wittig condensation. On a mmole scale of potassium cyanide-^{14}C, the overall yield of methoxsalen-5-^{14}C was 35% providing some 5 mCi of **3** having specific activity of 25 mCi/mmole.



EXPERIMENTAL

Melting Points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All solvents were distilled prior to use. Radiochemical purity was determined on thin layer chromatograms (Brinkmann precoated silica gel F-254) with a Packard Model 7201 Radiochromatogram Scanner System and radioactivity was measured by the liquid scintillation technique with a Packard Tricarb Model 2010 spectrometer. Spectral measurements were recorded as follows: infrared on either Perkin Elmer Model 137 or Model 621 or Beckman Model IR-9 spectrometers; ultraviolet on Cary 14 and 15 spectrophotometers; nmr on Varian T-60A, A-60 and HA-100 spectrometers and mass spectra on CEC 110-21B and Jeolco 015G double focusing and Hitachi RMU 6L-single focus spectrometers.

α-Chloro-2,4-dihydroxy-3-methoxyacetophenone (**4**).

From 19.6 g. (0.14 mole) of 2,6-dihydroxyanisole, 10.7 g. (0.14 mole) of chloroacetonitrile and 10 g. of freshly fused zinc chloride, the crude product, isolated as described (13) was purified by chromatography over silica gel (E. Merck 60), eluting with chloroform followed by crystallization from water-methanol to yield 24.9 g. (0.115 mole, 82%) of colorless solid, m.p. 71-72°; ir (potassium bromide): 3410, 1645 cm^{-1}; nmr (deuteriochloroform): δ 3.97 (s, 3, OCH_3), 4.59 (s, 2, CH_2), 6.53 and 7.38 (q, 2, Ar), 12.21 (s, 1, OH), 6.49 (s, 1, OH); ms: m/e (relative intensity) 216 (M^+, 31.8), 167 (100), 152 (20.5).

Anal. Calcd. for $C_9H_9ClO_4$: C, 49.9; H, 4.2; Cl; 16.4. Found: C, 50.0; H, 4.2; Cl, 16.3.

6-Hydroxy-7-methoxy-3(2*H*)benzofuranone (**5**).

As described (13), 23.4 g. (0.108 mole) of **4** was treated with a solution of 29 g. of anhydrous sodium acetate in 80 ml. of absolute ethanol. After recrystallization from methanol, 13.5 g. (0.075 mole, 69.4%) of product was isolated as a colorless solid, m.p. 160° (lit. m.p. (13) 156-157°), ms: m/e (relative intensity) 180 (M^+, 100), 165 (41.3), 151 (46.0).

Anal. Calcd. for $C_9H_8O_4$: C, 60.0; H, 4.5. Found: C, 60.3, H, 4.6.

2,3-Dihydro-7-methoxy-6-benzofuranol (**1**).

A solution of **5**, 233 mg. (1.29 mmoles) in 5 ml. of acetic acid was hydrogenated for 4 hours at room temperature under 53 psi of hydrogen gas using 50 mg. of 10% palladium on carbon as catalyst. The mixture was then filtered, concentrated *in vacuo* to a residue which was chromatographed over silica gel (E. Merck 60) eluting with chloroform to yield, after evaporation, 199 mg. (1.2 mmole, 93%) of colorless oil; nmr (deuteriochloroform): δ 3.18 (t, 2, CH_2), 4.05 (s, 3, OCH_3), 4.69 (t, 2, CH_2) 5.73 (s, 1, OH), 6.55 and 6.87 (q, 2, Ar); ms: m/e (relative intensity) 166 (M^+, 100), 151 (44.1), 133 (32.4), 123 (35.3).

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.1; H, 6.1. Found: C, 65.3; H, 6.1.

2,3-Dihydro-6-hydroxy-7-methoxy-5-benzofurancarboxaldehyde (**2**).

A mixture of 2.49 g. (15 mmoles) of **1**, 5.87 g. (50 mmole) of zinc cyanide and 100 ml. of dry ether was saturated with hydrogen chloride for 1 hour at 0°, then for 2 hours at room temperature. The mixture was then allowed to stand overnight at room temperature then concentrated *in vacuo* and the residue treated with 100 ml. of 0.1*N* hydrochloric acid for 1 hour at reflux. After cooling, ether extraction provided the product which was purified by chromatography over silica gel (E. Merck 60), eluting with chloroform, to yield 2.52 g. (13 mmoles, 87%) of colorless solid, m.p. 71-72°; ir (chloroform): 1640; nmr (deuteriochloroform): δ 3.23 (t, 2, CH_2), 3.97 (s, 3, OCH_3), 4.73 (t, 2, CH_2), 7.11 (s, 1, Ar), 9.75 (s, 1, CHO), 11.75 (s, 1, OH); ms: m/e (relative intensity) 194 (M^+, 100), 179 (11), 166 (20), 164 (21), 148 (31).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.9; H, 5.2. Found: 61.7; H, 5.3.

For ^{14}C labelling, potassium cyanide-^{14}C 53 mCi (specific activity of 58.2 mCi/mmole) was converted to zinc cyanide-^{14}C as described (10). On a 1 mmole scale, **2** labelled with ^{14}C was obtained as described above in a yield of 94.8%. Dilution with nonlabelled **2** to a specific activity of about 30 mCi/mmole was effected at this point.

6-Hydroxy-7-methoxy-5-benzofurancarboxaldehyde (**6**).

A solution of 817 mg. (3.6 mmole) of DDQ in 10 ml. of dioxane was added to 582 mg. (3 mmoles) of **2** in 15 ml. of dioxane and the resulting mixture was heated under reflux for 7 hours, cooled, and the formed solid removed by filtration.

The precipitate was thoroughly washed first with benzene then with chloroform. The washings were combined with the initial filtrate and the total concentrated *in vacuo* to a residue which was chromatographed first on a 20 ml. dry silica gel column (E. Merck 7734) with chloroform elution followed by conventional chromatography over 20 g. of silica (E. Merck 7734) packed in benzene-ethyl acetate (95:5) and elution with this solvent mixture provided, after workup, 405 mg. (2.11 mmoles, 70%) of yellow solid, m.p. 60-62°; nmr (deuteriochloroform): δ 4.09 (s, 3, OCH_3), 6.68 and 7.52 (q, 2, -CH=CH-), 7.38 (s, 1, CHO), 10.96 (s, 1, OH); m/e (relative intensity) 192 (M^+, 100), 177 (36), 146 (18).

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.5; H, 4.2. Found: C, 62.4; H, 4.2.

For ^{14}C labelling, 225 mg. of partially purified **2** was treated with 295 mg. of DDQ as described above. After extensive chromatography, 66 mg. (0.34 mmole) of **6** labelled with ^{14}C were obtained. By tlc, benzene-ethyl acetate (2:1) elution, the product was 99% radiochemically pure.

7-Oxo-9-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-6-carboxylic acid (**7**).

The aldehyde **6** (192 mg., 1 mmole) in 1 ml. of water was added to a solution of ethyl cyanoacetate (125 mg., 1.1 mmoles) in 1 ml. of water containing 200 mg. of sodium hydroxide. The mixture was stirred at room temperature for 20 hours then treated with 8 ml. of 2*N* hydrochloric acid under reflux for 30 minutes. After cooling, the product was isolated by centrifugation followed by crystallization from ethanol to yield 240 mg. (0.923 mmole, 92.3%) of yellow solid, m.p. 227-228°; nmr (deuteriochloroform): δ 4.23 (s, 3, OCH_3), 7.17 and 8.17 (q, 2, -CH=CH-), 7.93 (s, 1, Ar).

Anal. Calcd. for $C_{13}H_8O_6$: C, 60.0; H, 3.1. Found: C, 60.0; H, 3.4.

6-Hydroxy-7-methoxybenzofuran-5-*trans*-acrylic acid ethyl ester (**9**).

A mixture of the aldehyde **6** (192 mg., 1 mmole) and carbethoxymethylenetriphenylphosphorane (**8**), 666 mg., 1.9 mmoles, and prepared from triphenylphosphine and ethyl bromoacetate as described (15) in 20 ml. of benzene was heated under reflux for 2 hours. The solvent was removed by distillation *in vacuo* and the residue was chromatographed over silica gel (E. Merck 60) with benzene to provide 226 mg. (0.86 mmole, 86% of colorless solid, m.p. 127-128°; nmr (deuteriochloroform): δ 1.32 (t, 3, $-CH_2CH_3$), 4.26 (s, 3, $-OCH_3$), 4.28 (q, 2, $-CH_2CH_3$), 6.25 (s, 1, -OH), 6.67 and 8.10 (q, 2, $-CH=CHCO_2Et$), 6.76 and 7.59 (q, 2, ring-CH=CH-), 7.43 (s, 1, Ar).

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.1; H, 5.4. Found: C, 64.2; H, 5.4.

For ^{14}C labelling, 66 mg. (0.34 mmole) of labelled **6** was treated with 220 mg. of **8** as described above to provide 88 mg. (0.336 mmole, 98.8%) of ^{14}C labelled **9** which by tlc (5% ethyl acetate in benzene elution) was greater than 99% radiochemically pure.

9-Methoxyfuro[3,2-*g*]coumarin (**3**; 9-Methoxypsoralen, Methoxsalen).

A. By decarboxylation of **7**.

A 240 mg. (0.923 mmole) sample of **7** was intimately mixed with 300 mg. of calcium carbonate and the mixture was heated under nitrogen at 210° for 45 minutes. After cooling, the mixture was slurried with chloroform, filtered and the filtrate concentrated *in vacuo* to a residue which was chromatographed over silica gel (E. Merck 60) with benzene elution to yield 61 mg. (0.282 mmole, 31%) of colorless solid, m.p. 146-148° and identical to authentic methoxsalen by tlc (5% ethyl acetate in benzene elution; nmr (deuteriochloroform): δ 4.25 (s, 3, OCH_3), 7.31 (s, 1, Ar), 6.33 and 7.72 (q, 2, CH=CH-COO-, J = 9.7 Hz), 6.78 and 7.65 (q, 1, -CH=CH-O-, J = 2.1 Hz).

B. By heat conversion of **9**.

A 216 mg. (0.83 mmole) sample of **9** was heated, under nitrogen to 200° and held at that temperature for 30 hours. The resulting material was dissolved in benzene and chromatographed over silica gel (E. Merck 60) with benzene elution thereby providing 153 mg. (0.71 mmole, 85.3%) of methoxsalen, again identical to authentic methoxsalen.

Methoxsalen-5-^{14}C was prepared by this method starting with 88 mg. (0.336 mmole) of ^{14}C labelled **9** and 42 mg. (0.194 mmole, 58%) of product was obtained. Radiochemical purity exceeded 99% and specific activity was determined to be 115 μCi/mg (24.86 mCi/mmole).

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REFERENCES AND NOTES

(1) The ambiguity in the numbering of this molecule is due to its consideration as a furanocoumarin (8-methoxypsoralen) or as a furobenzopyran (9-methoxypsoralen). The latter is consistent wiht numbering according to the Ring Index and has therefore been followed in this work.

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