Synthesis of Isocoumarins *via* Indanones

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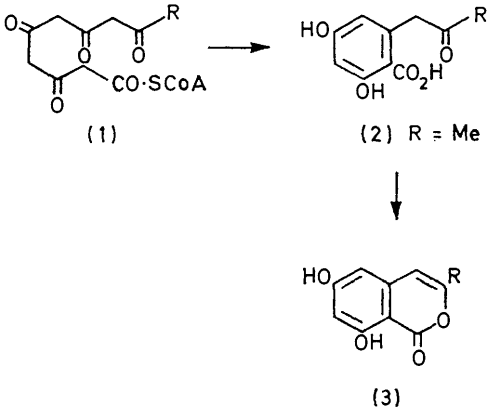
Two improved methods for the oxidative cleavage of indan-1-ones to give isocoumarins have been developed. Syntheses of 6,8-dimethoxy-3-methyl- and 8-methoxy-3-methyl-isocoumarin are described.

A LARGE number of fungal metabolites are considered [1] to arise by cyclisation of a polyketide chain (1) of the

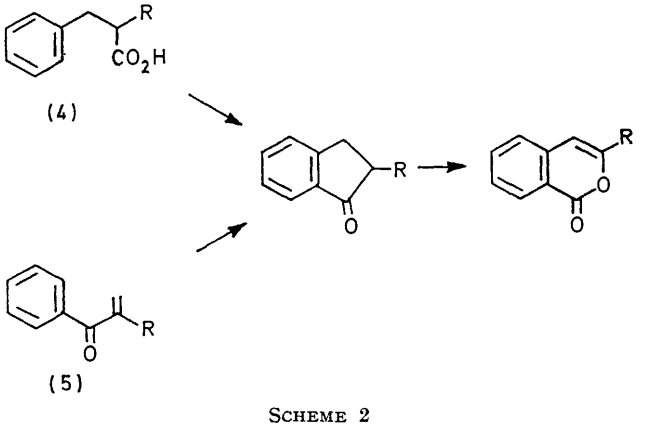


SCHEME 1

appropriate length folded as shown in Scheme 1. The *C*-acetylorsellinic acid (2) or isocoumarin (3) which results from this mode of cyclisation would then be converted into compounds such as the pentaketides citrinin and sepedonin or the hexaketides ascochitine and rubropunctatin, by a variety of oxidation, reduction, and alkylation reactions.[2]

We plan to test some of these biosynthetic proposals by carrying out incorporation experiments with the appropriate hypothetical precursors, and have therefore sought a convenient synthetic route to 3-alkylisocoumarins. Apart from being suitable for the introduction of isotopic labels at selected positions in the target molecules, the chosen route had to be sufficiently flexible to allow the synthesis of a wide range of differently substituted isocoumarins, including compounds with (*a*) one or more hydroxy-groups at C-4, -5, -6, -7, or -8, (*b*) one or more methyl groups at C-4, -5, or -7, and (*c*) a methyl or other alkyl substituent at C-3.

Of the established synthetic routes to isocoumarins,[3] that based on the oxidative cleavage of indanones



SCHEME 2

(Scheme 2) seemed most likely to meet these requirements. A wide range of suitable indanones can be prepared, by cyclisation of either an arylpropionic acid (4) or an acrylophenone (5).

It is essential for the success of this approach to have a reliable general method of effecting the key oxidative

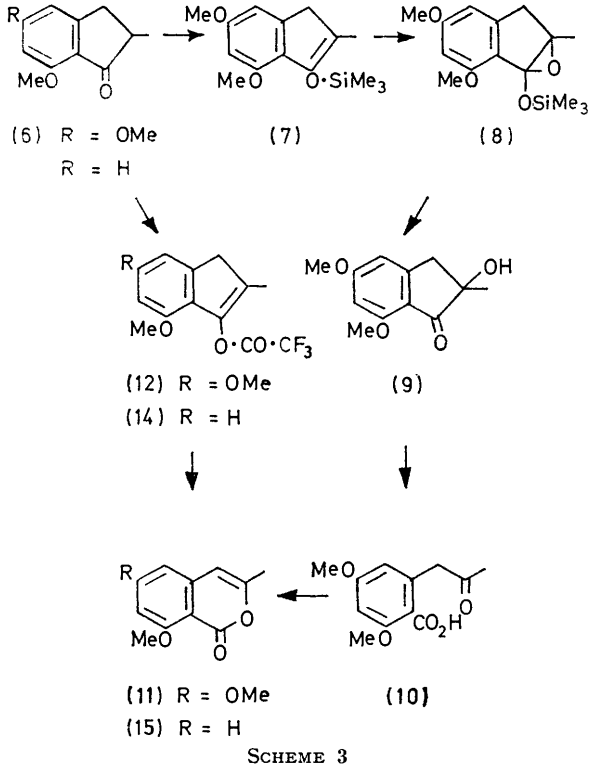
[1] W. B. Turner, 'Fungal Metabolites,' Academic Press, London and New York, 1972.

[2] A. J. Birch and F. W. Donovan, *Austral. J. Chem.*, 1953, **6**, 360.

[3] R. D. Barry, *Chem. Rev.*, 1964, 229.

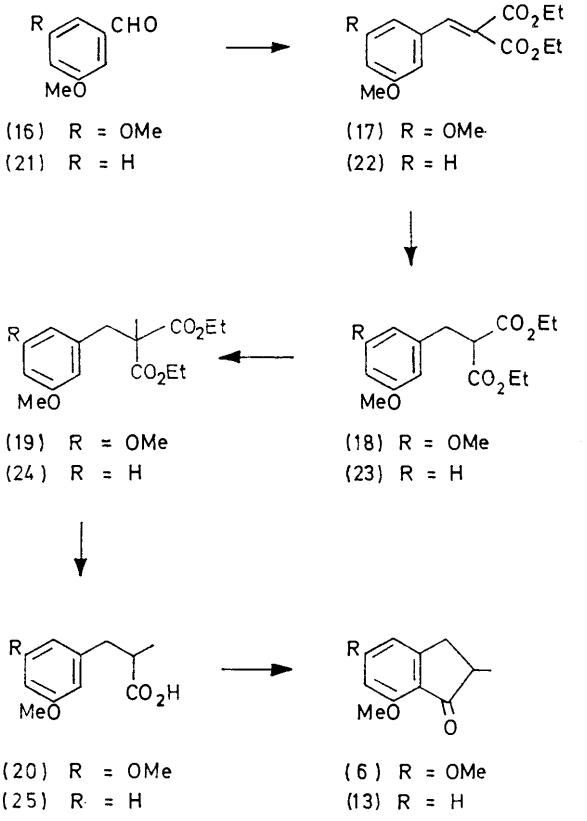
cleavage of the indanone to the isocoumarin. The transformation has been carried out successfully with a highly substituted indanone [4] by use of Triebs reagent,[5] but we have not found this to be a generally applicable method. Bayer–Villiger oxidation of a 2-alkylindanone leads to a coumarin rather than an isocoumarin.[6]

We have therefore investigated the oxidative cleavage of enol derivatives of 2-alkylindanones, and as a result have developed two convenient methods for the desired transformation. Exploratory studies were carried out on 5,7-dimethoxy-2-methylindan-1-one (6). In the first method (Scheme 3) this was converted into the silyl ether (7) by treating the enolate with chlorotrimethylsilane. On ozonolysis followed by oxidative work-up this derivative afforded the hydroxy-ketone (9) rather than the expected oxo-acid (10). Presumably the initial product of ozonolysis is an epoxide rather than an ozonide; this anomalous behaviour has been observed [7] with other highly hindered alkenes. The conversion of (7) into (9) can also be effected by *m*-chloroperbenzoic acid, though in lower yield. The final step of the desired transformation leading to (11) can be readily carried out by oxidative cleavage of (9) with periodate, presumably *via* the oxo-acid (10).



SCHEME 3

The overall transformation of (6) into (11) could be carried out more conveniently, however, by ozonolysis of the enol trifluoroacetate (12). The derivative was readily prepared by mild treatment of the indanone with



SCHEME 4

trifluoroacetic anhydride; the ozonolysis proceeded in a straightforward manner and the isocoumarin (11) was isolated directly and in excellent yield on work-up with dimethyl sulphide. This method proved equally effective for the conversion of 7-methoxy-2-methylindan 1-one into the corresponding isocoumarin [(13) ⟶ (14) ⟶ (15)].

The indanones (6) and (13) required for this study were conveniently prepared by cyclisation of the corresponding arylpropionic acids (Scheme 4). Differently substituted indanones may, however, be more readily prepared by cyclisation of an acrylophenone.[8] Both types of synthetic precursor can be labelled specifically at a number of positions by using standard labelled building blocks, so a convenient approach is now established for the preparation of the wide range of specifically labelled isocoumarins required for our biosynthetic investigations.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 257 spectrophotometer for solutions in chloroform unless otherwise

[4] T. Sassa, H. Aoki, and K. Munakata, *Tetrahedron Letters*, 1968, 5703.

[5] W. Triebs, *Ber.*, 1939, **72**, 1194; *Angew. Chem. Internat. Edn.*, 1964, **3**, 802.

[6] P. E. Sonnet and J. E. Oliver, *J. Heterocyclic Chem.*, 1974, **11**, 263.

[7] P. D. Bartlett and M. Stiles, *J. Amer. Chem. Soc.*, 1955, **77**, 2806; P. S. Bailey and A. G. Lane, *ibid.*, 1967, **89**, 4473; R. Criegee, Amer. Chem. Soc. Advances in Chemistry Series, No. 21, 1959, p. 133.

[8] J. H. Burckhalter and R. C. Fuson, *J. Amer. Chem. Soc.*, 1948, **70**, 4184; D. B. Bruce, A. J. S. Sorrie, and R. H. Thomson, *J. Chem. Soc.*, 1953, 2403.

stated. ^{1}H N.m.r. spectra were recorded with a Varian HA100 or HA100 D instrument for solutions in deuteriochloroform unless otherwise stated (Me_4Si as internal standard).

Diethyl 3,5-*Dimethoxybenzylidenemalonate* (17).—A solution of 3,5-dimethoxybenzaldehyde (1.83 g), diethyl malonate (1.60 g), piperidine (0.05 ml), and glacial acetic acid (0.15 ml) in dry benzene (10 ml) was heated at reflux in a Dean–Stark apparatus for 20 h. After cooling and dilution with ether (20 ml) the solution was washed with 3N-sulphuric acid (20 ml), 10% sodium hydrogen carbonate solution (20 ml), 5% acetic acid (20 ml), and water (2 × 20 ml). Evaporation of the dried ethereal solution gave a pale yellow oil which crystallised (yield 3.26 g, 96%). Distillation (b.p. 160—170° at 0.1 mmHg) gave diethyl 3,5-dimethoxybenzylidenemalonate as crystals, m.p. 47.5—48.5° (from pentane) (lit.,[9] 45—48°); $\nu_{max.}$ 1 720s, 1 630w, and 1 590s cm^{-1}; τ 2.36 (1 H, s, ArH), 3.40 (2 H, d, J 2 Hz, ArH), 3.52 (1 H, t, J 2 Hz), 5.66 (2 H, q, J 7 Hz, $OCH_2{\cdot}CH_3$), 5.70 (2 H, q, J 7 Hz, $O{\cdot}CH_2{\cdot}CH_3$), 6.24 (6 H, s, OCH_2), 8.66 (3 H, t, J 7 Hz, $O{\cdot}CH_2{\cdot}CH_3$), and 8.70 (3 H, t, J 7 Hz, $O{\cdot}CH_2{\cdot}CH_3$).

Diethyl 3,5-*Dimethoxybenzylmalonate* (18).—A solution of diethyl 3,5-dimethoxybenzylidenemalonate (1.07 g) in dry ethyl acetate (25 ml), was hydrogenated over 5% palladium–charcoal (0.1 g) at 20 °C and atmospheric pressure for 2 h (uptake 90 ml). The filtered solution was evaporated and the resulting oil distilled (b.p. 150—152° at 0.05 mmHg) to give diethyl 3,5-dimethoxybenzylmalonate (0.945 g, 88%) (lit.,[9] b.p. 140—145° at 0.2 mmHg); $\nu_{max.}$ (film) 1 730s and 1 600s cm^{-1}; τ 3.68 (3 H, s, ArH), 5.86 (4 H, q, J 6 Hz, $O{\cdot}CH_2{\cdot}CH_3$), 6.30 (6 H, s, $O{\cdot}CH_3$), 6.36 (1 H, t, J 8 Hz, $CH_2{\cdot}CH$), 6.86 (2 H, d, J 8 Hz, $CH_2{\cdot}CH$), and 8.80 (6 H, t, J 6 Hz, $O{\cdot}CH_2{\cdot}CH_3$).

3-(3,5-*Dimethylphenyl*)-2-*methylpropionic Acid* (20).—Sodium (0.7 g) was allowed to react with dry ethanol (120 ml). A solution of diethyl 3,5-dimethoxybenzylmalonate (6.9 g) in ethanol (20 ml) was then added and the mixture heated to reflux. After 1 h a solution of methyl iodide (3.9 g) in ethanol (20 ml) was added slowly and heating was continued for 1 h. The solution was concentrated, diluted with ether (50 ml), and then washed with water (50 ml), 3N sulphuric acid (50 ml), and 10% sodium hydroxide (50 ml), dried, and evaporated. The product was a yellow oil (6.5 g, 90%); $\nu_{max.}$ (film) 1 730s and 1 600s cm^{-1}; τ 3.70 (2 H, s, ArH), 3.74 (1 H, s, ArH), 5.82 (4 H, q, J 8 Hz, $O{\cdot}CH_2{\cdot}CH_3$), 6.30 (6 H, s, $O{\cdot}CH_3$), 6.84 (2 H, s, $ArCH_2$), 8.66 (3 H, s, CH_3), and 8.76 (6 H, t, J 8 Hz, $O{\cdot}CH_2{\cdot}CH_3$).

This product (11.5 g) was added to a solution of potassium hydroxide (6 g) in water (60 ml) and the mixture was heated at reflux for 30 h. After cooling, sulphuric acid (12 g) in water (18 ml) was added and heating continued for 25 h. The product was extracted with ether (2 × 50 ml). The ethereal solution was extracted in turn with 10% sodium hydrogen carbonate solution (2 × 50 ml). The acidified aqueous solution was extracted with ether (2 × 50 ml) and the ethereal solution dried and evaporated to give a yellow oil (4.9 g, 61%). At 4 °C a sample slowly crystallised; recrystallisation from pentane at −25° gave 3-(3,5-*dimethoxyphenyl*)-2-*methylpropionic acid*, m.p. 54—56° (Found: C, 64.2; H, 7.0. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.2%); $\nu_{max.}$ 3 200—2 800m, 1 690—1 710s, and 1 590s cm^{-1}; τ −0.84 (1 H, s, CO_2H), 3.68 (3 H, s, ArH), 6.26 (6 H, s, $O{\cdot}CH_3$), 6.8—7.5 (3 H, complex m, $CH_2{\cdot}CH$), and 8.80 (3 H, d, J 6 Hz, CH_3).

5,7-*Dimethoxy*-2-*methylindan*-1-*one* (6).—Trifluoroacetic anhydride (18 ml) was added to a solution of 3-(3,5-dimethoxyphenyl)-2-methylpropionic acid (4.5 g) in trifluoroacetic acid (80 ml) at 0 °C. The mixture was stirred at this temperature for 0.5 h, then evaporated, and the residue was dissolved in ether (50 ml). The ethereal solution was washed with 10% sodium hydroxide solution (2 × 50 ml) and water (2 × 50 ml), then dried and evaporated to give an oil which crystallised to afford solid 5,7-dimethoxy-2-methylindan-1-one (3.5 g, 85%). The product could be purified by distillation (b.p. 135—140° at 0.1 mmHg) and by recrystallisation from ethyl acetate–hexane (1 : 1) as prisms, m.p. 76—79° (Found: C, 68.5; H, 6.5. $C_{12}H_{14}O_3$ requires C, 68.2; H, 6.3%); $\nu_{max.}$ 1 700s and 1 610s cm^{-1}; τ 3.56 (1 H, s, ArH), 3.72 (1 H, s, ArH), 6.14 (3 H, s, $O{\cdot}CH_3$), 6.17 (3 H, s, $O{\cdot}CH_3$), 6.6—6.9 (1 H, m, $CH_2{\cdot}CH$), 7.3—7.5 (2 H, m, $CH_2{\cdot}CH$), and 8.76 (3 H, d, J 8 Hz, CH_3).

2-*Hydroxy*-5,7-*dimethoxy*-2-*methylindan*-1-*one* (9).—To a solution of di-isopropylamine (34 mg) in tetrahydrofuran (5 ml) cooled to −20 °C under nitrogen, was added 15% butyl-lithium in hexane (0.20 ml) followed, after 15 min by a solution of 5,7-dimethoxy-2-methylindan-1-one (49 mg) in tetrahydrofuran (2 ml). After 3 h at room temperature, chlorotrimethylsilane (120 mg) was added. After 15 min the solvent was evaporated off and the residue dissolved in ether (15 ml). The ethereal solution was washed with water (15 ml), dried, and evaporated. The silyl ether was purified by chromatography on silica gel [ethyl acetate–cyclohexane (1 : 1) as eluant] to give the silyl ether (43 mg, 65%); $\nu_{max.}$ (film) 1 630s and 1 600s cm^{-1}; τ 3.45 (1 H, d, J 1 Hz, ArH), 3.63 (1 H, d, J 1 Hz, ArH), 6.12 (6 H, s, $O{\cdot}CH_3$), 6.91 (2 H, s, CH_2), and 8.12 (3 H, s, CH_3).

(a) *Ozonolysis of the silyl ether.* A solution of the foregoing product (39 mg) in ethyl acetate (10 ml) was cooled to −70 °C and ozonised oxygen (*ca.* 5%; 20 l h^{-1}) was bubbled through for 15 min. The excess of ozone was removed by passing nitrogen through the solution, which was then evaporated, and the residue was treated with 4N-hydrochloric acid (20 ml) for 2 h. The product was extracted with ether (2 × 20 ml) and purified by chromatography on silica gel (ethyl acetate–cyclohexane as eluant) to give 2-*hydroxy*-5,7-*dimethoxy*-2-*methylindan*-1-*one* (17 mg, 45%). The product crystallised from ether–hexane; m.p. 122—124° (Found: C, 64.9; H, 6.1. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); $\nu_{max.}$ 3 400m, 1 700s, and 1 600s cm^{-1}; τ 3.56 (1 H, s, ArH), 3.70 (1 H, s, ArH), 6.12 (3 H, s, $O{\cdot}CH_3$), 6.16 (3 H, s, $O{\cdot}CH_3$), 6.91 (2 H, s, CH_2), and 8.64 (3 H, s, CH_3).

(b) *Oxidation with* m-*chloroperbenzoic acid.* A solution of the silyl ether (42 mg) and *m*-chloroperbenzoic acid (29 mg) in dichloromethane (25 ml) was stirred for 3 h. Water (25 ml) was added and the organic layer separated. The aqueous layer was extracted with ether (2 × 25 ml) and the organic extracts were dried and evaporated to give a mixture of products. The major product, separated by chromatography on silica gel [ethyl acetate–cyclohexane (1 : 1) as eluant] was 2-hydroxy-5,7-dimethoxy-2-methylindanone (13 mg, 25%).

Conversion of the Ketone (9) *into* 6,8-*Dimethoxy*-3-*methylisocoumarin* (11).—2-Hydroxy-5,7-dimethoxy-2-methylindan-1-one (50 mg) was dissolved in a mixture of 1,4-dioxan (2 ml) and 2N-sulphuric acid (8 ml), sodium periodate (110 mg) was added, and the mixture was stirred at room temperature for 18 h. Water (50 ml) was added and the

[9] H. Newman and R. B. Angier, *J. Org. Chem.*, 1966, **31**, 1451.

solution was extracted with ethyl acetate (2 × 50 ml). Evaporation of the dried organic layer gave a residue which was purified by chromatography (dichloromethane as eluant) to yield 6,8-dimethoxy-3-methylisocoumarin (27 mg, 54%), m.p. 157—160° (lit.,[10] 157—158°); $\nu_{max.}$ 1 740s, 1 700m, 1 640s, and 1 610s cm^{-1}; τ 3.59 (1 H, d, *J* 2 Hz, ArH), 3.71 (1 H, d, *J* 2 Hz, ArH), 3.92 (1 H, s, 4-H), 6.06 (3 H, s, O·CH_3), 6.12 (3 H, s, O·CH_3), and 7.80 (3 H, s, CH_3).

4,6-Dimethoxy-2-methylinden-3-yl Trifluoroacetate (12).—A solution of 5,7-dimethoxy-2-methylindan-1-one (510 mg) in trifluoroacetic anhydride (10 ml) was stirred at room temperature for 20 min. Evaporation gave dark blue-green iridescent plates, which on distillation (114—116° and 0.05 mmHg) afforded the *trifluoroacetate* as a pale yellow solid (640 mg, 85%). Repeated distillation gave a white powder, m.p. 90—99° (Found: C, 55.7; H, 4.3%; *m/e*, 302.0776. $C_{14}H_{13}F_3O_4$ requires C, 55.6; H, 4.2%; *M*, 302.0764); $\nu_{max.}$ 1 800s, 1 660w, 1 590s, and 1 460m cm^{-1}; τ 3.44 (1 H, s, ArH), 3.66 (1 H, s, ArH), 6.26 (3 H, s, O·CH_3), 6.30 (3 H, s, O·CH_3), 6.74 (2 H, s, CH_2), and 8.08 (3 H, s, CH_3).

Conversion of the Trifluoroacetate (12) *into 6,8-Dimethoxy-3-methylisocoumarin* (11).—Ozonised oxygen (*ca.* 5%; 20 l h^{-1}) was passed through a solution of the trifluoroacetate (12) (750 mg) in ethyl acetate (50 ml) at −70 °C until the solution became blue. The excess of ozone was removed by bubbling nitrogen through the solution, which was then treated with dimethyl sulphide and allowed to warm up to room temperature. After 1 h at this temperature the solvent was evaporated off and the product recrystallised from methanol to give 6,8-dimethoxy-3-methylisocoumarin as plates (490 mg, 90%).

Diethyl 3-Methoxybenzylidenemalonate (22).—By the method for the preparation of (17), 3-methoxybenzaldehyde (3.0 g) gave *diethyl 3-methoxybenzylidenemalonate* (5.88 g, 95%), b.p. 205—210° (Found: C, 64.8; H, 6.6. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%); $\nu_{max.}$ (film) 1 715s, 1 660m, 1 600m, and 1 580m cm^{-1}; τ 2.32 (1 H, s, ArC*H*), 2.7—3.2 (4 H, m, ArH), 5.67 (2 H, q, *J* 7 Hz, O·CH_2·CH_3), 5.70 (2 H, q, *J* 7 Hz, O·CH_2·CH_3), 6.23 (3 H, s, O·CH_3), 8.68 (3 H, t, *J* 7 Hz, O·CH_2·CH_3), and 8.72 (3 H, t, *J* 7 Hz, O·CH_2·CH_3).

Diethyl 3-Methoxybenzylmalonate (23).—By the method for the preparation of (18), diethyl 3-methoxybenzylidenemalonate (1.9 g) gave *diethyl 3-methoxybenzylmalonate* (1.7 g, 90%), b.p. 190—195° (Found: C, 64.3; H, 7.1. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.2%); $\nu_{max.}$ (film) 1 730s, 1 600s, and 1 580s cm^{-1}; τ 2.7—3.3 (4 H, m, ArH), 5.85 (4 H, q, *J* 7 Hz, O·CH_2·CH_3), 6.35 (1 H, t, *J* 8 Hz, CH_2·C*H*), 6.81 (2 H, d, *J* 8 Hz, CH_2·CH), and 8.81 (6 H, t, *J* 7 Hz, CH_3).

Diethyl (3-Methoxybenzyl)methylmalonate (24).—By the method for the preparation of (19), diethyl 3-methoxybenzylmalonate (3 g) gave *diethyl (3-methoxybenzyl)methylmalonate* (2.1 g, 70%), b.p. 255—260° (Found: C, 65.4; H, 7.8. $C_{16}H_{22}O_5$ requires C, 65.3; H, 7.5%); $\nu_{max.}$ (film) 1 730s, 1 600m, and 1 580m cm^{-1}; τ 2.7—3.4 (4 H, m, ArH), 5.82 (4 H, q, *J* 7 Hz, O·CH_2·CH_3), 6.29 (3 H, s, OMe), 6.82 (2 H, s, CH_2), and 8.69 (3 H, s, CH_3).

(3-Methoxybenzyl)methylmalonic Acid.—Diethyl (3-methoxybenzyl)methylmalonate (7 g) in 30% sodium hydroxide solution (150 ml) was heated at reflux for 19 h. After cooling, the mixture was extracted with ether (3 × 50 ml), then acidified with concentrated hydrochloric acid. The cloudy white solution was extracted with ethyl acetate (3 × 50 ml). The organic layer was dried and evaporated to give *(3-methoxybenzyl)methylmalonic acid* (4.2 g, 75%), which crystallised from ether–hexane as needles, m.p. 145—146° (Found: C, 60.5; H, 6.0. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%); $\nu_{max.}$ (Nujol) 3 000br, s, 1 700s, and 1 600m cm^{-1}; τ [$(CD_3)_2CO$] −0.89 (2 H, s, CO_2H), 2.83 (1 H, t, *J* 8 Hz, ArH), 3.18 (4 H, m, ArH), 6.27 (3 H, s, OCH_3), 6.79 (2 H, s, CH_2), and 8.67 (3 H, s, CH_3).

7-Methoxy-2-methylindan-1-one (13).—A solution of (3-methoxybenzyl)methylmalonic acid (1 g) in 30% sulphuric acid (50 ml) was heated at reflux for 16 h. After cooling, the solution was extracted with ether (3 × 50 ml). Evaporation of the dried ethereal solution gave *3-(3-methoxyphenyl)-2-methylpropionic acid* (650 mg, 78%) as a viscous oil, $\nu_{max.}$ (film) 3 200br, s, 1 700s, 1 600s, and 1 450s cm^{-1}; τ 0.7br (1 H, s, CO_2H), 2.7—3.4 (4 H, m, ArH), 6.29 (3 H, s, O·CH_3), 6.9—7.5 (3 H, m, CH_2·C*H*), and 8.85 (3 H, d, *J* 6 Hz, CH_3). The crude product was cyclised as in the preparation of (6) to give a mixture of indanones from which could be isolated (by chromatography on silica gel with ether as solvent), *7-methoxy-2-methylindan-1-one* (70 mg, 15%), b.p. 170—180° (Found: C, 74.8; H, 7.0. $C_{11}H_{12}O_2$ requires C, 75.0; H, 6.9%); $\nu_{max.}$ (film) 1 690s, 1 600s, 1 460m, and 1 260s cm^{-1}; τ 2.39 (1 H, d, *J* 8 Hz, ArH), 3.20 (2 H, m, ArH), 6.14 (3 H, s, O·CH_3), 6.68 (1 H, m, *J* 8 Hz, C*H*·CH_3), 7.39 (2 H, m, *J* 14 Hz, CH_2), and 8.75 (3 H, d, *J* 7 Hz, CH_3). The major product was *5-methoxy-2-methylindan-1-one* (280 mg, 60%), m.p. 62—65° (from ether–hexane) (Found: C, 75.1; H 6.7. $C_{11}H_{12}O_2$ requires C, 75.0; H, 6.9%).

8-Methoxy-3-methylisocoumarin (15).—After 30 min at room temperature, a solution of 7-methoxy-2-methylindan-1-one (100 mg) in trifluoroacetic anhydride (10 ml) was evaporated to give the enol derivative (14) as an oil (120 mg, 80%), $\nu_{max.}$ (film) 1 800s, 1 600s, 1 260s, 1 230s, and 1 160s cm^{-1}; τ (CF_3·CO_2H) 3.08 (3 H, m, ArH), 6.14 (3 H, s, O·CH_3), 6.65 (2 H, s, CH_2), and 7.99 (3 H, s, CH_2). This oil (55 mg) was treated with ozonised oxygen as in the preparation of (11) to give 8-methoxy-3-methylisocoumarin (34 mg, 90%), which crystallised from ethanol as prisms, m.p. 109—110° (lit.,[11] 104.5—110.5°), $\nu_{max.}$ 1 725s, 1 660s, 1 595s, and 1 565s cm^{-1}; τ 1.8—3.1 (3 H, m, ArH), 3.80 (1 H, s, 4-H), 6.13 (3 H, s, OCH_3), and 7.75 (3 H, s, CH_3).

We thank the S.R.C. for support and Roche Products Ltd. for a CAPS award to R. H. C.

[6/028 *Received*, 6th *January*, 1976]

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