A New Approach to Rethrolone Synthesis

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Rearrangement of the 4-ylidenebutenolides (4) and (5), with sodium methoxide in methanol, leads to the cyclopent-2-ene-1,4-diones (6), which when heated with sodium chloride in dimethyl sulphoxide give the 1,4-diones (7). The latter can be reduced using zinc in acetic acid, to the dihydrorethrolones (8). In a similar manner, rearrangement of (10) produces (11a) which can be demethoxycarbonylated to (11b), an intermediate used previously in a synthesis of natural jasmololone (8; R = EtCH:CH).

The prop-2-enyl substituted cyclopentenolones (8; R = MeCH=CH, EtCH=CH, CH_2=CH·CH=CH) known collectively as 'rethrolones', are the alcohol components of the insecticidal pyrethrin esters found in pyrethrum *Chrysanthemum cinerariaefolium*.[1] The commercial importance of pyrethrin insecticides has resulted in the development of a range of methods for the synthesis of the rethrolone portions of the molecules.[2] In this paper, we describe a new approach to this interesting problem, which is based on a novel rearrangement of the 4-ylidenebut-2-enolides (4) and (5) derived from an appropriately substituted maleic anhydride (3).

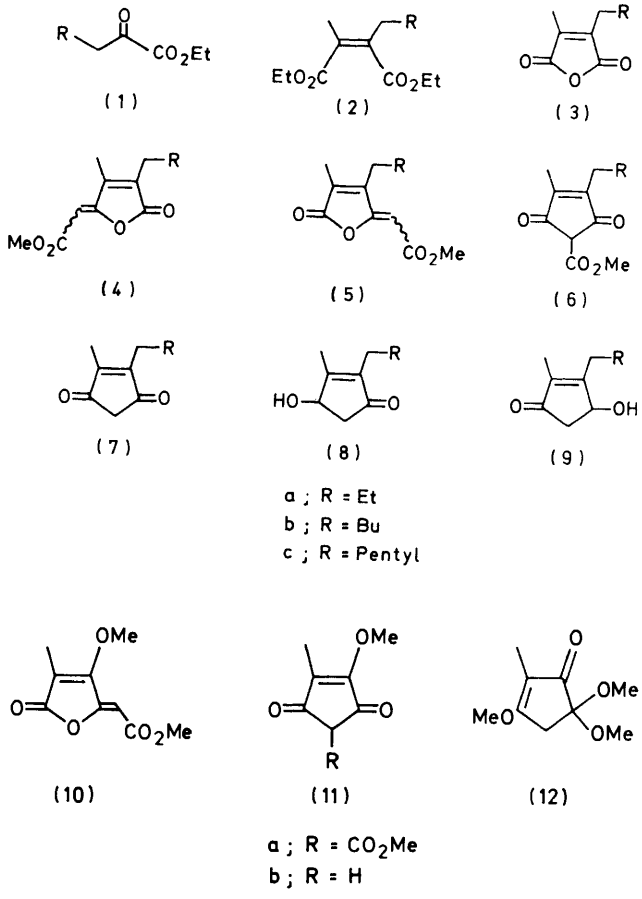
Olefination of the alkyl substituted α-keto- esters (1) with diethyl 1-ethoxycarbonylethylphosphonate, in agreement with investigations by Sutherland *et al.*[3] produced mainly the substituted maleate esters (2) and negligible amounts (<5%) of the corresponding fumarate esters. Attempts to olefinate the allyl substituted α-keto-ester (1; R = CH:CH_2) with the same phosphonate were unsuccessful, due to competing enolate formation in the keto-ester.

Saponification of the maleate esters (2), followed by cyclohydration of the resulting maleic acids in the presence of acetic anhydride, then led to the corresponding 2-alkyl-3-methylmaleic anhydrides (3).

Treatment of the maleic anhydrides (3) with methoxycarbonylmethylenetriphenylphosphorane in refluxing chloroform resulted in the formation of a mixture of *E*-(major) and *Z*-isomers of the methoxycarbonylmethylidenebut-2-enolides (4; major) and (5).[4] The isomers were not separated, but instead treated collectively with sodium methoxide in methanol at 0 °C, whereupon they rearranged to the cyclopentenediones (6) in high yield.[5] Heating the methoxycarbonylated diones (6) with sodium chloride in aqueous dimethyl sulphoxide [6] at reflux, then effected smooth demethoxycarbonylation leading to the cyclopentene-1,4-diones (7).

Reduction of the diones (7), using zinc in acetic acid, following the work of Vandewalle *et al.*,[7] was found to be regioselective producing largely the dihydrorethrolones (8), accompanied by smaller amounts of the positional isomers (9).

In a parallel investigation of the potential for maleic anhydride in the synthesis of rethrolones we also synthesised the ylidenebut-2-enolide (10) from 2-methoxy-3-methylmaleic anhydride. The butenolide was smoothly rearranged to the dione (11a) [5] which was demethoxycarbonylated to 2-methoxy-3-methylcyclopentene-1,4-dione (11b). Treatment of the dione (11b) with trimethyl orthoformate then led to the ketal (12), a central intermediate in Vandewalle's synthesis of jasmololone (8; R = EtCH=CH).[8]



Experimental

For general experimental details see ref. 5.

Preparation of α-Keto-esters (1).—The general procedure described by Eliel and Hartmann [9] was followed, and the following esters were prepared: ethyl 2-oxoheptanoate,[10] b.p. 98—104 °C at 3 mmHg, $\nu_{max.}$ (film) 1 730 cm^{-1}, δ 4.28 (q, *J* 7, OCH_2CH_3), 2.8 (t, *J* 8, CH_2CH_2CO), 1.12—1.92 (m, 9 H), and 0.92 (t, *J* 7, CH_2CH_3) (Found: *m/z* 172.1094. $C_9H_{16}O_3$ requires *M* 172.1095); ethyl 2-oxohexanoate,[9] $\nu_{max.}$ 1 730 cm^{-1}, δ 4.32 (q, *J* 7, OCH_2CH_3), 2.84 (t, *J* 8, CH_2CH_2-CO), 1.16—1.8 (m, 7H), and 0.96 (t, *J* 7, CH_2CH_3) (Found: *m/z* 158.0933. $C_8H_{14}O_3$ requires *M* 158.0943); ethyl 2-oxopentanoate, $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1}, δ 4.28 (q, *J* 7, OCH_2CH_3), 2.8 (t, *J* 8, CH_2CH_2CO), 1.68 (sextet, *J ca.* 7.5, $CH_2CH_2CH_3$), 1.36 (t, *J* 7, OCH_2CH_3), and 0.92 (t, 7.5, CH_2CH_3); ethyl 2-oxopent-4-enoate, b.p. 40—42 °C at 0.5 mmHg, $\nu_{max.}$ (film) 1 725 and 1 640 cm^{-1}, δ 5.6—6.2 (m, CH:CH_2), 5.1—5.4 (m, : CH_2), 4.3 (q, *J* ~ 7, OCH_2CH_3), 3.6br (d, *J* ~ 8, CH_2CO), and 1.28 (t, *J* 7, OCH_2CH_3) (*m/z* 142, $C_7H_{10}O_3$).

Diethyl 2-Alkyl-3-methylmaleates (2).—The general procedure described by Huff *et al.*[3] was followed, and the follow-

ing maleates were prepared: diethyl 2-methyl-3-n-pentylmaleate, $\nu_{max.}$ 1 720 and 1 640 cm^{-1}; δ 4.1—4.6 (m, OCH_2CH_3), 2.2—2.5 (m, CH_2C:), 1.96 (:CMe), 1.2—1.8 (m, 6 H), 1.2—1.5 (OCH_2CH_3), and 0.96 (t, *J* 7, CH_2CH_3) (*m/z* 256, $C_{14}H_{24}O_4$); diethyl 2-n-butyl-3-methylmaleate, b.p. 98—100 °C at 0.01 mmHg, $\nu_{max.}$ 1 720 and 1 640 cm^{-1}; δ1.94 (:CMe); diethyl 2-methyl-3-n-propylmaleate, $\nu_{max.}$ 1 720 and 1 640 cm^{-1}; δ 1.96 (:CMe).

2-Alkyl-3-methylmaleic Anhydrides (3).—A solution of the diethyl 2-alkyl-3-methylmaleate (1g) in ethanol (8 ml) and 2M-sodium hydroxide (4 ml) was stirred at 25 °C for 7 h under nitrogen, then diluted with water (20 ml) and washed with ether. The aqueous layer was acidified with dilute hydrochloric acid, and then extracted with ether. Evaporation of the dried ether layer left the crude 2-alkyl-3-methylmaleic acid (*ca.* 75%) as an oil. A solution of the maleic acid (0.5 g) in acetic anhydride (20 ml) was heated under reflux in an atmosphere of nitrogen for 12 h, and then evaporated to dryness. Chromatography of the residue on silica gel impregnated with formic acid using benzene as eluant gave the anhydride (*ca.* 80%) as a colourless oil.

The following maleic anhydrides were prepared: 2-methyl-3-n-pentylmaleic anhydride, $\nu_{max.}$ ($CHCl_3$) 1 860, 1 820, 1 760, and 1 640 cm^{-1}; δ 2.52 (t, *J* 7, :C·CH_2), 2.08 (:CMe), 1.12—1.84 (m, 6 H), 0.92 (t, *J* 7, CH_2CH_3) (Found: *m/z* 182.0932. $C_{10}H_{14}O_3$ requires *M* 182.0943); 2-n-butyl-3-methylmaleic anhydride,[11] $\nu_{max.}$(film) 1 820 and 1 760 cm^{-1}; δ 2.08 (:CMe) (Found: *m/z* 168.0787. $C_9H_{12}O_3$ requires *M* 168.0786); 2-methyl-3-n-propylmaleic anhydride $\nu_{max.}$ 1 860, 1 820, and 1 760 cm^{-1}; δ 2.06 (:CMe).

2-Alkyl-5-methoxycarbonyl-3-methylcyclopent-2-ene-1,4-diones (6).—A solution of the 2-alkyl-3-methylmaleic anhydride and methoxycarbonylmethylenetriphenylphosphorane (1.5 equiv.) in chloroform was heated under reflux in an atmosphere of nitrogen for 20 h, and then evaporated to dryness.[4] Chromatography of the residue on silica gel using dichloromethane–hexane (4 : 1) as eluant led to a mixture of *Z*- and *E*-isomers of 4- and 5- methoxycarbonylmethylidenebut-2-enolides (*ca.* 80%) as an oil. By the general procedure described previously,[5] the mixture of methoxycarbonylmethylidenebut-2-enolides was rearranged in methanolic sodium methoxide to give the corresponding cyclopent-2-ene-1,4-diones. The following cyclopentenediones were prepared: 5-methoxycarbonyl-3-methyl-2-n-pentylcyclopent-2-ene-1,4-dione, $\nu_{max.}$(film) 1 760, 1 725, and 1 700 cm^{-1}; δ 3.88 (OMe), 3.92 (1 H), 2.46 (t, *J ca.* 7, :C·CH_2CH_2), 2.16 (:CMe), 1.1—1.7 (m, 6H), 0.92 (t, *J ca.* 7, CH_2CH_3) (Found: *m/z* 238.1211. $C_{13}H_{18}O_4$ requires *M* 238.1205); 5-methoxycarbonyl-3-methyl-2-n-propylcyclopent-2-ene-1,4-dione, $\nu_{max.}$ 1 740 and 1 700 cm^{-1}; δ 3.86 (OMe), 3.9 (1 H), 2.5 (t, *J ca.* 7, :C·CH_2CH_2), 2.16 (:CMe), 1.6 (sextet, *J ca.* 7, CH_2CH_3), and 1.0 (t, *J ca.* 7, CH_2CH_3).

2-Alkyl-3-methylcyclopent-2-ene-1,4-diones (7).—A mixture of the 2-alkyl-5-methoxycarbonyl-3-methylcyclopent-2-ene-1,4-dione (0.6 g) and sodium chloride (0.15 g) in water (1 ml) and dimethyl sulphoxide (5 ml) was heated under reflux for 1 h; it was then evaporated to dryness and extracted with ether. Evaporation of the washed (H_2O) and dried ($MgSO_4$) ether extracts, followed by chromatography of the residue on silica gel using ether as eluant gave the cyclopent-2-ene-1,4-dione (*ca.* 90%) as an oil. The following cyclopentenediones were prepared: 2-methyl-3-n-pentylcyclopent-2-ene-1,4-dione,[7] $\nu_{max.}$ (film) 1 700 and 1 630 cm^{-1}; δ 2.95 ($COCH_2$), 2.54 (t, *J ca.* 7, :C·CH_2), 2.1 (2.1 (:CMe), 1.2—1.6 (m, 6 H), 0.94 (t, *J ca.* 7, CH_2CH_3), (*m/z* 180, $C_{11}H_{16}O_2$); 2-n-butyl-3-methylcyclopent-2-ene-1,4-dione,[12] $\nu_{max.}$ 1 700 and 1 630 cm^{-1}, δ 2.88 ($COCH_2$), 2.48 (t, *J* 7, :C·CH_2), 2.08 (:CMe), 1.2—1.6 (m, 4H), 0.98 (t, *J ca.* 7, CH_2CH_3) (*m/z* 166, $C_{10}H_{14}O_2$); 2-methyl-3-n-propylcyclopent-2-ene-1,4-dione,[12] $\nu_{max.}$ 1 700 and 1 635 cm^{-1}; δ 2.95 ($COCH_2$), 2.52 (t, *J* 7, :C·CH_2), 2.10 (:CMe), 1.64 (sextet, *J ca.* 7 $CH_2CH_2CH_3$), 0.98 (t, *J* 7, CH_2CH_3) (Found: *m/z* 152.0841. $C_9H_{12}O_2$ requires *M* 152.0837).

2-Methoxy-3-methylcyclopent-2-ene-1,4-dione (11*b*).—The general procedure for demethoxycarbonylation described above was followed, and gave the dione[13] as colourless crystals (85%), m.p. 45—46 °C, $\nu_{max.}$ ($CHCl_3$) 1 700 and 1 635 cm^{-1}; δ 4.48 (OMe), 3.0 (CH_2), and 2.04 (:CMe) (Found: *m/z* 140.0477. Calc. for $C_7H_8O_3$: *M* 140.0473).

2-Alkyl-4-hydroxy-3-methylcyclopent-2-enones(Dihydrorethrolones) (8).—The general procedure for reduction using zinc–acetic acid, described by Vandewalle *et al.*[7] was followed, and the following dihydrorethrolones were prepared: 4-hydroxy-3-methyl-2-n-pentylcyclopent-2-enone(dihydrojasmololone), $\nu_{max.}$ ($CHCl_3$) 3 600, 1 710, and 1 650 cm^{-1}, δ 4.73 (d, *J* 6, C*H*OH), 2.78 (dd, *J* 18 and 6, C*H*H·CHOH), 2.28 (dd, *J* 18 and 2, CH*H*·CHOH), 2.17 (t, *J* 7, :C·CH_2), 2.09 (:CMe), 1.2—1.6 (m, 6 H), and 0.90 (t, *J* 7, CH_2CH_3) (Found: *m/z* 182.1283. Calc. for $C_{11}H_{18}O_2$: 182.1306) [^{1}H n.m.r. data, δ 4.86 (C*H*·OH), 1.75 (:CMe) showed the presence of 15—20% of the alternative positional isomer]; 2-n-butyl-4-hydroxy-3-methylcyclopent-2-enone, δ 4.73 (d, *J* 6, C*H*·OH) and 2.09 (:CMe) (Found: *m/z* 168.1140. Calc. for $C_{10}H_{16}O_2$: *M* 168.1150) [^{1}H n.m.r. data, δ 4.85 (C*H*OH), and 1.75 (:CMe), showed the presence of 15% of the alternative positional isomer]; 4-hydroxy-3-methyl-2-n-propylcyclopent-2-enone (dihydroallethrolone), δ 4.76 (C*H*OH), 2.12 (:CMe) (Found: *m/z* 154.0992. Calc. for $C_9H_{14}O_2$: *M* 154.0994) [^{1}H n.m.r. data, δ 1.73 (:CMe), showed the presence of 33—40% of the alternative positional isomer].

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