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CYCLOPENTANONES—III*

A NEW SYNTHESIS OF (±) ALLETHROLONE

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Abstract—A new synthesis of (±) allethrolone, starting from 3-methyl-1,2,4-cyclopentanetrione, is described. The key intermediate for this synthesis is 2-methyl-3,5,5-triethoxy-2-cyclopentene-1-one. Starting from this compound, allethrin, the ester of allethrolone and chrysanthemic acid, has been obtained in an overall yield of 52%. The method has a general applicability in the synthesis of cyclopentenolones.

ALLETHROLONE (Ia) is a synthetic homologue of the natural occurring rethrolones; cinerolone (Ib), jasmololone (Ic) and pyrethrolone (Id). These cyclopentenolones are the alcohol components of the principal insecticidal constituents of pyrethrum flowers.[1] Esterified with chrysanthemic acid (IIa) and pyrethric acid (IIb) they form the pyrethrins (IIIb,c,d) of which allethrin (IIIa) is a commercially available synthetic homologue.

A general route leading to the cyclopentenolones I has been developed by Schechter, *et al.*[2]; recently an elegant improvement of this synthesis has been described by Crombie, *et al*[3]. The key step to their synthesis consists of the condensation of an appropriately substituted acetoacetate with pyruvaldehyde and subsequent cyclization to the ketols I.

This paper presents a new synthesis of the cyclopentenolones I starting from a cyclic key intermediate. In a general study of 3-alkyl-1,2,4-cyclopentanetriones, examining specific reactions at the 2-carbonyl function, it was found that the 1- and 4-carbonyl groups can suitably be protected by means of orthoformic esters.[4] Starting from the easily accessible 3-methyl-1,2,4-cyclopentanetrione (occurring as the enol-form IV), 2-methyl-3,5,5-triethoxy-2-cyclopentene-1-one (V) is obtained in 78% yield. Compounds of the general type V are key intermediates for the introduction of a second substituent in a 5-membered ring. Organomagnesium and organolithium reactions, followed by acid hydrolysis, leads to 2,3-dialkyl-2-cyclopentene-1,4 diones (VII) in good yields. For the synthesis of allethrolone (Ia) the ene-dione VIIa was obtained in 87% yield starting from V and allylmagnesium bromide. The only remaining problem was the specific reduction of the 4-carbonyl function. A suitable intermediate for this step in the synthesis should be compound VIa. The organomagnesium reaction product was therefore hydrolysed with water. Indeed one can expect that allylic rearrangement would lead to the enone part in the molecule without cleavage of the acetal function. Although compound VIa was formed (as shown by spectroscopic evidence) its isolation and purification was impossible. The same results were obtained for the other organometallic reactions when the alkyl group contains a double or triple

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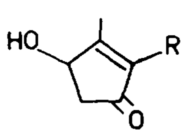
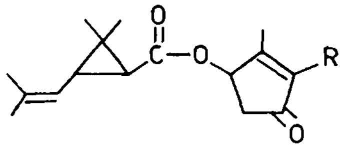
bond.[5] However, when the chain introduced is a saturated alkyl group (as for the synthesis of Ie) the intermediate can easily be isolated in high yield. Subsequent reduction of the carbonyl function in VIe with sodium borohydride led to tetrahydropyrethrolone (Ie) with a yield of 55% starting from VI.

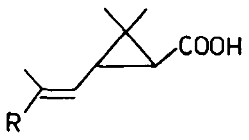
For the selective reduction of the carbonyl function next to the Me substituent in compounds VII several methods were investigated. Only reduction with lithium tri-t-butoxy-aluminum hydride and zinc–acetic acid[6] gave acceptable results. Tetrahydropyrethrolone (Ie) was obtained in 78% yield by means of the complex metal hydride reduction (GC analysis showed only 3% of the isomer). For Ia however this method led to a poor yield, mainly due to the formation of more complex reaction mixture. (±) Allethrolone (Ia) was however obtained in high yield by the zinc–acetic acid reduction in methylene chloride at −10°. This method led to a practically quantitative yield of a mixture of ca. 92% Ia and 8% of the isomer (occurring from the reduction of the other carbonyl function) as shown by GC analysis. The assignation of the structure as allethrolone is based on the PMR spectrum, which is identical with the one described in the literature.[7] The signal of the 4-methylene protons (δ = 2·85) is



I



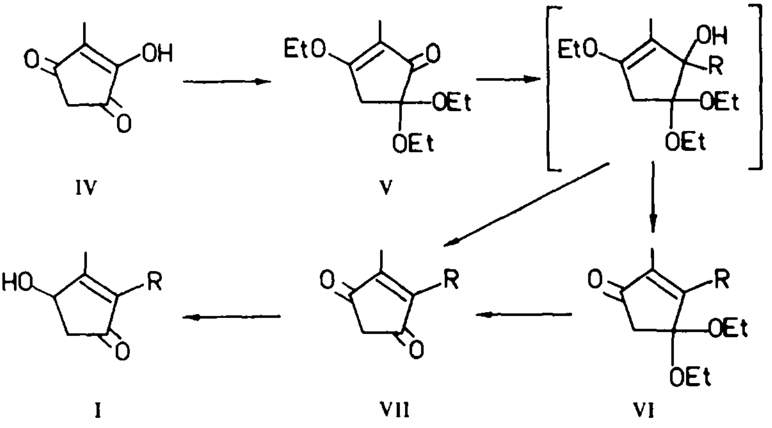
III



II

a: $R = -CH_2-CH=CH_2$
b: $R = -CH_2-CH\overset{cis}{=}CH_2-CH_3$
c: $R = -CH_2-CH\overset{cis}{=}CH-CH_2CH_3$
d: $R = -CH_2-CH\overset{cis}{=}CH-CH=CH_2$
e: $R = n.C_5H_{11}$

a: $R = CH_3$
b: $R = COOCH_3$



IV V

I VII VI

a: $R = -CH_2-CH=CH_2$
e: $R = n.\ C_5H_{11}$

shifted upfield compared to the signal in the starting material VIIa (δ = 3·15); in the latter compound the protons considered are more deshielded (γ-position of an α,β-enone system).

By distillation (0·02 mm) only ca. 50% can be recovered because of pronounced resinification. The IR, NMR and mass spectra before and after distillation are however practically identical. The crude (±) allethrolone was therefore esterified directly with chrysanthemic acid chloride to give allethrin (IIIa) which can be purified by distillation (starting from VIIa the yield of IIIa is 61%). Esterification of a purified sample gave 76% yield (37% overall from VIIa).

The synthesis of the natural rethrolones (Ib,c,d) is now being investigated.

EXPERIMENTAL

2-*Allyl*-3-*methyl*-2-*cyclopentene*-1,4-*dione* (IIa)

To a stirred suspension of Mg (36 g; 1·5 mole) in dry ether (100 ml) was added dropwise a mixture of allyl bromide (180 g; 1·5 mole) and 2-methyl-3,5,5-triethoxy-2-cyclopentene-1-one (57 g; 0·25 mole) in dry ether. The mixture was heated under reflux for 10 hr, and was then acidified with 0·1 N cold H_2SO_4. The ether layer was separated, washed (water) and dried (Na_2SO_4). After evaporation of the ether, the residue was distilled (b.p. 94°/0·05 mm) as a pale yellow oil. The yield of VIIa was 32·6 g, 87%. (Found: C, 71·85; H, 6·55. Calc for $C_9H_{10}O_2$: C, 72·0; 6·67%); UV spectrum (MeOH) λ_{max} = 245 mµ; IR spectrum: peaks at 3080, 1750, 1720 and 1640 cm^{-1}; PMR spectrum (CCl_4): 3-Me, δ=1·99; 5-H, =2·74; 2-CH_2, δ=3·15 (m=2, *J*=6 c/s); =CH_2, δ=5·1 (m); ═CH_2 δ 5·7 (m). Mass spectrum: *M/e* at: 150 (M^+, 100%), 135 (18%), 122 (18%), 121 (7%), 107 (22%), 80 (30%), 79 (97%), 77 (29%).

4,4-*Diethoxy*-2-*methyl*-3-*n.pentyl*-2-*cyclopentene*-1,4-*dione* (VIe)

To a stirred soln of n-pentylmagnesium bromide (0·048 mole) in dry ether (50 ml) was added dropwise IIa (4·56 g; 0·02 mole) in dry ether (40 ml) at 0°. The reaction mixture was heated for 8 hr and was then poured on crushed ice. Ether was added and the inorganic salts were removed by centrifugation. The ether layer was dried (Na_2SO_4); after evaporation under reduced press, the residue is distilled (b.p. 122–125°/0·5mm) yielding VIe (4·2 g; 80%) as a light yellow liquid, UV spectrum (MeOH) λ_{max} = 231 mµ ε = 9760); IR spectrum: peaks at 1720, 1450, 1330 and 1050 cm^{-1}; PMR spectrum (CCl_4): $OCH_2\ {-C\underline{H}_3}$, δ = 1·16 (m = 3, *J* = 4·2 c/s; $OC\underline{H}_2{-}CH_3$, δ = 3·4 (m, complex because of hindered rotation); 2-CH_3, δ = 1·68; 5-H, δ = 2·40; 3-CH_2—, δ = 2·32 (m = 3, *J* = 6 c/s); Mass spectrum: *m/e* at: 254 (M^+, 2%), 208 (87%), 124 (100%).

2-*Methyl*-3-*n.pentyl*-2-*cyclopentene*-1,4-*dione* (VIIe)

The same procedure was followed as for VIe except that the hydrolysis was carried out with 10% H_2SO_4. The compound VIIe (yield 82%) was distilled as a yellow oil (b.p. 70–73°/0·2 mm). (Found: C, 73·68; H, 8·62. Calc for $C_{11}H_{16}O_2$: C, 73·30; H, 8·94%); UV spectrum (MeOH) λ_{max} = 246 mµ (ε = 11·400); IR spectrum: peaks at 1750, 1710 and 1650 cm^{-1}; PMR spectrum (CCl_4): 2-Me, δ = 1·97; 5-H, δ = 2·68; 3-CH_2—, δ = 2·4 (m = 3, *J* = 7 c/s); Mass spectrum: peaks at *m/e*: 180 (M^+, 16%), 165 (15%), 152 (57%), 137 (28%), 124 (100%), 123 (31%), 96 (21%) and 95 (22%).

3-*Allyl*-4-*hydroxy*-2-*methyl*-2-*cyclopentene*-1-*one*, *allethrolone* (Ie)

Zn dust (30 g; 0·5 mole) was added in portions over a period 20 min to a stirred soln of 2-allyl-3-methyl-2-cyclopentene-1,4-dione (15 g; 0·1 mole) in CH_2Cl_2 (500 ml) and AcOH (200 ml) at −10°. The mixture was stirred at −10° for a further 90 min, and the solvents were then removed under reduced press. Ether (100 ml) was added to the residue, and the soln was filtered to remove Zn. The filtrate was washed (10% Na_2CO_3aq), dried (Na_2SO_4) and evaporated under reduced press. The residue (14·7 g) was almost pure allethrolone, and was used without further purification in the next stage. GC analysis (2 m PTMO column at 200°) showed a practically qualitative yield of the reduction: allethrolone (92%) and the isomeric ketol 8%). Distillation (b.p. 85–90°/0·05 mm) of a portion of the residue occurred with resinification (54% recovered) and gave the same distribution of the isomers; UV spectrum (MeOH)

$\lambda_{max} = 230$ mμ; IR spectrum: peaks at 3380 (broad) 3080, 1720, 1650, 1100 cm^{-1}; PMR spectrum (CCl_4): 2-Me, $\delta = 2{\cdot}03$; 5-H ($\underline{A}$BX), $\delta_A = 2{\cdot}62$ ($J = 18$ c/s and $J = 6$c/s), $\delta_B = 2{\cdot}12$ ($J = 18$ c/s and $J = 2$ c/s); 4-H (AB$\underline{X}$), $\delta = 4{\cdot}58$ ($J = 6$ c/s and $J = 2$ c/s); 3-CH_2—, $\delta = 2{\cdot}85$ ($m = 2$, $J = 6$ c/s); Mass spectrum *m/e* at 152 (M^+, 44%), 137 (27%), 124 (24%), 123 (19%), 111 (29%), 109 (89%), 135 (4%), 134 (4%), 133 (5%).

4-Hydroxy-2-methyl-3-pentyl-2-cyclopentene-1-one; tetrahydropyrethrolone(Ie)

(a) To a stirred soln of VIe (2·54 g, 0·01 mole) in EtOH (20 ml was added $NaBH_4$ (0·28 g; 0·015 mole) in ethanolic 0·1 N NaOH (20 ml) at room temp. After 3 hr the mixture was diluted with water (200 ml), acidified and extracted with ether. The ether soln was washed (5% Na_2CO_3aq), dried (Na_2SO_4) and evaporated under reduced press. The residue was distilled yielding Ie (1 g, 55%), b.p. 132°/1·5 mm (lit.[8] 125°/0·5 mm).

(b) To a soln of lithium tri-t-butoxyaluminum hydride (from LAH, 0·57 g, 0·015 mole and t-BuOH 3·33 g, 0·045 mole) in THF (25 ml) was added dropwise VIIe (1 g, 0·0055 mole) in THF (95 ml) at 0°.

The mixture was stirred for 30 min at 0° and 1 hr at room temp and then hydrolysed with 0·1 N HCl. After extraction with ether the organic layer was dried (Na_2SO_4) and evaporated under reduced press. On distillation, Ie was obtained (yield 0·78 g, 78% b.p. 120°/0·3 mm). GC analysis (2 m PTMO column at 205°) showed about 3% of the isomer; UV spectrum (MeOH): $\lambda_{max} = 234$ mμ; IR spectrum: peaks at 3400, 1700 and 1660 cm^{-1}; PMR spectrum (CCl_4): 2-Me, $\delta = 2{\cdot}04$; 5-H ($\underline{A}$BX), $\delta_A = 2{\cdot}61$ ($J = 17{\cdot}4$ c/s and $J = 5{\cdot}8$ c/s), $\lambda_B = 2{\cdot}14$ ($J = 17{\cdot}4$ c/s and $J = 2{\cdot}2$c/s); 4-H (AB$\underline{X}$), $\delta = 4{\cdot}57$ ($J = 5{\cdot}8$ c/s and $J = 2{\cdot}2$ c/s); 3-CH_2—, $\delta = 2{\cdot}1$; O—H, $\delta = 3{\cdot}84$; Mass spectra: *m/e* at 182 (M^+, 56%), 167 (73%), 153 (15%), 139 (27%), 126 (90%), 111 (69%).

Allethrin (IIIa)

Chrysanthemic acid chloride (2·18 g; 0·011 mole) in dry ether (25 ml) was added dropwise to a cooled (ice) stirred soln of allethrolone (1·52 g; 0·01 mole) and pyridine (0·8 g; 0·01 mole) in dry ether (25 ml). The mixture was then heated under reflux for 2 hr, cooled, filtered from pyridine hydrochloride, washed (10% $NaHCO_3$aq) and dried (Na_2SO_4). The solvent was removed under reduced press, and the residue was distilled to give the insecticide allethrin (2·3 g, 76%) as a pale yellow oil, b.p. 140°/0·01 mm (lit.[8]: 135–138°/0·05 mm). Preparative GC was carried out on a 6 m SE.30 column at 230°; IR spectrum: peaks at 1720, 1650, 1150 cm^{-1}; PMR spectrum (CCl_4): 2-Me, $\delta \simeq 1{\cdot}98$; 5-H ($\underline{A}$BX), $_A \simeq 2{\cdot}75$ (partly obscured); $\delta_B \simeq 2{\cdot}10$ (partly obscured); 4-H (AB$\underline{X}$), δ–5·6 (partly obscured); 3-CH_2 ≃, $\delta = 2{\cdot}89$ ($J = 6$ c/s; mass spectrum: *m/e* at: 302 (M^+, 4%); 168 (14%); 153 (10%); 151 (7%); 136 (32%); 123 (100%); 107 (32%).

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