64. *Acylcyclopentanones. Part I. The Synthesis of 3-Acylcyclopentane-1,2,4-triones.*

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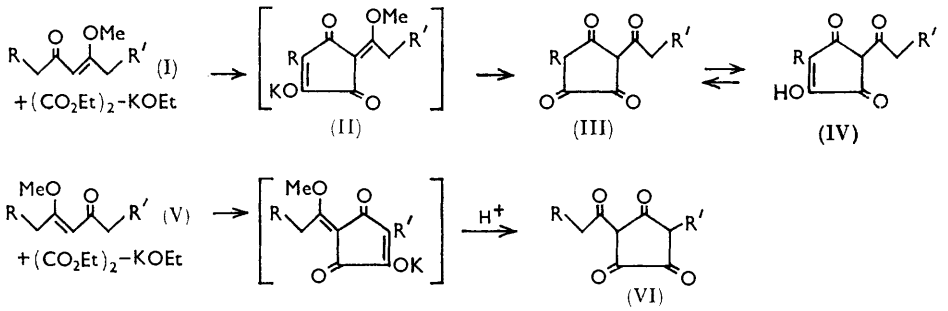
3-Acylcyclopentane-1,2,4-triones are obtained by condensation of the enol ethers of β-diketones with diethyl oxalate. They are monoenolic, monobasic acids with pK_a 2·7—2·8. Their spectra, which are discussed in detail, are in agreement with the structures advanced.

SYNTHESIS of 3-acylcyclopentane-1,2,4-triones (III) has not yet been reported, although several attempts to prepare them appear to have been made.[1] A method of synthesis of these compounds has now been found in the condensation of the αβ-unsaturated ketones or enol ethers (I) with diethyl oxalate. Physical properties show that the compounds exist in a monoenolic form (*e.g.*, IV).



a, R = R′ = H. b: R = R′ = Me. c: R = H, R′ = Pr^i. d: R = H, R′ = Bu^n.

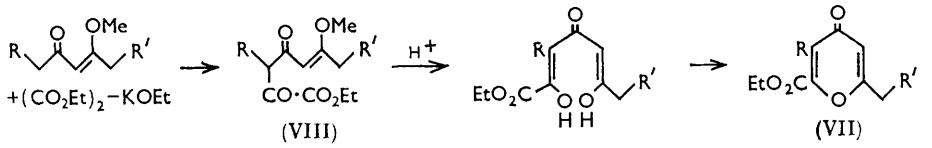
The enol ethers (I) were prepared from the corresponding 1,3-diketones with diazomethane by Eistert and Arndt's method.[2] With asymmetric diketones (c and d), a 1 : 1 mixture of the isomers (I) and (V) is obtained. These mixtures cannot be separated by distillation and are used in the further reactions as such. The salts (II or similar structure) cannot be purified but, on treatment with acid, they yield the cyclopentanetriones (III) directly. Compound (IIIa) was purified by crystallization, but (IIIb) required counter-current distribution. In the series (c and d) [starting from a mixture of (I) and (V)], two isomeric cyclopentanetriones (III and VI) can be expected, and it was necessary to subject the reaction mixtures to counter-current distribution; this showed that only the isomer (III) was present. It must thus be concluded that terminal methyl groups react preferentially, before methylene groups. We are investigating this problem further.

The yields are low and the best results (10—30%) were obtained when two mol. of potassium ethoxide were used. In the reactions of series (b and c) the pyrones (VII) were isolated as by-products after acidification. These structures are supported by infrared

[1] Harris, Howard, and Pollock, *J.*, 1952, 1906.
[2] Eistert, Arndt, Loewe, and Ayça, *Chem. Ber.*, 1951, **84**, 156.

(i.r.) and nuclear magnetic resonance spectra (n.m.r.) and show that an intermediate (VIII) occurs during the formation of the acylcyclopentanetriones (III).

The 3-acylcyclopentane-1,2,4-triones (III) are monobasic acids with pK_a (in 1 : 1 water–methanol) 2·7—2·8.

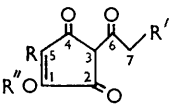


Infrared spectra (recorded with a Perkin-Elmer spectrophotometer 21 for potassium bromide discs) of 3-acylcyclopentane-1,2,4-triones show a very characteristic pattern, with strong peaks at 1565—1580, 1640—1650, and 1720—1730 cm.$^{-1}$, a broad ($\pm$150 cm.$^{-1}$) band of variable and medium size at 1900 cm.$^{-1}$, and a very broad band at 3000—2300 with two maxima (2750 and 2450 cm.$^{-1}$). Except for the band at 1900 cm.$^{-1}$ which we cannot explain, this spectrum supports the enolic structure of the compounds.

Ultraviolet spectra (recorded with a Perkin-Elmer spectrophotometer 137) for 0·1N-hydrochloric acid–methanol solutions of 3-acylcyclopentane-1,2,4-triones show a maximum at 261—265 mμ (ε 8000—8800), and for 0·1N-sodium hydroxide–methanol solution at 256—258 mμ (ε 10,000—11,500).

The n.m.r. spectra were obtained for 10% solutions in deuterated chloroform with

Nuclear magnetic resonance of compounds,



Compound	See notes	1-OR″	5-R	3-H	7-CH_2	R′ CH	R′ CH_2	R′ CH_3
R = R′ = H, R″ = Me.....	1	6·07	3·05	3·82				7·63
	2	1	2	2				1
	3	—	2·3	2·3				—
	4	3	1	1				3
R = R′ = R″ = Me	1	6·1	7·77	3·81	7·4			8·76
	2	1	1	1	4			3
	3	—	—	—	7·6			7·6
	4	3	3	1	2			3
R = R″ = H, R′ = Pr^i ...	1	−2·8 *	2·7	3·54	7·44	7·8		9·04
	2	1	2	2	2	m †		2
	3	—	— ‡	2·0	6·4	—		6·4
	4	1	1	1	2	1		6
R = R″ = H, R′ = Bu^n ...	1	−2·8 *	2·7	3·51	7·31		8—9	9·1
	2	1	2	2	3		m †	3
	3	—	— ‡	2·3	—		—	—
	4	1	1	1	2		6	3

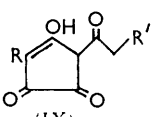
Compounds (VII).

		3-R	5-H	8-CH_2	7-CH_2	9-CH_3	R′ CH	R′ CH_3
R = R′ = Me	1	7·74	3·83	5·6	7·4	8·61		8·74
	2	1	1	4	4	3		3
	3	—	—	7·1	7·5	7·2		7·6
	4	3	1	2	2	3		3
R = H, R′ = Pr^i	1	2·99	3·8	5·57	7·51	8·58	8	9
	2	2	2	4	2	3	m †	2
	3	2·3	2·3	7·0	6·0	7	—	6·1
	4	1	1	2	2	3	1	6

Column 2: 1, τ value; 2, multiplicity; 3, spin–spin coupling constant (c./sec.); 4, no. of H atoms.

* Very broad hydroxyl resonance; m†, badly resolved multiplet; ‡ obscured by chloroform peak.

tetramethylsilane (0·5%) as internal reference. A Varian D.P. spectrometer was used at 56·4 Mc. τ values are given to 0·03 p.p.m. A 100 c./sec. a.f. signal was used to calibrate the spectra. The 3-acylcyclopentane-1,2,4-triones (IIIa and b) are very sparingly soluble in deuteriochloroform. In deuterium oxide the solubility is higher, but the ring protons are too rapidly replaced by deuterium. The substances were therefore converted (in good yield) into the more soluble monomethyl enol ethers. Substances (IIIc and d) are sufficiently soluble in deuteriochloroform. Their spectra (see Table) indicate that the free acids are completely enolized in this medium. The enolization occurs *via* H-5 (see IV or IX); the enol form (X) should give a ring-proton resonance for H-5 at much higher field than does H-3 in (IV or IX). Moreover, there should be a quadruplet for R = Me instead of the observed singlet at τ 3·8. For compound (Xa; R = R′ = H) we expect to find a single line at τ ~7 with intensity 2. The observed doublets at τ 3·05 and 3·82 not only prove formula (IV or IX) but also reveal the existence of long-range spin–spin coupling H-3/H-5 of 2·3 c./sec. (±0·05), which can be compared with the allylic coupling in a number of steroids.[3] We found the same value for the H-3/H-5 spin–spin coupling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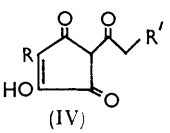
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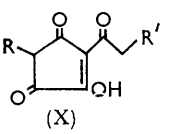
(X)

in the pyrone (VIIc). Since an analogous coupling was found in several other more or less rigid systems, this point is under further study. The spectra recorded in the Table are in complete agreement with the structures proposed.

Experimental

4-Methoxypent-3-en-2-one (Ia).—This compound, prepared by the method of Eistert *et al.*[2] from pentane-2,4-dione and diazomethane, in 75% yield, had b. p. 68—69°/15 mm. (lit., 58—59°/10 mm.).

3-Acetylcyclopentane-1,2,4-trione (IIIa).—To a solution of potassium ethoxide (0·28 mole), in absolute alcohol (15 ml.) and dry ether (60 ml.) was added diethyl oxalate (20·2 g., 0·14 mole) in dry ether (20 ml.). After 15 min. the enol ether (Ia) (15·7 g., 0·14 mole) was added slowly with stirring. The mixture quickly became dark red and gelatinous. After 2 days at room temperature the brown amorphous potassium salt (II) (29 g.) was filtered off and washed with ethanol and ether. It was dissolved in cold water (200 ml.) the solution was acidified with concentrated hydrochloric acid. The *trione* (IIIa) was precipitated and, recrystallized from ethanol (charcoal) (yield, 6·7 g., 32%), sublimed at 186—190° without melting; it had pK_a (by titration in 1 : 1 water–methanol) 2·70 (Found: C, 54·9, 54·7; H, 4·0, 4·1%; *M*, 156. $C_7H_6O_4$ requires C, 54·6; H, 3·9%; *M*, 154).

The triketone (208 mg.) was treated in methanol with ethereal diazomethane; the *methyl ether* sublimed at 95° (yield, 180 mg., 82%) (Found: C, 57·6, 57·6; H, 4·9, 5·2. $C_8H_8O_4$ requires C, 57·8; H, 4·85%).

5-Methoxyhept-4-en-3-one (Ib).—The above method, applied to heptane-3,5-dione,[4] gave the *enol ether* (93%), b. p. 93—97°/15 mm. (Found: C, 67·45, 67·15; H, 10·3, 10·5. $C_8H_{14}O_2$ requires C, 67·6; H, 9·85%).

5-Methyl-3-propionylcyclopentane-1,2,4-trione (IIIb).—The ether (Ib) (5 g., 0·035 mole) was allowed to react with a solution of potassium ethoxide (0·07 mole) and diethyl oxalate (5·14 g., 0·035 mole) in ethanol–ether. After 2 days, the mixture was poured into water (50 ml.). The aqueous layer was acidified and ammonium sulphate added to saturation. The aqueous layer was extracted thoroughly with ether and the extracts were evaporated to ~0·5 l. and extracted with small portions of saturated potassium carbonate solution until the aqueous layer was almost colourless. The latter was acidified, saturated with ammonium sulphate, and extracted

[3] Collins, Hobles, and Sternhell, *Tetrahedron Letters*, 1963, **4**, 197.
[4] Adams and Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1220.

with ether. After drying (Na_2SO_4), the ether was evaporated and a dark brown solid (3·9 g.) obtained. This residue (2 g.) was subjected to counter-current distribution in ether and 50% ammonium sulphate buffer (pH 3·81). After 200 transfers, the material in cells 60—140 was extracted with ether after further acidification and saturation with ammonium sulphate. The ether layer was dried (Na_2SO_4) and evaporated, yielding the *trione* (IIIb) (380 mg., 11·6%). After recrystallization from ethanol–benzene or from dioxan–" iso-octane," the product melted at 187° with sublimation and had pK_a (by titration as above) 2·78 (Found: C, 59·0, 59·4; H, 5·65, 5·55%; *M*, 186. $C_8H_{10}O_4$ requires C, 59·35; H, 5·55%; *M*, 182).

The fraction insoluble in potassium carbonate solution was an oil from which, on storage at 0° for several months, a white solid was precipitated, a further crop being recovered by adding " iso-octane " to the mother-liquor. In this way *ethyl 6-ethyl-3-methyl-4-pyrone-2-carboxylate* (VIIb) (0·85 g.), m. p. 59·5—61°, was obtained (after recrystallization from " iso-octane ") (Found: C, 61·5, 61·8; H, 6·4, 6·7. $C_{11}H_{14}O_4$ requires C, 62·85; H, 6·7%). Distillation of the mother-liquor yielded a further quantity of less pure ester (1·2 g.), b. p. 168—169°/18 mm., which solidified on cooling. The yield was 13·5% (from a condensation with 1 mole of potassium ethoxide).

The enol ether (134 mg.), m. p. 79—83°, was obtained from the trione (IIIb) by use of diazomethane as above and recrystallization from " iso-octane."

Mixed Enol Ethers from 6-Methylheptane-2,4-dione.—The dione [5] (15·9 g.) yielded a mixture (14·8 g.), of ethers (Ic) and (Vc) on reaction with diazomethane; this had b. p. 102·5—115°/6 mm. (90·5%). Vapour-phase chromatography showed two peaks of about equal height.

3-Isovalerylcyclopentane-1,2,4-trione (IIIc).—The reaction was carried out as for the analogue (IIIb), but after pouring of the mixture into water, acidification, and saturation with ammonium sulphate, the ether extract was dried and evaporated. This yielded a dark oil (3·7 g.) from (3·8 g.). This oil (1 g.) was subjected to counter-current distribution in ether–10% ammonium sulphate (pH 2·90), yielding material (210 mg.) from tubes 21—40 (77 transfers) that, when recrystallized from benzene, gave pure *3-isovalerylcyclopentane-1,2,4-trione*, m. p. 168° with sublimation, pK_a (as above) 2·70 (Found: C, 61·95, 61·35; H, 6·4, 6·2%; *M*, 200. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%; *M*, 196).

The oil (800 mg.) recovered from tubes 66—77 was purified by chromatography on silica gel (100 g.) (column of 3 cm. diameter). After elution with benzene (400 ml.), ether was passed through the column; the percolate contained *ethyl 6-isobutyl-4-pyrone-2-carboxylate* (VIIc) (263 mg., 15%). Recrystallization from " iso-octane " gave the pure product, m. p. 55—56·5° (Found: C, 64·3, 64·7; H, 7·2, 7·15. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·2%).

3-Hexanoylcyclopentane-1,2,4-trione (IIId).—Nonane-2,4-dione [6] (16 g.) yielded a 1 : 1 mixture (16 g.) of ethers (Id) and (Vd), b. p. 117—131°/13—16 mm. (92%). Condensation was carried out as for the analogue (IIIb). Counter-current distribution was carried out in ether–10% ammonium sulphate (pH 3·08). After 200 transfers, the cells 90—160 contained *3-hexanoylcyclopentane-1,2,4-trione* (IIId). Recrystallization from ethanol–benzene gave a product (16%) having m. p. 137—137·5°, pK_a (as above) 2·79 (Found: C, 62·95, 62·8; H, 6·65, 6·8%; *M*, 214. $C_{11}H_{14}O_4$ requires C, 62·85; H, 6·7%; *M*, 210).

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[5] Sprague, Beckham, and Adkins, *J. Amer. Chem. Soc.*, 1934, **56**, 2665.
[6] Meyer and Hauser, *J. Org. Chem.*, 1960, **25**, 158.