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ALICYCLIC DIKETONES AND DIOLS—IV*

THE CYCLIZATION OF ETHYL 6-OXO-5-PHENYLHEPTOATE

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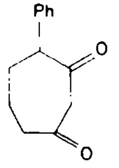
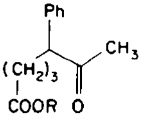
Abstract—The cyclization of ethyl 6-oxo-5-phenylheptoate, by sodium ethoxide in ethanol, has now been shown to give 6-oxo-5-phenylheptoic acid, 2-acetyl-5-phenylcyclopentanone, 3-ethoxycarbonyl-2-methyl-1-phenylcyclopent-1-ene and 3-ethoxycarbonyl-2-methyl-1-phenylcyclopent-2-ene. The material previously described as a hydrate of 4-phenylcycloheptane-1,3-dione is in fact a mixture of 6-oxo-5-phenylheptoic acid and 2-acetyl-5-phenylcyclopentanone.

EISTERT[1] *et al.* have differentiated between two categories of 1,3-diones; the "*cis*-fixed", which form chelate compounds (i.e. acyclic 1,3-diones and acyl cyclanones), and the "*trans*-fixed" diones, which do not form chelate compounds and behave as vinylogous acids (i.e. C_4, C_5 and C_6 cyclic 1,3-diones). The report[2] that 4-phenylcycloheptane-1,3-dione (I) has properties peculiar to both "*cis*-fixed" diones (violet colouration with methanolic ferric chloride), and "*trans*-fixed" diones (I.R. spectrum of a vinylogous acid), appeared to contradict these ideas and warranted investigation.

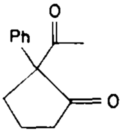
Bergmann and Yaroslavsky[2] cyclized ethyl 6-oxo-5-phenylheptoate (II; R = Et) by means of sodium ethoxide in ethanol, and separated the product with sodium carbonate into a soluble fraction, which they believed to be a hydrate of 4-phenylcycloheptane-1,3-dione (I; H_2O), and an insoluble fraction to which they assigned the structure 2-acetyl-2-phenylcyclopentanone (III).



I



II



III

We have repeated this cyclization and separation a number of times and have consistently obtained the following results:

Carbonate soluble fraction. This material gave a weak violet colouration with methanolic ferric chloride, and had the properties and spectra previously ascribed[2] to the 1,3-dione hydrate $C_{13}H_{14}O_2 \cdot H_2O$ (I; H_2O). It was, however, a mixture which could be further separated, either by distillation or by sodium bicarbonate extraction, into two components. One of these, an acid $C_{13}H_{16}O_3$, was identified as 6-oxo-5-phenylheptoic acid (II; R = H) by direct comparison. The other, the bicarbonate insoluble component $C_{13}H_{14}O_2$, gave an intense violet colouration with methanolic

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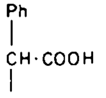
* Part III, *Tetrahedron*, **18**, 821 (1962).

[1] B. Eistert and W. Reiss, *Chem. Ber.* **87**, 92, 108 (1954).

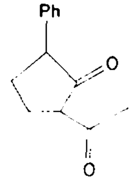
[2] E. D. Bergmann and S. Yaroslavsky, *Tetrahedron* **11**, 154 (1960).

ferric chloride. Its N.M.R. spectrum[3] indicated the presence of C_6H_5 (δ 7·1 to 7·24, *m*, 5 protons) and CH_3CO (keto form, δ 2·2, *s*; enol form δ 1·9). This, together with the U.V. spectrum in neutral solution (λ_{max} 2450 and 2880 Å) and in alkaline solution (λ_{max} 2420 and 3110 Å), indicated that the substance was a phenyl 2-acetylcyclopentanone. Alkaline hydrolysis gave 6-oxo-2-phenylheptoic acid (IV) identified by direct comparison with an authentic specimen. These facts prove that the compound $C_{13}H_{14}O_2$, which is responsible for the violet colouration given by the original carbonate soluble fraction with methanolic ferric chloride, is a mixture of the keto and enol forms of 2-acetyl-5-phenylcyclopentanone (V and VI).

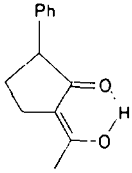


$$\begin{array}{l}Ph\\ |\\ CH\cdot COOH\\ |\\ (CH_2)_3COCH_3\end{array}$$

IV

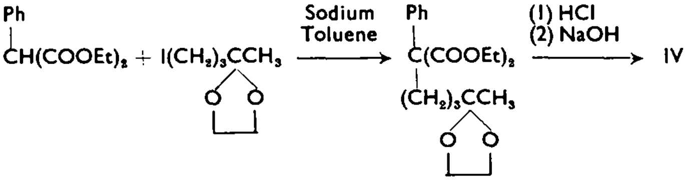


V

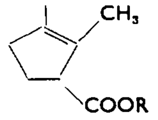


VI

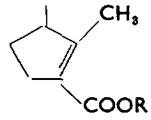
The authentic specimen of 6-oxo-2-phenylheptoic acid (IV) was synthesized by the route outlined below.



Carbonate insoluble fraction. This material possessed the molecular formula $C_{15}H_{18}O_2$; its I.R. and U.V. spectra indicated the presence of a phenyl group, and a double bond conjugated with an ester group. Catalytic reduction, to the dihydro compound $C_{15}H_{20}O_2$, confirmed the presence of the double bond; alkaline hydrolysis, to the acid $C_{13}H_{14}O_2$, confirmed the presence of the ester group. The acid (VII; R = H), $C_{13}H_{14}O_2$, was characterised as its crystalline amide and anilide. The N.M.R. spectrum[4] of the anilide indicated the presence of C_6H_5 (δ 7·39 and 7·34), an allylic proton (δ 3·98, *m*), allylic CH_2 (δ 2·91, *m*), alicyclic CH_2 (δ 2·35, *m*) and $CH_3.C = C$ (δ 1·92, *m*). The I.R. spectrum indicated the presence of an unconjugated amido grouping ($\nu_{max}^{CCl_4}$ 1695 cm^{-1}), and the U.V. spectrum (λ_{max} 2500 Å) established that the double bond was in conjugation with the aromatic nucleus. These facts prove the compound to be the anilide of 2-methyl-1-phenylcyclopent-1-ene-3-carboxylic acid (VII; R = H)



VII



VIII

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[3] The N.M.R. spectra are for CCl_4 solutions, the chemical shift δ, in p.p.m., is based on δ $(CH_3)_4Si = O$ in CCl_4, the signals are defined s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, and the coupling constant J is in c.p.s.

[4] The chemical shift, δ, in p.p.m., is based on $\delta(CH_3)_4$ Si = O in CF_3COOH

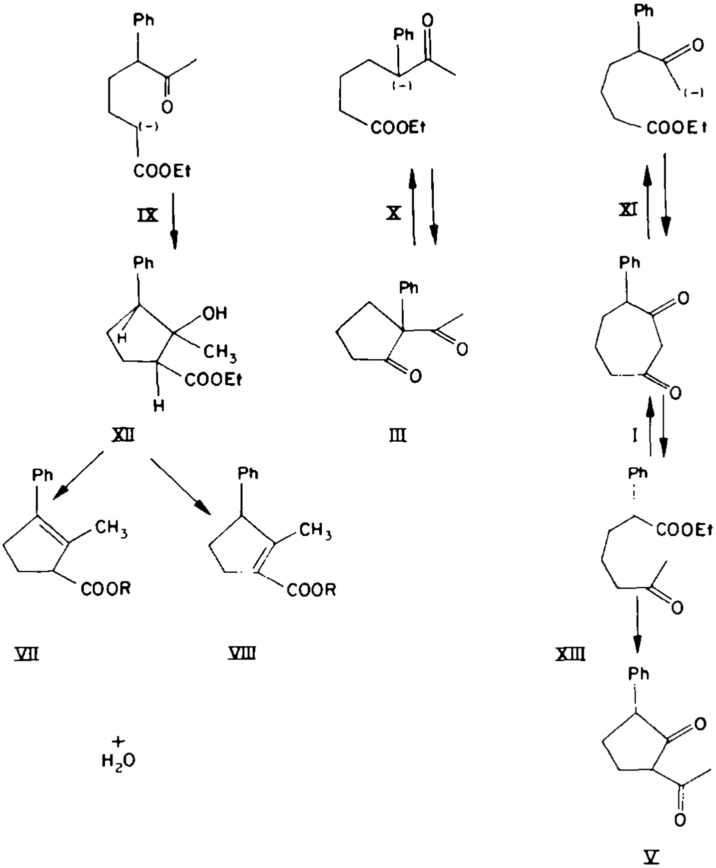
The parent ethyl ester (VII; R = Et), however, has $\nu_{\max}^{CCl_4}$ 1730 cm^{-1} (alkyl COOEt), shoulder at 1710 cm^{-1} (conjugated COOEt) and 1645 cm^{-1} (conjugated C = C). The N.M.R. spectrum[3] also shows the presence of two types of COOEt groups (δ 1·26 and 1·28, two triplets each with J = 7; δ 4·11 and 4·15, two quadruplets each with J = 7). These facts establish that the ester is a mixture of the isomers VII (R = Et) and VIII (R = Et).

Formation of reaction products. In the presence of sodium ethoxide, the ester II (R = Et) can give rise to three anions—IX, X, and XI.

Anion IX can cyclize to the alcohol XII in which two protons are available for the irreversible dehydration to the isomers VII (R = Et) and VIII (R = Et). The water produced in this reaction would be removed from the system by the hydrolysis of the ester II (R = Et) to the corresponding acid.

Anion X could cyclize to the non-enolizable 1,3-dione III. The latter, however, would be readily cleaved with sodium ethoxide in ethanol, regenerating the ester II (R = Et).

Anion XI can cyclize to the cycloheptane-1,3-dione I, which, however, would not be stable to sodium ethoxide and ethanol[5] and would undergo cleavage either to the



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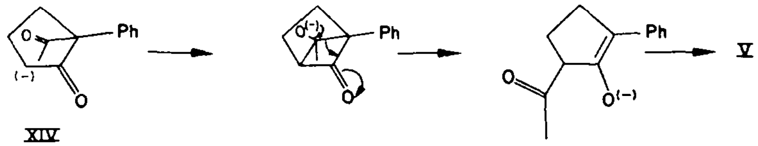
[5] It has been shown that cycloheptane-1,3-dione rearranges to 2-acetyl-cyclopentanone by the action of sodium ethoxide in ethanol. (I. Maclean and R. P. A. Sneeden, forthcoming publication.)

original ester II (R = Et) or to the ester XIII. The latter can cyclize to the stable, enolizable, 1,3-dione V.

The above scheme accounts satisfactorily for the formation of all the observed products. However, from Robinson and Pinder's work on non-enolizable 1,3-diones[6] there is an alternative route which would account for the formation of V. The anion XIV of the non-enolizable 1,3-dione III could undergo rearrangement to give V, in the following manner:



EXPERIMENTAL

U.V. absorption spectra were recorded on a Perkin Elmer 137 spectrometer in ethyl alcohol, unless otherwise stated.

Ethyl 6-oxo-5-phenylheptoate, (II; R = Et). The keto-ester (II; R = Et), obtained in 40% yield by the method of Bergmann and Yaroslavsky,[2] had b.p. 118°/0·03 mm (Found: C, 72·55; H, 7·8. Calc. for $C_{15}H_{20}O_3$: C, 72·6; H, 8·0%), λ_{max} 2200, 2620, 2850 Å (ε 5660, 256 and 285), ν_{max} 1725 alkyl COOEt), 1700 (alkyl C=O), 1600, 1495, 760, 704 cm^{-1} (Ph), n_D^{24} 1·4970, NMR[3]: δ 1·19 (t, J = 7), 4·03 (q, J = 7) CH_3CH_2 of COOEt, δ 1·96 (s) CH_3 of CH_3CO-, δ 3·57 (t, J = 7) H of PhCH—, δ 7·22 (m) C_6H_5.

2,4-*Dinitrophenylhydrazone of* II (R = Et). Ethyl 6-oxo-5-phenylheptoate (2·47 g) in methanol was treated with excess Brady's reagent, the whole diluted with water and extracted with chloroform. Chromatography of the dried extract on alumina (grade III) with benzene, gave the 2,4-*dinitrophenylhydrazone* (3·61 g; 86%) as golden yellow needles, m.p. 96·5–97·5° (MeOH) [Lit. 78°[2]] (Found: C, 58·7; H, 5·8; N, 13·1. $C_{21}H_{24}N_4O_6$ requires: C, 58·9; H, 5·65; N, 13·1%).

6-*Oxo-5-phenylheptoic acid.* (II, R = H). The ester II (R = Et; 1·97 g) was readily hydrolysed with 10% sodium hydroxide (20 ml) to give the *acid* as a viscous clear oil (1·44 g; 82%), b.p. 143–147°/0·4 mm. (Found: C, 71·1; H, 7·4. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), λ_{max} 2510, 2600, 2840 Å (ε 302, 309 and 315), ν_{max} 3200–2650, 1715–1700, 1600, 1495, 760, 700 cm^{-1}. This acid gave a positive iodoform test, thereby excluding its possible formulation as 6-oxo-7-phenylheptoic acid.

The acid formed a *semicarbazone*, m.p. 182–183° (from aqueous ethanol) (Found: C, 60·8; H, 7·05; N, 15·25. $C_{14}H_{19}N_3O_3$ requires: C, 60·6; H, 6·9; N, 15·15%).

Regenerated from the semicarbazone, the acid was obtained as a colourless solid, m.p. 35–37·5°.

Cyclization of ethyl 6-oxo-5-phenylheptoate. Following the technique of Bergmann,[2] the ester II (R = Et; 19·47 g) was cyclized using sodium ethoxide (from sodium [1·73 g] in 40 ml dry EtOH) to give a carbonate soluble fraction (6·54 g; 41·2%) and a carbonate insoluble fraction (8·60 g; 54·2%). [These yields are for crude material and are based on products of M.Wt. 202].

Carbonate soluble fraction. Carbonate extraction of the cyclization products gave a colourless, viscous, oil, b.p. 160–166°/0·45 mm. (Found: C, 71·8; H, 7·45. Calc. for $C_{13}H_{14}O_2$: C, 77·2; H, 7·0. Calc. for $C_{13}H_{14}O_2.H_2O$: C, 71·0; H, 7·3. Lit values[2]: C, 72·1; H, 7·3%), ν_{max} 3200–2650, 1740–1700, 1600, 1495, 760, 704 cm^{-1}. This material gave a weak violet colour with methanolic ferric chloride.

Further separation of this oil was possible by either careful fractional distillation, or, more readily, by extraction with sodium bicarbonate.

Bicarbonate soluble. Acidification, extraction, and distillation of the bicarbonate extracts gave 6-oxo-5-phenylheptoic acid, b.p. 130–140°/0·09 mm. (Found: C, 70·6; H, 7·5. $C_{13}H_{16}O_3$ requires: C, 70·9; H, 7·3%) U.V. and I.R. spectra were identical with those reported above for 6-oxo-5-phenylheptoic acid.

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[6] A. R. Pinder and R. Robinson, *J. Chem. Soc.* 3341 (1955); N. H. Bromham and A. R. Pinder, *ibid.* 2688 (1959).

The semicarbazone, alone and admixed with an authentic specimen, had m.p. 182–185° (Found: C, 60·6; H, 6·9; N, 15·05. $C_{14}H_{19}N_3O_3$ requires: C, 60·6; H, 6·9; N, 15·15%). Hydrolysis of this derivative regenerated the acid, m.p. 35–39°.

Bicarbonate insoluble. The ethereal layer after bicarbonate extraction gave, on drying and distillation, *2-acetyl-5-phenylcyclopentanone* (as a mixture of keto and enol forms) b.p. 114–116°/0·04 mm. (Found: C, 77·0; H, 7·2. $C_{13}H_{14}O_2$ requires: C, 77·2; H, 7·0%). λ_{max} 2450, 2880 Å (ε 3438 and 5693) $\lambda_{max}^{OH^-}$ 2410, 3110 Å (ε 3602 and 14,860) ν_{max} 1740 (5-membered cyclic C=O), 1705 (acyclic C=O), 1650 (conj. C=O), 1605 (conj. C=C), 1595, 1500, 760, 700 cm^{-1} (Ph).

The material gave an intense violet colouration with methanolic ferric chloride.

Hydrolysis of bicarbonate insoluble fraction. This product on hydrolysis with 10% sodium hydroxide gave *6-oxo-2-phenylheptoic acid*, b.p. 142–148°/0·07 mm. (Found: C, 71·45; H, 7·55. $C_{13}H_{16}O_3$ requires: C, 70·9; H, 7·3%), ν_{max} 3300–2600, 1720, 1700, 1600, 1495, 760, 700 cm^{-1}, positive iodoform.

The *semicarbazone* crystallized from ethanol as prisms, m.p. 164–165°, alone or admixed with a synthetic specimen (Found: C, 60·4; H, 6·7; N, 14·9. $C_{14}H_{19}N_3O_3$ requires: C, 60·6; H, 6·9; N, 15·15%).

6-Oxo-2-phenylheptoic acid (IV). 5-Chloropentan-2-one[7] (93 g, b.p. 62–64°/12 mm, n_D^{17} 1·4394), ethylene glycol (124 ml) in benzene (450 ml) containing *p*-toluene-sulphonic acid (1 g) were heated under reflux, the returning condensate being passed through a Dean-Stark water separator. When no more water separated (12 hr) the cooled solution was washed with 1N NaOH (2 × 50 ml), water (3 × 50 ml), dried (Na_2SO_4) and fractionally distilled. The ethylene ketal of 5-chloropentan-2-one was obtained (109 g) as a colourless oil, b.p. 92°/12 mm, n_D^{20} 1·4501.

The chloroketal (109 g), sodium iodide (400 g), and acetone (2·3 l.) were stored overnight at room temp. The acetone was removed by slow distillation, the residue diluted with water, and ether extracted. The extracts were washed with sodium bisulphite (to ensure freedom from iodine), water, and then dried (Na_2SO_4) and distilled. Thus was obtained the ketal of 5-iodopentan-2-one (40 g) as a colourless oil, b.p. 108–110°/12 mm, n_D^{26} 1·4840. The oil darkened rapidly on standing and was therefore used immediately.

Diethyl phenylmalonate (29·75 g) was added dropwise to a refluxing suspension of sodium (2.95 g) in toluene (200 ml) with vigorous stirring. Refluxing was continued a further 30 min before cooling. The ketal of 5-iodopentan-2-one (33·1 g) was added over 40 min and the solution stirred and refluxed a further 6 hr. The cooled solution was washed with water, dried (Na_2SO_4), and distilled to give the *ketal of ethyl 2-ethoxycarbonyl-6-oxo-2-phenylheptoate* (14·9 g), b.p. 150–154°/0·15 mm. (Found: C, 66·25; H, 7·8. $C_{20}H_{28}O_6$ requires: C, 65·9; H, 7·75%) ν_{max} 1740, 1360, 1070, 1040, 945, 690 cm^{-1} n_D^{22} 1·4970.

The ketal ester (2·21 g) was left overnight in aqueous methanolic hydrochloric acid (20 ml), diluted with water and ether extracted. On evaporation of the ether, the extract was refluxed with 10% sodium hydroxide (20 ml) for 2 hr, and the cooled solution washed with ether, acidified, and extracted with ether to give 6-oxo-2-phenylheptoic acid (1·16 g; 87%) b.p. 150–154°/0·2 mm, ν_{max} 3000–2600, 1720, 1700 cm^{-1}.

The semicarbazone, from ethanol, had m.p. 164–165° (Found: C, 60·5; H, 6·7; N, 15·1. $C_{14}H_{19}N_3O_3$ requires: C, 60·6; H, 6·9; N, 15·15%)

Carbonate insoluble. The organic layer from the cyclization of II, after washing with carbonate, was dried and evaporated to give an inseparable mixture of *3-ethoxycarbonyl-2-methyl-1-phenylcyclopent-1-ene and 3-ethoxycarbonyl-2-methyl-1-phenylcyclopent-2-ene*, b.p. 102–104°/0·05 mm. (Found: C, 78.1; H, 7·95. $C_{15}H_{18}O_2$ requires: C, 78·2; H, 7·9%), λ_{max} 2420 Å (ε 12,300), $\nu_{max}^{CCl_4}$soln. 1734, 1710, 1645 cm^{-1}, n_D^{24} 1·5439. This oil gave a scarlet colouration with tetranitromethane.

The above mixture of esters was hydrolysed with 10% sodium hydroxide (50 ml) to give *2-methyl-1-phenylcyclopent-1-ene-3-carboxylic acid* and *2-methyl-1-phenylcyclopent-2-ene-3-carboxylic acid*, b.p. 134–136°/0·1 mm. (Found: C, 76·8; H, 7·1. $C_{13}H_{14}O_2$ requires: C, 77·2; H, 7·0%), λ_{max} 2370 Å (ε 5580), ν_{max} 3300–2650, 1700 (broad), 1655, 1600, 1500, 760, 705 cm^{-1}, n_D^{24} 1·5660. The conjugated acid was characterized as its crystalline *anilide* and *amide*.

The anilide, obtained via the acid chloride, recrystallized from aqueous ethanol as white plates, m.p. 172–173° (Found: C, 82·0; H, 6·9; N, 5·05. $C_{19}H_{19}NO$ requires: C, 82·3; H, 7·1; N, 5·1%) NMR in text.

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[7] *Organic Synthesis* Vol. 31; p. 74. J. Wiley, New York (1951).

The amide, also obtained via the acid chloride, recrystallized from aqueous ethanol as pale yellow plates, m.p. 147–148° (Found: C, 77·8; H, 7·6; N, 6·7. $C_{13}H_{15}NO$ requires: C, 77·6; H, 7·5; N, 7·0%).

Hydrogenation of the mixed esters. The ester mixture was hydrogenated with palladium charcoal (10%) to give a mixture of stereoisomers of *1-ethoxycarbonyl-2-methyl-5-phenylcyclopentane*, b.p. 92–93°/0·05 mm. (Found: C, 77·55; H, 9·0. $C_{15}H_{20}O_2$ requires: C, 77·55; H, 8·7%), λ_{max} 2590 Å (ε 256), ν_{max} 1720, 1600, 1495, 705 cm^{-1}. This product gave no colouration with tetranitromethane.

In a typical experiment, cyclization of II (29·66 g) with sodium ethoxide gave 6-oxo-5-phenylheptoic acid (7·98 g; 31%), 2-acetyl-5-phenylcyclopentanone (1·00 g; 4%) and a mixture of 3-ethoxycarbonyl-2-methyl-1-phenyl-cyclopent-1-ene and 3-ethoxycarbonyl-2-methyl-1-phenylcyclopent-2-ene (10·40 g; 38%). [Yields based on purified reaction products].

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