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ALICYCLIC DIKETONES AND DIOLS—V[*]

THE PREPARATION AND PROPERTIES OF CYCLOHEPTANE-1,3-DIONE

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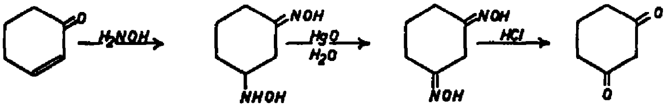
Abstract—The preparation and properties of cyclohept-2-enone and cycloheptane-1,3-dione are described.

WHEN it proved impracticable to prepare medium and large ring cyclic-β-diketones by the conventional base catalysed cyclization of long chain keto-esters,[1–3] attention was turned to their synthesis by the modification of preformed cyclic ketones or potential ketones.[‡]

KOTZ and Grethe[5] describe the synthesis of cyclohexane-1,3-dione, from cyclohex-2-enone, outlined below:



Such a scheme could provide a general synthetic route to cyclic-1,3-diones, and we were interested in applying the reaction to the synthesis of cycloheptane-1,3-dione. However, for this, substantial quantities of pure cyclohept-2-enone were required. Braude and Evans[6] were the first to point out that the usual "cyclophept-2-enone", prepared by the dehydrohalogenation of 2-brom- and 2-chlor-cyclopheptanone was in fact a mixture of cyclohept-2-enone and cyclohept-3-enone, and from the present work it is evident that based on the quoted extinction coefficient at λ_{max} 235 mμ, the content of conjugated isomer varied from 25 to 50%.

Using preparative gas chromatography we were able to separate the "cycloheptenone mixture", obtained by the degradation of tropidine,[7] into pure cyclohept-2- and -3-enone,[8] the skeletal structure of both compounds being established by catalytic hydrogenation to cycloheptanone, identified as its 2,4-dinitrophenylhydrazone. Both

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[*] Part IV, *Tetrahedron* **19**, 1307 (1963).

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[‡] Whilst this work was in progress, two elegant syntheses of cycloheptane-1,3-dione appeared.[4]

[1] A. W. Allan and R. P. A. Sneeden, *Tetrahedron* **18**, 821 (1962).

[2] I. Maclean and R. P. A. Sneeden, *Tetrahedron* **19**, 1307 (1963).

[3] I. Maclean, Ph.D., Thesis, Glasgow University.

[4] B. Eistert, F. Haupter and K. Schank, *Liebigs Ann.* **665**, 55 (1963).

[5] A. Kotz and Th. Grethe, *J. Prakt. Chem.* **80**, 473 (1909).

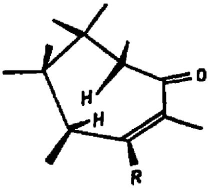
[6] E. A. Braude and E. A. Evans, *J. Chem. Soc.* 607 (1954).

[7] G. Merling, *Ber. Dtsch. Chem. Ges.* **24**, 3108 (1891).

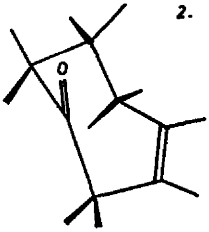
[8] A. C. Cope. S. Moon and C. H. Park, *J. Amer. Chem. Soc.* **84**, 4843 (1962).

cyclohept-2-enone (λ_{max}^{EtOH} 228 mμ: ε_{max} 10,060: ν_{max} 1670–1655, 1635 cm^{-1}) and cyclohept-3-enone (λ_{max}^{EtOH}, only weak carbonyl adsorption: ν_{max} 1704, 1660 cm^{-1}) were stable to dilute acid, however, when a drop of alkali was added to a solution of cyclohept-2-enone in ethanol the extinction at λ_{max} 228 mμ dropped from 10,060 to 2,500. This ready isomerization of the α,β-unsaturated ketone to the β,γ-form is a reflection of the steric strain in the former, occasioned by the coplanarity of the C=C and C=O[9] (1, R=H), in the β,γ-isomer (2) this strain is not present.

1.



2.



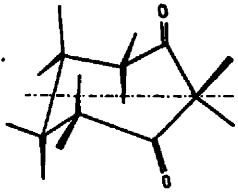
Unfortunately, the overall yield of pure cyclohept-2-enone was very poor, and attempts to use the mixture of cycloheptenones in the Kotz and Grethe[5] synthesis led to intractable tars.

The synthesis of cycloheptane-1,3-dione was finally achieved from 1,3-dimethoxy-cycloheptatriene, recently described by Chapman and Fitton.[10] Catalytic reduction of the triene gave an impure mixture of 1,3-dimethoxy-cycloheptadienes, which on careful hydrolysis, with oxalic acid, gave cycloheptane-1,3-dione as a colourless hygroscopic liquid, characterized as its crystalline bis-2,4-dinitrophenylhydrazone and bis-oxime.*

From the IR, UV and NMR spectra, it was evident that cycloheptane-1,3-dione, in contrast to C_4, C_5, and C_6 cyclic-1,3-diones, exists in the diketo- form (3), in the pure state, in carbon tetrachloride and in deuterochloroform solutions, and furthermore it is a weaker acid (pK_a = 8·64) than cyclohexane-1,3-dione (pK_a = 7·02). In alcohol solution, the dione is only slightly enolized (λ_{max}^{EtOH} 265 mμ: ε_{max} 3440).

This lack of enolization and low acidity can be ascribed to the steric strain present in the enolic form (1, R=OH) and the anion (1, R=O$^{(-)}$) making them less stable than the strain free diketo- form (3).

3.



In contrast to cyclohexane-1,3-dione, the C_7-dione did not give crystalline condensation products with either formaldehyde or benzaldehyde; furthermore, whereas

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* The IR and UV spectra of the liquid dione, and the m.p. of the bis-2,4-dinitrophenylhydrazone and bis-oxime, were in agreement with those published subsequently by Eistert *et al.*[4]

[9] H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.* **78**, 4394 (1956).

[10] O. L. Chapman and P. Fitton, *J. Amer. Chem. Soc.* **85**, 41 (1963).

the C_6-dione is stable in ethanolic sodium hydroxide solution, the C_7-dione is readily cleaved, under these conditions, to 6-oxo-heptoic acid.

The most striking difference between the C_6- and C_7-diones is in their behaviour towards ethanolic sodium ethoxide, thus whereas the former is stable, the C_7-dione is smoothly converted, presumable by ring opening and recyclization to 2-acetylcyclopentanone.

The foregoing facts clearly demonstrate that cycloheptane-1,3-dione has none of the characteristics typical of *trans*-fixed C_4, C_5 and C_6-1,3-diones. Furthermore, the instability of the C_7-dione towards base explains the failure of earlier attempts to prepare it by base catalysed cyclizations.[1–3]

EXPERIMENTAL

Cyclohept-2-enone and cyclohept-3-enone

Tropilene,[7] b.p. 182–184°, n_D^{20} 1·4910 (0·5 ml samples) were subjected to gas chromatography on a column of celite with 20% apiezon M, at a temp of 100°, gas inlet press. 18 mm Hg to give finally:

(i) *Cyclohept-2-enone*, as a colourless oil, b.p. 76°/18 mm λ_{max}^{EtOH} 228 mμ ε_{max} 10,060 ν_{max} 3030 (enolic OH), 1670–1655 (conjugated C═O), 1635 (C═C), 890, 820, 790 and 690 cm^{-1} (*cis* double bond): (Found: C, 75·9: H, 9·3. $C_7H_{10}O$ requires: C, 76·3: H, 9·15%).

The ketone, in ethanol, was hydrogenated in the presence of Pt: when the uptake of hydrogen had ceased, the filtered solution was treated with 2,4-dinitrophenylhydrazine sulphate, also in ethanol, to give only the 2,4-dinitrophenylhydrazone of cycloheptanone, m.p. and mixed m.p. 148–151°, the IR spectrum was superposable on that of an authentic specimen.

(ii) *Cyclohept-3-enone*, as a colourless oil, b.p. 180–181°, λ_{max}^{hexane} only weak carbonyl adsorption, ν_{max} 1704 (unconjugated C═O in seven membered ring). 1660 (double bond), 995, 790 and 690 cm^{-1} (*cis* double bond): (Found: C, 75·9: H, 8·9, $C_7H_{10}O$ requires: C, 76·3: H, 9·15%).

The ketone in ethanol was hydrogenated in the presence of Pt. The reduction product, isolated as its 2,4-dinitrophenylhydrazone, m.p. 148–151°, was shown to consist only of the 2,4-dinitrophenylhydrazone of cycloheptanone by a direct comparison.

The isomerization of cyclohept-2-enone. A solution of cyclohept-2-enone (1·1 mg) in ethanol (25 ml) was treated with a drop of 5N NaOH and allowed to stand at room temp. Periodically, aliquots were taken and their UV spectrum recorded; the extinction coefficient at λ_{max} 228 mμ, which was initially 11,100 fell within 2 hr to the equilibrium value of 2,500.

Attempted preparation of cycloheptane-1,3-dione.[5] A solution of the mixed cycloheptenones (7·2 g), hydroxylamine hydrochloride (8·8 g) and sodium methoxide (from 2·92 g Na and 25 ml methanol) in methanol (40 ml) was allowed to stand at room temp for 8 days. The solvent was removed by distillation under red. press., and the product, isolated with the aid of ether, dissolved in water (200 ml). The boiling aqueous solution was treated portionwise with HgO (50 g), and the reaction product isolated with the aid of ether. Thus crude material, a brown syrup, was hydrolysed with dil. H_2SO_4 (50 ml of 10%). The final reaction product, isolated with the aid of ether, was a very dark intractable tar, from which no pure substance could be isolated either by distillation or by chromatography.

Cycloheptane-1,3-dione. 1,3-Dimethoxycycloheptadiene (1·152 g), prepared by the catalytic reduction of 1,3-dimethoxycycloheptatriene[10] (1·756 g), was stirred for 4 hr at 40–50° in an aqueous solution of oxalic acid (5 g in water 50 ml). The cooled solution was washed with hexane and the extracted with chloroform, the dried chloroform extract was evaporated and the residue distilled to give cycloheptane-1,3-dione, b.p. 119–122°/15mm, $\nu_{max}^{CCl_4}$ 3415 (very weak), 1728 and 1704 (strong, twin carbonyl) and 929 cm^{-1}: $\lambda_{max}^{CCl_4}$ transparent: λ_{max}^{EtOH} 265 mμ, ε_{max} 3440: $\lambda_{max}^{EtOH/NaOH}$ 288 mμ, ε_{max} 24,060: (Found: C, 66·75: H, 7·8. Calc. for $C_7H_{10}O_2$: C, 66·65: H, 8·0%): pK_a, 8·64: NMR, in CCl_4, $\delta = 3{\cdot}47$ (s, 2 protons)-CO.CH_2.CO, $\delta = 2{\cdot}52$ (m, 4 protons)-CH_2, CO-, $\delta = 2{\cdot}00$ (m, 4 protons)-CH_2-. NMR in MeOH, (1:1), $\delta = 3{\cdot}7$ s, 2 protons)-CO.CH_2.CO-, $\delta = 2{\cdot}57$ (m, 4 protons)-CH_2.CO, $\delta = 2{\cdot}00$ (m, 4 protons)-CH_2-.

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[11] L. Ruzicka, C. F. Seidel, H. Schinz and M. Pfeiffer, *Helv. Chim. Acta* **31**, 422 (1948).

The *bis-2,4-Dinitrophenydrazone* of cycloheptane-1,3-dione was obtained from chloroform–ethanol as orange-yellow needles m.p. 208–212° (Eistert[4] quotes m.p. 205–206°). (Found: C, 46·7: H, 3·95: N, 23·1. Calc. for $C_{19}H_{18}N_8O_8$: C, 46·9: H, 3·7: N, 23·0%).

The *bis-oxime* of cycloheptane-1,3-dione was obtained from methanol as white prisms m.p. 164–166° (Eistert[4] quotes m.p. 162–163°) (Found: C, 54·15: H, 7·9: N, 17·95. Calc. for $C_7H_{12}N_2O_2$: C, 53·85: H, 7·75: N, 17·95%).

*The reaction of cycloheptane-*1,3*-dione with aqueous sodium hydroxide.* Cycloheptane-1,-3dione (0·094 g) was warmed with 10%. NaOHaq (5 ml) on a steam bath for 2 hr, the cooled reaction mixture washed with ether and the aqueous layer acidified. The product, isolated by continuous ether extraction (18 hr), was distilled giving 6-oxoheptanoic acid (0·110 g) as a colourless oil, b.p. 125°/0·1 mm, whose IR spectrum was identical with that of an authentic specimen.[11] The semicarbazone was obtained from ethanol as white needles m.p. 142–144°, alone or mixed with an authentic specimen, (Found: C, 47·65: H, 7·15: N, 21·2. Calc. for $C_8H_{15}N_3O_3$: C, 47·75: H, 7·5: N, 20·9%).

*The reaction of cycloheptane-*1,3*-dione with ethanolic sodium ethoxide.* Cycloheptane-1,3-dione (0·402 g) was added to a solution of sodium ethoxide (from 0·09 g Na) in ethanol (1·8 ml) and the whole heated under reflux for 2 hr. The cooled solution was acidified with acetic acid, the product extracted with ether, and the ether layer shaken with copper acetate aq. The derivative obtained in this way (0·146 g), m.p. 260° (dec.) was shown to be identical with an authentic specimen of the copper derivative of 2-acetylcyclopentanone[1] by a direct comparison, ν_{max} 1595, 1162, 1015, 947 and 725 cm^{-1}: λ_{max} 254 and 309 mμ, ε_{max} 6300 and 12050 respectively (lit[1]., m.p. 240° (dec) λ_{max} 254 and 309 mμ, ε_{max} 6390 and 12630 respectively). The copper derivative was hydrolysed with dil. mineral acid, and the product, isolated with the aid of ether, was identified as 2-acetylcyclopentanone, b.p. 130°/20 mm, by a direct comparison with an authentic specimen.[1]

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