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BRIDGED RING SYSTEMS—IX

A NEW ROUTE TO CYCLOHEPTENE CARBOXYLIC ACIDS

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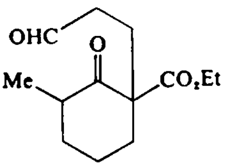
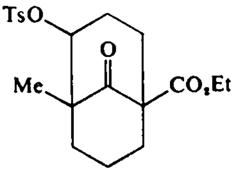
Abstract—Bridge fission of certain bicyclo (3.2.1) octane derivatives has been applied to the synthesis of cycloheptene carboxylic acids, and the mechanism of the reaction has been studied.

In a recent publication,[1] it was reported that the keto-aldehyde (I) was converted to a mixture of epimetric tosylates (II) by ring closure followed by tosylation, and that under appropriate basic conditions this mixture afforded the cyclo-octene diester (III) together with unreacted tosylate. It was further suggested that the returned tosylate was the axial epimer, whilst the facile bridge-fission reaction stemmed entirely from the stereochemically apposite equatorial isomer by a concerted β-elimination process (IV). This interpretation of the reaction presumed a difference in reactivity between the tosylate epimers, large enough to account for the simplicity of the conversion II → III, but such an assumption seemed to be justified.[2] In particular, it had been observed,[2a] that the epimeric tosylates (V), each reacted with ethoxide uniquely, and at a different rate. The less reactive tosulate afforded VI whilst the more reactive epimer yielded the cyclo-octene derivative (VII). Nevertheless the lack of strict stereochemical



I



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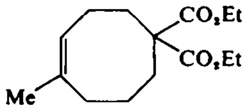
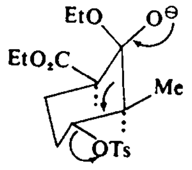


III



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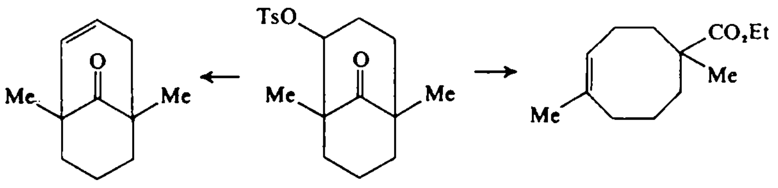

VI V VII

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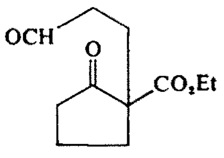
[1] G. L. Buchanan, A. McKillop and R. A. Raphael, *J. Chem. Soc.* 833 (1965).

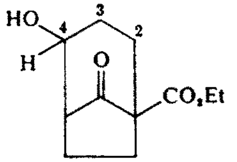
[2a] J. Martin, W. Parker and R. A. Raphael, *J. Chem. Soc.* 289 (1964); [b] J. A. Marshall and C. J. V. Scanio, *J. Org. Chem.* **30**, 3019 (1965); [c] C. A. Grob, *I.U.P.A.C. Kekulé Symposium*, p. 114. Butterworths, London (1959).

assignments and the absence of an ethoxycarbonyl function in this model system was less than satisfactory and the reaction has now been re-examined.

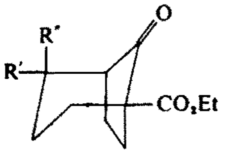
Although the components of the mixture (II) could not be separated for individual study, a closely related mixture of epimers has proved to be more amenable. In the presence of triethylamine, acrolein and 2-ethoxycarbonylcyclopentanone condensed smoothly yielding VIII, which was cyclized by acid to a mixture of bicyclic alcohols (IX). This ring closure could also be effected by prolonged treatment with triethylamine, and indeed, the overall preparation of IX could be carried out in one operation.



VIII



IX



X R′ = OH: R″ = H
XI R′ = OAc: R″ = H
XII R′ = OTs: R″ = H
XIII R′ = H: R″ = OH
XIV R′ = H: R″ = OAc
XV R′ = H: R″ = OTs

The epimeric alcohols (X and XIII) were separated by chromatography, and characterized as O-acetates, but the tosylates (XII and XV) prepared directly from the mixture (X) or from the crude reaction mixture could be separated by crystallization. The three related epimeric pairs were thus available, and their configurations were established by an examination of the C_4 proton signal in the NMR (Table 1). In each epimeric pair, the axial proton could be identified as that which absorbed at higher field, in accordance with known principles,[3,4] and showed also the broader multiplet originating from axial-axial coupling.[5] In the alcohols the latter effect was partially obscured by the —CH_2—O— signal of the ester function, but it was clearly visible in the acetates and in the tosylates. Although stereochemical assignments could be made by inspection, it was noted that the half-band widths ($W^{1/2}$) of the multiplets lay within the limits quoted[5] for axail and equatorial protons.

TABLE 1. NMR data

		$\overset{4}{>}$CH·O- signal (τ)	$W^{1/2}$ c/s	C^4 proton Assignment
Alcohols	X	~5·95	~30	a
	XIII	~5·75	~12	e
Acetates	XI	5·05	20·4	a
	XIV	4·9	9·0	e
Tosylates	XII	5·35	18·0	a
	XV	4·95	9·0	e

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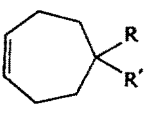
[3] L. M. Jackman, *Application of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry* p. 116, Pergamon Press, London (1959).

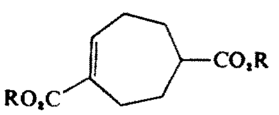
[4] In this instance the axial H also lies closer to the shielding cone of the C=O.

[5] A. Hassner and C. Heathcock, *J. Org. Chem.* **29**, 1350 (1964).

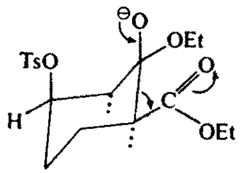
These criteria were sufficient to establish the configurations of the tosylates, and it was now possible to test the β-elimination mechanism. Contrary to expectations *both tosylates reacted with equal facility.* On heating with ethoxide for 15 min, the equatorial tosylate (XII) gave mainly the *gem*-diester (XVI) which could be identified by the extreme simplicity of its NMR spectrum,[6] by the absence of UV absorption and by its IR spectrum ($\nu_{CO}^{CCl_4}$ 1734 cm^{-1}; $\nu_{C=C}^{CS_2}$ 684 cm^{-1}). This structure was confirmed by hydrolysis and decarboxylation to XVII, which was shown to be identical with an authentic specimen.[7] Under the same conditions, the axial tosylate (XV) yielded mainly the unsaturated diester (XVIII; λ_{max}^{EtOH} 224 mμ ε 8,000; $\nu_{CO}^{CCl_4}$ 1739 and 1711 cm^{-1}) whose NMR spectrum showed 1 × H vinyl proton as a triplet at 2·93 τ (J 6 c/s). Hydrolysis afforded the stable dicarboxylic acid (XIX). The diester (XVIII) must arise by a retro-Claisen ester reaction (XX) followed by β-elimination of the tosylate function. An alternative mechanism involving XXI seems much less plausible in the light of past experience.[1,2a]



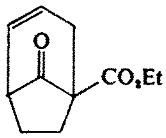
XVI; R = R' = CO_2Et
XVII; R = H; R' = CO_2H



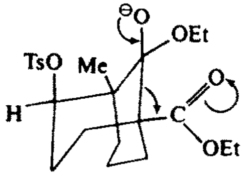
XVIII; R = Et
XIX; R = H



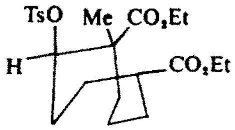
XX



XXI



XXII



XXIII

It can now be seen that the smoothness of the conversion II → III was due, not to differential reactivities of the epimers but solely to the presence of the bridgehead methyl group. In its absence, a mixture of isomeric cyclo-octene diesters corresponding to XVI and XVIII would have resulted. By blocking the tosylate elimination step, the retro-Claisen process XXII → XXIII would be encouraged to reverse, leaving unreacted axial tosylate. A similarly decisive intervention by a bridgehead methyl function has already been described.[1]

Interestingly the aldehyde (VIII) reacted with methanolic alkali to give the acid (XIX) in 50% yield. It must be presumed that the aldol product (IX) is formed and that, in the absence of a good leaving group, a process akin to XX takes place, followed by dehydration.

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[6] The spectrum was even simpler than expected, for the ring methylenes (8H) appeared as a thick singlet at 7·85 τ (in CCl_4); the corresponding dicarboxylic acid showed the same phenomenon, 8H at 7·6 τ (in $F_3C{\cdot}CO_2H$). Presumably the non-allylic methylenes are deshielded by the two adjacent ester carbonyls.

[7] G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.* **78**, 5129 (1956). We are grateful to Professor Stork for providing a specimen of this acid.

EXPERIMENTAL

UV and IR spectra were measured on Unicam S.P.500 and S.P.100 spectrophotometers respectively and NMR spectra (in $CDCl_3$) on a Perkin–Elmer 60 mc instrument.

2-Ethoxycarbonyl-2-(3′-oxopropyl)-cyclopentanone (VIII)

Redistilled acrolein (50 ml) was added dropwise to a stirred solution of 2-carbethoxycyclopentanone (100 g) and triethylamine (7·5 ml) in anhydrous benzene (500 ml) at 0°, stirred at room temp for 24 hr, neutralized with AcOH, washed with brine and dried ($MgSO_4$). Distillation furnished the aldehyde-ester (100·2 g, 73·7%), b.p. 115–138°/0·2–0·5 mm, contaminated by small quantities of the isomeric ring-closed alcohol (IX). Repeated distillation failed to effect a separation but chromatography and redistillation afforded a pure sample of VIII, b.p. 75–78°/0·02 mm. (Found C, 61·9; H, 7·5. $C_{11}H_{16}O_4$ requires: C, 62·25. H, 7·60%), $\nu(CCl_4)$ 2720, 1754 and 1735 cm^{-1}. The NMR spectrum (CCl_4) showed a signal at 0·28 τ (1H).

Ethyl 4-hydroxybicyclo-(3.2.1)-octan-8-one carboxylates (IX).

(a) A solution of the aldehyde (20 g) and triethylamine (20 ml) in anhydrous benzene (200 ml) was refluxed for 48 hr, then cooled and neutralized with acetic acid. The reaction mixture was washed with 4N NaOH, then with brine and dried ($MgSO_4$). The combined brine washes were extracted with $CHCl_3$ and dried ($MgSO_4$). Removal of the benzene gave an oil shown by TLC (40% AcOEt in petrol) to consist of the epimeric alchols and VIII. Chromatography on silica initially afforded mixtures of the three components and subsequently mixtures of the epimeric alcohols. The $CHCl_3$ solution, on concentration yielded only the epimeric alcohols which were purified by chromatographic filtration. The total yield of the alcohols was 12·5 g (62·5%).

Comparable yields of the alcohols were obtained by reacting 2-carbethoxycyclopentanone and acrolein as previously described and then treating the crude reaction mixture with additional triethylamine for 48 hr at reflux in the manner detailed above.

The epimeric mixture of alcohols (1 g), in ether, was chromatographed on fine mesh silica (30 g). Elution with ether afforded initially the pure equatorial isomer X (280 mgm) then mixtures of both epimers and finally the pure axial isomer XIII, (440 mgm). Attempts to distil these compounds (for analysis) resulted in each case in a mixture of both epimers together with VIII. Epimerization and retro-aldolization also occurred during GLC analysis. The equatorial alcohol showed $\nu_{OH}^{CCl_4}$ 3629 and 3440–3540 cm^{-1}, $\nu_{CO}^{CCl_4}$ 1760 and 1733 cm^{-1}, and afforded an O-*acetate* (XI) b.p. 122–128°/0·8 mm. (Found: C, 61·35; H, 7·2, $C_{13}H_{18}O_5$ requires: C, 61·4; H, 7·1%), $\nu_{CO}^{CCl_4}$ 1762 and 1736 cm^{-1}. The axial alcohol showed $\nu_{OH}^{CCl_4}$ 3620 and 3420–3540 cm^{-1}; $\nu_{CO}^{CCl_4}$ 1761 and 1733 cm^{-1}, and afforded an O-*acetate* (XIV) m.p. 77–77·5° (benzene–light petroleum). (Found: C, 61·8; H, 7·35, $C_{13}H_{18}O_5$ requires: C, 61·4; H, 7·1%), $\nu_{CO}^{CCl_4}$ 1765, 1746 and 1735 cm^{-1}.

(b) The aldehyde-ester (15 g) and conc. HCl (15 ml) in acetic acid (120 ml) and water (40 ml) was heated at 100° for 4·5 hr then allowed to stand at room temp overnight, neutralized with $NaHCO_3$ aq. and extracted with ether and $CHCl_3$. The organic solutions were separately washed with brine, dried ($MgSO_4$) and evaporated. The oily residue (5·36 g) was shown by chromatography to be a mixture of the alcohols (X and XIII) and their acetates (XI and XIV).

Tosylates XII *and* XV. A stirred solution of 2-ethoxycarbonylcyclopentanone (100 g) and triethylamine (7·5 ml) in anhydrous benzene (500 ml) at 0° was treated dropwise with acrolein (50 ml) and stirred for 24 hr at room temp. Thereafter triethylamine (80 ml) was added and the solution boiled under reflux for 48 hr, then cooled at 0° and finally treated with a solution of toluene-*p*-sulphonyl chloride (78 g) in anhydrous pyridine (150 ml). After standing for 4 days, this mixture was poured on to crushed ice and extracted with benzene. The organic extract was washed with 6N HCl then saturated $NaHCO_3$ aq and finally brine and dried. Removal of solvent afforded a gum 180 g which slowly solidified and was triturated with ether, yielding the mixture of tosylates. Fractional crystallization (EtOH) furnished the *equatorial tosylate* (XII) m.p. 96° (Found: C, 59·1; H, 6·2. $C_{18}H_{22}O_6S$ requires: C, 59·0; H, 6·05%) identical (TLC) with the tosylation product of X, $\nu_{CO}^{CCl_4}$ 1766 and 1733 cm^{-1} $\nu_{SO_2}^{CCl_4}$ 1375 and 1175 cm^{-1}, and the *axial tosylate* XV m.p. 95–96°. (Found: C, 59·25; H, 6·0. $C_{18}H_{22}O_6S$ requires: C, 59·0; H, 6·05%) identical (TLC) with the tosylation product of XIII, $\nu_{CO}^{CCl_4}$ 1766 and 1736 cm^{-1} $\nu_{SO_2}^{CCl_4}$ 1375 and 1175 cm^{-1}. Successive crops were analysed by TLC (40% EtOAc in light petroleum), the equatorial epimer being the less polar, and separation could also be effected by chromatography on silica.

Diethyl cycloheptene-5,5-dicarboxylate (XVI)

A solution of XII (1·83 g) in hot anhydrous EtOH (10 ml) was added to a solution of EtONa [from Na (0·15 g)] in dry EtOH (20 ml) at 60° and the reaction mixture stirred and refluxed for 15 min, then cooled, poured on to ice, acidified (6N HCl) and extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$) and evaporated yielding 1·16 g of an oil consisting of the desired diester together with <10% of the isomeric compound (XVIII) identified by its GLC retention time. Distillation afforded pure *gem-diester*(XVI) b.p. 120°/0·6 mm. (Found: C, 64·55; H, 8·1. $C_{13}H_{20}O_4$ requires: C, 65·0; H, 8·4%), $\nu_{CO}^{CCl_4}$ 1734 cm^{-1}, $\nu_{C=C}^{CS_2}$ 684 cm^{-1}.

Cycloheptene-5-carboxylic acid (XVII)

The diester (XVI; 780 mgm) and KOH (2 g) in MeOH (50 ml) was allowed to stand for 18 hr at room temp. The MeOH was removed under red. press., the residue diluted with water, washed with ether, acidified (6N HCl) and extracted with ether. The ethereal extract was washed with water and dried ($MgSO_4$) yielding 509 mgm, (81%) of XVI (H for Et) m.p. 152–159° (dec) from EtOH. (Found: C, 58·9; H, 6·6. $C_9H_{12}O_4$ requires: C, 58·7; H, 6·6%.) The diacid (1·78 g) and Cu powder in pyridine (50 ml) was refluxed for 40 min. The pyridine was removed under red. press., the residue diluted with ether and extracted with 4N NaOH. The basic extracts were acidified, extracted with ether and the organic solution washed with brine and dried ($MgSO_4$). Concentration afforded XVII (1·1 g; 83·3%). Recrystallization from petrol furnished a sample m.p. 66·5–69·5° (lit.[7] m.p. 65–67°). (Found: C, 68·6; H, 8·8. $C_8H_{12}O_2$ requires: C, 68·55; H, 8·6%.) The IR spectrum showed $\nu_{CO}^{CCl_4}$ 1755, 1707 cm^{-1} and $\nu_{C=C}^{CS_2}$ 682 cm^{-1}. The NMR spectrum (CCl_4) showed peaks at 4·23 τ (triplet, 2H) for the olefinic protons, at $-2·05$ τ for the carboxyl proton and a complex band at 8·4–7·4 τ (9H). An authentic sample of XVII kindly supplied by Professor Stork[7] was identical (IR spectrum and mixed m.p.) with the above material.

Cycloheptene-1,5-*dicarboxylic acid* (XIX)

(a) When the axial tosylate (XV; 1·83 g) was treated with NaOEt as described above, it yielded the *diester* XVIII, b.p. 95°/0·5 mm. (Found: C, 64·7; H, 8·4. $C_{13}H_{20}O_4$ requires: C, 65·0; H, 8·4%), $\nu_{CO}^{CCl_4}$ 1739, 1711 cm^{-1}. The oleofinic proton appeared as a subsplit triplet at 2·93 τ and the UV spectrum showed absorption λ_{max}^{EtOH} 223 mμ (ϵ = 8,000).

Hydrolysis (KOH–CH_3OH) afforded the *di-carboxylic* acid (XIX), m.p. 162–165° from EtOH. (Found: C, 58·5; H, 6·3. $C_9H_{12}O_4$ requires: C, 58·7; H, 6·6%.) λ_{max}^{EtOH} 223 mμ (ϵ = 5,210).

(b) The aldehyde-ester (VIII; 10 g) was dissolved in a solution of KOH (6 g) in MeOH (250 ml) and allowed to stand at room temp for 4 hr. The MeOH was evaporated and the residual oil dissolved in water and washed with ether. After acidification (6N HCl), the aqueous solution was extracted with ether. Concentration yielded a white solid which was recrystallized from EtOH to give 4·5 g (50%) of the diacid m.p. 161–164°, identical with that described above.

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