# BRIDGED RING SYSTEMS—XIII<sup>1</sup> THE SYNTHESIS OF CYCLOHEPTENE CARBOXYLIC ACIDS

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Abstract— $\beta$ -(2-Oxocyclopentyl)ethylaryl ketones are transformed under acid conditions *via* a 2-arylbicyclo[3.2.1]oct-2-en-8-one intermediate into a mixture of arylcycloheptene carboxylic acids. The scope and the mechanism of the reaction are both discussed.

RECENTLY<sup>2</sup> we reported the acid catalysed conversions of the 1.5-diketone I into the carboxylic acid III and the lactone IV, and identified as the reaction intermediate the unstable bicyclic ketone II which could be isolated only under special conditions.

No mechanism which we could visualize would account for the formation of only these products: indeed, we had expected, on mechanistic grounds, that the main product would be V. A re-examination of the reaction product has now shown that although the (oily) acid appeared to be homogeneous it is in fact a 1:1 mixture.



It has not been possible to isolate either component by GLC or TLC, but the structure V of the second product can be inferred (assuming skeletal integrity) from the UV of the mixture,<sup>2</sup> which shows typical styrene absorption ( $\varepsilon$  10,000). Experimental confirmation of structures III and V has now been obtained (*vide infra*).

The true course of the reaction is therefore  $I \rightarrow [II] \rightarrow III + IV + V$ , and it is now possible to visualize the mechanism as a fragmentation of the bicyclic intermediate as in VI, followed by equilibration of the C=C. Presumably the hydration<sup>3</sup> step (II  $\rightarrow$  VI) and the subsequent fragmentation, result from ring strain; the absence of strain in the related bicyclo [3.3.1] nonenone and bicyclo [4.3.1] decenone systems accounts for their stability.<sup>2</sup> This being so, it would be expected that the corresponding



<sup>1</sup> Part XII J. Martin, W. Parker and R. A. Raphael, J. Chem. Soc. in press.

<sup>&</sup>lt;sup>2</sup> G. L. Buchanan, C. Maxwell and W. Henderson, Tetrahedron 21, 3273 (1965).

<sup>&</sup>lt;sup>3</sup> cf. H. O. House, P. P. Wickmann and H. C. Muller, J. Am. Chem. Soc. 84, 3139 (1962).

bicyclo [3.1.1] heptenone system would be even less stable and more readily fragmented. In fact chrysanthenone (VII), a member of this class, occurs in nature and fragments under acid conditions yielding not a carboxylic acid but piperitenone (VIII).<sup>4</sup> It is now clear that this behaviour is atypical, and is promoted by the *gem*dimethyl group, for the cyclobutanone derivative IX behaved as expected under acid conditions, giving the phenylcyclohexene carboxylic acid (X).

As visualized above, the transformation  $VI \rightarrow V$  is initiated by protonation of the C=C and in turn, ease of protonation must be influenced by substituents in the aromatic ring. In order to test this feature, as well as to explore the scope of the reaction, the aryl ketones XI have been treated under standard conditions and the yields of mixed acids are recorded in Table 1. Even this crude measure of the effect of substituents shows that the ease of protonation is an important factor and is consistent with the postulated mechanism. From a practical standpoint, it should be noted in case e where standard conditions gave a poor yield, forcing conditions (Experimental) gave a 75% yield. An o-hydroxyl on the other hand obstructs the reaction, probably by H-bonding at the initial aldol step (I  $\rightarrow$  II).

				TABLE I				
XII	a	ь	c	đ	e	ſ	g	h
R % yield	Ph 75	<b>4BrPh</b> 80	4 McOPh 88	4 McPh 82	4 NO <sub>2</sub> Ph 26*	2-Naphth 75	2 McOPh 70	2 HOPh 0*

\* Starting material returned.



That the reaction produces a *mixture* of carboxylic acids reduces its usefulness as a synthetic route to cycloheptene carboxylic acids. However, there are exceptions; the chalcone adduct XIII gave only one acid (XIV), together with small amounts of the  $\gamma$  and  $\delta$  lactones.<sup>5</sup> The reason for this is not clear, but the location of the C=C in XIV follows from its NMR spectrum (1 × H triplet 3.85  $\tau$ , J = 6 c/s). In particular a substituent on the 3 or 5 positions stabilizes the C=C; thus the dione XV gives only the lactone XVI, and its isomer XVII gives only the cycloheptene carboxylic acid XVIII.<sup>6</sup> This process is therefore eminently suited to the construction of tricyclic

- <sup>4</sup> M. Kotake and H. Nonaka, Liebigs Ann. 607, 153 (1957); E. P. Blanchard, Chem. & Ind. 293 (1958).
- <sup>5</sup> This is the only case in which any  $\delta$  lactone has been detected.
- The presence of a substituent at position 5 in the cyclopentanone ring inhibits the transformation and the yield is low but good yields (79 %) are achieved under forcing conditions.



compounds of type XX, and indeed the diketones XIX derived from indan-1-one,  $\alpha$ -tetralone and 2,3-benzosuberone readily afford the carboxylic acids XX<sup>7</sup> together with traces of the related  $\gamma$ -lactones. The use of a methoxylated benzosuberone has also been studied and will be reported later.

Although the mixture of isomeric acids (XII) could not be separated in any of the cases investigated, it was frequently possible to isolate a pure isomer of unknown orientation by repeated sacrificial crystallization. It was of interest to identify this isomer. It was also desirable to establish rigorously that the components of the mixture XII were in fact the 3-ene and 4-ene carboxylic acids, and these problems were tackled concurrently.

The mixed cycloheptene acids (III and V) were esterified and hydroborated. The resulting mixture of diols was oxidized, and after esterification could be separated into a liquid and a solid ester. These were identified as XXI and XXII by reaction, separately with MeMgBr and subsequent hydrolysis and dehydration, when they yielded, respectively, the lactone XVI and the unsaturated acid XVIII. The liquid keto-ester (XXI) was also obtained from the  $\gamma$ -lactone (IV) by LAH followed by oxidation and esterification.



Thus the structures III, IV and V are all verified. In the p-tolyl case (XIId), a solid acid isolated by repeated recrystallizations was correlated with the isomeric lactone by the hydroboration procedure outlined above and was thus identified as XXIII.

<sup>1</sup> These acids showed the appropriate styrene chromophore (UV) but no vinyl proton (NMR).

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Any attempt to extend the fragmentation reaction to a wholly aliphatic system such as XXIV is frustrated by the alternative aldol reaction leading to the hydroindanone XXV. Nevertheless, evidence is available from studies<sup>8</sup> on a related system that such reactions proceed *via* a kinetically favoured bridged bycyclic intermediate, analogous to XXVI. There are also indications<sup>9</sup> speculative but significant— that a completely aliphatic bicyclo[3.2.1]octen-8-one is capable of fragmentation in the fashion described above for the aromatic analogues. However, although the formation of either bridged (e.g. XXVI) or fused (e.g. XXV) aldol products depends on reaction conditions<sup>9-10</sup> rather than on stereochemical factors, as was once suggested.<sup>11</sup> the



conditions necessary for the fragmentation step are precisely those which would lead to the thermodynamically favoured enone XXV. Accordingly, we can only hope to observe the fragmentation process dominant in cases where enone formations is impossible, or under special conditions.

The t-butyl ketone (XXVIIa) was completely unaffected under the usual reaction conditions, but the isopropyl ketone (XXVIIb) afforded 15% of the mixture of acids XXVIIIb as well as the unconjugated enone XXIX, and even the isobutyl analogue XXVIIc gave a 24% yield of XXVIIIc in addition to XXX. More convincingly the



- <sup>8</sup> W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta, J. Am. Chem. Soc. 82, 614 (1960).
- <sup>9</sup> W. G. Dauben and J. W. McFarland, J. Am. Chem. Soc. 82, 4245 (1960).
- <sup>10</sup> For a pertinent example see E. J. Corey and S. Nozoe, J. Am. Chem. Soc. 87, 5728 (1965).
- <sup>11</sup> R. D. Sands, J. Org. Chem. 28, 1710 (1963); S. Julia, Bull Soc. Chim. Fr. 780 (1954).

diketone XXXI yielded, according to conditions, the lactone XXXII or the methyl ester XXXIII. The homologous diketone XXXIV, which can afford either a bicyclo-[3.3.1]nonenone (XXXV) or a bicyclo[3.2.1]octenone XXXVI<sup>12</sup> intermediate, gave rise to a mixture of both plus the lactone XXXVII which arises from fragmentation of the latter. Unexpectedly, the isopropyl ketone XXVIIb was observed to give a 73% yield of acid (XXVIIb) under *forcing* conditions, and thus encouraged we reinvestigated the isobutyl (XXVIIc) and methyl (XXIV) ketones. Under forcing conditions, these afforded respectively 73% and 60% yield of the acids XXVIIIc and XXVIIId. These results illustrate convincingly how the ultimate fate of a ketone such as XXIV is governed by two equilibria, for under high temperature conditions, the kinetically favoured bicycle XXVI appears to undergo fragmentation (to XXVIIId) more rapidly than isomerization to XXV.



Another species which should afford fragmentation products is the aldehyde XXXVIII. In practice, acid treatment of this molecule was complicated by retro-Michael products, but the bicyclic keto-ester XXXIX behaved as expected, yielding, after esterification, a mixture of the esters XL and XLI. The latter was identified by comparison (IR; GLC) with an authentic specimen;<sup>13</sup> its isomer was shown to possess the same carbon skeleton by reduction of both products to diethyl cyclo-heptane-1,1-dicarboxylate, and its structure XL was inferred spectroscopically and by analogy with the foregoing results. Interestingly, the ratio of isomers XL and XLI was 4:1 and when a pure sample of the latter<sup>13</sup> was re-subjected to the reaction conditions, the same ratio was re-established. We suggest that this is a conformational effect. In the preferred chair conformation<sup>14</sup> a 5-axial substituent experiences two non-bonded interactions (XLIa) whereas in the isomer XLa there is only one. This argument also explains our observation that under standard conditions, the diketone XLII

yields mainly the lactone XLIII ( $v_{CC}^{CC1}$  1777 cm<sup>-1</sup>;  $\mathbf{H} \rightarrow \mathbf{C} \rightarrow \mathbf{O}$  5.18  $\tau$  as subsplit doublet;  $\mathbf{H} \rightarrow \mathbf{C} \rightarrow \mathbf{P}$  7.25  $\tau$  unresolved).

12 S. Julia and D. Varech, Bull. Soc. Chim. Fr. 1127 (1959).

<sup>13</sup> G. L. Buchanan and G. W. McLay, Tetrahedron 22, 1521 (1966).

<sup>14</sup> G. L. Buchanan and J. M. McCrae, Tetrahedron 23, 279 (1967); S. Kabus, H. Friebolin and H. Schmid, Tetrahedron Letters 469 (1965).

## EXPERIMENTAL

UV and IR Spectra were measured on Unicam SP 800 and SP 100 Spectrophotometers respectively and NMR Spectra (in CDCl<sub>3</sub>) on a Perkin-Elmer (R.S.10) 60 mc instrument. Mass-spectra were measured on an A.E.I. MS9.

## 2-Dimethylaminomethylhydrindan-1-one

A soln of  $\alpha$ -hydrindone (24 g), paraformaldehyde (114 g) and dimethylamine hydrochloride (162 g) in EtOH (100 ml) containing conc HCl (3 ml) was boiled under reflux for 2 hr. When the soln had cooled it was poured into excess acetone and allowed to crystallize overnight. The *Mannich base hydrochloride* (yield 86°) was recrystallized from EtOH acetone m.p. 148–150°. (Found: C, 636; H, 74; N, 61. C<sub>12</sub>H<sub>16</sub> ONCl requires: C, 63/8; H, 71; N, 6/2°). The free base was liberated by alkali and used immediately.

## 3-Dimethylamino-o-methoxypropiophenone

A soln of o-methoxyacetophenone (47 g), dimethylamine hydrochloride (33 g) and paraformaldehyde (12 g) in 150 ml EtOH containing conc HCl (0.5 ml) was boiled under reflux for 2 hr, diluted with water, washed with ether, basified and re-extracted with ether. The crude Mannich base (75°, yield) was characterized as its picrate m.p. 138–139° from EtOH. (Found: C, 49.5; H, 4.6; N, 12.8,  $C_{18}H_{20}O_9N_4$  requires: C, 49.4; H, 4.8; N, 13.1°,).

## 1,5-Diketones

Except in a few cases which are separately described, the 1,5-diketones were prepared from cyclopentanone and the appropriate Mannich base by the thermal Michael process which has already been described<sup>15</sup> for XIa. In each case, the crude product was distilled to separate it from di-condensation product and crystallized to purity. The data are listed in Table 2.

## 2-(3'-Phenyl-3'-oxopropyl)cyclobutanone (1X)

Cyclobutanone (1.6 g) and  $\beta$ -dimethylaminopropiophenone (1.23 g) were refluxed with stirring for 1 hr, neutralized with AcOH and extracted with ether. The extract afforded the *dione* 0.7 g, 60 °<sub>0</sub>) b.p. 125 130°:003 mm v  $\mathcal{C}_{13}^{L_4}$  1783 and 1693 cm<sup>-1</sup>; *m/e* 202. (Found: C, 77.3, H, 70. C<sub>13</sub>H<sub>14</sub>O<sub>2</sub> requires: C, 77.2; H, 70° °<sub>0</sub>.)

## 2-(B-Benzolyethyl) 2-methylcyclopentanone (XLII)

An ice-cooled ethereal soln of 2-methylcyclopentanone (3.92 g) was treated with KOH (0.17 g) in 1.5 ml EtOH, followed by slow (30 min) addition of phenylvinyl ketone (3.0 g) dissolved in ether (10 ml) to the stirred reaction mixture. The ice-bath was then removed and the heterogeneous mixture was stirred for a further hr. After dilution with water and acidification (6NHCl), the mixture was ether extracted and the ethereal soln was washed with brine, dried and concentrated. The *diketone* was isolated by distillation (121 135<sup>c</sup>:001 mm) and thereafter solidified m.p. 40-42<sup>c</sup>. (Found: C, 77.9, H, 7.8. C<sub>15</sub>H<sub>18</sub>O<sub>2</sub> requires: C, 78.2; H. 7.9<sup>o</sup>, )  $v_{\infty}^{CCl_{16}}$  1736 and 1689 cm<sup>-1</sup>. The NMR showed a 3H singlet at 8.98 r.

## Cycloheptene Carboxylic Acids

The previously described<sup>2</sup> general procedure was used throughout, with reflux time varying (8-24 hr) according to convenience except in the case of XVI, where an 8-day reflux was used. The acid mixture was extracted by alkali, and the neutral fraction, which sometimes contained starting material and occasionally a trace of the bicyclo[3.2.1] octenone intermediate as well as  $\gamma$ -lactone, could be purified by treatment with NaBH<sub>4</sub> followed by chromatography,<sup>2</sup> when is afforded the  $\gamma$ -lactone ( $v_{cc1}^{CC1} \sim 1778 \text{ cm}^{-1}$ ). In view of recent comments<sup>16</sup> on the  $v_{cc}$  of certain  $\delta$ -lactones, the lactone structure was confirmed, where possible,

by the presence of a  $\mathbf{H}_{\perp} \stackrel{l}{\leftarrow} -\mathbf{O}$  signal at  $\sim 5.2 \tau$  in the NMR. Results are shown in Table 3. Analytical

figures and m ps quoted for carboxylic acids relate to pure isomers isolated by repeated recrystallizations. The acidic product obtained from I (i.e. XIIa) was esterified (diazomethane) yielding a yellow oil b.p.

134°:01 mm v<sup>CC1+</sup> 1730 cm<sup>-1</sup>. (Found: C, 78-6; H, 8-1. C<sub>13</sub>H<sub>18</sub>O<sub>2</sub> requires: C, 78-2; H, 79%), which was

<sup>15</sup> N. S. Gill, K. B. James, F. Lions and K. T. Potta, J. Am. Chem. Soc. 74, 4923 (1952).

<sup>&</sup>lt;sup>16</sup> K. K. Cheung, K. H. Overton and G. A. Sim, Chem. Comm. 634 (1965).

TABLE	2.	1.5-	Dix	ETONE
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Compound	Mannich base		Found	Requires	b.p.	m.p.	% Yield
		C14H1.03Br	C 569	569	166 176°/0∢ mm	 70-∶72°	62.5
			H 5-15	5-1		petrol	
			Br 27.2	27.1		•	
XIc	B	C, H, O,	C 73·3	73-1	196 198°/0.5 mm	78–79°	76
			H 70	7-3		EtOH	
XId	С	$C_{13}H_{18}O_{2}$	C 78·5	78·2	160-170°/0·3 mm	72 74°	76
			H 7-9	79		petrol	
Xle	D4	CIAH, OAN	C 64-4	64-1	-	75 77°	65
			H 5-8	5-6		petrol	
			N 54	5·2		•	
XIf	Ε	C <sub>1</sub> H <sub>1</sub> O <sub>2</sub>	C 809	81-2	190-200°/002 mm	75–76°	50
			H 68	6.8		petrol	
Xig	F	C1.H1.O1	C 72.5	73.15	150-155°/0-15 mm	• _	59
Ū			H 7·1	74			
XIh	G	CIAHIAO,	C 72-6	72-4	140°/0-02 mm	105 106°	63
			H 6-65	69		petrol	
xv	A	C1,H10,	C 77·8	78·2	125 127°/0·15 mm	-	50
			H 8-2	79			
XVII*	Н	$C_1,H_1,O_2$	C 78·2	78-2	130-140°/005 mm	68 - 70°	76
			H 8-05	79		EtOH	
XIX	F	$C_1$ , $H_1$ , $O_2$	C 78.7	78-0	176°/007 mm	60-64°	42
(n = 1)			H 70	7.1		petrol	
XIX	1	•				•	
(n = 3)							
XXVIIa	J	C18H24O3N4*	C 57·7	57-4	84 ·86°/0·02 mm	-	80
			H 6-2	64			
			N 14-8	14-9			
ХХУПЬ	ĸ	C11H18O2	C 72-4	72·5	94–98°/0·5 mm	-	31
			H 99	995			
XXVIIc	ĸ	C12H202	C 740	73-5	102-104°/0·3 mm		75
			H 104	10-3			

<sup>A</sup> E. B. Knott, J. Chem. Soc. 1190 (1947). <sup>B</sup> C. Mannich and D. Lammering, Chem. Ber. 55, 3510 (1922). <sup>C</sup> D. W. Adamso and J. W. Billinghurst, J. Chem. Soc. 1039 (1950). <sup>D</sup> H. F. Ginsburg, I. Lederman and D. Papa, J. Am. Chem. Soc. 75, 458 (1953). <sup>B</sup> F. F. Blicke and C. E. Maxwell, J. Am. Chem. Soc. 64, 428 (1942). <sup>P</sup> vide supra. <sup>G</sup> E. M. Padfield and M. L. Tomlir son, J. Chem. Soc. 2272 (1950). <sup>B</sup> Org. Synthesis Coll. Vol.; 3, 305. <sup>I</sup> D. S. Tarbell, H. F. Wilson and E. Ott, J. Am. Chem. Soc. 74, 6263 (1952). <sup>J</sup> A. N. Kost and V. V. Ershov, Zh. Obsh. Khim. 27, 1722 (1957) [Chem. Abstr. 52, 3789 g]. <sup>K</sup> G. I. Buchanan and A. C. W. Curran, Chem. Comm. 773 (1966).

<sup>a</sup> Mono-D.N.P., m.p. 127–129° (MeOH). <sup>b</sup> For structure see G. L. Buchanan and G. W. McLay, *Chem. Comm.* 504 (1965 <sup>c</sup> For structure see G. L. Buchanan and A. C. W. Curran, *Chem. Comm.* 773 (1966). <sup>d</sup> Free base obtained by treatment wit Na<sub>2</sub>CO<sub>3</sub> solution at 0°, *picrate* m.p. 160–161° (T.H.F./EtOH). (Found: C, 45·2; H, 3·8.  $C_{17}H_{17}O_{10}N_3$  requires: C, 45·2 H, 3·9%.) <sup>e</sup> Crude product used.

found by GLC analysis (1% PEG-A; 150°; 45 ml/min) to be a 45/55% mixture of two components with retention times of 54 min, and 6 min. On 1% F-60 at 140°, they had R, 120 and 128 min respectively.

## Forcing conditions

The diketone (2 g) and toluene-*p*-sulphonic acid (2 g) in ethylene glycol (ca. 3 g) was boiled for 1 hr. cooled and made alkaline with KOH (3 g) in  $\sim 10$  ml water. The soln was then boiled for a further 2 hr.

	1,5-dione		γ-Lacton <del>es</del> Found	Required	b.p. or m.p.	°, Yield		Acids Found	Required	b.p. or m.p.	(xvii) % Yield	Notes
 . x	- XI						 C <sub>13</sub> H <sub>14</sub> O <sub>2</sub>	C 77-75			8 (x)	(xiii)
Allb	ЯIХ						C <sub>14</sub> H <sub>15</sub> O <sub>2</sub> Br	с 57-2 Н 5-2	569 5.1	155 -157°	8	(xiv)
XIIc	XIc						C <sub>15</sub> H <sub>18</sub> O <sub>3</sub>	Br 27:2 C 72:8 H 7:7	27-1 73-1 7-3	137 139*	88	(xiv)
PIIX	PIX	C1,5H1,02	C 78-25	78·2 7.0	105°	Į	C <sub>15</sub> H <sub>16</sub> O <sub>2</sub>	C 780	78:2	127 129°	82	(x v)
XIIc	XIe		5	r.	6	<u>,</u>	C <sub>14</sub> H <sub>15</sub> O <sub>4</sub> N	н С в С <b>2</b> 6 С <b>6</b> 6	- <b>2</b> - <b>2</b> - <b>2</b> - 2	116-118°	(xvi) 26	(xiv)
XIIC	хіг						C <sub>18</sub> H <sub>16</sub> O <sub>2</sub>	C 815 C 815 F	54 81-2 6.6	(ii) 100 102° 611	75	(XIV)
XIIg	XIg	C1,H1,O3	C 73-1 H 7-3	73-15 7-4	123-124° (vi)	24	C <sub>16</sub> H <sub>20</sub> O <sub>3</sub>	с 730 Н 730	73.8	145–148° 0-25 mm	70	(xiv)
XIV	XIII (i)	C20H2002	С 82-1 Н 7-1	82.2 6.9	() 182° (v)	5	C20H2002	С 824 Н 64	82.2 64	194-196	85	
١٨X	X	C <sub>15</sub> H <sub>18</sub> O <sub>2</sub>	C 78-2 H 79	78:2 7.9	90-92° (vi)			:	5	Ì		(x viii)
ΙΙΙΛΧ	ΪΛΧ						C <sub>13</sub> H <sub>18</sub> O <sub>2</sub>	C 78-3 H 8-0	78·2 7.9	150 152° 0-25 mm	9 (xi)	(XIX)
XX = 1	XIX 1 = 1						C1,H1,O2	C 78.9 H 7.1	78.9 7.0	168-169° (vi)	6	(xx)
xx	XIX (iii)	C <sub>16</sub> H <sub>14</sub> O <sub>2</sub>	C 794 H 7:5	79-3 7-5	128 -130° (v)		C <sub>16</sub> H <sub>16</sub> O <sub>2</sub>	C 79-1 H 7-2	79.3 7:5	113-115° (vi)	4	(XXI)
×× ™	XIX (ii) 						C1,H2002	C 790 H 74	796 79	156 159° (vi)	17 (xii)	(ххі)

TARLE 3. CARBOXYLIC ACIDS AND LACTONES

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	1.5-dione		y-Lactones Found	Required	b.p. or m.p.	% Yiekd	Acids Found	Required	b.p. or m.p.	(avii) °° Yick	Notes
IIXXX	XXXI (iv)	C <sub>11</sub> H <sub>16</sub> O <sub>2</sub>	С 729 Н 88	73-3 8.95	 1 <i>57°</i> 12 тт	27					(xxii)
XLIII	XLII	C <sub>15</sub> H <sub>14</sub> O <sub>2</sub>	C 78-1 H 805	78·2 79	140 141° (v)	6 4					(xxiii)
<sup>(1)</sup> R. Gec J. Chem. S forcing con starting ma of purified a	oc. 825 (194 oc. 825 (194 ditions gave ditions gave ditions gave ditions gave ditions gave ditions gave ditions gave ditions gave ditions gave ditions gave	<i>t. Chem.</i> <b>86</b> , 232 9); J. Colonge 5 80%, <sup>(vi1)</sup> Med ered. <sup>(ui1)</sup> Overal vn. <sup>(uv)</sup> d <sup>3</sup> -isomer 78 cm <sup>-1</sup> , NMR	(1912) <sup>(11)</sup> S. Ju J. Dreux and F hyl ester. <sup>(13)</sup> Cr II yield from M. r. <sup>(111)</sup> S2 % start shows 3H sin	lia and D. Va H. Delplace, J yst. from ben annich base. <sup>(1</sup> ting material I glet at 8.82 r.	arech, Bull. S Bull. Soc. CH Vzene-petrol. (****) Indepen recovered ; f (************************************	ioc. Chim. Fr. 1127 () tim. Fr. 1635 (1956). (1) 60 % starting ma dently synthesized fr orcing conditions ga H singlet 8:33 r. <sup>(11)</sup> .	(959), <sup>(III)</sup> Crude dione <sup>10</sup> Cryst from EtOH. terial recovered : forci om ethyl 4-oxocycloh ve 75% yield. <sup>(wil)</sup> Yiel	(1) used direct. (1) used direct. (1) used direct. (1) used direct from an conditions are carboxy used are carboxy are to mi	<sup>1</sup> J. R. Nunr <sup>1</sup> petrol. <sup>(+10)</sup> <b>petrol.</b> (+10) <b>pave 87% o</b> <b>late and Ph</b> tture of ison 1µ (c 5000).	n and W. S. Yield very of the acid X if the acid X imgBr. <sup>(ath</sup> ) S	Rapson. low, but (a) 88 % itructure mixture 75 cm <sup>-1</sup> .

and flooded with water. Neutral products were extracted at this stage and, after acidification, acids were extracted with ether.

## Methyl 4-phenyl-3 and 5-oxocycloheptane carboxylates XXI and XXII

(a) The mixture of esters (24 g) derived from the isomeric acids XIIa (i.e. III + V) was added to a suspension of NaBH<sub>4</sub> (0.84 g) in anhyd diglyme (12 ml) and treated dropwise with a soln of redistilled BF<sub>3</sub> etherate (5 ml) in diglyme (6 ml). The reaction mixture was stirred at room temp for 1 hr, then treated cautiously with 8 ml H<sub>2</sub>O followed by 4N NaOH (6 ml) and 30°,  $H_2O_2$  (6 ml), stirred for a further 1 hr at room temp and finally extracted with ether. The ether soln was washed with FeSO<sub>4</sub> aq and then with brine, dried (MgSO<sub>4</sub>) and evaporated. The resulting oil (1.5 g), which was a mixture of diols, was dissolved in acetone and stirred overnight with an excess of Jones' reagent.<sup>17</sup> The soln was flooded with water (100 ml) and extracted with ether. The acids were isolated from the extract via a N NaOH extraction and esterified (diazomethane) yielding 0.65 g oil. This oil was chromatographed on fine mesh silica (10 g) and the fractions eluted with 40, 45 and 50°, ether in petrol, were rechromatographed affording the 3-oxo ester b.p. 136–138/0.02 mm (Found: C, 72.6; H, 74. C<sub>1.5</sub>H<sub>1.8</sub>O<sub>3</sub> requires: C, 73.1; H, 74°, ),  $v_{CO}^{CGL}$  1730 and 1710 cm<sup>-1</sup>. GLC R, 20.2 min under identical conditions.

(b) A soln of the  $\gamma$ -lactone IV, (100 mg) in dry THF (1 ml) was added to a stirred suspension of LAH (2 mg) in dry THF (2 ml) and the mixture was refluxed for 7.5 hr. Thereafter  $(NH_4)_2$  SO<sub>4</sub> aq was added followed by enough dil HCl to dissolve salts. Extraction with AcOEt afforded an oil which was oxidized for 20 hr in acetone soln with excess Jones' reagent. The acidic material isolated by the normal work-up was esterified (diazomethane) and shown by GLC and IR to be identified with the liquid oxo ester ( $R_r$  J8.1 min) described in (a) above.

By an identical process, the mixture of acids XIId was transformed into the oxo-ester XXI (p-tolyl for phenyl) b.p. 174–176°, 1-2 mm  $v_{CC}^{CCI_{4}}$  1743 and 1712 cm<sup>-1</sup>. (Found: C, 73:55; H, 748. C<sub>1.6</sub>H<sub>20</sub>O<sub>3</sub> requires: C, 73:8; H, 7:7°, ). GLC  $R_{t} = 20.6$  min on 7°, F-60.1°, Z at 200°, and XXII(p-tolyl for phenyl) m.p. 80–81° (petrol)  $v_{CC}^{CCI_{4}}$  1742 and 1712 cm<sup>-1</sup>. (Found: C, 73:8; H, 79–C<sub>1.6</sub>H<sub>20</sub>O<sub>3</sub> requires: C, 73:8; H, 7:7°, ). GLC  $R_{t} = 20.6$  min on 7°, F-60.1°, Z at 200°, and XXII(p-tolyl for phenyl) m.p. 80–81° (petrol)  $v_{CC}^{CCI_{4}}$  1742 and 1712 cm<sup>-1</sup>. (Found: C, 73:8; H, 79–C<sub>1.6</sub>H<sub>20</sub>O<sub>3</sub> requires: C, 73:8; H, 7:7°, ). GLC  $R_{t} = 23.4$  min on the same column. The liquid oxo ester was identified as the 3-oxo isomer by independent synthesis from the  $\gamma$ -lactone by-product of XIId (see Table 3). by LAH reduction as in (b) above. Moreover, a pure sample of the acid XIId, m.p. 127-129° (Table 3) isolated by repeated recrystallization, was identified as the  $d^{3}$  isomer XXIII by esterification-hydroboration-oxidation as detailed in (a) above.

## Grignard reaction on oxo-ester

The liquid XXI (66 mg) in anhyd ether (5 ml) was treated, under  $N_3$ , with ethereal MeMgI [from Mg (29 mg) and McI (220 mg) in ether (7 ml)] and stirred under reflux for 45 min. After cooling, 6N HCI (12 ml) was added and the 2-phase system was stirred and refluxed overnight; during this time the ether evaporated. The reaction mixture was then extracted with ether and the latter, re-extracted with 4N NaOH. The basic extract yielded 18 mg of acid on acidification, and this was shown (GLC on methyl ester) to be starting oxo-ester. The ethereal soln yielded 38 mg of XVI, m.p. 90–92' (benzene petrol) identical in all respects with the product already described (Table 3)

A stirred ethereal soln of solid XXII (60 mg) was similarly reacted with MeMgI for 2.5 hr, and worked up as before, yielding 45 mg of a complex mixture of neutral products and 20 mg of an acid which was esterified (diazomethane) The resulting ester was identical (GLC and IR) with that derived from the acid XVIII.

## 4-Isopropylcyclohept-3 and 4-ene carboxylic acids (XXVIIIb)

(a) The diketone XXVIIb (2.6 g) and conc HCl (6 ml) in 18 ml glacial AcOH was refluxed for  $_{-4}$  nr, concentrated *in vacuo*, flooded with water and extracted with other. The ethereal soln was washed with NaOH aq and evaporated, affording an oil (1.7 g) containing trace amounts of the dione (GLC). It was chromatographed on silica from which the *enone* XXIX was eluted with 4° AcOEt petrol, ( $v_{CO}^{CL}$  1717 cm<sup>-1</sup>  $\lambda_{max}$  end abostrption) and characterized as its 2.4-DNP, m.p. 142–144° from EtOH. (Found: C. 59-6; H. 54; N. 16.6.  $C_{17}H_{20}O_4N_4$  requires: C. 59-3; H. 5/8; N. 16.3° a.) On acidification, the alkaline washings afforded 400 mg acidic material which was esterified (diazomethane) ( $v_{CO}^{CC}$  1740 cm<sup>-1</sup>) and shown to be a

<sup>&</sup>lt;sup>17</sup> K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc. 39 (1946).

3:1 mixture (GLC) of methyl esters of XXVIIIb. (Found: C, 73.6; H, 10.1.  $C_{12}H_{20}O_2$  requires: C, 73.4; H, 10.3°<sub>6</sub>.) The NMR showed a 6H doublet at 8.9  $\tau$  ( $J = 6 c_1$ s) and a poorly resolved triplet (1 × H) at 4.07  $\tau$ .

(b) The diketone (3 g), toluene-p-sulphonic acid (3 g) and ethylene glycol (5 g) afforded 2.2 g ( $73^{\circ}_{o}$ ) of the same acid mixture when subjected to the forcing experimental procedure previously described (*vide supra*).

#### Effect of acid on 2-(5'-methyl-3'-oxohexyl) cyclopentanone (XXVIIc)

(a) On standard treatment<sup>2</sup> with conc HCl (8 ml) in glacial AcOH (24 ml) the diketone (4·2 g) gave 3·4 g neutral oil b.p. 90-94°.1 mm ( $\lambda_{max}^{EOH}$  247 mµ  $\varepsilon$  10.000 M/e 178;  $\nu_{CO}^{CO+}$  1678 cm<sup>-1</sup>) and 100 mg of acidic material. The neutral enone XXX was characterized as its 2.4-DNP m.p. 155–157° mm EtOH. (Found: C, 60·2; H, 60; N, 15·7. C<sub>18</sub>H<sub>22</sub>O<sub>4</sub>N<sub>4</sub> requires: C, 60·3; H, 6·2; N, 15·6°<sub>0</sub>); the acidic product was esterified (diazomethane) and shown by GLC to be a 1:1 mixture of esters derived from the *isopropylcycloheptene carboxylic acids* (XXVIIIc). (Found: C, 73·8; H, 10·7. C<sub>13</sub>H<sub>22</sub>O<sub>2</sub> requires: C, 74·2; H, 10·5°<sub>0</sub>.)

(b) The diketone (1.5 g) and toluene-*p*-sulphonic acid (1.5 g) in ethylene glycol (2.5 g) was boiled under reflux for 1 hr, cooled and after adding KOH (2.5 g) in 8 ml water, boiled for a further 2 hr. Finally the mixture was flooded with water, washed with ether, acidified and re-extracted with ether. The neutral product (200 mg) was identical (GLC and 2.4-DNP) with that described above. The acidic product (1.1 g)was also identical (GLC on methyl esters) in nature and in composition with that described above.

## Methyl 1.2.4.5.6.7.3.8-Octahydroazulene-5-carboxylate (XXXIII)

The diketone XXXI (3 g) in MeOH (60 ml) containing 6 ml conc  $H_2SO_4$  was boiled under reflux for 2 days, concentrated, dissolved in ether and washed with saturated brine. On evaporation, the ethereal soln afforded the *methyl ester* XXXIII, b.p. 85-90<sup>o</sup>/0.25 mm (Found: C, 74.2; H, 89.  $C_{12}H_{18}O_2$  requires: C, 74.2; H, 9.2<sup>o</sup>,)  $v_{CO}^{CO_4}$  1738 cm<sup>-1</sup>, yield 2.6 g (87<sup>o</sup><sub>o</sub>) GLC analysis (10<sup>o</sup><sub>o</sub> APL, 175<sup>o</sup>; 50 ml/min) showed it to be a single substance  $R_i$  7.75 min and alkaline hydrolysis followed by acidification gave XXXII, already described (Table 3). The position of the double bond follows from the absence of NMR signals in the 4  $\tau$  region

#### Acid treatment of 2-(2'oxocyclopentylmethyl) cyclohexanone (XXXIV)

The diketone<sup>15</sup> XXXIV (4 g) in AcOH (25 ml) containing cone HCI (8 ml) was boiled under reflux for 24 hr, concentrated *in vacuo*, diluted with water and extracted with ether. The ethereal soln was washed with 4N NaOH, then brine Acidification afforded a negligible amount of acid from the washings: the ethereal soln yielded 3.6 g of neutral oil which was shown (GLC) to comprise starting material  $(3^{\circ}_{o})$  and three other components A, B and C ( $R_1$  4.25, 7.25 and 17.0 min respectively on  $10^{\circ}_{o}$  PEG-A at 175°; 45 ml/min) in  $32^{\circ}_{o}$ ,  $24^{\circ}_{o}$  and  $40^{\circ}_{o}$  yields.

The mixture (2 g) was chromatographed on 100 g silica and eluted with petrol AcOEt mixture. This operation afforded A + B as an inseparable mixture, and pure C (750 mg b.p. 80° 0.5 mm). (Found: C, 744; H, 9.6  $C_{12}H_{18}O_2$  requires: C, 742; H, 9.3°,)  $v_{CO}^{CO*}$  1776 cm<sup>-1</sup>. The NMR spectrum showed no absorption below 8.3 x and this product is therefore the *lactone* XXXVII. The mixture (A + B) showed  $v_{CO}^{IO*}$  1750 and 1720 cm<sup>-1</sup>. It was boiled for 2 days in MeOH (25 ml) containing conc H<sub>2</sub>SO<sub>4</sub> (2 ml), diluted with water and concentrated. Ether extraction gave a colourless oil (750 mg) which was chromatographed as above, and so yielded lactone (C: 400 mg) and XXXV (205 mg) b.p. 60°:0.01 mm. (Found: C. 81-2; H, 9.65,  $C_{12}H_{16}O$  requires: C, 81.7; H, 9.15°, )  $v_{CO}^{CO*}$  1722 cm<sup>-1</sup>. The NMR spectrum showed three unresolved multiplets – 2H at 7.5 x (CH—CO), 6H at 8.2 x (allylic) and 8H at 8.5x. GLC analysis showed that the acid-MeOH treatment had converted component A into the lactone XXXVII, and A is therefore XXXVI.

#### Acid treatment of 2-(3'-oxopropyl) cyclopentanone (XXIV)

(a) The dione<sup>15</sup> (6 g) and conc HCl (10 ml) in AcOH (30 ml) was boiled under reflux for 6 hr, concentrated under vacuum, flooded with water and extracted in ether. The ether soln was washed with NaOH and concentrated, affording the enone XXV v(CCl<sub>4</sub>) 1630 and 1667 cm<sup>-1</sup>,  $\lambda_{max}^{EOH}$  240 mµ (e 11,000) b.p. 113–115<sup>9</sup>/12 mm, which was further characterized as its 2,4-DNP,<sup>18</sup> m.p. 198–199°. Acidification of the alkali washings gave a trace of acidic material.

<sup>10</sup> A. J. Birch, J. Chem. Soc. 430 (1944); G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrel, J. Am. Chem. Soc. 85, 207 (1963).

(b) Using 3 g diketone, the toluene-*p*-sulphonic acid-ethylene glycol procedure afforded 1.8 g acids which was converted to a mixture of *methyl esters* (XXVIIId) b p. 60/0.8 mm  $v_{CC}^{CC}$  1740 cm<sup>-1</sup>. (Found: C, 710; H, 9.4.  $C_{10}H_{16}O_2$  requires: C, 714; H, 9.6 °<sub>0</sub>.)

## Ethyl bicyclo-[3.2.1]-oct-3-en-8-one carboxylate (XXXIX)

The epimeric mixture of ethyl 4-hydroxybicyclo-[3,2,1]octan-8-one carboxylates<sup>13</sup> (2 g) and polyphosphoric acid (40 g) were stirred together for 1 hr on the steam bath, diluted with ice-water and extracted with ether. The ethereal extract was washed with NaHCO<sub>3</sub> aq and evaporated. Distillation afforded the *unsaturated keto-ester* b p. 70–75':006 mm,  $v_{C0}^{C0}$  1735, 1763 cm<sup>-1</sup>.  $v_{C1}^{C2}$  680 cm<sup>-1</sup>. (Found: C, 68-2; H, 79. C<sub>11</sub>H<sub>14</sub>O<sub>3</sub> requires C, 68-0; H, 7-3°<sub>0</sub>.) NMR showed 2(vinyl) H 4-3  $\tau$  (mult.) and a 2H (allylic) doublet at 7.88  $\tau$ .

## Diethyl cyclohept-3 and 4-ene-1,1-dicarboxylates (XL and XLI)

The bicyclic keto-ester (0.33 g) was boiled overnight with conc HCl (2 ml) in glacial AcOH (6 ml), poured into ice-water and extracted with ether. The extract was re-extracted with 6N NaOH, and on acidification a semi-solid product was obtained. Esterification (diazomethane) yielded 0.138 g of a pale yellow oil which was found (GLC) to contain a trace of diethyl cyclohept-4-en-1,5-dicarboxylate<sup>13</sup> in addition to the two main constituents. These occurred in a 4:1 ratio [the less abundant being identified (GLC) as XLI] and were isolated by preparative TLC. The structure of the minor component was confirmed by hydrolysis and decarboxylation to cyclohept-4-ene carboxylic acid as previously described.<sup>13</sup> The major component, bp. 95-97°/001 mm.  $v_{CO}^{CO}$  1729 cm<sup>-1</sup>;  $v_{CS}^{CS}$  685 cm<sup>-1</sup>. (Found: C. 64·8; H, 8·7. C<sub>13</sub>H<sub>20</sub>O<sub>4</sub> requires: C, 650; H, 8·4°°) showed only end absorption in the UV and a 2H (vinyl) multiplet at 40 r. It is formulated as the  $A^3$  isomer XL since catalytic reduction (5°° Pd:C in acetic acid) afforded the saturated diester b:p. 70°/001 mm.  $v_{CO}^{CO}$  1729 cm<sup>-1</sup>. (Found: C. 64·6; H. 9·3, C<sub>13</sub>H<sub>22</sub>O<sub>4</sub> requires: C. 64·4; H, 9·15°°) which was also formed by catalytic reduction of XLI.

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