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THE THERMAL-MICHAEL REACTION—I

ORIENTATION FEATURES[1]

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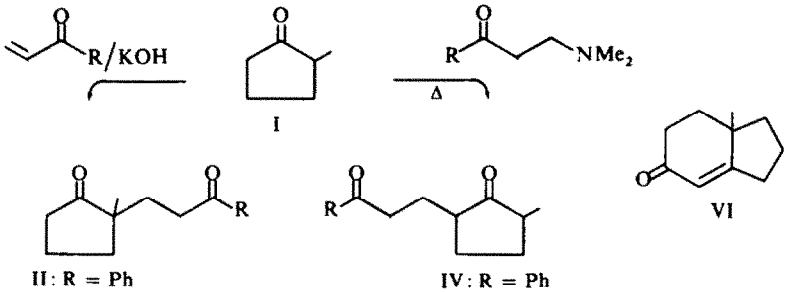
Abstract—Mannich bases react thermally with ketones to give 1,5-diketones by what appears to be a Michael reaction. In some cases the orientation of the product differs significantly from that observed in the Michael reaction, and Mannich bases lacking a hydrogen β to the N atom are able to react *via* an intermediate migration.

IN THE Michael reaction, which is normally defined as the condensation of a carbanion with an electrophilic olefin, the latter may be conveniently replaced by a Mannich base or its methiodide.[2] This (Robinson–Michael) modification is base-catalyzed and appears to proceed via an elimination step[3] in which the conjugated enone is liberated *in situ* and thereafter reacts by the standard mechanism. A second, less popular modification, involving the thermal condensation of a Mannich base with a reactive methylene compound, was described a short time ago[4] and has been classified[5] as a Robinson–Michael reaction. In fact this is not so; mechanistically it is a separate reaction and we propose to call it the *thermal*-Michael reaction.

The work of the Australian group[4] has established that the Thermal reaction offers certain practical advantages over either the classical or Robinson procedures. The reaction is cleaner, yields are frequently higher, little polymer is formed and competing condensations* are minimized. In our hands[6] the thermal-Michael has been the method of choice for the synthesis of a wide variety of 1,5-diketones. However, the true nature of the reaction is not apparent until it is applied to unsymmetrical ketones. When these react with enones under classical-Michael conditions or with Mannich base methiodides under Robinson–Michael conditions, the condensation takes place mainly, or even exclusively at the more highly substituted carbon.[7] Thus



II: R = Ph
III: R = Me

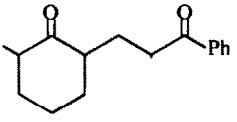
IV: R = Ph
V: R = Me

* e.g. Self-condensation of cyclopentanone to give cyclopentylidene cyclopentanone, or ring-closure of 2-(3'-oxobutyl)-cyclohexanones to give octalones.

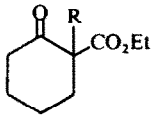
when phenyl vinyl ketone was condensed[6] with 2-methylcyclopentanone (I) in the presence of KOH, the NMR spectrum of the product showed a Me singlet (τ 8·98) as expected of structure II. On the other hand, the thermal reaction of I with β-dimethylaminopropiophenone gave[6] an isomer (76% yield) which showed a Me doublet (τ 8·93; J = 7·0 c/s), and must be formulated as IV. Chemical proof of structures II and IV is implicit in their conversion by HCl to isomeric phenylcycloheptene carboxylic acids.[6]

Similarly methylvinyl ketone reacted with I in the presence of KOH affording III (3H singlet τ 9·03) and the Robinson variation has been shown to give the derived bicyclic-enone VI,[7c] whilst thermal decomposition of 4-dimethylaminobutan-2-one in I, yielded *almost exclusively* the isomer V (3H doublet τ 8·94; J = 6 c/s). With 2-methylcyclohexanone the same orientations were observed. Both the classical Michael and Robinson–Michael processes are known to lead mainly to 2,2-disubstituted derivatives,[7] and as expected, phenylvinyl ketone reacted with 2-methylcyclohexanone in the presence of KOH to give the 2,2-disubstituted product. On the other hand, the thermal reaction afforded the 2,6-disubstituted product VII, whose structure was indicated by NMR (3H doublet τ 9·03; J = 6 c/s) and confirmed by a synthesis using the enamine route.[8]

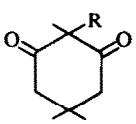
In thermal-Michael reactions cyclopentanone affords small amounts of dicondensation product and it has been noted[9] that here too the orientation is 2,5. It is apparent from these observations that although it apparently resembles the



VII

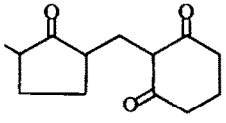


VIII



IX

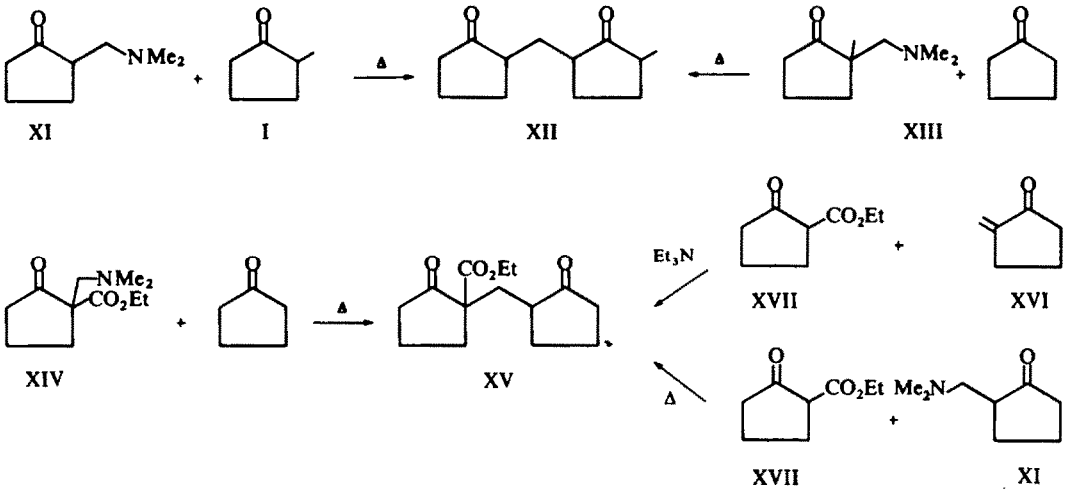
a: R = H
b: R = CH_2CH_2COPh



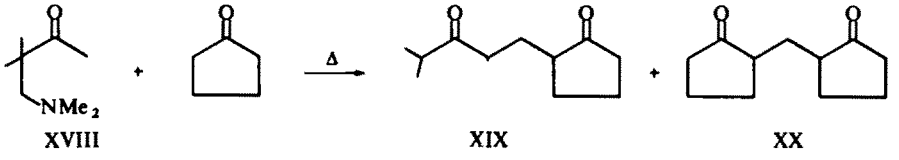
X

Robinson–Michael reaction, the thermal-Michael reaction is in fact *complementary* to it, bringing about substitution specifically at the less substituted C atom. Accordingly, it must proceed by an *independent mechanism*. An exploration of the scope of the reaction is under way, but it is pertinent to note here that, in contrast to alkyl-substituted ketones, the β-ketoester VIIIa and the β-diketone IXa both reacted at the more highly substituted site, to yield the conventional Michael-products VIIIb and IXb.

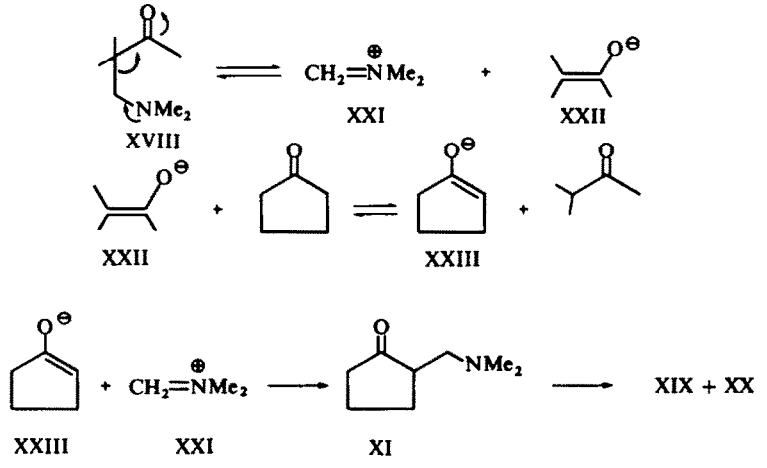
The Mannich base (XI) of cyclopentanone reacted with I to give the "expected" product XII; surprisingly, the Mannich base of 2-methylcyclopentanone which was recently shown[10] to be XIII, reacted with cyclopentanone to give *the same* product, and with dihydroresorcinol to give X. Similarly the Mannich base XIV reacted[11] with cyclopentanone under thermal conditions to give the non-enolisable β-ketoester XV which was also obtained from XVI and XVII under classical conditions or thermally, by the reaction of XI with XVII.



It is possible to envisage several mechanisms for the thermal Michael reaction (I → IV) but less easy to accommodate the reactions XIV → XV or XIII → XII *unless* it can be assumed that these cases involve an initial transformation (XIII → I + XI) peculiar to ββ-disubstituted Mannich bases. Positive evidence for such a

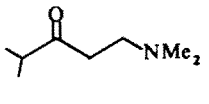


transformation has arisen out of the reaction of cyclopentanone with XVIII,[12] the Mannich base of isopropylmethyl ketone. This reaction afforded not only the product XIX now expected, but a small amount of XX which must have arisen from cyclopentanone and the Mannich base XI. Thus it appears that ββ-disubstituted

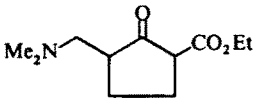


Mannich bases (e.g. XVIII) can undergo a thermal retroprocess leading via XXI, by a trans-aminomethylation,[13] to XI from which both products (XIX and XX) are derived by the thermal-Michael reaction. The same mechanism explains the formation of XII from XIII, and XV from XIV without contravening the substitution rules for the thermal-Michael as set out earlier in this paper.

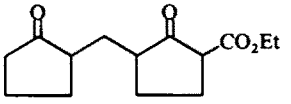
It seems probable that the transaminomethylation process is indeed *intermolecular*,



XXIV



XXV



XXVI

as shown above, and not intramolecular (e.g. XVIII → XXIV → XIX). This follows from the reaction XIV → XV, for in this instance, an intramolecular migration would have led via XXV to an enolizable β-ketoester XXVI.

EXPERIMENTAL

UV and IR spectra were measured on Unicam S.P. 800 and S.P. 100 spectrophotometers respectively, and NMR spectra on a Perkin–Elmer (R.S. 10) 60 mc instrument (in $CDCl_3$). Mass spectra were measured on an A.E.I. M.S.9.

2-Methyl-2-(3'-oxobutyl)-cyclopentanone (III)

A soln of 2-methylcyclopentanone (3·92 g) in anhyd ether (15 ml) was cooled to 0° and treated with a soln of KOH (0·17 g) in anhyd EtOH (1·5 ml). Methyl vinyl ketone (1·4 g) dissolved in anhyd ether (10 ml), was added dropwise over a period of 30 min to the stirred reaction mixture then the ice bath was removed and the heterogeneous system stirred for 1 hr. After dilution with water and acidification (6N HCl), the mixture was extracted with ether and the extracts washed with brine and dried ($MgSO_4$). Concentration and removal of the excess 2-methylcyclopentanone yielded 2·3 g of an oil which showed OH and complex CO absorption in the IR spectrum. The oil was dissolved in petrol and chromatographed on silica (60 g), elution with 20% ether in petrol furnishing the desired *diketone* III, b.p. 135°/11 mm. (Found: C, 71·06; H, 9·28. $C_{10}H_{16}O_2$ requires: C, 71·39; H, 9·59%); $\nu_{C=O}^{CCl_4}$ 1736 and 1720 cm^{-1}. The NMR spectrum showed the protons of the Me group on the cyclopentanone ring as a singlet at 9·03 τ; GLC retention time, 13·2 min (10% APL at 125°).

Further elution afforded material which showed OH absorption in the IR spectrum, but this was shown by GLC analysis to be a mixture of 3 compounds.

GLC analysis of the crude reaction product showed that two impurities with retention times of 15·9 min and 28·6 min (10% APL at 125°) were present in considerable quantities. Neither corresponded to the isomeric 2,5-substituted cyclopentanone (V) of the α,β-unsaturated ketone (VI).

2-(3'-Oxobutyl)-5-methylcyclopentanone (V)

A stirred soln of diethylaminobutan-3-one (8·58 g) in 2-methylcyclopentanone (17·3 g) was refluxed for 1·25 hr at 140° then cooled, neutralized with AcOH and diluted with ether. The ethereal soln was washed with brine and dried ($MgSO_4$), then concentrated and the excess 2-methylcyclopentanone removed by distillation on a water bath at water-pump press. The residue showed a major spot on TLC with a trace of a slightly less polar material. Distillation afforded 4·01 g (40%) of a colourless oil b.p. 122–126°/10 mm, a sample (500 mgm) of which was chromatographed on fine silica (10 g). Elution with 30% ether in petrol furnished pure *diketone* V (TLC and GLC analysis on 10% APL at 125°, R_t = 15 min), b.p. 124–127°/mm. (Found: C, 70·74; H, 9·59. $C_{10}H_{16}O_2$ requires: C, 71·39; H, 9·59%); $\nu_{C=O}^{CCl_4}$ 1739 and 1723 cm^{-1}. The NMR spectrum showed a doublet at 8·94 τ (J = 6 c/s) for the Me group on the cyclopentanone ring. GLC analysis of the product prior to chromatography showed the presence of a trace of the 2,2-substituted isomeric diketone (III) (10% APL at 125°, R_t = 13·2 min).

An earlier reaction which was heated at 120° for 90 min yielded only 8% of an oil shown by GLC analysis to consist of 70% of V together with 30% of the III and an unidentified compound.

2-Methyl-6-(β-benzoylethyl)-cyclohexanone VII

(a) A mixture of 2-methylcyclohexanone (10 g) and β-dimethylaminopropiophenone (5·15 g) was refluxed under an air condenser for 30 min at 165° by which time evolution of dimethylamine from the reaction mixture has ceased. On cooling, the mixture was neutralized with glacial AcOH, diluted with ether and washed with brine. The ethereal soln was dried ($MgSO_4$), the ether and excess 2-methylcyclohexanone removed *in vacuo* and the residue distilled *in vacuo* to give 5·5 g (76%) of a yellow oil (b.p. 145–150°/0·05 mm) which solidified on standing.

GLC on 5% QFI at 200° showed the presence of 3 compounds with retention times of (a) 5·55 min; (b) 6·00 min; (c) 7·57 min in the proportions 85%; 10%; 5%.

The major component VII was purified by crystallization, m.p. 52° (pet ether). (Found: C, 78·79; H, 7·95. $C_{16}H_{20}O_2$ requires: C, 78·65; H, 8·25%), and showed $\nu_{CO}^{CCl_4}$ 1712 and 1688 cm^{-1}; *m/e* 244, NMR 3H doublet τ 9·03, $J = 6$ c/s.

Compound (b) showed similar IR features but no CH_3 signal in the NMR. It was shown to be 2-(β-benzoylethyl)-cyclohexanone by comparison with an authentic sample,[4] and is derived from cyclohexanone present in the 2-methylcyclohexanone. Compound (c) showed a singlet CH_3 signal $\nu_{CO}^{CCl_4}$ 1707 and 1689 cm^{-1} and was shown to be 2-methyl-2-(β-benzoylethyl)-cyclohexanone by direct comparison (see below).

(b) A mixture of 2-methyl-1-pyrrolidinocyclohex-6-ene[9] (5 g) and phenyl vinyl ketone (4 g) in dry benzene (30 ml) was refluxed for 24 hr in a stream of dry nitrogen. A buffer soln of glacial AcOH (15 ml), water (15 ml) and NaOAc (7·5 g) was added and refluxing continued for a further 4 hr. The mixture was allowed to cool, the benzene layer separated and the aqueous layer extracted with benzene. The combined benzene extracts were washed with 10% HCl and sat $NaHCO_3$aq. After the removal of the solvent under reduced press, 5·7 g of material remained which gave on distillation 5·4 g (74%) of a viscous yellow oil (b.p. 140–145°/0·04 mm) which solidified on standing to give the dione VII, m.p. 52° (pet ether) identical in all respects with the product from (a) above.

2-Methyl-2-(β-benzoylethyl)-cyclohexanone

Phenyl vinyl ketone (4·3 g) in 25 ml ether was added over 1 hr to a mixture of 2-methylcyclohexanone (7·25 g) and ethanolic KOH (1 g/4 ml) in 30 ml ether at 0°. The mixture was then stirred at room temp for 1 hr, poured on to ice, acidified with conc HCl and extracted with ether. The ethereal extracts were washed with brine, dried over $MgSO_4$ and the ether and excess 2-methylcyclohexanone removed under reduced press. The residue was distilled *in vacuo* to yield 5·1 g (64%) of a yellow viscous oil (b.p. 145–150°/0·06 mm). GLC analysis on 5% QFI at 200° showed the major product to be the expected 2-(β-benzoylethyl)-2-methylcyclohexanone with trace amounts of the other two products described in (a) above. A pure sample isolated by thick plate chromatography showed $\nu_{C=O}^{CCl_4}$ 1690 and 1707 cm^{-1} in the IR and a singlet Me signal at τ 8·94 in the NMR. (Found: C, 78·07; H, 8·35. $C_{16}H_{20}O_2$ requires: C, 78·65; H, 8·25%).

2-(β-Benzoylethyl)-2-carbethoxycyclohexanone (VIIIb)

(a) A mixture of β-dimethylaminopropiophenone (3·4 g) and VIIIa (9·8 g) was heated under reflux (160°) for 30 min. The usual work-up procedure yielded 4·1 g (70%) of an oil b.p. 136–140°/0·01 min. GLC analysis indicated the presence of two components R_t 2·00 and 9·25 min on 5% QFI at 200° and 55 ml/min and R_t 5·5 and 17·75 min on 1% SE30 at 175° and 45 ml/min respectively and in ratio 1:3. Combined GLC-mass spectrometry showed that the minor component had mol.wt. 244 and the major 302.

The former was identified as 2-(β-benzoylethyl)-cyclohexanone by GLC and mass spectrum comparison with an authentic specimen. The major product, isolated by thick plate chromatography was identical (IR, NMR and GLC) with the expected β-keto-ester described in (b) below.

(b) Phenylvinyl ketone (0·775 g) in dry ether (5 ml) was added dropwise to a mixture of 2-carbethoxycyclohexanone (2·0 g) and ethanolic KOH (0·175 g/2 ml) in ether (5 ml) at 0°. The mixture was stirred at room temp for 2 hr, poured on to crushed ice, acidified with HCl aq and extracted with ether. The extract was washed (brine) dried ($MgSO_4$) and distilled. After removal of ether and excess keto-ester, the product VIIIb (1·2 g, 68%) distilled at 155–160°/0·2 mm. It showed a single peak on GLC (R_t 9·25 min on 5% QFI at 200° and 55 ml/min. (Found: C, 71·31; H, 7·54. $C_{18}H_{22}O_4$ requires: C, 71·50; H, 7·33%); $\nu_{CO}^{CCl_4}$ 1692, 1716 and 1739 cm^{-1}. The product gave no colouration with $FeCl_3$ (alc) and no displacement in the UV spectrum on the addition of base.

2-Methyl-2-(2'-benzoylethyl)-dimedone (IXb)

β-Dimethylaminopropiophenone (12 g) was added to IXa (11·3 g) and slowly heated to 140°. The temp was maintained at 140° for 45 min and, after cooling, the reaction mixture was dissolved in ether, washed with $NaHCO_3$aq, then with water, dried over $MgSO_4$ and evaporated. The residue crystallized from light petrol (60–80°) in colourless needles, m.p. 99°, ($\nu_{CO}^{CCl_4}$ 1731, 1698 cm^{-1}), yield 5 g. (Found: C, 75·21; H, 7·22. $C_{18}H_{22}O_3$ requires: C, 75·53; H, 7·69%); NMR 3H singlet 8·7 τ.

2-Methyl-5-(2'-oxocyclopentylmethyl)cyclopentanone XII

(a) Compound XIII (9·9 g) was dissolved in cyclopentanone (17·64 g) and the mixture refluxed with stirring for 3 hr. Standard work up procedure gave the *diketone* XII as a colourless oil (2·5 g, 40%) b.p. 105–108°/0·5 mm; R_t = 12·05 min on 10% A.P.L. at 135°. (Found: C, 73·98; H, 8·98. $C_{12}H_{18}O_2$ requires: C, 74·19; H, 9·34%); $\nu_{C=O}^{CCl_4}$ 1742 cm^{-1}. NMR 8·95 τ (2 overlapping doublets: J = 6 c/s), suggesting a mixture of stereoisomers.

(b) The base XI (6·5 g) and 2-methylcyclopentanone (18 g) were heated at reflux temp for 90 min. Standard work up procedure gave a pale yellow oil from which the same diketone XII was obtained as a colourless oil (5·2 g, 50%), b.p. 110°(0·5 mm; R_t = 12·05 min on 10% A.P.L. at 175°, NMR and IR spectra identical with those described under (a) above.

2-(3'-Methyl-2'-oxocyclopentylmethyl)cyclohexan-1,3-dione (X)

Cyclohexane-1,3-dione (11 g) was dissolved in XIII (4·65 g) and the mixture refluxed with stirring for 6 hr. Standard work up procedure gave X (5 g, 55%) b.p. 140–145°/0·1 mm; m.p. 115–116° (petrol). (Found: C, 70·58; H, 7·70. $C_{13}H_{18}O_3$ requires: C, 70·24; H, 8·10%); λ_{max}^{EtOH} 263 mμ (ε 22,000) with bathochromic shift λ_{max}^{EtOH} 291 in alkali; NMR showed τ 8·85 (3H, doublet).

2-Carbethoxy-2-(2'-oxocyclopentylmethyl)cyclopentanone XV

(a) The base XIV was dissolved in cyclopentanone (2·52 g) and the mixture refluxed with stirring for 2 hr. Work up as before gave the *diketone* XV as a colourless oil (1·5 g, 48%) b.p. 115–119°/0·1 mm; R_t = 5·5 min on 5% QFl at 225°; 14·25 min on 10% P.E.G.A. at 175° and 13·12 min on 10% A.P.L. at 175°. (Found: C, 66·28; H, 7·68. $C_{14}H_{20}O_4$ requires: C, 66·65; H, 7·99%); $\nu_{C=O}^{CCl_4}$ 1733 and 1740 cm^{-1}; NMR showed τ 5·8 (2H, quartet); τ 8·75 (3H, triplet); λ_{max}^{EtOH} 219 mμ (ε 12,000).

(b) The base XI (3 g) was dissolved in 2-carbethoxycyclopentanone (5·3 g) and the mixture refluxed for 90 min. Standard work up procedure gave the same diketone as a colourless oil (2·5 g, 45%) b.p. 155°/1 mm; R_t = 5·5 min on 5% QFl at 225° and 14·25 min on 10% P.E.G.A. at 175°; λ_{max}^{EtOH} 219 mμ (ε 9,500).

(c) Recrystallized 2-β-dimethylaminomethylcyclopentanonehydrochloride (5 g) was heated gradually to 200° under reduced press (12 mm) and the methylenecyclopentanone[14] distilled at 60°/12 mm (2·5 g, 88%).

The vinyl ketone (2 g) in 2-carbethoxycyclopentanone (9 g) was basified with Et_3N (1·18 g) and refluxed with stirring for 90 min. The cooled residue was treated with glacial AcOH and extracted into ether. The ethereal soln was brine washed, dried and evaporated to afford the *diketone* XV as a colourless oil (3·2 g, 60%) b.p. 150–152°/1 mm; R_t = 5·5 min on 5% QFl at 225° and 14·25 min on 10% P.E.G.A. at 175°; λ_{max}^{EtOH} 219 mμ (ε 11,000).

Hydrolysis

The diketone XV (100 mg) in EtOH (10 ml) was treated with 4N NaOH (5 drops) and the mixture shaken for 5 min. The EtOH was evaporated and the residue diluted with water and ether extracted. The combined ethereal extracts were discarded and the aqueous soln was acidified and ether extracted. The ethereal extract was washed ($NaHCO_3$aq and brine) dried and evaporated to afford a colourless oil (20 mg) identified as 2-carbethoxycyclopentanone by GLC retention times (2·25 min on 5% QFl at 225°; 2·75 min on 10% P.E.G.A. at 175° and 8·01 min on 10% A.P.L. at 175°) and by UV (λ_{max}^{EtOH} 218 mμ ε 8300 with shifts to λ_{max}^{EtOH} 284 mμ in alkali).

The acidic material was isolated from the bicarbonate washings as a colourless oil (70 mg) which was decarboxylated at 200°/10 mm, to the known[6,15] dione XX, m.p. and mixed m.p. 71–73° $\nu_{max}^{CCl_4}$ 1742 cm^{-1}.

2-(4'-Methyl-3'-oxopentyl)cyclopentanone XIX

The base XVIII[12] (5·5 g) in cyclopentanone (10 g) was refluxed with stirring for 4 hr, neutralized with AcOH and taken up in ether. The ethereal soln was washed with brine, dried, and distilled. Following the removal of ether and excess cyclopentanone, the residual oil (3·5 g) was chromatographed on silica in

EtOAc/pet. ether. Elution gave successively cyclopentylidenecyclopentanone (100 mg, $\nu_{CO}^{CCl_4}$ 1690 cm^{-1} λ_{max}^{EtOH} 258 mμ ε 28,000, 2:4 D.N.P. m.p. and mixed m.p. 227–229°) then the *dione* XIX (2·2 g) as a colourless oil, b.p. 90–95°/0·5 mm. (Found: C, 72·4; H, 9·9. $C_{11}H_{18}O_2$ requires: C, 72·5; H, 9·95%); *m/e* 182 $\nu_{CO}^{CCl_4}$ 1714 and 1738 cm^{-1}; NMR, 6H doublet τ 8·9, J = 6 c/s) and finally the dione XX (50 mg) m.p. and mixed[15] m.p. 70–72°.

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