The Constitution of Some 3-Methylcyclohex-2-enone Dimers.

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A chemical proof is given for the relationship between the hydroxyl and the αβ-unsaturated carbonyl group in the alkaline dimerisation product of of 3 : 5-dimethyl*cyclo*hex-2-enone. This result uniquely determines the structure of the dimer as well as of α- and β-dipiperitone.

KNOEVENAGEL AND REINECKE (*Ber.*, 1899, **32**, 418) first found that 3-methyl*cyclo*hex-2-enones could be dimerised in hot concentrated alkali but they did not propose a structure for the products. Later Ruzicka (*Helv. Chim. Acta*, 1920, **3**, 781) discovered that good yields of the dimers were obtained when powdered sodamide in ether was used in place of aqueous alkali. In the case of 3 : 5-dimethyl*cyclo*hex-2-enone, as a typical example, he proposed the structure (I) for the dimer. Treibs (*Ber.*, 1930, **63**, 2738), in a study of piperitone dimers, suggested a formula for the alkaline dimerisation product, m. p. 105°, but did not present evidence in its support. Briggs, Harland, Ralph, and Simmonds (*J.*, 1953, 3788) in an exhaustive investigation of α- and β-dipiperitone (by-products in the commercial processing of piperitone) showed that Treibs's dimer was a mixture of these two compounds. They also brought considerable evidence forward to support the constitution of the dimer as (II) in which the only difference between the α- and the β-form lay in the stereochemistry of the carbon atom marked with an asterisk. The infrared evidence was claimed to be in good agreement with this assignment. Taylor (*Chem. and Ind.*, 1954, 252), however, has re-interpreted their data to take into account the presence of a strongly hydrogen-bonded αβ-unsaturated carbonyl group (cf. piperitone and the dimers in the Table) and revised the formula to (III) with which all the other evidence agreed. We have remeasured the infra-red spectra of some of the dipiperitone derivatives and have found some systematic errors in the results reported by Briggs *et al.* (*loc. cit.*) ; however, we have not discussed them in this paper since a correction is in the press (Briggs, personal communication).

Cole (*Chem. and Ind.*, 1954, 661) recently pointed out that since these infrared spectra were measured in the solid state this permitted *a priori* the possibility of inter- as well as intra-molecular hydrogen bonding and that spectra should be taken in dilute solution in order to establish the latter type firmly. As can be seen from the Table the spectral results in solution (where taken) were almost identical with those for the solid phase, thus proving intramolecular hydrogen bonding which fully substantiates Taylor's earlier conclusion.

In considering the dimerisation of piperitone it should be noted that of the various

anions (Va—c) only the simple enol ion (Va) and the transoid anion (Vc) are important. For example the former partakes in the ready racemisation mechanism of optically active piperitones and the latter in condensation reactions under basic conditions, as with benzaldehyde to yield the styryl compound (VI). Hence the Michael addition of piperitone to itself under basic conditions would be expected to give the diketone (IV), subsequent ring closure of which to dipiperitone (III) through an anion of type (Vc) is clear.
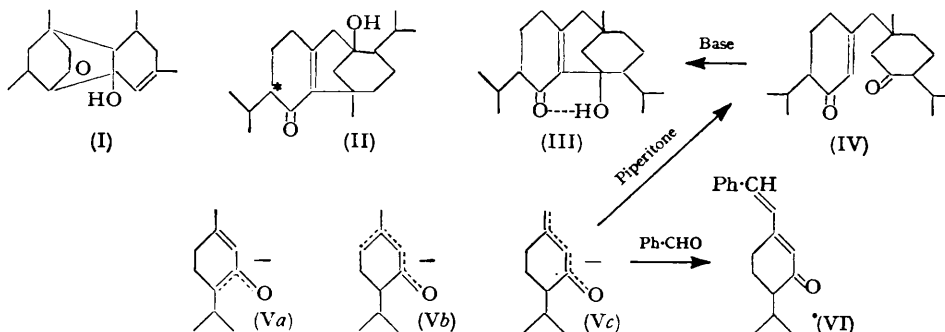

It would be expected then that dimers from other 3-methyl*cyclo*hex-2-enones would have similar structures, and 3 : 5-dimethyl*cyclo*hex-2-enone dimer was chosen for study because it was readily prepared and was crystalline. In agreement with its predicted formula (VII), its infrared and ultraviolet absorption spectra closely resembled those of dipiperitone (see Table). However, it was desirable to obtain more rigid proof and this was done by the following degradation. Reduction of the dimer (VII) in liquid ammonia with a limited

Infrared and ultraviolet maxima of the dimers and their acetates.†

Compound	ν_{OH} (cm.$^{-1}$)	ν_{CO} (cm.$^{-1}$)	$\nu_{C:C}$ (cm.$^{-1}$)	Ultraviolet max. (mμ) (log ε)
α-Dipiperitone (III)	3450	1638	1615	253 (7960), 321 (120)
α-Dipiperitone acetate	—	1735, 1680	1625	247 (8650), 320 (53)
3 : 5-Dimethyl*cyclo*hexenone dimer (VII)	3450, 3472 •	1645, 1650 •	1626, 1625 •	249 (10,200), 315 (100)
Acetate of (VII)	—	1729,• 1673 *	1628 *	246 (10,800)
Piperitone	—	1680	1650	—

* Infrared spectra were taken in KBr mulls unless marked • which were in *ca.* 0·02м-solution in CCl$_4$.

amount of lithium gave the saturated ketone (X) which despite the proximity of the hydroxy-group had the carbonyl stretching frequency in the normal region. Reduction of the dimer (VII) with excess of lithium in liquid ammonia furnished the saturated diol, and catalytic hydrogenation on the other hand afforded the allylic diol (VII; CH·OH in place of CO) in which the tetrasubstituted double bond was stable to further reduction. The ketone (X) reacted with sodium ethoxide and pentyl nitrite to give in poor yield the hydroxyimino-ester (XI) which on vigorous hydrolysis followed by remethylation with dizaomethane furnished

(VII) R = H
(VIII) R = Br
(IX) R = OEt

(X)

(XI) R' = Et; R = :N·OH
(XII) R' = Me; R = :O
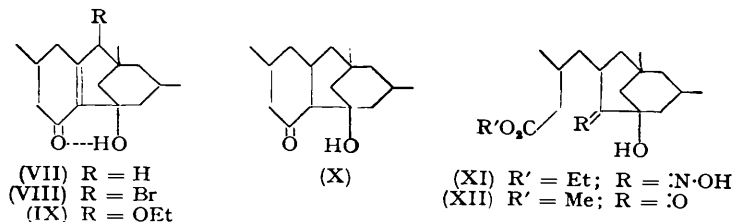
the oily oxo-ester (XII). In agreement with this formulation this ketol-ester (XII) consumed one mol. of lead tetra-acetate; the reaction was slow (24 hours for completion), undoubtedly owing to steric hindrance about the carbonyl group (cf. hydrolysis of its oxime above). This result, which confirms the deductions made from infrared measurements, uniquely

determines the structure of the dimer as (VII) since none of the other possible formulations could have given this last reaction.

Bromination of the dimer (VII) gave, as in the preparation of 6β-bromocholest-4-en-3-one (Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534), the bromo-compound (VIII) with which structure the ultraviolet spectrum was in good agreement (Dorfmann, *Chem. Rev.*, 1953, **53**, 84). Analogously to cases observed by Barton and Miller (*J. Amer. Chem. Soc.*, 1950, **72**, 370, 1066, 5309) attempted formation of the 2 : 4-dinitrophenylhydrazone of (VIII) in ethanol gave the corresponding derivative of the ethoxy-compound (IX). Finally we have found that addition of cyanide ion to piperitone gave the expected cyano-ketone and not the dicyclic anhydro-amide postulated by Read and Watters (*J.*, 1929, 2168), and the resistance to hydrolysis of the tertiary cyano-group must be due to steric hindrance.

EXPERIMENTAL

Absorption spectra were taken in 95% EtOH.

1-*Hydroxy*-5 : 9 : 11-*trimethyl*tricyclo[7 : 3 : 1 : $0^{2 \cdot 7}$]*tridec*-2(7)-*en*-3-*one*   (VII).—This was prepared by dimerisation of 3 : 5-dimethyl*cyclo*hex-2-enone and had m. p. 120° from aqueous ethanol [Found : C, 77·3; H, 9·7%; *M* (Rast), 214. Calc. for $C_{16}H_{24}O_2$: C, 77·4; H, 9·7%; *M*, 248]. The 2 : 4-*dinitrophenylhydrazone* had m. p. 191° (from ethanol) (Found : C, 61·6; H, 6·6. $C_{22}H_{28}O_5N_4$ requires C, 61·6; H, 6·6%) and had absorption max. at 260 and 378 mμ (log ε 3·97 and 4·28). The acetate prepared by the acetic anhydride–perchloric acid method was a viscous oil, b. p. 115—120°/0·1 mm. (Found : Ac, 17·8. Calc. for $C_{18}H_{26}O_3$: Ac, 14·8%). The infrared spectrum is unsymmetrical on the high-frequency side, indicating the presence of a little enol acetate and thus accounting for the relatively high acetyl value.

Ketone (X).—The dimer (9·4 g.) in dry ether (500 ml.) was slowly added with stirring to liquid ammonia (400 ml.), and lithium (760 mg.) was added portionwise at the same time at such a rate that the solution remained blue. After completion of the reaction the solution was stirred for 15 min., then *tert.*-butyl alcohol (25 ml.) in ether (25 ml.) was added and ½ hr. later the whole was diluted with more ether, followed by water (200 ml.). The ethereal layer was dried (Na_2SO_4) and yielded on evaporation an oil which, crystallised readily from light petroleum (b. p. 60—80°) and then from ethanol, gave the *ketone*, m. p. 124° (Found : C, 76·7; H, 10·4. $C_{16}H_{26}O_2$ requires C, 76·8; H, 10·5%). The 2 : 4-*dinitrophenylhydrazone*, crystallised from chloroform–ethanol, had m. p. 208° (Found : C, 61·4; H, 7·1; N, 13·1. $C_{22}H_{30}O_5N_4$ requires C, 61·4; H, 7·0; N, 13·0%).

1 : 3-*Dihydroxy*-5 : 9 : 11-*trimethyl*tricyclo[7 : 3 : 1 : $0^{2 \cdot 7}$]*tridecane*.—Reduction of the above ketone with lithium aluminium hydride in ether afforded the *diol*, a viscous oil which was purified by distillation at 0·5 mm. (bath-temp. 150°) (Found : C, 76·2; H, 11·2. $C_{16}H_{28}O_2$ requires C, 76·1; H, 11·2%).

1 : 3-*Dihydroxy*-5 : 9 : 11-*trimethyl*tricyclo[7 : 3 : 1 : $0^{2 \cdot 7}$]*tridec*-2(7)-*ene*.—The dimer (2·6 g.) took up only one mol. of hydrogen in acetic acid in the presence of Adams catalyst. The *diol* (2·2 g.), crystallised from ether, had m. p. 111—114°; it did not react with Brady's reagent and showed only strong end-absorption in the ultraviolet region. Oxidation of the diol by chromic acid in pyridine regenerated the dimer in high yield.

Ketol-ester (XII).—Pentyl nitrite (0·4 ml.) was added to an ice-cold solution of the ketone (X) (1 g.) in dry ethanol (15 ml.) in which sodium (100 mg.) was dissolved. After 1 hr. the solution was allowed to warm to room temperature during several hours, then diluted with water, whereupon a precipitate (0·6 g.) of unchanged ketone was recovered. Carbon dioxide was bubbled through the mother-liquor until the pH was 7·5, then the solution was extracted with ether. The resulting aqueous solution was acidified and yielded from its ether extract the oily hydroxyimino-acid (0·2 g.) which was refluxed vigorously for 8 hr., to furnish the ketol-acid (180 mg.). Esterification with diazomethane in ether gave the oily *ketol-ester* (130 mg.), which distilled at 170—175°/1 mm. (Found : C, 68·4; H, 9·2. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%). The ketol-ester had a final uptake of one mol. of lead tetra-acetate in acetic acid in 24 hr. ·

Bromo-compound (VIII).—Bromine (1·30 g.) in acetic acid (10 ml.) was slowly added to the dimer (1·47 g.) in acetic acid (25 ml.). The mixture was poured into ice-water (200 ml.), and the precipitated 8-*bromo-compound* was filtered off and washed successively with water, sodium hydrogen carbonate, and water then crystallised from ethanol; it had m. p. 114—115° (Found :

C, 58·2; H, 7·3. $C_{16}H_{23}O_2Br$ requires C, 58·7; H, 7·1%). The ultraviolet absorption spectrum showed a max. at 259 mμ (log ε 3·92).

Ethoxy-compound (IX).—The above bromo-compound (100 mg.), 2 : 4-dinitrophenylhydrazine (73 mg.), and concentrated hydrochloric acid (0·3 ml.) were refluxed for 5 min. in ethanol. On cooling, the 2 : 4-*dinitrophenylhydrazone* of the 8-ethoxy-compound crystallised and was pure after four crystallisations from the same solvent, having m. p. 185° (Found : C, 60·7; H, 7·1; N, 12·1; OEt, 8·2. $C_{24}H_{32}O_6N_4$ requires C, 61·0; H, 6·8; N, 11·9; OEt, 9·5%).

5-*Cyano*-5-*methyl*-2-*iso*propyl*cyclohexanone*.—This *ketone* was prepared from piperitone and potassium cyanide according to Read and Watters's method (*loc. cit.*) and had b. p. 151—153°/13 mm. (Found : C, 73·5; H, 9·7; N, 7·4. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·5; N, 7·9%). The infrared spectrum showed bands at 1708 (CO) and 2240 cm.⁻¹ (CN). The compound did not form a 2 : 4-dinitrophenylhydrazone.