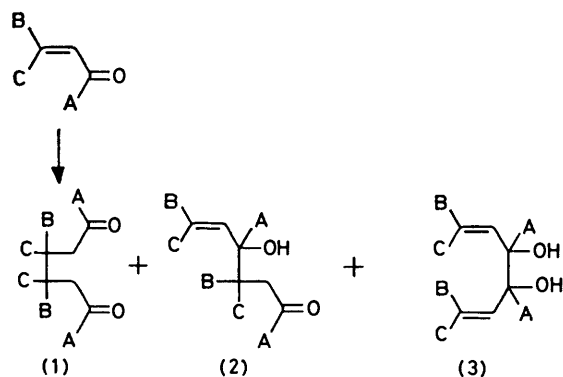


Electrochemical Reactions. Part 21.¹ Stereochemistry of the Hydrodimers from Cyclohexenone, Isophorone, and (\pm)-Piperitone

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The photodimerisation of cyclohexenone, isophorone, and piperitone leads to tricyclic diketones of established stereochemistry. Birch reduction of the head-to-head photodimers causes cleavage of the cyclobutane bond α to two carbonyl groups followed by reduction of the carbonyl functions. Oxidation of each alcohol so formed affords one of the two isomeric diketonic hydrodimers obtained by either electrochemical or dissolving metal reduction of the initial cyclohexenone. These reactions establish the stereochemistry of the diketonic hydrodimers of cyclohexenone, isophorone, and (\pm)-piperitone.

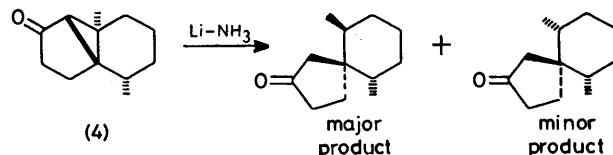
THE hydrodimerisation of $\alpha\beta$ -unsaturated ketones can be brought about either electrochemically or by means of dissolving metals and leads, among other products, to 1,6-diketones (1). Where two stereoisomeric diketones are formed the relative stereochemistry of the products is often not known and a complete characterisation of these products is necessary before attempting to explain any stereoselectivity in the hydrodimerisation process. In electrochemical reduction, stereoselectivity could be brought about by orientation of the substrate in the adsorption layer prior to reduction. A recent study² of the ratio of stereoisomers formed in an electro-oxidation of 2,5-dimethylfuran found that the ratio changed with substrate concentration and this was thought to be due to the influence of concentration on substrate orientation in the adsorption layer.



Here³ we report on the stereochemistry of the known diketonic hydrodimers of cyclohexenone,^{4,5} isophorone,^{6,7} and piperitone⁸ by relating them to the well characterised enone photodimers. We have previously examined the stereochemistry of the diketonic hydrodimers derived from other cyclohexenones, carvone⁹ and apoverbenone.¹⁰ The hydrodimerisation of enones can lead to other products (2) and (3) along with the diketones.¹¹

Photoreaction of cyclohexenone and some substituted compounds affords tricyclic diketonic dimers by a $[2\pi + 2\pi]$ addition of the olefin functions. The head-to-head photodimers readily undergo reductive cleavage of the carbon-carbon bond which is α to both ketone functions thus affording one of the isomeric cyclohexenone hydrodimers. This regiospecific cleavage reaction, which can be rationalised, has been noted

previously for a cyclopentenone photodimer.¹² Reduction is effected with lithium and alcohol in liquid ammonia and yields a diol, a hexahydro-product, which can be oxidised to the diketonic hydrodimer. The reaction is related to the reductive ring cleavage of cyclopropyl ketones¹³ and the stereochemistry of this carbon-carbon bond cleavage has been established using a conformationally rigid cyclopropyl ketone (4).¹⁴ Re-



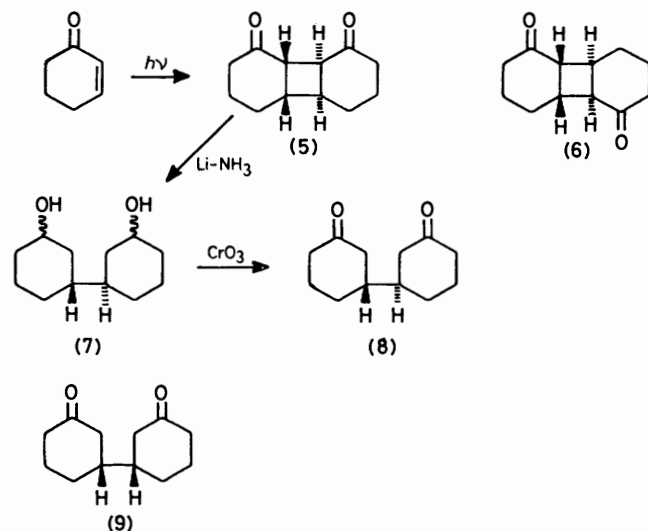
duction of the ketone function to its dianion occurs prior to cleavage.¹⁵ The transition state for cleavage is stabilised by overlap between the breaking σ -bond and the π -orbital of the carbonyl group so that one developing carbanion centre is stabilised as the enolate and relief of the cyclopropane strain energy contributes to the driving energy for reaction. In our cyclobutane examples, the σ -bond most likely to break is that flanked on both sides by carbonyl groups so that cleavage affords two enolate ions. A related carbon-carbon bond cleavage in unstrained 1,4-diketones, including cyclohexane-1,4-dione to give hexane-2,5-dione, is readily effected by reduction with zinc and acid.¹⁶

Cyclohexenone.—The photodimerisation of cyclohexenone has been studied in detail and the relative configurations of the head-to-head (5) and head-to-tail (6) dimers determined.¹⁷ The head-to-head dimer (5) predominates in polar media and is obtained in satisfactory yield by photoreaction in acetonitrile. Reduction of this photodimer with lithium and *t*-butyl alcohol in liquid ammonia afforded a diol which oxidised to a diketone, $C_{12}H_{18}O_2$, m.p. 80°, which must be the hydrodimer (8) of cyclohexenone.

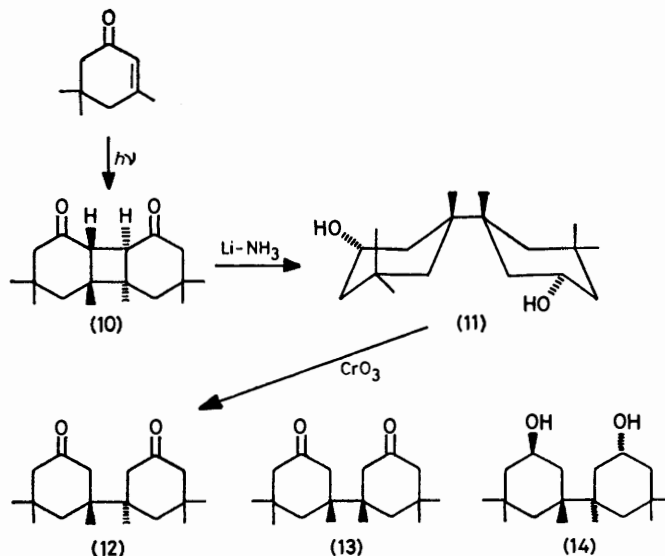
Wiemann⁴ has described two hydrodimers of cyclohexenone and these compounds, m.p. 97 and 55–64° (lit., 63–65°), were prepared. Mixed m.p.s led us to suspect that the material, m.p. 55–64°, was a mixture of the two ketones, m.p. 97 and 80°. The suspected mixture was resolved by g.l.c. on two columns into two components which were shown by enrichment procedures to be the two ketones mentioned.

Thus the pure hydrodimers from cyclohexenone have

m.p. 80 and 97°. Because of its preparation from (5), the lower melting hydrodimer is the (\pm)-form (8) and the higher melting hydrodimer is the *meso*-form (9).



Isophorone.—Photoreaction of isophorone leads to one head-to-head dimer (10) and two head-to-tail dimers whose structures have been established by *X*-ray crystallography.¹⁸ Birch reduction of the dimer (10) gave a diol



which was oxidised to the diketone (12), m.p. 128°. Reduction of isophorone with lithium in ether and fractional crystallisation of the products gave the two hydrodimers, m.p. 128 and 166°. Electroreduction is reported to yield the higher melting isomer only.⁷ Thus the hydrodimer, m.p. 128°, is the (\pm)-form (12) and the hydrodimer, m.p. 166°, is the *meso*-form (13). These hydrodimers give n.m.r. spectra in which lines for all the protons can be seen and interpreted but the spectra were not sufficiently different to allow the analysis of mixtures.

For these hydrodimers, whatever chair conformation

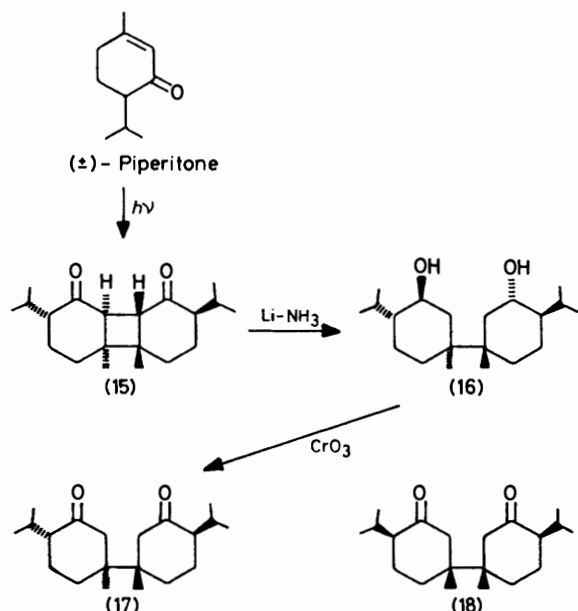
is adopted by the cyclohexanone rings, there will be severe 1,3-diaxial interactions. Such interactions give rise to compression energy terms of the same order of magnitude as the energy difference between the chair and flexible boat forms of cyclohexanone.¹⁹ Thus the hydrodimers will adopt either flattened chair or flexible boat conformations. The alcohol (11) is formed by reduction under equilibrating conditions and so it can be assigned the relative stereochemistry and conformation shown with equatorial hydroxy functions. Conformations with an axial cyclohexyl substituent can be excluded since the standard free energy for the equatorial to axial inversion of cyclohexyl (ΔG_0 2.15 kcal mol⁻¹ for unsubstituted cyclohexyl) is numerically greater than that for the axial to equatorial inversion of methyl (ΔG_0 -1.70 kcal mol⁻¹). Both quoted values were obtained using the same technique.²⁰ In (11), the other axial substituents will ensure that the conformation with equatorial cyclohexyl is further favoured. An isomeric diol (14) was obtained by reaction of the diketone (12) with sodium borohydride which can be expected to give the more hindered epimer of each alcohol function.²¹ Since both cyclohexane rings are equivalent in the n.m.r. spectrum, (14) must have the structure shown. It is unlikely to adopt a conformation like (11) but with axial hydroxy groups since this involves 1,3,5-axial interaction. Diol (14) can either have the alternative chair conformation, or a flexible boat conformation if interactions with axial cyclohexyl are severe.

Piperitone.—Hydrodimerisation of piperitone has been carried out under mildly alkaline conditions which would be expected to epimerise the isopropyl substituent. However it is still important to characterise the relative stereochemistry of the methyl substituents in the resulting hydrodimers.

The photodimerisation of piperitone was first investigated by Triebs²² and later by Ziffer *et al.*²³ The principal product is the head-to-head dimer (15) which is obtained optically active from (-)-piperitone and as the racemate, m.p. 142°, from (\pm)-piperitone. The optically active material can be recovered unchanged from attempted epimerisation by alkali and so must have the *cis-anti-cis*- rather than *cis-syn-cis*-fusion of rings. The latter would undergo epimerisation of the isopropyl groups to give a *meso*-form. This is all the stereochemical information necessary for our purpose but Ziffer has defined the stereochemistry of (15) as shown on the basis of the o.r.d. curve for the optically active form.

Birch reduction of the photodimer, m.p. 142°, yielded a diol which was oxidised to the diketone (17), m.p. 168°. This diketone was identical with the hydrodimer, m.p. 168°, and the second hydrodimer had m.p. 142–145°. The relative stereochemistry of (17) can be assigned since it is prepared from (15) under alkaline conditions which ensure that, for each cyclohexane ring, in the most abundant epimer the cyclohexyl and isopropyl substituents will occupy equatorial positions. Interaction

between the isopropyl group and ketone function in 2-isopropylcyclohexanones does however give rise to appreciable concentrations of the axial isopropyl epimer



at equilibrium.²⁴ The presence of this epimer must contribute to the difficulty experienced in isolating a second pure hydrodimer from the products of electroreduction. The hydrodimer, m.p. 141—144°, can be assigned the relative stereochemistry (18), although since this material has a broad melting range it may not have been obtained pure.

EXPERIMENTAL

I.r. spectra were measured using KBr discs. N.m.r. spectra were determined in CDCl_3 .

Procedure for Birch Reduction.—A solution of the enone photodimer (2 g) in tetrahydrofuran (30 ml) and *t*-butyl alcohol (15 ml) was added to freshly distilled liquid ammonia (100 ml) and chopped lithium (2 g) slowly added. After 5 h excess of lithium was destroyed by addition of methanol and ammonium chloride and the ammonia allowed to evaporate. Water was added to the residue and the product isolated with dichloromethane, washed with dilute hydrochloric acid and water, dried (MgSO_4), and the solvent removed. Chromatography of the residue on neutral alumina and elution with ether afforded unchanged photodimer; elution with ether-methanol (3%) yielded the required diol. This diol in ether (200 ml) was stirred with chromium trioxide (1.3 g) in sulphuric acid (25 ml, 20%) for 15 h. The ether layer was then separated, washed with sodium hydrogencarbonate and water, dried (MgSO_4), and the solvent removed to give the enone hydrodimer.

Cyclohexenone Derivatives.—Reduction of cyclohexenone photodimer (5), m.p. 77—79° (lit.,¹⁷ 78°), afforded 3-(3-hydroxycyclohexyl)cyclohexanol (11%), m.p. 114—130°, probably a mixture of stereoisomers (7), m/e 198 (2%, M^+), 180 (8, $M^+ - \text{H}_2\text{O}$), and 162 (100, $M^+ - 2\text{H}_2\text{O}$). Oxidation of the diol gave (±)-3-(3-oxocyclohexyl)cyclohexanone (8), needles from aqueous ethanol, m.p. 80—81° (Found: C, 74.4; H, 9.3. $\text{C}_{12}\text{H}_{14}\text{O}_2$ requires C, 74.2; H, 9.3%), depressed on admixture with starting material, ν_{CO} 1700

cm^{-1} , m/e 194 (32%, M^+), 136 (30), and 97 (100). Reduction of cyclohexenone with sodium amalgam in aqueous dimethoxymethane and fractional crystallisation of the products from aqueous ethanol afforded *meso*-3-(3-oxocyclohexyl)cyclohexanone (9), m.p. 97—98° (lit.,⁴ 97°), and a mixture of the (±)- and *meso*-diketones, m.p. 55—64° [lit.,⁴ 63—65° for the (±)-isomer]. G.l.c. of the mixture on 2½% silicone gum rubber column (2 m; 160 °C) and on Antarax CO-990 (2 m; 215 °C) gave two partially resolved peaks with retention times identical with those for the *meso*- and (±)-diketones.

Isophorone Derivatives.—Reduction of the photodimer (10), m.p. 187—188° (lit.,^{18,25} 187°), afforded 5-(5-hydroxy-1,3,3-trimethylcyclohexyl)-3,3,5-trimethylcyclohexanol (11) (18%), rhombs from ether, m.p. 206—208° (Found: C, 76.5; H, 12.1. $\text{C}_{18}\text{H}_{34}\text{O}_2$ requires C, 76.6; H, 12.1%); ν_{OH} 3410 cm^{-1} ; m/e 264 (25%, $M^+ - \text{H}_2\text{O}$), 249 (8), 242 (15), and 123 (100); δ 0.94, 0.99, 1.03 (s, CH_3 groups), and 3.96 (m, total J 32 Hz, CHOH). Oxidation of this diol afforded authentic (±)-5-(1,3,3-trimethyl-5-oxocyclohexyl)-3,3,5-trimethylcyclohexanone, laths from aqueous ethanol, m.p. 128—129° (lit.,⁶ 126°), undepressed on admixture with material from reduction of isophorone with lithium in ether.⁶ The *meso*-hydrodimer (13) had m.p. 166—168° (lit.,^{6,7} 163°).

N.m.r. spectra of isophorone hydrodimers

| <i>meso</i> -Isomer (13) δ (CDCl_3) | (±)-Isomer (12) δ (CDCl_3) | Assignment |
|--|---|---|
| 1.04, 1.07, 1.09 | 1.06, 1.07 | } $\geq \text{C}-\text{CH}_2-\text{C} \leq$ |
| 1.40 (d, J 14.5 Hz) | 1.40 (d, J 14.0 Hz) | |
| 1.80 (d, J 14.5 Hz) | 1.76 (d, J 14.0 Hz) | } $-\text{CH}_2\text{CO}-$ |
| 2.18 (s) | 2.16 (s) | |
| 2.08 (d, J 14.5 Hz) | 2.04 (d, J 14.0 Hz) | } $-\text{CH}_2\text{CO}-$ |
| 2.36 (d, J 14.5 Hz) | 2.33 (d, J 14.0 Hz) | |

Reduction of the hydrodimer, m.p. 128—129°, with sodium borohydride in propan-2-ol afforded 5-(5-hydroxy-1,3,3-trimethylcyclohexyl)-3,3,5-trimethylcyclohexanol (14), laths from aqueous ethanol, m.p. 124—126° (Found: C, 76.6; H, 12.0%); ν_{OH} 3350 cm^{-1} ; δ 0.94, 1.12, 1.13 (s, CH_3 groups), 1.08 and 1.23 (both d, J 7 Hz, $\geq \text{C}-\text{CH}_2-\text{C} \leq$), 1.47 (d, J 6 Hz, $-\text{CH}-\text{CH}_2-\text{C} \leq$), 1.14 and 1.85 (both dd, J 4, 5, and 14 Hz, $-\text{CHCH}_2\text{C} \leq$), and 3.98br (quintet, total J 25 Hz, $-\text{CH}_2\text{CHOHCH}_2-$).

(±)-Piperitone Derivatives.—Birch reduction of (±)-piperitone photodimer (15), m.p. 141—144° (lit.,²³ 144°), afforded 3-(3-hydroxy-4-isopropyl-1-methylcyclohexyl)-6-isopropyl-3-methylcyclohexanol (16), rhombs from ether, m.p. 186—188° (Found: C, 77.2; H, 12.5. $\text{C}_{20}\text{H}_{38}\text{O}_2$ requires C, 77.4; H, 12.3%); ν_{OH} 3480 cm^{-1} ; δ 0.87 (s, CH_3), 0.83 and 0.93 (both d, J 8 Hz, CHMe_2), 2.16br (1 H, 7 lines, J 8 Hz, CHMe_2), and 3.63 (1 H, m, total J 25 Hz, CHOH). Oxidation of this diol afforded 3-(4-isopropyl-1-methyl-3-oxocyclohexyl)-6-isopropyl-3-methylcyclohexanone (17), m.p. 169—171° (lit.,⁸ 166—167°), undepressed on admixture with material prepared by electroreduction of piperitone, δ 0.84 (s, CH_3), 0.85 and 0.93 (both d, J 7 Hz, CHMe_2), and 2.09 and 2.34 (ABq, J 12 Hz, $\geq \text{CCH}_2\text{CO}$). Fractional crystallisation of the mother liquors from electroreduction of piperitone afforded a second product, m.p. 141—144° (lit.,⁸ 135—136°), which may be the second hydrodimer (18). Sodium and ethanol reduction of the hydrodimer, m.p. 169°, reformed the diol, m.p. 186—188°, and this is identical with the 1,1'-bismenthyl described by Read.^{8b}

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