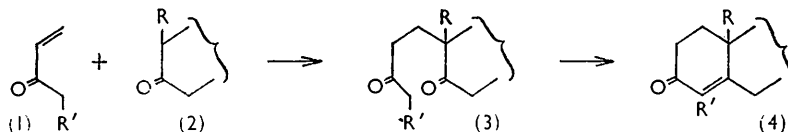


430. *Experiments in the Synthesis of Structures Related to Ring A of the Triterpenes*

By D. J. BAISTED and J. S. WHITEHURST

Attempts have been made, with varying success, to cyclise the adducts obtained from isopropyl vinyl ketone and some six-membered cyclic ketones.

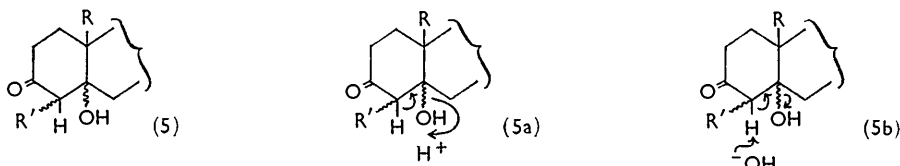
THE Robinson annelation reaction,¹ *i.e.*, the conversion of (1; R' = H or alkyl) (or the equivalent Mannich-base compounds) into (4), has been most fruitful for the synthesis of naturally occurring carbocyclic compounds. The adducts (3) have sometimes been



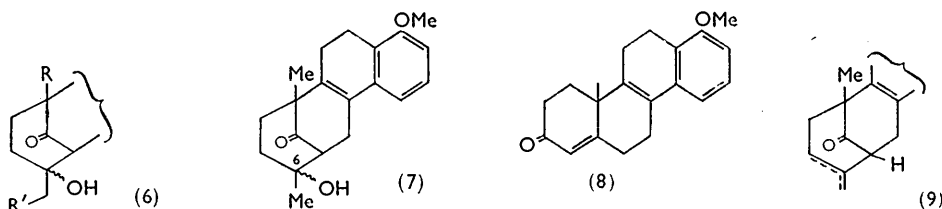
isolated,² and it is generally agreed that the step from (3) to (4) proceeds by way of the ketols (5), whose dehydration [acid- and base-catalysed mechanisms (5a) and (5b), respectively] is aided by the conjugation resonance energy of the products (4).

¹ E. C. du Feu, F. J. McQuillen, and R. Robinson, *J.*, 1937, 53.

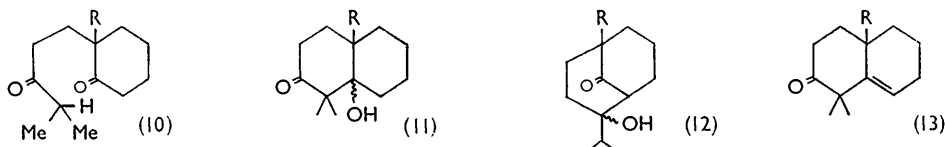
² *E.g.*, V. Prelog, M. M. Wirth, and L. Ruzicka, *Helv. Chim. Acta*, 1946, 29, 1425.



Although ketols of structure (5) are known, in several cases those isolated have had the bridged structure (6).³ Treatment of the ketols of structure (7) with sodium methoxide in methanol gave the hydrochrysenone (8), but dehydration with phosphorus oxychloride in pyridine yielded the bridged products (9). Ketols such as (7) are thus intervenient rather than precursory to the normal Robinson-type products.



We considered that compounds such as (10) might undergo cyclisation to ketols, *e.g.*, (11) and/or (12), which on subsequent dehydration might yield compounds such as (13), thus offering a useful variant on the methylation route so far known.⁴ Also, these structures resembled those found in the triterpenes.



The route chosen to the compounds (10) was that involving the addition of isopropyl vinyl ketone (and its equivalent Mannich-base compounds) to suitably substituted cyclohexanones. The vinyl ketone⁵ was made by the aluminium chloride catalysed addition of isobutyryl chloride to ethylene in carbon disulphide. Use of methylene chloride as solvent gave an improved yield but the product contained 1-chloro-4-methylpentan-3-one. Addition of diethylamine to isopropyl vinyl ketone in the presence of acetic acid gave 1-diethylamino-4-methylpentan-3-one, from which a methiodide was prepared.

2-Hydroxymethylenecyclohexanone,⁶ when heated with the above Mannich base in benzene-pyridine solution gave the aldehyde (10; R = CHO). A change of conditions to the Mannich-base methiodide in methanol-sodium methoxide solution furnished the compound (10; R = H) without the formyl group. The reaction between 2-hydroxymethylenecyclohexanone and isopropyl vinyl ketone in the absence of solvent gave, surprisingly,⁷ polymeric material only.

Treatment of the adduct (10; R = CHO) with potassium hydroxide in aqueous methanol gave, in good yield, a crystalline solid which appeared, from analysis, to be isomeric with the starting material; it showed ν_{\max} 3444 (OH) and 1686 cm^{-1} (C=O). The low value⁸

³ W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Amer. Chem. Soc.*, 1960, **82**, 614.

⁴ R. B. Woodward and A. A. Patchett; D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J.*, 1957, 1131.

⁵ M. Brown and W. S. Johnson, *J. Org. Chem.*, 1962, **27**, 4706, have made this compound by the reaction between isobutyryl chloride and ethylene in chloroform containing anhydrous aluminium chloride. The chloro-ketone was converted into 1-dimethylamino-4-methylpentan-3-one hydrochloride and the latter then heated to give the vinyl ketone.

⁶ Pl. A. Plattner, P. Treadwell, and C. Scholz, *Helv. Chim. Acta*, 1945, **28**, 771.

⁷ D. J. Baisted and J. S. Whitehurst, *J.*, 1961, 4089.

⁸ J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *J.*, 1957, 753.

for the carbonyl absorption is noteworthy; that it was not due to conjugation followed from the molecular formula established by analysis, from ultraviolet spectroscopy, and from the preparation of derivatives. The compound was clearly a ketol (11; R = H) or (12; R = H). Successful crystallisation depended on rapid working, owing to its transformation in solution, even at room temperature, into a new compound, a liquid which, from infrared ($\nu_{\text{max.}}$ 3560 and 1702 cm.^{-1}) and elemental analysis, was also ascribed a ketol structure (11; R = H) or (12; R = H).

These two ketols were extremely labile. Thus, under ordinary conditions, they both gave the bis-2,4-dinitrophenylhydrazone of the adduct (10; R = H), which must have arisen from a reverse aldol condensation. By cautious experimentation both compounds gave a mono-2,4-dinitrophenylhydrazone which, surprisingly, was not that of the adduct (10; R = H) as there was no infrared carbonyl absorption. The compound was therefore derived from either (11; R = H) or (12; R = H), but as there are two racemates corresponding to each of these it need not necessarily correspond to either of the above ketols. The possibility that the liquid ketol was simply a solution of the solid ketol in the adduct (10; R = H) was ruled out since such a solution, made from the two pure components, had completely different properties.

A decision between the gross structures (11; R = H) and (12; R = H) was made by n.m.r. spectroscopy carried out for us in Oxford by Mrs. E. E. Richards. The solid ketol gave two sharp methyl resonances * at τ 8.84 and 8.93 with a separation of 3 c./sec. at 30 Mc. and 6 c./sec. at 60 Mc, whereas the liquid ketol showed a methyl doublet ($J = 6.5$) centred at τ 8.95. The former result is that expected from two methyl groups in different environments (*e.g.*, axial-equatorial) whilst the latter is that found for the coupling of the methyl groups in an isopropyl group. Therefore, the solid ketol has the structure (11; R = H) and the liquid ketol is (12; R = H).

Though compound (11; R = H) is stable at its melting point, it undergoes gradual conversion into the ketol (12; R = H) in solution, especially in proton-donating solvents. The reverse transformation, (12) \longrightarrow (11) (R = H), is brought about by treatment of ketol (12; R = H) with alkali in methanol solution.

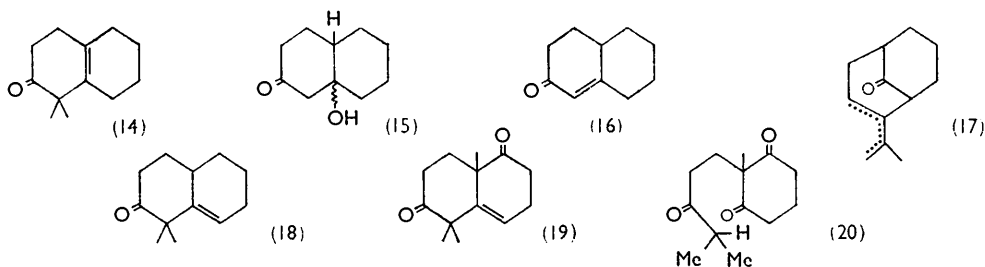
The cyclisation with alkali of the adduct (10; R = H) gave results identical with those described above, from which it follows that the first step in the cyclisation of (10; R = CHO) is loss of the aldehyde group. Unlike the formyl compound (10; R = H), in ether solution, underwent slow cyclisation on a column of prepared alkaline alumina,⁹ and the reaction could be followed by infrared spectroscopy. Hydroxyl absorption characteristic for the liquid ketol first appeared; after repeated passage of the eluates through the column, this band diminished in intensity, with concomitant rise in intensity of the band due to the solid ketol. Final work-up gave the solid ketol, a small amount of the liquid ketol most probably arising during the purification of the solid ketol, and, surprisingly, unchanged material.

All the compounds (11; R = H), (12; R = H), and (10; R = H and CHO) underwent dehydration with toluene-*p*-sulphonic acid (the adducts requiring more than catalytic amounts of the latter) to give the compound (14), a camphor-smelling oil. Both ketols were also dehydrated by heating with oxalic acid, but in neither case was pyridine-phosphorus oxychloride or thionyl chloride-pyridine effective at 0°. These results may be compared with those of Johnson, *et al.*³ who found oxalic acid to be effective for the ketol (15) [yielding the octalone (16)] but not for the compound (7) (6*S*-epimer), whereas both epimers of (7) gave bridged anhydro-products with phosphorus oxychloride in hot pyridine.

The structure of the dimethyloctalone (14) rests on the following evidence. Ozonolysis did not yield formaldehyde or acetone [cf. structure (17)], and hydroxylation with osmium tetroxide yielded a diol not acylable with acetic anhydride-pyridine. The spectra were consistent with the proposed structure; moreover, the compound was not identical with

* These values are close to those of the appropriate methyl groups in similarly constituted 4,4-dimethyl steroids which have been examined by Mrs. E. E. Richards (personal communication).

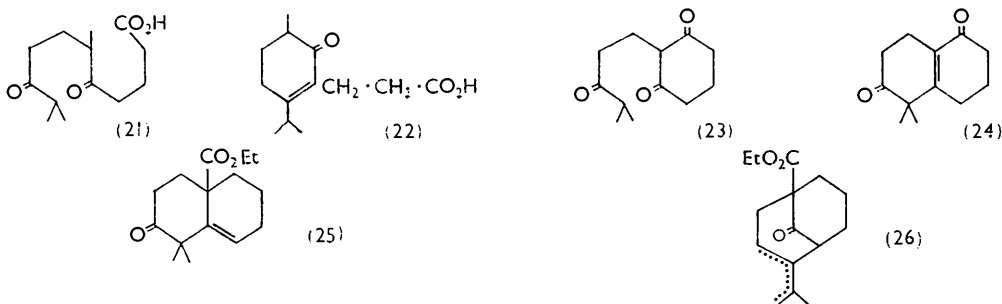
⁹ P. Wieland and K. Miescher, *Helv. Chim. Acta*, 1950, **33**, 2215.



the dimethyloctalone (18) obtained by methylation of the potassium enolate of the octalone (16).

Hydrogenation of compound (14) proceeded with difficulty, attack occurring at both unsaturated positions. The product, after chromic acid oxidation, furnished the *cis*-fused ketone. Hydrogenation of the isomer (18) gave the *trans*-fused ketone. The course of the latter reaction thus parallels that of 4,4-dimethyl- Δ^5 -steroids¹⁰ and inspection of a model of (18) shows the β -face of the molecule to be similarly hindered.

Work was then directed towards the synthesis of compound (19) by a similar approach. Unlike compound (14), compound (19) has considerable 1,3-diaxial interaction of methyl groups. 2-Methylcyclohexane-1,3-dione, treated with either 1-diethylamino-4-methylpentane-3-one in benzene-pyridine¹¹ or isopropyl vinyl ketone in methanol containing potassium hydroxide,¹² gave, in good yield, the adduct (20), which, on mild treatment with alkalis,¹³ gave the acid (21); more prolonged contact gave the compound (22) [λ_{\max} ,



245 $m\mu$ (ϵ 13,240)]. Under acid conditions the same two compounds were formed, as well as a neutral product which appeared to be a mixture of unsaturated lactones evidently formed by the further cyclisation of the acid (22). No variation in either method or procedure gave the compound (19).

From the contrast between the results obtained with the compound (10; R = H and CHO) and (20) it was inferred that 1,3-diaxial repulsion of the methyl groups in compound (19) prevents its formation by this route. Compound (14) has no such interaction; moreover, the transannular double bond permits some flexibility in the two rings. It seemed logical to study the cyclisation of compound (23) in the hope that it might form the unsaturated ketone (24). Though the former could be readily prepared from cyclohexane-1,3-dione and 1-diethylamino-4-methylpentan-3-one in benzene-pyridine, neither it nor its isobutyl enol ether would undergo cyclisation.¹⁴

Finally, studies were made on the compounds (10; R = Me and CO₂Et). The former

¹⁰ F. Gautschi and K. Bloch, *J. Biol. Chem.*, 1958, **233**, 1343.

¹¹ R. Robinson and C. A. Freedman, *Chem. and Ind.*, 1951, 777.

¹² I. N. Nazarov, S. T. Zav'yalov, M. S. Burmistrova, I. A. Gurvich, and L. I. Shmonina, *Zhur. obshchei Khim.*, 1956, **26**, 819.

¹³ N. L. Wendler, H. L. Slaters, and M. Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 3817.

¹⁴ A. L. Wilds, J. W. Ralls, W. C. Wildman, and K. E. McCaleb, *J. Amer. Chem. Soc.*, 1950, **72**, 5794.

was made from 2-methylcyclohexanone, sodium, and either isopropyl vinyl ketone or its diethylamino-Mannich base, the latter being prepared either from ethyl 2-oxocyclohexanecarboxylate and 1-diethylamino-4-methylpentan-3-one methiodide in sodium methoxide-methanol or from ethyl 2-oxocyclohexanecarboxylate and isopropyl vinyl ketone in methanol containing potassium hydroxide. The methyl compound could not be induced to undergo cyclisation, but treatment of the ethoxycarbonyl compound with aqueous methanolic potassium hydroxide gave the ketols (11; R = H) and (12; R = H), the results exactly paralleling those obtained with the adducts (10; R = H and CHO). With warm polyphosphoric acid, the ester (10; R = CO₂Et) gave a mixture of products from which a 2,4-dinitrophenylhydrazone of a keto-ester was obtained. This compound was not identical with the 2,4-dinitrophenylhydrazone of an authentic specimen of the ester (25), prepared by methylation of 10-ethoxycarbonyl- $\Delta^{1(9)}$ -2-octalone,^{6,15} and is therefore that derived from the bridge structure (26).

EXPERIMENTAL

Isopropyl Vinyl Ketone.—Isobutyryl chloride (50 g.) was added during 20 min. to a stirred mixture of dry aluminium chloride (64 g.) and carbon disulphide (170 ml.), the solution was cooled to 0°, and dry ethylene bubbled in for 7 hr. The solution was cautiously warmed to evolve hydrogen chloride and left overnight. The product was poured on to ice and the organic layer washed with dilute hydrochloric acid, water, and dilute sodium hydrogen carbonate solution until just alkaline. Solvent was distilled off through a packed column, water was added to the residue, and the mixture distilled at the water-pump. The two-phase distillate was redistilled through a fractionating column at atmospheric pressure, and gave the ketone as a water azeotrope, b. p. 88–97°, which slowly separated into two layers; the organic layer was separated, dried (K₂CO₃), and redistilled at atmospheric pressure, to yield isopropyl vinyl ketone (14 g., 30%), b. p. 115–116°, n_D^{21} 1.4215 (Found: C, 72.55; H, 10.15. Calc. for C₆H₁₀O: C, 73.45; H, 10.25%), λ_{\max} . (in EtOH) 212 m μ (ϵ 12,290), ν_{\max} . (film) (main bands) 1670, 1620, 1410, 1390, 1374, 1218, 1056, 984, and 790 cm.⁻¹.

1-Diethylamino-4-methylpentan-3-one.—To a stirred ice-cold solution of diethylamine (24.1 g.) and acetic acid (0.7 ml.) was added dropwise, during 3 hr., isopropyl vinyl ketone (26.0 g.). The solution was stirred for a further 16 hr. at room temperature and poured into ether. The ether solution was washed with potassium hydroxide solution and the aqueous washings were re-extracted once with an equal volume of ether. The ether extracts were combined, washed with water, and dried (MgSO₄). After removal of solvent, the residual liquid was distilled, to afford the *Mannich base* (39.5 g., 88%), b. p. 88–92°/30 mm., n_D^{17} 1.4300 (Found: C, 69.1; H, 12.2. C₁₀H₂₁NO requires C, 70.2; H, 12.3%).

1-Diethylamino-4-methylpentan-3-one Methiodide.—A solution of methyl iodide (12.0 g.) in dry ether (20 ml.) was added during 20 min. to an ice-cold, stirred solution of the ketone (9.0 g.) in dry ether (15.0 ml.). The mixture was stirred for a further 1 hr., the ether removed under reduced pressure, and the product washed with an equal volume of ether and dried in a vacuum. The viscous gum weighed 19.2 g. (90%).

2-Formyl-2-(4-methyl-3-oxopentyl)cyclohexanone (10; R = CHO).—2-Hydroxymethylenecyclohexanone (6.3 g.), 1-diethylamino-4-methylpentan-3-one (10.7 g.), pyridine (4.3 ml.), and dry benzene (62.0 ml.) were heated under reflux for 17 hr. After cooling, the solution was washed with dilute hydrochloric acid, water, and saturated sodium chloride solution. Removal of solvent gave a yellow liquid which afforded the *adduct* (3.6 g., 32%), b. p. 110°/0.1 mm., n_D^{18} 1.4765 (Found: C, 69.15; H, 9.4. C₁₃H₂₀O₃ requires C, 69.6; H, 9.0%). A 2,4-dinitrophenylhydrazone was obtained from chloroform-ethanol as an amorphous powder, m. p. 192–200° (Found: C, 50.1; H, 4.85. C₂₅H₂₈N₈O₉ requires C, 51.35; H, 4.8%. C₃₁H₃₂N₁₂O₁₂ requires C, 48.7; H, 4.2%).

2-(4-Methyl-3-oxopentyl)cyclohexanone (10; R = H).—To a stirred solution of 2-hydroxymethylenecyclohexanone (7.6 g.) and sodium methoxide in methanol [from sodium (1.6 g.) in absolute methanol (250 ml.)] was added, during 1 hr., a solution of 1-diethylamino-4-methylpentan-3-one methiodide (32 g.) in absolute methanol (80 ml.). After 17 hr. at room temperature

¹⁵ A. S. Hussey, H. P. Liao, and R. H. Baker, *J. Amer. Chem. Soc.*, 1953 **75**, 4727.

the solution was refluxed for 5 hr., cooled, poured into ether, washed with water, and dried (MgSO_4). Distillation of the residual liquid, after removal of solvent, gave the *adduct* (8.8 g., 74%), b. p. $93^\circ/0.25$ mm., n_D^{23} 1.4696 (Found: C, 73.1; H, 10.45. $\text{C}_{12}\text{H}_{20}\text{O}_2$ requires C, 73.45; H, 10.25%), ν_{max} . (film) (principal bands) 1705, 1440, 1376, 1366, 1306, and 1120 cm^{-1} . The *bis-2,4-dinitrophenylhydrazone* formed needles, m. p. $212\text{--}213^\circ$ (from chloroform) (Found: C, 51.7; H, 4.8; N, 20.4. $\text{C}_{24}\text{H}_{28}\text{N}_8\text{O}_8$ requires C, 51.8; H, 5.05; N, 20.15%).

1,1-Dimethyl-9-hydroxy-2-decalone (11; R = H) and 2 ξ -hydroxy-2 ξ -isopropyl-9-oxobicyclo-[3,3,1]nonane (12; R = H).—2-Formyl-2-(4-methyl-3-oxopentyl)cyclohexanone (7.3 g.), in methanol (100 ml.), was stirred for 3 hr. at room temperature with a solution of potassium hydroxide (80 g.) in water (160 ml.) and methanol (2 l.). The solution was then poured into saturated sodium chloride solution (2 l.) and extracted with ether. The extracts were washed with water and dried (MgSO_4). Removal of solvent gave a yellow oil (6.1 g., 96%) which solidified on cooling, to give the *ketol* (2.5 g., 40%) as colourless flakes, m. p. $97.5\text{--}98.5^\circ$ (from ether—light petroleum) (Found: C, 73.65; H, 10.55. $\text{C}_{12}\text{H}_{20}\text{O}_2$ requires C, 73.45; H, 10.25%). It gave a positive Zimmermann test; ν_{max} . (Nujol) 3444, 1686, 1444, 1384, 1356, 1250, 1222, 1172, 1144, 1123, 1092, 1078—1058 (complex absorption), 968, 944, and 838 cm^{-1} . A *bis-2,4-dinitrophenylhydrazone*, needles (from chloroform—methanol), m. p. $212\text{--}213^\circ$, was identical with the *bis-2,4-dinitrophenylhydrazone* of 2-(4-methyl-3-oxopentyl)cyclohexanone (above) (mixed m. p.) (Found: C, 51.5; H, 4.8; N, 19.9%). A *mono-2,4-dinitrophenylhydrazone* was obtained from ethanol as needles, m. p. $177.5\text{--}179^\circ$ (Found: C, 56.9; H, 6.2; N, 15.4. $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}_4$ requires C, 57.4; H, 6.4; N, 14.9%), ν_{max} . (Nujol) no absorption in the 1700—1710 cm^{-1} region. A *monoxime* crystallised from ethanol—water as prisms, m. p. $134\text{--}135^\circ$ (Found: C, 64.95; H, 10.0; N, 5.8. $\text{C}_{12}\text{H}_{21}\text{NO}_2, \text{C}_2\text{H}_5\text{OH}$ requires C, 65.35; H, 10.55; N, 5.45%).

Evaporation of the mother-liquors from the crystallisation of the solid ketol afforded an oil (3.6 g., 56%). Distillation of this gave the *liquid ketol* (12; R = H) (3.0 g., 46%) as a colourless liquid, b. p. $116\text{--}118^\circ/0.3$ mm., n_D^{17} 1.4818 (Found: C, 73.9; H, 10.15. $\text{C}_{12}\text{H}_{20}\text{O}_2$ requires C, 73.45; H, 10.25), ν_{max} . (film) 3560, 1702, 1444, 1386, 1372, 1252, 1126, 1090, 984, 936, and 838 cm^{-1} . A *mono-2,4-dinitrophenylhydrazone*, isolated as small needles, m. p. $178\text{--}179^\circ$, was identical with that from the solid ketol (mixed m. p.) (Found: C, 56.95; H, 6.4; N, 15.5%). A *bis-2,4-dinitrophenylhydrazone* crystallised from chloroform as needles, m. p. $212\text{--}213^\circ$, and was identical with that obtained from the solid ketol. The liquid ketol gave a positive Zimmermann test.

Dr. W. G. Paterson (Oxford) kindly carried out one of the n.m.r. spectra on the liquid ketol.

The cyclisation of 2-(4-methyl-3-oxopentyl)cyclohexanone (10; R = H) and of ethyl 1-(4-methyl-3-oxopentyl)-2-oxocyclohexanecarboxylate (10; R = CO_2Et), when carried out in an exactly similar manner for the formyl compound above, gave identical results.

2-(4-Methyl-3-oxopentyl)cyclohexanone (10; R = H) (1 g.), in dry ether (10 ml.), was poured on to a column of prepared alkaline alumina (75 g.) (obtained by washing alumina with sodium carbonate solution and water until the washings had pH 10, then with methanol followed by heating at 200° for 1 hr.), and the column developed with ether. The eluates were poured back on to the column. After the tenth cycle, absorption at 3524 cm^{-1} occurred in the evaporated eluate. After 6 hr. the recovered material had a band at 3470 cm^{-1} and, on crystallisation from ether—light petroleum, afforded the solid ketol (0.4 g., 40%). The residual oil from the crystallisation was virtually pure starting material.

The liquid ketol (0.40 g.) was stirred for 3 hr. with a solution of potassium hydroxide (4 g.) in water (8 ml.) and methanol (100 ml.). Work-up gave a crude product (0.34 g.) which solidified completely. Crystallisation gave the solid ketol (0.20 g.).

1,1-Dimethyl- Δ^9 -2-octalone.—(a) A solution of the solid ketol (0.50 g.) in dry benzene (60 ml.) was treated with toluene-*p*-sulphonic acid (0.50 g.) and heated under reflux for 4 hr. After cooling, the mixture was washed with water and dried (MgSO_4). The residual oil, after removal of solvent, was distilled, to give a colourless *liquid*, strongly smelling of camphor (0.41 g., 90%), b. p. $60^\circ/0.08$ mm., n_D^{22} 1.5020 (Found: C, 80.45; H, 9.95. $\text{C}_{12}\text{H}_{18}\text{O}$ requires C, 80.9; H, 10.1%). The product gave a yellow coloration with tetranitromethane, and a positive Zimmermann reaction; ν_{max} . (film) (principal bands) 1710, 1669, 1452, 1440, 1380, 1360, 1330, 1274, 1168, 1090, and 968 cm^{-1} . The 2,4-dinitrophenylhydrazone formed needles (from methanol) (Found: C, 60.4; H, 6.7; N, 15.55. $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_4$ requires C, 60.3; H, 6.2; N, 15.65%), λ_{max} .

(in CHCl_3) 368 μ (ϵ 25,740). The same reaction repeated with the liquid ketol gave an identical product in similar yield.

(b) The solid ketol (0.40 g.) and oxalic acid (0.50 g.) were heated at 140–150° for 15 min. After cooling, the mixture was extracted with ether, and the extracts washed with sodium hydrogen carbonate solution, water, and dried (MgSO_4). Distillation of the residual oil, after removal of solvent, gave the same unsaturated ketone as that obtained by method (a) (0.32 g., 88%). A similar result was obtained when the above reaction was repeated with the liquid ketol.

9,10-*Dihydroxy-1,1-dimethyl-cis-2-decalone*.—1,1-Dimethyl- Δ^8 -2-octalone (500 mg.), in dry dioxan (8 ml.), was treated with a solution of osmium tetroxide (860 mg.) in the same solvent (8 ml.) at room temperature. After 65 hr., the solution was saturated with hydrogen sulphide and filtered. Evaporation of solvent from the filtrate gave a colourless, viscous oil (550 mg., 93%) which crystallised from ether–light petroleum as *prisms*, m. p. 104–105° (Found: C, 68.7; H, 9.75. $\text{C}_{12}\text{H}_{20}\text{O}_3$ requires C, 67.9; H, 9.45%). No coloration was given with tetranitromethane; ν_{max} (solid film) (principal bands) 3440, 1702, 1456, 1396, 1378, 1266, 1132, 1068, 1016, 1000, 956, 906, and 882 cm^{-1} .

1,1-*Dimethyl-cis-2-decalone*.—The dimethyl-octalone (0.5 g.) in acetic acid (25 ml.) was hydrogenated over a platinum oxide catalyst until 1.05 moles of hydrogen had been absorbed (1 hr.). Evaporation of solvent, after removal of catalyst, gave an oil (0.5 g.), ν_{max} (film) 3530, 3430, and 1702 cm^{-1} (no absorption at 1670). The oil, in acetone (30 ml.), was treated with a slight excess of 8N-chromic acid. The mixture was quenched with water and extracted with ether, which was washed with sodium hydrogen carbonate solution and water, dried (MgSO_4), and evaporated. The 2,4-*dinitrophenylhydrazone* of 1,1-dimethyl-*cis*-2-decalone formed plates, m. p. 141.5–142.5° (from ethanol) (Found: C, 60.4; H, 6.35; N, 15.05. $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}_4$ requires C, 60.0; H, 6.7; N, 15.55%).

1,1-*Dimethyl-trans-2-decalone*.—1,1-Dimethyl- Δ^8 -2-octalone (*q.v.*) (0.5 g.) in acetic acid (25 ml.) was hydrogenated over a platinum oxide catalyst (0.03 g.) until 1 mole of hydrogen had been absorbed (50 min.). After removal of catalyst the solution was evaporated and gave an oil (0.5 g.) whose infrared spectrum (film) was close to that of the starting ketone. The oil, in light petroleum (10 ml.), was chromatographed on alumina (20 g.). Elution with light petroleum gave some starting material; further elution with benzene and benzene–ether gave an oil which, when treated with 2,4-dinitrophenylhydrazine, gave the 2,4-*dinitrophenylhydrazone* of 1,1-dimethyl-*trans*-2-decalone, needles, m. p. 162–163° (from ethanol) (Found: C, 59.8; H, 6.55; N, 15.55%).

2-*Methyl-2-(4-methyl-3-oxopentyl)cyclohexane-1,3-dione*.—(a) A mixture of 2-methylcyclohexane-1,3-dione (5 g.) and freshly-distilled 1-diethylamino-4-methylpentan-3-one (8.5 g.) in dry benzene (65 ml.) was treated with pyridine (3.3 ml.) and then refluxed for 20 hr. The yellow solution was cooled, washed with 2N-hydrochloric acid and water, and dried (MgSO_4). Removal of the solvent and distillation of the residue gave the *product* (7.5 g., 85%), b. p. 123–124°/0.4 mm., n_D^{18} 1.4800 (Found: C, 69.6; H, 9.0. $\text{C}_{13}\text{H}_{20}\text{O}_3$ requires C, 69.6; H, 9.0%), ν_{max} (film) 1696, 1462, 1425, 1368, 1315, 1282, 1100, and 1024 cm^{-1} . The *tris-2,4-dinitrophenylhydrazone* formed microprisms, m. p. 252–253° (decomp.) (from chloroform) (Found: C, 48.6; H, 4.35; N, 22.05. $\text{C}_{31}\text{H}_{32}\text{N}_{12}\text{O}_{12}$ requires C, 48.7; H, 4.2; N, 22.0%).

(b) A mixture of 2-methylcyclohexane-1,3-dione (6.3 g.), absolute methanol (20 ml.), freshly-distilled isopropyl vinyl ketone (7.2 g.), and potassium hydroxide (1 pellet) was refluxed for 5 hr. The solution was poured into chloroform and water, and the organic layer was then washed brine and dried (MgSO_4). After removal of solvent the pale yellow residual oil was distilled, and gave the adduct (9.47 g., 85%), b. p. 115–116°/0.1 mm., n_D^{17} 1.4790.

6,10-*Dimethyl-5,9-dioxoundecanoic Acid*.—The above adduct (300 mg.), in either ether (20 ml.) or methanol (20 ml.), was treated for 5 min. at room temperature with 5% aqueous potassium hydroxide (20 ml.). Ether (40 ml.) was added, and the organic layer separated, washed with water, dried (MgSO_4), and evaporated, to leave a neutral product (10 mg.) which was not further investigated. The aqueous extract was acidified with dilute hydrochloric acid and shaken with ether. The ether layer was separated, washed with water, dried (MgSO_4), and evaporated, to leave a clear viscous oil (220 mg., 70%). Distillation gave the *acid*, b. p. 140–145°/0.5 mm., n_D^{14} 1.4825 (Found: C, 65.3; H, 9.65. $\text{C}_{13}\text{H}_{22}\text{O}_4$ requires C, 64.45; H, 9.15%), ν_{max} (film) 3200 (hydrogen bonded), 1730sh 1710br, 1470, 1420, 1388, 1250 (complex), and 1104 cm^{-1} . Treatment with 2,4-dinitrophenylhydrazine in ethanolic sulphuric acid gave the

bis-2,4-dinitrophenylhydrazone of the ethyl ester as felted needles, m. p. 168—169.5° (from chloroform) (Found: C, 51.65; H, 5.45; N, 17.85. $C_{27}H_{34}N_8O_{10}$ requires C, 51.45; H, 5.4; N, 17.8%), λ_{\max} . (in $CHCl_3$) 363 μ (ϵ 41,740).

2-(2-Carboxyethyl)-3-isopropyl-5-methylcyclohex-2-en-1-one.—The adduct (0.5 g.) was stirred with methanol (150 ml.) and aqueous potassium hydroxide (30 ml.; 15%) for 3 hr. The solution was acidified, poured into ether, and the organic layer separated, washed with water, dried ($MgSO_4$), and evaporated, to give a solid (0.38 g., 74%) which crystallised from benzene-light petroleum to yield colourless prisms, m. p. 80°, of the *product* (Found: C, 69.85; H, 9.05. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%), λ_{\max} . 245 μ (ϵ 13,240), ν_{\max} . (Nujol) 3250—2500, 1703, 1667, 1628, 1456, 1372, 1310, 1286, 1226, 1186, 964, and 912 cm^{-1} . The 2,4-dinitrophenylhydrazone of the ethyl ester formed needles, m. p. 98—99° (from ethanol) (Found: C, 58.55; H, 6.55; N, 12.8. $C_{21}H_{30}N_4O_6$ requires C, 58.3; H, 6.55; N, 12.95%), λ_{\max} . (in $CHCl_3$) 392 μ (ϵ 27,675).

2-(4-Methyl-3-oxopentyl)cyclohexane-1,3-dione.—Cyclohexane-1,3-dione (5.7 g.) was heated under reflux for 20 hr. with pyridine (4.4 ml.) and 1-diethylamino-4-methylpentan-3-one (11.0 g.) in dry benzene (65 ml.). Working-up gave a yellow-brown oil from which, by means of ether-light petroleum, the *product* was obtained as colourless rosettes (2.7 g., 25%), m. p. 101—101.5° (Found: C, 68.55; H, 8.7. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.65%), λ_{\max} . (in EtOH) 264 μ (ϵ 14,790), ν_{\max} . (Nujol) 1701, 1572, 1452, 1370, 1284, 1016, and 916 cm^{-1} , ν_{\max} . (in CCl_4) 3230, 1688, 1612—1500, 1450, 1420, 1390, 1360, 1340, 1290, 1180, 1120, 1056, and 920 cm^{-1} . A *mono*-2,4-dinitrophenylhydrazone formed needles (from chloroform), m. p. 235—235° (decomp.) (Found: C, 55.5; H, 5.9; N, 13.7. $C_{18}H_{22}N_4O_6$ requires C, 55.4; H, 5.7; N, 14.35%).

3-Isobutoxy-2-(4-methyl-3-oxopentyl)cyclohex-2-en-1-one.—The above adduct (1.05 g.) was refluxed with isobutyl alcohol (1 ml.), toluene-*p*-sulphonic acid (0.05 g.), and benzene (12 ml.). After 2 hr. the solution was cooled, ice and cold saturated sodium hydrogen carbonate were added, and the mixture was extracted with ether. Working-up gave an oil (1.18 g.), b. p. 120—124°/0.7 mm., $n_D^{17.5}$ 1.5200 (Found: C, 73.25; H, 8.4. $C_{16}H_{26}O_3$ requires C, 72.15; H, 9.75%), ν_{\max} . (film) 1714, 1670, 1634, 1484, 1452, 1410, 1378, 1314, 1266, 1234, 1202, 1150, 1122, 1080, 1052, 992, 936, and 854 cm^{-1} , λ_{\max} . (in EtOH) 271 μ (ϵ 8210).

Ethyl 1-(4-Methyl-3-oxopentyl)-2-oxocyclohexanecarboxylate.—(a) A solution of 1-diethylamino-4-methylpentan-3-one methiodide (17 g.) in absolute methanol (70 ml.) was added gradually to a well-stirred solution of ethyl 2-oxocyclohexanecarboxylate (6.32 g.) in a solution of sodium methoxide (from sodium, 0.90 g.) in absolute methanol (150 ml.). After 17 hr. at room temperature, the mixture was refluxed for a further 5 hr. The solution was cooled, extracted with ether, washed with water, and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was distilled to afford the *product* as a very pale green liquid (7.97 g., 80%), m. p. 111°/0.05 mm., n_D^{18} 1.4680 (Found: C, 66.85; H, 9.1. $C_{15}H_{24}O_4$ requires C, 67.15; H, 9.0%), ν_{\max} . (film) 1724, 1708, 1464, 1384, 1368, 1340, 1250 (region complex), 1134, 1094, 1060, 1020, 974, 943, 822, and 812 cm^{-1} . The 2,4-dinitrophenylhydrazone was a powder, m. p. 182—184° (from chloroform-methanol).

(b) Ethyl 2-oxocyclohexanecarboxylate (10 g.) was refluxed at 130° for 3 hr. with isopropyl vinyl ketone (8.7 g.), potassium hydroxide (1 pellet), and a trace of quinol. The mixture was cooled, chloroform added, and the organic layer separated, washed with water, dried ($MgSO_4$), and evaporated, to give an oily product which was distilled. The first fraction was ethyl 2-oxocyclohexanecarboxylate (4.2 g.). The second fraction was the adduct (5.6 g., 61% based on reacted keto-ester), b. p. 128°/0.15 mm., $n_D^{19.5}$ 1.4675.

Polyphosphoric Acid Cyclisation.—The adduct (3.2 g.) was heated on a water-bath with polyphosphoric acid [from phosphoric acid (11.5 g.) and phosphorus pentoxide (18.0 g.)]. After 4 min. the mixture became dark brown and began to effervesce; it was then cooled and poured on to ice. Trituration gave a pale yellow gum which produced a yellow colour with tetranitromethane. The crude product resisted all attempts at crystallisation and was treated as follows. An ether solution was washed with aqueous potassium carbonate, water, dried ($MgSO_4$), and evaporated. The remaining yellow gum in benzene-light petroleum (1:1) (50 ml.) was poured on to alumina, activity 1 (100 g.). Elution with benzene-petroleum spirit (1:1 to 2:1) and then pure ether gave two distinct fractions. From the last a 2,4-dinitrophenylhydrazone was isolated with some difficulty (total yield 43%). After filtration through bentonite and crystallisation from ethanol, *prisms*, m. p. 139—140°, were obtained (Found: C, 58.55; H, 6.1; N, 13.15. $C_{21}H_{26}N_4O_6$ requires C, 58.6; H, 6.1; N, 13.0%), λ_{\max} . (in $CHCl_3$)

366 $m\mu$ (ϵ 25,450). The m. p. was depressed to 124° on admixture with an authentic specimen of the 2,4-dinitrophenylhydrazone of 10-ethoxycarbonyl 1,1-dimethyl- Δ^8 -2-octalone.

2-Methyl-2-(4-methyl-3-oxopentyl)cyclohexanone.—(a) Sodium (0.1 g.) was dissolved in redistilled methylcyclohexanone (5.6 g.). Isopropyl vinyl ketone (5.9 g.) was added slowly to the chilled (0°) solution. The mixture was then warmed on a steam-bath for 3 hr. After cooling, chloroform was added, and the organic layer, after being separated, was washed with dilute hydrochloric acid, water, and brine. Evaporation of solvent gave an oil which was distilled to afford unchanged methylcyclohexanone (1.2 g.) and the *product* (1.67 g., 20% based on converted methylcyclohexanone), b. p. 105—108°/0.01 mm., n_D^{25} 1.4685 (Found: C, 74.2; H, 10.45. $C_{13}H_{22}O_2$ requires C, 74.25; H, 10.55%), ν_{max} (film) 1700, 1450, 1310, 1124, 1100, 1060, 1000, and 858 cm^{-1} . A 2,4-dinitrophenylhydrazone was obtained as a powder from chloroform-ethanol, m. p. 200.5—201.5°.

A fraction, b. p. 140°/0.15 mm., obtained in the above experiment possessed a small but distinct hydroxyl band in the infrared spectrum (liquid film).

(b) Methylcyclohexanone (5.6 g.), the Mannich base of isopropyl vinyl ketone (10.26 g.), a trace of quinol, and sodium (0.1 g.) were heated to 135° on an oil-bath for 3 hr. After cooling, the mixture was treated with 10% hydrochloric acid and extracted with ether. The extracts were combined, washed with water, dried ($MgSO_4$), and evaporated, to give an oil which was distilled. The first fraction was unchanged methylcyclohexanone (0.65 g.), the second the adduct (2.4 g., 26% based on converted methylcyclohexanone), b. p. 116—120°/0.2 mm., $n_D^{16.5}$ 1.4731.

A 2,4-dinitrophenylhydrazone was obtained as a powder from chloroform-ethanol, m. p. 198—199.5°, undepressed on admixture with the specimen obtained above.

2,2-Di-(4-methyl-3-oxopentyl)cyclohexane-1,3-dione.—Cyclohexane-1,3-dione (11.2 g.), isopropyl vinyl ketone (11.8 g.), absolute methanol (2 ml.), and potassium hydroxide (1 pellet) were heated on a water-bath for 5 hr. After being cooled, the solution was poured into ether. The organic layer was separated, washed with water and brine, and dried ($MgSO_4$). Removal of solvent gave a pale yellow oil which crystallised as fine colourless *needles* (19.8 g., 65%), m. p. 68—69° (from ether-light petroleum) (Found: C, 70.1; H, 9.25. $C_{18}H_{28}O_4$ requires C, 70.1; H, 9.15%), λ_{max} (in EtOH) 288 $m\mu$ (ϵ 113), ν_{max} (Nujol) 1722, 1698, 1468, 1392, and 1040 cm^{-1} ; in carbon tetrachloride solution only the peaks at 1715 and 1690 cm^{-1} were prominent.

1,1-Dimethyl- Δ^8 -2-octalone.— $\Delta^{1(9)}$ -2-Octalone (5 g.) in dry t-butyl alcohol (210 ml.) at 40° was treated with a solution of potassium t-butoxide [from potassium (3.9 g.) in dry t-butyl alcohol (80 ml.)]. Immediately, methyl iodide (12.8 ml.) in the same solvent (15 ml.) was added, and the mixture was refluxed for 1 hr. After cooling, it was acidified with dilute hydrochloric acid and extracted with ether. The extract was thoroughly washed with water, dried ($MgSO_4$), and evaporated, to give a dark brown oil (5.16 g.). Chromatography of the oil in benzene on acid-washed alumina (60 g., activity 1—2) gave an initial fraction containing a colourless oil (1.25 g.), λ_{max} (in EtOH) 286 $m\mu$. A second fraction (2.38 g.) possessed a broad shoulder in the ultraviolet spectrum at 246 $m\mu$. Re-chromatography of this fraction gave a further 1.74 g. of oil, free from ultraviolet absorption in the 230—250 $m\mu$ region. The combined products were distilled and gave a colourless *liquid* (2.5 g., 42%), b. p. 86°/0.9 mm., $n_D^{14.5}$ 1.5070 (Found: C, 80.75; H, 9.55. $C_{12}H_{18}O$ requires C, 80.9; H, 10.1%), ν_{max} (film) 1706, 1666, 1434, 1378, 1358, 1140, 1112, 1088, 962, 878, 846, and 814 cm^{-1} . The 2,4-dinitrophenylhydrazone was obtained as plates, m. p. 124—125° (from ethanol) (Found: C, 60.3; H, 5.8; N, 15.55. $C_{18}H_{22}N_4O_4$ requires C, 60.3; H, 6.2; N, 15.65%), λ_{max} (in $CHCl_3$) 368 $m\mu$ (ϵ 21,880).

10-Ethoxycarbonyl-1,1-dimethyl- Δ^8 -2-octalone.—10-Ethoxycarbonyl- $\Delta^{1(9)}$ -2-octalone (11.10 g.) in dry t-butyl alcohol (320 ml.) was treated with a solution of potassium t-butoxide [from potassium (3.8 g.) in dry t-butyl alcohol (120 ml.)]. Methyl iodide (19.0 ml.) in the same solvent (20 ml.) was immediately added, and the mixture refluxed for 1 hr. The product was worked up in the usual way and gave a *liquid* (7.8 g.), b. p. 126—127°/0.7 mm. The oil in light petroleum-benzene (1:1) was chromatographed on alumina, and gave a series of fractions (total 4.93 g.) which had no absorption in the 230—250 $m\mu$ region and all of which gave a positive Zimmermann reaction. Later fractions (eluted with benzene) furnished clear oils (1.46 g.) having some absorption in the 245—250 $m\mu$ region. These were re-chromatographed on alumina, to yield material (1.25 g.) showing no selective absorption in the 230—250 $m\mu$ region. The total material (6.18 g.) was distilled, to yield the *product* (5.02 g., 42%), b. p. 87°/0.04 mm., n_D^{20}

1·4990 (Found: C, 71·8; H, 8·8. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%). The 2,4-dinitrophenylhydrazone formed prisms (from alcohol), m. p. 139—140° (Found: C, 58·65; H, 6·25; N, 13·55. $C_{21}H_{26}N_4O_6$ requires C, 58·6; H, 6·1; N, 13·0%), λ_{max} (in $CHCl_3$) 368 $m\mu$ (ϵ 21,380).

1,1,10-Trimethyl- Δ^8 -2-octalone.—This compound was made essentially by the methylation procedure described above, using 10-methyl- $\Delta^{1(9)}$ -2-octalone (yield 23%). The 2,4-dinitrophenylhydrazone, plates from alcohol, m. p. 159—159·5°, λ_{max} (in $CHCl_3$) 369 $m\mu$ (ϵ 22,900), was identical with an authentic specimen ¹⁶ kindly provided by Professor Yanagita.

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¹⁶ M. Yanagita, M. Hirakura, and F. Seki, *J. Org. Chem.*, 1958, **23**, 841.
