677. *Studies in the Vitamin D Field. Part III.* Approaches to Derivatives of 5-Hydroxy-2-methyl*cyclo*hexanone.*

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Some reactions of 4-methyl*cyclo*hex-3-enol are described. Experiments on the addition of water, alcohols, etc., to the olefinic bond in 6-methyl*cyclo*hex-2-enone were successful (though in poor yield) only with benzyl alcohol. Some experiments on the synthesis of related intermediates are outlined.

IN connection with synthetical approaches to calciferol and its relatives,[1] protected derivatives (I) of 5-hydroxy-2-methyl*cyclo*hexanone were required; the methoxy-ketone (I; R = Me) has previously been prepared [2,3] by an eight-stage synthesis from *p*-cresol.

p-Methoxytoluene was reduced by lithium and ethanol in ether–liquid ammonia [3,4,5] to 4-methoxy-1-methyl*cyclo*hexa-1 : 4-diene, which was hydrolysed without purification to 4-methyl*cyclo*hex-3-enone (II) in 80% yield; this is a considerable improvement over that obtained by using sodium.[6,7] Reduction of the ketone (II) with lithium aluminium hydride gave the alcohol (III; R = H) which readily furnished the acetate (III; R = Ac) and the tetrahydropyranyl ether.[3] This acetate has previously been prepared [3,8] by a different route, but the present method is more convenient. Attempts to transform the double bond in the alcohol (III; R = H) directly into the >CH·CO– grouping by reaction with performic acid [9] gave only 6-methyl*cyclo*hex-2-enone (IV). Reaction of the acetate (III; R = Ac) with monoperphthalic acid readily furnished the epoxide (V), the

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* Part II, Braude and Wheeler, *J.*, 1955, 329.

[1] Braude and Wheeler, *J.*, 1955, 320.

[2] U.S.P. 2,511,815; G.P. 800,573; *Chem. Abs.*, 1950, **44**, 9981; 1951, **45**, 1624; cf. Corsano and Capitò, *Gazzetta*, 1955, **85**, 1590.

[3] Inhoffen, Weissermel, and Quinkert, *Chem. Ber.*, 1955, **88**, 1313.

[4] Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5360, 5366.

[5] Soffer and Jevnik, *ibid.*, 1955, **77**, 1003.

[6] Birch, *J.*, 1944, 430.

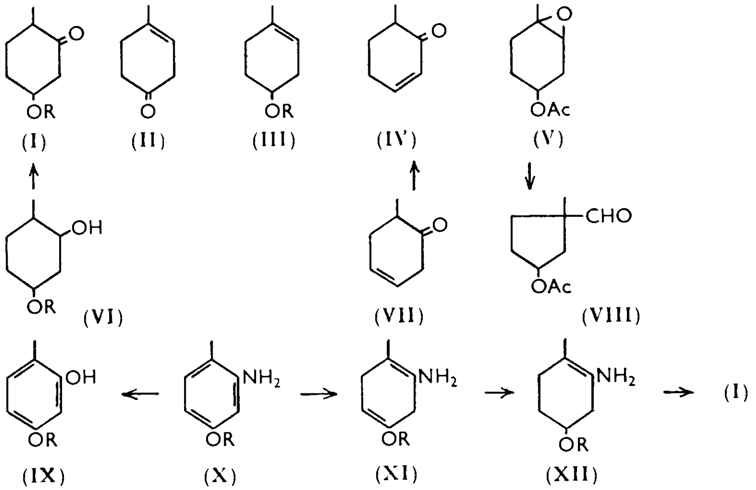
[7] *Idem, J.*, 1946, 593.

[8] Jones and Sondheimer, *J.*, 1949, 615.

[9] Cf. Mousseron, Jacquier, and Christol, *Compt. rend.*, 1953, **236**, 927.

preparation of which was described by Inhoffen[3] after this part of the investigation was completed. Isomerisation of the epoxide by mineral acids[10,11] or by boron trifluoride[11,12] was accompanied by loss of acetic acid, and again 6-methyl*cyclo*hex-2-enone (IV) was formed.

The epoxide was isomerised by magnesium bromide in boiling ether[13,14] to a carbonyl compound, which gave a yellow 2 : 4-dinitrophenylhydrazone, m. p. 140°, prepared under acidic conditions and exhibiting light-absorption properties ($\lambda_{max.}$ 3600 Å) characteristic of the derivative of a saturated aldehyde or ketone. This stability towards acid, however, was clearly incompatible with the desired structure (I; R = Ac), and as it gave a positive Schiff test, and reduced Fehling's solution it is formulated as 3-acetoxy-1-methyl*cyclo*pentylformaldehyde (VIII); a similar acid-catalysed rearrangement, of 1 : 2-epoxymethyl*cyclo*hexane to 1-methyl*cyclo*pentylformaldehyde, has long been known.[15] The aldehyde showed only a single carbonyl absorption band in the infrared spectrum, at 1739 cm.$^{-1}$, but this was of very high intensity, evidently owing to the combined effect of the aldehyde group and the acetate-carbonyl group.



The course of isomerisation of the epoxide is highly dependent on the conditions used. Conversion into the *cyclo*pentane system (VIII) is best effected by the use of magnesium bromide prepared from the metal and purified ethylene dibromide.[14] When the salt was prepared from its elements[16] the isomerisation products contained variable proportions of 6-methyl*cyclo*hex-2-enone (IV); in one experiment a bromohydrin was obtained. Replacement of magnesium bromide with zinc chloride, reported[17] to be highly effective in the isomerisation of aliphatic epoxides to ketones, gave only unchanged starting material.

Although it is clear that the β-hydroxy-ketone (I; R = H) and its derivatives readily

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[10] Cf. Maclean, Silverstone, and Spring, *J.*, 1951, 935; Elks, Evans, Oughton, and Thomas, *J.*, 1954, 463.

[11] Schoenwaldt, Turnbull, Chamberlin, Rheinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696.

[12] Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921; Heusler, Heusser, and Anliker, *Helv. Chim. Acta*, 1953, **36**, 398; Grigor, Laird, Maclean, Newbold, and Spring, *J.*, 1954, 2333; Inhoffen and Mengel, *Chem. Ber.*, 1954, **87**, 146.

[13] Tschoubar, *Compt. rend.*, 1942, **214**, 117; Gaylord and Becker, *Chem. Rev.*, 1951, **49**, 413; Bachmann, Horwitz, and Warzynski, *J. Amer. Chem. Soc.*, 1953, **75**, 3268.

[14] Stevens and Dykstra, *ibid.*, 1954, **76**, 4402.

[15] Tiffeneau, *Compt. rend.*, 1932, **195**, 1284; cf. Naqvi, Horwitz, and Filler, *J. Amer. Chem. Soc.*, 1957, **79**, 6283.

[16] Rowley, *J. Amer. Chem. Soc.*, 1950, **72**, 3305.

[17] Gasson, Graham, Millidge, Robson, Webster, Wild, and Young, *J.*, 1945, 2170.

undergo conversion into the ethylenic ketone (IV) such reactions are usually measurably reversible. 6-Methyl*cyclo*hex-3-enone (VII) was therefore prepared by reduction of *o*-methoxytoluene with lithium and ethanol under essentially the same conditions as for the *para*-isomer, and it was converted into the conjugated compound (IV) by hot dilute sulphuric acid. The attempted additions to this of acetic acid, formic acid, and hydrogen bromide were fruitless, but with benzyl alcohol, which reacts favourably in related cases,[18] and with boron trifluoride–mercuric oxide as catalyst, a small amount of the benzyloxy-ketone (I; R = CH_2Ph) was isolated as its 2 : 4-dinitrophenylhydrazone. A solution of the unsaturated ketone (IV) in 0·1N-methanolic potassium hydroxide showed at room temperature (and rapidly when heated) a steady diminution in the intensity of the absorption maximum at 2260 Å, but only the original ketone and resinous material could be isolated from the product; several variations in conditions failed to yield any methoxy-compound.

Another possible route to ketones (I) is a Birch reduction of the amino-ether (X) to the dihydro-compound (XI), followed by selective hydrogenation to the tetrahydro-compound (XII) and acid hydrolysis to (I). In a model experiment, *o*-toluidine was reduced with lithium and ethanol in liquid ammonia,[19] and the crude dihydro-compound was hydrogenated in ethanol–ether–acetic acid; hydrolysis of the product gave mainly 2-methyl*cyclo*hexanone, thus establishing the feasibility of the route, but application of the method to 2-amino-4-methoxytoluene (X; R = Me) failed to give any of the ether (I; R = Me). In some other exploratory experiments, reduction of *o*- and *p*-anisidine with lithium–ethanol–ammonia gave, after acid hydrolysis, *cyclo*hex-2-enone and *cyclo*hexane-1 : 4-dione respectively; reductive removal of the methoxy-group, as observed in certain other cases,[20] had thus occurred with the *ortho*-isomer.

A method described [2,3] for the preparation of the methyl ether (I; R = Me) is by oxidation of 5-methoxy-2-methyl*cyclo*hexanol (VI; R = Me), but the preparation of the latter involves a lengthy series of reactions. Investigations were therefore made of other possible routes to compounds of type (VI) or suitable precursors. Clemmensen reduction of 2 : 4-dihydroxybenzaldehyde has been reported to be unsatisfactory,[21] and we found no improvement by the use of variations recommended [22] in other difficult cases. Wolff–Kishner reduction of the aldehyde has not been reported (though 2 : 4-dimethoxybenzaldehyde is quite readily reduced [23]) but again we obtained no 4-methylresorcinol under a variety of conditions. This is probably due to the fact that even with an excess of hydrazine the aldehyde gives the azine rather than the hydrazone, and although azines have been used for Wolff–Kishner reductions this one appears to be exceptionally stable; it was isolated from the reaction products on several occasions. Catalytic hydrogenation of 2 : 4-dihydroxybenzaldehyde over platinum is known [21] to give a small yield of 4-methylresorcinol but it has now been found that hydrogenation in methanol over highly active Raney nickel gives an excellent yield of 4-methyl*cyclo*hexane-1 : 3-diol (VI; R = H), probably as a mixture of stereoisomers; benzoylation under controlled conditions gave a product which, although non-crystalline, was a monobenzoate as shown by analysis and infrared spectrum. On oxidation with chromic acid it gave a product which furnished the 2 : 4-dinitrophenylhydrazone of 6-methyl*cyclo*hex-2-enone (IV); benzoylation had therefore occurred in the 1-position to give (VI; R = Bz), but the usual elimination had taken place under the acidic oxidation conditions.

The monobenzoylation of 2 : 4-dihydroxybenzaldehyde was described by Leon and Robinson,[24] who obtained the 4-monobenzoate, in unstated yield, as the chief product.

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[18] Hoffman, *J. Amer. Chem. Soc.*, 1927, **49**, 530; Hirschmann, Hirschmann, and Daus, *ibid.*, 1952, **74**, 539; Bernstein, Heller, and Stolar, *ibid.*, 1954, **76**, 5674.

[19] Stork and White, *ibid.*, 1956, **78**, 4604.

[20] Birch, *J.*, 1947, 102.

[21] Bell, Bridge, and Robertson, *J.*, 1937, 1542.

[22] Robinson and Shah, *J.*, 1934, 1491; Steiger and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 161.

[23] Cram, *J. Amer. Chem. Soc.*, 1948, **70**, 4240.

[24] Leon and Robinson, *J.*, 1931, 2732.

A detailed reinvestigation of this reaction has now shown that a considerable proportion of the 2-monobenzoate is also formed. Hydrogenation of the 4-monobenzoate over Raney nickel in ether gave a small yield of a solid, the analysis and infrared spectrum of which were compatible with its formulation as 3-hydroxy-4-methyl*cyclo*hexyl benzoate (VI; R = Bz).

Reduction of the acetate or benzoate of 4-methyl-3-nitrophenol gave the corresponding *O*-derivative (X; R = Ac or Bz) of the aminophenol; diazotisation of this *O*-benzoate gave 3-hydroxy-4-methylphenyl benzoate (IX; R = Bz).

EXPERIMENTAL

In this and the following paper, analyses were by Mr. F. H. Oliver, Miss J. Cuckney and their staff, and absorption spectra by Mr. R. L. Erskine, B.Sc., A.R.C.S., and Mrs. A. I. Boston.

Unless otherwise stated, 2 : 4-dinitrophenylhydrazones were chromatographed on alumina in benzene.

*4-Methyl*cyclo*hex-3-enone.*—*p*-Methoxytoluene (122 g., 1 mol.) was added to a stirred mixture of anhydrous ether (600 ml.) and liquid ammonia (1·6 l.). After 15 min., lithium (26·4 g., 3·8 equiv.) was added in small strips (0·1 g.) during 30 min. Stirring was continued for 15 min. and then dry ethanol (193 g., 4·2 mol.) was added dropwise during 30 min. Stirring was continued until the blue colour of the solution had been discharged (*ca.* 1 hr.) and most of the ammonia was then allowed to evaporate. Ice (750 g.) was added to the residue, which was then extracted with ether. The ether layer was washed with water, concentrated to about 250 ml. under reduced pressure, and stirred overnight with aqueous 2M-oxalic acid (250 ml.). The ether layer was again separated, combined with ether extracts of the aqueous layer, washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and distilled, giving 4-methyl*cyclo*hex-3-enone (88 g., 80%), b. p. 36°/4 mm., n_D^{21} 1·4693, $\lambda_{max.}$ (in EtOH) 2800 Å (ε 24) (Found: C, 76·1; H, 9·5. Calc. for $C_7H_{10}O$: C, 76·3; H, 9·15%) (lit.,[7] b. p. 74°/17 mm.). The 2 : 4-dinitrophenylhydrazone, prepared in ethanol–phosphoric acid,[25] crystallised from aqueous ethanol in orange prisms, m. p. 119—121°, $\lambda_{max.}$ (in EtOH) 3650 Å (ε 22,600) (lit.,[7] m. p. 120—121°, $\lambda_{max.}$ 3680 Å, ε 20,200).

*4-Methyl*cyclo*hex-3-enol.*—The foregoing ketone (82 g., 0·74 mol.) in ether (300 ml.) was added dropwise during 1·5 hr. to a stirred solution of lithium aluminium hydride (16 g., 0·42 mol.) in ether (300 ml.) heated under reflux. Heating and stirring were continued for a further 2·5 hr., then excess of 10% hydrochloric acid was added to the cooled mixture; the ether layer was separated and combined with the ether extracts of the aqueous layer, washed with water, dried (Na_2SO_4), and distilled giving 4-methyl*cyclo*hex-3-enol (75 g., 90%), b. p. 61—62°/5 mm., n_D^{24} 1·4810, $\nu_{max.}$ (liquid film) 3330 (OH), 1669 (C=C) cm.$^{-1}$ (lit.,[8] b. p. 89°/26 mm., n_D^{22} 1·4803). The 3 : 5-dinitrobenzoate crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 115—116° (Found: C, 54·9; H, 4·8; N, 9·3. Calc. for $C_{14}H_{14}O_6N_2$: C, 54·9; H, 4·6; N, 9·15%) (lit.,[3, 8] m. p. 113—113·5°, 107°). The *α-naphthylurethane* crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 146—147° (Found: C, 76·5; H, 6·9; N, 5·1. $C_{18}H_{19}O_2N$ requires C, 76·8; H, 6·8; N, 5·0%).

*Reaction of 4-Methyl*cyclo*hex-3-enol with Performic Acid.*—The alcohol (3·4 g.) was dissolved in 98% formic acid (15 ml.), and 30% hydrogen peroxide (10 ml.) was added, followed by two drops of concentrated sulphuric acid. The solution was stirred for 2 hr. at 40—45° and became green. Sulphuric acid (7 ml.) was added to the cooled solution and stirring was continued for 2 hr. at room temperature. Isolation of the product with ether and treatment with Brady's reagent gave the 2 : 4-dinitrophenylhydrazone (form *A*) of 6-methyl*cyclo*hex-2-enone, m. p. and mixed m. p. 125—126°. (Two forms, m. p.s 122—125·5° and 162—164°, are known.[26])

*4-Methyl*cyclo*hex-3-enyl Tetrahydropyran-2-yl Ether.*—Freshly distilled 2 : 3-dihydro-4*H*-pyran (20·5 g.) was added to a solution of 4-methyl*cyclo*hex-3-enol (5·5 g.) in ether (50 ml.), followed by phosphorus oxychloride (0·3 ml.). After 12 hr. at room temperature, solid potassium hydroxide (5 g.) was added and after a further 48 hr. the mixture was filtered and

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[25] Johnson, *J. Amer. Chem. Soc.*, 1951, **73**, 5888.

[26] Yanagita, Inayama, and Kitagawa, *J. Org. Chem.*, 1956, **21**, 612.

distilled, giving the ether (6·2 g., 65%), b. p. 77—79°/0·2 mm., n_D^{22} 1·4740 (Found: C, 73·5; H, 10·5. Calc. for $C_{12}H_{20}O_2$: C, 73·4; H, 10·3%) (lit.,[3] b. p. 90—91·5°/3 mm.).

*4-Acetoxy-1-methyl*cyclo*hexene.*—Acetyl chloride (42 g.) in benzene (100 ml.) was added dropwise during 1 hr. to a stirred solution of 4-methyl*cyclo*hex-3-enol (57 g.) in light petroleum (b. p. 40—60°) (200 ml.) and pyridine (45 g.) at −10° to 0°. Stirring was continued for 30 min. and the mixture was then kept at room temperature for 24 hr. The pyridine hydrochloride was filtered off and washed with light petroleum, and the combined filtrates were washed with 2N-hydrochloric acid and water, dried (Na_2SO_4), and distilled, giving 4-acetoxy-1-methyl*cyclo*hexene (64 g., 82%), b. p. 64—65°/5 mm., n_D^{18} 1·4591, $\nu_{max.}$ (liquid film) 1735 (C=O), 1677 (C=C), and 1245 (C–O in acetate) cm.$^{-1}$ (lit.,[3, 8] b. p. 90°/23 mm., n_D^{24} 1·4548).

*4-Acetoxy-1 : 2-epoxy-1-methyl*cyclo*hexane.*—The foregoing acetate (13·5 g.) in ether (20 ml.) was added to a solution (200 ml.; 14% w/v) of monoperphthalic acid in ether at 0°. After 1 hr., the mixture was allowed to attain room temperature and kept for 24 hr. The precipitate of phthalic acid was filtered off and the solution was washed with sodium hydrogen carbonate and water, dried (Na_2SO_4), and distilled, giving the epoxide as a sweet-smelling liquid (9·6 g., 64%), b. p. 85—87°/4 mm., n_D^{23} 1·4528, $\nu_{max.}$ (liquid film) 1736 (C=O), 1244 (C–O in acetate), 1212, 848, and 835 (epoxide?) cm.$^{-1}$ (Found: C, 63·5; H, 8·4. Calc. for $C_9H_{14}O_3$: C, 63·5; H, 8·3%) (lit.,[3] b. p. 113—119°/24 mm.).

Treatment of the epoxide (1 ml.) with 2 : 4-dinitrophenylhydrazine (1 g.) in concentrated hydrochloric acid (30 ml.), water (30 ml.), and ethanol (5 ml.) gave very little precipitate at room temperature, but after 10 min. at 90° a red oil separated which after chromatography furnished 6-methyl*cyclo*hex-2-enone 2 : 4-dinitrophenylhydrazone (form *A*) (0·25 g.), m. p. and mixed m. p. 124—126°.

Treatment of the epoxide (1 ml.) with boron trifluoride–ether complex (1 ml.) in ether (10 ml.) for 72 hr. at 5—10°, followed by addition of aqueous sodium hydrogen carbonate, isolation of the product with ether, and reaction with 2 : 4-dinitrophenylhydrazine in 5N-hydrochloric acid, also gave the derivative of 6-methyl*cyclo*hex-2-enone, m. p. and mixed m. p. 125—126° (form *A*), $\lambda_{max.}$ (in EtOH) 3800 Å (ε 28,500) (Found: C, 54·2; H, 5·1; N, 19·3. Calc. for $C_{13}H_{14}O_4N_4$: C, 53·8; H, 4·9; N, 19·3%) (lit.,[26] m. p. 122—125·5°).

When the epoxide (1·0 g.) was treated for 24 hr. at room temperature with 2 : 4-dinitrophenylhydrazine (5 g.) and sulphuric acid (10 ml.) in methanol (75 ml.) it gave 5-(2 : 4-dinitrophenylhydrazino)-2-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, orange plates (from pyridine–methanol), m. p. and mixed m. p. 187—188° (decomp.), $\lambda_{max.}$ (in EtOH) 3500 Å (ε 36,600) (lit.,[7] m. p. 176—177°).

*3-Acetoxy-1-methyl*cyclo*pentylformaldehyde.*—Freshly distilled ethylene dibromide (6 g.) was added to dry magnesium turnings (3 g.) in ether (50 ml.) and when the vigorous reaction had subsided the mixture was refluxed for 15 min., then cooled to 0°. On addition of the foregoing epoxide (5 g.) a copious flocculent white precipitate of the epoxide–magnesium bromide complex was formed immediately. The mixture was heated under gentle reflux for 60 hr. Water was then added and the ether layer was separated, combined with ether extracts of the aqueous layer, washed with water, dried (Na_2SO_4), and distilled, giving a main fraction (3·3 g.), which on redistillation furnished *3-acetoxy-1-methyl*cyclo*pentylformaldehyde* (0·75 g.), b. p. 61—64°/0·1 mm., n_D^{23} 1·4518, $\lambda_{max.}$ (in EtOH) 2720 Å (ε 12), $\nu_{max.}$ (in CCl_4) 2778 and 2703 (C–H in CHO), 1739 (C=O in aldehyde and in acetate), 1242 (C–O in acetate) cm.$^{-1}$ (Found: C, 63·6; H, 8·7. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%). It gave a positive test with Schiff's reagent, and reduced boiling Fehling's solution. The 2 : *4-dinitrophenylhydrazone,* prepared in ethanol–phosphoric acid, was chromatographed and then crystallised from aqueous methanol in yellow plates, m. p. 139—141°, $\lambda_{max.}$ (in $CHCl_3$) 3600 Å (ε 23,000) (Found: C, 51·65; H, 5·4; N, 16·1. $C_{15}H_{18}O_6N_4$ requires C, 51·4; H, 5·2; N, 16·0%).

Reaction of the epoxide (3 g.) with magnesium bromide (15 g., from the elements) in ether (60 ml.) for 72 hr. at 5—10° gave *5-acetoxy-2-bromo-2-methyl*cyclo*hexanol* (?) (2·8 g.), b. p. 106—114°/0·7 mm., n_D^{26} 1·4950—1·5028, ε <100 at λ 2200—4000 Å (Found: C, 44·2; H, 6·2; Br, 31·3. $C_9H_{15}O_3Br$ requires C, 43·0; H, 6·0; Br, 31·8%). From a lower-boiling fraction there was obtained 6-methyl*cyclo*hex-2-enone 2 : 4-dinitrophenylhydrazone, orange prisms [from benzene–light petroleum (b. p. 40—60°)], m. p. 162—163° (form *B*) (Found: C, 54·5; H, 5·2; N, 19·6. Calc. for $C_{13}H_{14}O_4N_4$: C, 53·8: H, 4·9; N, 19·3%).

*2-Acetoxy-5-methyl*cyclo*hexanone 2 : 4-Dinitrophenylhydrazone.*—Prepared from the ketone[27]

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[27] Treibs and Bast, *Annalen*, 1949, **561**, 165.

this *derivative* crystallised from methanol–ethyl acetate in orange prisms, m. p. 168—170° (Found: C, 51·7; H, 5·5; N, 16·4. $C_{15}H_{18}O_6N_4$ requires C, 51·4; H, 5·2; N, 16·0%).

6-*Methyl*cyclo*hex*-3-*enone*.—*o*-Methoxytoluene (122 g., 1 mol.) in ether (500 ml.) was added in one lot to a stirred solution of lithium (30 g., 4·29 equiv.) in liquid ammonia (1·7 l.). After 15 min., dry ethanol (230 g., 5 mol.) was added dropwise during 30 min. After a further 5 min., when the intense blue colour of the solution had faded, the ammonia was allowed to evaporate, and the residue was stirred with 2N-sulphuric acid (800 ml.) at *ca.* 5° for 1 hr. The mixture was extracted with ether and the ether solution was separated, washed with dilute potassium hydroxide and water, dried (Na_2SO_4), and distilled, giving 6-*methyl*cyclo*hex*-3-*enone* (86 g., 78%), b. p. 59—60°/15 mm., n_D^{23} 1·4648, $\lambda_{max.}$ (in EtOH) 2730 Å (ε 70), $\nu_{max.}$ (liquid film) 1704 (C=O), 1653 (C=C) cm.$^{-1}$ (Found: C, 76·3; H, 9·4. $C_7H_{10}O$ requires C, 76·3; H, 9·15%). The 2 : 4-dinitrophenylhydrazone, prepared in ethanol–phosphoric acid, crystallised from aqueous ethanol in light orange prisms, m. p. 139°, $\lambda_{max.}$ (in EtOH) 3650 Å (ε 22,000) (lit.,[7] m. p. 135—137°).

Reaction of 6-*Methyl*cyclo*hex*-3-*enone with* 30% *Sulphuric Acid*.—When the crude ketone (40 g.) was boiled under reflux with 30% sulphuric acid (cf. ref. 7) for 30 min. it gave mainly a viscous, pale yellow *dimer* (27 g.), b. p. 120° (bath)/10^{-4} mm., n_D^{23} 1·5205, $\nu_{max.}$ (in CCl_4) 1718 (C=O) cm.$^{-1}$ (Found: C, 77·0; H, 9·2%; *M* in camphor, 235. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%; *M*, 220). A lower-boiling fraction, b. p. 67—70°/15 mm., n_D^{24} 1·4825, gave a 2 : 4-dinitrophenylhydrazone, crimson plates (from chloroform–methanol), m. p. 194—195°, $\lambda_{max.}$ (in $CHCl_3$) 3800 Å (ε 26,000), probably the derivative of 2-methyl*cyclo*hex-2-enone (see below); the latter ketone is known [28] to be present in small amount in the acid-rearrangement products from crude 6-methyl*cyclo*hex-3-enone.

6-*Methyl*cyclo*hex*-2-*enone*.—Crude 6-methyl*cyclo*hex-3-enone (85 g.), prepared as above, was heated under reflux with 2N-sulphuric acid (200 ml.) and methanol (10 ml.) for 3 hr. The product was isolated with ether, and the ether solution was washed, dried (Na_2SO_4), and distilled, giving crude ketone, b. p. 29—30°/0·2 mm. The combined product (176 g.) from two such runs was separated by fractionating through a 6″ Stedman column into 2-methyl*cyclo*hexanone (8 g.), b. p. 49—50°/15 mm., and 6-methyl*cyclo*hex-2-enone (103 g., 47%), b. p. 50—51°/15 mm., n_D^{20} 1·4834, $\lambda_{max.}$ (in EtOH) 2270 Å (ε 12,000), $\nu_{max.}$ (liquid film) 1680 (C=O), 1626 (C=C) cm.$^{-1}$ (Found: C, 76·5; H, 9·2. Calc. for $C_7H_{10}O$: C, 76·3; H, 9·15%) (lit.,[7] b. p. 164—167°, $\lambda_{max.}$ 2263 Å, ε 4490).

With 2 : 4-dinitrophenylhydrazine in ethanol–phosphoric acid, the ketone gave two derivatives which were separated by crystallisation. One was the 2 : 4-dinitrophenylhydrazone (form *B*) of 6-methyl*cyclo*hex-2-enone, which crystallised from ethyl acetate–methanol in light orange prisms, m. p. 155—156°, $\lambda_{max.}$ (in $CHCl_3$) 3790 Å (ε 24,000) (Found: C, 54·5; H, 5·2; N, 19·6. Calc. for $C_{13}H_{14}O_4N_4$: C, 53·8; H, 4·9; N, 19·3%) (lit.,[7,19,26] m. p. 156—157°, 161—162°, 162—164°). The other derivative, 5-(2 : 4-dinitrophenylhydrazino)-2-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, crystallised from chloroform–dimethylformamide in orange plates, m. p. 187—188° (decomp.), $\lambda_{max.}$ (in $CHCl_3$) 3450 Å (ε 24,000) (Found: C, 46·3; H, 4·2; N, 22·9. Calc. for $C_{19}H_{20}O_8N_8$: C, 46·7; H, 4·1; N, 22·9%) (lit.,[7] m. p. 176—177°).

5-*Benzyloxy*-2-*methyl*cyclo*hexanone*.—A mixture of 6-methyl*cyclo*hex-2-enone (4·8 g.), benzyl alcohol (6·3 g.), boron trifluoride–ether complex (0·2 ml.), and yellow mercuric oxide (20 mg.) was kept at 100° for 3 hr. and then at room temperature for 35 days. Potassium carbonate (0·5 g.) was added and the mixture was distilled, giving unchanged ketone, benzyl alcohol, and a fraction (2·3 g.), b. p. 120°/0·2 mm., n_D^{22} 1·5367, which was treated with 2 : 4-dinitrophenylhydrazine in ethanol–phosphoric acid. The mixture of derivatives formed was separated by chromatography and gave (i) 6-methyl*cyclo*hex-2-enone 2 : 4-dinitrophenylhydrazone (?), m. p. 163° (Found: C, 53·0; H, 5·0; N, 19·8. Calc. for $C_{13}H_{14}O_4N_4$: C, 53·8; H, 4·9; N, 19·3%) (a mixture with the authentic specimen, m. p. 156—157°, described above, had m. p. 154—155°); and (ii) 5-*benzyloxy*-2-*methyl*cyclo*hexanone* 2 : 4-*dinitrophenylhydrazone*, orange plates (from ethyl acetate–pentane), m. p. 159—163°, $\lambda_{max.}$ (in $CHCl_3$) 3670 Å (ε 24,000) (Found: C, 59·9; H, 5·7; N, 14·1. $C_{20}H_{22}O_5N_4$ requires C, 60·3; H, 5·6; N, 14·1%).

Reduction of o-*Toluidine*.—(i) A solution of *o*-toluidine (10·5 g.) in dry ether (50 ml.) was added to a stirred solution of lithium (3·0 g.) in liquid ammonia (200 ml.). After 15 min., ethanol (30 ml.) was gradually added (20 min.), and stirring was maintained until the solution became colourless (13 min.). The ammonia was then allowed to evaporate, and the residue was decomposed with ice-water and extracted with ether. The ether solution was hydrogenated

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[28] Birch and Hextall, *Austral. J. Chem.*, 1955, **8**, 96.

over Raney nickel W7 (*ca.* 1 ml.) until absorption ceased (1790 ml.); distillation of the product gave mainly 2-methyl*cyclo*hexylamine (6·75 g.), b. p. 70—78°/51 mm., n_D^{22} 1·4611 (Found: C, 74·0; H, 13·1; N, 12·0. Calc. for $C_7H_{15}N$: C, 74·3; H, 13·35; N, 12·4%).

(ii) In a similar experiment, acetic acid (5 c.c.) was added to the ether extract; an oil separated. Raney nickel W7 (*ca.* 1 ml.) was added but no gas was absorbed when the mixture was shaken in hydrogen. More catalyst (1 ml.) was added, followed by sufficient ethanol (100 ml.) to render the sludge granular; hydrogen was then absorbed, and ceased after 16 hr. (950 ml.). Removal of solvent from the filtered solution gave an oil, which was heated to 90° in 20 min. with 2N-hydrochloric acid (100 ml.). Extraction of the cooled solution with ether gave 2-methyl*cyclo*hexanone (2·5 g.), b. p. 64°/19 mm., n_D^{22} 1·4483 (lit.,[29] b. p. 165°, n_D^{20} 1·4483), which showed light absorption in ethanol ($\lambda_{max.}$ 2270 Å, ε *ca.* 400) indicating the presence of a very small proportion of 6-methyl*cyclo*hex-2-enone.

Reduction of Anisidines.—(i) *o*-Anisidine (12·3 g.) was reduced with lithium in liquid ammonia in the same way as *o*-toluidine. After evaporation of the ammonia the residue was dissolved in ice-water and extracted with ether. Evaporation of these extracts gave an oil, which was treated for a few minutes on the steam-bath with 2N-hydrochloric acid and worked up with ether, to give *cyclo*hex-2-enone (3·5 g.), b. p. 77—80°/12 mm., n_D^{23} 1·4817, $\lambda_{max.}$ (in EtOH) 2250 Å (ε 4800) [semicarbazone, m. p. 164—166°, $\lambda_{max.}$ (in EtOH) 2300, 2700 Å (ε 8000, 7000)] (lit.,[30] b. p. 169—171°, n_D^{18} 1·4842; semicarbazone, m. p. 171—172°).

(ii) *p*-Anisidine (12·3 g.) on similar reduction gave *cyclo*hexane-1 : 4-dione (1·3 g.), m. p. 78° (lit.,[30] m. p. 78°).

2 : 4-*Dihydroxybenzaldehyde.*—Prepared by Bisagni, Buu-Hoï, and Royer's method,[31] except that the product was not distilled but was directly recrystallised from water, it was obtained in better yield (55% on a 2 mole scale), and had m. p. 135—136° (lit.,[31] m. p. 135°), $\lambda_{max.}$ (in Et_2O) 2320, 2800, and 3100 Å (ε 8600, 13,800, and 6600), $\nu_{max.}$ (in $CHCl_3$) 3509 (O–H), 1658, and 1634 (chelated –CHO) cm.$^{-1}$.

2 : 4-*Dihydroxybenzaldehyde Azine.*—A mixture of the aldehyde (2 g.) with a large excess of 100% hydrazine hydrate (5 g.) was heated at 100° for 5 min., then cooled and acidified with dilute acetic acid. The yellow precipitate on recrystallisation from hot water or aqueous dioxan gave yellow needles of the *azine* (1·7 g.), which sublimed at *ca.* 270° and did not melt at 315°; it had $\lambda_{max.}$ (in EtOH) 2220, 2500, 3100, and 3650 Å (ε 16,300, 13,600, 12,800, and 48,000) (Found: C, 61·8; H, 4·8; N, 10·7. $C_{14}H_{12}O_4N_2$ requires C, 61·8; H, 4·4; N, 10·3%).

Treatment of the azine (5 g.) with potassium hydroxide (5 g.) and sodium (0·5 g.) in ethylene glycol (20 ml.) for 2·5 hr. at 170° under nitrogen gave only a brown resin. A similar result was obtained by reaction of the azine with a fused 1 : 1 mixture of sodium hydroxide and potassium hydroxide at 150—300°.

4-*Methyl*cyclo*hexane*-1 : 3-*diol.*—A solution of 2 : 4-dihydroxybenzaldehyde (13·8 g.) and sodium hydroxide (0·2 g.) in methanol (100 ml.) was hydrogenated over freshly prepared Raney nickel W7 (*ca.* 5 g.) at 100°/140 atm. until absorption ceased (4 hr.). The filtered solution was then neutralised with hydrochloric acid and distilled to give 4-*methyl*cyclo*hexane*-1 : 3-*diol* (12 g., 92%), b. p. 150° (bath)/10^{-5} mm., $\nu_{max.}$ (in CCl_4) 3630 (free O–H), 3542 (bonded O–H) cm.$^{-1}$ (Found: C, 63·9; H, 10·7. $C_7H_{14}O_2$ requires C, 64·6; H, 10·8%). A small amount of solid was collected from the last fraction; on recrystallisation from acetone–light petroleum (b. p. 40—60°) it formed plates, m. p. 107—108°, $\nu_{max.}$ (paraffin mull) 3268 (O–H) (Found: C, 63·9; H, 10·9%). Purity of the aldehyde and high activity of the catalyst are essential for the success of this reduction.

With ether as solvent in place of methanol, the product was *trans*-2-methyl*cyclo*hexanol (71%), b. p. 33—35°/0·02 mm., n_D^{22} 1·4607—1·4619 (Found: C, 73·7; H, 12·5. Calc. for $C_7H_{14}O$: C, 73·6; H, 12·4%), identified as the 3 : 5-dinitrobenzoate, m. p. 112—115° (lit.,[32] m. p. 117°).

Monobenzoylation of 4-*Methyl*cyclo*hexane*-1 : 3-*diol.*—Benzoyl chloride (40 g.) in chloroform (100 ml.) was gradually added to the diol (37 g.) in pyridine (40 g.), vigorously stirred at −10°. The mixture was set aside overnight, then heated at 100° for 1 hr., cooled to −10°, diluted with water, and acidified with hydrochloric acid. The chloroform layer was washed with dilute

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[29] Skita, *Ber.*, 1923, **56**, 1014.
[30] Bartlett and Woods, *J. Amer. Chem. Soc.*, 1940, **62**, 2933.
[31] Bisagni, Buu-Hoi, and Royer, *J.*, 1955, 3693.
[32] Jackman, Macbeth, and Mills, *J.*, 1949, 1717.

hydrochloric acid, aqueous sodium carbonate and water, then dried ($MgSO_4$) and evaporated to give the *monobenzoate* (mainly 5-benzoyloxy-2-methyl*cyclo*hexanol) as a viscous oil (52 g.). A portion was distilled at 150—180° (bath)/10^{-5} mm., and showed $\nu_{max.}$ (in CCl_4) 3610 and 3497 (O–H), 1718 (C=O), 1274 and 1112 (benzoate) cm.$^{-1}$ (Found: C, 71·6; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%).

Oxidation. This monobenzoate (23·4 g.) in acetic acid (30 g.) and water (10 g.) was added dropwise to a stirred solution of chromium trioxide (14 g.) in acetic acid (60 g.) and water (20 g.) at 0°. Stirring was maintained for 3 hr. at 0° and 24 hr. at room temperature, and most of the acetic acid was then neutralised with aqueous sodium hydroxide. Continuous extraction with ether, and distillation of the washed (aq. Na_2CO_3) extract, gave an oil (4·5 g.), b. p. 50—90°/10^{-4} mm., n_D^{24} 1·4936—1·5002, and a sublimate of benzoic acid, m. p. and mixed m. p. 122°. Treatment of the oil with 2 : 4-dinitrophenylhydrazine in phosphoric acid gave 5-(2 : 4-dinitrophenylhydrazino)-2-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. 187—188°, mixed m. p. 184—185°.

Monobenzoylation of 2 : 4-*Dihydroxybenzaldehyde*.—(i) Benzoyl chloride (4·6 ml.) was added dropwise, with shaking, to the aldehyde (5·6 g.) in 0·24N-potassium hydroxide (185 ml.), the precipitated lumps of derivative being removed at intervals. A solution of the crude product in benzene–light petroleum (b. p. 60—80°) slowly deposited 2-*benzoyloxy*-4-*hydroxybenzaldehyde* (2·1 g.) which on recrystallisation from benzene formed plates, m. p. 136—137° (Found: C, 69·7; H, 4·3. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·2%). The 4-benzoyloxy-compound, m. p. 102—103° (see below), was isolated from the mother-liquors.

(ii) A similar procedure was carried out on the aldehyde (45 g.), and the crude product was crystallised twice from ethanol to give 4-benzoyloxy-2-hydroxybenzaldehyde (27 g.), m. p. 101—102°. Leon and Robinson,[24] who proved its structure, give m. p. 103°.

Hydrogenation of 4-*Benzoyloxy*-2-*hydroxybenzaldehyde*.—The aldehyde (4·8 g.) in dry ether (100 ml.) was hydrogenated over Raney nickel W7 for 14 hr. at 100°/100 atm. Distillation of the product gave a series of fractions the last of which (0·5 g.), b. p. 164—192° (bath)/10^{-4} mm., solidified. Recrystallisation from benzene–light petroleum gave prisms of (?) 3-hydroxy-4-methyl*cyclo*hexyl benzoate, m. p. 100—101°, $\nu_{max.}$ (paraffin mull) 3304 (O–H), 1714 (C=O in aromatic ester), 1606 and 1509 (benzenoid) cm.$^{-1}$ (Found: C, 71·7; H, 8·0. Calc. for $C_{14}H_{18}O_3$: C, 71·75; H, 7·7%).

4-*Methyl*-3-*nitrophenol*.—Prepared by Copisarow's method,[33] this had m. p. 78—79° (lit.,[33] m. p. 76—77°). The *acetate*, m. p. 70—71° (Found: C, 55·3; H, 4·75; N, 7·3. $C_9H_9O_4N$ requires C, 55·4; H, 4·65; N, 7·2%), and the *benzoate*, m. p. 94—95° (Found: C, 65·1; H, 4·3; N, 5·65. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3; N, 5·4%), both formed pale yellow needles from ethanol.

3-*Amino*-4-*methylphenyl Acetate*.—4-Methyl-3-nitrophenyl acetate (2·0 g.) was hydrogenated in methanol (20 ml.) over Raney nickel W7 (*ca* 1 ml.) and magnesium sulphate (0·1 g.) at 25°/40 atm. for 24 hr. to give the *amine* (1·4 g.), m. p. 72—73° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 65·9; H, 6·6; N, 8·6. $C_9H_{11}O_2N$ requires C, 65·5; H, 6·7; N, 8·5%).

3-*Amino*-4-*methylphenyl Benzoate*.—4-Methyl-3-nitrophenyl benzoate (2·6 g.), water (20 ml.), and acetic acid (0·3 ml.) were boiled under reflux during the gradual addition (1·5 hr.) of iron filings (2 g.). Boiling was continued for another hour, and the mixture was then filtered and evaporated. Recrystallisation of the residue from ethanol gave colourless needles of the *amine* (1·3 g.), m. p. 113—114° (Found C, 73·6; H, 5·8; N, 6·5. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·8; N, 6·2%). The same product was obtained, in poorer yield, by hydrogenation, as described above for the acetate.

3-*Hydroxy*-4-*methylphenyl Benzoate*.—The precipitate formed by the addition of 3-amino-4-methylphenyl benzoate (5·1 g.) to a solution of stannic chloride (8 ml.) in concentrated hydrochloric acid (20 ml.) was collected, suspended in concentrated hydrochloric acid (20 ml.), and cooled.[34] A solution of sodium nitrite (1·4 g.) in water (4·5 ml.) was added slowly (20 min.) at *ca.* 5° with stirring, which was maintained for a further hour. The precipitate was collected and added during 10 min. to boiling water (150 ml.). Extraction of the cooled solution with ether gave a solid which was dissolved in ethanol, filtered from some insoluble material, and evaporated to an oil, which after distillation at 230° (bath)/10^{-4} mm. solidified (1·5 g.).

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[33] Copisarow, *J.*, 1929, 251.

[34] Cf. Woodward and Doering, *J. Amer. Chem. Soc.*, 1945, **67**, 860.

Recrystallisation from aqueous ethanol gave 3-*hydroxy*-4-*methylphenyl benzoate*, colourless prisms, m. p. 107—109° (Found: C, 73·4; H, 5·6. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%).

The residual aqueous solution was made alkaline and extracted with ether; 3-amino-4-methylphenyl benzoate (1·1 g.), m. p. 110—113°, was recovered.

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