

90. Experiments on the Synthesis of Simple C-Substituted Derivatives of Dihydroxyacetone.

By J. R. MARSHALL and JAMES WALKER.

Recorded observations concerning the anomalous course of reactions designed to yield derivatives of 1:3-dihydroxy-1-phenylacetone from *O*-acetylmandelyldiazomethane have been largely confirmed and extended. The diacetate and 3-monoacetate have now, however, been obtained. 1-Phenylpropane-1:2-dione and, probably, *O*-acetylmandelaldehyde were obtained together with the diacetate; the 3-monoacetate readily underwent decomposition to give 1-phenylpropane-1:2-dione. A mechanism is suggested for the formation of the diketone which can be applied to the analogous conversion of dihydroxyacetone into methylglyoxal.

When the protecting *O*-acetyl group was removed from 1-diazoacetyl-cyclohexyl acetate by alkaline hydrolysis, the resulting diazo-ketone decomposed on treatment with acetic acid to give, as major product, 1-oxa-spiro[3:5]nonan-3-one; the mechanism of this reaction is discussed and analogies are provided. Evidence for the formation of the parent oxetan-3-one from chloroacetyldiazomethane was obtained.

With a view to use in the synthesis of analogues of cortisone, a study has been made of the application of the diazo-ketone synthesis to the chlorides of *O*-acylated derivatives of two representative α -hydroxy-carboxylic acids, mandelic acid and cyclohexanol-1-carboxylic acid. This reaction, however, is unlikely to be of value in the synthesis of cortisone itself in view of the inaccessibility of appropriate 17-hydroxyetic acids in the correct stereochemical configuration, as well as the difficulty of protecting a non-acylable 17 α -hydroxyl group (cf. Fieser, *Experientia*, 1950, **6**, 312) and the unfavourable stereochemical course of the cyanohydrin reaction when applied to 17-keto-steroids.

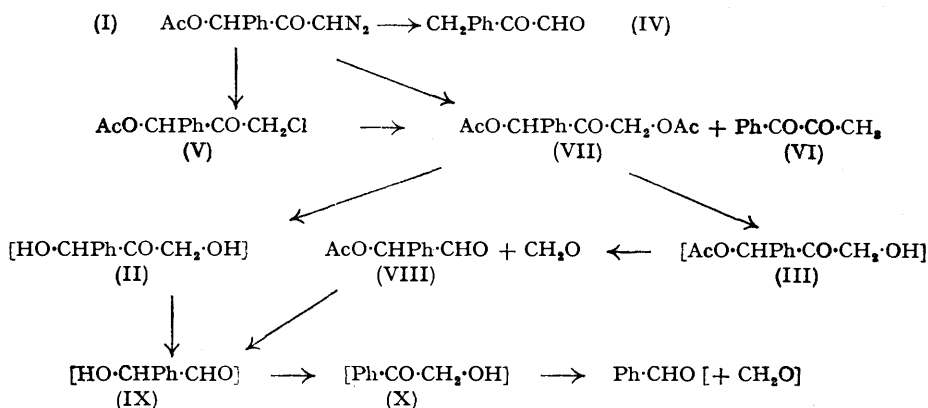
Although the diazo-ketone synthesis has been used successfully in the synthesis of L-sorbose from diethylidene L-lyxonoyl chloride (Gätzi and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 186), of D-erythrose from isopropylidene D-glyceroyl chloride (Iwadare, *Bull. Chem. Soc. Japan*, 1939, **14**, 131), and of a series of homologous ketoses from the appropriate fully acetylated aldonyl chlorides (Wolfson *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 201, 632; 1942, **64**, 1701, 2329; 1943, **65**, 1021, 1516; 1944, **66**, 204; 1945, **67**, 1793; 1946, **68**, 791, 1453), Bradley and Eaton (*J.*, 1937, 1913) found that the diazomethyl ketone (I) derived from *O*-acetylmandelyl chloride behaved anomalously when treated with various acids, and neither 1:3-dihydroxy-1-phenylacetone (II) nor its 1-*O*-acetyl derivative (III) was obtained by these authors. 1:3-Dihydroxy-1-phenylacetone (II) has been mentioned without details in a patent (U.S.P. 2,043,950/1936), but, in view of the work of Bradley and Eaton and that to be described below, it is unlikely that free dihydroxyphenylacetone has been prepared or, indeed, that it is capable of other than transient existence.*

Bradley and Eaton stated that the diazomethyl ketone (I) in dilute sulphuric acid gave benzylglyoxal (IV) as the only crystalline reaction product, while benzaldehyde (identified as the 2:4-dinitrophenylhydrazone) was also produced. The chloromethyl ketone (V), on the other hand, they found to react with methyl-alcoholic sodium acetate to give 1-phenylpropane-1:2-dione (VI); benzoic acid was also isolated and doubtless originated by slow decomposition of (VI) (cf. Müller and von Pechmann, *Ber.*, 1889, **22**, 2127). Except when it was carefully purified, decomposition of the chloromethyl ketone (V) to (VI) occurred on storage. Although Bradley and Eaton stated, without details, that the diazo-ketone (I) "did not react easily with acetic acid," we readily effected this reaction, noted

* [Added in proof, December 18th, 1951.] Since this paper was written, Smith and Anderson (*J. Org. Chem.*, 1951, **16**, 963) have described the successful preparation of phenyldihydroxyacetone, m. p. 71–73°, by deacetylation of the diacetate at 0° with aqueous barium hydroxide, and note its ready transformation into (VI); we had made several tentative attempts to effect the deacetylation of (VII), at room temperature with methanolic sodium methoxide or with methanol containing a trace of hydrogen chloride without, however, achieving a satisfactory result.

the production of traces of the diketone (VI), and isolated 1 : 3-diacetoxy-1-phenylacetone (VII) and a substance $C_{10}H_{10}O_3$ (see below) possessing one acetyl group.

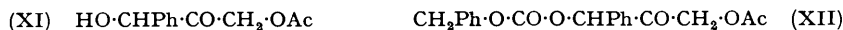
We found the chloro-ketone (V) to react with sodium acetate, in acetic acid containing acetic anhydride (*i.e.*, in an anhydrous medium), to give the diketone (VI), a fraction "b" corresponding in properties with the substance $C_{10}H_{10}O_3$, and 1 : 3-diacetoxy-1-phenylacetone (VII), which appears to be stable indefinitely at room temperature. Immediately after collection, fraction "b" had an odour of formaldehyde. Fraction "b" itself had strong reducing properties and gave with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid a dinitrophenylhydrazone, m. p. 134—136.5°, corresponding to a carbonyl compound $C_{10}H_{10}O_3$, and, in smaller amount, a second derivative, m. p. 179—184°, which appeared to correspond to a carbonyl compound $C_8H_8O_2$. The detection of formaldehyde, the composition of the substance, and the analytical data for the two 2 : 4-dinitrophenylhydrazones allow one to conclude that the compound $C_{10}H_{10}O_3$ was *O*-acetylmandelaldehyde (VIII) of which the dinitrophenylhydrazone, m. p. 134—136.5°, was a derivative; the somewhat impure dinitrophenylhydrazone, m. p. 179—184°, was probably crude mandelaldehyde (IX) 2 : 4-dinitrophenylhydrazone and was distinct from the 2 : 4-dinitrophenylhydrazone of benzoylcarbinol (X).



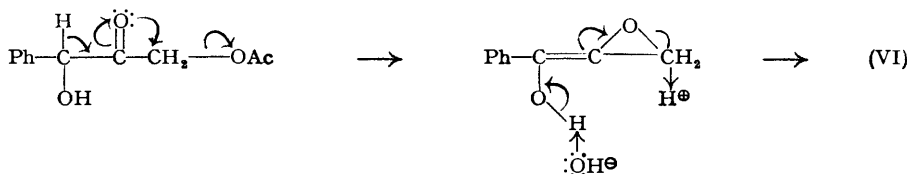
The formation of *O*-acetylmandelaldehyde (VIII) and formaldehyde from what had initially been 1 : 3-diacetoxy-1-phenylacetone (VII) requires the reasonable assumption that the 3-acetoxy-group had been hydrolysed during working-up of the mixture with sodium hydrogen carbonate with production of 1-acetoxy-3-hydroxy-1-phenylacetone (III). The facile decomposition of (III) to (VIII) and formaldehyde is analogous with the reversibility of the benzoin condensation (Lachman, *J. Amer. Chem. Soc.*, 1924, **46**, 708; cf. Buck and Ide, *ibid.*, 1931, **53**, 2350, 2784), the thermal decomposition of acetol to acetaldehyde and formaldehyde (Nef, *Annalen*, 1904, **335**, 250; Urion, *Compt. rend.*, 1932, **194**, 2145), and the more facile cleavage of benzoylcarbinol (X) to benzaldehyde (Zincke, *Annalen*, 1883, **216**, 286), although formaldehyde has not been detected in the last decomposition. Although mandelaldehyde (IX) has only been described once (Rinkes, *Rec. Trav. chim.*, 1920, **39**, 709) and earlier experiments designed to produce it gave, instead, benzoylcarbinol (X) (Evans and Parkinson, *J. Amer. Chem. Soc.*, 1913, **35**, 1772) the acetate (VIII) may have been obtained by Nef (*loc. cit.*, p. 268), and it yielded benzoylcarbinol (X) instead of (IX) on hydrolysis. The formation of benzaldehyde, noted by Bradley and Eaton, and the other observed transformations, for which valid analogies have been noted above, may therefore be summarised in the above scheme.

As it was obviously of interest, 3-acetoxy-1-hydroxy-1-phenylacetone (XI) was sought by way of the 1-benzyloxycarbonyl derivative (XII). Methoxycarbonylation of mandelic acid was described by Fischer and Fischer (*Ber.*, 1913, **46**, 2659) but their technique was not satisfactory when applied to benzyl chloroformate and mandelic acid; at a low temperature, however, methyl mandelate was converted in good yield to methyl *O*-benzyloxycarbonyl-mandelate by the action of benzyl chloroformate in the presence of a minimal amount of

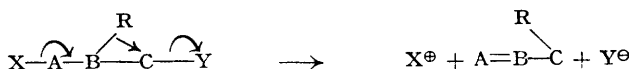
pyridine, notwithstanding the decomposition of the acid chloride in the presence of pyridine expected as a side reaction (cf. Carré and Passedouet, *Compt. rend.*, 1935, **200**, 1767). The benzyloxycarbonyl group was extremely sensitive to cold methanolic potassium hydroxide, which gave a mixture of mandelic acid and methyl mandelate (cf. Fischer and Fischer, *loc. cit.*), but acid hydrolysis afforded *O*-benzyloxycarbonylmandelic acid in good yield. Conversion into the acid chloride and the diazo-ketone proceeded normally, and reaction of the latter with acetic acid readily gave (XII). Hydrogenolysis of this proceeded smoothly but the resulting monoacetate (XI), which was characterised as a semicarbazone, could not be crystallised and, on attempted distillation in a high vacuum, decomposed to give the diketone (VI) in good yield; similar decomposition also took place on storage.



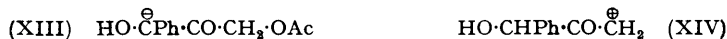
The formation of 1-phenylpropane-1 : 2-dione (VI), and also of benzylglyoxal (IV) as observed by Bradley and Eaton, from dihydroxyphenylacetone derivatives is analogous with the well-known transformation of dihydroxyacetone into methylglyoxal (cf., e.g., Bernier and Evans, *J. Amer. Chem. Soc.*, 1938, **60**, 1381). Exemplified by the present instance, the reaction may be interpreted as :



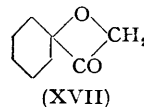
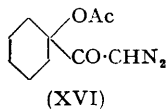
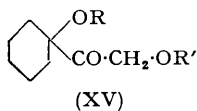
In this the initial stage is reminiscent of Ingold and Shoppee's generalised scheme for the pinacolin and related transformations (*J.*, 1928, 371) :



The first phase is presumably formation of the carbanion (XIII) and not the carbonium ion (XIV).



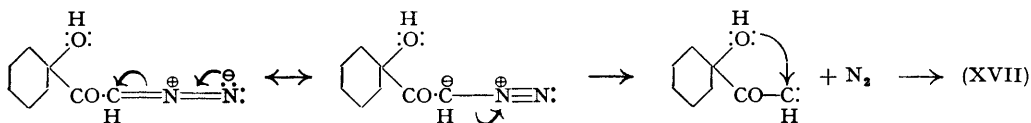
The synthesis of 1-acetoxyacetyl*cyclohexyl* acetate (XV; R = R' = Ac) from 1-hydroxycyclohexanecarboxylic acid proceeded smoothly and, since our work was concluded, a similar synthesis has been intimated by Alexander, Cocker, Cocker, and Lipman (*Chem. and Ind.*, 1951, 112). Hydrolysis of (XV; R = R' = Ac) with potassium hydrogen carbonate yielded 1-hydroxyacetyl*cyclohexan-1-ol* (XV; R = R' = H) in excellent yield, compared with the less satisfactory conversion of 1-bromoacetyl*cyclohexyl* bromide into (XV; R = R' = H) (Wagner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 1873). Hydrolysis of (XV; R = R' = Ac) with methanolic sodium methoxide was abnormal and the only identifiable products were *cyclohexanone* and 1-hydroxycyclohexanecarboxylic acid.



Hydrolysis of the crude diazo-ketone (XVI) with methanolic potassium hydroxide and treatment of the product with acetic acid gave the novel *spiro*-compound, 1-oxa*spiro*[3 : 5]-nonan-3-one (XVII), with only a small proportion of the expected product (XV; R = H, R' = Ac). which has since been prepared by Billimoria and Maclagan (*Nature*, 1951, **167**, 81*) by the action of silver acetate on 1-bromoacetyl*cyclohexan-1-ol*. The formation of (XVII) requires decomposition of the hydrolysed diazo-ketone to take place yielding a carbon atom with a sextet of electrons, the deficiency being made good by the oxygen

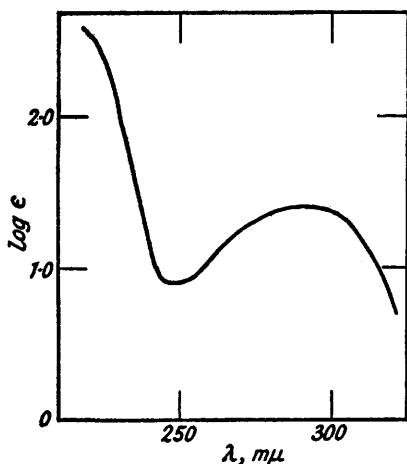
* Also *J.*, 1951, 3067.

atom of the alcoholic hydroxyl group presenting a pair of its unshared electrons to this carbon atom with migration of the proton. Analogies for this reaction, with formation of 5-membered heterocyclic rings, are the formation of the coumaranones (XVIII, XIX) by



the action of acids on 3-diazoacetyl-2-naphthol (Krzikalla and Eistert, *J. pr. Chem.*, 1935, **143**, 50) and 6-diazoacetylbumbelliferone propionate (von Bruchhausen and Hoffmann, *Ber.*, 1941, **74**, 1584) respectively; coumaranone itself is obtained in excellent yield from

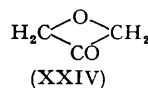
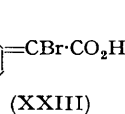
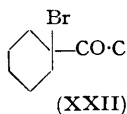
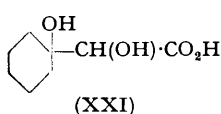
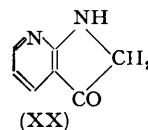
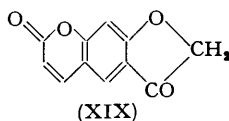
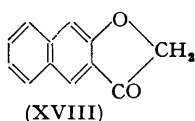
*Light absorption of
1-oxaspiro[3:5]nonan-3-one in hexane.*



o-anisoyldiazomethane (Marshall, Kuck, and Elderfield, *J. Org. Chem.*, 1942, **7**, 444; Pfeiffer and Enders, *Chem. Ber.*, 1951, **84**, 247), and 7-pyriodoxyl (XXI) is produced as an intermediate from 2-amino-3-diazoacetylpyridine (Kägi, *Helv. Chim. Acta*, 1941, **24**, 141E).

The only previous instance of the deliberate removal of the protecting group in a blocked α' -hydroxy- α -diazomethyl ketone before transformation of the diazo-group appears to be that described by Wolfrom, Brown, and Evans (*J. Amer. Chem. Soc.*, 1943, **65**, 1025) who deacetylated 1-deoxy-1-diazo-*D*-galaheptulose penta-acetate with methanolic ammonia before reaction of the resulting 1-deoxy-1-diazo-*D*-galaheptulose with formic acid, which gave an unidentified product and not, apparently, *D*-galaheptulose; it now appears that their material may have analogously contained a 5-membered ring.

Although Wolff rearrangement could conceivably have given the isomeric β -lactone* of 1-hydroxycyclohexylacetic acid, the structure of (XVII) followed from the typically ketonic ultra-violet light absorption (see figure) and from oxidative experiments (see p. 474). For example, alkaline hypoiodite gave, in small yield, 1-hydroxycyclohexylglycollic acid



(XXI), implying substitution in the methylene group and rearrangement of the Favorski type (*Bull. Soc. chim.*, 1926, **39**, 216) to the α -hydroxy- β -lactone as intermediate stages. An authentic specimen of (XXI) was obtained by brominating hexahydroacetophenone and treating the resulting tribromo-derivative (XXII) with aqueous potassium hydroxide following Favorski's method for the preparation of $\beta\beta$ -dimethylglyceric acid from methyl isopropyl ketone (*J. pr. Chem.*, 1913, **88**, 693), while it is noteworthy that the use of alcoholic potassium hydroxide afforded α -bromocyclohexylideneacetic acid (XXIII) (Wagner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 3655).

* This structure is erroneously ascribed by the "Ring Index" (no. 556; p. 99) to what is really the γ -lactone of cyclohexanol-2-acetic acid (von Braun and Münch, *Annalen*, 1928, **465**, 61).

The substance (XVII) was acidic ($pK_a \sim 12.5$) and dissolved readily in aqueous alkali, being reprecipitated unchanged by carbon dioxide; in these respects its behaviour was reminiscent of that of coumaranone (cf. Friedlaender and Neudörfer, *Ber.*, 1897, **30**, 1081) but its reducing action on Fehling's solution and ammoniacal silver nitrate appeared to be much weaker. In an attempt to prepare the parent compound, oxetan-3-one (XXIV), chloroacetyl chloride was treated with diazomethane and the crude chloroacetyldiazomethane was hydrolysed with aqueous methanolic potassium carbonate. Reaction with acetic acid and fractionation then afforded ketonic material distilling below the b. p. of acetic acid and giving a 2 : 4-dinitrophenylhydrazone of the composition expected for that of (XXIV).

We are indebted to our colleague Dr. D. A. Long for his kindness in examining (VII) and (XV; $R = R' = H$) for any effect on the sensitivity of tuberculin-sensitized guinea pigs to tuberculin of the type shown by cortisone and A.C.T.H. (Long and Miles, *Lancet*, 1950, **I**, 492); neither substance had any action.

EXPERIMENTAL.

1 : 3-Diacetoxy-1-phenylacetone (VII).—(a) *Action of acetic acid on O-acetylmandelyldiazomethane.* O-Acetylmandelyl chloride (*Org. Synth.*, **4**, 1) (10 g.) in dry ether (40 c.c.) was added to a solution (dried for 3 hours over potassium hydroxide pellets) of diazomethane (4.2 g.) in dry ether (380 c.c.). Next morning part of the ether was removed to demonstrate the presence of excess of diazomethane. After the addition of glacial acetic acid (25 c.c.) the remainder of the ether was removed and the residual orange liquid was heated on the boiling water-bath for $1\frac{1}{2}$ hours. The mixture was then treated with aqueous sodium hydrogen carbonate to pH 8, and the product was recovered in ether as a brown syrup (11.6 g.). Fractionation afforded a yellow fore-running, presumably containing 1-phenylpropane-1 : 2-dione, followed by a viscous, slightly yellow syrup (8.1 g.), b.p. (mainly) $140\text{--}148^\circ/1$ mm. Fractionation yielded (i) a liquid, probably O-acetylmandelaldehyde (VIII), b. p. $95^\circ/0.6$ mm., n_D^{18} 1.5345 (Found: C, 67.6; H, 5.5; OAc, 26.3. $C_{10}H_{10}O_3$ requires C, 67.5; H, 5.6; OAc, 24.2%), and (ii) 1 : 3-diacetoxy-1-phenylacetone as a colourless liquid (3.2 g.), b. p. $110^\circ/0.04$ mm., n_D^{21} 1.5085 (Found: C, 62.8; H, 5.8; OAc, 37.0. $C_{13}H_{14}O_5$ requires C, 62.4; H, 5.6; OAc, 34.4%).

The acetyl determinations were carried out in the apparatus described by Clark (*Ind. Eng. Chem., Anal.*, 1936, **8**, 487), and occasional somewhat high values found are attributable to the production, besides acetic acid, of traces of acidic by-products appreciably volatile in steam; in the above cases the formation of traces of benzoic acid is probable.

(b) *Reaction between α -acetoxybenzyl chloromethyl ketone (V) and sodium acetate.* Anhydrous sodium acetate (15 g.) was heated under reflux for an hour with acetic anhydride (30 c.c.) and acetic acid (100 c.c.). After cooling, α -acetoxybenzyl chloromethyl ketone (Bradley and Eaton, *loc. cit.*) (18.2 g.) was added, and the mixture was heated on the water-bath for 3 hours, sodium chloride being precipitated. The solvent was removed as far as possible in a vacuum and the residue was distributed between ether and water. Fractionation of the dried ethereal extract afforded (a) a yellow fore-running (2 g.), (b) a nearly colourless fraction (8 g.), b. p. $83^\circ/0.1$ mm., n_D^{20} 1.5339, corresponding with fraction (i) of the previous experiment, (c) an intermediate fraction (3 g.), and (d) 1 : 3-diacetoxy-1-phenylacetone (2 g.) as a viscous colourless syrup, apparently stable indefinitely at room temperature, b.p. $105\text{--}110^\circ/0.03$ mm., n_D^{20} 1.5151 (Found: C, 62.2; H, 5.6; OAc, 34.9%).

Fraction (a) was distributed between ether and aqueous sodium hydrogen carbonate solution, the latter yielding benzoic acid on acidification. The ethereal solution yielded 1-phenylpropane-1 : 2-dione (0.54 g.) which, on treatment with *o*-phenylenediamine (0.39 g.) in hot acetic acid (5 c.c.), afforded 2-methyl-3-phenylquinoxaline (0.6 g.), m. p. $56\text{--}59^\circ$, after distillation at $120\text{--}130^\circ/0.002$ mm. and recrystallisation from light petroleum (lit., m. p. $57\text{--}58^\circ$) (Found: N, 13.1. Calc. for $C_{15}H_{12}N_2$: N, 12.7%).

Immediately after distillation, fraction (b) had an odour of formaldehyde, the presence of which was confirmed by the reddish-brown colour given by the vapours with benzene and concentrated sulphuric acid on a glass rod. The product reduced Fehling's solution and ammoniacal silver nitrate readily in the cold. It gave a gummy semicarbazone. The product obtained from this fraction (0.46 g.) and 2 : 4-dinitrophenylhydrazine (0.35 g.) in cold ethyl alcoholic sulphuric acid contained at least three compounds. After rejection of a sparingly soluble and relatively high-melting substance, fractional crystallisation from alcohol afforded

O-acetylmandelaldehyde 2 : 4-dinitrophenylhydrazone as orange-yellow flattened needles, m. p. 134—136.5° (Found : C, 55.8; H, 3.7; N, 16.4. $C_{16}H_{14}O_6N_4$ requires C, 55.3; H, 4.0; N, 16.1%); successful separation of this material depended on rapid collection of the crystals by centrifugal filtration a few minutes after crystallisation from the hot solution had set in. After evaporation of pooled mother-liquors, crystallisation of the residue from alcohol gave orange-yellow plates, m. p. 179—184°, probably essentially mandelaldehyde 2 : 4-dinitrophenylhydrazone (Found : C, 52.2; H, 3.2; N, 19.0. Calc. for $C_{14}H_{12}O_5N_4$: C, 53.1; H, 3.8; N, 17.7%).

Attempted Alkaline Hydrolysis of O-Acetylmandelyldiazomethane.—The diazoketone (from 12 g. of *O*-acetylmandetyl chloride) was treated with a cold solution of potassium hydroxide (10 g.) in methanol (200 c.c.). The solution rapidly became dark reddish-brown and effervescence took place for about 10 minutes. Slight evolution of heat was controlled by external cooling. After 3 hours, water (200 c.c.) was added and the methanol was removed at 40° under reduced pressure. A small amount of neutral material was extracted with ether. On acidification of the aqueous solution a brown syrup (7 g.) was obtained by extraction with ethyl acetate. Sublimation of part of this product at 120—125°/25 mm. showed it to consist largely of benzoic acid, m. p. and mixed m. p. 123° (Found : C, 68.8; H, 5.3. Calc. for $C_7H_6O_2$: C, 68.8; H, 4.9%); no other identifiable product was isolated.

Methyl O-Benzoyloxyacetylmandelate.—Benzyl chloroformate (*Org. Synth.*, 23, 13) (45 c.c.) was added dropwise during 2 hours to a vigorously stirred mixture of methyl mandelate (32.4 g.) and dry pyridine (25 c.c.), cooled to 0°. Stirring was continued for a further hour. On the following day, the semi-solid orange-brown mixture was treated with 3*N*-hydrochloric acid (125 c.c.) and extracted with ether. The residue after removal of the ether was heated to 165°/0.7—1.0 mm. to remove any benzyl chloride and methyl mandelate. The resulting product was poured into methanol (150—200 c.c.), and the solution was cooled to 0°, whereupon *methyl O-benzoyloxyacetylmandelate* (43.7 g., 75%) crystallised in stout colourless needles, m. p. 48° (Found : C, 67.7; H, 5.4. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%). The yield was reduced to 55% when a greater proportion of pyridine was used and was not improved by carrying out the reaction at -30°.

The acidic washings were basified and exhaustively extracted with ether. The aqueous solution was then acidified with hydrochloric acid and evaporated as far as possible, yielding a syrup. On treatment with mercuric chloride a portion of this syrup afforded 1-benzylpyridinium mercurichloride, which separated from water in colourless plates, m. p. 85—87° after desiccation; Ferns and Lapworth (*J.*, 1912, 101, 283) record m. p. 86—89°. Another portion of the syrup yielded with aqueous sodium picrate an oily picrate, which slowly crystallised; recrystallisation from alcohol gave orange prisms of 1-benzylpyridinium picrate, m. p. 116—118° (Found : C, 54.1; H, 3.2; N, 13.9. $C_{18}H_{14}O_7N_4$ requires C, 54.3; H, 3.5; N, 14.1%).

O-Benzoyloxyacetylmandelic Acid.—A mixture of the above methyl ester (48 g.), acetic acid (192 c.c.), and concentrated hydrochloric acid (16 c.c.) was kept at 37° for 14 hours, during which there was a slight evolution of carbon dioxide without obvious effervescence. The solvent was removed in a vacuum at 40° as far as possible and the residue was treated with excess of dilute aqueous sodium hydrogen carbonate. Extraction with ether afforded essentially unchanged starting material (20 g.). The aqueous phase was acidified to pH 2 and extracted with ether. The residue left on removal of the ether was washed with water to remove traces of mandelic acid and dried, affording pure *O-benzoyloxyacetylmandelic acid* (24 g.; 53%, or 87% on amount hydrolysed), m. p. 123—125° (Found : C, 67.3; H, 5.2. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9%).

The acid is readily soluble in methanol, ethyl acetate, and ether, soluble in benzene, but sparingly soluble in water and ligroin. It is best recrystallised from 50% acetic acid from which it separates in colourless needles.

O-Benzoyloxyacetylmandelyldiazomethane.—The acid chloride, prepared from the foregoing acid (24 g.) and thionyl chloride (60 c.c.) on the water-bath and freed from excess of thionyl chloride in a vacuum at 100°, was dissolved in dry ether (150 c.c.) and added to a solution of diazomethane (from 41 g. of nitrosomethylurea) in dry ether (400 c.c.) with continual shaking. The product crystallised rapidly. Next day the substance (16.5 g., 63%) was collected and washed with ether, only traces remaining in the mother-liquors and washings. Recrystallisation from ethyl acetate or, better, from methanol gave pale yellow prisms of *O-benzoyloxyacetylmandelyldiazomethane*, m. p. 121° (Found : C, 65.6; H, 4.7; N, 9.3. $C_{17}H_{14}O_4N_2$ requires C, 65.8; H, 4.5; N, 9.0%).

3-Acetoxy-1-benzoyloxyacetyl-1-phenylacetone (XII).—A solution of the preceding diazoketone (3.7 g.) in glacial acetic acid (20 c.c.) was heated on the water-bath for 2½ hours. The

excess of acetic acid was removed in a vacuum and crystallisation of the residue from methanol (20 c.c.) afforded colourless prisms of 3-acetoxy-1-benzoyloxy-1-phenylacetone (2.9 g., 71%), m. p. 78.5–80° (Found: C, 66.3; H, 5.2; OAc, 13.4. $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3; OAc, 12.6%).

3-Acetoxy-1-hydroxy-1-phenylacetone Semicarbazone.—The above ketone (1.2 g.) in methanol (25 c.c.) was shaken with palladised charcoal (0.2 g.) in a stream of hydrogen. Evolution of carbon dioxide ceased after 40–45 minutes and the reaction was stopped after 50 minutes. After removal of the catalyst, removal of the solvent in a vacuum at 30–40° left a viscous colourless syrup, which was treated with semicarbazide hydrochloride (0.42 g.) and sodium acetate (0.35 g.) in water with addition of methanol to homogeneity. After being kept overnight the methanol was partly removed and addition of water precipitated 3-acetoxy-1-hydroxy-1-phenylacetone semicarbazone (0.65 g.), which separated from aqueous methanol in colourless elongated prisms, m. p. 133° (Found: C, 54.2; H, 5.7; N, 15.4. $C_{12}H_{15}O_4N_3$ requires C, 54.4; H, 5.8; N, 15.8%).

In further experiments, all attempts to crystallise the parent ketone (XI) failed. It was converted in good yield into 1-phenylpropane-1:2-dione, b. p. 65°/0.3 mm., on attempted distillation in a high vacuum at 100°. The ketone also became bright yellow and acquired the odour of the diketone when kept.

1-Acetoxy-cyclohexanecarbonyl Chloride.—1-Acetoxy-cyclohexanecarboxylic acid (Bucherer and Dahlem, *J. pr. Chem.*, 1934, **140**, 251) (56 g.) was refluxed with thionyl chloride (70 c.c.) on the boiling water-bath for 10 minutes, a reddish-brown colour developing. The excess of thionyl chloride was removed in a vacuum and colourless 1-acetoxy-cyclohexanecarbonyl chloride (49 g., 84%) passed over at 87°/1.4 mm. (Found: C, 52.9; H, 6.4. Calc. for $C_9H_{13}O_3Cl$: C, 52.8; H, 6.4%). Alexander *et al.* (*loc. cit.*) record b. p. 121°/18 mm.

No advantage was gained by the use of pyridine in ether (cf. Carré and Libermann, *Compt. rend.*, 1934, **199**, 1422), and, in the above experiment, the yield was considerably reduced when the time of reflux exceeded 10 minutes.

1-Acetoxyacetylcyclohexyl Acetate (XV; R = R' = Ac).—The above acid chloride (15 g.) in dry ether was added during 5 minutes to a dried ethereal solution of diazomethane (from 41 g. of nitrosomethylurea) in the usual manner. The following day the ether was removed, glacial acetic acid (25 c.c.) was added, and the mixture was heated on the water-bath for an hour. Lest any of the chloromethyl ketone should have been present, heating was continued for 2½ hours after the addition of anhydrous sodium acetate (3 g.). The crude product (17 g.) was isolated by neutralisation with sodium hydrogen carbonate and extraction with ether. A preliminary distillation at 1.2 mm. freed the product from 20–30% of a dark still residue and fractionation of the distillate afforded 1-acetoxyacetylcyclohexyl acetate in good yield as a colourless liquid, b. p. 117.5–119°/0.3 mm., n_D^{20} 1.4710 (Found: C, 59.4; H, 7.8; OAc, 32.8. Calc. for $C_{12}H_{18}O_5$: C, 59.5; H, 7.5; OAc, 35.5%). The low acetyl value may be attributable to some deacetylation by the action of the sodium hydrogen carbonate occurring during working up (cf. following experiment). Alexander *et al.* (*loc. cit.*) record b. p. 165°/18 mm.

1-Hydroxyacetylcyclohexanol (XV; R = R' = H).—Potassium hydrogen carbonate (3.0 g.) was added to 1-acetoxyacetylcyclohexyl acetate (1 g.) in methanol (15 c.c.), and the mixture was left for 48 hours. Addition of water and extraction (thrice) with ether yielded a colourless syrup (0.61 g.) with a slight odour of cyclohexanone. Recrystallisation from benzene afforded colourless prisms (0.51 g., 85%) of 1-hydroxyacetylcyclohexanol, m. p. 87–89.5° (Found: C, 61.3; H, 8.9. Calc. for $C_8H_{14}O_3$: C, 60.8; H, 8.9%). Wagner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1874) record m. p. 86–87°.

The substance rapidly reduced Fehling's solution and ammoniacal silver nitrate in the cold.

Hydrolysis of 1-Acetoxyacetylcyclohexyl Acetate with Sodium Methoxide.—1-Acetoxyacetylcyclohexyl acetate (0.73 g.) was treated with dry methanol (10 c.c.) containing sodium methoxide (from 0.1 g. of sodium). After 24 hours, the orange solution was diluted with water, saturated with carbon dioxide, and extracted with ether. The product (0.26 g.) would not crystallise from benzene, indicating non-identity with the foregoing 1-hydroxyacetylcyclohexanol. The presence of cyclohexanone was established by distillation and preparation of the 2:4-dinitrophenylhydrazone, m. p. and mixed m. p. 162°. Acidification of the alkaline aqueous layer to Congo-red and extraction with ether afforded a gum which subsequently crystallised, the solid being identified as 1-hydroxycyclohexanecarboxylic acid, m. p. and mixed m. p. 107°.

1-Oxaspiro[3:5]nonan-3-one (XVII) and *1-Acetoxyacetylcyclohexanol* (XV; R = H, R' = Ac).—1-Acetoxy-cyclohexanecarbonyl chloride (25 g.) in dry ether was added to a dried solution of diazomethane (11 g.) in dry ether (420 c.c.). After being kept overnight the ether

and excess of diazomethane were removed on a water-bath at 50°. A chilled solution of potassium hydroxide (25 g.) in methanol (500 c.c.) was added to the cooled oily residue, and the solution became orange-coloured immediately. After 6 hours at room temperature, the orange-red solution was diluted with water (350 c.c.), and the methanol was removed in a vacuum at 30°. The filtered solution was exhaustively extracted with ether, and the extract dried (K_2CO_3) and evaporated at $>50^\circ$ on the water-bath, yielding a yellow oil (15 g.). Addition of glacial acetic acid (90 c.c.) produced effervescence and slight evolution of heat. The mixture was heated on the boiling water-bath for 2 hours, cooled, treated with excess of aqueous sodium hydrogen carbonate, and thoroughly extracted with ether. Fractionation of the dried extract yielded (i) 1-oxaspiro[3 : 5]nonan-3-one (XVII) (see below) (8.5 g., 49% based on the acid chloride) having a camphoraceous odour, b. p. 86°/28 mm., n_D^{19} 1.4631, absorption max. in hexane 290 $m\mu$ ($\log \epsilon = 1.4$) (Found : C, 68.5; H, 8.9. $C_8H_{12}O_2$ requires C, 68.6; H, 8.6%), and (ii) 1-acetoxyacetylcyclohexanol (XV; R = H, R' = Ac) as a colourless oil (1.5 g.), b. p. 126—133°/1.5 mm., 118—124°/0.6 mm. (Found : C, 60.3; H, 7.9; OAc, 23.2. Calc. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.0; OAc, 21.5%). Billimoria and Maclagan (*loc. cit.*) record b. p. 90—92°/10⁻⁶ mm., m. p. 42—43°. The semicarbazone crystallised from aqueous alcohol in colourless needles, m. p. 163—168° (Found : C, 51.5; H, 7.3; N, 16.5. Calc. for $C_{11}H_{19}O_4N_3$: C, 51.4; H, 7.4; N, 16.4%). Billimoria and Maclagan (*loc. cit.*) record m. p. 172—173°.

When kept for several months 1-oxaspiro[3 : 5]nonan-3-one gradually deteriorated and quantitative recovery was not possible on redistillation. The substance was sparingly soluble in water but readily soluble in 2N-sodium hydroxide, being reprecipitated therefrom by carbon dioxide. A solution of the substance (3.95 g.) in cold 2N-sodium hydroxide (50 c.c.) was set aside at room temperature for 24 hours. Acidification, extraction with ether, and fractionation afforded unchanged material (3 g.), b. p. 76°/22 mm., n_D^{19} 1.4628, and a brown tarry still residue. Potentiometric titration using a lithium glass electrode indicated a pK_a of ~ 12.5 .

The 2 : 4-dinitrophenylhydrazone crystallised from alcohol in orange needles, m. p. 165—167° (Found : C, 52.9; H, 4.9; N, 17.6. $C_{14}H_{16}O_5N_4$ requires C, 52.5; H, 5.0; N, 17.5%). The semicarbazone separated from alcohol in colourless prisms, m. p. 191—194° (Found : C, 54.9; H, 7.7; N, 21.8. $C_9H_{15}O_2N_3$ requires C, 54.9; H, 7.6; N, 21.3%).

Degradation of 1-Oxaspiro[3 : 5]nonan-3-one.—(a) *Oxidation to adipic acid.* Potassium permanganate (1.69 g.) was added gradually to a solution of the substance (0.50 g.) in water (15 c.c.) containing potassium hydroxide (0.3 g.), addition of the oxidising agent being stopped when the rate of oxidation became slow. Filtration, extraction with ether, acidification with hydrochloric acid, and further extraction with ether yielded adipic acid, m. p. and mixed m. p. 151°. Adipic acid was also isolated in small yield when a cold solution in 2N-sodium hydroxide was treated with 20-vol. hydrogen peroxide solution.

(b) *Oxidation to 1-hydroxycyclohexylglycollic acid* (XXI). Iodine (7.2 g., 4 at.) was added to a solution of the substance (2.0 g.) in water (80 c.c.) containing potassium hydroxide (4 g.), the mixture being shaken until all the iodine dissolved. On the following day, the pale yellow solution was extracted with ether, and then treated with 3N-hydrochloric acid (26 c.c.) and enough sodium metabisulphite to react with the iodine liberated. Extraction with ether gave a greenish-brown gum (0.63 g.), affording a crystalline solid (0.20 g.) on treatment with benzene. Crystallisation from benzene-ethyl acetate yielded colourless prisms, m. p. 117—119°, not depressed on admixture with authentic 1-hydroxycyclohexylglycollic acid (see below) (Found : C, 55.3; H, 8.3. $C_8H_{14}O_4$ requires C, 55.2; H, 8.1%). On treatment of the acid (43.5 mg.) in water (2 c.c.) with 0.5M-periodic acid (0.5 c.c.), the odour of cyclohexanone developed rapidly. Next day the mixture was basified with sodium hydroxide and extracted with aldehyde-free ether. Treatment of the extract with Brady's reagent afforded cyclohexanone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 162° (Found : N, 19.8; Calc. for $C_{12}H_{14}O_4N_4$: N, 20.1%).

(c) *Oxidation to 1-hydroxycyclohexanecarboxylic acid.* A solution of benzenediazonium chloride [from aniline (0.67 g.), 3N-hydrochloric acid (5 c.c.), and sodium nitrite (0.5 g.)] was added to a solution of the substance (0.9 g.) in 2N-sodium hydroxide (15 c.c.) containing added potassium hydroxide (1.5 g.). The solution became dark reddish-brown and a small amount of a dark tar was precipitated. After half an hour, during which some nitrogen was evolved, the acidity was brought to 5N. by the addition of concentrated hydrochloric acid. The mixture was then heated on the water-bath for 3 hours. Extraction with ether yielded an oil (0.5 g.) distilling above 100°/0.002 mm. The distillate was separated into neutral and acidic fractions by partition between ether and dilute aqueous alkali. The acidic fraction, recovered by acidification and extraction with ether, was essentially 1-hydroxycyclohexanecarboxylic acid, the product

obtained by recrystallisation from carbon tetrachloride and then from benzene having m. p. 107°, alone and in admixture with an authentic specimen (Found : C, 58.6; H, 8.3. Calc. for $C_7H_{12}O_3$: C, 58.3; H, 8.3%). A small quantity was converted into the acetyl derivative which showed no depression in m. p. when mixed with an authentic specimen.

1-Bromo-1-dibromoacetylcyclohexane (XXII).—Bromine (38.5 g.) was added gradually in a slow stream of carbon dioxide to warm hexahydroacetophenone (10 g.). After the addition of the bromine the reaction was completed by $\frac{1}{2}$ hour's heating on the water-bath. The tribromo-ketone solidified on cooling. Crystallisation from ligroin, with alumina treatment to remove coloured impurities, afforded colourless needles (20 g.), m. p. 74–76° (Found : C, 27.0; H, 3.1; Br, 66.4. Calc. for $C_6H_{11}OBr_3$: C, 26.5; H, 3.0; Br, 66.2%). Wagner and Moore (*loc. cit.*) record m. p. 72.5–74°.

1-Hydroxycyclohexylglycollic Acid (XXI).—The above tribromo-ketone (2.0 g.) was treated with potassium hydroxide (1.6 g.) in water (10 c.c.) and boiled until dissolution was complete. The solution was then strongly acidified and repeatedly extracted with ether. Removal of the ether from the dried extract yielded 1-hydroxycyclohexylacetic acid (0.21 g.), which separated from benzene in colourless prisms, m. p. 117° (Found : C, 55.5; H, 7.9%).

Oxetan-3-one 2 : 4-Dinitrophenylhydrazone.—Freshly distilled chloroacetyl chloride (5 c.c.), in dry ether, was added slowly to a dried solution of diazomethane (6 g.) in ether (390 c.c.). After being kept overnight, the ether and excess of diazomethane were removed in a vacuum at 50°, and the residue was treated in methanol (20 c.c.) with potassium carbonate (10 g.) and water (8 c.c.). The mixture was stirred from time to time during 4 hours, during which it became dark brown in colour and effervesced continually. The methanol was removed as far as possible in a vacuum at 50° and the residue was extracted twice with ether by stirring and decantation. Evaporation of the ethereal solution afforded a yellowish-brown syrup. This was treated with glacial acetic acid (10 c.c.) and the mixture was warmed under reflux until obvious reaction ceased. Thereafter the mixture was carefully fractionated through a 10-cm. fractionating column. Three fractions (each of 0.5–1 c.c.) were collected while the b. p. rose to that of acetic acid. When tested with 2 : 4-dinitrophenylhydrazine in ethanolic sulphuric acid, the first fraction gave a strongly positive test, the second a weakly positive, and the third a negative test. A control experiment with the acetic acid gave no sign of a ketonic fore-running. The 2 : 4-dinitrophenylhydrazone separated from alcohol in pale orange-coloured flattened needles, m. p. 152–155° (Found : C, 42.7; H, 3.4. $C_9H_8O_5N_4$ requires C, 42.8; H, 3.2%).

A chloride ion determination on the spent potassium carbonate solution showed the presence of 75% of the amount calculated for formation and hydrolysis of chloroacetyldiazomethane.