678. *Simple Analogues of Cortisone. Part I. Some Monocyclic Compounds.*

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1-Acetoxyacetyl*cyclo*hexanol, the parent ketol, and 1-hydroxyacetyl*cyclo*pentanol have been prepared by reaction of 1-hydroxy*cyclo*hexane- and 1-hydroxy*cyclo*pentane-1-carboxylic acid, respectively, with methyl-lithium and subjection of the resulting ketones to halogenation and acetolysis or hydrolysis. Ethyl phenylglyoxylate and ethyl 1-hydroxy*cyclo*hexylchloroacetate were also examined as starting materials for the preparation of 1-hydroxyacetyl*cyclo*hexanol and the corresponding triol but were found unsuitable.

The preparation of simple alicyclic compounds containing the dihydroxy-keto-grouping characteristic of cortisone as in (I) and the corresponding triol (II) was undertaken to see if such compounds possessed useful biological activity.

(I) $HO\cdot X\cdot CO\cdot CH_2\cdot OH$ $HO\cdot X\cdot CH(OH)\cdot CH_2\cdot OH$ (II) (X = alicyclic)

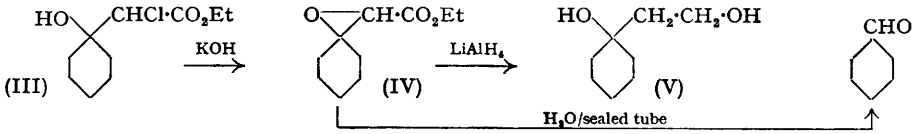
During our present investigations, Wagner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1874) published an account of a preparation of 1-hydroxyacetyl*cyclo*hexanol. Following a totally different route, we have been able to prepare the monoacetate of this compound, the free ketol in higher yields, and also 1-hydroxyacetyl*cyclo*pentanol (cf. Billimoria and Maclagan, *Nature*, 1951, **167**, 81).

In a preliminary attempt to synthesise the triol (II; $X = C_6H_{10}$) the hydrogenation of ethyl phenylglyoxalate was studied. However, a product was obtained which had the composition $C_{10}H_{14}O_3$; lithium aluminium hydride reduction of this yielded a compound $C_8H_{12}O_2$, whereas oxidation with alkaline potassium permanganate gave an unidentified acid, m. p. 136—137°, and further experiments on this line were therefore abandoned.

The chloro-ester (III) (Darzens and Lévy, *Compt. rend.*, 1937, **204**, 272) was converted quantitatively into the epoxide (IV); fission of this which might have furnished a diol ester led, however, to undesirable products. The epoxide (IV) was recovered unchanged on treatment with dilute mineral acids whilst heating it with water at 180° resulted in the isolation of *cyclo*hexanealdehyde.

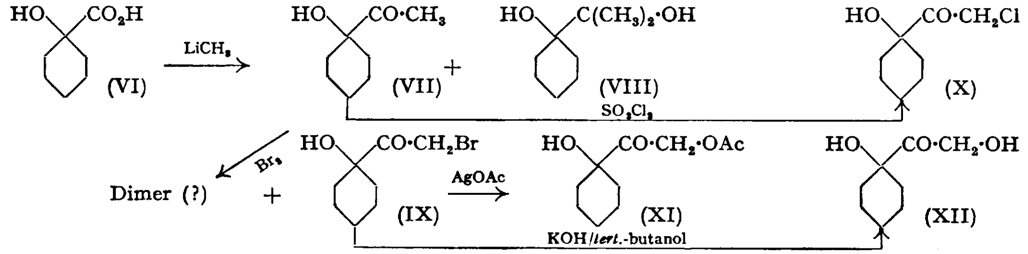
With the object of replacing the halogen atom by an acetoxy-radical, (III) was heated with silver acetate in acetic acid; the unexpected product may be the 1-acetoxy-chloro-ester.

Reduction of (IV) by means of lithium aluminium hydride resulted in the formation of 2-1′-hydroxy*cyclo*hexylethanol (V). The alternative αβ-diol structure was unlikely as the compound did not react with benzaldehyde or acetone. Selective reduction of the ester group in (IV) by use of 0·5 mol. of lithium aluminium hydride gave the same compound and some unchanged epoxide.



Ultimately, 1-hydroxy*cyclo*hexane-1-carboxylic acid (VI) proved to be a more useful intermediate. The acid when treated with ethereal methyl-lithium gave a mixture of acetyl*cyclo*hexanol (VII), and 2-1′-hydroxy*cyclo*hexylpropan-2-ol (VIII); under selected experimental conditions, the formation of the alcohol could be almost eliminated and the desired ketone obtained in 73% yield.

Attempts to brominate the hydroxy-ketone (VII) with *N*-bromosuccinimide failed completely and bromine itself ultimately proved satisfactory. Bromination of (VII) in chloroform in the presence of calcium carbonate was slow and incomplete; when bases such as pyridine or sodium acetate were used there was no bromination even at 100°. Rapid absorption of bromine took place, however, at 40° when light petroleum was used as solvent, the product being a readily separable mixture of 1-bromoacetyl-1-hydroxy*cyclo*hexanol (characterised as a crystalline pyridine adduct) (IX) and a dimer, m. p. 117—118°; the latter was resistant to boiling alcoholic potassium hydroxide and boiling dimethylaniline. Acid catalysts had a marked effect in promoting the bromination and in minimising the formation of the dimeric product.



The reaction of the ketone (VII) with one equivalent of sulphuryl chloride in light petroleum at 40° afforded the crystalline 1-chloroacetyl*cyclo*hexanol (X). Attempts to increase the yield by using an excess of sulphuryl chloride led only to the formation of complex mixtures.

The bromide (IX) when treated with silver acetate in acetic acid gave 1-acetoxyacetyl*cyclo*hexanol (XI). The hydrolysis of the bromide (IX) to the free ketol (XII) presented considerable difficulties; the most efficacious procedure (*ca.* 50% yield) was the gradual addition of potassium hydroxide solution to the aqueous phase of a solution in *tert.*-butanol in the presence of a saturated solution of sodium chloride.

Direct oxidative acetolysis of the ketone (VII) with mercuric acetate (Treibs, *Naturwiss.*, 1948, **35**, 125) led to an intractable mixture from which none of the ketol acetate (XI) could be isolated. Again, an attempted oxidation of the ketone (VII) with selenium dioxide in dioxan gave none of the expected keto-aldehyde.

A similar series of reactions was also carried out with 1-hydroxy*cyclo*pentane-1-carboxylic acid. Bromination of 1-acetyl*cyclo*pentanol and subsequent hydrolysis afforded the 1-hydroxyacetyl compound which in our hands was an undistillable liquid. It was characterised as a semicarbazone; regeneration from the derivative again yielded a liquid which readily reduced ammoniacal silver nitrate and alkaline copper sulphate. Since our earlier communication (*loc. cit.*) Cocker, Cocker, and Lipman (*Chem. and Ind.*, 1951, 112) have described this compound as a solid, m. p. 109°.

A number of these compounds and their homologues (details of which will be published shortly) are being subjected to biological tests, the results of which will be reported elsewhere.

EXPERIMENTAL.

All m.p.s are uncorrected; the micro-analyses have been carried out by Dr. Sobotka, University of Graz, and in the Micro-analytical Laboratory, Organic Chemistry Department, Imperial College of Science and Technology (Mr. F. H. Oliver).

Hydrogenation of Ethyl Phenylglyoxalate.—The ester (72 g.) in acetic acid (200 c.c.) was hydrogenated at 70°/50 atmos. in the presence of the Adams's platinum catalyst (1 g.). Approximately two mols. of hydrogen were taken up (theory : 3 mols.). Raising the temperature to 125° and continuing the experiment for 5 hours did not result in further hydrogen uptake. The product was ether extracted, and the residual oil distilled through a 6″ column packed with helices; the bulk distilled at 101—102°/1 mm. On redistillation the *substance* (55 g.) had b. p. 84—85°/2 × 10^{-3} mm. (bath temp. 115—120°) (Found : C, 65·8, 65·4; H, 7·7, 7·8%; *M*, 199. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%; *M*, 182). It did not decolourise bromine in chloroform but evolved hydrogen bromide on being heated. Neutral aqueous potassium permanganate was decolourised only very slowly and no keto-derivative was obtained.

Reduction of the Compound $C_{10}H_{14}O_3$.—The compound (7 g.) was dissolved in ether (100 c.c.) and, with stirring, lithium aluminium hydride (2·5 g.) was added in small portions during 0·75 hour; the mixture was then stirred at room temperature for 1 hour, acidified with hydrochloric acid (crushed ice), and extracted with ether. A *substance* (3 g.), b. p. 93—95°/7 × 10^{-3} mm., was obtained as a viscous oil which, on trituration with light petroleum (40—60°), gave a crystalline solid. Recrystallisation of this from benzene–light petroleum gave needles, m. p. 80° (Found : C, 68·2; H, 8·9. $C_8H_{12}O_2$ requires C, 68·57; H, 8·6%).

Oxidation of the Compound $C_{10}H_{14}O_3$.—The compound (4 g.), suspended in 5% aqueous sodium hydroxide, was treated dropwise at 70° with aqueous potassium permanganate (6 g.), and the reaction completed on the steam-bath for 15 minutes. The solution was filtered, cooled to 0°, and just acidified with aqueous sulphuric acid. The oil obtained by ether extraction crystallised on trituration with light petroleum. Recrystallisation from light petroleum (b. p. 100—120°) gave plates of an acid, m. p. 136—137° (Found : C, 60·5; H, 8·5%).

*Ethyl 1-Hydroxy*cyclo*hexylchloroacetate.*—This was prepared by Darzens and Lévy's method (*Compt. rend.*, 1937, **204**, 272) [the magnesium amalgam was prepared from magnesium (25 g.) and mercury (1200 g.) in a high vacuum instead of in hydrogen]. The ester (150 g.; from 100 g. of *cyclo*hexanone) had b. p. 88—90°/2 × 10^{-3} mm. (bath temp. 125—130°), n_D^{27} 1·4755 (Found : C, 54·25; H, 7·85; Cl, 16·1. Calc. for $C_{10}H_{17}O_3Cl$: C, 54·55; H, 7·7; Cl, 16·1%). Darzens and Lévy (*loc. cit.*) give b. p. 136—138/4 mm.

Reaction of the Above Chloro-ester with Potassium Hydroxide. Ethyl α : *1-Epoxy*cyclo*hexylacetate.*—(*a*) The ester (20 g.) in dry ethanol (150 c.c.) was cooled to 0° and potassium hydroxide (5 g.) in dry ethanol (150 c.c.) was added dropwise with stirring until the solution was just alkaline (phenolphthalein). After concentration and repeated removal of the potassium chloride, distillation gave ethyl α : 1-epoxy*cyclo*hexylacetate (14·5 g.), b. p. 72°/4 × 10^{-3} mm., $n_D^{27.5}$ 1·4610.

(*b*) The chloro-ester in aqueous ethanol was titrated against 2N-potassium hydroxide (phenolphthalein). On working up of the product the epoxide was again obtained; the b. p. and $n_D^{27.5}$ were identical with those of the previous sample (Found : C, 65·1; H, 9·0. Calc. for $C_{10}H_{16}O_3$: C, 65·2; H, 8·8%).

Reaction of the Chloro-ester with Silver Acetate.—Ethyl 1-hydroxy*cyclo*hexylchloroacetate (15 g.) was heated under reflux with acetic acid (150 c.c.) and silver acetate (15 g.) for 4 hours. On distillation of the product, a colourless liquid (13 g.), b. p. 78°/10^{-6} mm., was obtained (Found : C, 55·3; H, 7·8; Cl, 13·2. $C_{12}H_{19}O_4Cl$ requires C, 55·0; H, 7·3; Cl, 13·5%). This is believed to be *ethyl 1-acetoxy*cyclo*hexylchloroacetate.*

Reactions of the Epoxide.—(*a*) The epoxide (10 g.) was heated with water at 180° for 12 hours. A considerable pressure of carbon dioxide developed; the product was extracted with ether, the extract washed with sodium hydrogen carbonate, and the solvent evaporated, and the residual oil distilled, giving *cyclo*hexanealdehyde (b. p. 157—158°) (Zelinsky and Gutt, *Ber.*, 1907, **40**, 3051, give b. p. 159—160°). The semicarbazone, m. p. 174—176° (*idem, ibid.*, m. p. 173—174°), separated from aqueous pyridine.

(*b*) The epoxide was recovered unchanged when a suspension in 2N-sulphuric acid was heated for 15 minutes at 100° with stiring.

(*c*) *Reduction of the epoxide. 2-1′-Hydroxy*cyclo*hexylethanol.* The epoxide (10 g.) was added dropwise to a solution of lithium aluminium hydride (5 g.) in absolute ether (500 c.c.) at 0°; after complete addition (1 hour) stirring was continued for 2 hours at 0° and overnight at room temperature. The mixture was decomposed with 2N-sulphuric acid (crushed ice), and the ether layer was separated and the aqueous layer extracted with chloroform (3 × 100 c.c.). The extracts were combined, washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and the solvents removed, giving *2′-1′-hydroxy*cyclo*hexylethanol* (6·4 g.), b. p. 95°/4 × 10^{-3} mm., n_D^{25} 1·4870 (Found : C, 66·6; H, 11·2. $C_8H_{16}O_2$ requires C, 66·7; H, 11·15%).

cyclo*Hexanone Cyanohydrin.*—*cyclo*Hexanone (1000 g.) was dissolved in ether (2·5 l.), and finely powdered sodium cyanide (735 g.) added. With vigorous stirring and cooling to −15°, concentrated hydrochloric acid (1500 c.c.) was added dropwise; thereafter the temperature was kept below 0° for 6 hours. The cyanohydrin was extracted into ether, and the solution washed with saturated sodium hydrogen sulphite solution followed by aqueous sodium hydrogen carbonate and dried (Na_2CO_3), and the cyanohydrin distilled slowly (wide-bore retort), b. p. 63°/10^{-6} mm. (bath temp. 75°). When the washings were omitted or distillation was at higher pressure, decomposition occurred. The liquid

(900 g.) crystallised on cooling; recrystallisation from light petroleum gave pure *cyclo*hexanone cyanohydrin, m. p. 27—28° (Found : C, 67·1; H, 8·8; N, 11·0. Calc. for $C_7H_{11}ON$: C, 67·2; H, 8·8; N, 11·2%).

1-*Hydroxy*cyclo*hexane*-1-*carboxylic Acid*.—This was obtained by the smooth hydrolysis of the nitrile (900 g.) with concentrated hydrochloric acid (1500 c.c.) on the steam-bath for 6 hours. The acid formed needles, m. p. 110°, from benzene–light petroleum (Found : C, 58·7; H, 8·3. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·3%), and was characterised as the 3 : 5-*dinitrobenzoate*, m. p. 165—168°, needles from ethanol (Found : C, 49·6; H, 3·9. $C_{14}H_{14}O_8N_2$ requires C, 49·7; H, 4·1%).

Reactions of the Acid with Methyl-lithium. 1-*Acetyl*cyclo*hexanol and* 2-1′-*Hydroxy*cyclo*hexylpropan*-2-*ol*.—(*a*) The acid (47 g.) in ether (1000 c.c.) was added dropwise to a solution of methyl-lithium (from 20 g. of lithium) during 3 hours, and the mixture was then stirred overnight at room temperature. The mixture was poured on crushed ice (1000 g.) and concentrated hydrochloric acid (300 c.c.), the ether layer was separated, and the aqueous layer extracted with ether (6 × 500 c.c.). After evaporation of the ether, the residual oil was fractionated; two fractions were obtained : (1) 26 g., b. p. 42—50°/10^{-6} mm.; and (2) 10 g., b. p. 60—90°/10^{-6} mm. Redistillation of (1) gave 1-acetyl*cyclo*hexanol (22 g.), b. p. 46°/10^{-6} mm. (bath temp. 60°), b. p. 57°/10^{-5} mm. (bath temp. 98°), $n_D^{24.5}$ 1·4672 (Found : C, 67·4; H, 9·9. Calc. for $C_8H_{14}O_2$: C, 67·7; H, 9·9%).

Fraction (2) on trituration with light petroleum (40—60°) deposited a solid (8 g.), which when recrystallised from light petroleum (b. p. 100—120°) yielded 2-1′-*hydroxy*cyclo*hexylpropan*-2-*ol* as needles, m. p. 87° (Found : C, 67·9; H, 11·4. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%).

(*b*) In a similar experiment, in which the mixture obtained on the addition of the organic acid to the methyl-lithium solution was allowed to warm and was then heated under reflux for 1 hour, only small quantities of the ketone (4 g.) and the carbinol (10 g.) were obtained.

(*c*) Lithium metal (50 g.) in short lengths of 1-mm. ribbon was introduced into anhydrous ether (2000 c.c.) in an atmosphere of nitrogen. Methyl iodide (507 g.) in absolute ether (1000 c.c.) was added dropwise with stirring during 2 hours (carbon dioxide–acetone cooled condensers). By titration of an aliquot portion of the ethereal methyl-lithium against standard acid the metal content was found to be 40 g. 1-Hydroxy*cyclo*hexane-1-carboxylic acid (144 g.) in ether (1500 c.c.), externally cooled to 15°, was vigorously stirred and the methyl-lithium solution added dropwise (nitrogen atmosphere) until two moles had been added (3 hours). The rest of the methyl-lithium solution was run in during 0·5 hour. When the solution was worked up in the usual manner, without acidification, an oil (128 g.) was obtained, which on distillation gave 1-acetyl*cyclo*hexanol (100 g.), together with a negligible quantity of the carbinol.

Derivatives of 1-*Acetyl*cyclo*hexanol*.—The *semicarbazone* was prepared in aqueous pyridine and recrystallised from aqueous ethanol; it had m. p. 221—222° (Found : C, 54·7; H, 8·9; N, 21·2. $C_9H_{17}O_2N_3$ requires C, 54·3; H, 8·5; N, 21·1%). The *phenylhydrazone* was prepared in ether and crystallised from light petroleum (b. p. 80—100°) forming needles, m. p. 163° (decomp.) (Found : C, 72·5; H, 8·9. $C_{14}H_{20}ON_2$ requires C, 72·5; H, 8·6%). The 2 : 4-*dinitrophenylhydrazone* separated from ethanol in orange needles, m. p. 206° (decomp.) (Found : N, 16·9. $C_{14}H_{18}O_5N_4$ requires N, 17·3%).

1-*Acetyl*cyclo*hexyl benzoate*. 1-Acetyl*cyclo*hexanol (5·7 g.) was dissolved in dry pyridine (10 c.c.) and, with cooling to 0°, benzoyl chloride (5·6 g.) was added. After the reaction mixture had been heated for 2 hours at 120° and worked up in the usual manner, 1-*acetyl*cyclo*hexyl benzoate* was obtained as a viscous liquid, b. p. 124—125°/10^{-6} mm. (Found : C, 73·45; H, 7·3. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%).

Bromination of 1-*Acetyl*cyclo*hexanol*. 1-*Bromoacetyl*cyclo*hexanol*.—(*a*) The hydroxy-ketone (21·6 g.) in dry petroleum (100 c.c.; b. p. 40—43°) was treated dropwise with stirring under reflux (nitrogen atmosphere) with bromine (24 g.; during 2·5 hours). The light petroleum and residual hydrogen bromide were removed in vacuum and the viscous pale yellow liquid triturated with aqueous ethanol (60% by vol.; 100 c.c.) and cooled to −5°. After 0·5 hour the crystalline material (15 g.; m. p. 103—106°) was filtered off. The filtrate was evaporated *in vacuo* (without being heated), the residual oil taken up in a little ether, the solution dried (Na_2SO_4), the solvent removed, and the residue distilled in high vacuum; 1-*bromoacetyl*cyclo*hexanol* (14 g.) was obtained as a pale yellow liquid, b. p. 122—125°/10^{-5} mm. The bromide contained some unreacted ketone which could not be removed by fractionation. The impure bromide (2·2 g.) was therefore warmed at 60° with pyridine (1 g.) for 5 minutes and set aside at 0° for several hours. The crystalline adduct was dissolved in methanol and precipitated with ether. Recrystallisation from methanol–ether yielded the *pyridine adduct*, m. p. 148°, as needles (Found : C, 49·6; H, 6·4; N, 4·2; Br, 24·5. $C_8H_{13}O_2Br,C_5H_5N,CH_4O$ requires C, 50·5; H, 6·4; N, 4·2; Br. 24·2%).

The crystalline by-product (m. p. 103—106°) after repeated crystallisation from ethanol yielded needles, m. p. 117—118°, of a *dimer* (Found : C, 45·4; H, 5·8; Br, 36·4%; *M*, 397. $C_{16}H_{26}O_4Br_2$ requires C, 43·4; H, 5·8; Br, 36·2%; *M*, 442).

(*b*) 1-Acetyl*cyclo*hexanol (198·8 g.) was dissolved in acetic acid (198 c.c.) and bromine (74·2 c.c.) in acetic acid (1388 c.c.) was added at room temperature all in one lot. A 50% solution of hydrogen bromide in acetic acid (5 c.c.) was then added and the mixture agitated at short intervals; after 30 minutes all the bromine had reacted. The solution was diluted with ether (1000 c.c.) and poured on crushed ice (2000 g.); most of the acetic acid was neutralised with concentrated aqueous sodium hydroxide at 0°, and the solution was then carefully neutralised with aqueous sodium carbonate and thoroughly extracted into ether (8 × 500 c.c.). The ether extract was dried (Na_2SO_4) and distilled, yielding pure 1-bromoacetyl*cyclo*hexanol (207 g.) as a viscous liquid, b. p. 70°/10^{-6} mm. (bath temp. 100°). The compound rapidly coloured in the atmosphere (Found : C, 42·4; H, 5·6; Br, 35·3. $C_8H_{13}O_2Br$ requires C, 43·3; H, 5·9; Br, 36·2%). It afforded the pyridine adduct described above.

A higher-boiling fraction, b. p. 140° (bath temp. 180°), was obtained as a viscous pale yellow oil (33 g.) which solidified when seeded with a crystal of the dimer (described above), and afforded needles (from ethanol), m. p. 117—118°. This dimer was unchanged when heated under reflux for several hours with 30% alcoholic potassium hydroxide or with dimethylaniline.

1-*Chloroacetyl*cyclo*hexanol*.—1-Acetyl*cyclo*hexanol (14·2 g.) in light petroleum (50 c.c.; b. p. 40—43°) was heated under reflux in an atmosphere of nitrogen and, with stirring, sulphuryl chloride (13·5 g.) was added dropwise during 0·5 hour. The solution was then heated under reflux for a further 0·5 hour. After distillation of the solvent, the residual oil was fractionated under reduced pressure giving the unchanged ketone (7 g.), b. p. 45—80°/10^{-5} mm. (bath temp. 90—100°), and 1-*chloroacetyl*cyclo*hexanol* (6 g.), b. p. 80—90°/10^{-5} mm. (bath temp. 100—110°); on redistillation the latter had b. p. 88°/10^{-5} mm. (bath temp. 110°), m. p. 69—70° (needles from aqueous ethanol) (Found: C, 54·5; H, 7·8; Cl, 19·8. $C_8H_{13}O_2Cl$ requires C, 54·4; H, 7·4; Cl, 20·1%).

Acetolysis of 1-*Bromoacetyl*cyclo*hexanol*. 1-*Acetoxyacetyl*cyclo*hexanol*.—The bromide (12 g.) in 50% aqueous acetic acid (500 c.c.) was heated under reflux with silver acetate (20 g.) for 1 hour, and the solution then stirred at 80° for 2 hours. After filtration and evaporation to a small bulk (60 c.c.) the filtrate was again refluxed with silver acetate (5 g.) for 1 hour. The acetic acid was neutralised and the solution ether-extracted; distillation yielded a product, b. p. 90°/3 × 10^{-5} mm., which solidified on cooling; crystallisation from light petroleum afforded 1-*acetoxyacetyl*cyclo*hexanol* (4 g.) as rods, m. p. 42—43° (Found: C, 60·25; H, 8·24. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%).

The same compound could be obtained in lesser yields by the acetolysis of the bromide in glacial acetic acid, fused sodium or potassium acetate being used instead of silver acetate.

The ketol acetate (0·5 g.), aqueous pyridine (5 c.c.), and semicarbazide hydrochloride (1 g.) at 0° overnight slowly deposited the *semicarbazone* (0·3 g.), which recrystallised from hot water in long needles, m. p. 171—172° (Found: C, 51·05; H, 7·65; N, 16·5. $C_{11}H_{19}O_4N_3$ requires C, 51·35; H, 7·4; N, 16·35%).

1-*Hydroxyacetyl*cyclo*hexanol*.—(*a*) The bromide (100 g.) in 60% aqueous ethanol, was rapidly treated under nitrogen with sodium hydroxide (18·5 g.) dissolved in 60% aqueous ethanol (500 c.c.). After 5 minutes the excess of alkali was neutralised with aqueous acetic acid (phenolphthalein), and the solution then concentrated in a vacuum (bath temp. 40°) to 100 c.c. By ether extraction of this concentrate an oil which solidified was obtained; when crystallised from ether–light petroleum this gave needles (29 g.), m. p. 86—87°. Although the alcohol could not be distilled without decomposition it readily sublimed in a high vacuum, giving needles, m. p. 89—90° (Wagner and Moore, *loc. cit.*, give 86—87°) (Found: C, 61·0; H, 8·9. Calc. for $C_8H_{14}O_3$: C, 60·8; H, 8·9%).

(*b*) The bromide (100 g.) was dissolved in *tert.*-butanol (200 c.c.), and a saturated aqueous solution of sodium chloride (250 c.c.) added. With vigorous shaking, potassium hydroxide (20·8 g.) in water (250 c.c.) was added in ten portions during 15 minutes, allowing neutralisation of each portion (phenolphthalein). After complete addition the mixture was just acidified with aqueous sulphuric acid and the aqueous layer saturated with sodium chloride. The *tert.*-butanol layer was separated and the aqueous layer thoroughly extracted with chloroform (5 × 100 c.c.). The extracts were dried (Na_2SO_4) and the solvents distilled off; an almost colourless liquid remained which solidified on cooling. 1-Hydroxyacetyl*cyclo*hexanol (38 g.), m. p. 88—89°, was obtained after a single crystallisation from ether–light petroleum (b. p. 40—60°).

1-*Acetyl*cyclo*pentanol*.—*cyclo*Pentanone cyanohydrin was obtained as described for the hexanone cyanohydrin, but unlike the latter it could not be distilled without decomposition even in a high vacuum. The crude cyanohydrin (500 g.) was readily hydrolysed by hydrochloric acid (1000 c.c.) to yield needles (from benzene–light petroleum) of 1-hydroxy*cyclo*pentane-1-carboxylic acid (325 g.), m. p. 103—105° (Wislicenus and Gastner, *Annalen*, 1893, **257**, 333, give m. p. 103°).

The acid (153 g.) was treated with an ethereal solution of methyl-lithium (lithium content, 51 g.). After the mixture had been stirred overnight and the lithium complex decomposed with water, the solution was constantly extracted with ether (24 hours). 1-*Acetyl*cyclo*pentanol* (81·6 g.) had b. p. 72°/10 mm. (bath temp. 135—140°), n_D^{19} 1·4650 (Found: C, 65·8; H, 9·3. $C_7H_{12}O_2$ requires C, 65·6; H, 9·3%). The *semicarbazone* separated slowly from aqueous pyridine, forming needles (from ethanol), m. p. 206—208° (decomp.) (Found: C, 52·4; H, 8·1; N, 23·1. $C_8H_{15}O_2N_3$ requires C, 51·9; H, 8·1; N, 22·7%).

1-*Acetyl*cyclo*pentyl Acetate*.—The ketone (11·5 g.) was dissolved in pyridine (15 c.c.), acetic anhydride (15 c.c.) added at 0°, and the mixture refluxed for 2 hours. The *acetate* (10 g.) had b. p. 100—103°/10 mm. (Found: C, 63·7; H, 8·6. $C_9H_{14}O_3$ requires C, 63·5; H, 8·2%).

Bromination of the Ketone. 1-*Bromoacetyl*cyclo*pentanol*.—1-Acetyl*cyclo*pentanol (5·8 g.) was dissolved in acetic acid (10 c.c.), and bromine (2·5 c.c.) in acetic acid (100 c.c.) added in one lot, followed by a 50% solution of hydrogen bromide in acetic acid (0·5 c.c.). After 15 minutes decolorisation of the bromine occurred, and the solution was worked up in the usual manner. Distillation yielded 1-*bromoacetyl*cyclo*pentanol* (7·2 g.), b. p. 85—95°/10^{-6} mm. (slight decomposition during distillation) (Found: Br, 38·1. $C_7H_{11}O_2Br$ requires Br, 38·6%).

Hydrolysis of the Bromide.—The bromide (7·2 g.) in 60% aqueous ethanol (60 c.c.) was treated in the usual manner with sodium hydroxide (1·35 g.) in 60% aqueous ethanol (30 c.c.). The product was isolated as an oil which could not be distilled. It was dissolved in aqueous pyridine (5 c.c.) and treated with semicarbazide hydrochloride (5 g.) in water (5 c.c.); after 24 hours at 0° the crystalline precipitate (2 g.) was collected, and recrystallisation afforded 1-*hydroxyacetyl*cyclo*pentanol semicarbazone* as microneedles, m. p. 211° (decomp.) (Found: C, 47·8; H, 7·2; N, 20·9. $C_8H_{15}O_3N_3$ requires C, 47·8; H, 7·4; N, 20·9%).

The semicarbazone was suspended in light petroleum and stirred at 70° for 0·5 hour with 2N-sulphuric acid (15 c.c.). On evaporation of the petroleum layer a liquid was obtained which reduced ammoniacal silver nitrate solution and alkaline copper sulphate solution. The liquid could not, however, be distilled without decomposition even in a high vacuum.

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