Simple Analogues of Cortisone. Part III. Some Monocyclic Compounds.*

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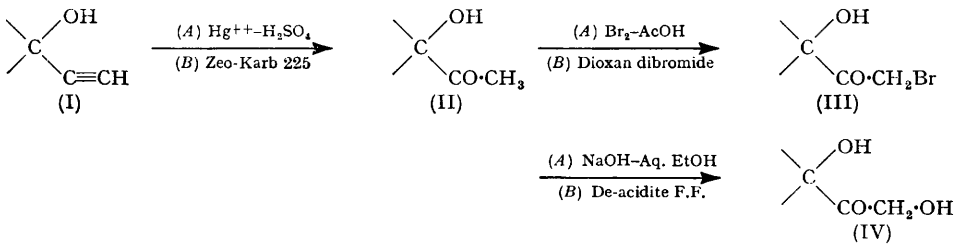
[Reprint Order No. 5274.]

The hydration of some ethynylcarbinols (I) to acetylcarbinols (II) has been catalysed by an acid ion-exchange resin (Zeo-Karb 225) impregnated with mercuric ions. Bromination of (II) with dioxan dibromide has yielded the bromoacetylcarbinols (III). A basic ion-exchange resin (De-acidite F.F.) has been found to hydrolyse the α-keto-bromides (III) very smoothly to the glycolloylcarbinols (IV). Thus, 1-glycolloyl*cyclo*heptanol, 1-glycolloyl-4-methyl*cyclo*hexanol, 1-glycolloyl-3-methyl*cyclo*hexanol and 1-glycolloyl-2 : 2-dimethyl*cyclo*hexanol have been prepared. 1-Glycolloyl*cyclo*heptanol showed slight biological activity in the mouse-liver glycogen test.

In view of a slight but significant biological activity shown by (*sol.*)-1-glycolloyl-2-methyl*cyclo*hexanol * in the liver glycogen test (see below), we have prepared some more simple alicyclic compounds incorporating the dihydroxy-acetone moiety of cortisone.



The general scheme shown above has been used; some of the transformations (I) to (IV) were carried out by previously used reagents (marked *A*) and others by new ones (marked *B*).

Newman (*J. Amer. Chem. Soc.*, 1953, **75**, 4740) hydrated 1-ethynyl*cyclo*hexanol to 1-acetyl*cyclo*hexanol by using the ion-exchange resin Dowex-50 previously impregnated with 1% mercuric sulphate. We have independently found the resin Zeo-Karb 225 (a polystyrenesulphonic acid), impregnated with 1% mercuric ions, very effective in hydrating 1-ethynyl*cyclo*hexanol. With 1-ethynyl-2-methyl*cyclo*hexanol, however, pretreatment of the resin with 20% mercuric sulphate was necessary, and 1-acetyl-2-methyl*cyclo*hexanol was then rapidly obtained in excellent yield. Other ethynyl compounds were equally readily hydrated by use of this resin.

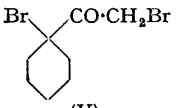
The bromination of acetylcarbinols (II) (Part I, *J.*, 1951, 3067), previously regarded as an acid-catalysed reaction, has now been carried out by treating their ethereal solutions with an equivalent of dioxan dibromide (Yanosskaya, Terent'ev, and Belen'kii, *Zhur. Obshchey Khim.*, 1952, **22**, 1594; *Chem. Abs.*, 1953, **47**, 8032) and irradiating the mixture with strong visible light. Anhydrous conditions were maintained by preparing the dioxan dibromide in light petroleum.

Wagner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1874) hydrolysed the dibromide (V) with aqueous potassium carbonate and found that, although a large portion was rearranged to the acid (VI), about 20% was converted into the required ketol (VII; R = H).

Similar treatment of (*sol.*)-1-bromoacetyl-2-methyl*cyclo*hexanol (VIII) failed, the unchanged bromide being recovered as a pyridinium adduct. The hydrolyses of such α-keto-bromides, a major obstacle in our route for the introduction of the keto-alcohol side-chain into simple compounds, has now been overcome by the use of the basic ion-exchange resin De-acidite F.F. Thus, the bromide (VIII), treated in hot methanol with De-acidite F.F., gave the keto-alcohol (VII; R = Me) in high yield.

* Part II, *J.*, 1953, 2626.

1-Ethynyl*cyclo*heptanol was hydrated with aqueous sulphuric acid–mercuric sulphate, or by the ion-exchange process, to 1-acetyl*cyclo*heptanol in 60% and 85% yields, respectively. Conversion into 1-bromoacetyl*cyclo*heptanol followed by hydrolysis yielded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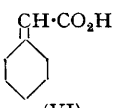
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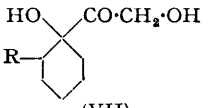
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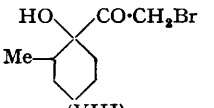
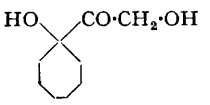

(VIII)

1-glycolloyl*cyclo*heptanol (IX). The latter readily reduced alkaline copper sulphate and furnished a semicarbazone.

1-Ethynyl-4-methyl*cyclo*hexanol formed an unstable mercury complex during the sulphuric acid hydration, but was smoothly converted into 1-acetyl-4-methyl*cyclo*hexanol by the ion-exchange process. This ketone when irradiated in ether in the presence of dioxan dibromide gave 1-bromoacetyl-4-methyl*cyclo*hexanol which when refluxed with aqueous methanol and De-acidite F.F. yielded 1-glycolloyl-4-methyl*cyclo*hexanol (X; $R^1 = R^2 = R^3 = H$, $R^4 = Me$).

Similarly, 1-ethynyl-3-methyl*cyclo*hexanol gave a liquid 1-glycolloyl-3-methyl*cyclo*hexanol (X; $R^1 = R^2 = R^4 = H$, $R^3 = Me$).

Crude 2 : 2-dimethyl*cyclo*hexanone was purified through its semicarbazone (Adamson, Marlow, and Simonsen, *J.*, 1938, 774). The derived 1-acetyl-2 : 2-dimethyl*cyclo*hexanol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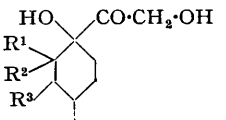
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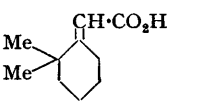
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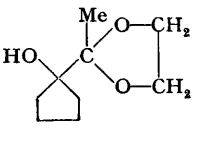
(XII)

furnished a crystalline 1-bromoacetyl-2 : 2-dimethyl*cyclo*hexanol, which on hydrolysis with aqueous ethanolic sodium hydroxide, followed by chromatography (alumina), gave only a trace of a keto-alcohol. This gave analytical data agreeing with formulation as 1-glycolloyl-2 : 2-dimethyl*cyclo*hexanol (X; $R^1 = R^2 = Me$, $R^3 = R^4 = H$) and reduced alkaline copper sulphate, but the quantity was insufficient for characterisation. An acid, probably the rearranged acid [XI (?), cf. Wagner and Moore, *loc. cit.*], was also isolated from the hydrolysate.

Ethynylation of *cyclo*pentanone with sodium acetylide in liquid ammonia gave poor yields of 1-ethynyl*cyclo*pentanol, due mainly to the formation of *cyclo*pentylidene*cyclo*pentanone. Hydration of the ethynylcarbinol by the sulphuric acid–mercuric sulphate method was unsatisfactory. Better results were obtained when 1-ethynyl*cyclo*pentanol and ethylene glycol reacted in the presence of a boron trifluoride–ether complex–mercuric oxide catalyst. The ketal (XII) was thus obtained in 60% yield from which the parent acetyl-carbinol was readily obtained by mild acid hydrolysis. Hydration of the ethynylcarbinol with Zeo-Karb 225–mercuric ion catalyst, however, gave directly 1-acetyl*cyclo*pentanol in 80% yield. Some modifications in the methods of ethynylation of *cyclo*pentanone and the hydration of the acetylenic alcohol with mercuric sulphate, leading to better yields, have been reported since the completion of this work (Stacey and Mikulie, *J. Amer. Chem. Soc.*, 1954, **76**, 525).

Infra-red spectra * of 1-glycolloyl*cyclo*heptanol and 1-glycolloyl-4-methyl*cyclo*hexanol show the following absorption bands (in $cm.^{-1}$; % absorption in parentheses):

	C=O	Ring OH	Ketol-OH
1-Glycolloyl*cyclo*heptanol	1710 (95)	3250 (92)	2900 (85)
1-Glycolloyl-4-methyl*cyclo*hexanol	1710 (65)	3100—3175 (80)	2900 (70)

* These will appear in Sadtler's "Catalogue of Infra-red Spectrograms," Philadelphia. They were determined on a Baird double-beam instrument, that of 1-glycollolyl-4-methyl*cyclo*hexanol as a film from chloroform and that of 1-glycollolyl*cyclo*heptanol in 10% solution in chloroform.

Biological Activity.—Three of the compounds referred to were tested for adrenocortical activity by the mouse-liver glycogen method described below with the following results :

Compound	Dosage, g./kg.	No. of mice	Liver glycogen, mg./100 g. bodyweight, control	test	Significance
1-Glycolloyl*cyclo*heptanol	1	16	12·6 ± 1·4	34·5 ± 5·4	P = 0·001
1-Glycolloyl-2-methyl*cyclo*hexanol	0·7	19	14·4 ± 1·6	22·2 ± 3·0	P = 0·02—0·05
1-Glycolloyl-4-methyl*cyclo*hexanol	1	21	24·9 ± 3·5	17·5 ± 3·0	none

It will be seen that two compounds displayed a small but significant activity at high dosages. Control tests with equivalent doses of dihydroxyacetone gave negative results indicating that this activity was not due to direct conversion of the compounds into carbohydrate.

Experimental

The microanalyses were carried out in the Microanalytical Laboratory, Organic Chemistry Department, Imperial College of Science and Technology (Mr. F. H. Oliver) and by Dr. Sobotka, University of Graz.

Preparation of the Resins.—Zeo-Karb 225–mercuric ion. The damp Zeo-Karb 225 (British Permutit; mesh 200—400; 1000 g.) was suspended in a column (3″ diam.) and washed under suction with hydrochloric acid (4 l.; 10% w./v.) followed by distilled water (8 l.). After being dried in air (2 days), and then in a vacuum at 50°, the resin (200 g.) was vigorously shaken with 2N-aqueous sulphuric acid (2 l.) containing mercuric sulphate (40 g.) for 1 hr. The resin was filtered off and air-dried (2 days) before use.

Regeneration. The spent resin was washed with ether, ethanol, and water and stirred with aqueous nitric acid (25% w./v.) for 2 days. It was then washed with acid and water, dried, and impregnated with mercuric sulphate, as described above.

De-acidite F.F. The damp resin (mesh 200—400; 250 g.) was washed on a column with 2N-aqueous sodium hydroxide (2 l.) and distilled water (4 l.), and vacuum dried at 60° before use. After use it was regenerated with 2N-aqueous sodium hydroxide.

Dioxan Dibromide.—Bromine (320 g.) was added with vigorous hand stirring to dioxan (160 g.; distilled over sodium), and the warm solution (*ca.* 60°) was poured into light petroleum (2 l.; b. p. <40°), precooled to −20°. The yellow precipitate was filtered off under suction and freed from solvent under vacuum as rapidly as possible (there is a considerable loss due to volatility of the dibromide). The compound, m. p. 60—61°, was used without further purification and could be stored at 0°.

1-*Acetyl*cyclo*heptanol.—Method* A. To an aqueous sulphuric acid solution (140 c.c. of acid and 1300 c.c. of water) of mercuric sulphate (52 g.) was added with stirring a solution of 1-ethynyl-*cyclo*heptanol (240 g.) in carbon tetrachloride (500 c.c.), the temperature being maintained below 25°. The white precipitate first formed decomposed to an oil after 2 hours' stirring. The organic layer was separated and the mother liquor extracted with carbon tetrachloride (2 × 250 c.c.). The combined extracts were run into mercuric sulphate (15 g.), sulphuric acid (80 c.c.), and water (625 c.c.) under steam distillation. From the distillate, after extraction (carbon tetrachloride) and distillation, 1-*acetyl*cyclo*heptanol* was obtained (163 g., 60%), b. p. 100—101°/9 mm., n_D^{21} 1·4765 (Found : C, 69·1; H, 10·5. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). The *semicarbazone*, prepared in aqueous pyridine, crystallised from ethanol in needles, m. p. 198° (Found : C, 56·1; H, 8·9; N, 19·4. $C_{10}H_{19}O_2N_3$ requires C, 56·2; H, 8·9; N, 19·7%).

Method B. A solution of ethynyl*cyclo*heptanol (100 g.) in methanol (250 c.c.) and water (70 c.c.) was refluxed with stirring and Zeo-Karb 225–mercuric ion resin (25 g.) added. (After 1 hr. a test portion of filtered reaction mixture gave no precipitation with ammoniacal silver nitrate. A second portion with aqueous silver nitrate was only weakly acid to universal-indicator paper, showing absence of the acetylenic group.) The solution was refluxed for a further 1 hr. Removal of the resin by filtration, evaporation of solvent, and distillation of the residue gave 1-acetyl*cyclo*heptanol (91 g., 80%), n_D^{21} 1·4766 (Found : C, 69·1; H, 10·3%). This gave a semicarbazone, m. p. 198° (undepressed when melted in admixture with the material prepared by method A).

1-*Bromoacetyl*cyclo*heptanol.—Method* A. 1-Acetyl*cyclo*heptanol (100 g.) in acetic acid (100 c.c.) was treated with bromine (34 c.c.) in acetic acid containing hydrogen bromide (0·25 g.). After 6 min., the bromine was decolorised with evolution of hydrogen bromide. The solution

was poured on crushed ice and extracted with ether, and the extract was neutralised ($NaHCO_3$), dried (Na_2SO_4), and distilled, giving 1-*bromoacetyl*cyclo*heptanol* (100 g.), b. p. 75°/10^{-5} mm. (evaporative distillation; bath temp. 100—110°), n_D^{21} 1·5150 (Found: Br, 33·7. $C_9H_{15}O_2Br$ requires Br, 34·0%).

1-*Glycolloyl*cyclo*heptanol*.—*Method* A. 1-Bromoacetyl*cyclo*heptanol (110 g.), dissolved in ethanol (360 c.c.) and water (240 c.c.), was treated with a solution of sodium hydroxide (18·8 g.) in aqueous ethanol (300 c.c.; 60% w./v.) added in portions (25 c.c.) with vigorous shaking. Subsequent additions were made only after each portion of the alkali was neutralised (phenolphthalein). The solution was evaporated in vacuum (50°) and the residual oil was dissolved in ether and dried (Na_2SO_4). The ether was distilled off and the residue crystallised from ether (sodium dried; 70 c.c.) by cooling to −40°. After the crystals (19 g.) had been filtered off, the filtrate on dilution with light petroleum (b. p. <40°) deposited a further crop (2 g.), m. p. 58—59°. Sublimation in high vacuum followed by crystallisation from ether–light petroleum (b. p. 40—60°) yielded 1-*glycolloyl*cyclo*heptanol* (19 g.) as plates, m. p. 62—63° (Found: C, 62·7; H, 9·3. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%).

1-*Ethynyl*-4-*methyl*cyclo*hexanol*.—This alcohol (110 g., 80%) was obtained by the reaction of 4-methyl*cyclo*hexanone (112 g.) with sodium acetylide (from sodium, 24 g.) in liquid ammonia (2 l.). After distillation, the product was obtained as a crystalline mass, m. p. 15—24°. Laborious fractional crystallisation of a small portion from light petroleum (b. p. 40—60°) gave a trace of a pure *isomer*, m. p. 36° (Found: C, 78·1; H, 10·1. $C_9H_{14}O$ requires C, 78·3; H, 10·1%). For further work the mixture, m. p. 15—24°, was used.

1-*Acetyl*-4-*methyl*cyclo*hexanol*.—*Method* B. 1-Ethynyl-4-methyl*cyclo*hexanol (100 g.), Zeo-Karb 225–mercuric ion (25 g.), methanol (300 c.c.), and water (70 c.c.) were refluxed with stirring for 2 hr. The mixture was worked up as previously described giving the ketone (92 g., 80%), b. p. 90—95°/10 mm. The semicarbazone, formed in aqueous pyridine, was crystallised from ethanol to constant m. p. 181—182°. This appeared to be homogenous and on regeneration with warm aqueous sulphuric acid gave a pure isomer of 1-*acetyl*-4-*methyl*cyclo*hexanol* (64 g.), b. p. 99—100°/10 mm. (Found: C, 69·5; H, 10·2. $C_9H_{16}O_2$ requires C, 69·3; H, 10·3%). The *semicarbazone* of this ketone, without further crystallisation, had m. p. 182—183° (Found: C, 56·5; H, 9·0; N, 20·0. $C_{10}H_{19}O_2N_3$ requires C, 56·3; H, 8·9; N, 19·7%)

1-*Bromoacetyl*-4-*methyl*cyclo*hexanol*.—*Method* B. 1-Acetyl-4-methyl*cyclo*hexanol (31·2 g.) in dry ether (50 c.c.) was added to dioxan dibromide (50 g.) in ether (500 c.c.). The red solution was irradiated with a 250-watt G.E.C. lamp; after 3 min. the ether was colourless and a small quantity of red oil separated. On further irradiation (2—3 min.) the solution was again homogeneous and colourless. The mixture was rapidly washed with water and dried (Na_2SO_4), and 1-*bromoacetyl*-4-*methyl*cyclo*hexanol* was obtained, by evaporative distillation, as a pale yellow liquid (38 g.), b. p. 75—80°/10^{-6} mm. (bath temp. 100—110°) (Found: Br, 34·1. $C_9H_{15}O_2Br$ requires Br, 34·0%).

Pyridinium adduct. The bromide (3 g.; not distilled), anhydrous ether (100 c.c.), and pyridine (5 c.c.) were kept at 0° for 24 hr., an oil separating. The ether was decanted off, and the residue, on trituration with chloroform and light petroleum (40—60°), solidified. A solution of the solid in cold methanol (2 c.c.) was diluted with ether and kept at 0°, the *pyridinium* adduct (4 g.) then separating in needles, m. p. 194—195° (Found: C, 53·4; H, 6·5; N, 4·5; Br, 25·2. $C_{14}H_{20}O_2NBr$ requires C, 53·5; H, 6·3; N, 4·5; Br, 25·4%).

1-*Glycolloyl*-4-*methyl*cyclo*hexanol*.—*Method* B. The bromide (20 g.), De-acidite F.F. (50 g.), methanol (350 c.c.), and water (100 c.c.) were refluxed with vigorous stirring (20 hr.). The resin was filtered off, and the filtrate concentrated under vacuum (<60°). The residual oil was dissolved in ether and dried (Na_2SO_4); removal of the solvent followed by crystallisation from light petroleum (b. p. 40—60°) containing a little ether, gave 1-*glycolloyl*-4-*methyl*cyclo*hexanol* (8 g.) as plates, m. p. 80—81° (Found: C, 63·1; H, 9·4. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%). The compound deposited cuprous oxide when heated on the water-bath with Somogyi's reagent, and further addition of Nelson's arsenomolybdate reagent to this mixture gave a dark blue solution (Somogyi, *J. Biol. Chem.*, 1945, **160**, 61; Nelson, *J. Biol. Chem.*, 1944, **153**, 375).

1-Ethynyl-3-methyl*cyclo*hexanol (100 g.), prepared in 80% yield by the sodium acetylide–liquid ammonia method, was suspended in light petroleum and stirred with a solution (2 l.) of aqueous ammoniacal silver nitrate (containing 125 g. of silver nitrate). The mixture was kept for 12 hr. at 0°, and the silver salt filtered off, washed with ether, suspended in light petroleum (b. p. 80—100°), and shaken with a solution (3 l.) of saturated aqueous ammonium thiocyanate. The regenerated acetylenic carbinol had b. p. 56—60°/1 mm., n_D^{25} 1·4702. At 0—5° it crystallised

in fine needles but was liquid at room temperature (Found : C, 78·5; H, 10·1. Calc. for $C_9H_{14}O$: C, 78·3; H, 10·1%). (Rupe and Kambli, *Annalen*, 1927, **459**, 195, give two isomers, one of m. p. 55° and the other a liquid. The present compound was essentially the liquid isomer.)

1-*Acetyl*-3-*methyl*cyclo*hexanol*.—*Method* A. The acetylenic carbinol (200 g.) was hydrated with mercuric sulphate (52·5 g.) in aqueous sulphuric acid (140 c.c. of H_2SO_4; 1200 of c.c. H_2O). The mercury complex was decomposed by steam distillation as previously described, 1-*acetyl*-3-*methyl*cyclo*hexanol* (140 g.) being obtained, b. p. 68°/1 mm., n_D^{21} 1·4641 (Found : C, 69·1; H, 10·5. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). The ketone was converted into the *semicarbazone*, needles (from methanol), m. p. 211—212° (Found : C, 56·6; H, 9·2; N, 19·5. $C_{10}H_{19}O_2N_3$ requires C, 56·3; H, 8·9; N, 19·7%).

1-*Bromoacetyl*-3-*methyl*cyclo*hexanol*.—*Method* A The above ketone (31 g ; regenerated from the semicarbazone), dissolved in chloroform (20 c.c.) was added to a solution of bromine (32 g.), hydrogen bromide (0·25 g.), and acetic acid (0·5 c.c.) in chloroform (200 c.c.). After 20 min., the solution became colourless, and it was worked up in the usual manner, 1-*bromoacetyl*-3-*methyl*cyclo*hexanol* (29 g.), b. p. 75°/10^{-6} mm., being obtained by evaporative distillation. The bromide was too labile to be analysed and a portion was characterised as the *pyridinium* adduct, crystallising from dry methanol–ether in needles, m. p. 172—173° (Found : C, 53·2; H, 6·4; N, 4·3; Br, 25·5. $C_{14}H_{20}O_2NBr$ requires C, 53·5; H, 6·3; N, 4·5; Br, 25·4%).

1-*Glycolloyl*-3-*methyl*cyclo*hexanol*.—*Method* A. The bromoacetyl compound (20 g.) in ethanol (150 c.c.) and water (60 c.c.) was titrated as previously described with sodium hydroxide (3·5 g.) in aqueous ethanol (100 c.c.; 60% w./v.). The solvents were removed *in vacuo* (below 50°) and the *keto-alcohol* (6 g.), b. p. 60°/10^{-6} mm., n_D^{20} 1·4921 (Found : C, 62·4; H, 9·1. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%), obtained by evaporative distillation. The *thiosemicarbazone* separated from methanol as pale yellow needles, m. p. 208° (decomp.) (Found : C, 49·0; H, 7·8; N, 17·2; S, 13·0. $C_{10}H_{19}O_2N_3S$ requires C, 49·0; H, 7·8; N, 17·1; S, 13·2%).

(*sol.*)-1-*Acetyl*-2-*methyl*cyclo*hexanol*.—*Method* B. The hydration of (*sol.*)-1-ethynyl-2-methyl*cyclo*hexanol (100 g.) with Zeo-Karb 225–mercuric ions (25 g.) in aqueous methanol (350 c.c.; 70% w./v.) yielded (*sol.*)-1-acetyl-2-methyl*cyclo*hexanol (92 g.), m. p. 36° undepressed when melted on admixture with a previously prepared sample (Part II, *loc. cit.*).

(sol.)-1-*Bromoacetyl*-2-*methyl*cyclo*hexanol*.—*Method* B. When the ketone (15·6 g.) was brominated with dioxan dibromide (25 g.) in ether (200 c.c.), there was obtained the bromide, m. p. 62—63° undepressed on admixture with a previously prepared sample (Part II).

(sol.)-1-*Glycolloyl*-2-*methyl*cyclo*hexanol*.—*Method* B. The bromide (7·8 g.), De-acidite F.F. (15 g.), and aqueous methanol (300 c.c.) were heated under reflux (20 hr.) The hydroxy-ketol (3·9 g.), isolated in the usual manner, had m. p. 81—82° undepressed on admixture with an authentic specimen (Part II).

1-*Acetyl*-2 : 2-*dimethyl*cyclo*hexanol*.—Crude 2 : 2-dimethyl*cyclo*hexanone semicarbazone was fractionally crystallised from methanol to constant m. p. 199—200° (Adamson, Marlow, Simonsen, *loc. cit.*). 2 : 2-Dimethyl*cyclo*hexanone (126 g.), regenerated from this semicarbazone, gave with sodium acetylide (39 g.), 1-ethynyl-2 : 2-dimethyl*cyclo*hexanol (120 g.), b. p. 78°/6 mm., n_D^{22} 1·4788 (Found : C, 78·5; H, 10·9. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·5%). The acetylenic alcohol (100 g.) was converted with mercuric sulphate (27 g.) and aqueous sulphuric acid (70 c.c. of H_2SO_4 and 600 c.c. of H_2O) into 1-*acetyl*-2 : 2-*dimethyl*cyclo*hexanol* (80 g.), b. p. 101°/8 mm., n_D^{21} 1·4733 (Found : C, 70·5; H, 10·8. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%). The *semicarbazone* separated from ethanol as cubes, m. p. 204—205° (Found : C, 58·4; H, 9·2; N, 18·6. $C_{11}H_{21}O_2N_3$ requires C, 58·2; H, 9·3; N, 18·5%).

1-*Bromoacetyl*-2 : 2-*dimethyl*cyclo*hexanol*.—*Method* A. 1-Acetyl-2 : 2-dimethyl*cyclo*hexanol (17 g.) was brominated in chloroform (170 c.c.) with bromine (16·2 g.) containing hydrogen bromide (0·25 g.) and acetic acid (5 c.c.). On distillation, the bromide had b. p. 80°/10^{-6} mm., and solidified on cooling to 0°. 1-*Bromoacetyl*-2 : 2-*dimethyl*cyclo*hexanol* crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 65° (Found : C, 48·3; H, 6·8; Br, 32·3. $C_{10}H_{17}O_2Br$ requires C, 48·2; H, 6·8; Br, 32·1%).

Hydrolysis of the bromide. The bromide (14 g.) in aqueous ethanol (60% w./v.; 100 c.c.) was neutralised with sodium hydroxide (2·3 g.) in aqueous ethanol (60% w./v.; 100 c.c.). The solution was concentrated under reduced pressure and water (50 c.c.) added. The solution was extracted into ether, the two layers separated, and the ether layer dried (Na_2SO_4). (*a*) The ether extract, after removal of solvent, left an oil which was dissolved in a minimum of light petroleum (b. p. 40—60°)–ether and chromatographed on alumina (nitrogen atmosphere). A portion eluted with light petroleum (b. p. 40—60°), twice crystallised from the same solvent, gave only a trace of the *hydroxy-ketol* as needles, m. p. 56° (Found : C, 64·1; H, 9·3. $C_{10}H_{18}O_3$

requires C, 64·5; H, 9·6%). The compound readily reduced the Somoygi reagent and gave a deep blue colour with the Nelson reagent (*loc. cit.*).

(*b*) The aqueous layer was acidified and extracted into ether. Purification of the acid gave, after evaporation of the solvent, an oily residue which eventually solidified. Crystallisation from hot aqueous acetic acid gave 2 : 2-*dimethyl*cyclo*hexylideneacetic acid* (?) as a dihydrate, m. p. 70° (indefinite) (Found : C, 59·2; H, 9·5. $C_{10}H_{16}O_2,2H_2O$ requires C, 58·8; H, 9·8%). On dehydration at 100° in vacuum it had m. p. 145—146° (Found : C, 71·1; H, 9·3. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%). This compound readily decolorised aqueous acidified potassium permanganate.

*Ethynyl*cyclo*pentanol and* cyclo*Pentylidene*cyclo*pentanone*.—Sodium acetylide, from sodamide (195 g.) in liquid ammonia (5 l.), was treated with *cyclo*pentanone (420 g.) in the usual manner. Distillation yielded 1-ethynyl*cyclo*pentanol (280 g.), b. p. 52—54°/2 mm., m. p. *ca.* 20°. A higher-boiling fraction (b. p. 60—90°/2 mm.; 130 g.) on refractionation gave *cyclo*pentylidene*cyclo*pentanone, b. p. 119°/8 mm., $n_D^{20\cdot5}$ 1·5220 (Found : C, 79·8; H, 10·5. Calc. for $C_{10}H_{14}O$: C, 80·0; H, 10·6%). The compound decolorised acidified potassium permanganate.

1-*Acetyl*cyclo*pentanol*.—1-Ethynyl*cyclo*pentanol (100 g.), Zeo-Karb 225–mercuric ion (25 g.), and aqueous methanol (70% w./v.; 300 c.c.) were refluxed (2 hr.) with stirring. Filtration followed by distillation of the filtrate gave 1-acetyl*cyclo*pentanol, b. p. 71—74°/11 mm., n_D^{20} 1·4650 (Found : C, 65·4; H, 9·1. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·3%). The semicarbazone had m. p. 185—186° (Found : C, 57·7; H, 8·1; N, 23·0. $C_8H_{15}O_2N_3$ requires C, 57·9; H, 8·1; N, 22·7%). Both compounds were identical with previously prepared specimens (Billimoria and Maclagan, *J.*, 1951, 3067. The m. p. of the semicarbazone was erroneously reported as 206—208°).

2-1′-*Hydroxy*cyclo*pentyl*-2-*methyl*-1 : 3-*dioxolan*.—Mercuric oxide (4·5 g.) was covered with freshly distilled boron trifluoride–ether complex (2 c.c.) and dried ethylene glycol (5 g.). The mixture was warmed for a few minutes and then externally cooled, whilst a mixture of ethylene glycol (20 g.) and 1-ethynyl*cyclo*pentanol (35 g.) was run in dropwise with stirring. After the addition, the mixture was stirred (1·5—2 hr.), and then left overnight. Next day, anhydrous potassium carbonate (5 g.) was added and the solution stirred for a few minutes. The liquid was separated by centrifugation and distilled through a 6″ Vigreux column. The *ketal* (34 g.) was obtained as a viscous liquid, b. p. 69—70°/1 mm. (bath temp. 100°), $n_D^{23\cdot5}$ 1·4695 (Found : C, 62·5; H, 9·1. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%).

Hydrolysis. A portion of the ketal dissolved in a little methanol containing a few c.c. of aqueous 5% hydrochloric acid was warmed on the water-bath for 20 min. Addition of an excess of pyridine followed by the addition of semicarbazide hydrochloride gave the semicarbazone of 1-acetyl*cyclo*pentanol; this had m. p. and mixed m. p. 185—186°.

Biological Assay.—Groups of thirty mice (each 18—20 g.) were adrenalectomised on Day 1 and kept at 23° ± 1°. 8—10 animals were used for each of the control and the experimental groups. Drugs or control vehicle (arachis oil) were injected on the evening of Day 3 and again on the morning of Day 4. At 4 p.m. on Day 4 the animals were killed and the glycogen content of the livers was estimated by a slightly modified version of Venning, Kazmin, and Bell's method (*Endocrinol.*, 1946, **38**, 79).

We are indebted to the Empire Rheumatism Council and the Governors' Discretionary Fund, Westminster Hospital, for generous financial assistance, to Miss Patricia Maxwell for technical assistance, and to Samuel P. Sadtler & Son Inc., Philadelphia, for the infra-red spectra. We gratefully acknowledge the assistance of Mr. A. J. Feetham in the biological testing of the compounds.

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Westminster Medical School, London, S.W.1. [*Received, April 2nd*, 1954.]