Simple Analogues of Cortisone. Part IV. Some Benzyl-substituted Glycolloyl*cyclo*hexanols.*

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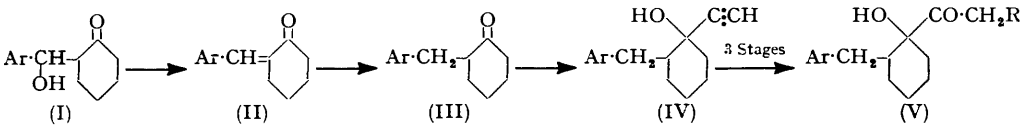
A preparative method for 2-benzyl*cyclo*hexanone and similar compounds substituted in the aromatic nucleus has been devised. Three of these compounds have been converted into the corresponding glycolloyl*cyclo*hexanols or their acetates (V; R = OH or OAc). The stereoisomers were separated at the substituted acetyl*cyclo*hexanol (V; R = H) stage.

Although 2 : 6-dibenzylidene*cyclo*hexanone is well known, the corresponding monobenzylidene compound is obtained only with difficulty. Vorlander and Kunze's method (*Ber.*, 1926, **59**, 2078) was not satisfactory.

In the present method *cyclo*hexanone and benzaldehyde suspended in water and treated with a small quantity of aqueous alkali, under carefully chosen experimental conditions, gave an excellent yield of 2-α-hydroxybenzyl*cyclo*hexanone (I) which, on further treatment with alkali gave a mixture of mono- and di-benzylidene*cyclo*hexanone, the latter predominating. However, the alcohol (I) was smoothly dehydrated by hot aqueous oxalic acid to monobenzylidene*cyclo*hexanone (II). In this manner, *o*-, *m*-, and *p*-methoxy-



and *p*-nitro-benzaldehyde also gave good yields of the respective alcohols (I). Benzaldehyde with *cyclo*pentanone gave mixtures from which only 2 : 5-di-α-hydroxybenzyl*cyclo*pentanone was isolated in small yield but with 2-decalone a mono-α-hydroxybenzyl-2-decalone was obtained in 25% yield.

2-Benzylidene*cyclo*hexanone was hydrogenated over palladium–strontium carbonate to 2-benzyl*cyclo*hexanone, which with sodium acetylide in liquid ammonia gave an inseparable mixture of *cis*- and *trans*-2-benzyl-1-ethynyl*cyclo*hexanol (IV; Ar = Ph); this was hydrated with sulphuric acid in the presence of mercuric sulphate and fractional crystallisation of the resulting mixture yielded crystalline *cis*- and *trans*-1-acetyl-2-benzyl*cyclo*hexanol. The absolute configuration of these compounds is not known; the suffixes A and B used below refer to the higher- and lower-melting ketones and their derivatives respectively.

The ketones (V; Ar = Ph, R = H) were separately brominated in acetic acid to give the two 1-bromoacetyl*cyclo*hexanols (V; R = Br). The bromide A on hydrolysis with alkali in 60% aqueous ethanol gave the 2-benzyl-1-glycolloyl*cyclo*hexanol A as a viscous glass which was characterised as a semicarbazone. However, each isomer of the bromide, on treatment with silver acetate in acetic acid, gave the corresponding crystalline 1-acetoxyacetyl-2-benzyl*cyclo*hexanol (V; R = OAc). All compounds of the A series were distinct from those of the B series and mixed melting points were depressed.

2-(2-Methoxy-α-hydroxybenzyl)*cyclo*hexanone (I, Ar = *o*-hydroxyphenyl) was successfully converted into 2-2′-methoxybenzyl*cyclo*hexanone and thence into 1-ethynyl-2-2′-methoxybenzyl*cyclo*hexanol. Hydration of the last compound yielded no ketonic material.

In similar experiments the 1-acetyl-2-4′-methoxybenzyl*cyclo*hexanol (V; Ar = *p*-hydroxyphenyl, R = H) was obtained from the keto-alcohol (I) and separated into two isomers. Isomer A was crystalline and after bromination with dioxan dibromide in ether and hydrolysis of the bromide with Deacidite F.F. (cf. Part III, *loc. cit.*) gave 1-glycolloyl-2-4′-methoxybenzyl*cyclo*hexanol (V; R = OH). Isomer B (V; R = H) was liquid, probably contained some isomer A, and was not further pursued.

* Part III, *J.*, 1954, 3257.

The three keto-alcohols, 1-acetoxyacetyl-2-benzyl*cyclo*hexanol A and B and 1-glycolloyl-2-4'-methoxybenzyl*cyclo*hexanol A, were found to have no cortisone-like activity when assayed by the mouse liver-glycogen (Part III, *loc. cit.*) and the cold-stress method.

Experimental

The microanalyses were carried out in the Microanalytical Laboratory, Organic Chemistry Department, Imperial College (Mr. F. H. Oliver).

2-α-*Hydroxybenzyl*cyclo*hexanone*.—*cyclo*Hexanone (300 g.) and benzaldehyde (212 g.) were suspended in water (6 l.), and sodium hydroxide (21 g.) in water (1 l.) was added. The mixture was stirred at room temp. for 4 hr., light petroleum (b. p. 40—60°) (500 c.c.) added, and the precipitated keto-alcohol (450 g.) collected and washed with cold light petroleum (b. p. 40—60°) (1·5 l.). A portion of the 2-α-hydroxybenzyl*cyclo*hexanone was crystallised from aqueous acetone, forming colourless needles, m. p. 99—100° (Vorlander and Kunze, *loc. cit.*, give m. p. 101—102°) (Found: C, 76·5; H, 7·9. Calc. for $C_{13}H_{16}O_2$: C, 76·5; H, 7·8%).

2-*Benzylidene*cyclo*hexanone*.—The above compound (crude, 400 g.) was heated under reflux for 2 hr. with water (1500 c.c.) and oxalic acid (400 g.). The mixture was cooled and extracted with ether, and the organic layer repeatedly washed with sodium hydrogen carbonate solution and dried (Na_2SO_4). Distillation in a high vacuum gave an oil (337 g.) which crystallised (m. p. 52—53°). Recrystallisation from light petroleum (b. p. 40—60°) gave pale yellow needles of 2-benzylidene*cyclo*hexanone, m. p. 53—54° (Found: C, 83·8; H, 7·5. Calc. for $C_{13}H_{14}O$: C, 83·9; H, 7·5%).

2-*Benzyl*cyclo*hexanone*.—The above compound (300 g.) in ethanol (1 l.) was hydrogenated over 2% palladium–strontium carbonate (25 g.) at 100 atm. (initial). Distillation gave colourless 2-*benzyl*cyclo*hexanone* (300 g.), b. p. 142°/1 mm., n_D^{18} 1·5356 (Found: C, 83·0; H, 8·8. $C_{13}H_{16}O$ requires C, 82·9; H, 8·5%).

2-*Benzyl*-1-*ethynyl*cyclo*hexanol*.—Sodium acetylide (from sodium, 33 g.) was formed in liquid ammonia (3 l.) by using Nieuwland's catalyst (Vaughan, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120), and 2-benzyl*cyclo*hexanone (188 g.) in dry ether (200 c.c.) was run in during 1·5 hr. whilst a rapid stream of acetylene was passed through the solution. The stream of acetylene was continued for 2 hr. after complete addition of the ketone, and the mixture stirred overnight. Working up in the usual manner afforded 2-*benzyl*-1-*ethynyl*cyclo*hexanol* (180 g.), b. p. 152°/1 mm. (bath-temp. 170°), n_D^{21} 1·5431 (Found: C, 84·0; H, 8·3. $C_{15}H_{18}O$ requires C, 84·1; H, 8·4%). The liquid was a mixture of *cis*- and *trans*-isomers and could not be separated by fractionation.

1-*Acetyl*-2-*benzyl*cyclo*hexanol*.—2-Benzyl-1-ethynyl*cyclo*hexanol (200 g.) was run into a solution of mercuric sulphate (110 g.) in sulphuric acid (300 c.c.) and water (2500 c.c.) during 1 hr. at 30—40°. Stirring was continued until the precipitated complex again became liquid (3—4 hr.). Light petroleum (b. p. 80—100°) (1 l.) was added and the mixture heated under reflux for 2 hr. The mixture was cooled and the organic layer separated. After filtering, the aqueous layer was extracted with ether (2 × 500 c.c.), and the precipitate washed under suction with ether (500 c.c.). The combined organic solvents were evaporated in a vacuum and the mixture of *cis*- and *trans*-ketone was obtained as a crystalline mass (180 g.), m. p. 45—75°.

These crystals (435 g.; from two experiments) were dissolved in a mixture of light petroleums (b. p. 40—60°, 1 l.; b. p. 80—100°, 400 c.c.) and cooled to room temperature. After 24 hr. crop (I) (123 g.; m. p. 82—84°) was separated. Subsequent concentration to half-bulk and cooling gave crop (II) (61 g.; m. p. 60—65°); further cooling to 0° gave crop (III) (31 g.; m. p. 63—65°); further evaporation gave crop (IV) (m. p. 45—50°; 215 g.). A portion of crop (I) after a number of crystallisations from light petroleum (b. p. 80—100°) gave a compound, m. p. 86—87°, and similar crystallisation of crop (IV) from light petroleum (b. p. 40—60°) gave a compound m. p. 55—56°. Crops (I)—(III) were combined, dissolved in light petroleum (b. p. 80—100°), and seeded with the higher-melting ketone, yielding 1-*acetyl*-2-*benzyl*cyclo*hexanol A* (190 g.), m. p. 86—87° unaltered on further crystallisation. Seeding of a solution of crop (IV) gave 1-*acetyl*-2-*benzyl*cyclo*hexanol B* (151 g.), m. p. 55—56°. A mixed m. p. was 46° (not sharp) (Isomer A, found: C, 77·8; H, 8·8. Isomer B, found: C, 77·6; H, 8·7. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·7%). The *semicarbazone A*, prepared in aqueous-alcoholic sodium acetate, separated from ethanol in needles, m. p. 236—237°, and the *semicarbazone B* from ethanol in needles, m. p. 214° (mixed m. p. 200—205°) (Isomer A, found: C, 66·8; H, 8·2; N, 14·5. Isomer B, found: C, 66·7; H, 8·2; N, 14·5. $C_{16}H_{23}O_2N_3$ requires C, 66·8; H, 8·0; N, 14·5%).

2-*Benzyl*-1-*bromoacetyl*cyclo*hexanol*.—1-Acetyl-2-benzyl*cyclo*hexanol A (23·2 g.) was dissolved in chloroform (200 c.c.), and bromine (16 g.) in chloroform (100 c.c.) containing hydrogen bromide in acetic acid (0·5 c.c., 50% by weight) was added. After the colour of bromine had disappeared (15 min.), the mixture was washed with water (2 × 50 c.c.), the aqueous layers were extracted with chloroform (2 × 20 c.c.), and the chloroform layers combined, dried (Na_2SO_4), and evaporated *in vacuo*. The residue on crystallisation from light petroleum (b. p. 80—100°) gave colourless needles of 2-*benzyl*-1-*bromoacetyl*cyclo*hexanol A* (18 g.), m. p. 114—115° (Found: C, 57·8; H, 6·3; Br, 25·9. $C_{15}H_{19}O_2Br$ requires C, 58·0: H, 6·2; Br, 25·7%).

The ketone B (23·2 g.) and bromine (16 g.) in the same manner gave the *bromide B* (15·5 g.), crystallising from light petroleum (b. p. 80—100°) in needles, m. p. 105° (Found: C, 57·7; H, 6·4; Br, 25·6%).

1-*Acetoxyacetyl*-2-*benzyl*cyclo*hexanol*.—The bromide A (48 g.) in acetic acid (500 c.c.) was refluxed under nitrogen with silver acetate (100 g.) for 24 hr. The solution was filtered, the silver halide was washed thoroughly with ether, and the combined filtrates were evaporated *in vacuo*. The residue was dissolved in ether and washed with aqueous sodium hydrogen carbonate. Removal of the solvent followed by distillation in a high vacuum yielded a pale yellow glass (20 g.), b. p. 130—140°/10^{-5} mm. (bath temp. 160—165°). On crystallisation from light petroleum (b. p. 80—100°), colourless needles of 1-*acetoxyacetyl*-2-*benzyl*cyclo*hexanol A* (12 g.), m. p. 86°, were obtained (Found: C, 70·3; H, 7·8. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%).

The bromide B (10 g.) similarly gave the *acetoxy-ketol B* (1·2 g.) which crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 69—70° (Found: C, 69·9; H, 7·7%). The *semicarbazone B* separated from ethanol in needles, m. p. 182—183° (Found: C, 62·3; H, 7·4; N, 12·3. $C_{18}H_{25}O_4N_3$ requires C, 62·2; H, 7·2; N, 12·1%).

2-*Benzyl*-1-*glycolloyl*cyclo*hexanol A*.—2-Benzyl-1-bromoacetyl*cyclo*hexanol A (11·8 g.) in aqueous ethanol (100 c.c.; 60% w/v) was treated with aqueous-ethanolic sodium hydroxide (2 g. in 50 c.c. of 60% ethanol w/v) in nitrogen. Each portion of alkali was allowed to be neutralised (phenolphthalein) before subsequent additions were made. Evaporation *in vacuo* followed by extraction with ether and removal of solvent left a colourless glass (4 g.) which gave a *semicarbazone*, needles (from ethanol), m. p. 195—198° (decomp.) (Found: C, 62·8; H, 7·7; N, 13·4. $C_{16}H_{23}O_3N_3$ requires C, 63·0; H, 7·6; N, 13·7%).

2-(2-*Methoxy*-α-*hydroxybenzyl*)cyclo*hexanone*.—*o*-Methoxybenzaldehyde (68 g.) was mechanically shaken with *cyclo*hexanone (69 g.) and sodium hydroxide (6 g.) in water (2 l.). After 3 hr. the precipitate (116 g.) was collected and a portion on crystallisation from aqueous ethanol gave the *keto-alcohol* in colourless plates, m. p. 113—114° (Found: C, 72·0; H, 7·7. $C_{14}H_{18}O_3$ requires C, 72·0; H, 7·8%).

2-2′-*Methoxybenzylidene*cyclo*hexanone*.—The above compound (500 g.), refluxed with oxalic acid (600 g.) and water (2 l.) for 2½ hr., gave the required *benzylidene compound* (430 g.) which separated from ether in large yellow rods, m. p. 79—80° (Found: C, 78·0; H, 7·4. $C_{14}H_{16}O_2$ requires C, 78·0; H, 7·4%).

2-2′-*Methoxybenzyl*cyclo*hexanone*.—2-2′-Methoxybenzylidene*cyclo*hexanone (400 g.) in ethanol (1 l.), hydrogenated as above, afforded the saturated *compound* (400 g.), b. p. 102—106°/0·1 mm., $n_D^{21·5}$ 1·5399 (Found: C, 77·0; H, 8·5. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%) [*semicarbazone*, needles (from ethanol), m. p. 201° (Found: C, 65·5; H, 7·8; N, 15·4. $C_{15}H_{21}O_2N_3$ requires C, 65·5; H, 7·8; N, 15·4%)].

1-*Ethynyl*-2-2′-*methoxybenzyl*cyclo*hexanol*.—2-2′-Methoxybenzyl*cyclo*hexanone (300 g.) was treated with sodium acetylide (from sodium, 48 g.) in liquid ammonia (5 l.). After distillation the acetylenic *alcohol* was obtained as a pale yellow liquid, b. p. 145°/2 mm., $n_D^{24·5}$ 1·5468 (Found: C, 78·1; H, 7·9. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%).

2-(4′-*Methoxy*-α-*hydroxybenzyl*)cyclo*hexanone*.—*p*-Methoxybenzaldehyde (272 g.) and *cyclo*hexanone (245 g.) were stirred with sodium hydroxide (6 g.) in water (2 l.) for 4 hr. The mixture was added to light petroleum (b. p. 40°) and set aside at 0° for 12 hr. The precipitate was filtered off, rapidly dissolved in acetone (1 l., preheated to its b. p.), and allowed to cool to 0°. (The *compound* is thermolabile when heated with the solvent.) The colourless plates (390 g.), m. p. 117—119°, were filtered off. A specimen recrystallised from hot acetone gave plates, m. p. 119—120° (Found: C, 72·0; H, 7·8. $C_{14}H_{18}O_3$ requires C, 72·0; H, 7·7%).

2-4′-*Methoxybenzylidene*cyclo*hexanone*.—This compound was obtained in 90% yield from the above product by treatment with aqueous oxalic acid as previously described. After distillation in a high vacuum it separated from *n*-hexane in yellow needles, m. p. 71—73° (Found: C, 77·8; H, 7·4. Calc. for $C_{14}H_{16}O_2$: C, 77·8; H, 7·4%).

2-4′-*Methoxybenzyl*cyclo*hexanone*.—Hydrogenation of the above benzylidene compound (200 g.) in methanol as above and distillation gave 2-4′-*methoxybenzyl*cyclo*hexanone* (195 g.), b. p. 138°/0·5 mm., n_D^{21} 1·5381 (Found: C, 65·5; H, 7·9; N, 15·6. $C_{15}H_{21}O_2N_3$ requires C, 65·5; H, 7·6; N, 15·2%).

1-*Ethynyl*-2-4′-*methoxybenzyl*cyclo*hexanol*.—2-4′-Methoxybenzyl*cyclo*hexanone (151 g.) was treated with lithium acetylide (from lithium, 7 g.) in liquid ammonia (2·5 l.). The acetylenic *alcohol* (122 g.) was obtained by distillation as a colourless liquid, b. p. 138—140°/10^{-6} mm., n_D^{18} 1·5455 (Found: C, 78·3; H, 7·9; $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%).

1-*Acetyl*-2-4′-*methoxybenzyl*cyclo*hexanol*.—The above alcohol (100 g.) in methanol (270 c.c.) and water (70 c.c.) was refluxed under stirring with "Zeokarb 225" (mesh below 50 μ; 100 g.; previously treated with a solution of 20% mercuric sulphate in 2N-sulphuric acid). The test for an acetylenic alcohol (liberation of acid by aqueous silver nitrate) was weak after 6 hr. The resin was then filtered off and distillation of the filtrate gave 1-acetyl-2-4′-methoxybenzyl-*cyclo*hexanol (mixed isomers) as a viscous liquid (70 g.), b. p. 132°/10^{-6} mm. The mixture was converted into the semicarbazone, which separated from ethanol in needles, m. p. 194—200° (Found: C, 64·1; H, 7·9; N, 13·4. Calc. for $C_{17}H_{25}O_3N_3$: C, 64·0; H, 7·8; N, 13·1%). The semicarbazone (34 g.) on treatment with acid gave the ketone (25 g.) which after distillation was kept at 0° for several weeks. One pure isomer crystallised and recrystallisation from light petroleum (b. p. 40—60°) gave 1-*acetyl*-2-4′-*methoxybenzyl*cyclo*hexanol A* (13 g.), m. p. 74·5° (Found: C, 73·3; H, 8·4. $C_{16}H_{22}O_3$ requires C, 73·5; H, 8·4%). The liquid fraction gave the impure B-isomer, b. p. 136°/10^{-6} mm. (Found: C, 73·1; H, 8·6%).

1-*Glycolloyl*-2-4′-*methoxybenzyl*cyclo*hexanone A*.—The above ketone (solid isomer, 6·5 g.) was dissolved in ether (100 c.c.), and dioxan dibromide (6·1 g.) in ether (50 c.c.) was added. The solution was irradiated with a 250-w lamp until colourless, then washed with water and evaporated, to yield the crude bromide (5 g.). This oil, in methanol (200 c.c.) and water (80 c.c.), was heated on the water-bath for 2 hr. with "Deacidite F.F." (25 g.) under nitrogen. After isolation in the usual manner 1-glycolloyl-2-4′-methoxybenzyl*cyclo*hexanol A (1·3 g.) separated from ether–light petroleum (b. p. 40—60°) in cubes, m. p. 64—67° (Found: C, 69·9; H, 8·1. $C_{16}H_{22}O_4$ requires C, 69·5; H, 8·0%).

2-(4-*Nitro*-α-*hydroxybenzyl*)cyclo*hexanone*.—The *compound* obtained in 90% yield by condensation of *p*-nitrobenzaldehyde and *cyclo*hexanone under conditions already described separated from methanol in colourless needles, m. p. 150—151° (Found: C, 62·2; H, 6·1; N, 5·8. $C_{13}H_{15}O_4N$ requires C, 63·0; H, 6·1; N, 5·6%).

2 : 5-*Di*-(α-*hydroxybenzyl*)cyclo*pentanone*.—The *compound* (10% yield) separated from ethanol in needles, m. p. 144—145° (Found: C, 77·1; H, 6·9. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

x-(α-*Hydroxybenzyl*)-2-*decalone* separated from methanol in colourless needles, m. p. 116—117° (Found: C, 79·2; H, 8·7. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·5%).

Biological Assay.—The cold-stress test, as developed by D'Arcy (*J. Pharm.*, 1954, **6**, 65) and Buttle, D'Arcy, and Howard (*J. Physiol.*, 1954, **123**, 5P), was applied to bilaterally adrenalectomised mice of 12—15 g. Groups of 9—11 mice were injected with two equal doses of test material dissolved in arachis oil, one dose on the evening of the first and one on the morning of the second postoperative day. A simultaneously run control group was injected with arachis oil only. An hour after the final injection, the mice were stressed at 5°, being observed at half hourly intervals until all were dead.

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