36. *Perhydroindanes. Part I. Some Products from* 1-*Hydroxy*cyclo*hexylpropiolic Acid.*

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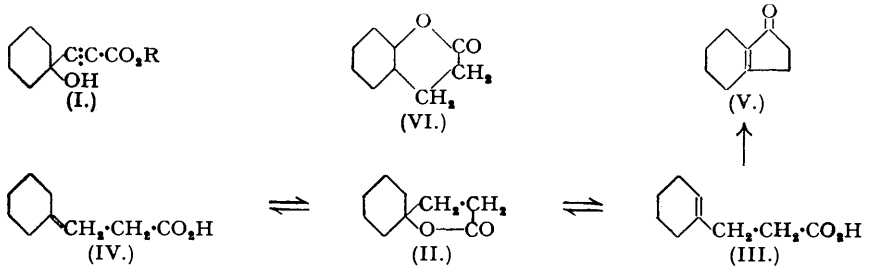
The synthesis is described of 4 : 5 : 6 : 7-tetrahydroindan-1-one from *γ-cyclo*hexane*spiro*butyrolactone and some related products.

In connection with the synthesis of perhydroindanes the investigation was undertaken of certain methods for the introduction of a propionic acid residue in place of the carbonyl-oxygen atom of a pre-formed *cyclo*hexanone nucleus. The difficulties and side reactions besetting

attempts to utilise ethyl β-bromopropionate in a Reformatsky-type reaction prompted an approach *via* the readily available 1-hydroxy*cyclo*hexylpropiolic acids. After this work had been completed, Bachmann and Raunio (*J. Amer. Chem. Soc.*, 1950, **72**, 2530) reported work along similar lines.



In place of a one-stage condensation utilising methyl sodiopropiolate (Bachmann and Raunio, *loc. cit.*), the synthesis of the required propiolic acid (I; R = H) has been carried out in two stages. *cyclo*Hexanone was converted into ethynyl*cyclo*hexanol which was carboxylated as described by Jones and Whiting (*J.*, 1949, 1423), to yield the known 1-hydroxy*cyclo*hexylpropiolic acid (I; R = H). Hydrogenation of this in ethyl acetate with Adams's platinum oxide led to the rapid uptake of two moles of hydrogen and the subsequent isolation of crystalline γ-*cyclo*hexane*spiro*butyrolactone (II). From the mother-liquors *cyclo*hexylpropionic acid was isolated as *p*-bromophenacyl ester, presumably produced by dehydration of the β-1-hydroxy*cyclo*hexylpropionic acid during the somewhat exothermic saturation of the triple bond.

In view of Johnson, Petersen, and Sneider's work (*J. Amer. Chem. Soc.*, 1947, **69**, 74), the possibility was considered that the *spiro*lactone (II) in presence of acids would exist in equilibrium with β-*cyclo*hex-1-enylpropionic acid (III) and possibly with *cyclo*hexylidenepropionic acid

Substance.	Conditions.	Products, %. Acid (IV).	Lactone (II).
(II)	$KHSO_4$, 200°, 45 mins.	14	80
	$(CO_2H)_2$, 200°, 60 mins.	16	80
	Reagent A,* 4 hrs. (reflux)	2	94
	,, 8 hrs. ,,	2	93
(III)	Reagent A, 4 hrs. ,,	30	65
	,, 8 hrs. ,,	10	82
(IV)	Reagent A, 4 hrs. ,,	57 (mixture)	33

* AcOH : HCl : H_2O = 7 : 3·5 : 5 parts by vol. (Johnson, Petersen, and Sneider, *loc. cit*).

(IV). The lactone (II) was therefore treated with certain acid reagents as described in a preliminary note (Linnell and Mathieson, *Nature*, 1950, **165**, 1010), and at the same time equilibration of the other two possible tautomerides was investigated in like fashion. The results, shown in the table, agree with those of Johnson and Hunt (*J. Amer. Chem. Soc.*, 1950, **72**, 935), whose paper prompted the publication of our note. Linstead, Wang, Williams, and Errington (*J.*, 1937, 1136) record a 50% conversion of *cyclo*hexylidenepropionic acid (IV) into the *spiro*lactone in presence of 50% sulphuric acid after 4 hours at room temperature. The acid fraction from *cyclo*hexylidenepropionic acid is complex. Although isomerism of (IV) to β-*cyclo*hexylacrylic acid is known to occur under the influence of alkali, it is possible, as pointed out by Johnson and Hunt (*loc. cit.*), that this change also occurs under acid conditions. In addition, however, it is shown below that ring closure of (IV) with acid reagents affords 4 : 5 : 6 : 7-tetrahydroindan-1-one in 5% yield. Since ring closure must presumably take place *via* β-*cyclo*hex-1-enylpropionic acid (III), the presence of this acid—in addition to β-*cyclo*hexylacrylic acid—is likely in the acid fraction.

As the equilibrium (II) ⇌ (III) under acid conditions was so far in favour of the lactone (II), direct conversion of the latter into the indanone (V) seemed likely to be disappointing. Ring closure of such *spiro*lactones must proceed *via* the intermediate β-*cyclo*hexenylpropionic acids, and the work of Johnson *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 1366; 1947, **69**, 74) has shown that where the acid-catalysed equilibrium mixture contains a significant proportion of the enoic acid, ring closure of a sample of the *spiro*lactone by Fieser and Hershberg's method (*J. Amer. Chem. Soc.*, 1937, **59**, 1028) proceeds in fair yield. As expected in the present case, ring closure of (II) to form (V) could be achieved in only 16% yield with

phosphoric oxide in benzene, or 7·5% with zinc chloride–acetic anhydride–acetic acid (yields being based on semicarbazone isolated from the reaction mixture). The structure of the ketone (V), previously described by Nenitzescu and Przmetsky (*Ber.*, 1941, **74**, 676), was confirmed by the fact that its 2 : 4-dinitrophenylhydrazone showed maximum absorption at 388 mμ., as required for an αβ-unsaturated ketone (Braude and Jones, *J.*, 1945, 498).

By Cason, Adams, Bennett, and Register's method (*J. Amer. Chem. Soc.*, 1944, **66**, 1764), the lactone (II) yielded ethyl β-*cyclo*hex-1-enylpropionate as described by Johnson and Hunt (*loc. cit.*). Hydrolysis of this, however, proved disappointing. With aqueous sodium hydroxide, the acid resulted in 16% yield (identified by comparison of its *p*-bromophenacyl ester with a sample synthesised by Arndt–Eistert homologation of *cyclo*hexenyl-1-acetic acid). The remainder of the hydrolysis product was a lactone of the same empirical formula and melting point, but it had a different crystalline form, and on admixture with the lactone (II) it immediately liquefied. It is tentatively assigned the constitution of a δ-lactone (VI), a substance described as an oil by Nenitzescu and Przmetsky (*loc. cit.*). Attempted hydrolysis of ethyl β-*cyclo*hex-1-enylpropionate with 4N-hydrochloric acid gave 8% of the required acid (III) and, mainly, the lactone (II).

Ring closure of the acid (III) with zinc chloride–acetic anhydride–acetic acid afforded the indanone (V) in 37% yield (based on once recrystallised semicarbazone).

Several modifications in the above reactions were equally fruitless. (i) The methyl ester of the acid (I) behaved similarly to the acid itself, yielding on reduction a mixture of the *spiro*-lactone (II) and methyl β-*cyclo*hexylpropionate. (ii) Treatment of the *spiro*lactone (II) with the theoretical amount of sodium hydroxide gave sodium β-1-hydroxy*cyclo*hexylpropionate, but treatment of this with phosphorus pentachloride and then stannic chloride (cf. Haberland and Heinrich, *Ber.*, 1939, **72**, 1215; 1943, **76**, 621) failed to afford any ketone.

Experimental.

γ-cyclo*Hexane*spiro*butyrolactone*.—1-Hydroxy*cyclo*hexylpropiolic acid (Jones and Whiting, *loc. cit.*) (50 g.) in ethyl acetate (250 ml.) was shaken with hydrogen under laboratory conditions in presence of Adams's platinum oxide (0·5 g.). Uptake of hydrogen, which was exothermic, was complete in 2 hours. Evaporation of the filtered solution yielded an oil, b. p. 125°/5 mm., n_D^{20} 1·4765 (supercooled specimen) (46 g., 98%). When this was kept overnight at 0°, large colourless prisms separated; recrystallised from light petroleum (b. p. 40—60°), they had m. p. 28—29° (Linstead, Wang, Williams, and Errington, *loc. cit.*, give m. p. 20—25° for a sample synthesised by an alternative route) (Found : C, 70·5; H, 9·2%; sap. equiv., 154. Calc. for $C_9H_{14}O_2$: C, 70·0; H, 9·1%; sap. equiv., 154). By dissolving the *spiro*lactone in the theoretical amount of aqueous barium hydroxide and concentrating the solution, *barium β-hydroxy*cyclo*hexylpropionate* was obtained (Found : Ba, 28·6. $C_{18}H_{30}O_6Ba$ requires Ba, 28·6%).

The mother-liquors after removal of the crystalline lactone showed an acid fraction 31% by weight on direct titration in 40% aqueous methanol against N/10-sodium hydroxide. The oil failed to decolorise aqueous potassium permanganate or bromine in carbon tetrachloride, and was transparent to light of 215 mμ., unlike 1-hydroxy*cyclo*hexylpropiolic acid (Haynes and Jones, *J.*, 1946, 503). The acid fraction, separated by extraction with sodium hydrogen carbonate, was a colourless oil, b. p. 115—120°/2 mm. (bath-temp.). Chromatography on alumina of the derived *p*-bromophenacyl ester yielded the p-*bromophenacyl* ester of *β-cyclo*hexylpropionic acid, m. p. 93—94° (from light petroleum). It was identified by mixed m. p. with an authentic specimen (see below) (Found : Br, 22·4. $C_{17}H_{21}O_3Br$ requires Br, 22·6%).

Hydrogenation of Methyl 1-*Hydroxy*cyclo*hexylpropiolate*.—The methyl ester (13·4 g.) was hydrogenated in presence of Adams's platinum oxide (0·1 g.) as described for the free acid. The resulting material yielded two fractions : (*a*) B. p. 37—38°/0·05 mm., 3·46 g. (27%), n_D^{20} 1·4475 (Found : C, 70·9; H, 10·8%; sap. equiv., 169. Calc. for $C_{10}H_{18}O_2$: C, 70·6; H, 10·6%; sap. equiv., 170); this was methyl *β-cyclo*hexylpropionate, and on hydrolysis with 20% sodium hydroxide it afforded an acid, b. p. 115—118°/3 mm., of which the *p*-bromophenacyl ester, formed in the usual way, had m. p. and mixed m. p. with *p*-bromophenacyl *β-cyclo*hexylpropionate 93—94°. (*b*) B. p. 70—72°/0·05 mm., 5·87 g. (49%), n_D^{20} 1·4758, m. p. 24—25° not depressed on admixture with γ-*cyclo*hexane*spiro*butyrolactone.

1-*cyclo*Hexenylacetic acid, prepared (80% yield) by iodine dehydration of ethyl 1-hydroxy*cyclo*hexylacetate followed by hydrolysis, had b. p. 94—95°/0·1 mm., m. p. 35—36°.

β-cyclo*Hex*-1-*enylpropionic Acid*.—*cyclo*Hexenylacetic acid (26 g.) in dry benzene (50 ml.) was added, with stirring, to pure thionyl chloride (35 ml.) during 2 hours, and the whole heated under reflux for 30 minutes; excess of solvent and reagent was removed *in vacuo*, and the residual acid chloride distilled (b. p. 60—65°/3 mm.; 25 g.). It was dissolved in dry ether and treated overnight at 0° with an ethereal solution of diazomethane (800 ml.) (from *N*-nitrosomethylurea, 37 g.). Evaporation of the solvent yielded an oily yellow diazo-ketone (27 g.) which in dry dioxan (60 ml.) was slowly added to a stirred solution of freshly precipitated silver oxide (25 g.) and sodium thiosulphate (30 g.) in water (300 ml.). After the addition was complete, stirring was continued at 40° for 1½ hours, the mixture was filtered, and the mother-liquors were acidified with dilute nitric acid to yield an oil which was extracted with ether.

Purification of this acid fraction *via* the sodium salt yielded *β-cyclo*hex-1-enylpropionic acid as a colourless oil, b. p. 88—91°/0·1 mm., n_D^{20} 1·4884; 11·02 g. (38%) (Found: C, 69·5; H, 9·4%; equiv., 154. Calc. for $C_9H_{14}O_2$: C, 70·0; H, 9·1%; equiv., 154). The p-*bromophenacyl* ester crystallised from ethanol in colourless plates, m. p. 108—109° (Found: Br, 22·2. $C_{17}H_{19}O_3Br$ requires Br, 22·7%).

β-cyclo*Hexylpropionic Acid.*—*β-cyclo*Hex-1-enylpropionic acid (1 g.) in ethanol (10 ml.) was hydrogenated in presence of Adams's platinum oxide (0·1 g.), uptake being complete in 20 minutes. The product, a colourless oil, b. p. 90—91°/0·2 mm., n_D^{17} 1·4665, gave a *p*-bromophenacyl ester crystallising from light petroleum (b. p. 60—80°) in colourless plates, m. p. 92—93° (Found: Br, 22·3%).

*β-cyclo*Hexylidenepropionic acid was synthesised by the method of Linstead, Wang, Williams, and Errington (*loc. cit.*).

Equilibration Studies.—General procedure. A sample of the material under investigation (1 g.) was heated with the reagent used [twice its weight of anhydrous oxalic acid or potassium hydrogen sulphate, or reagent A (15 ml.; see p. 178)] for the times and at the temperatures stated in the table (p. 178). After addition of water (10 ml.), or evaporation of the acetic acid in the last case, an ethereal extract was separated into neutral and acidic fractions by sodium hydrogen carbonate extraction. The constituents were then identified as follows: *γ-cyclo*hexane*spiro*butyrolactone by b. p., m. p., refractive index, and saponification equivalent; *β-cyclo*hex-1-enylpropionic acid by equivalent (titration) and formation of its *p*-bromophenacyl ester. Equilibration of both these compounds yielded substantially pure end-products. The *p*-bromophenacyl ester of the acid fraction from *β-cyclo*hexylidenepropionic acid (IV) had m. p. 96—109° not raised by further recrystallisation from ethanol or light petroleum.

Ethyl *β-cyclo*hex-1-enylpropionate, prepared (yield 76%) essentially as described by Johnson and Hunt (*loc. cit.*), had b. p. 83—85°/3 mm., n_D^{16} 1·4656 (Found: C, 72·4; H, 10·0%; sap. equiv., 181. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 9·9%; sap. equiv., 182).

Alkaline hydrolysis. Ethyl *β-cyclo*hex-1-enylpropionate (2 g.), 10% sodium hydroxide solution (10 ml.), and ethanol (3 ml.) were refluxed for 40 minutes, by which time the oily layer had passed into solution. After acidification, both the acidic and the lactonic fraction were removed by ether-extraction, then separated with sodium hydrogen carbonate in the usual way. There thus resulted: (*a*) An acid fraction, 282 mg. (16%), equiv. by titration, 154; *p*-bromophenacyl ester, m. p. 107—108° undepressed on admixture with the corresponding ester of *β-cyclo*hex-1-enylpropionic acid. (*b*) A neutral fraction with a typical lactonic odour (1·18 g., 75%), slowly soluble in sodium hydroxide on warming. When it was cooled in carbon dioxide–acetone, colourless needles were obtained, m. p. 29—30° (from light petroleum, b. p. 40—60°) (Found: C, 69·6; H, 9·2%; sap. equiv., 151. $C_9H_{14}O_2$ requires C, 70·0; H, 9·1%; sap. equiv., 154); on admixture with a sample of *γ-cyclo*hexane*spiro*butyrolactone, the whole immediately liquefied.

Acid hydrolysis. Ethyl *β-cyclo*hex-1-enylpropionate (1·35 g.) was refluxed for 3 hours with 4N-hydrochloric acid (15 ml.). After separation there resulted: (*a*) Acid fraction, 80 mg. (8·7%); *p*-bromophenacyl ester, m. p. 106—108°, undepressed on admixture with *p*-bromophenacyl *β-cyclo*hex-1-enylpropionate. (*b*) Lactonic fraction, 0·96 g. (83%), b. p. 130—135°/10 mm. (bath-temp.), n_D^{20} 1·4745; after this had solidified in a carbon dioxide–acetone bath, several recrystallisations from light petroleum (b. p. 60—80°) gave *γ-cyclo*hexane*spiro*butyrolactone, m. p. and mixed m. p. with an authentic specimen 28—29°.

Ring-closure Experiments.—(i) *β*-cyclo*Hex-1-enylpropionic acid.* This acid (5 g.) in acetic anhydride (85 ml.) was refluxed for 4 hours in a nitrogen atmosphere with a 2% solution of anhydrous zinc chloride in acetic acid (20 ml.). The solution was then concentrated to half bulk, and any residual anhydride decomposed by shaking the mixture with ice and excess of 20% sodium hydroxide solution. The alkaline liquors were steam-distilled till the distillate no longer gave a positive reaction with 2 : 4-dinitrophenylhydrazine. The distillate, saturated with sodium chloride, was thoroughly extracted with ether, and the dried extract evaporated. The residue distilled at 85—90°/0·5 mm. (bath-temp.) (2·28 g., 51·5%) and proved to be 4 : 5 : 6 : 7-tetrahydroindan-1-one. The semicarbazone from the above (2·3 g.; 37% yield based on this derivative) crystallised in pale yellow needles, m. p. 245—246° (placed in bath at 235°) (Found: N, 21·4. Calc. for $C_{10}H_{15}ON_3$: N, 21·7%), from aqueous acetic acid. The 2 : 4-dinitrophenylhydrazone crystallised in dark red needles, m. p. 238°, from ethanol; $\lambda_{max.}$ 388 mμ., $\varepsilon_{max.}$ 27,000; Johnson, Hunt, and Stork (*J. Amer. Chem. Soc.*, 1948, **70**, 3022) give m. p. 242·5—243° and 238—239·5°, respectively, for the semicarbazone and dinitrophenylhydrazone.

(ii) *γ*-cyclo*Hexane*spiro*butyrolactone.* (*a*) The *spiro*lactone (17·15 g.) in acetic anhydride (300 ml.) with zinc chloride solution (as above; 100 ml.) was refluxed for 4 hours in a nitrogen atmosphere; after working up as described above there resulted 4 : 5 : 6 : 7-tetrahydroindan-1-one as a light yellow oil, b. p. 60—65°/0·05 mm. (bath-temp.), 2·02 g. (13%); 2 g. of crystalline semicarbazone were obtained from this material as small, pale yellow needles (from dilute acetic acid), m. p. 245—246°. (*b*) The *spiro*lactone (2 g.) in dry benzene (50 ml.) was refluxed for 2½ hours with phosphoric oxide (4 g.) and an equal bulk of acid-washed kieselguhr. The dark viscous residue was decomposed by addition of water, the benzene layer was removed, and the aqueous layer extracted with benzene. Evaporation of the combined extracts gave a residue which was warmed for 2 hours on the steam-bath with 10% sodium hydroxide to cleave any lactone. Non-alkali-soluble material was extracted with benzene to yield the required ketone, 463 mg. (24·6%), b. p. 60—67°/0·05 mm., which gave a semicarbazone (400 mg.), m. p. 245—246°, from aqueous acetic acid (16% yield based on semicarbazone).

(iii) *β*-cyclo*Hexylidenepropionic acid.* The acid (2 g.), acetic anhydride (35 ml.), and stock solution of zinc chloride (12 ml.) were refluxed for 4 hours. There resulted after working up as above 314 mg. of a light yellow oil, from which 115 mg. of semicarbazone were obtained, m. p. 243—245° (from aqueous acetic acid) (4·6% yield based on semicarbazone).

All m. p.s are uncorrected. Absorption spectra were determined by use of a " Uvispek " photoelectric spectrophotometer and a cell-path of 1 cm., with ethanol as solvent. Microanalyses were carried out by Mr. G. S. Crouch.

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