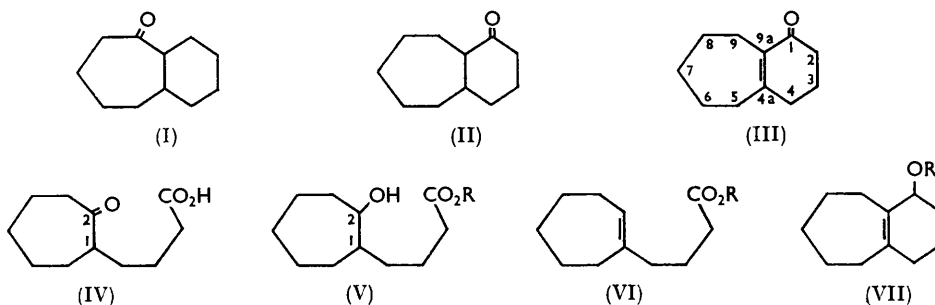


1054. *Synthetical and Stereochemical Studies in the Perhydrobenzocyclohepten-1-one System.*

By DVORA KIMCHI and SHLOMO BIEN.

The preparation of 2,3,4,5,6,7,8,9-octahydrobenzocyclohepten-1-one (III)* is described, and the stereochemistry of its ketonic and alcoholic reduction products is determined.

THE relative stabilities of several *cis*- and *trans*-fused α -ketonic bicyclo-systems, in which one of the rings is six-membered, are known. In the perhydroindan-1-one system the *cis*-isomer has proved to be the more stable,¹ but the reverse situation applies to α -decalone.² The next higher homologues, *cis*- and *trans*-perhydrobenzosuberone (I), were synthesised only a few years ago and the *trans*-ketone was the more stable.³ The object of the present work was the synthesis and the stereochemical study of the hitherto unknown *cis*- and *trans*-perhydrobenzocyclohepten-1-ones (II).



A precursor (III) of both the *cis*- and the *trans*-isomer of compound (II) was synthesised from methyl 2-oxocycloheptanecarboxylate. This β -keto-ester was alkylated with methyl γ -bromobutyrate in the presence of sodium ethoxide in dry ethanol.⁴ A second method, in which the carbanion was obtained by the use of metallic potassium in dry benzene,⁵ gave large amounts of dimethyl suberate, formed by coupling of the halogeno-ester. Similar side reactions are common in the Reformatsky reaction.⁶

The alkylated keto-ester was hydrolysed and decarboxylated in one step by refluxing it with barium hydroxide solution, giving the keto-acid (IV), which was in turn purified through its semicarbazone. Reduction with sodium borohydride and esterification of the crude intermediate hydroxy-acid with diazomethane afforded the hydroxy-ester (V; R = Me), which was dehydrated by using phosphorus pentoxide in dry benzene or (best) phosphorus oxychloride and pyridine, or by boiling its toluene-*p*-sulphonate with collidine. Hydrolysis of the resulting ester (VI; R = Me), followed by cyclisation with acetic anhydride and zinc chloride in acetic acid, gave the desired unsaturated ketone (III) through the intermediate acid (VI; R = H).

Analysis of the unsaturated ketone (III) showed low carbon and higher oxygen values, even after purification by chromatography and distillation, manganese dioxide oxidation

* The nomenclature used in this paper is that of I.U.P.A.C. rule A-21.4 [*Chem. Soc. Special Publ.* 14 (1960), p. 68] whereby benzocycloheptene denotes the 6,7-ring compound containing (formally) five double bonds.

¹ Linstead, *Ann. Reports*, 1935, **32**, 311.

² Hückel and Brinkmann, *Annalen*, 1925, **441**, 21.

³ Ginsburg and Rosenfelder, *Tetrahedron*, 1957, **1**, 3; Gutsche and Peter, *J. Amer. Chem. Soc.*, 1955, **77**, 5971.

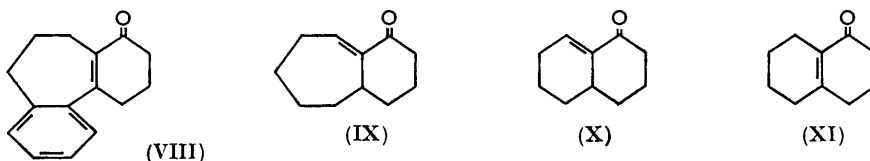
⁴ Cf. Tinker, *J. Org. Chem.*, 1951, **16**, 1417.

⁵ Büchi and Jeger, *Helv. Chim. Acta*, 1949, **33**, 538.

⁶ "Organic Reactions," John Wiley and Sons, Inc., New York, 1947, Vol. I, p. 4.

of the corresponding allylic alcohol (VII; R = H) (obtained from ketone III by hydride ion reduction), or hydrolysis of the semicarbazone. On the other hand, its 2,4-dinitrophenylhydrazone, semicarbazone, and oxime, as well as its reduction product (VII; R = H), gave correct analyses. An analogous system⁷ (VIII) and the lower homologue⁸ (XI) showed the same analytical discrepancies.

It is known that under acidic cyclisation conditions, used in the last step of the synthesis, the double bond of an alkenoic acid is highly labile.⁹ On the other hand, a double-bond shift might be expected in the cyclised product if a more stable compound is formed thereby. Consequently one must decide whether the resulting unsaturated ketone is (III) or (IX). In a very similar case, Campbell and Harris¹⁰ assigned structure (X) to α -octalone on the basis of the ultraviolet absorption maximum observed at 243 m μ . In the light of Woodward's rules¹¹ (published later), no conclusive choice can be made between structures (X) and (XI), whose calculated absorption maxima are at 240 and 247 m μ respectively. More recently,⁸ Quartey found λ_{max} 244 m μ for the same α -octalone and claimed structure (XI) for it. In the present work, the unsaturated ketone showed an absorption maximum at 249 m μ , which rules out structure (IX) and favours (III).



The same structure (III) appears to be correct as the compound shows the following nuclear magnetic resonances: (a) a single sharp line at 438 c./sec. (7.31 p.p.m., $\tau = 2.69$) which is the residual chloroform in the deuteriochloroform used as solvent; (b) a complex multiplet at 141.7 c./sec. (2.36 p.p.m., $\tau = 7.64$) representing the protons adjacent to the carbonyl group and those allylic to the double bond; (c) a complex multiplet at 97.3 c./sec. (1.62 p.p.m., $\tau = 8.38$) representing the remaining methylene protons; (d) the single sharp line of the tetramethylsilane used as an internal standard. The compound shows no resonances, even at high gain, in the $\tau = 3.5$ —5.5 region in which one would expect to find any simple, cyclic conjugated or non-conjugated olefinic protons.

Catalytic reduction of compound (III) in a neutral medium led to a mixture of saturated ketones (subsequently referred to as mixture "A"), containing mainly one stereoisomer and altering its isomer ratio on alkaline equilibration. From molecular models, as well in analogy with perhydrobenzosuberone (I) and the well-investigated α -decalone system, we can expect the *trans*-ketone (XIII) to be the more stable stereoisomer.

Mixture "A" was directly reduced with lithium aluminium hydride to the corresponding alcohols, separable by chromatography on basic alumina. The *trans*-alcohols were eluted from the column in small amounts, followed by the main fraction of the *cis*-alcohol (XIV).^{*} The latter was oxidised to the pure *cis*-ketone (XII) by chromic oxide in pyridine, a method proved to be stereospecific.¹² On the other hand, when mixture "A" was reduced after alkaline epimerisation, chromatography on basic alumina gave the *trans*-fused alcohols (XV) and (XVI) as the main products and only a minute amount

* All such formulæ include those of the mirror images.

⁷ Crabb and Schofield, *J.*, 1958, 4276.

⁸ Quartey, *J. Indian Chem. Soc.*, 1960, **37**, 731.

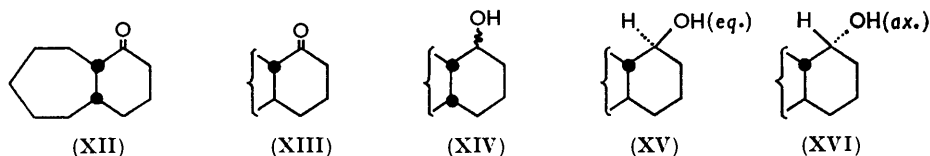
⁹ Ansell and Brown, *J.*, 1958, 2955.

¹⁰ Campbell and Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 2721.

¹¹ Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 72, 76; Dorfman, *Chem. Rev.*, 1953, **53**, 59.

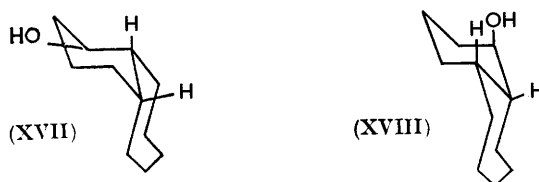
¹² Cope, Brown, and Hiok-Huang Lee, *J. Amer. Chem. Soc.*, 1958, **80**, 2855; Cope, Berchtold, Peterson, and Sharman, *ibid.*, 1960, **82**, 6371.

of *cis*-fused alcohol (XIV). Both *trans*-fused alcohols led to the same *trans*-fused ketone (XIII) on oxidation by chromic oxide in pyridine. The same *trans*-fused ketone resulted from the *cis*-fused isomer (XII) in high yield on epimerisation by sodium methoxide.



The rates of oxidation of the *trans*-alcohols, as well as those of saponification of their acetates, made it possible to assign to them the equatorial (XV) and the axial conformation (XVI), respectively. The axial epimer was eluted from the column before the equatorial, in accordance with the generality that equatorial alcohols are the more polar.¹³ Their infrared spectra showed at 1046 and 1000 cm^{-1} the strong single bands characteristic of equatorial and axial C–O stretching frequencies, respectively.¹⁴

In the *cis*-series only one alcohol could be isolated; it showed the characteristic bands of both equatorial and axial alcohols at 1050 and 1010 cm^{-1} , respectively. The compound may exist as an equilibrium mixture of the two conformations (XVII and XVIII) and possesses both equatorial and axial character, as is known in the case of *cis*- α -decalol.¹⁵



On hydrogenation of the unsaturated ketone (III) in acid or basic medium, the *cis*-isomer content of the resulting mixture was always lower than that of the hydrogenation mixture obtained in neutral medium. Reduction was apparently followed by epimerisation in both cases.

The unsaturated ketone (III) was then reduced with lithium and liquid ammonia, and a mixture containing preponderantly the *trans*-ketone (XIII) was obtained. When this reaction was repeated in the presence of absolute alcohol, the quantity of the *cis*-isomer in the resulting mixture (in this case the *cis*-alcohol) was greatly increased. This suggests that kinetically controlled protonation of the intermediate lithium enolate gave the unstable *cis*-isomer, as the main product. Several examples were given by Zimmerman¹⁶ in which kinetically controlled ketonisation of enols leads to the formation of the thermodynamically less stable of two possible stereoisomers. Recently, a number of authors^{16b,17,18} reported the formation of an unstable *cis*-epimer as the main product in the metal-ammonia reduction of $\alpha\beta$ -unsaturated ketones and the formation of the *trans*-isomer was attributed to epimerisation occurring during the working up. This exploration was supported in the present work by showing that a new equilibrium mixture was obtained when a known mixture of saturated ketones was reduced with lithium and liquid ammonia.

¹³ Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

¹⁴ Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1951, **73**, 3215; Dauben, Hoeringer, and Freeman, *ibid.*, 1952, **74**, 5206; Cole, Jones, and Dobriner, *ibid.*, 1952, **74**, 5571.

¹⁵ Braude and Nachod, "Determination of Organic Structures by Physical Methods," Academic Press Inc., New York, 1955, p. 689.

¹⁶ Zimmerman, (a) *J. Org. Chem.*, 1955, **20**, 549; (b) *J. Amer. Chem. Soc.*, 1956, **78**, 1168; (c) Zimmerman and Giallombardo, *ibid.*, p. 6259; (d) Zimmerman and Mais, *ibid.*, 1959, **81**, 3644.

¹⁷ Birch, Smith, and Thornton, *J.*, 1957, 1339.

¹⁸ Loewenthal, *J.*, 1958, 1367.

Quantitative Infrared Analysis.—The *cis*:*trans*-isomer ratios in the different ketone and alcohol mixtures were estimated by the method of Zimmerman *et al.*^{16b,c,d} The *trans*-ketone had a strong peak at 1176 cm^{-1} and one of medium intensity at 913 cm^{-1} . The *cis*-isomer showed two sharp absorptions, at 1093 and 1136 cm^{-1} , and one of medium intensity at 781 cm^{-1} . For calculation the pair at 1176 and 1093 cm^{-1} was chosen. The

TABLE 1.

Mixtures of known composition.						
<i>cis</i> -Isomer (%):	exptl.	15	30	50	72.5	83
	calc.	16.6	27.75	50.2	72.5	85

TABLE 2.

Calculated isomer content in the different reaction products.

Reaction	<i>cis</i> -Isomer (%)
Hydrogn. of (III) in neutral medium	83 \pm 2.5
Hydrogn. of (III) in acidic medium	43 \pm 2.5
Hydrogn. of (III) in alkaline medium	42 \pm 2.5
Epimern. of mixture "A" with NaOMe for 3 hr.	15 \pm 2.5
Epimern. of mixture "A" with NaOMe for 20 hr.	13 \pm 2.5
Epimern. of mixture "A" on basic alumina overnight	13 \pm 2.5
Epimern. of (XII) with NaOMe for 5 hr.	14 \pm 2.5
Li-liq. NH_3 reduction of (III)	21 \pm 2.5
Li-liq. NH_3 redn. of (III) in the presence of alcohol	55 \pm 2.5
Epimern. of mixture "A" under the conditions of Li-liq. NH_3 reduction.....	50 \pm 2.5

isomer ratio of the epimeric *trans*-alcohols could be determined by using the two bands at 1000 and 1046 cm^{-1} , characteristic of axial and equatorial alcohols, respectively. Calibration data for ketone mixtures of known composition are recorded in Table 1, and those obtained for different reaction mixtures in Table 2.

EXPERIMENTAL

γ -(2-Oxocycloheptyl)butyric Acid (IV).—(a) Sodium (4.2 g.) was dissolved in absolute ethanol (53 ml.), and methyl 2-oxocycloheptanecarboxylate (20 g.) was added without heating. The mixture was stirred for 5 min., and methyl γ -bromobutyrate (35 g.) was added rapidly. The solution was then stirred and refluxed for 8 hr., cooled, poured into water (60 ml.), and extracted with ether. On distillation of the dried (MgSO_4) ether solution, an oil was formed, which was purified by distillation in a short-path still at 120–130°/0.01 mm. The distillate (15 g.) was refluxed in water (260 ml.) and methanol (125 ml.) containing barium hydroxide (40 g.) for 20 hr. The larger part of the methanol was then distilled off, the mixture acidified with concentrated hydrochloric acid, and the separated oil extracted with ether. The ether layer was washed several times with saturated sodium hydrogen carbonate solution, and the combined alkaline fractions were acidified with concentrated hydrochloric acid and re-extracted with ether. Evaporation of the dried (MgSO_4) ether solution gave an oil, which on distillation (138–140°/0.01 mm.) yielded the crude keto-acid (IV) (9.9 g.).

For purification this keto-acid (27 g.) was converted into its *semicarbazone* (33 g.), m. p. 177–179° (from methanol) (Found: C, 56.9; H, 8.0; O, 19.0; N, 16.5. $\text{C}_{12}\text{H}_{21}\text{N}_3\text{O}_3$ requires C, 56.45; H, 8.3; O, 18.8; N, 16.5%).

The semicarbazone (33 g.) was refluxed with oxalic acid (35 g.) in water (140 ml.) for 1 hr. The mixture was then cooled and extracted with ether, and the ether solution dried (MgSO_4). After removal of the solvent, distillation yielded the pure *keto-acid* (IV) (25 g.), b. p. 140–141°/0.01 mm., n_D^{20} 1.4810 (Found: C, 66.5; H, 9.1; O, 25.0. $\text{C}_{11}\text{H}_{18}\text{O}_3$ requires C, 66.6; H, 9.15; O, 24.2%). The *S*-benzylthiuronium salt melted at 155–156° (from aqueous ethanol) (Found: C, 62.55; H, 7.65; O, 13.6; S, 9.0. $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_3\text{S}$ requires C, 62.6; H, 7.7; O, 13.2; S, 8.8%).

(b) To a suspension of metallic potassium (9 g.) in dry benzene (150 ml.) methyl 2-oxocycloheptanecarboxylate (40 g.) was added dropwise during 0.5 hr. The reaction was exothermic and the solution became orange. Sodium iodide (0.8 g.) in absolute ethanol (4 ml.), followed

by methyl γ -bromobutyrate (42.5 g.) in dry benzene (70 ml.), was added dropwise and the mixture boiled and stirred for 38 hr. It was then poured on ice-salt, and the oil which separated was extracted with ether. From the dried (MgSO_4) ether solution a heavy oil was obtained, which was purified by distillation in a short-path still at 120—130°/0.01 mm. The product (63 g.) was hydrolysed and decarboxylated with barium hydroxide as described in (a), giving an oil (40 g.), which partially solidified on distillation at 140—144°/0.01 mm. Trituration with ether separated the oil (22 g.) from ether-insoluble crystals (16.5 g.). The solid was identified by its m. p., mixed m. p., and infrared spectrum as suberic acid. The oil was identical with the keto-acid (IV) obtained in method (a).

γ -(2-Hydroxycycloheptyl)butyric Acid (V; R = H).—To a methanol solution of the keto-acid (IV) (31.5 g.) sodium borohydride (10 g.) was added in small portions under cooling. The mixture was set aside overnight and the solvent evaporated under reduced pressure. Water and dilute hydrochloric acid were added and the mixture was extracted with ether. Drying (MgSO_4) and evaporation of the solvent gave a quantitative yield of the hydroxy-acid (V; R = H). The *S*-benzylthiuronium salt melted at 146—147° (from water) (Found: C, 61.9; H, 8.4; N, 7.7; S, 8.75. $\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}_3\text{S}$ requires C, 62.3; H, 8.2; N, 7.65; S, 8.7%). The 3,5-dinitrobenzoate had m. p. 88—89° (from ethanol) (Found: C, 54.8; H, 5.5; N, 7.2. $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_8$ requires C, 54.8; H, 5.6; N, 7.1%).

Methyl γ -(2-Hydroxycycloheptyl)butyrate (V; R = Me).—The crude hydroxy-acid (V; R = H) (30 g.) was treated with an excess of ethereal diazomethane. The solution was kept for 2 hr. at room temperature (under the hood!), washed with sodium hydrogen carbonate solution, and water, and dried (MgSO_4). The hydroxy-ester (26 g.) had b. p. 108—110°/0.01 mm., n_D^{20} 1.4815 (Found: C, 67.3; H, 10.6; O, 22.3. $\text{C}_{12}\text{H}_{22}\text{O}_3$ requires C, 67.25; H, 10.35; O, 22.4%), ν_{max} (in CHCl_3) 3630, 3450, 1725 cm^{-1} .

Methyl γ -(Cyclohept-1-enyl)butyrate (VI; R = Me).—(a) A solution of hydroxy-ester (V; R = Me) (2 g.) in dry benzene was shaken with phosphorus pentoxide (2 g.) overnight. Cold water (20 ml.) was then added and the mixture extracted with ether. The ether solution was washed with dilute sodium hydrogen carbonate solution and water and dried (MgSO_4). Evaporation gave the olefinic ester (1 g.), b. p. 67—70°/0.01 mm., n_D^{18} 1.4700 (Found: C, 72.85; H, 10.3; O, 17.0. $\text{C}_{12}\text{H}_{20}\text{O}_2$ requires C, 73.4; H, 10.3; O, 16.3%), ν_{max} (in CHCl_3) 1725 cm^{-1} . It showed a strong positive test with tetranitromethane.

(b) The hydroxy-ester (V; R = Me) (8 g.) was dissolved in dry pyridine (15 ml.) and redistilled phosphorus oxychloride (6 g.) was added at 0°. The solution was set aside overnight at room temperature and then heated on a steam-bath for 1 hr. The mixture was cooled and decomposed with ice-water (20 ml.). The separated oil was extracted with ether, and the organic layer washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water and dried on MgSO_4 . After evaporation of the solvent, the olefinic ester (6.5 g.) was obtained, identical in properties and spectrum with that obtained in (a).

(c) The hydroxy-ester (V; R = Me) (8 g.) in dry pyridine (15 ml.) was treated overnight at room temperature with toluene-*p*-sulphonyl chloride (8 g.). The mixture was decomposed with ice-water (20 ml.) and worked up as usual. The crude dry toluene-*p*-sulphonate was refluxed in dry pyridine (40 ml.) for 2 hr. The cooled mixture was acidified with dilute sulphuric acid and extracted with ether-hexane. The olefinic ester (6 g.), obtained from the organic layer, was identical in its properties and spectrum with those obtained in (a) and (b).

The above ester (6.5 g.) was heated under reflux for 4 hr. with an excess of 15% aqueous potassium hydroxide. The cooled solution was acidified with dilute hydrochloric acid and extracted with ether. After the organic layer had been washed with water and dried (MgSO_4), the solvent was removed, and the residual oil distilled, yielding the pure olefinic acid (4.5 g.), b. p. 120—122°/0.01 mm., n_D^{18} 1.4867 (Found: C, 72.3; H, 9.95; O, 16.7. $\text{C}_{11}\text{H}_{19}\text{O}_2$ requires C, 72.5; H, 9.95; O, 17.5%). The *S*-benzylthiuronium salt had m. p. 148—149° (from aqueous ethanol) (Found: C, 65.5; H, 7.8; N, 8.0; S, 9.25. $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$ requires C, 65.5; H, 8.0; N, 8.0; S, 9.2%).

2,3,4,5,6,7,8,9-Octahydrobenzocyclohepten-1-one (III).—In a three-necked flask redistilled acetic anhydride (1030 ml.), acetic acid (64 ml.) and a solution of freshly melted zinc chloride (1.28 g.) in acetic acid were mixed. The olefinic acid (VI; R = H) (90 g.) was added dropwise and the mixture kept overnight under nitrogen. The solution was then boiled for 2 hr., concentrated under reduced pressure, diluted with ice-water, and extracted with ether. The extract was washed with sodium hydrogen carbonate solution, then water, dried (MgSO_4), and

evaporated, giving a crude oil (88 g.) which according to its infrared spectrum was a mixture of the unsaturated ketone and a lactone.

The crude oil was heated under reflux for 2 hr. with an excess of 10% sodium hydroxide solution. After the usual working up the crude oil (48 g.) showed only the infrared absorption of the unsaturated carbonyl group. From the acidified alkaline solution the acid (VI; R = H) (34 g.) was isolated.

The crude ketone (48 g.) was chromatographed in hexane on basic alumina (1900 g.; Fisher). Elution with hexane-benzene (3 : 1) gave a mobile oil (38 g.) which was distilled at 80–82°/0.01 mm. The ketone was finally purified by preparing its semicarbazone, which was smoothly cleaved by refluxing it with dilute oxalic acid. The ketone (III) has a terpene-like odour, b. p. 80°/0.01 mm., and n_D^{25} 1.5265 (Found: C, 79.75; H, 9.7; O, 10.7. Calc. for $C_{11}H_{16}O$: C, 80.4; H, 9.8; O, 9.7%), ν_{max} . (in $CHCl_3$) 1650, 1625 cm^{-1} , λ_{max} . (in EtOH) 249, 308 $m\mu$ (log ϵ 4.112, 2.106 respectively). Repeating the purification did not improve the analytical results.

The deep-red 2,4-dinitrophenylhydrazone had m. p. 261–262° (from ethanol-chloroform) (Found: C, 59.2; H, 5.8; O, 18.6; N, 16.5. $C_{17}H_{20}N_4O_4$ requires C, 59.3; H, 5.85; O, 18.6; N, 16.3%). The semicarbazone (from aqueous methanol) melted at 206–207° (Found: C, 65.3; H, 8.3; O, 7.5; N, 18.9. $C_{12}H_{19}N_3O$ requires C, 65.1; H, 8.65; O, 7.2; N, 19.0%). The oxime had m. p. 148–149° (from aqueous methanol) (Found: C, 73.15; H, 9.35; O, 9.0; N, 7.8. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.6; O, 8.9; N, 7.8%).

2,3,4,5,6,7,8,9-Octahydrobenzocyclohepten-1-ol (VII; R = H).—To a solution of ketone (III) (1 g.) in dry tetrahydrofuran (40 ml.) was added lithium hydridotri-*t*-butoxyaluminate (1.6 g.) under nitrogen, and the solution refluxed for 2 hr. The mixture was decomposed with Rochelle salt solution and extracted with ether. The oily residue (0.85 g.) obtained after removal of the solvent was chromatographed in pentane on basic alumina (35 g.; Fisher). Elution with pentane gave an unidentified mixture of cycloalkenes (0.12 g.), and with hexane-benzene (1 : 1) the solid allylic alcohol (0.38 g.), m. p. 55–56°, b. p. 100° (bath)/0.01 mm. (Found: C, 79.3; H, 10.7; O, 9.5. $C_{11}H_{18}O$ requires C, 79.5; H, 10.9; O, 9.6%).

The same compound was obtained on reduction with lithium aluminium hydride in dry ether.

The alcohol (1 g.), dry pyridine (4 ml.), and acetic anhydride (4 ml.) were kept together at room temperature overnight, giving an acetate (1.1 g.), b. p. 68–70°/0.2 mm., n_D^{20} 1.4970 (Found: C, 74.8; H, 9.7; O, 15.5. $C_{13}H_{20}O_2$ requires C, 75.0; H, 9.7; O, 15.4%).

Hydrolysis of the Acetate (VII; R = Ac) and Oxidation of the Resulting Alcohol (VII; R = H).—The distilled acetate (0.8 g.) in 2% sodium methoxide solution was kept overnight at room temperature. After removal of the methanol, saturated sodium chloride (10 ml.) was added, and the oil taken up in ether. After drying ($MgSO_4$) and removal of the solvent, the allylic alcohol (0.63 g.) was obtained. The alcohol (0.6 g.) was shaken overnight with activated manganese dioxide¹⁹ (4 g.) in carbon tetrachloride (10 ml.). The dried filtrate gave the crude unsaturated ketone (0.52 g.), which was purified by chromatography and successive distillation (b. p. 80°/0.01 mm.). The ketone was identical in its infrared spectrum as well as in m. p. of its derivatives with compound (III), described above.

Catalytic Reduction of Compound (III).—(a) *Neutral medium*. The unsaturated ketone (III) (2 g.) was hydrogenated in ethanol (100 ml.) in the presence of 10% palladised carbon (0.1 g.) at room temperature. After about 3 hr. 1 mol. of hydrogen had been taken up. Filtration and concentration of the filtrate under reduced pressure gave an oil (1.95 g.), b. p. 52–53°/0.01 mm. This was subjected to quantitative infrared analysis, which showed it to be a mixture (subsequently referred to as mixture "A") of the *cis*- and *trans*-ketone (XII and XIII) containing $83 \pm 2.5\%$ of the former.

(b) *Acidic or basic medium*. A mixture of the unsaturated ketone (III) (0.25 g.), ethanol (10 ml.), 10% palladised carbon (0.05 g.), and 10% hydrochloric acid (1 ml.) or 10% sodium hydroxide solution (1 ml.) was hydrogenated at room temperature. After 1 mol. of hydrogen had been taken up (in the acidic medium after about 3 hr., in basic medium after about 2 days), the reaction stopped. Filtration and concentration gave an oil (0.24 g.), b. p. 53–54°/0.01 mm., shown by quantitative infrared analysis to contain about 43% of *cis*- and 57% of *trans*-ketone.

Epimerisation of Mixture "A".—(a) *With sodium methoxide*. The mixture "A" (1 g.) in dry methanol (50 ml.) containing 10% sodium methoxide solution (3 ml.) was refluxed for 2 hr. The new equilibrium mixture (0.95 g.) was isolated by adding saturated sodium chloride

¹⁹ Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

solution (20 ml.) after most of the methanol had been removed and subsequent ether-extraction; it had b. p. 60—61°/0.2 mm. The same reaction was repeated and the reaction time increased to 20 hr.

(b) *On basic alumina.* Mixture "A" (0.5 g.) in pentane was kept overnight on a column prepared from basic alumina (6 g.; Merck). The equilibrated ketone mixture was then eluted with pentane-ether (95 : 5), and had b. p. 60°/0.2 mm.

The infrared spectra of mixtures showed that in each case (a) and (b) 85—87% of the *trans*-epimer had been formed.

*trans-Perhydrobenzocyclohepten-cis(eq)-1-ol*²⁰ (XV) and *-trans(ax)-1-ol*²⁰ (XVI).—Epimerised (with sodium methoxide in methanol; see foregoing reaction), mixture "A" (2 g.) in dry tetrahydrofuran (80 ml.) was stirred overnight with lithium hydridotri-*t*-butoxy-aluminate (5 g.) at 50°. The usual working-up (decomposition with Rochelle salt solution) gave the oily crude mixture (2 g.) of the saturated alcohols, which was purified by chromatography on basic alumina (80 g.; Alcoa) in hexane. Elution with hexane and increasing amounts (up to 30%) of methylene chloride separated the epimeric *trans*-alcohols, the axial being eluted before the equatorial epimer (total 1.7 g.). In the last fractions a minute amount of *cis*-alcohol (XIV) was eluted.

The *trans-trans(ax)-alcohol* (XVI) had b. p. 77—78°/0.5 mm., n_D^{25} 1.5000 (Found: C, 78.3; H, 11.9; O, 9.6. $C_{11}H_{20}O$ requires C, 78.5; H, 12.0; O, 9.5%), ν_{max} (in CS_2) 3640, 3500, 1000 cm^{-1} . The *p-nitrobenzoate* had m. p. 70° (from methanol) (Found: C, 68.2; H, 7.2; O, 20.3; N, 4.5. $C_{18}H_{23}NO_4$ requires C, 68.1; H, 7.3; O, 20.2; N, 4.4%). The *acetate*, prepared by acetic anhydride in pyridine, had b. p. 59—60°/0.05 mm., n_D^{20} 1.4792 (Found: C, 74.4; H, 10.6; O, 15.3. $C_{13}H_{22}O_2$ requires C, 74.2; H, 10.5; O, 15.2%), ν_{max} (in CS_2) 1240 (composed), 1218 (shoulder), 1202 cm^{-1} (shoulder).

The *trans-cis(eq)-alcohol* (XV) had m. p. 56° (from pentane at liquid-air temperature) (Found: C, 78.3; H, 11.8; O, 9.7%), ν_{max} (in CS_2) 3640, 3500, 1046 cm^{-1} . The *p-nitrobenzoate* melted at 100—101° (from methanol) (Found: C, 68.1; H, 7.3; O, 20.3; N, 4.6%). The *acetate* had b. p. 63°/0.01 mm., n_D^{25} 1.4780 (Found: C, 74.3; H, 10.3; O, 15.3%), ν_{max} (in CS_2) 1240 cm^{-1} .

When the epimeric *trans*-alcohols were eluted from the column (see above) without separation (in one fraction), the proportions of the equatorial and axial isomers was found to be $53 \pm 2.5\%$ and $47 \pm 2.5\%$ respectively.

cis-Perhydrobenzocyclohepten-1-ol (XIV).—Mixture "A" (1 g.) in dry ether (50 ml.) was added dropwise to a stirred and cooled slurry of lithium aluminium hydride (0.25 g.) in dry ether (50 ml.). After being stirred overnight at room temperature, the mixture was worked up as usual (with Rochelle salt). The crude mixture of isomeric alcohols (0.95 g.) was chromatographed in a minimum volume of pentane on alumina (40 g.; Alcoa). Elution was with a large volume of pentane-ether (95 : 5). The first fractions gave a mixture of *trans*-alcohols (XV, XVI) (0.12 g.) (identified by their infrared spectra and derivatives), followed by the pure *cis-alcohol* (0.6 g.), m. p. 60° (from pentane at liquid-air temperature) (Found: C, 78.4; H, 11.9; O, 9.7%), ν_{max} (in CS_2) 3640, 3400, 1050, 1010 cm^{-1} . The *p-nitrobenzoate* had m. p. 75° (from ethanol) (Found: C, 67.9; H, 7.3; O, 20.3; N, 4.6%). The *acetate* had b. p. 68°/0.02 mm., n_D^{18} 1.4810 (Found: C, 74.5; H, 10.5; O, 15.4%), ν_{max} (in CS_2) 1240, 1228 (shoulder), 1220 cm^{-1} (shoulder).

trans-Perhydrobenzocyclohepten-1-one (XIII).—The *trans-alcohol* (XVI) (0.6 g.) in pyridine (1 ml.) was added to the cooled chromic oxide-pyridine complex (from 0.6 g. of chromic oxide and 6 ml. pyridine), and the mixture kept overnight at room temperature. Ether and benzene were added and the suspension was filtered, washed with 10% acetic acid solution containing ferrous sulphate, then with water, 5% sodium hydrogen carbonate solution, and again with water, and dried ($MgSO_4$). On removal of the solvent the *trans-perhydrobenzocyclohepten-1-one* (XIII) was obtained in almost quantitative yield, with b. p. 55°/0.01 mm., n_D^{20} 1.4948 (Found: C, 79.2; H, 10.7; O, 9.9. $C_{11}H_{18}O$ requires C, 79.5; H, 10.9; O, 9.6%), ν_{max} (in CS_2) 1710, 1176, 913 cm^{-1} . The *2,4-dinitrophenylhydrazone* had m. p. 226° (from methanol-chloroform) (Found: C, 59.1; H, 6.3; N, 16.0. $C_{17}H_{22}N_4O_4$ requires C, 58.9; H, 6.4; N, 16.2%). The *semicarbazone* melted at 209—210° (from aqueous ethanol) (Found: C, 64.5; H, 9.1; N, 19.0. $C_{12}H_{21}N_3O$ requires C, 64.5; H, 9.5; N, 18.8%). The *oxime* had m. p. 141—142° (from ethanol) (Found: C, 73.0; H, 10.7; N, 7.7. $C_{11}H_{19}NO$ requires C, 72.9; H, 10.6; N, 7.7%).

²⁰ The *trans*-1 and *cis*-1 designation refer to the relation of the 1-substituent to the neighbouring hydrogen atom of the ring junction.

The same *trans*-ketone (XIII) was obtained when the alcohol (XV) was oxidised by the same method.

cis-Perhydrobenzocyclohepten-1-one (XII).—The *cis*-perhydrobenzocyclohepten-1-ol (XIV) was oxidised with the chromic oxide-pyridine complex as described for preparation of the *trans*-ketone (XIII), to give the *cis*-ketone, b. p. 53°/0.1 mm., n_D^{20} 1.4959 (Found: C, 78.7; H, 10.9; O, 9.95%), ν_{\max} (in CS₂) 1706, 1093, 781 cm.⁻¹. The *semicarbazone* had m. p. 182—183° (from methanol) (Found: C, 64.4; H, 9.3; N, 18.6%). The *oxime* had m. p. 88—89° (from light petroleum) (Found: C, 72.7; H, 10.5; N, 7.9%).

Epimerisation of *cis*-ketone (XII) with sodium methoxide in methanol for 5 hr. (method described above for epimerisation of mixture "A") gave a mixture containing 86% of the *trans*-isomer (XIII).

The semicarbazones of the saturated *cis*- and *trans*-ketones (XII and XIII respectively) behaved as homogeneous compounds, and known mixtures of them were readily separated when chromatographed on basic alumina.

Reduction of Unsaturated Ketone (III) with Lithium in Liquid Ammonia.—(a) The unsaturated ketone (III) (1 g.) in dry ether (5 ml.) was added to a mixture of lithium (0.1 g.) and liquid ammonia (500 ml.), prepared in a three-necked flask and cooled with acetone-solid carbon dioxide. After a few minutes more lithium (*ca.* 1.5 g.) was added in grain-sized pieces to the stirred solution until the blue colour persisted for 2 hr. The colour was then discharged by addition of solid ammonium chloride (*ca.* 1 g.). The ammonia was allowed to evaporate slowly and the residue taken up in water and extracted with ether. The ether solution was washed with dilute hydrochloric acid and then water, dried (MgSO₄), and evaporated. The resulting oil (0.85 g.) was shown to be a mixture of starting material and saturated ketones (XII and XIII). Separation in this stage was difficult; therefore the mixture was directly reduced by adding its ethereal solution (20 ml.) to a stirred and cooled slurry of lithium aluminium hydride (0.25 g.) in dry ether (20 ml.). The mixture was stirred at room temperature for 1 hr. and worked up on the usual way. The crude alcoholic product (0.8 g.) was chromatographed in pentane on basic alumina (35 g.; Alcoa). With a large volume of pentane-ether (9:1) the saturated alcohols (0.6 g.) were eluted before the unsaturated one (0.1 g.). The mixture of saturated alcohols was directly oxidised with the chromic oxide-pyridine complex as described above. The ketone mixture thus obtained was analysed by the infrared method and shown to contain 21 ± 2.5% of the *cis*- and 79 ± 2.5% of the *trans*-isomer.

(b) To a cooled (acetone-carbon dioxide) and stirred solution of lithium (2 g.) in liquid ammonia (500 ml.), absolute ethanol (10 ml.) was added, followed by a solution of the unsaturated ketone (III) (1 g.) in dry ether (5 ml.). Stirring was continued for 2 hr., ammonium chloride (1 g.) added, and the mixture worked up as described in (a). The oily product (0.65 g.) was chromatographed in pentane on basic alumina (30 g.; Alcoa). Elution with pentane-ether (9:1) gave a good separation between small amount of ketonic mixture (0.08 g.; partly starting material) and a mixture of saturated alcohols (0.5 g.). The alcohol mixture was oxidised with chromic oxide in pyridine, as described above, to give the mixture of saturated ketones (XII and XIII), containing 55 ± 2.5% of *cis*-isomer (estimated by the infrared method).

Epimerisation of Mixture "A" with Lithium-Liquid Ammonia.—To the stirred and cooled (acetone-carbon dioxide) mixture prepared by adding mixture "A" (0.25 g.) in dry ether (1 ml.) to liquid ammonia (100 ml.), lithium (0.2 g.) was added and the blue solution stirred for 2 hr. After the usual working up, the saturated ketone mixture was found by the infrared method to contain 50 ± 2.5% of *cis*-ketone.

Measurement of Relative Oxidation Rates of Alcohols.—These were kindly determined by Professor A. Eschenmoser and Mr. L. Moldovanyi at the Eidgenössische Technische Hochschule, Zürich. The concentrations were 6.0 × 10⁻⁴ mole/l. for the alcohols and 8.0 × 10⁻⁴ mole/l. for chromic oxide, in 90.5% acetic acid at 20° ± 1°. The rate constants (see Table 3) were calculated as described previously.²¹

TABLE 3.
Relative oxidation rates.

Alcohol	<i>k</i>	Half-life (min.)	Suggested conformation
(XV)	1.9	63	<i>eq</i>
(XVI)	5.1	18	<i>ax</i>

²¹ Eschenmoser, *Helv. Chim. Acta*, 1955, **38**, 1529.

Measurement of Relative Rates of Saponification of Acetates.—The acetate (0.03 g.) was dissolved in 95% ethanol (5 ml.) and the volume was made up to 25.0 ml. with $N/40$ -alcoholic sodium hydroxide. The solution was kept at $25.0^\circ \pm 1^\circ$, and 1.00 ml. portions were withdrawn at intervals and titrated with 0.01*N*-hydrochloric acid. The results, which were checked against a control solution, are shown in Table 4.

TABLE 4.

		Relative hydrolysis rates.							
		(% of the acetates saponified after (hr.))							
Alcohol		2	5	12	24	29	36	48	Suggested conformation
(XV)	6.5	15.5	32.75	49.15	62.25	73.75	82.0		<i>eq</i>
(XVI)	0.0	0.0	0.0	0.9	7.15	11.75	16		<i>ax</i>

Infrared Spectra.—Measurements were made with a Perkin-Elmer model 21 spectrometer. In the quantitative analysis, the spectra of the ketones were measured at a total of 20.0 mg./10.50 ml. of CS_2 in 0.50 mm. cells, and those of the alcohols at 10.0 mg./0.50 ml. of CS_2 in 0.50 mm. cells.

Nuclear Magnetic Resonance Spectra.—The spectra were run at a frequency of 60 Mc./sec. on a Varian spectrometer model V-4300-c, and chemical shifts were determined by the side-band technique. The spectral sample consisted of 66.9 mg. of ketone in 0.6 ml. of deuteriochloroform containing 2% of dissolved tetramethylsilane and was observed immediately after preparation in a thin-walled 5 mm. tube, while spinning.

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