117. *Epimeric Alcohols of the* cyclo*Hexane Series. Part I.* cis- *and* trans-*Dihydrocryptol.*

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Dihydrocryptol is available in two forms, one prepared by reduction of cryptone with sodium and alcohol or by the Ponndorf method, and the other by electrolytic reduction of the ketone or its hydrogenation under pressure in the presence of a suitable catalyst.

The pure alcohols become available through the hydrogen phthalates, as the ester of the *cis*-epimer (electrolytic, Raney nickel, etc.) forms a soluble magnesium salt by means of which the isomers are readily separated and assayed.

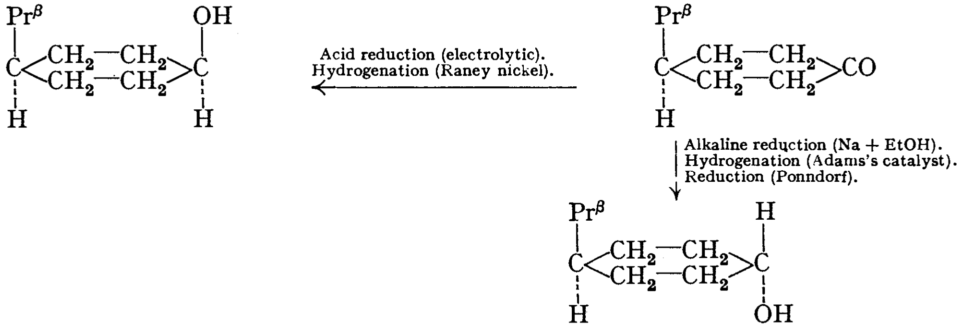
The epimer obtained on pressure hydrogenation depends on the catalyst used. Raney nickel at 120° gives practically pure cis-*dihydrocryptol*, platinum oxide (Adams) gives approximately 90% of the trans-*form*, and copper–barium–chromium oxide gives about 60% of the *cis*-epimer and 40% of the *trans*-form.

The configurations of the alcohols are deduced by the application of the Auwers–Skita rule and consideration of the chemical differences of the two epimers.

FURTHER work on the dihydrocryptols (Gillespie, Macbeth, and Swanson, J., 1938, 1820) has been carried out with a view to their preparation in quantity and the determination of their configurations.

It has long been known that one form of an epimeric pair has the higher density, refractive index, etc., the differences in general being most marked when the substituted radical and the hydroxyl group are attached to adjacent carbon atoms. Von Auwers (*Annalen*, 1920, **420**, 92) concluded that the higher values were associated with the *cis*-epimer, and the experimental support for this opinion adduced by Skita (*ibid.*, 1922, **427**, 255; 1923, **431**, 1) led to the Auwers–Skita rule. Hückel (*ibid.*, 1937, **533**, 1) has shown that the rule applies rigidly only to 1 : 2-derivatives of *cyclo*hexanes and *cyclo*pentanes, exceptions being found in other position isomers. Chemical differences in the epimers, however, are also observed, the *cis*-compound, for example, being produced by catalytic hydrogenation of monosubstituted *cyclo*hexanones in acid solution, and the *trans*-form by alkaline reduction with sodium and alcohol. Vavon and his co-workers (*Bull. Soc. chim.*, 1931, **49**, 937) showed that the *cis*-alcohols were esterified with greater difficulty than the *trans*-forms, and the esters of the latter were more readily hydrolysed.

Experimental evidence along these lines enables the configurations of the two dihydrocryptols to be established with some degree of certainty, as summarised below :



cis-Dihydrocryptol.	*trans*-Dihydrocryptol.
Greater density : $d_{20^\circ}^{20^\circ}$ 0·9212, $d_{50^\circ}^{50^\circ}$ 0·9084	Lesser density : $d_{20^\circ}^{20^\circ}$ 0·9156, $d_{50^\circ}^{50^\circ}$ 0·9053
Higher refractivity : $n_D^{20^\circ}$ 1·4671	Lower refractivity : $n_D^{20^\circ}$ 1·4658
Slower hydrolysis :	Quicker hydrolysis :
H phthalate, k^{55°, 0·954 × 10^{-4}	H phthalate, k^{55°, 2·48 × 10^{-4}
acetate, k^{55°, 0·762 × 10^{-3}	acetate, k^{55°, 2·08 × 10^{-3}
Hydrogen phthalate, m. p. 130°	Hydrogen phthalate, m. p. 115°
Phenylurethane, m. p. 89°	Phenylurethane, m. p. 114·5°
α-Naphthylurethane, m. p. 113°	α-Naphthylurethane, m. p. 159·5°
p-Nitrobenzoate, m. p. 69·5°	*p*-Nitrobenzoate, m. p. 75—75·5°
3 : 5-Dinitrobenzoate, m. p. 112°.	3 : 5-Dinitrobenzoate, m. p. 124·5°.

The dihydrocryptols readily form hydrogen phthalates, and the less soluble *cis*-ester is readily obtained free from the *trans*-compound by crystallisation from light petroleum. The best method of separation is by means of magnesium chloride: when a solution of this salt is added to a hot solution (about 2%) of the sodium salts of the phthalates, the magnesium salt of the *trans*-ester is precipitated.

The pure *alcohols* are obtained by steam distillation of the hydrogen phthalates in presence of alkali; a white solid formed during the hydrolysis of the *cis*-phthalate is a hydrate of the *cis*-alcohol containing 3·5 molecules of water and having a transition point at 34·2—34·4°. The readiness with which the *cis*-alcohol forms this hydrate distinguishes it immediately from its epimer.

The assay of the amounts of the two hydrogen phthalates derived from samples of crude dihydrocryptol isolated as experimental products shows that the reduction of cryptone by sodium and alcohol gives a dihydrocryptol consisting essentially of the *trans*-form. The product of reduction of dihydrocryptone by Ponndorf's method, or the similar treatment of cryptone, followed by saturation of the double bond, consists approximately of 95% of the *trans*-alcohol together with the balance of the *cis*-epimer. The best method for preparing the *cis*-alcohol is undoubtedly the hydrogenation of cryptone at 120° and a pressure of 100 atms., with Raney nickel as the catalyst; the double bond is rapidly reduced, the conversion into the alcohol is completed in a few hours, and the product is contaminated with traces only of the *trans*-isomer. The proportion of the latter is much increased when the hydrogenation is carried out at laboratory temperature. Hydrogenation with the Adams's platinum oxide catalyst gives the *trans*-alcohol as the main product, some 10% of the *cis*-form being present. A mixture of the alcohols containing approximately 60% of the *cis*-form is obtained by the hydrogenation of cryptone at 120° and 100 atms. with copper–barium–chromium oxide (*J. Amer. Chem. Soc.*, 1932, **54**, 1138) as the catalyst.

The rates of hydrolysis of the pure hydrogen phthalates of *cis*- and *trans*-dihydrocryptol were measured at 55° to obtain further data on which to base configuration determinations. The reaction velocities are in agreement with the evidence of the other factors considered, as are also the reaction velocities for the saponification of the acetates of the two alcohols. All the available evidence is in favour of the configurations of the two alcohols in the sense stated above, and it therefore appears valid to use them as reference substances in the configuration determination of *d*- and *l*-cryptol (Macbeth and Winzor, this vol., p. 264) and other related compounds.

EXPERIMENTAL.

Hydrogenation Experiments.—The hydrogenation of cryptone or dihydrocryptone was carried out with various catalysts and at different temperatures, the initial pressure being usually 100 atms. The proportions of *cis*- and *trans*-alcohols formed were assayed by separation of the magnesium salts of the hydrogen phthalates (see below). In all cases the ketone was reduced in neutral absolute-alcoholic solution. Typical experiments are described below.

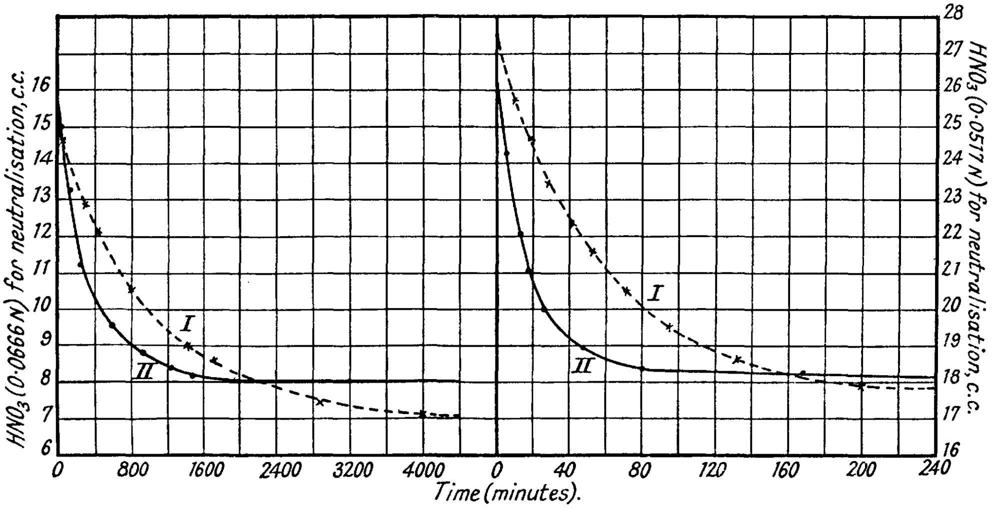
(a) *Raney nickel.* Cryptone (75 g.) in alcohol (50 c.c.) containing freshly prepared Raney nickel (10 g.) was placed in a glass reaction vessel and introduced into a bomb hydrogenation apparatus. The temperature was raised to 120°, the pressure of the hydrogen then being about 100 atms. After 10 minutes' shaking, half the total absorption of hydrogen occurred, representing the saturation of the double bond; hydrogenation was complete after 4—5 hours. The cooled product was filtered from the catalyst, poured into water, and extracted with ether, and the extract was treated with sodium bisulphite solution (35%) to remove any traces of unchanged ketone, washed, and dried. Removal of the solvent and distillation gave the dihydrocryptol fraction (50 g.) at 68°/0·6 mm. The product consisted essentially of the *cis*-alcohol together with some non-alcoholic material. In another experiment dihydrocryptone was the initial material, and under the above conditions the *cis*-alcohol was similarly isolated.

(b) *Platinum oxide (Adams) catalyst.* Cryptone or dihydrocryptone (25 g.) in alcohol (80 c.c.) containing the catalyst (0·3 g.) was shaken in the bomb at the ordinary temperature for 4 hours, the initial pressure of the hydrogen being 70 atms. The product, worked up as in the preceding case, gave crude dihydrocryptol (20 g.), which was shown by the magnesium ester phthalate method to consist of approximately 90% of the *trans*-alcohol, with the balance of the *cis*-epimer.

(c) *Copper–barium–chromium oxide catalyst.* Hydrogenation of cryptone (50 g.) in alcohol (80 c.c.) containing the catalyst (6 g.) at 120° and 100 atms. was complete in 2 hours. The product (40 g.), isolated in the usual way, was shown by examination of the phthalates to consist of approximately 60 and 40% of the *cis-* and the *trans*-alcohol respectively.

Sodium Reduction of Dihydrocryptone.—The ketone (25 g.) in ethanol (500 c.c.) was heated under reflux while sodium (50 g.) was added during 3 hours. The partly cooled mixture was diluted with water, the greater part of the alcohol distilled off, and the dihydrocryptol steam-distilled. After being worked up in the usual way, crude dihydrocryptol (22 g.) was collected at 72°/1 mm., from which a pure sample of the *trans*-hydrogen phthalate was prepared (see below).

Phthalate Formation.—The hydrogen phthalates were prepared (10 hours' heating) by the method described by Gillespie, Macbeth, and Swanson (J., 1938, 1823). The ester separating on acidification of the sodium carbonate solution was extracted with chloroform, and the residue after removal of the solvent was crystallised from light petroleum (b. p. 60—90°). The *cis*-ester was readily purified by this treatment, but fractional crystallisation of the *trans*-ester was laborious when any appreciable quantity of the less soluble *cis*-phthalate was present. Typical examples are as follows : (a) *Sodium reduction product.* The product from the crude dihydrocryptol (22 g.) and phthalic anhydride (25 g.) gave an oily by-product (10 g.) containing unchanged dihydrocryptone (3 g.) ; the regenerated phthalate formed large plates, m. p. 113°, of pure *trans*-hydrogen phthalate after one crystallisation from light petroleum. (b) *Raney nickel product.* The dihydrocryptol (22 g.) gave a by-product (6 g.), together with the pure *cis*-phthalate (27 g.), long flat needles, m. p. 130°, after three recrystallisations from light petroleum. In another experiment with the same catalyst, the product (50 g.) with phthalic anhydride (55 g.) gave an oil (15 g.) and the pure phthalate (46 g.), m. p. 130° (Found : C, 70·2; H, 7·5. Calc. : C, 70·3; H, 7·6%). (c) *Ponndorf reduction product.* Dihydrocryptol (54 g.) prepared by reduction with aluminium *iso*propoxide (Gillespie, Macbeth, and Swanson, *loc. cit.*) was esterified by heating with phthalic anhydride (60 g.). The non-alcoholic fraction (15 g.) was recovered on ether extraction of the solution of the product in sodium carbonate, and bulk recrystallisation of the recovered phthalate from light petroleum gave a product which became more and more impure owing to accumulation of the less soluble *cis*-ester initially present; (one crystallisation) 67 g., m. p. 109—112°; (three crystallisations) 52 g., m. p. 105—110°; after a further crystallisation the m. p. was 102—110°. The product was then purified by the magnesium chloride method.



I cis-*Dihydrocryptol hydrogen phthalate.*
II trans-*Dihydrocryptol hydrogen phthalate.*

I cis-*Dihydrocryptol acetate.*
II trans-*Dihydrocryptol acetate.*

Purification of the Hydrogen Phthalates by Magnesium Chloride.—A solution of the crude hydrogen phthalate in an excess of aqueous sodium carbonate was neutralised with hydrochloric acid and diluted until the concentration of the phthalate was approximately 2%. To the warmed solution (60—70°), hot neutral magnesium chloride solution was slowly added with shaking as long as precipitation occurred. After cooling, the granular precipitate of the magnesium salt was collected and washed with hot water. Acidification of the filtrate and washings precipitated the *cis*-hydrogen phthalate, which, extracted with chloroform and recrystallised from light petroleum, was obtained in long flat needles, m. p. 130°. [The magnesium salt of the *trans*-ester may be further purified by solution in boiling alcohol, from which, after addition of cold water (4 vols.), it separates, on cooling, in flat pearly plates, m. p. 127—128°]. When decomposed by hydrochloric acid, the magnesium salt yielded the *trans*-hydrogen phthalate; after extraction with chloroform and crystallisation from light petroleum, this was obtained in plates, m. p. 115° (Found: C, 70·5; H, 7·55. Calc.: C. 70·3; H, 7·6%).

The application of the method to the crude phthalate obtained from the copper–barium-chromite hydrogenation gave the *trans*-ester (6 g.), m. p. 115° after one crystallisation, and the *cis*-derivative (8 g.), m. p. 130°.

The method of separation was also tested on the phthalates in the still residues after recovery of the light petroleum from the considerable quantities of mother-liquors accumulated during the work. The crude product (34 g.) gave pure samples of the two phthalates after one crystallisation from light petroleum. The method is therefore not only convenient but efficient.

Pure cis- *and* trans-*Dihydrocryptol.*—The pure alcohols were obtained from the purified hydrogen phthalates by steam distillation in the presence of potassium hydroxide. The possibility of transmutation of the alcohol is thus minimised, as it is removed from the alkaline medium almost as quickly as it is formed in the hydrolysis.

In a typical experiment the *trans*-ester (30 g., m. p. 115°) was added to 4% potassium hydroxide solution (580 c.c.; 4 mols.) and steam distilled. Frothing occurred at first, but was quickly suppressed by the separation of the alcohol. After the major part of the alcohol had been removed, frothing again set in, and the rate of steam distillation was then slowed down. All the alcohol was collected in less than 40 minutes. After extraction of the distillate with ether, drying with anhydrous magnesium sulphate, and removal of the solvent, the *trans*-dihydrocryptol was bulked with the products of two other separations and distilled under reduced pressure. From 77 g. of the hydrogen phthalate a yield of pure trans-*dihydrocryptol* (32·5 g.) was obtained, b. p. 79·5°/1·8 mm., 81°/2·2 mm., $n_{\mathrm{D}}^{20^\circ}$ 1·4658, $d_{20^\circ}^{20^\circ}$ 0·9156, $d_{50^\circ}^{50^\circ}$ 0·9053 (Found: C, 76·05; H, 12·75. $C_9H_{18}O$ requires C, 76·0; H, 12·7%).

Similar treatment of pure *cis*-dihydrocryptol hydrogen phthalate (30 g., m. p. 130°) yielded the free *alcohol*, but the hydrolysis was much slower and extended over 2·5 hours. The distillate solidified in the condenser, a white solid collecting in the receiver also. On working up as described in the preceding case, pure *cis*-dihydrocryptol was collected, b. p. 72°/1·9 mm., 74·5°/2·2 mm, $n_{\mathrm{D}}^{20^\circ}$ 1·4671, $d_{20^\circ}^{20^\circ}$ 0·9212, $d_{50^\circ}^{50^\circ}$ 0·9084 (Found: C, 75·8; H, 12·7%). The alcohol did not solidify on standing or on nucleation with a crystal of the white solid previously collected. The solid itself could not be crystallised from any solvent, and soon disappeared when placed on a tile in a vacuum desiccator. This suggested a hydrate, and the alcohol was found to solidify immediately on the addition of water. cis-*Dihydrocryptol hydrate* contains 3·5 molecules of water, and dilatometer readings fixed its transition point at 34·2—34·4° (Found: C, 52·4; H, 12·4. $C_9H_{18}O,3{\cdot}5H_2O$ requires C, 52·6; H, 12·3%).

Dihydrocryptol Acetates.—The alcohols were esterified with excess of glacial acetic acid and 3% of concentrated sulphuric acid. After standing at room temperature for 48 hours, followed by refluxing on the steam-bath for 30 minutes, the mixture was poured into water, and the ester extracted with ether and worked up in the usual way. cis-*Dihydrocryptol acetate* had b. p. 70·5°/1·1 mm., $n_{\mathrm{D}}^{20^\circ}$ 1·4485 (Found: C, 71·9; H, 11·1. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·95%). trans-*Dihydrocryptol acetate* had b. p. 76°/2 mm., $n_{\mathrm{D}}^{20^\circ}$ 1·4490 (Found: C, 71·9; H, 11·05%). The refractive indices of the esters prepared by this method are therefore no guide to configuration on the Auwers–Skita rule.

The esters were also prepared from the respective alcohols by the Fischer–Speier method; *cis*-dihydrocryptol acetate, b. p. 86—87°/5 mm., $n_{\mathrm{D}}^{20^\circ}$ 1·4484, $d_{30^\circ}^{30^\circ}$ 0·9348; *trans*-dihydrocryptol acetate, b. p. 89—90°/5 mm., $n_{\mathrm{D}}^{20^\circ}$ 1·4488, $d_{30^\circ}^{30^\circ}$ 0·9312. The densities conform to the Auwers–Skita rule, and the configurations are supported by the rates of hydrolysis of the esters. The isolation of the respective alcohols after hydrolysis further showed that no change of configuration occurred during esterification.

Rates of Hydrolysis of Dihydrocryptol Esters.—The hydrolysis were carried out at 55° in a constant-temperature oven. An excess of 0·05N-sodium hydroxide (200 c.c.) was warmed to about 55° and placed in the oven for about 40 minutes to attain its temperature. A weighed quantity of the phthalate (1·5—2·0 g.) was then added, the time being taken as zero on a stop-watch. The time taken for solution of the phthalate was about 2 minutes, but the error due to this was negligible, as the rate of hydrolysis was slow. At appropriate intervals during 40—50 hours, 20 c.c. of the mixture were drawn off and run into 25 c.c. of 0·05N-nitric acid, to which alcohol (50 c.c.) had been added to prevent separation of the products. Titration with 0·117N-barium hydroxide (phenolphthalein) gave a measure of the volume of nitric acid neutralised by the mixture. In the figure these volumes are plotted against time, and the hydrolysis constants are calculated therefrom by substitution in the equation

$$k = 2{\cdot}3026\ [\log N_t + \log (N_0 - N_\infty) - \log N_0 - \log (N_t - N_\infty)]/N_\infty t$$

where N_0, N_t, and N_∞ are the volumes of nitric acid (in c.c.) required for neutralisation at time t_1, time t_2, and at the end of reaction respectively.

Alcoholic solutions of the acetates were used, as these esters do not form water-soluble salts, and an alcoholic (60%) solution of 0·05N-nitric acid was used in the titrations. Graphs similarly constructed to those above are shown in the figure. The reaction velocities were much greater in the case of the acetates, the N_∞ value being taken after 24 hours.

The values of $k^{55°}$ calculated from the curves for the hydrogen phthalates and the acetates are given in the table on p. 518. The rates of hydrolysis are in accord with the figures for refractive indices and densities of the alcohols and are also in agreement with the configurations expected for the alcohols formed by acid and by alkaline reduction.

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