49. *Epimeric Alcohols of the* cyclo*Hexane Series. Part VI. The Optically Active* 3-*Methyl*cyclo*hexanols.*

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The resolution of *dl-cis*-3-methyl*cyclo*hexanol is described, the *d*- and the *l*-form being characterised by a series of derivatives. The alkaloidal salts of the hydrogen phthalate of the *dl-trans*-alcohol give a separation of *l-trans*-3-methyl*cyclo*hexanol, but the isolation of the *d*-component was not satisfactorily achieved by the use of such salts. The use of *l*-menthylaminoacetic acid as a resolving agent has also been examined.

The preparation and characterisation of *dl-cis*- and *dl-trans*-3-methyl*cyclo*hexanols has already been described (*J.*, 1945, 709) and the resolution of the compounds has now been examined. The separation of the *dl-cis*-alcohol into its components is much easier than with the *dl-trans*-compound, for the hydrogen phthalate gives a reasonably stable series of salts with the common alkaloids, and of these the quinine salt may advantageously be used to give the initial separation of the *l*-component, and the strychnine salt may be used to obtain the pure *d*-component from the mother liquors. Although the cinchonidine salt of the *dl-cis*-hydrogen phthalate crystallises well, the physical properties of the *d*-, *l*-, and *dl*-compounds are so much alike that no appreciable resolution can be effected by the use of this salt. The best method of getting a good initial separation of the *l-cis*-quinine salt is to use the modification of Pickard's method (*J.*, 1907, **91**, 1973) in which half of the hydrogen phthalate is combined with the alkaloid and half with an alkali metal by the simultaneous use of quinine and sodium carbonate. Under these conditions the *l*-isomer separates as the quinine salt and the *d*-component mainly concentrates in the mother liquors which are used again thrice. The most satisfactory method for recovery of the *d*-component was found to be treatment with strychnine of the optically crude *d-cis*-hydrogen phthalate isolated from the mother liquors, and fractional crystallisation of the alkaloidal salt.

Clark and Read (*J.*, 1934, 1777) recorded the successful use of *l*-menthylaminoacetic acid in the resolution of *dl*-menthol, and this reagent gave with *dl-trans*-3-methyl*cyclo*hexanol a good yield of the ester as a non-crystallisable syrup which formed a solid sulphate. Repeated crystallisation of this salt ultimately yielded a small quantity of optically pure 1-trans-3-*methyl*cyclo*hexyl* 1-*menthylaminoacetate*, but the yield of the ester was unpromisingly small and the attempted recovery of further solid from the mother liquors led to extensive decomposition. Other salts of the menthylglycine ester were tried with no better results, and we were unable to recover the pure *d*-component by this method.

Alkaloidal salts of the hydrogen phthalate of the *dl-trans*-alcohol were examined. Brucine, cinchonidine, and strychnine all gave well-defined salts, and of these the strychnine salts were found to be best for resolution work. On the addition of 70% of the theoretical amount of strychnine to *dl-trans*-3-methyl*cyclo*hexyl hydrogen phthalate in ethyl acetate the impure strychnine salt was mainly derived from the *l*-compound. Systematic fractional crystallisation from ethyl acetate gave a fair yield of the optically pure salt. As the melting point of the strychnine salt was not a good indication of optical purity and as the rotation of the salt was inconveniently low, the progress of the resolution was followed by occasional decomposition of the salt and examination of the isolated hydrogen phthalate. Some difficulty was at first experienced in getting a complete decomposition of the strychnine salt, but it was ultimately found satisfactory to form a concentrated solution in hot dioxan and run this into excess of dilute hydrochloric acid.

The hydrogen phthalate recovered from the mother liquors after the initial removal of the *l*-compound as the strychnine salt had a rotation which indicated some 70% of the *d*-component. No crystallisable alkaloidal salt, however, could be prepared of lower solubility than that derived from the *l*-ester which would have enabled the separation of the optically pure *d-trans*-compound to be effected.

Trial tests indicated that the phenylurethane might be used, and the crude *d*-hydrogen phthalate was hydrolysed to the alcohol and condensed with phenyl *iso*cyanate. Fractional crystallisation of the product gave a good yield of optically pure *d-trans*-3-methyl*cyclo*hexyl-phenylurethane. This constitutes a resolution of the alcohol, but is unsuitable inasmuch as the drastic conditions required for the hydrolysis of a phenylurethane do not lend themselves to the production of an optically pure alcohol.

When preparing derivatives of *l-cis*-3-methyl*cyclo*hexanol particular attention was paid to the phenylurethane and hydrogen phthalate to see if, like the *dl*-compounds, they were

dimorphic. Only one form of each could be isolated corresponding to the lower-melting of the *dl-cis*-derivatives.

Oxidation of the optically pure 3-methyl*cyclo*hexanols with chromic acid gave optically pure 3-methyl*cyclo*hexanones with rotations of the opposite sign: thus the *l-cis* and *l-trans*-alcohols gave the *d*-ketone, whereas the *d-cis*-alcohol gave *l*-3-methyl*cyclo*hexanone. Resolution of the *dl*-ketone with *l*-menthylhydrazide was described by Adams, Smith, and Loewe (*J. Amer. Chem. Soc.*, 1942, **64**, 2087), but their results show that it is a tedious and wasteful process. In view of this it would seem best to prepare the active forms of the ketone by the above oxidations when they are needed in quantity.

Experimental.

Resolution of dl-cis-3-*Methyl*cyclo*hexyl Hydrogen Phthalate*.—Both quinine and cinchonidine gave salts with the ester which could readily be recrystallised, but quinine proved to be the better alkaloid to use. The *dl*-ester (10 g.), anhydrous sodium carbonate (1·0 g.), and anhydrous quinine (6·2 g.) were dissolved in boiling aqueous alcohol (50%; 90 c.c.) and, after being seeded, the solution was allowed to cool slowly. After separation of the quinine salt (8·4 g.) the mother liquors were again used with *dl*-ester (11·7 g.), quinine (7·2), and sodium carbonate (1·2), and a further quantity (11·0 g.) of quinine salt was collected. A third lot of salt (4·1 g.) was prepared by the addition of *dl*-ester (5·0 g.) and equivalent quantities of alkaloid and sodium carbonate to the mother liquors. It was inadvisable to use the mother liquors more than thrice as the accumulation of the sodium salt made the separation of the quinine salt very slow. The combined quinine salt crystallised well from moist ethyl acetate, and systematic fractional crystallisation (the head fraction being crystallised five times) gave optically pure *l-cis*-3-methyl*cyclo*hexyl quinine phthalate (14·3 g.) of indefinite m. p., $[\alpha]_D$ −95·0° (chloroform; *c*, 2·0). The quinine salt was decomposed by running a solution in boiling alcohol into cold dilute hydrochloric acid and working up in the usual way. The resulting ester when recrystallised from light petroleum gave *l-cis*-3-methyl*cyclo*hexyl hydrogen phthalate as coarse aggregates of large white prisms, m. p. 70—72°, $[\alpha]_D$ −27·0° (benzene; *c*, 5·0) (Found: C, 69·3; H, 6·95. Calc.: C, 68·7; H, 6·9%). Hydrolysis of the hydrogen phthalate in the usual way gave a 95% recovery of *l-cis*-3-methyl*cyclo*hexanol, b. p. 84°/13 mm.; $n_D^{20°}$ 1·4582; $d_4^{30°}$ 0·9135; $\alpha_D^{20°}$ − 6·7° (homogeneous). A series of derivatives of the active alcohol was prepared, a sample of the hydrogen phthalate being formed because Godchot and Canquil (*Compt. rend.*, 1934, **198**, 663) reported it as a liquid whereas Gough, Hunter, and Kenyon (*J.*, 1926, 2052) recorded m. p. 70—71°. In agreement with the latter workers the prepared sample when recrystallised from light petroleum had m. p. 70—72° identical with that of the specimen from the quinine salt. *l-cis*-3-Methyl*cyclo*hexyl *p*-nitrobenzoate, pale yellow glistening needles from methanol, had m. p. 81·5—82·5°, $[\alpha]_D$ − 27·2° (chloroform; *c*, 5·0) (Found: C, 64·1; H, 6·6. Calc.: C, 63·85; H, 6·5%). l-cis-3-*Methyl*cyclo*hexyl* 3 : 5-*dinitrobenzoate* separated as pale yellow fluffy needles from aqueous alcohol, m. p. 134—135°, $[\alpha]_D$ − 15·2° (chloroform; *c*, 2·0) (Found: C, 54·5; H, 5·35; N, 8·9. $C_{14}H_{16}O_6N_2$ requires C, 54·5; H, 5·2; N, 9·1%). *l-cis*-3-Methyl*cyclo*hexyl-phenylurethane, needles from light petroleum, had m. p. 90—91·5°, $[\alpha]_D$ − 15·5° (chloroform; *c*, 5·0) (Found: C, 72·4; H, 8·15. Calc.: C, 72·05; H, 8·2%). l-cis-3-*Methyl*cyclo*hexyl-α-naphthylurethane*, needles from aqueous alcohol, had m. p. 117·5—118·5°, $[\alpha]_D$ − 19·4° (chloroform; *c*, 5·1) (Found: C, 76·55; H, 7·5. $C_{18}H_{21}O_2N$ requires C, 76·25; H, 7·45%).

d-cis-3-*Methyl*cyclo*hexanol*.—The mixture of hydrogen phthalates recovered from the mother liquors after the initial separation of the quinine salt (above) had $[\alpha]_D$ + 14° approx., indicating a content of about 75% of the *d*-ester. The crude hydrogen phthalate (13 g.) and strychnine (11·7 g.) were dissolved in chloroform–light petroleum (1 : 1 by volume; 130 c.c.). After removal of the first crop of crystals further quantities of ester (10 g.) and alkaloid (9 g.) were dissolved in the mother liquor, and after removal of the alkaloidal salt the process was repeated twice, using in all hydrogen phthalate (43 g.) and strychnine (38·5 g.; 0·7 mol.). The combined strychnine salt was systematically crystallised from chloroform–light petroleum (1 : 1; 8 vols.), the head fraction being recrystallised five times and the tail fraction nine times. Pure *d-cis*-3-methyl*cyclo*hexyl strychnine phthalate (41 g.) was obtained having m. p. 131—133°, $[\alpha]_D$ − 11·6° (chloroform; *c*, 5·0). The salt effervesced on melting and apparently retained some chloroform very tenaciously and concordant analysis could not be obtained. It was decomposed by adding a concentrated solution in alcohol to excess of cold, dilute hydrochloric acid. d-cis-3-*Methyl*cyclo*hexyl hydrogen phthalate*, isolated and purified in the usual way, had m. p. 70—72°, $[\alpha]_D$ + 27·2° (benzene; *c*, 5·0) (Found: C, 68·8; H, 7·1. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). Hydrolysis of the hydrogen phthalate gave *d-cis*-3-methyl*cyclo*hexanol, $\alpha_D^{21°}$ + 6·67° (homogeneous), $n_D^{20°}$ 1·4581, $d_4^{30°}$ 0·9137. This yielded a *p*-nitrobenzoate, m. p. 80—81°, $[\alpha]_D$ + 27·8° (chloroform; *c*, 5·0).

dl-trans-3-*Methyl*cyclo*hexyl* l-*Menthylaminoacetate*.—A sample of the *dl*-alcohol (10 g.) was dissolved in dry benzene and chloroacetyl chloride (10 g.) in the same solvent (30 c.c. in all) added, and the mixture was refluxed ($CaCl_2$ tube) until no more hydrogen chloride was evolved (1·5 hours). The cooled solution was washed successively with water, dilute sodium carbonate solution, and water, and dried ($MgSO_4$). After removal of the solvent on the water-bath, distillation under reduced pressure gave *dl-trans*-3-methyl*cyclo*hexyl chloroacetate (16·1 g.) as a colourless liquid, b. p. 99°/2 mm., $d_4^{20°}$ 1·0765, with the fragrant odour characteristic of chloroacetates of *cyclo*hexane alcohols. The chloroacetate was dissolved in dry benzene (100 c.c.) and after the addition of *l*-menthylamine (32 g.; 2·5 mols.) the solvent was distilled off from a glycerol-bath and the temperature of the mixture raised to 150°. This temperature was maintained for 3·5 hours, and solid *l*-menthylamine hydrochloride slowly separated. The cooled mixture was poured into dilute sulphuric acid, chloroform added, and all well shaken to give an aqueous extract of menthylamine. After the chloroform layer had been washed successively with

water, 10% sodium carbonate solution, and water, and dried ($MgSO_4$), the solvent was removed (finally under reduced pressure) and left the menthylglycine derivative as a brownish oil (26 g.) which did not solidify. Accordingly the menthylglycine derivative was dissolved in chloroform and shaken with *N*-sulphuric acid, and the acid layer was separated and extracted with chloroform. The combined chloroform solutions were washed with water and dried, and the solvent was removed. The hard yellow solid residue (30 g.) was washed with a little light petroleum to remove colour, and after crystallisation from ethyl acetate (200 c.c.) the menthylglycine sulphate was obtained as a white crystalline solid, m.p. 141—143°, $[\alpha]_D$ — 45·6° (chloroform; *c*, 2·0). Systematic fractional crystallisation from ethyl acetate (five times) gave l-trans-3-*methyl*cyclo*hexyl* l-*menthylaminoacetate sulphate* (1·6 g.), fine white needles, m. p. 171—172·5°, $[\alpha]_D$ — 57·3° (chloroform; *c*, 2·0) identical with an authentic sample prepared from a sample of *l*-trans-3-methyl*cyclo*hexanol derived from pulegone [Found: C, 63·75; H, 10·1; N, 3·95; S, 4·3. $(C_{19}H_{35}O_2N)_2,H_2SO_4$ requires C, 63·6; H, 10·1; N, 3·9; S, 4·45%]. Subsequent preparations gave similar results, but as less than 10% of the optically pure sulphate was obtained from the crystallisations, and as little satisfactory material was isolated from the less pure fractions the method was abandoned. The picrate prepared from the *dl*-menthylglycine separated as yellow prisms from light petroleum and had m. p. 112—113°, $[\alpha]_D$ — 9·0°. Repeated crystallisation failed to alter the rotation. As a sample of the picrate prepared from the *l*-menthylglycine had the same crystalline form and m. p., with $[\alpha]_D$ — 20·5°, it was evident that this salt was of no value as a resolving agent. The *d*-tartrate, hydrochloride, and phosphate, and the *p*-nitrobenzoyl derivative were prepared from the menthylglycine, but none of them could be induced to crystallise.

Resolution by the Strychnine Salt.—Of the common alkaloids, brucine, cinchonidine, and strychnine gave crystalline salts with the *dl-trans*-hydrogen phthalate, and of these the strychnine *salt* appeared to have the sharpest m. p. and the best crystallising power. The salt has a low solubility in all organic solvents apart from chloroform and dioxan, even at the boiling point. In ethyl acetate it has a solubility of about 1 in 60 at the boiling point and 1 in 1000 at laboratory temperature. Recrystallised from this solvent it separated as large transparent rods with pyramidal ends, and showed marked birefringence. It had m. p. 168—170° $[\alpha]_D$ — 29·0° (chloroform; *c*, 2·0) (Found: C, 71·7; H, 6·9. $C_{36}H_{40}O_6N_2$ requires C, 72·4; H, 6·7%). In the preparation of the strychnine salt for resolution it was found best to add only 65—70% of the required amount of the alkaloid to a 2% solution of the hydrogen phthalate in boiling ethyl acetate. To the phthalate (25 g.) in boiling ethyl acetate (1·5 l.) finely powdered strychnine (23 g.) was added and boiling continued for 1 hour. Traces of undissolved solid were separated, and the filtrate was left overnight at room temperature after seeding with pure *l-trans*-strychnine salt. The alkaloidal salt (25·5 g.) was separated and the filtrate used again for a second preparation. The combined yield of strychnine salt (63 g.) represented 64% of the *dl*-hydrogen phthalate used. It was fractionally crystallised from ethyl acetate, each fraction being left at room temperature for at least 8 hours before being filtered. The head fraction was recrystallised seven times and the tail fraction twelve times before optical purity was reached. It was found necessary to follow the course of the resolution by occasional hydrolysis of the salt and isolation of the methyl*cyclo*hexanol, as after a certain stage very slight changes in the physical constants of the strychnine salt are accompanied by considerable alteration in optical purity. The strychnine salt had m. p. 168—171°, $[\alpha]_D$ — 30·0° (chloroform; *c*, 2·0), and represented a recovery of about 30% of the original hydrogen phthalate.

Decomposition of the Strychnine Salt.—The strychnine salt was easily soluble in boiling dioxan, and this simplified its decomposition. The salt (50 g.) in boiling dioxan (150 c.c.) was stirred into cold dilute hydrochloric acid (1 l. of 1%). The free hydrogen phthalate separated as an oil, but with this dilution of acid no separation of strychnine hydrochloride took place. The phthalate was quickly extracted with ether (thrice) and the combined extracts were washed with water and dried ($CaCl_2$). Solvent was removed on the water-bath, and traces of dioxan under reduced pressure. The residue, when boiled with a little light petroleum and cooled, gave transparent, acicular crystals of *l-trans*-3-methyl*cyclo*hexyl hydrogen phthalate having m. p. 94°, $[\alpha]_D$ — 13·0° (Found: C, 68·75; H, 7·0. Calc.: C, 68·65; H, 6·9%). Hydrolysed in the usual way, the ester gave 95% yield of *l-trans*-3-methyl*cyclo*hexanol, b. p. 94°/12 mm., $\alpha_D^{28°}$ — 3·62° (homogeneous), $n_D^{20°}$ 1·4573, $d_4^{30°}$ 0·9070.

Resolutions of the *dl*-hydrogen phthalate were also carried out with brucine and cinchonidine, but strychnine was more suitable. *l-trans*-3-Methyl*cyclo*hexyl brucine phthalate separated as sheaves of fine white needles having m. p. 179—180°, $[\alpha]_D$ — 31·0° (chloroform; *c*, 2·0). *l-trans*-3-Methyl*cyclo*hexyl cinchonidine phthalate formed large white needles which melted indefinitely at 102—108°, and had $[\alpha]_D$ — 62·5°.

Derivatives of *l-trans*-3-methyl*cyclo*hexanol were prepared by standard methods. The *p*-nitrobenzoate, pale yellow, shining scales from methanol, had m. p. 46—47° (Found: C, 64·15; H, 6·65. Calc.: C, 63·85; H, 6·5%). The 3 : 5-*dinitrobenzoate*, yellow needles from aqueous alcohol, had m. p. 97—98° (Found: C, 54·4; H, 5·35. $C_{14}H_{16}O_6N_2$ requires C, 54·5; H, 5·2%). The phenylurethane, stout shining needles from aqueous alcohol, had m. p. 117—118°, $[\alpha]_D$ — 20·0° (chloroform; *c*, 5·0) (Found: C, 71·9; H, 8·2. Calc.: C, 72·05; H, 8·2%). The *α-naphthylurethane*, woolly mass of needles from light petroleum, had m. p. 147—148° (Found: C, 76·4; H, 7·4. $C_{18}H_{21}O_2N$ requires C, 76·25; H, 7·45%).

d-trans-3-*Methyl*cyclo*hexanol.*—The mother liquors from the initial separation of the crude *l*-strychnine salt when decomposed yielded a hydrogen phthalate having $[\alpha]_D$ + 8° approx. As no alkaloidal salt could be prepared which allowed the *d-trans*-salt to be freed by crystallisation from a more soluble *l*-salt, attempts were made to effect a resolution by precipitation of the *l*-strychnine salt from solutions of the crude *d*-alkaloidal salt. This was in fact achieved by dissolving the dextrorotatory phthalate in chloroform and adding as much strychnine as would dissolve in the boiling solution. Light petroleum was added to incipient precipitation, and slow cooling then gave a deposit consisting of some free strychnine, heavy grains of the *l-trans*-strychnine salt, and many fine white needles. These were separated as far as possible mechanically, and recrystallised from hot chloroform by the addition of light petroleum. Free strychnine separated at each stage, indicating that the *d-trans*-salt was dissociating in solution. By continuing this method crude *d-trans*-hydrogen phthalate (60 g.) gave fine

needles (7·7 g.). The salt was decomposed to the hydrogen phthalate and the ester hydrolysed to *d-trans*-3-methyl*cyclo*hexanol, which had α_D + 3·31° (homogeneous), indicating a content of about 96% of the *d*-alcohol. In view of the poor yield of the product and the optical impurity, the method was not regarded as satisfactory.

Separation of d-trans-3-*Methyl*cyclo*hexanol as Phenylurethane*.—Experiments with mixtures showed that it was possible to separate the phenylurethane of the *l-trans*-alcohol from the *dl*-form by crystallisation from dilute alcohol, in which the *l-trans*-derivative is much less soluble. Accordingly part of the impure *d-trans*-hydrogen phthalate (above) was hydrolysed and the derived alcohol converted to the phenylurethane (10·5 g.); when systematically crystallised from aqueous alcohol (70%), this ultimately yielded pure d-trans-3-*methyl*cyclo*hexylphenylurethane* (6 g.), m. p. 117—118°, $[\alpha]_D$ + 19·8° (chloroform; *c*, 5·0) (Found: C, 72·15; H, 8·3. $C_{14}H_{19}O_2N$ requires C, 72·05; H, 8·2%).

Oxidation of Optically Pure 3-*Methyl*cyclo*hexanols*.—*l-cis*-3-Methyl*cyclo*hexanol (3 g.) in water (20 c.c.) containing potassium dichromate (3 g.) was oxidised by gradual addition of dilute sulphuric acid (3 c.c. of concentrated acid in 10 c.c. of water) so that the temperature rose to and was maintained at 50—60°. Worked up in the usual way, *d*-3-methyl*cyclo*hexanone (2·3 g.) was obtained having b. p. 63°/10 mm., $\alpha_D^{21°}$ + 11·5° (homogeneous), $n_D^{20°}$ 1·4454, $d_4^{30°}$ 0·9089. Oxidation of the *l-trans*-alcohol gave a sample of ketone having $\alpha_D^{23°}$ + 11·7°. The *l*-menthylhydrazone had m. p. 131—133°, $[\alpha]_D$ − 65·3° (chloroform; *c*, 2·1), − 60·9° (ethanol; *c*, 5·0).

Oxidation of *d-cis*-3-methyl*cyclo*hexanol in a similar way gave a good yield of *l*-3-methyl*cyclo*hexanone having $\alpha_D^{21°}$ − 11·5° (homogeneous), $n_D^{20°}$ 1·4452, $d_4^{30°}$ 0·9088. The *l*-menthylhydrazone had m. p. 146°, $[\alpha]_D$ − 18·5° (chloroform; *c*, 2·0), − 31·7° (ethanol; *c*, 4·8).

One of us (J. A. M.) wishes to thank the Federal Research Fund for a Fellowship which enabled him to participate in this work.

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