147. dl-2 : 2-*Dimethyl*cyclo*hexylacetic Acid.*

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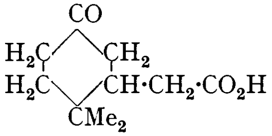
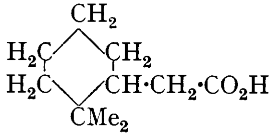
dl-2 : 2-*Dimethyl*cyclo*hexylacetic acid* has been synthesised and resolved into its optical enantiomorphs in order that the dextrorotatory form of the acid might be compared with an acid having the same composition obtained by the degradation of hydroxyeremophilone. The two acids were not identical.

By the oxidation of the benzoate of hydroxyeremophilone Bradfield, Hellström, Penfold, and Simonsen (preceding paper) obtained a keto-acid, $C_{10}H_{16}O_3$, m. p. 105—107°, which they thought might be *d*-5-keto-2 : 2-dimethyl*cyclo*hexylacetic acid (I). Its product of reduction by the Clemmensen method was a liquid acid, $C_{10}H_{18}O_2$, which might be *d*-2 : 2-dimethyl*cyclo*hexylacetic acid (II). The *dl*-modification of the latter acid was readily prepared by

(I.)





(II.)

the condensation of 2 : 2-dimethyl*cyclo*hexanone (Cornubert, Bornel, and Bihan, *Bull. Soc. chim.*, 1931, **49**, 1385) with ethyl bromoacetate in the presence of zinc. The resulting *hydroxy*-ester, on dehydration with potassium hydrogen sulphate, yielded a mixture of ethyl 2 : 2-dimethyl*cyclo*hexylideneacetate and ethyl 2 : 2-dimethyl-Δ^6-*cyclo*hexenylacetate, since oxidation gave 2 : 2-dimethyl*cyclo*hexanone, oxalic acid, and δ-acetyl-δ-methylhexoic acid, the last being identified by the preparation of its semicarbazone, decomp. 169° (Crossley and Renouf, J., 1911, **99**, 1111). Catalytic hydrogenation of the mixture of unsaturated esters gave *ethyl* dl-2 : 2-*dimethyl*cyclo*hexylacetate*, from which the dl-*acid* was obtained on hydrolysis. By means of the half molecule method the l-*ephedrine* salt of the lævorotatory form of the acid was easily obtained, and the pure d-*acid* was isolated in a similar manner *via* the *cinchonidine* salt. The p-*phenylphenacyl* esters of the *d*- and the *l*-acid had m. p. 87—88°, whereas the same derivative of the acid obtained from hydroxyeremophilone benzoate had m. p. 65—67°.

Experimental.

For the preparation of 2 : 2-dimethyl*cyclo*hexanone the following modification of the method used by Cornubert *et al.* (*loc. cit.*) was adopted. To a mechanically stirred suspension of finely powdered sodamide (28 g.) in benzene (300 c.c.), 2-methyl*cyclo*hexanone (80 g.) was gradually added, the mixture being heated on the water-bath in a stream of dry nitrogen. After 3 hours evolution of ammonia ceased and methyl sulphate (100 g.) was slowly added to the cooled mixture (ice). After digestion for a further 3 hours ice was added to the neutral solution, and the benzene layer separated and shaken with concentrated aqueous ammonia to remove the excess of methyl sulphate. The benzene extract was washed with dilute sulphuric acid, sodium carbonate solution and water, and dried, and the solvent removed through a column. The residue (72 g.) had b. p. 162—169°/765 mm. The crude ketone was shaken mechanically with sodium bisulphite solution to remove unchanged 2-methyl*cyclo*hexanone (32 g.).

The methylated ketone (166 g.) which did not react with sodium bisulphite, was converted into the semicarbazone and this was fractionally crystallised from alcohol, yielding 2 : 2-dimethyl*cyclo*hexanonesemicarbazone (93 g.), m. p. 197—198°, which gave on hydrolysis with sulphuric acid 2 : 2-dimethyl*cyclo*hexanone, b. p. 169—170°/768 mm., $d_{25^\circ}^{25^\circ}$ 0·9147, $n_D^{25^\circ}$ 1·4460. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in golden needles, m. p. 140—142° (Found : N, 18·0. $C_{14}H_{18}O_4N_4$ requires N, 18·3%).

Ethyl 1-*Hydroxy*-2 : 2-*dimethyl*cyclo*hexylacetate*.—Ethyl bromoacetate (35 g.) and 2 : 2-dimethyl*cyclo*hexanone (20 g.) were added to benzene (100 c.c.) containing zinc filings (12·5 g.) in suspension. On warming on the water-bath a vigorous reaction ensued, necessitating the removal of the source of heat; after this reaction had moderated, the mixture was heated for 4 hours, cooled, and mixed with an equal volume of dilute sulphuric acid (10%). The benzene layer was separated, washed with sodium bicarbonate solution and water, dried, and evaporated; the residue (25 g.) had b. p. 135—136°/18 mm. The *hydroxy*-ester was redistilled for analysis, b. p. 137°/20 mm. (Found : C, 67·0; H, 10·2. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3%).

For the preparation of the unsaturated ester the hydroxy-ester (10 g.) was heated with finely powdered potassium hydrogen sulphate (10 g.) at 180—200° for 4 hours. After addition of water the oil was dissolved in ether, the ethereal solution washed with sodium carbonate solution, and dried, and the solvent evaporated. Analysis showed that the residual oil, b. p. 120—125°/18 mm., still contained some hydroxy-ester and it was therefore treated again with potassium hydrogen sulphate. The unsaturated *ester*, b. p. 121°/18 mm., was a mobile oil with a somewhat pungent odour (Found : C, 73·5; H, 10·0. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%).

Ozonolysis of the Unsaturated Ester.—The ester (2·3 g.) in methyl acetate was ozonised at 0° until excess of ozone passed freely through the solution. The solvent was removed under diminished pressure, and the ozonide mixed with water (5 c.c.) and decomposed by heating on the water-bath for 1 hour. Distillation in steam separated a volatile oil, identified as 2 : 2-dimethyl*cyclo*hexanone by the preparation of the semicarbazone and 2 : 4-dinitrophenylhydrazone. The residue from the steam distillation was a somewhat viscid oil giving a red coloration with ferric chloride. After digestion with dilute sulphuric acid (10%) for 1 hour to hydrolyse and decarboxylate the ester, the oil (0·6 g.) was isolated by ether in the usual manner and converted into the semicarbazone. δ-Acetyl-δ-methylhexoic acid semicarbazone crystallised from alcohol in rosettes of needles, decomp. 169° (Found : C, 52·7; H, 8·5. Calc. for $C_{10}H_9O_3N_3$: C, 52·4; H, 8·3%).

dl-2 : 2-*Dimethyl*cyclo*hexylacetic Acid*.—The unsaturated ester (32·5 g.) in alcohol (120 c.c.) was shaken with hydrogen in the presence of palladium–norit (10%, 1 g.), the reduction being slow. After removal of the alcohol from the filtered solution, *ethyl* 2 : 2-*dimethyl*cyclo*hexylacetate* was obtained as a mobile oil, b. p. 122—123°/23 mm. (Found : C, 72·4; H, 11·0. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·1%). Hydrolysis of the ester with methyl-alcoholic potassium hydroxide solution in the usual manner gave dl-2 : 2-*dimethyl*cyclo*hexylacetic acid*, b. p. 153°/17 mm., which crystallised in needles, m. p. *ca.* 30° (Found : C, 70·6; H, 10·5. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%). The p-*phenylphenacyl* ester crystallised from methyl alcohol in needles, m. p. 86—87° (Found : C, 79·1; H, 7·7. $C_{24}H_{28}O_3$ requires C, 79·1; H, 7·7%). The *quinine* salt crystallised from ethyl acetate in needles, m. p. 97—100° after softening at 90°, $[\alpha]_{5461}$ − 125·3° in chloroform (*c*, 1·037) (Found : C, 69·1; H, 8·4. $C_{10}H_{18}O_2,C_{20}H_{24}O_2N_2,2H_2O$ requires C, 69·0; H, 8·8%).

l-2 : 2-*Dimethyl*cyclo*hexylacetic Acid*.—To a warm solution of the *dl*-acid (4·0221 g.) in water (30 c.c.) and alcohol (4 c.c.), sodium hydroxide solution (2·204N, 5·36 c.c.) and *l*-ephedrine (1·953 g.) were added. The *ephedrine* salt (3 g.), m. p. 87°, $[\alpha]_{5461}$ − 29·8° in alcohol (*c*, 3·291), crystallised on cooling; the mother-liquor deposited a further quantity (0·2 g.) of the salt on standing overnight. The salt (2·5 g.) crystallised from a mixture of benzene (17 c.c.) and ligroin (b. p. 60—80°, 100 c.c.) in fine needles (1·8 g.), m. p. 90—91°, $[\alpha]_{5461}$ −31·1° in alcohol (*c*, 3·277). This was unaltered by further crystallisation (Found : C, 67·9; H, 10·2. $C_{10}H_{18}O_2,C_{10}H_{15}ON,H_2O$ requires C, 68·0; H, 9·9%).

For the isolation of the acid, the salt (13 g.) was suspended in ether and shaken with an excess of 10% sodium hydroxide solution. The alkaline solution was separated and acidified with dilute sulphuric acid, and the liquid acid dissolved in ether. Evaporation of the ether from the dried extract gave l-2 : 2-*dimethyl*cyclo*hexylacetic acid* (5·6 g.), b. p. 149—150°/13 mm., m. p. *ca.* 43—44° after softening at 38°, $[\alpha]_{5461}$ −14·57° in alcohol (*c*, 10·2). Attempts to recrystallise the acid failed (Found : C, 70·6; H, 10·5. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%). The p-*phenylphenacyl* ester crystallised from methyl alcohol in leaflets, m. p. 87—88°, $[\alpha]_{5461}$ −2·9° in ethyl acetate (*c*, 7·342) (Found : C, 79·0; H, 7·4. $C_{24}H_{28}O_3$ requires C, 79·1; H, 7·7%).

The acid recovered from the soluble ephedrine salt had b. p. 153°/18 mm., $[\alpha]_{5461}$ + 5·7° in alcohol (*c*, 3·610).

d-2 : 2-*Dimethyl*cyclo*hexylacetic Acid*.—To a warm solution of the crude *d*-acid (1·09 g.) in alcohol (3 c.c.), sodium hydroxide solution (2·204N, 0·88 c.c.) and cinchonidine (1·31 g.) were added. The salt (1·2 g.) rapidly crystallised and a second fraction (0·8 g.) separated from the mother-liquor on long standing. The first fraction of the *cinchonidine* salt crystallised from ethyl acetate (5 c.c.) in rosettes of prismatic needles, m. p. 120—122°, $[\alpha]_{5461}$ $-85{\cdot}7°$ in alcohol (*c*, 1·241). A further crystallisation from ethyl acetate raised the rotatory power to 86·6° in alcohol (*c*, 1·254) and this together with the m. p. was unaltered by a further crystallisation (Found : C, 72·6; H, 8·8. $C_{10}H_{18}O_2,C_{19}H_{22}ON_2,H_2O$ requires C, 72·2; H, 8·7%). The second fraction of the salt, after crystallisation from ethyl acetate, had m. p. *ca.* 105°, $[\alpha]_{5461}$ $-86{\cdot}6°$.

For the separation of the acid the cinchonidine salt was decomposed with sodium hydroxide solution, the cinchonidine extracted with chloroform, the alkaline solution acidified, and the d-*acid* dissolved in ether. After removal of the solvent the acid had b. p. 150°/13 mm., m. p. *ca.* 37—40°, $[\alpha]_{5461}$ $+ 14{\cdot}1°$ in alcohol (*c*, 10·36) (Found : C, 70·7; H, 10·6. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%). The p-*phenylphenacyl* ester crystallised from methyl alcohol in leaflets, m. p. 87—88° (Found : C, 79·0; H, 7·5. $C_{24}H_{28}O_3$ requires C, 79·1; H, 7·7%).

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