88. *Experiments on the Synthesis of* 1 : 2-*Dimethyl*cyclo*hexyl-acetic Acid.*

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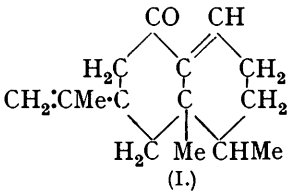
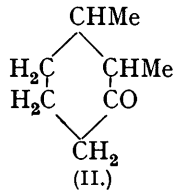
One of the theoretically possible forms of dl-1 : 2-*dimethyl*cyclo*hexylacetic acid* (IV) has been prepared by the reduction of the *lactone* (VI). This lactone was obtained by the action of methylmagnesium iodide on *ethyl* 2-*keto*-1-*methyl*cyclo*hexylacetate* (V). The acid (IV) was partially resolved into its optically active enantiomorphs and direct comparison of the l-p-*phenylphenacyl* ester with the *p*-phenylphenacyl ester of the *cyclo*hexyl acid obtained from hydroxyeremophilone benzoate established their identity. 6-*Keto*-1 : 2-*dimethyl*cyclo*hexylacetic acid* (III; R = H) also has been synthesised.

One of the grounds for the assignment to eremophilone of the structure (I) (Penfold and Simonsen, J., 1939, 87) was the observation that the acid, $C_{10}H_{18}O_2$, obtained by the reduction of the keto-acid, $C_{10}H_{16}O_3$, resulting from the ozonolysis of hydroxyeremophilone benzoate, gave on selenium dehydrogenation *o*-xylene. Since direct comparison showed that the dextrorotatory *p*-phenylphenacyl ester of this acid was not identical with the ester prepared from *d*-2 : 2-dimethyl*cyclo*hexylacetic acid (Adamson, Marlow, and Simonsen, J., 1938, 774), it was obviously desirable to synthesise the isomeric *dl*-1 : 2-dimethyl*cyclo*hexylacetic acid (IV) and to resolve it into its optical enantiomorphs. It was of course recognised that this acid can exist in two *dl*-modifications.


(I.)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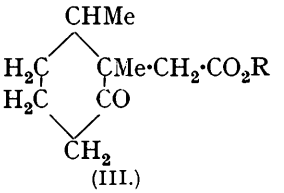
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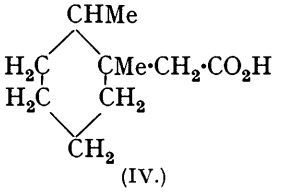
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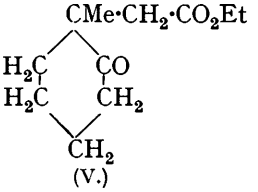
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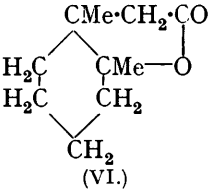
(VI.)

The most direct method for the synthesis appeared to be the reduction of 6-keto-1 : 2-dimethyl*cyclo*hexylacetic acid (III, R = H). For this purpose 2 : 3-dimethyl*cyclo*hexanone (II) was prepared by methods given in the literature (Knoevenagel, *Annalen*, 1894, **281**, 94; Rabe and Rahm, *ibid.*, 1904, **332**, 13; *Ber.*, 1905, **38**, 970; Kötz, Blenckermann, Mähnert, and Rosenbüsch, *Annalen*, 1913, **400**, 82; Cornubert and Morel, *Bull. Soc. chim.*, 1931, **49**, 1519) with certain modifications. Condensation of the sodio-derivative of this ketone with ethyl bromoacetate gave in very poor yield the ester (III, R = Et), which was separated from *ethyl* 2-*keto*-3 : 4-*dimethyl*cyclo*hexylacetate* by condensation with ethyl oxalate as detailed on p. 416. Hydrolysis of the ester gave a mixture of keto-acids, which were separated by crystallisation of their semicarbazones. The *α-semicarbazone*, m. p.

197—198°, gave on hydrolysis α-6-*keto*-1 : 2-*dimethyl*cyclo*hexylacetic acid* (III, R = H), m. p. 107—108°, and the more soluble β-*semicarbazone*, m. p. 192°, gave on hydrolysis a gum. Unfortunately the crystalline acid was insufficient in quantity for further investigation.

The second and more successful method adopted for the synthesis of the required acid (IV) involved the condensation of the sodio-derivative of 2-methyl*cyclo*hexanone with ethyl bromoacetate to *ethyl* 2-*keto*-1-*methyl*cyclo*hexylacetate* (V), which also was formed in poor yield. The *keto-acid*, m. p. 77—78°, obtained by the hydrolysis of the ester was characterised by the preparation of the *semicarbazone*, decomp. 183°. By treatment of the ester (V) with methylmagnesium iodide the *lactone* (VI), m. p. 73°, was prepared. Unfortunately no satisfactory method could be found for the reduction of the lactone to the required acid (IV). With the Clemmensen reagent the *acid*, b. p. 153°/16 mm., was formed in very small amount, and with hydriodic acid and red phosphorus at 150° polymerisation occurred. The *dl*-acid, characterised by the preparation of its p-*phenylphenacyl* ester, m. p. 61—62°, was too limited in amount for complete resolution into its optical enantiomorphs. By means of the half molecule method a sparingly soluble *cinchonidine* salt, m. p. 142—143°, was prepared; the acid regenerated from this yielded a lævorotatory p-*phenylphenacyl* ester, m. p. 65—67°. The d-p-*phenylphenacyl* ester, prepared from the acid regenerated from the mother-liquor from which the cinchonidine salt had been separated, did not melt sharply and it could therefore not be compared with the corresponding derivative of the acid obtained from hydroxyeremophilone benzoate. The identity, however, of the synthetic acid and this acid was proved by mixing equal amounts of the synthetic *l*-*p*-phenylphenacyl ester and the *d*-ester of the natural acid. This mixture had m. p. 62—63°, both alone and in admixture with the synthetic *dl*-ester. There can in our opinion be no doubt that the acid derived from hydroxyeremophilone benzoate is *d*-1 : 2-dimethyl*cyclo*hexylacetic acid. It follows, therefore, that in eremophilone and hydroxyeremophilone the methyl groups must occupy the 1:10-positions and these ketones are not isoprene derivatives.

Experimental.

2 : 3-*Dimethyl*-Δ^2-cyclo*hexenone*.—Ethyl 4-keto-2 : 3-dimethyl-Δ^2-*cyclo*hexenecarboxylate (10 g.) was added to ethyl-alcoholic potassium hydroxide (KOH, 5 g.; alcohol, 30 c.c.) and heated under reflux for 12 hours. After saturation with carbon dioxide the mixture was distilled in steam; decarboxylation then occurred. The ketone, which passed over with the steam, was isolated by ether; it had b. p. 91°/15 mm. (the value, 118—119°/12 mm., given in the literature is incorrect) (Found : C, 77·2; H, 9·8. Calc. for $C_8H_{12}O$: C, 77·2; H, 9·7%). The semicarbazone had m. p. 225° in agreement with that given by Kötz *et al.* (*loc. cit.*). The alkaline solution from the steam-distillate was acidified; the acid, recovered by ether extraction and decomposed by distillation under diminished pressure, yielded a further quantity of the ketone (total yield, 5·6 g.).

2 : 3-*Dimethyl*cyclo*hexanone*.—The ketone, prepared by the catalytic hydrogenation of the unsaturated ketone with a palladium–norit catalyst, had b. p. 181—182°/769 mm., 69—70°/13 mm., in agreement with that, b. p. 78°/29 mm., found by Cornubert and Morel (*loc. cit.*) but not with that given by Kötz *et al.* (*loc. cit.*). The semicarbazone of the ketone was not homogeneous, but a fraction, m. p. 202—203°, was readily obtained.

6-*Keto*-1 : 2-*dimethyl*cyclo*hexylacetic Acid*.—A solution of 2 : 3-dimethyl*cyclo*hexanone (10 g.) in benzene (100 c.c.) was refluxed with finely powdered sodamide (3·1 g.) in a stream of nitrogen for 6 hours (mechanical stirring). To the solution, cooled in ice, ethyl bromoacetate (12·5 g.) was gradually added and after 1 hour the mixture was heated for 2 hours. Ice was added to the cooled solution, the benzene separated, washed with water, and dried, and the solvent removed. Distillation of the residual oil under diminished pressure gave a fraction (4 g.), b. p. 140—153°/19 mm. Without further purification this ester (5 g.) was added to a well-cooled solution (salt–ice) of sodium (0·55 g.) in alcohol (7·5 c.c.) and after the addition of ethyl oxalate (3·6 g.) the whole was kept at 0° for 17 hours. The mixture was poured on ice, the oil (A) dissolved in ether, and the aqueous alkaline solution acidified. The oil which separated was dissolved in ether, the solvent removed from the dried extract, and the residual oil (5 g.) distilled under diminished pressure. After decomposition was complete the oil (2·2 g.) had b. p. 160—180°/16 mm. A further small quantity (0·5 g.) of the ester was obtained when the oil (A) was again treated with ethyl oxalate.

The ester (8 g.) was hydrolysed by digestion with dilute sulphuric acid (10%; 25 c.c.), the resulting acid (3 g.) being a viscid oil. It was mixed with an excess of aqueous semicarbazide acetate; the gummy solid which separated was collected, washed with ether to remove resinous impurities, and crystallised from methyl alcohol. The less soluble α-*semicarbazone* separated in highly iridescent prisms, m. p. 197—198° (Found: C, 55·2; H, 7·8. $C_{11}H_{19}O_3N_3$ requires C, 54·8; H, 7·9%); a more readily soluble β-*semicarbazone* was obtained from dilute methyl alcohol in stout prisms, decomp. 192° after softening at 187° (Found: C, 55·0; H, 8·1%). Hydrolysis of the α-semicarbazone with dilute sulphuric acid gave α-6-*keto*-1 : 2-*dimethyl*cyclo*hexylacetic acid*, which crystallised from dilute methyl alcohol or dilute acetone in soft needles, m. p. 107° (Found: C, 65·3; H, 8·3. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). The acid from the β-semicarbazone was a gum and was not further examined.

The ester which did not react with ethyl oxalate, namely, *ethyl* 2-*keto*-3 : 4-*dimethyl*cyclo*hexylacetate*, b. p. 143—145°/16 mm., was redistilled for analysis; b. p. 144°/16 mm. (Found: C, 68·2; H, 9·7. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%).

Condensation of 2-*Methyl*cyclo*hexanone with Ethyl Bromoacetate. Ethyl* 6-*Keto*-5-*carbethoxy*-2-*methyl*cyclo*hexylacetate and* 2-*Keto*-1-*methyl*cyclo*hexylacetic Acid.*—To a suspension of finely powdered sodamide (25 g.) in ether (500 c.c.), 2-methyl*cyclo*hexanone (70 g.) was added, and the mixture heated in a current of nitrogen for 5 hours (mechanical stirring). Ethyl bromoacetate (90 g.) was added to the cooled solution, and the reaction mixture heated for 5 hours. The condensation product (50 g.), isolated in the usual manner, had b. p. 130—155°/21 mm., giving on refractionation a main fraction, b. p. 130—145°/16 mm. After treatment with ethyl oxalate in the manner previously described, the *keto-ester* was obtained as a somewhat viscid oil, b. p. 170—190°/20 mm., giving a purple coloration with alcoholic ferric chloride (Found: C, 62·5; H, 8·5. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·1%).

Hydrolysis of the ester with dilute sulphuric acid (10%) gave 2-*keto*-1-*methyl*cyclo*hexylacetic acid*, which, after isolation by ether, was obtained as a crystalline cake. For purification it was converted into the *semicarbazone*, which crystallised from methyl alcohol in feathery needles, decomp. 182° (Found: C, 53·0; H, 7·1. $C_{10}H_{17}O_3N_3$ requires C, 52·9; H, 7·5%). The acid, obtained from the semicarbazone by hydrolysis with dilute sulphuric acid, crystallised from *cyclo*hexane or dilute methyl alcohol in well-formed prisms, m. p. 77—78° (Found: C, 63·8; H, 8·1. $C_9H_{14}O_3$ requires C, 63·5; H, 8·2%). The *ethyl* ester had b. p. 142°/19 mm. (Found: C, 66·8; H, 9·2. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·1%). Treatment of the ethyl ester with *iso*amyl formate in ethereal solution in the presence of sodium gave the hydroxymethylene derivative as an oil, which developed a purple coloration with ferric chloride. The *semicarbazone* crystallised from dilute methyl alcohol in leaflets, m. p. 151°, analysis showing that alcoholysis had occurred with the formation of the *iso*amyl ester (Found: C, 59·6; H, 8·3. $C_{16}H_{27}O_4N_3$ requires C, 59·1; H, 8·3%). An analogous alcoholysis has been recorded by Bhagvat and Simonsen (J., 1927, 87).

Lactone of 6-*Hydroxy*-1 : 2-*dimethyl*cyclo*hexylacetic Acid.*—Methylmagnesium iodide (from magnesium, 1·34 g.) in ether (60 c.c.) was added gradually to a well-cooled solution of ethyl 2-keto-1-methyl*cyclo*hexylacetate (10 g.) in ether (60 c.c.). After being kept overnight, the reaction mixture was heated under reflux for ½ hour and cooled, and the Grignard compound decomposed with ice and dilute hydrochloric acid. The dried ethereal extract was evaporated, and the residual oil hydrolysed with methyl-alcoholic potassium hydroxide (KOH, 4 g.). After removal of the alcohol the aqueous solution was acidified, and the oil (6·5 g.) extracted with ether. For purification the crude lactone (17 g.) was mixed with an excess of aqueous semicarbazide acetate and after 2 days the semicarbazone of the unchanged keto-acid (5 g.) was collected and washed with ether to remove adhering oil. The filtrate, together with the ethereal washings, was distilled in steam, and the distillate made alkaline with sodium hydroxide, concentrated, acidified, and extracted with ether. The ethereal extract was washed with dilute aqueous sodium carbonate, which removed an acid (1 g.), the extract dried, and the solvent evaporated. The *lactone* (7 g.) rapidly crystallised in nacreous needles, which could not be recrystallised. After pressing on porous tile it had m. p. 73° (Found: C, 70·8; H, 9·6. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%).

dl-1 : 2-*Dimethyl*cyclo*hexylacetic Acid.*—The lactone (7 g.) was digested with amalgamated zinc (40 g.) and hydrochloric acid (200 c.c.) for 24 hours and then distilled in steam. The distillate was made alkaline, concentrated, acidified, and extracted with ether. The ethereal extract was washed with aqueous sodium carbonate, dried, and evaporated, yielding unchanged lactone (5·5 g.). Acidification of the sodium carbonate solution gave dl-1 : 2-*dimethyl*cyclo*hexylacetic acid* (1 g.) as an oil, b. p. 153°/16 mm. (Found: C, 70·5; 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 rosettes of leaflets, m. p. 61—62° (Found: C, 79·5; H, 7·9. $C_{24}H_{28}O_3$ requires C, 79·1; H, 7·7%). In admixture with the *d*-ester from hydroxyeremophilone benzoate or with the synthetic *l*-ester (see below) the m. p. was 62—64°.

The acid (0·45 g.) was mixed with 0·894N-sodium hydroxide (1·47 c.c.) and cinchonidine (0·338 g.) with sufficient methyl alcohol to give a clear solution on warming. The *cinchonidine* salt (0·55 g.) crystallised on keeping and was purified by two crystallisations from ethyl acetate, from which it separated in matted needles, m. p. 141—142°, $[\alpha]_{5461}$ −95° in chloroform (*c*, 1·06) (Found: N, 6·0. $C_{10}H_{18}O_2,C_{19}H_{22}ON_2$ requires N, 6·0%). The acid, regenerated from the cinchonidine salt, was converted into the p-*phenylphenacyl* ester, which crystallised from methyl alcohol in leaflets, m.p. 65—67°, $[\alpha]_{5461}$ − 6° in ethyl acetate (*c*, 4·0)* (Found: C, 79·4; H, 7·6%). This ester (2 mg.) was mixed in ether with an equal weight of the *d*-ester prepared from hydroxyeremophilone benzoate. After evaporation of the solvent the mixture had m. p. 62—63° both alone and in admixture with the *dl*-ester described above.

The alkaline solution from which the cinchonidine salt had been separated was acidified, and the acid recovered and converted into the p-*phenylphenacyl* ester, which crystallised from methyl alcohol in leaflets, m. p. 62—65°, $[\alpha]_{5461}$ +8° in ethyl acetate (*c*, 3·64)* (Found: C, 79·2; H, 7·6%).

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