14. *Studies in the* cyclo*Hexane Series. Part IV. The Isomeric 1-Carboxy-4-, -3-, and -2-methyl*cyclo*hexane-1-succinic Acids.*

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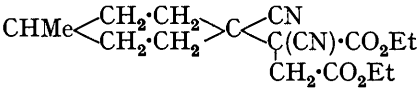
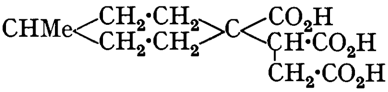
Condensation of the sodio-derivative of ethyl 1-cyano-4-methyl*cyclo*hexane-1-cyanoacetate with ethyl bromoacetate yields a *dicyanosuccinic* ester, which gives a pair of isomeric 1-*carboxy*-4-*methyl*cyclo*hexane*-1-*succinic acids* on hydrolysis. Similar pairs of isomeric carboxymethyl*cyclo*hexanesuccinic acids have been obtained from the corresponding 1-cyano-3-methyl- and 1-cyano-2-methyl-*cyclo*hexane-1-cyanoacetates.

THE general failure to isolate the strainless isomers of *cyclo*hexane derivatives required by the Sachse–Mohr hypothesis is usually attributed to the small energy required to convert the " boat " form of the *cyclo*hexane ring into the " armchair " form (Mills, Report of Fourth Chemical Solvay Conference, 1931). It seems possible, however, that suitable substitution of the hydrogen atoms of the *cyclo*hexane ring might increase the energy difference between these forms sufficiently to render possible their isolation as definite individuals.

Attention was therefore directed to the synthesis of 1-carboxymethyl*cyclo*hexane-1-succinic acids by Higson and Thorpe's method (J., 1906, **89**, 1455). Condensation of the sodio-derivative of ethyl 1-cyano-4-methyl*cyclo*hexane-1-cyanoacetate, prepared from the cyanohydrin of 4-methyl*cyclo*hexanone, with ethyl bromoacetate gave a *dicyanosuccinic* ester (I), which on hydrolysis furnished a pair of isomeric 1-*carboxy*-4-*methyl*cyclo*hexane*-1-*succinic acids* (II). A similar pair of isomeric acids was obtained from the condensation product of the sodio-derivative of ethyl 1-cyano-3-methyl*cyclo*hexane-1-cyanoacetate and ethyl bromoacetate.

(I.) 

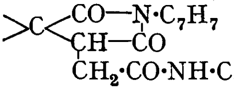
$$\mathrm{CHMe}{<}\begin{array}{l}\mathrm{CH_2{\cdot}CH_2}\\ \mathrm{CH_2{\cdot}CH_2}\end{array}{>}\mathrm{C}{<}\begin{array}{l}\mathrm{CN}\\ \mathrm{C(CN){\cdot}CO_2Et}\\ \mathrm{CH_2{\cdot}CO_2Et}\end{array}$$

 (II.)

$$\mathrm{CHMe}{<}\begin{array}{l}\mathrm{CH_2{\cdot}CH_2}\\ \mathrm{CH_2{\cdot}CH_2}\end{array}{>}\mathrm{C}{<}\begin{array}{l}\mathrm{CO_2H}\\ \mathrm{CH{\cdot}CO_2H}\\ \mathrm{CH_2{\cdot}CO_2H}\end{array}$$

Finally, two isomeric forms of 1-*carboxy*-2-*methyl*cyclo*hexane*-1-*succinic acid* were obtained from the hydrolysis of the dicyanosuccinic ester prepared from 1-cyano-1-hydroxy-2-methyl*cyclo*hexane.

No indication was therefore obtained of isomerism connected with multiplanar forms of the *cyclo*hexane ring.

In all three series the acids (B) gave p-*methylanil*-p-*toluidides*, 

$$>\mathrm{C}{<}\begin{array}{l}\mathrm{CO{-}N{\cdot}C_7H_7}\\ \mathrm{CH{-}CO}\\ \mathrm{CH_2{\cdot}CO{\cdot}NH{\cdot}C_7H_7},\end{array}$$

identical with those prepared from the more difficultly fusible (A) isomers. It is reasonable to interpret this as due to the conversion of the labile form into the more stable isomer, at the relatively high temperature (210—220°) used in the preparation of these derivatives.

When this work was in an advanced stage (Desai, Hunter, and Saharia, *Nature*, 1937, **139**, 718), a paper by Chatterji appeared (*J. Indian Chem. Soc.*, 1937, 127), in which the author stated that he could obtain only one 1-carboxy-4-methyl*cyclo*hexane-1-succinic acid, m. p. 188°. In the 3- and the 2-methyl*cyclo*hexane series, he obtained gums. The acid, m. p. 188°, is, however, a mixture, from which, with some difficulty, mainly 1-carboxy-4-methyl*cyclo*hexane-1-succinic acid (A), m. p. 207°, can be isolated.

EXPERIMENTAL.

1-*Carboxy*-4-*methyl*cyclo*hexane*-1-*succinic Acids*.—(i) *Condensation of ethyl* 1-*cyano*-4-*methyl*-cyclo*hexane*-1-*cyanoacetate with ethyl bromoacetate*. Ethyl 1-cyano-4-methyl*cyclo*hexane-1-cyanoacetate, prepared by condensing freshly distilled 1-cyano-1-hydroxy-4-methyl*cyclo*hexane (34·7 g.) with ethyl cyanoacetate (31 g.) in the presence of sodium ethoxide (prepared from 5·7 g. of sodium and 60 c.c. of absolute alcohol), was kept at laboratory temperature for 48 hours. The mixture was cooled during the addition of ethyl bromoacetate (44·2 g.) and the resulting mixture was kept at laboratory temperature for another 2 days and then heated on a water-bath under reflux for 24 hours; the alcohol was recovered, and the residue added to a large quantity of water. The precipitated ester was extracted in ether, dried, recovered, and distilled, giving a fraction, b. p. up to 120°/6 mm., a fraction, b. p. 120—195°/6 mm., and ethyl 1-cyano-4-methyl*cyclo*hexane-1-α-cyanosuccinate, b. p. 208—210°/6 mm. The first fraction was rejected. The yield was improved by condensing the second fraction (26 g.) with ethyl bromoacetate (19 g.) and sodium ethoxide (prepared from 2·5 g. of sodium and 30 c.c. of absolute alcohol), and working up the product as already described; the total yield was 65%. The *dicyanosuccinic* ester solidified in a vacuum; m. p. 75—78°, raised to m. p. 97° (previous sintering) by recrystallisation (Found: C, 63·7; H, 7·5. $C_{17}H_{24}O_4N_2$ requires C, 63·75; H, 7·5%). Yield, 53 g.

(ii) *Hydrolysis of the ester.* The ester (52 g.) was left in contact with concentrated sulphuric acid (100 c.c.) overnight, and water (135 c.c.) then added. The mixture was heated for 24 hours, diluted with water, cooled, and extracted with ether. The ethereal extract was shaken with aqueous sodium carbonate (10%); when the alkaline solution was acidified with concentrated hydrochloric acid, a mixture of acids separated. After saturation of the liquid with ammonium sulphate, the acids were extracted in ether, dried, and recovered; they solidified in a vacuum, m. p. 158—165°. Treatment with warm benzene left a solid, m. p. 195° (previous sintering), which, on being heated under reflux with further benzene for an hour, gave an acid, m. p. 205°. On recrystallisation of this from dilute alcohol, 1-*carboxy*-4-*methyl*cyclo*hexane*-1-*succinic acid* (*A*) was obtained in plates, m. p. 207° (Found: C, 55·5; H, 7·0. $C_{12}H_{18}O_6$ requires C, 55·8; H, 6·9%). The combined benzene mother-liquors on concentration deposited a fraction, m. p. 180—185°, which after several recrystallisations furnished the acid (A), m. p. 207°. The mother-liquors gave a fraction, m. p. 165—169°, which on recrystallisation from benzene furnished the isomeric (*B*) *acid*, m. p. 175—176°, and 178° after recrystallisation from aqueous alcohol (Found: C, 55·7; H, 6·9%). A mixture of this with the acid (A) melted at 155—156°. A mixture of the acid (B) with 1-carboxy-4-methyl*cyclo*hexane-1-acetic acid (A) (m. p. 173°) melted at 154—155°.

The benzene mother-liquor gave a sticky mass, which on rehydrolysis with concentrated hydrochloric acid for 15 hours gave a certain amount of the acid (A), m. p. 207°, accompanied by a gum.

(iii) *Esterification of the gum.* A solution of the gum (5—7 g.) in absolute alcohol (25 c.c.) was treated with concentrated sulphuric acid (2·5 c.c.) and heated under reflux on a water-bath for 24 hours. The oil precipitated on pouring into cold water was extracted with ether and washed with 2N-sodium carbonate. The residue obtained on removal of ether was distilled under reduced pressure, two fractions, b. p. 135—140°/6 mm. and 155—157°/6 mm., being collected. The first fraction, after alkaline hydrolysis, furnished 1-carboxy-4-methyl*cyclo*hexane-1-acetic acids (A) and (B), m. p. 173° and 137° respectively (Desai, Hunter, Ghulam Khan, and Saharia, J., 1936, 416). The second fraction gave, on hydrolysis, 1-carboxy-4-methyl*cyclo*hexane-1-succinic acid, m. p. 207° after purification.

During the separation of the two isomeric acids, we encountered an acid, m. p. 188° (previous sintering), which could be broken up with difficulty, furnishing mainly the acid (A), m. p. 207°. This appears to be a eutectic mixture (compare Desai, Hunter, Ghulam Khan, and Saharia, *loc. cit.*).

Derivatives of the Acid (*A*), *m. p.* 207°.—The anhydride, prepared by means of boiling acetic anhydride, was a liquid. It was converted, by treatment with aniline in benzene solution, into the *anilide-anilic acid*, m. p. 175—176°, after recrystallisation from alcohol–water (Found: C, 70·1; H, 6·7. $C_{24}H_{28}O_4N_2$ requires C, 70·5; H, 6·8%). The *anil-anilide*, prepared by heating the acid (0·5 g.) with aniline (1 g.) at 165—170° for 3—4 hours, crystallised from alcohol–water in plates, m. p. 187° (Found: C, 73·6; H, 6·7. $C_{24}H_{26}O_3N_2$ requires C, 73·8; H, 6·6%). The p-*methylanil*-p-*toluidide*, prepared by heating the acid (1 g.) and *p*-toluidine (1·7 g.) at 210—220° for 2 hours, on treatment with boiling hexane for an hour and crystallisation from alcohol–water, formed rectangular plates, m. p. 186° (Found: C, 74·4; H, 7·1. $C_{26}H_{30}O_3N_2$ requires C, 74·6; H, 7·2%).

The acid (B), m. p. 178°, gave a *p*-methylanil-*p*-toluidide, which after recrystallisation from dilute alcohol had m. p. 185—186° alone and when mixed with the *p*-methylanil-*p*-toluidide of the acid (A). This is attributed to isomeric change at the temperature (220°) of the reaction.

1-*Carboxy*-3-*methyl*cyclo*hexane*-1-*succinic Acids*.—Ethyl 1-cyano-3-methyl*cyclo*hexane-1-cyanoacetate, prepared from freshly distilled 1-cyano-1-hydroxy-3-methyl*cyclo*hexane (27·8 g.), ethyl cyanoacetate (25 g.), and sodium ethoxide (4·6 g. of sodium and 60 c.c. of absolute alcohol), was kept for 48 hours and treated with ethyl bromoacetate (33·5 g.). The ester was obtained as a dark brownish-yellow oil, which was extracted in ether, dried, and distilled. The fraction, b. p. up to 125°/10 mm., was rejected, and the fraction, b. p. 125—195°/10 mm., was re-treated with ethyl bromoacetate; the last fraction consisted of *ethyl* 1-*cyano*-3-*methyl*cyclo*hexane*-1-α-*cyanosuccinate*, b. p. 208—210°/10 mm. After retreatment of the second fraction (125—195°/10 mm., 24 g.) with ethyl bromoacetate in the presence of sodium ethoxide (2·4 g. of sodium and 30 c.c. of absolute alcohol), the yield of dicyanosuccinic ester was raised to 56% (Found: C, 63·5; H, 7·6. $C_{17}H_{24}O_4N_2$ requires C, 63·75; H, 7·5%). The ester (36 g.) was hydrolysed as in the preceding case. The crude mixture of acids isolated by ether solidified in a vacuum; after trituration with cold benzene, it was treated with warm benzene. This furnished a sparingly soluble acid, which was heated with benzene under reflux for an hour and recrystallised from a small quantity of alcohol–water, yielding 1-*carboxy*-3-*methyl*cyclo*hexane*-1-*succinic acid* (*A*) in plates, m. p. 210° (Found: C, 55·8; H, 6·9. $C_{12}H_{18}O_6$ requires C, 55·8; H, 6·9%). The benzene mother-liquors deposited a fraction, m. p. 185—187°, which consisted mainly of the acid (A); on treatment with fresh benzene the m. p. was raised to 210°. The combined benzene mother-liquors were evaporated, and the residue hydrolysed with concentrated hydrochloric acid and worked up in the usual way. The product, crystallised from alcohol–water, furnished 1-*carboxy*-3-*methyl*cyclo*hexane*-1-*succinic acid* (*B*), m. p. 171—172° (Found: C, 55·7; H, 6·9%). A mixture of this with the isomeric acid (A) melted at 148°. A mixture of the acid (B) with 1-carboxy-3-methyl*cyclo*hexane-1-acetic acid (A) (m. p. 165°) had m. p. 145—146°.

The benzene mother-liquors gave a considerable amount of gummy product. To a solution of this (2 g.) in absolute alcohol (20 c.c.), concentrated sulphuric acid (2 c.c.) was added, and the mixture was heated for 24 hours. The ester was obtained as a yellow oil, which was extracted with ether, and the ethereal solution was shaken with aqueous sodium carbonate to remove any acid ester present. The residue obtained by removal of ether gave a fraction, b. p. up to 180°/18 mm., which on hydrolysis furnished the two isomeric 1-carboxy-3-methyl*cyclo*hexane-1-acetic acids, m. p. 163° and 108°. The second fraction, b. p. 190—195°/18 mm. (Found: C, 62·8; H, 8·7. $C_{18}H_{30}O_6$ requires C, 63·1; H, 8·7%), gave, on alkaline hydrolysis, a mixture of the 1-carboxy-3-methyl*cyclo*hexane-1-succinic acids.

The p-*methylanil*-p-*toluidide*, prepared from the acid (A) (0·5 g.) and *p*-toluidine (0·85 g.) at 210—220°, separated from dilute alcohol in prismatic needles, m. p. 158—159° (Found: C, 74·5; H, 7·2. $C_{26}H_{30}O_3N_2$ requires C, 74·6; H, 7·2%). The same substance was also obtained from the B-acid.

1-*Carboxy*-2-*methyl*cyclo*hexane*-1-*succinic Acids.*—Ethyl 1-cyano-2-methyl*cyclo*hexane-1-cyanoacetate, prepared from freshly distilled 1-cyano-1-hydroxy-2-methyl*cyclo*hexane (27·8 g.), was condensed with ethyl bromoacetate (33·5 g.) in the usual way. The first fraction, b. p. up to 125°/6 mm., was rejected, and the second fraction, b. p. 125—185°/6 mm., was re-treated with ethyl bromoacetate. The third fraction consisted of *ethyl* 1-*cyano*-2-*methyl*cyclo*hexane*-1-α-*cyanosuccinate*, b. p. 206—208°/8 mm. After three treatments with ethyl bromoacetate, a 40% yield of the dicyanosuccinic ester was obtained, as a mobile liquid (Found: C, 63·5; H, 7·5. $C_{17}H_{24}O_4N_2$ requires C, 63·75; H, 7·5%). The ester (12 g.) was hydrolysed as in the preceding cases. The crude mixture of acids, after treatment with benzene, furnished a sparingly soluble portion, m. p. 185—186°. On recrystallisation from alcohol–water, this gave the *acid* (*A*) in plates, m. p. 195° (Found: C, 55·8; H, 6·9. $C_{12}H_{18}O_6$ requires C, 55·8; H, 6·9%). The benzene mother-liquors did not deposit any solid on concentration; the solvent was therefore completely removed, and the residue heated with concentrated hydrochloric acid for 15 hours. The product was worked up in the usual way, a crude mixture of acids, m. p. 145—147°, being obtained, which on treatment with benzene yielded the acid (A), m. p. 185—190°. The benzene mother-liquors deposited a solid, m. p. 169—170°, which on crystallisation from alcohol–water yielded 1-*carboxy*-2-*methyl*cyclo*hexane*-1-*succinic acid* (*B*) in plates, m. p. 175° (Found: C, 55·7; H, 6·9%). A mixture of this with the acid (A) melted at 165°, and a mixture with 1-carboxy-2-methyl*cyclo*hexane-1-acetic acid (B) had m. p. 148°.

The p-*methylanil*-p-*toluidide*, prepared by heating the acid (A) or (B) with *p*-toluidine at 210—220° for 2 hours, had m. p. 169—170° after being heated with hexane under reflux. On recrystallisation from dilute alcohol, it was obtained in pink needles, m. p. 172° (Found: C, 74·2; H, 7·1. $C_{26}H_{30}O_3N_2$ requires C, 74·6; H, 7·2%). The hexane extract, on being kept, deposited the *di*-p-*toluidide* in white granules, m. p. 95° (previous sintering) (Found: C, 71·9; H, 7·2. $C_{26}H_{32}O_4N_2$ requires C, 71·5; H, 7·3%).

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