98. *The Isomeric* 1-*Carboxy*-4-, -3-, *and* -2-*methyl*cyclo*hexane*-1-*acetic Acids.*

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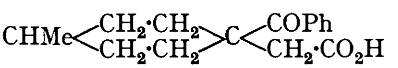
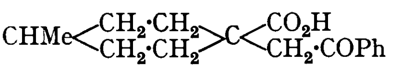
HYDROLYSIS of ethyl 1-cyano-4-methyl*cyclo*hexane-1-α-cyanoacetate, prepared by Higson and Thorpe's method (J., 1906, **89**, 1455), produced two 1-carboxy-4-methyl*cyclo*hexane-1-acetic acids, m. p. 137° and 173°, identical with the two acids previously obtained by oxidation of the isomeric α-keto-4-methyl*cyclo*hexane-1 : 1-diacetic acids (Desai, J., 1932, 1057). As Qudrat-i-Khuda (*J. Indian Chem. Soc.*, 1931, **8**, 277) claims to have obtained four acids by hydrolysis of the above ester, his work was repeated. The acids he describes as (A), (B), and (C) were isolated in accordance with his directions, but the fourth isomeride was not obtained. The acids (A) and (C), m. p. 137° and 173° respectively, were identical with the two acids mentioned above, but the " acid (B)," as has already been shown by Goldschmidt and Grafinger (*Ber.*, 1935, **68**, 279), whose paper appeared before the completion of our experiments, was a mixture of (A) and (C).

The anhydrides of the two 1-carboxy-4-methyl*cyclo*hexane-1-acetic acids on condensation with benzene gave, in addition to the expected 1-*benzoyl*-4-*methyl*cyclo*hexane*-1-*acetic acids* (I), which were characterised by their *semicarbazones*, neutral products to which the formula (IV) is assigned, it being assumed that they are produced from the alternative products of condensation (II) by dehydration of the intermediate hydroxy-lactones (III) under the influence of hydrogen chloride.

(I.)



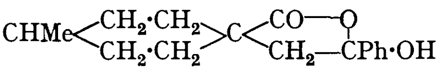
$$\mathrm{CHMe}{<}\begin{matrix}\mathrm{CH_2{\cdot}CH_2}\\ \mathrm{CH_2{\cdot}CH_2}\end{matrix}{>}\mathrm{C}{<}\begin{matrix}\mathrm{COPh}\\ \mathrm{CH_2{\cdot}CO_2H}\end{matrix}$$



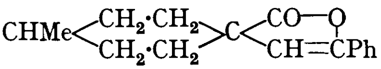
$$\mathrm{CHMe}{<}\begin{matrix}\mathrm{CH_2{\cdot}CH_2}\\ \mathrm{CH_2{\cdot}CH_2}\end{matrix}{>}\mathrm{C}{<}\begin{matrix}\mathrm{CO_2H}\\ \mathrm{CH_2{\cdot}COPh}\end{matrix}$$

(II.)

(III.)



$$\mathrm{CHMe}{<}\begin{matrix}\mathrm{CH_2{\cdot}CH_2}\\ \mathrm{CH_2{\cdot}CH_2}\end{matrix}{>}\mathrm{C}{<}\begin{matrix}\mathrm{CO{-}{-}O}\\ \mathrm{CH_2{-}CPh{\cdot}OH}\end{matrix}$$



$$\mathrm{CHMe}{<}\begin{matrix}\mathrm{CH_2{\cdot}CH_2}\\ \mathrm{CH_2{\cdot}CH_2}\end{matrix}{>}\mathrm{C}{<}\begin{matrix}\mathrm{CO{-}O}\\ \mathrm{CH{=}CPh}\end{matrix}$$

(IV.)

Support is lent to this view by the observation that α-phenylsuccinic anhydride gives a mixture of β-benzoyl-α-phenyl- and β-benzoyl-β-phenyl-propionic acid on condensation with benzene in the presence of aluminium chloride (unpublished results).

Synthesis of the 1-carboxy-3-methyl*cyclo*hexane-1-acetic acids both by Higson and Thorpe's method and by that of Lapworth and McRae (J., 1922, **121**, 2741) gave two isomerides, a somewhat sharp-melting mixture of which was at first mistaken for a third form of the acid (Desai and Hunter, *Nature*, 1935, **135**, 434).

Particular interest attaches to the synthesis of the 1-carboxy-2-methyl*cyclo*hexane-1-acetic acids in view of Thorpe's suggestion (J., 1931, 1023) that Qudrat-i-Khuda's second pair of acids might have arisen from the presence of 2-methyl*cyclo*hexanone in his 4-methyl*cyclo*hexanone. The melting points of the two 1-carboxy-2-methyl*cyclo*hexane-1-acetic acids obtained by both synthetic methods are quite different, however, from those of the acids (B) and (D) described by this author.

EXPERIMENTAL.

1-*Carboxy*-4-*methyl*cyclo*hexane*-1-*acetic Acids*.—(a) *Higson and Thorpe's method.* 4-Methyl*cyclo*hexanone (30 g.) was added to sodium bisulphite (26 g.) in water (100 c.c.) previously treated with sulphur dioxide. The oil which separated on addition of potassium cyanide (16 g. in 40 c.c. of water) was extracted in ether, dried (sodium sulphate), recovered, treated with two drops of concentrated sulphuric acid, and distilled under reduced pressure, 1-*hydroxy*-1-*cyano*-4-*methyl*cyclo*hexane* (30 g.) being obtained, b. p. 128°/20 mm. (Found : C, 68·9; H, 9·5. $C_8H_{13}ON$ requires C, 69·1; H, 9·3%). The cyanohydrin (16 g.) was gradually added to a solution of ethyl sodiocyanoacetate (sodium, 2·3 g.; absolute alcohol, 30 c.c.; ethyl cyanoacetate, 14 g.) and after 12 hours the mixture was heated on a water-bath for an hour and diluted with water. The oil produced was extracted and dried in ether and distilled, ethyl 1-cyano-4-methyl*cyclo*hexane-1-α-cyanoacetate passing over at 162—164°/15 mm. (Found : C, 66·4; H, 7·8. Calc. for $C_{13}H_{18}O_2N_2$: C, 66·7; H, 7·7%). Yield, 70%. The ester and concentrated hydrochloric acid (50 c.c.) were heated for 15 hours and the product was extracted in ether and shaken with aqueous sodium carbonate. The alkaline layer on acidification with concentrated hydrochloric acid gave a mixture of acids (12 g.), m. p. 120—136°. This was extracted with hot benzene (50 c.c.); the residue (m. p. 160—165°), recrystallised from benzene, yielded 1-carboxy-4-methyl*cyclo*hexane-1-acetic acid, m. p. 173° (efferv.). The benzene extract, on cooling, deposited a product, m. p. 140—160°, which on further extraction with hot benzene furnished more of the acid, m. p. 173°. The benzene mother-liquor from the acid of m. p. 140—160°, after being concentrated, furnished 1-carboxy-4-methyl*cyclo*hexane-1-acetic acid, m. p. 132—134°, and 137° after recrystallisation.

(b) *Lapworth and McRae's method.* The yield of ethyl 4-methyl*cyclo*hexylidenecyanoacetate obtained from ethyl cyanoacetate and 4-methyl*cyclo*hexanone in presence of piperidine was improved by the addition of anhydrous sodium sulphate and heating for 24 hours. The unsaturated ester was condensed with potassium cyanide according to the directions of Qudrat-i-Khuda, the product heated with concentrated hydrochloric acid for 15 hours, and the mixture of acids isolated in the usual way. The ethereal solution gave the imide of the acid of m. p. 173°, which crystallised from dilute alcohol in plates, m. p. 171°; the mother-liquor yielded the imide, m. p. 128—129° after several recrystallisations, of the acid of m. p. 137°.

Separation of the Acids by Qudrat-i-Khuda's Method.—The crude mixture of acids was neutralised with ammonia, the solution evaporated to dryness, and the residue extracted with absolute alcohol. An aqueous solution of the insoluble portion was acidified with hydrochloric acid and extracted with ether, the product heated with acetic anhydride for 3 hours, the excess removed, and the residue distilled under reduced pressure, a mixture of anhydrides passing over at 165—180°/39 mm., which set to a crystalline mass, m. p. 55—58°. On recrystallisation from light petroleum (b. p. 60—80°), this gave an anhydride in lustrous white laminæ, m. p. 104°, derived from the acid of m. p. 173°, and thereafter a second anhydride in thick plates, m. p. 77°, which yielded the 1-carboxy-4-methyl*cyclo*hexane-1-acetic acid of m. p. 137° on being treated with water. The mother-liquor furnished a solid, m. p. 57—61°, from which a pure individual could not be obtained by recrystallisation, but which, on decomposition with water, gave an acid, m. p. 129° (with previous sintering); this was shown to be an impure specimen of the acid of m. p. 137° (mixed m. p. 132—134°) by the preparation of derivatives.

The ammonium salts recovered from the alcoholic extract (above) were heated with concentrated hydrochloric acid for 4—5 hours; the product, m. p. 145—155°, on extraction with benzene, gave the acid of m. p. 173°. The mother-liquor deposited impure fractions and, after concentration to small bulk, the acid of m. p. 137°. From the impure fractions, the acid, m. p. 173°, was isolated, but no evidence of an acid, m. p. 146°, was obtained.

Derivatives of the Anhydride, m. p. 104°.—The *imide* crystallised from dilute alcohol in leafy plates, m. p. 171° (Found: C, 66·1; H, 8·3. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3%), and the *amic acid* in plates, m. p. 195° (Found: C, 60·2; H, 8·7. $C_{10}H_{17}O_3N$ requires C, 60·4; H, 8·5%). The anilic acid crystallised in needles, m. p. 186°, and the anil had m. p. 185° (Qudrat-i-Khuda, *loc. cit.*). The p-*toluidinic acid* separated from dilute alcohol in needles, m. p. 168—169° (Found: C, 70·9; H, 8·0. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 7·9%), the p-*tolylimide* in needles, m. p. 160° (Found: C, 75·6; H, 7·8. $C_{17}H_{21}O_2N$ requires C, 75·3; H, 7·8%), the α-*naphthylamic acid* in small plates, m. p. 140° (Found: C, 74·2; H, 7·1. $C_{20}H_{23}O_3N$ requires C, 73·8; H, 7·0%), and the α-*naphthylimide* formed needles, m. p. 163° (Found: C, 78·5; H, 6·9. $C_{20}H_{21}O_2N$ requires C, 78·4; H, 6·8%); the β-*naphthylamic acid* (Found: C, 74·1; H, 6·9%) and the β-*naphthylimide* (Found: C, 78·7; H, 6·8%) both had m. p. 185°, but the mixed m. p. was 165—170°.

Derivatives of the Anhydride, m. p. 77°.—The imide separated from dilute alcohol in plates, m. p. 130° (Qudrat-i-Khuda gives m. p. 119—120°), and the anilic acid in needles, m. p. 190°.

Derivatives of the Anhydride, m. p. 57—61°.—The imide after one crystallisation had m. p. 130°, undepressed by the imide of the acid of m. p. 137°. The anilic acid had m. p. 183° (previous sintering), and, after two recrystallisations, 190°, undepressed by the anilic acid obtained from the anhydride of m. p. 77°.

Condensation of the Anhydride, m. p. 104°, *with Benzene.*—A mixture of aluminium chloride (6·1 g.) and the anhydride (4·5 g.) in dry benzene, after being kept at laboratory temperature for 24 hours, was heated on a water-bath until the evolution of hydrogen chloride ceased. The residue obtained after removal of benzene was treated with cold dilute hydrochloric acid, and the residue from this was extracted with aqueous sodium carbonate (10%). On acidification of the extract, 1-*benzoyl*-4-*methyl*cyclo*hexane*-1-*acetic acid* (*A*) was obtained, which crystallised from benzene–petroleum in thick plates, m. p. 165° (Found: C, 73·4; H, 7·6; equiv., 258. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%; equiv., 260). The *semicarbazone* crystallised from alcohol in thick plates, m. p. 165° (Found : C, 64·0; H, 7·5. $C_{17}H_{23}O_3N_3$ requires C, 64·3; H, 7·3%). The neutral *compound* left after the extraction with aqueous sodium carbonate separated from alcohol in needles, m. p. 160° (Found : C, 78·9; H, 7·4. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%); mixed m. p. with the acid (A) 135—139°.

Reduction of 1-*Benzoyl*-4-*methyl*cyclo*hexane*-1-*acetic Acid* (*A*).—A mixture of the keto-acid (4 g.), amalgamated zinc (30 g.), and concentrated hydrochloric acid (35 c.c.) was boiled for 24 hours and kept at laboratory temperature for 2 hours. After removal of the excess of zinc, the mixture was extracted with ether, and 1-*benzyl*-4-*methyl*cyclo*hexane*-1-*acetic acid* (*A*) isolated by extraction with aqueous sodium carbonate; it crystallised from light petroleum in soft needles, m. p. 98° (Found : C, 77·9; H, 9·1; equiv., 245. $C_{16}H_{22}O_2$ requires C, 78·0; H, 9·0%; equiv., 246).

1-*Benzoyl*-4-*methyl*cyclo*hexane*-1-*acetic acid* (*B*), prepared from the anhydride of m. p. 77° and benzene, crystallised from petroleum in thick plates, m. p. 140—141° (Found : C, 73·5; H, 7·8%; equiv., 261); the *semicarbazone* separated from alcohol in plates, m. p. 150° (Found : C, 64·1; H, 7·6%). The neutral *compound* formed in the Friedel–Crafts reaction crystallised from dilute alcohol in plates, m. p. 89° (Found : C, 79·2; H, 7·3%). Reduction of the acid (B) by Clemmensen's method furnished 1-*benzyl*-4-*methyl*cyclo*hexane*-1-*acetic acid* (*B*), which crystallised from light petroleum in needles, m. p. 127° (Found : C, 77·7; H, 8·9%); the ethereal solution which had been extracted with aqueous sodium carbonate furnished a neutral *compound*, which crystallised in prismatic needles, m. p. 250° (Found : C, 78·5; H, 8·1. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%).

1-*Carboxy*-3-*methyl*cyclo*hexane*-1-*acetic Acids*.—(a) *Higson and Thorpe's method*. The preparative details are similar to those described for the 4-methyl compounds. 1-*Hydroxy*-1-*cyano*-3-*methyl*cyclo*hexane*, prepared from 3-methyl*cyclo*hexanone (yield, 80%), had b. p. 120°/15 mm. (Found : C, 68·8; H, 9·2%). *Ethyl* 1-*cyano*-3-*methyl*cyclo*hexane*-1-α-*cyanoacetate*, obtained from it (17 g.) and ethyl sodiocyanoacetate (sodium, 3 g.; alcohol, 40 c.c.; ethyl cyanoacetate, 15 g.), had b. p. 185°/15 mm. (Found : C, 66·5; H, 7·9. $C_{13}H_{18}O_2N_2$ requires C, 66·7; H, 7·7%). Yield, 75%. The dicyano-ester was heated with concentrated hydrochloric acid (3 vols.) for 48 hours. The acidic products, isolated by means of ether and aqueous sodium carbonate, became semi-solid on keeping, and on treatment with benzene furnished 1-carboxy-3-methyl*cyclo*hexane-1-acetic acid, m. p. 163° (efferv.), identical with the acid obtained by oxidation of α-keto-3-methyl*cyclo*hexane-1 : 1-diacetic acid with hydrogen peroxide (Desai, *loc. cit.*). The gum obtained by evaporation of the benzene mother-liquor was treated with excess of aqueous ammonia (*d* 0·880) and heated with the calculated amount of aqueous barium chloride. The precipitated barium salt on decomposition with dilute hydrochloric acid furnished an oily product, which yielded the acid, m. p. 163°, on treatment with benzene. The filtrate from the barium salt on acidification deposited an oil, which was isolated by means of ether; when triturated with benzene, it solidified, m. p. 85—90°. On treatment with petroleum (b. p. 60—80°) most of it dissolved, leaving a residue of the acid, m. p. 163°. The petroleum extract on slow evaporation deposited a second 1-*carboxy*-3-*methyl*-cyclo*hexane*-1-*acetic acid*, which crystallised from benzene in plates, m. p. 108° (Found : C, 59·9; H, 8·1. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%. Found for the *silver* salt : Ag, 52·0. $C_{10}H_{14}O_4Ag_2$ requires Ag, 52·2%). A mixture of this acid with the acid, m. p. 163°, melted at 90—92°.

(b) *Lapworth and McRae's method*. Solutions of ethyl 3-methyl*cyclo*hexylidenecyanoacetate (50 g., b. p. 170°/15 mm.; for improved yield, see p. 417) in rectified spirit (225 c.c.) and of potassium cyanide (32 g.) in water (75 c.c.) were mixed and kept for 24 hours. The product obtained on removal of the alcohol was heated with concentrated hydrochloric acid (100 c.c.) for 48 hours, and the resulting gum extracted with ether. The semi-solid mixture of acids isolated by means of aqueous sodium carbonate was treated with benzene, the acid, m. p. 163°, being obtained. The benzene mother-liquor deposited a further quantity of this acid, and the gummy residue, by the ammonia–barium chloride treatment, also yielded this isomeride. The gum obtained from the soluble barium salt gave, on fractional crystallisation from petroleum–benzene, a solid (m. p. 75—85°), which, recrystallised from petroleum, furnished the isomeric acid, m. p. 108°. The mother-liquor gave a substance (2 g.) containing nitrogen, m. p. 181°, which yielded the acid, m. p. 108°, on hydrolysis with concentrated hydrochloric acid.

Derivatives of the Acid, m. p. 163°.—The anhydride had b. p. 150°/15 mm., and solidified in a freezing mixture; m. p. 41°. The anilic acid and the anil had m. p. 176° (efferv.) and m. p. 143° respectively (Desai, *loc. cit.*). The *imide* crystallised from dilute alcohol in plates, m. p. 180—181° (Found : C, 66·3; H, 8·4. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3%), the p-*toluidinic* *acid* in needles, m. p. 180° (efferv.) (Found : C, 70·8; H, 8·1. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 7·9%), the p-*tolylimide* in small needles, m. p. 145° (Found : C, 75·5; H, 7·9. $C_{17}H_{21}O_2N$ requires C, 75·3; H, 7·8%), the *α-naphthylamic acid* in needles, m. p. 150° (Found : C, 74·0; H, 7·2. $C_{20}H_{23}O_3N$ requires C, 73·8; H, 7·0%), the *α-naphthylimide* had m. p. 142° (Found : C, 78·6; H, 7·0. $C_{20}H_{21}O_2N$ requires C, 78·4; H, 6·8%), the *β-naphthylamic acid* separated from alcohol in needles, m. p. 192° (efferv.) (Found : C, 74·2; H, 6·9%), and the *β-naphthylimide* formed plates, m. p. 189° (Found : C, 87·7; H, 6·8%). A mixture of the last and the β-naphthylamic acid melted at 165—170°.

Derivatives of the Acid, m. p. 108°.—The *anhydride* had b. p. 145—148°/15 mm. and crystallised from hexane in prismatic needles, m. p. 50° (Found : C, 66·1; H, 7·8. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%). The *anilic acid* crystallised from alcohol in needles, m. p. 207° (Found : C, 69·7; H, 7·8. $C_{16}H_{21}O_3N$ requires C, 69·8; H, 7·6%); the *anil* had m. p. 107° (Found : C, 74·5; H, 7·5. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4%). The *imide* separated from petroleum in needles, m. p. 92° (Found : C, 66·1; H, 8·5%). The p-*toluidinic acid* crystallised in needles, m. p. 185° (Found : C, 70·8; H, 7·8%); the *tolylimide* had m. p. 102—103° (Found : C, 75·5; H, 8·0%). The *α-naphthylamic acid*, m. p. 207° (Found : C, 73·5; H, 7·1%), the *α-naphthylimide*, m. p. 115° (Found : C, 78·1; H, 6·8%), and the *β-naphthylamic acid*, m. p. 183° (Found : C, 73·7; H, 7·3%), all crystallised in needles; the *β-naphthylimide* had m. p. 116° (Found : C, 78·5; H, 6·9%).

1-*Carboxy*-2-*methyl*cyclo*hexane*-1-*acetic Acids*.—1-*Hydroxy*-1-*cyano*-2-*methyl*cyclo*hexane* (28 g.), prepared from 2-methyl*cyclo*hexanone (28 g.), distilled at 114—116°/15 mm. (Found : C, 69·0; H, 9·4. $C_8H_{13}ON$ requires C, 69·1; H, 9·3%). *Ethyl* 1-*cyano*-2-*methyl*cyclo*hexane*-1-*α-cyanoacetate*, obtained in 50% yield from this ester and ethyl sodiocyanoacetate by the usual method, had b. p. 180°/15 mm. (Found : C, 66·4; H, 8·0. $C_{13}H_{18}O_2N_2$ requires C, 66·7; H, 7·7%). The dicyano-ester (20 g.) was heated with concentrated hydrochloric acid (50 c.c.) for 72 hours. The acids produced were extracted with ether, worked up in the usual way, and treated with benzene, a sparingly soluble 1-*carboxy*-2-*methyl*cyclo*hexane*-1-*acetic acid* being obtained, which crystallised from water in plates, m. p. 170° (efferv.) (Found : C, 59·9; H, 8·0; equiv., 101. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%; equiv., 100) [anhydride, b. p. 142—143°/12 mm.; *anilic acid*, thick cubes, m. p. 148°, from dilute alcohol (Found : C, 69·8; H, 7·7. $C_{16}H_{21}O_3N$ requires C, 69·8; H, 7·6%)]. More of this acid was obtained on concentration; the mother-liquor from this, on being kept for 24 hours, yielded a second *acid*, which separated from hot water in thick needles, m. p. 160° (Found : C, 60·2; H, 8·0%; equiv., 102), mixed m. p. with the first isomeride 135—140°. The anhydride of the second acid had b. p. 141—142°/12 mm., and the *anilic acid* separated from dilute alcohol in slender needles, m. p. 161—162° (Found : C, 70·1; H, 7·6%).

Ethyl 2-*Methyl*cyclo*hexylidenecyanoacetate*.—A mixture of 2-methyl*cyclo*hexanone (40 c.c.), ethyl cyanoacetate (35 c.c.), and piperidine (8—10 drops) was kept for 24 hours and, after addition of anhydrous sodium sulphate, heated for 48 hours. The unsaturated *ester* distilled at 150—160°/15 mm. (Found : C, 69·4; H, 8·4. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·2%). Yield, 50%. The unsaturated ester (25 g.) in rectified spirit (100 c.c.) was treated with potassium cyanide (16 g. in 40 c.c. of water), and the mixture was hydrolysed by heating with concentrated hydrochloric acid (75 c.c.) for 48 hours. From the acidic portion, worked up in the usual way, the two isomeric 1-carboxy-2-methyl*cyclo*hexane-1-acetic acids already described were obtained.

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