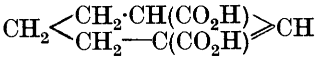
CCLXXXVII.—*The Chemistry of the Glutaconic Acids. Part XX. Tetrahydro*iso*phthalic Acid.*

By ERNEST HAROLD FARMER and HENRY LORIMER RICHARDSON.

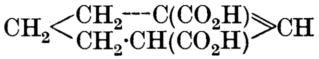
IN connexion with an examination of the structural mobility exhibited by cyclic systems containing the acylcrotonic grouping $\cdot CH_2\cdot CO\cdot CH_2\cdot CH{:}CH\cdot CO_2H$, it has become necessary, for purposes of comparison, to study the tautomeric capacity of the closely allied Δ^2-tetrahydro*iso*phthalic acid (I). This substance, in form an $\alpha\gamma$-disubstituted glutaconic acid, was obtained along with its Δ^3- and Δ^4-isomerides by Perkin and Pickles (J., 1905, **87**, 293) in an investigation of the reduction products of *iso*phthalic acid. The interconvertibility of the four isomeric tetrahydro-acids was explored by these authors and formulæ were assigned on the basis of the observations; the presence or absence of glutaconic tautomerism in the Δ^2-acid, however, was not determined. Owing to the number of substituents, this acid should not show the highest degree of glutaconic mobility, but would reasonably be expected to resemble in behaviour $\alpha\gamma$-dimethylglutaconic acid.

The ester of Perkin and Pickles's Δ^2-acid cannot be methylated under any conditions. Further, the methods applicable to the glutaconic acids have repeatedly failed to yield a hydroxy-anhydride, although the ordinary anhydride, as shown by the above authors, is readily obtainable. The acid, therefore, does not display two of the most important characteristics of glutaconic compounds. Whilst, however, with glutaconic acid, fixity of structure should result in geometrical isomerism, a semi-cyclic substance of formula (I) should exist in but one form whether the constitution be fixed, or mobile within the limits of the glutaconic three-carbon system. Distinction between the forms (I) and (II) is only to be perceived when the molecule is rendered unsymmetrical as in (III) or (IV). In testing the mobility of Perkin and Pickles's Δ^2-acid, the device represented in (IV) has been adopted, the half-ester of the acid being employed.

(I.)



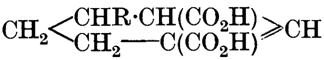
$$CH_2<\begin{matrix}CH_2\cdot CH(CO_2H)\\ CH_2—C(CO_2H)\end{matrix}>CH$$



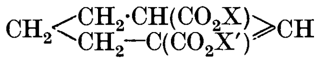
$$CH_2<\begin{matrix}CH_2—C(CO_2H)\\ CH_2\cdot CH(CO_2H)\end{matrix}>CH$$

(II.)

(III.)

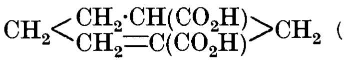


$$CH_2<\begin{matrix}CHR\cdot CH(CO_2H)\\ CH_2—C(CO_2H)\end{matrix}>CH$$



$$CH_2<\begin{matrix}CH_2\cdot CH(CO_2X)\\ CH_2—C(CO_2X')\end{matrix}>CH$$

(IV.)



$$CH_2<\begin{matrix}CH_2\cdot CH(CO_2H)\\ CH_2{=}C(CO_2H)\end{matrix}>CH_2$$

(V.)

When the anhydride of the tetrahydro-acid is heated with ethyl alcohol, not one, but two crystalline forms of the ethyl hydrogen ester are obtained, just as with *as*-dimethylsuccinic anhydride two forms of the corresponding ethyl hydrogen succinate are produced. Also, as with *as*-dimethylsuccinic anhydride, treatment with methyl alcohol yields one crystalline methyl hydrogen ester and only a trace of oily material which might represent a second form. When, however, bromine is added to this crystalline form and the product is treated with diethylamine, a somewhat impure monobromo-compound is obtained which yields on reduction a mixture of the original solid acid ester and a new substance; the latter appears to be the isomeric methyl hydrogen ester. There is, therefore, strong evidence of fixity of structure in the acid to which the formula (I) has been assigned, the forms (I) and (II) being potentially distinct and not possessing the degree of convertibility corresponding with glutaconic mobility. Moreover, it was found by Perkin and Pickles that boiling the acid represented by (I) with potash or hydrochloric acid led to double-bond movement, the new acid being the Δ^3-form (V). In our experiments, also, during the attempted methylation of the Δ^2-ester in the presence of sodium methoxide, the ester recovered was that not of the Δ^2- but of the Δ^3-acid.

Such behaviour for a glutaconic acid is most unusual; all experience goes to show that the tendency for a glutaconic system to appear, even under apparently adverse conditions, is extremely strong. The disappearance of glutaconic properties occasioned by movement of the double bond outside the system is without parallel; indeed, the tendency is rather for the migration of a double bond to establish such a system (compare Farmer, J., 1923, **123**, 3324). In view of these facts, the correctness of Perkin and Pickles's allocation of formulæ appeared extremely doubtful, and in the hope that degradation of the supposed Δ^2-acid by ozone would give useful information, where Perkin and Pickles had found permanganate and nitric acid to fail, the oxidation of this substance was attempted by us. Among the oxidation products a considerable amount of tricarballylic acid was found. Such a product cannot arise from the true Δ^2-form, but only from the Δ^3- or Δ^4-form * as seen in the fission formulæ (VI), (VII), and (VIII).

$\Delta^2 \longrightarrow HO_2C{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2H)_2$ . . . . . (VI.)
$\Delta^3 \longrightarrow HO_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CO_2H$. . . . . (VII.)
$\Delta^4 \longrightarrow HO_2C{\cdot}CH_2{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CH(CO_2H)_2$ . . . . (VIII.)

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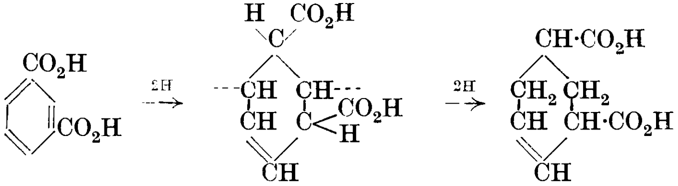
* We have been unable to complete the oxidation of the remaining isomerides or to apply other desirable tests owing to the exhaustion of our supply of material. A preliminary ozone oxidation of the *cis*-Δ^4-acid (P. and P.) yielded a considerable quantity of tricarballylic acid in accordance with the above scheme, but as the specimen employed did not, after numerous recrystallisations, quite attain the recorded melting point, it is intended to repeat the experiment.

There is little doubt, in view of the ease with which it yields an anhydride, that the Δ^2-acid of these authors is actually the *cis*-Δ^4-compound. Therefore the reduction of *iso*phthalic acid, which leads mainly to the production of this substance, may be represented thus:



It is hoped, when the further necessary evidence has been obtained, to investigate fully the properties of that isomeride possessing the glutaconic form.

EXPERIMENTAL.

*Tetrahydro*iso*phthalic Acids.**—The *iso*phthalic acid required was obtained in large quantities by the prolonged boiling of commercial xylene with a sufficient excess of aqueous permanganate to ensure the absence of toluic acids. The mixture of *iso*phthalic and terephthalic acids obtained by decolorising, filtering, and acidifying the product was separated into its components by the usual barium salt procedure. Reduction of the *iso*phthalic acid was effected by the method of Perkin and Pickles (*loc. cit.*), as were also the isolation and, where necessary, the interconversion of the tetrahydro-acids. Most of the Δ^2-acid used in the experiments was obtained by hydrolysis of the pure Δ^2-anhydride. A portion, however, derived directly from the less soluble calcium salt was used : this was carefully compared with the acid from the anhydride before employment.

Ethyl Hydrogen Δ^2-*Tetrahydro*iso*phthalate.*—The pure Δ^2-anhydride was refluxed for 3½ hours with twice the quantity of ethyl alcohol theoretically necessary. The excess of alcohol was evaporated in a vacuum, and the product freed from neutral ester by means of sodium carbonate solution. Thorough cooling of the acidic portion caused partial crystallisation ; filtration and repetition of the process resulted finally in the separation of the material into a crystalline acid ester and an oil from which no further crystals could thus be separated. The solid crystallised from light petroleum in colourless prisms, m. p. 44—45° (Found : C, 60·6 ; H, 7·1 ; *M*, monobasic, 199. $C_{10}H_{14}O_4$ requires C, 60·6 ; H, 7·1% ; *M*, 198). The oily acid ester, the basicity of which indicated that some free acid was present, was distilled and collected in two fractions, b. p. 169—171° and 171—173°/1 mm. The first of these completely

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* The description of compounds in the following pages is in accordance with the formulæ of Perkin and Pickles.

solidified on cooling; the second solidified but partly melted on resuming room temperature. The crystals from both specimens were identical and melted, after recrystallisation from light petroleum, at 40—41°. This substance was an acid ester, and was an isomeric form of that first isolated (mixed m. p. 31—37°) (Found: C, 60·4; H, 7·1%; *M*, monobasic, 197).

Methyl Hydrogen Δ^2-*Tetrahydro*iso*phthalate*.—This substance also was obtained from the anhydride. As with *as*-dimethylsuccinic acid, whilst ethyl alcohol yields two distinct acid esters (J., 1904, **85**, 534; *Ann. Chim.*, 1923, **19**, 335), methyl alcohol gives only one recognisable form. The crude product, after removal of the excess of alcohol, solidified almost entirely. Systematic fractional recrystallisation from hexane resulted only in the isolation of one isomeride. The crystallisation liquors yielded on evaporation a small quantity of oil. Part of this was the dimethyl ester of the Δ^2-acid; the remaining acidic portion crystallised when isolated from the mixture and was identical with the form already obtained. Only a minute quantity of acidic material remained. The second isomeride, therefore, if formed, was present only in an unrecognisable amount. The acid ester crystallised in soft, flat prisms, m. p. 59° (Found: C, 58·6; H, 6·6; *M*, monobasic, 184. $C_9H_{12}O_4$ requires C, 58·6; H, 6·6%; *M*, 184). The pure, dry crystals, when kept for some time in an evacuated desiccator or in the air, invariably became oily on the surface. Whether this was the result of isomerisation, or other change, could not be determined.

Interconversion of the Isomeric Acid-esters.—The reaction between pure methyl hydrogen Δ^2-tetrahydro*iso*phthalate (1 mol.) and bromine (1 mol.) in dry chloroform did not appear to be a simple addition of bromine: decoloration was rapid, but there was no end-point to mark the absorption of one molecular proportion of the halogen. The product, after removal of chloroform, was a viscous, pale yellow oil from which the pure dibromide could not be obtained in the solid condition. This crude substance, although somewhat deficient in bromine, was treated in ethereal solution with an excess of diethylamine. Diethylamine hydrobromide separated rapidly, and from the colourless filtrate an almost colourless, viscous oil was isolated, which also could not be obtained in the solid condition. This crude substance, containing 80% of the bromine necessary for the pure bromotetrahydro*iso*phthalic acid ester, was reduced with zinc dust and acetic acid. The product was separated into a small neutral portion and a much larger acidic portion. The former solidified and yielded a neutral, difficultly crystallisable solid (rosettes of colourless needles, m. p. 41—43°), the nature of which has not been discovered. The acidic portion, after a small quantity of the original acid ester had been removed, was distilled. The colourless distillate, b. p. 172—174°/1 mm., after a further very small quantity of the original easily crystallisable acid ester had been frozen out, remained liquid at room temperature. This substance, although not obtained in sufficient quantity to allow of adequate fractional distillation, approximated closely in composition and basicity to methyl hydrogen tetrahydro*iso*phthalate, and yielded the correct acid on hydrolysis. It distilled as a colourless oil, and is believed to represent the second isomeric form of the acid ester (Found : C, 59·8 ; H, 6·5%).

Methyl Δ^2-*tetrahydro*iso*phthalate* was obtained by the action of methyl iodide on the silver salt of the pure acid. The crude ester (after removal of a small quantity of the above-described solid acid ester by washing with sodium carbonate solution) was obtained on distillation as a colourless oil, b. p. 134—135°/7 mm. (Found : C, 60·45 ; H, 7·1. $C_{10}H_{14}O_4$ requires C, 60·5 ; H, 7·1%). To ensure that isomeric change had not taken place during esterification, a small portion of the ester was rapidly hydrolysed with dilute sulphuric acid ; only the Δ^2-acid could be isolated. The *amide*, which was readily obtained when the ester stood for 12 hours with concentrated aqueous ammonia at 40°, crystallised from water in flat prisms, m. p. 239°.

Methylation Experiments.—To the deep yellow solution obtained by mixing methyl Δ^2-tetrahydro*iso*phthalate with an equimolecular proportion of cold alcoholic sodium methoxide, an excess of methyl iodide was added. The temperature of the mixture rose somewhat, but as no change was apparent after 1½ hours, the mixture was heated for 4 hours on a steam-bath. The product isolated in the usual way consisted of a trace of acidic oil and a neutral ester that passed over on the first distillation at 138—143°/7 mm. On redistillation, almost the whole was obtained as a colourless oil, b. p. 140—141°/7 mm. This material was *methyl* Δ^3-*tetrahydro*iso*phthalate*, since on rapid hydrolysis with dilute sulphuric acid it yielded, not the Δ^2-acid, but an acid identical in all respects with Perkin and Pickles's Δ^3-acid. Unlike the Δ^2-ester, this isomeride did not yield a comparatively insoluble amide on standing with aqueous ammonia (Found : C, 60·4 ; H, 7·1. $C_{10}H_{14}O_4$ requires C, 60·5 ; H, 7·1%).

When the methylation mixture, prepared as above, was heated at 120—130° for 5 hours in a sealed tube, the same Δ^3-ester was obtained in good yield. In neither case could any methylated product be isolated. Attempts to secure methylation by the use of sodium and methyl iodide failed because finely-pulverised sodium was not appreciably affected by solutions of the Δ^2-ester in ether and xylene, even on prolonged refluxing.

Attempted Preparation of the Hydroxy-anhydride.—(*a*) Following the method of Thole and Thorpe (J., 1911, **92**, 2236), the pure Δ^2-acid was heated in a sealed tube with an excess of acetyl chloride for 6 hours at 110°. The product, consisting of a small amount of a white powder and a brown liquid, was freed from acetyl chloride and dissolved in dry ether. The ethereal solution was rapidly shaken with an excess of sodium bicarbonate solution, and the alkaline extract immediately acidified. The resulting aqueous solution was found on extraction to contain an acid which was largely precipitated on removal of the bulk of the solvent; the ethereal mother-liquor contained a very small amount of a more soluble crystalline solid. These were identified by direct comparison with authentic specimens as Δ^3-tetrahydro*iso*phthalic acid (m. p. 243°) and the anhydride of the corresponding Δ^2-acid (m. p. 78°), respectively. No trace of the hydroxy- or chloro-anhydride could be isolated. The aqueous mother-liquor from the recrystallisation of the Δ^3-acid contained a small amount of material, m. p. 165—205°, probably a mixture of the Δ^2- and Δ^3-acids. (*b*) The pure anhydride of the Δ^2-acid (m. p. 78°) was heated as directed by Thole and Thorpe (*loc. cit.*) for 15 minutes at 150°. There was no apparent decomposition and the melt, when recrystallised from ether, was found to consist entirely of the unchanged anhydride. More vigorous heating of the anhydride (15 minutes) at 300—310° resulted in considerable darkening in colour. From an ethereal solution of the cooled melt, crystals of unchanged anhydride were deposited, the mother-liquor yielding on evaporation a solid melting indefinitely at 72—187°. This was redissolved in ether and separated rapidly, as above, into neutral and acidic portions. The neutral portion was unchanged anhydride; the acidic portion, m. p. 225—235°, had none of the characteristics of a hydroxy-anhydride and was separated by fractional crystallisation from water into two portions, identified by direct comparison with authentic specimens as Δ^3- and Δ^2-tetrahydro*iso*phthalic acids. A portion of the melt insoluble in ether consisted partly of the Δ^3-acid and partly of resinous material from which no solid material could be obtained.

The possibility that the Δ^3-acid was formed by the fission of a hydroxy-anhydride under the conditions used for separation (use of aqueous sodium bicarbonate) seems discounted by the absence of the characteristics of such a compound in the various fractions obtained by use of non-aqueous solvents.

*Oxidation of Δ^2-Tetrahydro*iso*phthalic Acid.*—The acid derived from the pure Δ^2-anhydride ($2\frac{1}{2}$ g.) was dissolved in water and neutralised with a slight excess of sodium carbonate solution. A rapid stream of ozonised air was passed through the solution for about 12 hours. The product, after being freed from ozone by the passage of a rapid current of air, gave a strong aldehyde reaction with Schiff's reagent. It was accordingly cooled to 0° and treated with 3% permanganate solution (equivalent to 1 atom of oxygen based on the quantity of substance taken). The cold product was filtered, acidified, and extracted with pure ether. The mother-liquor, to which the aqueous extract of the manganese mud was added, was concentrated on the steam-bath and the evaporation completed in a vacuum. The residue was thoroughly extracted, first with ether, then with acetone. Each of the ethereal extracts yielded a syrupy acid which largely solidified. The bulk of the solid material (about 1 g.), after being thoroughly washed with dry ether and twice recrystallised from ether, was readily identified as tricarballylic acid, m. p. 163°. The ether washings and acetone extract contained other acids, the nature of which has not yet been ascertained.

Ozonisation of the Δ^2-acid was also conducted in chloroform suspension, but, owing to the insolubility of the acid, oxidation was extremely slow. The product, after being decomposed with water and the solvent removed, was freed as far as possible from the unchanged acid and kept for 3 days with hydrogen peroxide. The product was then evaporated almost to dryness several times with water and finally freed from water. From the syrupy residue, a quantity of impure tricarballylic acid slowly crystallised.

We desire to express our gratitude for grants from the Government Grant Committee of the Royal Society (to E.H.F.) and the Chemical Society (to H.L.R.) which have defrayed a considerable portion of the cost of the research.

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[*Received, May* 21*st*, 1926.]