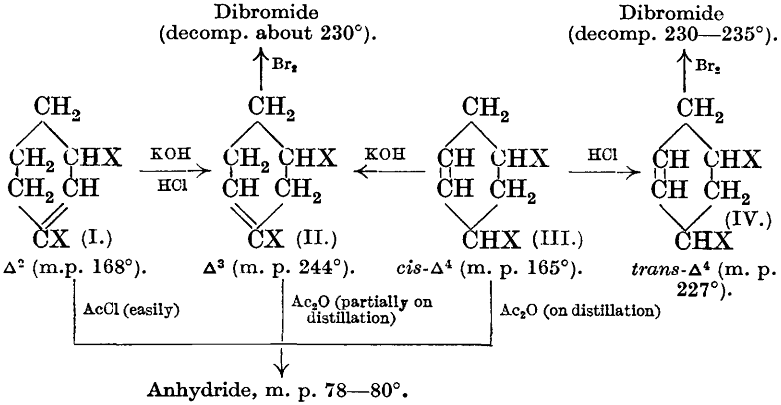
X.—*The Chemistry of the Glutaconic Acids. Part XXI. Non-formation of* Δ^2*-Tetrahydro*iso*phthalic Acid by Reduction of* iso*Phthalic Acid.*

By Ernest Harold Farmer and Henry Lorimer Richardson.

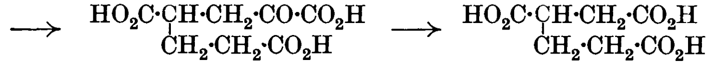
It was shown recently (Farmer and Richardson, J., 1926, 2173) that the Δ^2-tetrahydro*iso*phthalic acid of Perkin and Pickles (J., 1905, **87**, 293) does not possess glutaconic characteristics and should, on account of the ease with which it gives an anhydride and the nature of its oxidation products, be represented by the *cis*-Δ^4-formula. This correction quite precludes the possibility of a normal chemical relationship existing between the four tetrahydro-isomerides described by Perkin and Pickles: each of the possible ways of redistributing the formulæ involves a departure from customary chemical behaviour more serious than that connected with anhydride formation in the original scheme (below).



The most direct way of obtaining the necessary evidence for a reallotment of formulæ would appear to be oxidation of the remaining three isomerides. There are, however, two points which stand out from the evidence already recorded, and these have considerable importance in view of the later experimental results. The first concerns the conversion of the *cis-* into the *trans-*Δ^4-acid shown above; since the alleged *cis-*Δ^4-acid must have a structure other than that assigned to it in the scheme, the probability that the acid derived therefrom (by treatment with hydrochloric acid) is the *trans-*Δ^4-isomeride is greatly diminished. Secondly, the close similarity between the alleged Δ^3- and *trans-*Δ^4-acids and their similar behaviour on bromination strongly suggest their identity—a contingency which would reduce the number of isomerides isolated to three.

The main product of reduction of *iso*phthalic acid under the conditions described by Perkin and Pickles is the substance now regarded as the *cis-*Δ^4-acid (formerly Δ^2). Along with it appears a small quantity of an isomeric acid, m. p. 244° (Perkin and Pickles's Δ^3-acid) : this is obviously not a primary product of reduction, since it is produced in still smaller quantity when the temperature and alkalinity during reduction are diminished; also it is produced quite readily by boiling the pure *cis-*Δ^4-acid with alkali. The constitution of this substance follows from its oxidation by ozone to β-carboxyadipic acid, and therefore the Δ^3-formula assigned to it by Perkin and Pickles is correct.

(II.)



$$\longrightarrow \begin{array}{l} HO_2C\cdot CH\cdot CH_2\cdot CO\cdot CO_2H \\ \qquad\quad CH_2\cdot CH_2\cdot CO_2H \end{array} \longrightarrow \begin{array}{l} HO_2C\cdot CH\cdot CH_2\cdot CO_2H \\ \qquad\quad CH_2\cdot CH_2\cdot CO_2H \end{array}$$

The second primary product of the reduction—regarded by Perkin and Pickles as the *cis-*Δ^4-acid—must, therefore, if it is a tetrahydro*iso*phthalic acid, be either the true Δ^2- or the *trans-*Δ^4-form; both structures are difficult to reconcile with the recorded properties.

Considerable quantities of carefully purified *iso*phthalic acid have been reduced during these experiments, and the separation methods of Perkin and Pickles employed in isolating the products. We have been quite unable to satisfy ourselves that any portion of the reduction product contained a third isomeride. Not only has a third isomeride not been isolated, but oxidation of the entire residue after separation of the bulk of the pure Δ^3- and *cis-*Δ^4-acids has failed to yield any recognisable trace of adipic (or glutaric) acid.*

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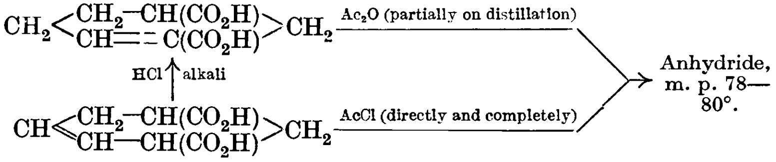
* Various portions approximating in melting point to that recorded for the "*cis-*Δ^4"-acid have been oxidised separately : one of these oxidations was referred to in a footnote of the previous memoir (p. 2173). Invariably the main product was tricarballylic acid.

The absence of the true Δ^2-acid from the reduction product therefore appears certain, and the remaining possibility, the occurrence of the *trans*-Δ^4-acid, is discounted on the following grounds : (1) non-isolability in the pure condition; (2) the inferior melting points of the residual portions of the reduction product; and (3) the strong indication afforded by the nature and analysis of the residues as to their consisting of mixtures of the Δ^3- and *cis*-Δ^4-acids with small quantities of non-isomeric impurities.* These results render the identity of Perkin and Pickles's Δ^3- and *trans*-Δ^4-forms all the more probable, and the relationship of the two veritable tetrahydro-acids, as represented below, is one which renders the direct conversion of the *cis*- into the *trans*-Δ^4-acid improbable of attainment.



$$\begin{tikzcd}
CH_2<\begin{matrix}CH_2-CH(CO_2H)\\CH=C(CO_2H)\end{matrix}>CH_2 \arrow[r, "Ac_2O\text{ (partially on distillation)}"] & \text{Anhydride, m. p. 78—80°.} \\
CH<\begin{matrix}CH_2-CH(CO_2H)\\CH-CH(CO_2H)\end{matrix}>CH_2 \arrow[u, "\text{alkali}"', shift right] \arrow[ur, "AcCl\text{ (directly and completely)}"'] &
\end{tikzcd}$$

It was noted by Perkin and Pickles that the dihydro*iso*phthalic acids appeared to be absent from their reduction products : this was the case also in our experiments. Yet the reduction may be regarded as normal in that it effects the hydrogenation of two CH:CH·CO groups. Further reduction experiments are being carried out and at the suggestion of Professor W. H. Perkin the synthesis of the Δ^2-tetrahydro-acid is being attempted.

EXPERIMENTAL.

Oxidation of Δ^3-*Tetrahydro*iso*phthalic Acid.*—The acid, m. p. 243—244°, was prepared by boiling the *cis*-Δ^4-acid (Perkin and Pickles's Δ^2-acid) with 30% aqueous potash and recrystallising the product from water (with the aid of charcoal) and from formic acid. A solution of 5 g. of it in a slight deficit of aqueous sodium carbonate was treated with ozonised oxygen for 20 hours; the product, after being freed from ozone by a rapid stream of air, gave a strong, aldehydic reaction with Schiff's reagent and with ammoniacal silver nitrate, but yielded no semicarbazone. The precipitate of *iso*phthalic acid (0·25 g., identified as methyl ester) obtained on acidification was removed and the filtrate was neutralised with alkali and carefully treated with dilute permanganate solution at 0° until the latter was no longer reduced. From the mixture, worked up in the usual way, ether extracted about 4 g. of a crystalline acid,

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* Nevertheless it has not been possible to demonstrate conclusively that the *trans*-Δ^4-acid is absent. It might quite well be produced in the reduction process and would yield tricarballylic acid on oxidation.

m. p. 110—115°; this, after recrystallisation from acetone–benzene and ethyl acetate, melted at 121° [Found: C, 44·3; H, 5·3: *M*(tribasic), 192. Calc. for $C_7H_{10}O_6$: C, 44·2; H, 5·3%; *M*, 190], alone or mixed with β-carboxyadipic acid prepared by Haworth and King's method (J., 1914, **105**, 1350).

Attempted Isolation of Perkin and Pickles's cis-Δ^4-*Acid.*—Since the Δ^2-acid of Perkin and Pickles is the true Δ^4-acid (almost certainly *cis*), the *cis*-Δ^4-acid of these authors must, if it represent a single isomeride of this series, be either the *trans*-Δ^4- or the Δ^2-form. On oxidation, the former of these should pass into tricarballylic acid, and the latter into adipic acid.

The earlier stages of Perkin and Pickles's calcium-salt method (*loc. cit.*, p. 302) for separating the reduction products of *iso*phthalic acid were followed. The calcium salt mother-liquors (the source of the "*cis*-Δ^4"-acid) yielded a glassy mass on evaporation. Fractional crystallisation of the acid regenerated from this (as described, *loc. cit.*, p. 311) yielded acid fractions of various melting points. Since samples approximating in m.p. to the recorded melting point "about 165°" * yielded considerable quantities of tricarballylic acid on oxidation with ozone, it was obvious that they did not consist of pure or nearly pure Δ^2-acid; the result, however, does not conflict with the Δ^4-structure for at least a portion of the material.

The acids obtained from a large quantity of the glassy calcium salts were regenerated and when solid were dissolved in hot water; almost pure Δ^3-acid separated on standing. The acids in the mother-liquor were reconverted into the calcium salts; a quantity of the less soluble calcium salt of the "Δ^2"-(true *cis*-Δ^4-)acid could then be removed. Again the mother-liquor yielded a glassy mass on evaporation. The alternate removal of Δ^3-acid and true *cis*-Δ^4-acid (as acid and calcium salt, respectively) was continued until less than 1 g. of acid (m. p. 165—200° after recrystallisation from formic acid) remained. This substance depressed the melting point of the pure *cis*-Δ^4-acid and gave very inferior analytical figures; it could not be regarded as a pure substance.

The acid material from the calcium salt mother-liquor appeared, therefore, to consist very largely of the Δ^3- and *cis*-Δ^4-acids. Of these, the former could readily be purified and identified beyond doubt; the purity of the latter, now free from all but the merest trace of the former, was not equally certain. Consequently, in

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* The above authors state that the melting point must be regarded as approximate only, as the acid obviously may have contained traces of "Δ^2"-tetrahydro*iso*phthalic acid.

demonstrating the absence of the Δ^2-acid (below) this portion of the reduction product was included.

Absence of the Δ^2-Acid from the Reduction Products.—The whole of the acid products derived from the calcium salt mother-liquors, except that portion removed as pure Δ^3-acid (above), was dissolved in aqueous sodium carbonate and treated with ozone as described above. Ether extracted from the acidified solution a sticky solid, m. p. 163—169° after recrystallisation from formic acid. This substance (amounting to about one-third of the material taken), which appeared to be slightly impure *cis*-Δ^4-acid (m. p. 172°) that had escaped oxidation, was re-submitted to oxidation (below). The aqueous mother-liquor, which gave a strong aldehyde reaction, was carefully reoxidised with dilute permanganate solution at 0°. The manganese-free liquor therefrom was acidified and evaporated to dryness in a vacuum. Extraction of the residue with acetone yielded a gummy mass, an aqueous solution of which, on concentration, deposited crystals of tricarballylic acid, representing nearly one-half of the material taken. No trace of adipic or glutaric acid could be isolated from the small residue.

The unoxidised portion (above) was combined with the ethereal extract of all the mother-liquors and porous tiles likely to contain acid derived from the more soluble calcium salt, and the whole was oxidised as before. The ethereal extract of the acidified product was a gummy mass (representing about 45% of the material taken). This and the aqueous mother-liquor were separately oxidised with permanganate. The former yielded a very small quantity of *iso*phthalic acid and some acid material readily soluble in water; the latter also yielded readily soluble, acid material. From the combined water-soluble portions, on concentration, tricarballylic acid separated in considerable quantity. No trace of adipic or glutaric acid could be isolated from the residue. Thus, whilst there is no evidence of the presence of the true Δ^2-acid in these portions of the *iso*phthalic acid reduction product, it is possible, although improbable, that a portion of the tricarballylic acid was derived from the *trans*-Δ^4-acid.

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