# CXCI.—*The Conditions underlying the Formation of Unsaturated and Cyclic Compounds from Halogenated Open-chain Derivatives. Part VIII. Products derived from Pimelic Acid. An Application of Bischoff's Dynamic Hypothesis.*

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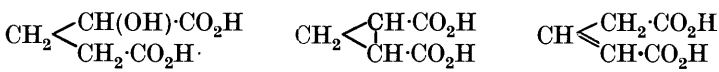
In general, the action of alkalis on the α-halogen derivatives of dibasic acids proceeds in three ways. Thus, monobromoglutaric acid yields a hydroxy-acid (I), a ring-acid (II), and an unsaturated acid (III), in addition to substances derived from the decomposition of these.



(I.) (II.) (III.)

If the quantity of unsaturated acid formed is small, the reaction may be regarded as a competition between hydroxylation and ring-formation, and may be used to estimate the relative ease of ring-formation in the different cases. This method has been applied to a number of glutaric and adipic acids, with results explicable on the assumption that the volumes of groups attached to a central carbon atom determine the inclination of its valencies and the consequent tendency of that atom to participate in a ring of given type (Ingold, J., 1921, **119**, 305, and later).

The halogen derivatives of pimelic acid have now been investigated, and, despite the fact that in this case there are difficulties in the way of a precise numerical comparison, the general results accord with the hypothesis. The ring formed is a five-membered one, and the ratio (ring-formation) : (hydroxylation) is much greater than in any case previously investigated.

In the case of the αα′-dihalogen-adipic esters (IV), concentrated

alkalis gave a small quantity of a *cyclo*butene acid (VI), and a considerable amount of muconic acid (VII) and of the hydroxy-acids (V).

$$CO_2R{\cdot}CHBr{\cdot}CH_2{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2R \quad \text{(IV.)}$$

$$\begin{matrix}CH_2{\cdot}CH(OH){\cdot}CO_2H\\ CH_2{\cdot}CH(OH){\cdot}CO_2H\end{matrix} \quad \begin{matrix}CH_2{\cdot}C{\cdot}CO_2H\\ \|\\ CH_2{\cdot}C{\cdot}CO_2H\end{matrix} \quad \begin{matrix}CH{:}CH{\cdot}CO_2H\\ CH{:}CH{\cdot}CO_2H\end{matrix}$$

(V; two forms.) (VI.) (VII.)

When αα′-dibromopimelic ester (VIII) was examined, a greatly increased tendency to ring formation was noticed Under various conditions, a considerable proportion of the material was transformed into the *cyclo*pentene acid (IX), although this acid did not always survive the conditions of its formation. When concentrated alkalis were employed, a second principal reaction gave rise to a doubly-unsaturated open-chain acid (X) (see below); the question as to whether this undergoes subsequent isomeric change is discussed below. So far as could be ascertained, dihydroxypimelic acids were not produced.

$$CH_2\!<\!\begin{matrix}CH_2{\cdot}CHBr{\cdot}CO_2R\\ CH_2{\cdot}CHBr{\cdot}CO_2R\end{matrix} \quad CH_2\!<\!\begin{matrix}CH_2{\cdot}C{\cdot}CO_2H\\ \|\\ CH_2{\cdot}C{\cdot}CO_2H\end{matrix} \quad CH_2\!<\!\begin{matrix}CH{:}CH{\cdot}CO_2H\\ CH{:}CH{\cdot}CO_2H\end{matrix}$$

(VIII.) (IX.) (X.)

The constitution of the ring-acid (IX) follows from its identity with the acid synthesised by Haworth and Perkin (J., 1894, **65**, 978) from the saturated *cyclo*pentane acid (XI), the dibromo-ester (XII) of which, on treatment with potassium iodide, yielded the ester (XIII):

$$CH_2\!<\!\begin{matrix}CH_2{\cdot}CH{\cdot}CO_2H\\ CH_2{\cdot}CH{\cdot}CO_2H\end{matrix} \rightarrow CH_2\!<\!\begin{matrix}CH_2{\cdot}CBr{\cdot}CO_2R\\ CH_2{\cdot}CBr{\cdot}CO_2R\end{matrix} \rightarrow CH_2\!<\!\begin{matrix}CH_2{\cdot}C{\cdot}CO_2R\\ \|\\ CH_2{\cdot}C{\cdot}CO_2R\end{matrix}$$

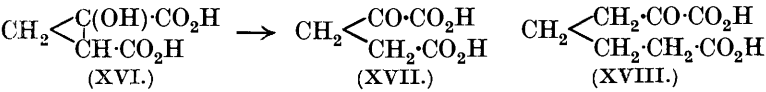
(XI.) (XII.) (XIII.)

In the presence of concentrated alkalis, the unsaturated ring-acid (IX) undergoes change into the isomeric acid (XIV), the reaction being analogous to the conversion of citraconic acid into itaconic acid, and of $\Delta^1$-tetrahydrophthalic acid into the $\Delta^2$-acid. The change is not complete, and definite evidence of its reversibility has been obtained. At the same time, a small amount of the saturated hydroxy-ring acid (XV) is produced.

(XIV.) $CH_2\!<\!\begin{matrix}CH{=}C{\cdot}CO_2H\\ CH_2{\cdot}CH{\cdot}CO_2H\end{matrix}$ $\qquad$ $CH_2\!<\!\begin{matrix}CH_2{\cdot}C(OH){\cdot}CO_2H\\ CH_2{\cdot}CH{\cdot}CO_2H\end{matrix}$ (XV.)

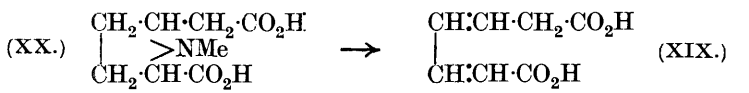
It is noteworthy that whereas the *cyclo*propane hydroxy-ring acid (XVI) is quantitatively converted into the isomeric ketoglutaric acid (XVII) by alkalis (Ingold, *loc. cit.*), the hydroxy*cyclo*pentane acid (XV) shows no tendency to pass into α-ketopimelic acid

(XVIII). The two cases evidently represent the two limiting conditions of the keto-cyclol change.



(XVI.) (XVII.) (XVIII.)

Although formula (X) must represent the structure of the unsaturated open-chain acid initially produced from dibromopimelic ester, it is possible that this acid changes into the isomeride (XIX) under the conditions of the experiment. It is known that under these conditions αβ-unsaturated acids readily come into equilibrium with their βγ-unsaturated isomerides, and in this case the βγ-compound possesses a conjugated system from which it might be expected to derive sufficient stability to render the isomeric change practically non-reversible. The acid appears to be identical with the " piperylenedicarboxylic acid " obtained by Willstätter (*Ber.*, 1895, **28**, 3287) by the exhaustive methylation of tropinic acid (XX):



(XX.) (XIX.)

These reactions do not, of course, prove the structure, but the tendency to the production of conjugated systems by the exhaustive methylation process is well known, and is illustrated by the exhaustive methylation of piperidine.

A remarkable reaction, which has not been observed in any of the shorter-chain series previously investigated, is that which leads to the formation of considerable quantities of the meso- and racemic forms of the dimethoxy-acid $CO_2H{\cdot}CH(OMe){\cdot}[CH_2]_3{\cdot}CH(OMe){\cdot}CO_2H$ when methyl-alcoholic potassium hydroxide is employed as the hydrolysing agent. Although the occurrence of this reaction creates difficulties when the attempt is made to extend to the pimelic acid series the method of numerical comparison previously employed, it is in accord with the view that the conditions governing all these reactions are essentially spatial; for whereas steric influences would prevent the accumulation of as many as four bulky groups (2MeO and $2CO_2H$) in 1 : 5- and 1 : 6-positions, there is no obstacle in the way of their occupying 1 : 7-positions, and hence this reaction is not encountered in the glutaric and adipic acid series, and is met with for the first time in the pimelic acid series. It may be predicted that the occurrence of this reaction, under the conditions specified, will be found to be a peculiarity of the higher series, and that it will be prominent in the suberic and azelaic acid series.

## EXPERIMENTAL.

Pimelic acid was prepared by hydrolysis of the ethyl pentane-tetracarboxylate produced from ethyl sodiomalonate and $\alpha\gamma$-dibromopropane. It was dibrominated in the form of its chloride, and the dibromo-chloride converted into ethyl dibromopimelate, which was treated with 6*N*-methyl-alcoholic potassium hydroxide, as in the previous investigations of this series. The acid product, a pale yellow syrup, was dissolved in water, neutralised with ammonia, and a concentrated aqueous solution of lead acetate was added in four or five successive portions until no further precipitation occurred, the solutions being kept cold throughout. The various fractions of lead salt were collected separately and decomposed with a small excess of dilute sulphuric acid, the filtrates from the lead sulphate being concentrated in a vacuum and extracted with ether. The acid regenerated in this way from the first fraction of lead salt solidified almost completely, and some of the intermediate fractions, on being seeded with the solid and kept for some weeks, deposited crystals. These fractions were then again submitted to the fractional precipitation of lead salts, and some further crops of crystalline acid were thus obtained.

*Piperylenedicarboxylic Acid* (XIX).—The solid acid, after two crystallisations from ether, melted at 169° (Found : C, 53·7; H, 5·3. $C_7H_8O_4$ requires C, 53·8; H, 5·1%), and corresponded closely in its properties with the acid obtained by Willstätter by exhaustive methylation of tropinic acid. The yield of purified material was 6·2% of the theoretical. The tetrabromide melted with decomposition at 217° (Found : Br, 67·0. Calc. : Br, 67·2%).

On oxidation with eight atoms of available oxygen in the form of 4% permanganate at the ordinary temperature, a small amount of malonic acid and much oxalic acid were obtained. On reduction by a large excess of sodium amalgam in boiling aqueous solution, a semi-solid product was obtained from which pimelic acid was isolated by draining and crystallisation from ether.

*cyclo Pentanol*-1 : 2-*dicarboxylic Acid* (XV).—The syrupy acids recovered from the lead salts, together with those obtained from the aqueous filtrates by extraction with ether after acidification, and desiccation over potassium hydroxide to remove acetic acid, were dissolved in ether and extracted with successive small quantities of water. The first extract, on evaporation in a vacuum, gave a residue which in course of time partly solidified. The remaining extracts gave syrups. The solid was drained (5·5% unpurified) and crystallised from acetone–benzene, from which it separated in small prisms, m. p. 159—160° (Found : C, 48·6; H, 5·8. $C_7H_{10}O_5$ requires C, 48·2; H, 5·7%).

The *silver* salt was prepared from the neutral ammonium salt (Found: Ag, 55·5. $C_7H_8O_5Ag_2$ requires Ag, 55·7%).

The *ethyl* ester was prepared by boiling the silver salt with ethyl iodide in ether solution; b. p. 168—171°/10—11 mm. (Found: C, 57·1; H, 7·8. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·8%). On heating with acetic anhydride in a sealed tube at 180°, an oil was obtained which, on hydrolysis by hydrochloric acid, gave *cyclo*pentene-1 : 2-dicarboxylic acid, m. p. 178°.

$\Delta^1$-cyclo*Pentene*-1 : 2-*dicarboxylic Acid* (IX).—The syrupy residues from the ethereal and the various aqueous solutions obtained in the preceding separation were combined and esterified with ethyl alcohol and sulphuric acid. The esters, after several distillations, yielded a fraction, b. p. 146°/11 mm., which was hydrolysed by boiling with hydrochloric acid under a condenser sufficiently short to permit the escape of alcohol vapour. On evaporation of the aqueous solution, a solid product was obtained, which melted indefinitely at 140—150°, and after several crystallisations from water yielded a small quantity of the $\Delta^1$-*cyclo*pentene acid, which was identified by analysis (Found: C, 53·9; H, 5·1. Calc.: C, 53·8; H, 5·1%) and by a mixed melting point determination.

$\Delta^2$-cyclo*Pentene*-1 : 2-*dicarboxylic Acid* (XIV).—This acid appears to be the main constituent of the mixture, m. p. 140—150° (19% of the theoretical yield), but the separation of the last traces of the 178°-acid necessitates several alternate crystallisations from water and ethyl acetate. This acid is very much more soluble in water than the $\Delta^1$-isomeride; it separates from water or ethyl acetate in small prisms, m. p. 146—147° (Found: C, 53·5; H, 5·1. $C_7H_8O_4$ requires C, 53·8; H, 5·1%).

2 : 3-*Dibromo*cyclo*pentane*-1 : 2-*dicarboxylic acid* was obtained when the $\Delta^2$-acid was exposed to bromine vapour for several days. The product, after being freed from bromine, was crystallised twice from glacial formic acid, from which it separated in small, dense prisms, which decompose with much frothing at 165° (Found: Br, 50·4. $C_7H_8O_4Br_2$ requires Br, 50·6%).

On heating for a few minutes with boiling 64% aqueous potassium hydroxide, both the $\Delta^1$- and $\Delta^2$-*cyclo*pentene acids yield a mixture consisting mainly of the $\Delta^2$-acid, along with a small amount of the $\Delta^1$-acid. In one experiment, starting with the $\Delta^1$-acid, a small amount of the hydroxy-ring acid was also isolated. The method of separation of these mixtures was substantially the same as that already described.

*Ethyl* $\alpha\alpha'$-*Dimethoxypimelate*.—In the distillation of esters (above) a large fraction (35% of the theoretical yield) was obtained, b. p. 160—175°/10 mm. This consisted essentially of a mixture of the

meso- and racemic forms of the dimethoxy-ester, and the central fraction, b. p. 166—169°/10 mm., gave correct figures on analysis (Found : C, 56·8; H, 8·7. $C_{13}H_{24}O_6$ requires C, 56·5; H, 8·7%).

Both the central fraction and the main fraction (the former, b. p. 166—169°/10 mm., and the latter, b. p. 160—175°/10 mm.), on hydrolysis by means of hydrochloric acid, gave a syrupy acid which could not be induced to crystallise, although it yielded a silver salt having the correct silver content for the dimethoxy-compound (Found : Ag, 50·2. $C_9H_{14}O_6Ag_2$ requires Ag, 49·8%). It was therefore digested with a small excess of pure thionyl chloride until sulphur dioxide ceased to be evolved, and after the excess of reagent had been removed at 100°, the acid chloride was treated with dry ammonia in ether solution. This process yielded a mixture of two crystalline amides.

The esters, b. p. 160—175°/10 mm., were mixed with concentrated aqueous ammonia (3 vols.), and the mixture was shaken frequently until it became homogeneous (3—6 days).

*αα'-Dimethoxypimelamide* (A-form).—This amide crystallised practically completely from the aqueous ammonia solution. It melted at 209—210°, and after one crystallisation from water was obtained pure, as prisms, m. p. 212°. The mixture of amides obtained from the ethereal ammonia solution yielded the A-amide in a pure condition after two crystallisations from water (Found : C, 49·2; H, 8·3. $C_9H_{18}O_4N_2$ requires C, 49·5; H, 8·3%). The amide is readily soluble in hot water, sparingly soluble in cold, fairly easily soluble in methyl or ethyl alcohol or acetone, and almost insoluble in ethyl acetate, chloroform, or benzene.

*αα'-Dimethoxypimelamide* (B-form).—The ammonia solution from the esters, after the A-amide had been collected, was evaporated on the water-bath until, on cooling, it set to a stiff paste of crystals, which were drained on porous porcelain and crystallised from water and ethyl acetate ; the compound separated in fluffy balls of minute needles, m. p. 167°. The aqueous solution from the decomposition of the acid chlorides, after the A-amide had been removed, was evaporated to dryness, and the residue extracted from the ammonium chloride with boiling ethyl acetate, from which, on concentration and cooling, the B-amide separated almost pure. It was crystallised from ethyl acetate (Found : C, 49·3; H, 8·2%). This amide is extremely soluble in hot water and very easily soluble in cold; it is fairly easily soluble in hot ethyl acetate, but almost insoluble in cold; it is easily soluble in acetone or methyl or ethyl alcohol, but insoluble in chloroform or benzene.

*αα'-Dimethoxypimelic Acid* (A-form).—A solution of the A-amide (1 g.) in 10 c.c. of concentrated sulphuric acid was treated between

0° and 5° with a strong aqueous solution of 0·6 g. of sodium nitrite delivered by a fine capillary tube dipping beneath the liquid, the addition occupying about 1·5 hours, during which the mixture was continually stirred. The solution was poured into water and extracted with ether, from which the A-acid was obtained as a clear gum (Found: C, 49·0; H, 7·3. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3%. Found for the *silver* salt: Ag, 49·6. $C_9H_{14}O_6Ag_2$ requires Ag, 49·8%).

*αα'-Dimethoxypimelic Acid* (B-form).—This acid was prepared similarly from the B-amide and had similar properties (Found: C, 49·1; H, 7·4%. Found for the *silver* salt: Ag, 49·5%).

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