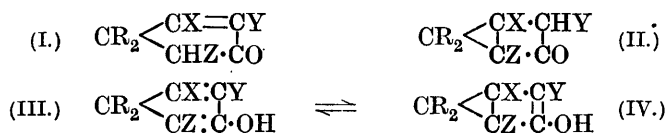


CLXXXIII.—*The Chemistry of Polycyclic Structures in Relation to their Homocyclic Unsaturated Isomerides. Part III. Intra-annular Tautomerism of α -Campholytic Acid.*

By JUAN PEDIGE CHARLES CHANDRASENA, CHRISTOPHER KELK INGOLD, and JOCELYN FIELD THORPE.

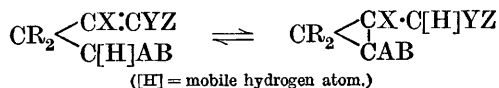
THE examples of intra-annular tautomerism previously discussed (T., 1920, **117**, 1362; this vol., p. 128) are characterised most especially by the extraordinary facility with which the two individuals composing the tautomeric system must be assumed to undergo interconversion. In no case, indeed, has it yet been found possible to isolate more than one crystalline variety of any of these substances, which in solution exhibit reactions characteristic of both the structures (I) and (II) :



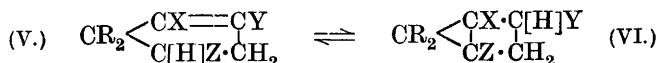
We may assume that the reason for this is the intimate connexion between the corresponding enolic forms (III and IV), which are valency-isomerides related to one another much like the two Kekulé individuals of a substituted benzene, and even more exactly like the bridged and double-bonded phases of the benzene nucleus by the aid of which the totality of aromatic transformations may, with large gain in uniformity, be interpreted (this vol., pp. 1133, 1143).

On general grounds, it may reasonably be said that the principal factor affecting the mobility of a tautomeric system is the simplicity of the mechanism of the isomeric change involved: valency-isomerides are more easily interconvertible than isomerides which

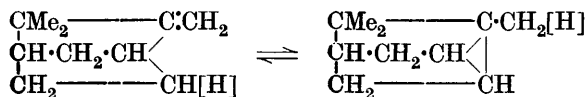
differ by the position of a hydrogen atom; the straight-chain, three-carbon system in the glutaconic esters is more mobile than the *cyclobutane* ring-chain three-carbon system (future communication), and so forth. If, therefore, means could be found of stopping the enolisation of the types (I) and (II), we should expect to observe a large decrease of mobility; for interchange between the bridged and double-bonded forms could now no longer occur by rearrangement of valencies alone, and the only available mechanism would be a *cyclopropane* ring-chain conversion



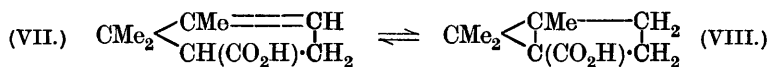
analogous to the *cyclobutane* changes referred to above. This change involves the migration of a hydrogen atom, and therefore we are led to anticipate that if the ketone groups in the types (I) and (II) were replaced by methylene groups the change



would occur only in the presence of acids or alkalis or at a high temperature. Such changes, occurring in the presence of reagents, are doubtless at the root of much that is difficult to understand in camphor chemistry; and, indeed, Meerwein and van Emster have already been forced to postulate an equilibrium between camphene and tricyclene in order to explain their observations on these compounds (*Ber.*, 1920, **53**, [B], 1828):



There are several well-known camphor derivatives belonging to type (V), one of the most familiar examples being α -campholytic acid, the usual formula for which is (VII). Obviously, however, the bridged formula (VIII) has to be taken into account, for, in view of what is known with regard to such reactions, there seems to be no a priori reason why either or both of the converse changes



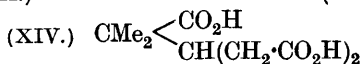
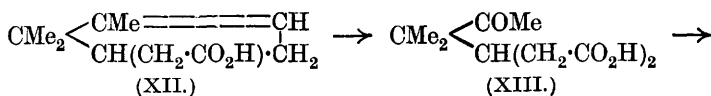
should not take place in the presence of suitable reagents.

The evidence usually quoted in favour of the accepted formula (VII) is far from satisfactory. The staple argument seems to be that Perkin and Thorpe obtained α -campholytic acid by the action of alkalis on the bromocyclopentane acid (IX) (*T.*, 1904, **85**, 147).

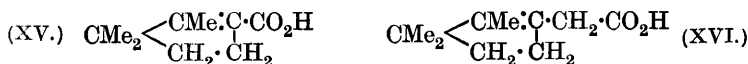
We know, however, that the production of a *cyclopropane* ring is the normal course of such a reaction. γ -Bromo- $\beta\beta$ -dimethylbutyric acid (X) gives dimethyl*cyclopropanecarboxylic acid* (XI) (Blanc, *Bull. Soc. chim.*, 1905, [iii], **33**, 902), α -bromo- $\beta\beta$ -dimethylglutaric acid gives caronic acid, and even α -bromoglutaric acid, which might perhaps be expected to yield glutaconic acid, gives chiefly *cyclopropanedicarboxylic acid* on treatment with alkalis; so great is the tendency for the hydrogen atom adjacent to a carboxyl group to suffer elimination as hydrogen bromide in these cases. Perkin and Thorpe's synthesis of α -campholytic acid from the γ -bromo-acid (IX) is therefore to be regarded as one of the strongest pieces of evidence against the formula which it is usually held to support; obviously, the elimination of hydrogen bromide from the acid (IX) should give rise to an acid of the bridged constitution (VIII), which, on other grounds, appears as a reasonable mode of formulation for α -campholytic acid :



There remain, however, reasons for retaining formula (VII), the chief consisting in the analogy with α -campholenic acid. No one, hitherto, appears to have succeeded in obtaining any definite oxidation products from α -campholytic acid, but the constitution of α -campholenic acid (XII) seems to be well established by its oxidation to *ketoisocamphoric acid* (XIII) and *isocamphoronic acid* (XIV) (Tiemann, *Ber.*, 1896, **29**, 3014), the structure of which has been proved by synthesis (Perkin, T., 1899, **75**, 897) :



Both α -campholytic acid and α -campholenic acid undergo isomeric change on heating with mineral acids giving *isolaunonic acid* (XV) and β -campholenic acid (XVI) respectively :

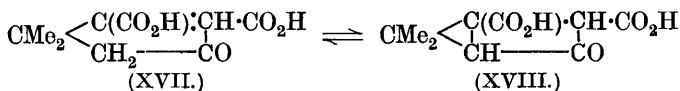


The constitutions of both these acids have been established by oxidation (Königs and Meyer, *Ber.*, 1894, **27**, 3466; Perkin, T., 1898, **73**, 802; Blanc, *Compt. rend.*, 1900, **130**, 840; Bouveault,

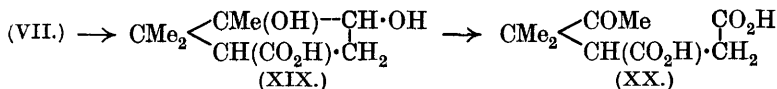
Bull. Soc. chim., 1896, [iii], **19**, 565), and there can be no reasonable doubt as to the similarity of mechanism of the changes by which they are produced. These considerations strongly suggest the retention of formula (VII) for α -campholytic acid owing to the analogy with the formula (XII) of α -campholenic acid.

Considered collectively, then, the existing evidence relating to the structure of α -campholytic acid is of a somewhat ambiguous character, and therefore it appeared desirable to apply to this acid the methods which were used in studying the cases of intra-annular tautomerism met with in the earlier investigations belonging to this series (*loc. cit.*). We have accordingly made a careful examination of the oxidation products obtained from α -campholytic acid under a variety of experimental conditions.

It will be recalled that the acid (XVII), for instance, is oxidised by alkaline permanganate very smoothly in accordance with the double-bonded formula assigned to it, whilst evidence of the bridged form (XVIII) can be obtained by the use of cold ferricyanide, which oxidises it to caronic acid :



On oxidising α -campholytic acid by alkaline permanganate, clear evidence was obtained of the unsaturated structure, the principal products being the dihydroxydihydro-acid (XIX) and δ -keto- β -carboxy- $\gamma\gamma$ -dimethylhexoic acid (XX) :

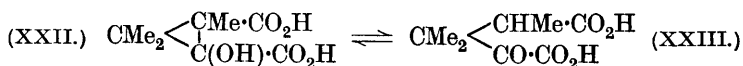


Similar results were obtained using alkaline chlorate in the presence of osmium tetroxide at 60° , but in this instance further evidence as to the mechanism of the oxidation was furnished by the isolation of $\alpha\alpha$ -dimethyltricarballic acid, $\text{CO}_2\text{H} \cdot \text{CMe}_2 \cdot \text{CH}(\text{CO}_2\text{H}) \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$ (XXI), which has been well characterised by other workers.

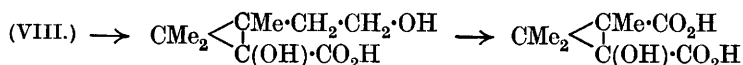
When, however, α -campholytic acid was oxidised over a period of several weeks with cold acidified chlorate and osmium tetroxide, the product contained, not only all the above acids, but also two others the formation of which plainly points to the existence in acid solution of the bridged individual (VIII).

One of these was the acid $\text{C}_8\text{H}_{12}\text{O}_5$, usually called Balbiano's acid, the constitution of which has been very recently established by Kon, Stevenson, and Thorpe (this vol., p. 654), who have proved that this substance is a hydroxycyclopropane acid of the formula

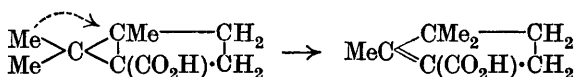
(XXII) in tautomeric relation with its open-chain isomeride (XXIII) and the lactonic modification of the latter :



It will at once be evident that neither of the individuals (XXII) or (XXIII) is capable of being represented as a direct oxidation product of the double-bonded form (VII) of α -campholytic acid. On the other hand, the hydroxy-ring acid (XXII) is the normal oxidation product of the bridged individual (VIII) :

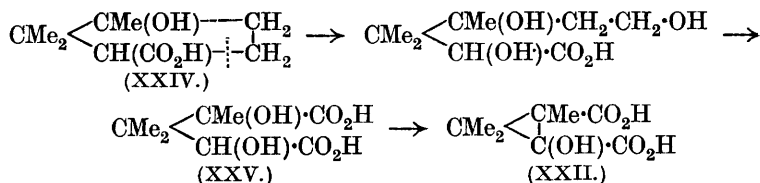


It appears significant, in view of the well-known influence of acids in accelerating the change from α -campholytic acid into *isola*uronic acid, that Balbiano's acid was not produced, and, in fact, no evidence of the bridged individual of α -campholytic acid was obtained, by oxidation in alkaline solution. The change from α -campholytic acid into *isola*uronic acid is a most remarkable one if considered from the point of view of the double-bonded formula for α -campholytic acid; it is, however, much more easily represented by the aid of the bridged formula (VIII), and in the earlier stages of these experiments we held the view that campholytic acid passes by way of its bridged form into *isola*uronic acid in the presence of acidic reagents :



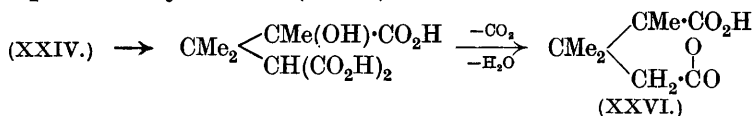
Towards the end of 1920, however, Meerwein and van Emster's paper appeared : these workers conclusively proved that tricyclene was not (as was then generally supposed) an intermediate product in the *isoborneol*-camphene transformation. About the same time, Professor Robinson told us of his explanation (since published, *Mem. Manchester Phil. Soc.*, 1920, 64, ii, 4) of the conversion of α -campholytic acid into *isola*uronic acid. Now, although we do not find in the results of our own experiments any clear evidence for or against Robinson's explanation of the mechanism, there can be no doubt that, from the point of view chosen, it is the most detailed and strictly logical explanation that has yet been proposed, and therefore it is necessary to examine its bearing on the interpretation of the experiments here described. We need only consider Robinson's first stage, which consists in the addition of the elements of water to the double-bonded formula for campholytic acid. It will be evident that the hydroxy-acid (XXIV) formed in

this way is capable of undergoing oxidation (similarly to the bridged form of campholytic acid), giving a dihydroxy-acid (XXV) which would at once pass into the hydroxy-ring form of Balbiano's acid (compare Kon, Stevenson, and Thorpe, *loc. cit.*, p. 657) :

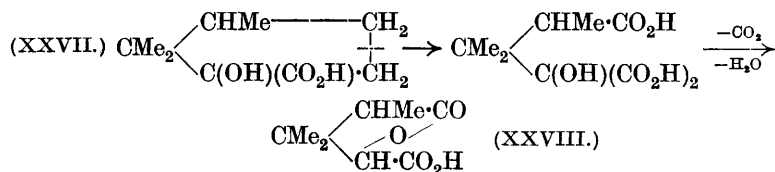


Evidently then, there are two alternative ways in which Balbiano's acid can be formed by oxidation, and therefore it became necessary to decide between them. This has been accomplished, and the results clearly show that, whatever may be the truth regarding the change which results in the formation of *isolaunonic* acid, the oxidation of α -campholytic acid cannot be accounted for by any mechanism depending on the preliminary addition of water to the double-bonded individual as suggested by Robinson.

The hydroxy-acid (XXIV) is evidently capable of oxidation to a lactonic acid of the composition $\text{C}_8\text{H}_{12}\text{O}_4$, its structure being represented by formula (XXVI) :



This lactonic acid is therefore to be regarded as capable of being derived from the double-bonded form of campholytic acid by addition of water and then oxidation. On the other hand, the bridged individual could, by a corresponding series of transformations, yield two such lactonic acids, corresponding with the two ways in which hydrolytic fission can occur at the bridge. According to one mode of fission, the primary product would be the hydroxy-acid (XXIV), and the ultimate oxidation product the lactonic acid (XXVI). According to the other mode, the primary product would be the isomeric hydroxy-acid (XXVII), and the ultimate product the lactonic acid (XXVIII) :



The lactonic acid (XXVI) may be formed, therefore, from either

modification of campholytic acid, but the lactonic acid (XXVIII) can only be obtained from the bridged individual. The lactonic acids (XXVI and XXVIII) are known and have very similar properties. However, the lactonic acid obtained along with Balbiano's acid by the oxidation of α -campholytic acid by cold chlorate and osmium tetroxide in acid solution was conclusively proved to have the structure (XXVIII) by direct comparison with a synthetic specimen. The production of this lactonic acid along with Balbiano's acid appears to leave no room for doubt as to the existence in acid solution of the bridged individual of campholytic acid.

EXPERIMENTAL.

The α -campholytic acid required for these experiments was prepared from sodium ethyl camphorate by the electrolytic method described by Walker (T., 1893, **63**, 475; 1895, **67**, 347; 1900, **77**, 383). This process was found to be much more convenient than the method of Noyes (*Amer. Chem. J.*, 1894, **16**, 310; 1895, **17**, 424; 1900, **24**, 290), depending on the action of bromine and alkali on camphoramic acid.

(A.) *Oxidation of α -Campholytic Acid by Cold Alkaline Permanganate; Formation of $\gamma\delta$ -Dihydroxydihydrocampholytic Acid and δ -Keto- β -carboxy- $\gamma\gamma$ -dimethylhexoic Acid.*

The α -campholytic acid (7 grams), dissolved in 25 c.c. of 2N-aqueous sodium carbonate, was treated with 3.16 per cent. aqueous potassium permanganate until no further decoloration took place in the cold. The quantity of permanganate decolorised corresponded with the absorption of three atoms of oxygen. The suspension was boiled and filtered, and the oxides of manganese thoroughly exhausted by suspending in water and passing a current of steam. The combined aqueous filtrates were acidified with hydrochloric acid, evaporated to a small bulk, and extracted with ether. The mixture of acids obtained in this way slowly set to a paste of crystals, which were drained as thoroughly as possible on porous porcelain, and then triturated with ether.

$\gamma\delta$ -Dihydroxydihydro- α -campholytic Acid.—The constituent insoluble in cold dry ether was crystallised, first from a large quantity of boiling ether, and then from ethyl acetate, and separated in large, lustrous prisms, m. p. 159–160°. It was identified by analysis and by direct comparison with the dihydroxy-acid obtained by the oxidation of α -campholytic acid with sodium chlorate and osmium tetroxide (Found: C = 57.6; H = 8.5. $C_9H_{16}O_4$ requires C = 57.4; H = 8.5 per cent.).

The *diacetyl* derivative was prepared by boiling the acid with an

excess of acetyl chloride for half an hour, after which the evolution of hydrogen chloride had ceased. The solution was evaporated over solid potassium hydroxide in an evacuated desiccator, and the crystalline residue purified by crystallisation from a mixture of light petroleum and ether. It separated in small needles, m. p. 122° , which were very soluble in all the usual solvents excepting water and light petroleum (Found: C = 57.7; H = 7.6. $C_{13}H_{20}O_6$ requires C = 57.3; H = 7.3 per cent.).

δ -Keto- β -carboxy- $\gamma\gamma$ -dimethylhexoic Acid.—The acid which dissolved in the cold dry ether (above) slowly solidified when the solvent had evaporated. It was crystallised first from ether and then from ethyl acetate, and was obtained in needles, m. p. 119 — 121° . It was identified with the substance (p. 1551) obtained by oxidation with sodium chlorate and osmic acid (Found: C = 54.2; H = 7.3. $C_9H_{14}O_5$ requires C = 53.5; H = 6.9 per cent.). Sufficient material was not available for an extended examination, but the substance certainly appeared to yield condensation products with the usual reagents for ketones.

(B.) *Oxidation of α -Campholytic Acid by Means of Sodium Chlorate and Osmium Tetroxide in Alkaline Solution at 60° ; Formation of $\gamma\delta$ -Dihydroxydihydrocampholytic Acid and $\alpha\alpha$ -Dimethyltricarballic Acid.*

A solution of α -campholytic acid (5 grams) in a small excess of 2*N*-aqueous sodium hydroxide was mixed with an aqueous solution (250 c.c.) of sodium chlorate (20 grams) and osmium tetroxide (0.3 gram). The mixture was kept in a thermostat at 60° for thirty-six hours, then acidified by means of hydrochloric acid, evaporated to a small bulk, and extracted with ether. The residue which was left when the ether had evaporated rapidly solidified. On triturating with cold dry ether, an insoluble residue remained, which, after several crystallisations from ethyl acetate, yielded the dihydroxy-acid (p. 1548) in a state of purity. The other main constituent of the product insoluble in ether was an acid, m. p. 170° , which contained chlorine and was not further investigated.

$\alpha\alpha$ -Dimethyltricarballic Acid.—The portion of the oxidation product soluble in cold dry ether was recovered as a gum, which refused to solidify. It was therefore dissolved in barium hydroxide solution, and the sparingly soluble barium salts were collected and decomposed by means of hydrochloric acid. The regenerated acids, which were isolated by extraction with ether, were obtained in a crystalline condition by rubbing with cold chloroform, and then crystallised twice from water. The product obtained in this way formed minute prisms, m. p. 156 — 157° , and was identified

as dimethyltricarballic acid by analysis (Found: C = 47.0; H = 6.1. Calc., C = 47.1; H = 5.9 per cent.), and by a careful comparison of its properties with the descriptions given by Barthe (*Compt. rend.*, 1897, **125**, 183) and by Haller and Blanc (*ibid.*, 1900, **131**, 21).

(C.) *Oxidation of α -Campholytic Acid by Means of Chloric Acid and Osmic Acid in Acid Solution at 20°; Formation of $\gamma\delta$ -Dihydroxy-dihydrocampholenic Acid, δ -Keto- β -carboxy- $\gamma\gamma$ -dimethylhexoic Acid, the Lactone of γ -Hydroxy- $\alpha\beta\beta$ -trimethylglutaric Acid, γ -Keto- $\alpha\beta\beta$ -trimethylglutaric Acid, and $\alpha\alpha$ -Dimethyltricarballic Acid.*

α -Campholytic acid (30 grams) was mixed with a solution of sodium chlorate (95 grams), glacial acetic acid (20 grams), and osmium tetroxide (1 gram) in 1500 c.c. of water. The mixture was kept at the ordinary temperature for several weeks, then filtered from a small amorphous deposit, and evaporated to dryness. The residue was evaporated twice with water in order to remove acetic acid, and then dissolved in water and extracted with ether. The residue from the ether was left until it had solidified, and was then boiled with dry ether in order to separate the main bulk of the sparingly soluble dihydroxy-acid. The residue from the ether was seeded with a trace of the original mixture and allowed to resolidify (this took several days), and then triturated with cold benzene until the more soluble portion appeared to have been completely removed.

Lactone of γ -Hydroxy- $\alpha\beta\beta$ -trimethylglutaric Acid.—The acids which were sparingly soluble in benzene were subjected to repeated fractional crystallisation from benzene and ethyl acetate employed alternately. In this way three products were obtained: (i) the dihydroxy-acid mentioned above, m. p. 159–160°; (ii) an acid which separated from benzene in long needles, m. p. 165–166°; (iii) an acid product, m. p. 148–150°. The last crystallised as a single substance and was free from chlorine, but its carbon and hydrogen content did not correspond with any definite formula, so that it was ultimately supposed to be a mixture and its investigation was abandoned. The substance, m. p. 165–166°, gave figures corresponding with the formula $C_8H_{12}O_4$, and on titration (by dissolving in excess of alkali and titrating the excess) behaved as a dibasic acid. It was at first supposed that this substance was α -methylcaronic acid (trimethylcyclopropanedicarboxylic acid), but on further investigation it was discovered that, when titrated by the direct method, the substance behaved as a monobasic acid, and, in fact, had all the properties of a lactone. Ultimately it was

identified with the lactonic acid which Balbiano prepared first by reduction of his oxidation product $C_8H_{12}O_5$ of camphoric acid (*Ber.*, 1894, **27**, 2136) and later by elimination of hydrogen bromide from γ -bromo- $\alpha\beta\beta$ -trimethylglutaric acid (*Atti R. Accad. Lincei*, 1899, [v], **8**, I, 426), by direct comparison and the mixed-melting-point test with a specimen obtained by the second of Balbiano's methods [Found: C = 55.8; H = 7.0. Calc., C = 55.8; H = 7.0 per cent. Equivalent (direct titration) = 171. Calc. 172. Equivalent (back titration) = 86.7. Calc. 86].

γ -Keto- $\alpha\beta\beta$ -trimethylglutaric Acid.—The acids which dissolved in cold benzene showed but little tendency to crystallise, and therefore were dissolved in a small excess of barium hydroxide and the insoluble barium salts collected. The main constituent of the acids regenerated from these insoluble salts was $\alpha\alpha$ -dimethyltricarballic acid (above). The soluble barium salts were decomposed with hydrochloric acid and the organic acids extracted with ether, and, after evaporating the ether, mixed with chloroform, which caused the separation in the crystalline state of a small amount of the ketonic acid described on p. 1549. The gummy acids were dissolved in an exact equivalent of ammonia, treated with calcium chloride, and the solution evaporated to a small bulk. The salt which separated was collected after cooling, washed with cold water, and decomposed with hydrochloric acid. The regenerated acid solidified fairly readily, but as it did not appear to crystallise well from solvents, was prepared for analysis by washing with chloroform. It was identified by its melting point, 119–120°, by analysis (Found: C = 51.3; H = 6.6. Calc., C = 51.1; H = 6.4 per cent.), by its conversion on heating with sulphuric acid into trimethylsuccinic anhydride, by the melting point of its condensation product with *o*-phenylenediamine, and, finally, by direct comparison and a mixed-melting-point determination with the substance described by Kon, Stevenson, and Thorpe (this vol., p. 663).

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