XXXVI.—*Campholytic and Isolauronolic Acids.*

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In former papers (Walker, Trans., 1893, **63**, 495; 1895, **67**, 347), it was shown that when sodium ortho-ethyl camphorate was electrolysed in aqueous solution, an unsaturated ethereal product was obtained at the anode in accordance with the following empirical equation:

$$CO_2Et\cdot C_8H_{14}\cdot CO_2Na + H_2O = C_8H_{13}\cdot CO_2Et + H_2 + NaHCO_3.$$

This ethereal product, when fractionated and hydrolysed, yielded two isomeric unsaturated acids of the formula $C_8H_{13}\cdot CO_2H$, one of which, campholytic acid, was a liquid, and the other, isolauronolic acid, a solid. These acids were also obtained by W. A. Noyes from β-camphoramic acid (*Amer. Chem. J.*, 1894, **16**, 505; 1895, **17**, 421), and isolauronolic acid in particular has recently been the subject of numerous investigations, chiefly by Blanc and by W. H. Perkin, jun.

By the action of alkalis on the dibromide of campholytic acid, a bromohydrocarbon is produced (Trans., 1893, **63**, 502), a decomposition which Fittig's researches have shown to be characteristic of $\alpha\beta$-dibromo-acids. Noyes found that the dibromide of isolauronolic acid undergoes a similar decomposition when neutralised with sodium carbonate, and was therefore led to regard the two unsaturated acids as stereoisomeric, a view which is strengthened by his discovery that campholytic acid is converted on standing with mineral acids into the isomeric isolauronolic acid. It is now generally admitted that isolauronolic acid is an unsaturated acid with the double bond in the $\alpha\beta$-position with regard to the carboxyl group (Blanc, *Ann. Phys. Chem.*, 1899, [vii], **18**, 181; Perkin, Trans., 1898, **73**, 810).

In view of the fact that the relationship of campholytic and isolauronolic acids to camphoric acid is of the greatest importance in

determining the relative position of the carboxyl groups in the molecule of the latter substance, we adduce in the present paper some further data bearing on this point.

Electrolysis of Sodium Ortho-methyl Camphorate.

Since hydrobromic acid was used by Walker in the production of isolauronolic acid from the ester $C_8H_{13}\cdot CO_2Et$, it does not follow that ethyl isolauronolate is a direct product of the electrolysis of sodium ortho-ethyl camphorate, for the isolauronolic acid, according to Noyes's researches, might conceivably have been produced by the isomeric transformation of campholytic acid. In order to decide this point, we repeated the electrolysis of the alkali salt of a hydrogen ortho-alkyl camphorate.

The sodium ortho-ethyl salt used in former experiments was the crude product obtained by the direct addition of sodium ethoxide to camphoric anhydride in presence of ethyl alcohol. This substance was liable to contain a little of the allo-ethyl salt, for experience with the corresponding methyl compounds had indicated that a perfectly pure ortho-alkyl salt is not produced by the direct addition of camphoric anhydride to sodium alkyloxide. To avoid any such source of uncertainty, we therefore in this case prepared pure hydrogen ortho-methyl camphorate, neutralised it with potassium carbonate, and electrolysed the potassium salt thus obtained.

Crude sodium ortho-methyl camphorate was obtained by the direct union of sodium methoxide and camphoric anhydride in presence of methyl alcohol according to the directions given by Walker (Trans., 1892, **61**, 1089). The corresponding hydrogen salt was liberated by hydrochloric acid, and dissolved out in ether. The residue from the ethereal solution crystallised on standing, and the crystals were freed from a slight syrupy admixture by spreading on a porous tile. The melting point of these crystals was 73°, that of the pure substance being 77°. Purification of large quantities of the substance by recrystallisation from most organic solvents is somewhat tedious (compare Wegscheider, *Monatsh.*, 1899, **20**, 685), but we find that a single recrystallisation from 25 per cent. acetic acid yields practically pure hydrogen ortho-methyl camphorate. Thus 13 grams of the crude crystals, on warming with 100 c.c. of 25 per cent. acetic acid, gave a solution which deposited 12·5 grams of crystals having the melting point 77°.

The acid thus purified was dissolved along with the calculated quantity of potassium carbonate in about its own weight of water. Contrary to the behaviour of the sodium ethyl salt on electrolysis, the potassium methyl salt was found to yield an ethereal product only

with great difficulty. The chief reaction on the passage of an electric current is here the production of hydrogen at the cathode and oxygen at the anode with regeneration of the original salt. There is thus little loss of substance, but the quantity of electricity which must be passed in order to produce a given quantity of ethereal product is out of all proportion greater than the theoretical amount. We tried numerous variations of concentration, current strength, voltage, temperature, and size of electrodes, but always with the same result—the yield of ethereal product was constant, but extremely small for the magnitude of the current. It seemed to us possible that the difference might be due to the salt electrolysed in the present instance being quite pure, whilst the sodium ethyl salt previously employed had been impure. We therefore prepared a solution of crude sodium ortho-methyl camphorate by direct union of sodium methoxide with camphoric anhydride and submitted it to electrolysis, but no difference in the result was thereby obtained. It thus appears that the replacement of ethyl by methyl in this particular instance greatly increases the difficulty of obtaining an ethereal substance, the chief electrolytic action being the decomposition of water with production of oxygen and hydrogen. A current of 10 ampères for 45 hours produced only 85 grams of ethereal salts instead of the approximate theoretical amount of 2,800 grams. The yield of ethereal product, however, when referred to the amount of potassium ortho-methyl salt electrolysed, amounted to nearly 50 per cent. of the theoretical quantity.

The ethereal product of electrolysis was subjected to fractional distillation, and in accordance with previous experience in similar cases, separated roughly into a fraction of high and one of low boiling point, ebullition beginning at about 190°. As methyl isolauronolate boils at 204° under a pressure of 760 mm., the portion of lower boiling point was investigated for this substance. 10 grams of the oil mixed with 10 c.c. of methyl alcohol, 5 c.c. of water, and 10 grams of caustic potash, were heated on the water-bath for 1 hour. The bulk of the methyl alcohol was driven off by evaporation in an open vessel, and water was then added. The solution was next extracted with ether in order to remove any ethereal salt which had escaped hydrolysis, and acidified with hydrochloric acid. A dark green oil separated, which was at once taken up by ether, in order to remove it from contact with the mineral acid, the last traces of which were removed from the ethereal solution by washing with water. The crude acid obtained after evaporation of the ether was distilled with steam. A small quantity of an oil (campholytic acid) first passed over, and then a white solid crystallised in the condenser. The solid, after one crystallisation from light petroleum, was found to melt at 135°, and proved to be isolauronolic acid.

Since none of the above operations would suffice to convert campholytic into isolauronolic acid, it must be accepted that methyl isolauronolate is, along with methyl campholytate, a direct product of the electrolysis of potassium ortho-methyl camphorate.

Optical Inactivity of Campholytic and Isolauronolic Acids.

The optical character of isolauronolic acid being of importance in determining its constitution, we examined in the polarimeter a saturated solution of the acid prepared by electrolysis, using methyl alcohol as solvent. No rotation could be detected with certainty, and a similar result followed the examination of a saturated aqueous solution of the sodium salt. The isolauronolic acid prepared by electrolysis must therefore be accounted optically inactive.

The original campholytic acid derived from sodium ortho-ethyl camphorate by electrolytic decomposition was stated to have a specific rotation of $[\alpha]_D$ $-5°$. This rotatory power is comparatively slight for a derivative of camphor, and it therefore appeared of interest to ascertain if it were real, or merely due to the admixture of a strongly active impurity with an inactive substance. A certain degree of probability is lent to this view by the circumstance that the crude isolauronolic acid obtained by electrolysis is slightly active, and loses its rotation only on repeated crystallisation.

Since campholytic acid is a liquid, the only method employed for its purification was fractional distillation, a process which is in general useless for removing the last traces of impurity from a liquid of high boiling point, unless very large quantities of material are available. In order to attempt the purification by another method, we prepared a quantity of campholytic acid by electrolysis. An investigation of the salts of the acid showed that magnesium campholytate was susceptible of purification by recrystallisation from water. The crude campholytic acid from which the magnesium salt was prepared had the specific rotation $[\alpha]_D$ $-9{\cdot}6°$. The magnesium salt obtained from this acid had also a well marked negative rotation. It was sparingly soluble in cold water, the saturated solution being of about 4 per cent. strength. The crude crystals were treated with successive small portions of hot water, allowed to cool, and filtered, the rotation of the filtrate being determined in each case. In three successive operations, the rotation of the filtrates in a 20 cm. tube were $-5°$, $-2°$, and $-1{\cdot}2°$ respectively, showing that the active substance was being removed by the water. The residual crystals were then reconverted into the acid, which now showed a specific rotation $[\alpha]_D$ $-2{\cdot}7°$. Crystallisation had thus reduced the rotatory power to one-fourth of that of the crude acid, and to about one-half of the value for the campholytic acid originally

prepared. With a sufficiency of material to permit a thorough systematic recrystallisation of the magnesium salt, the activity would doubtless altogether disappear, that observed being apparently due to some very active impurity. This conclusion is justified by the fact that the campholytic acid which we succeeded in preparing from isolauronolic acid, is entirely destitute of optical activity.

A portion of the campholytic acid purified by recrystallisation of the magnesium salt was converted into isolauronolic acid by warming with 25 per cent. sulphuric acid. The isolauronolic acid was driven over by steam, dried, and recrystallised from light petroleum. A 12 per cent. solution of the acid thus obtained showed no rotation when examined in a 20 cm. tube by the aid of a polarimeter reading to 0·01°.

It thus appears that isolauronolic acid, whether prepared by Blanc's method from camphoric anhydride and aluminium chloride (Blanc, *loc. cit.*), by the electrolytic decomposition of ortho-alkyl camphorates, or by the isomeric transformation of campholytic acid, is optically inactive.

Transformation of Isolauronolic Acid into Campholytic Acid.

Whilst the conversion of campholytic acid into isolauronolic acid may be effected with great readiness by the action of mineral acids, the reverse transformation has not so far been brought about directly. We have found it possible, however, to pass in an indirect way from isolauronolic acid to campholytic acid.

Noyes (*Amer. Chem J.*, 1895, **17**, 427) ascertained that fuming hydrobromic acid acts on campholytic acid in presence of a little light petroleum to form a hydrobromide, $C_8H_{14}Br{\cdot}CO_2H$, from which campholytic acid could be recovered by the action of alkalis and subsequent acidification. This bromo-acid melted with decomposition at 98—100°, and on neutralisation yielded a small quantity of an indifferent compound, which we have proved to be a hydrocarbon. An $\alpha\beta$-acid like campholytic acid would naturally assume the bromine in the β-position on taking up hydrogen bromide, and Fittig has shown that β-bromo-acids yield hydrocarbons on neutralisation, so that the action affords a further proof that campholytic acid is an unsaturated acid with the double bond in the $\alpha\beta$-position.

Noyes also studied the action of hydrobromic acid on isolauronolic acid, and on one occasion obtained a hydrobromide containing the theoretical amount of bromine for the formula $C_8H_{14}Br{\cdot}CO_2H$, and melting at 127—130°. This hydrobromide he considered to be the true hydrobromide of isolauronolic acid. He was, however, unable to prepare the substance a second time, and although operating under a

great variety of conditions, always obtained a bromo-acid of lower melting point.

We have repeated these experiments, since it appeared to us possible that some light might be thrown on the relation of the two isomeric unsaturated acids by the behaviour of the corresponding hydrobromides. Campholytic acid (2 grams), on being shaken up with 5 c.c. of hydrobromic acid solution saturated at 0°, became crystalline after one hour, and the solid after recrystallisation from light petroleum was found to be identical with the hydrobromide of campholytic acid prepared by Noyes. The melting point varied, according to the mode of heating, from 88° to 102°, and was always accompanied by darkening and evolution of gas.

On treating isolauronolic acid under similar conditions, we found that the hydrogen bromide was much more slowly absorbed. After the acids had remained in contact for 7 days, the solid was found to contain the theoretical quantity of bromine, but the product, instead of being Noyes's acid melting at 127—130°, proved to be identical with the hydrobromide of campholytic acid. This result was repeatedly obtained, and finally we prepared a considerable quantity of the hydrobromide of campholytic acid by keeping isolauronolic acid in contact with hydrobromic acid solution, which was retained at the saturation point by the passage of a slow current of the gaseous acid. The addition of hydrogen bromide could be effected in this way in about 24 hours, the bromo-acid then containing the calculated quantity of bromine, and melting with decomposition at a little over 90°.

The quantity of bromine in the bromo-acid was at first estimated in sealed tubes by Carius's method. We found, however, that the determination could be effected much more simply by decomposing a weighed quantity of the acid with caustic soda, all the bromine in the acid being thereby converted into sodium bromide, the bromine in which was afterwards estimated by titration according to Volhard's method. Too high results are obtained if the acid is recrystallised from light petroleum alone, since free hydrogen bromide clings to the crystals with remarkable persistence. This source of error may, however, be easily avoided by washing the crystals with a small quantity of cold water prior to drying and recrystallisation.

In order to prove that the bromo-acid obtained from isolauronolic acid is the hydrobromide of campholytic acid, we treated a quantity of it with excess of caustic soda solution. A small quantity of an indifferent oil separated as the acid dissolved, and this we removed by distillation with steam, the substance being extremely volatile. The steam distillate was extracted with ether, the ethereal solution dried, and the ether distilled off The residual oil distilled completely

between 108° and 110° at the ordinary pressure, and gave the following figures on analysis:

0·0484 gave 0·1540 CO_2 and 0·0542 H_2O. C = 86·7; H = 12·4.
C_8H_{14} requires C = 87·3; H = 12·7 per cent.

From its composition and boiling point, the substance is thus *isolaurolene*, formed according to the equation:

$$C_8H_{14}Br{\cdot}CO_2Na = C_8H_{14} + CO_2 + NaBr.$$

The hydrocarbon showed no optical activity when examined in a delicate polarimeter.

The formation of this hydrocarbon leaves no doubt that the bromine is in the β-position, as one would indeed expect from the mode of formation of the bromo-acid.

The solution of the sodium salt, from which the hydrocarbon had been removed by distillation with steam, was carefully acidified with hydrochloric acid and the oil which separated at once, dissolved by shaking up with ether. After washing with water, drying, and distillation of the ether, an oily acid remained, which, on combustion, yielded the following numbers:

0·1242 gave 0·3204 CO_2 and 0·1030 H_2O. C = 70·35; H = 9·21.
$C_9H_{14}O_2$ requires C = 70·13; H = 9·09 per cent.

The acid had thus the composition of campholytic acid, and its identity was proved by the conversion of a portion of it into isolauronolic acid by warming with 25 per cent. sulphuric acid.

A 60 per cent. ethereal solution of the campholytic acid, prepared from isolauronolic acid by the above method, gave a rotation in a 10 cm. tube which was less than a hundredth of a degree. The acid is therefore optically inactive.

Hydrobromide of Isolauronolic Acid.

Our first attempts to prepare the hydrobromide of isolauronolic acid were attended with but little success. If fuming hydrobromic acid is employed, the action proceeds in such a way that it is impossible to find a point at which the theoretical amount of hydrogen bromide has been taken up, and at which the isomeric transformation into the hydrobromide of campholytic acid is not yet effected. With weaker hydrobromic acid, however, the absorption is comparatively slow, and it was found to be possible, by stopping the action somewhat before the theoretical amount of hydrogen bromide had been absorbed, to isolate the hydrobromide of isolauronolic acid. The manner of operating which gave the most uniform results was as follows. The

isolauronolic acid was allowed to remain in contact in a test-tube with 50 per cent. hydrobromic acid in quantity little more than sufficient to cover it. The absorption, which is at first moderately rapid, is speedily retarded by the diminution of the strength of the hydrobromic acid solution as absorption progresses, and apparently a weak acid is unable to effect the isomeric transformation. At the expiration of 24 hours, the solution was again brought to the saturation point by passing in hydrogen bromide, and the action allowed to proceed. This operation was repeated at intervals of 24 hours until the solid contained between 25 and 30 per cent. of bromine, the theoretical amount being 34 per cent. The crystalline mass then consisted chiefly of the hydrobromide of isolauronolic acid along with a comparatively small amount of untransformed isolauronolic acid. Now isolauronolic acid is much less soluble in light petroleum than its hydrobromide. If therefore the dried and washed crystalline mass is dissolved in the minimum quantity of this solvent, the first portion which separates out on crystallisation contains the bulk of the isolauronolic acid, and the residual liquid yields the practically pure hydrobromide. Thus a mixture which initially contained 28 per cent. of bromine, and melted at 127—130°, yielded a first crop of crystals containing 11 per cent., and a second crop containing 32 per cent. of bromine. Heating is to be avoided in the recrystallisation, as the hydrobromide tends to lose hydrogen bromide when warmed in light petroleum. The melting point of the substance prepared and purified in this way is 132—133°, the fusion being unattended by any appreciable darkening or decomposition.

In order to ascertain if this bromo-acid were in reality the hydrobromide of isolauronolic acid, we subjected it to treatment with caustic soda. As in the case of the isomeric compound, a small quantity of an indifferent substance was produced, but the acid precipitated from the alkaline solution by hydrochloric acid was solid, and not liquid as in the former instance. On recrystallisation from light petroleum, the acid melted at 135°, and had the other properties of isolauronolic acid. A combustion resulted as follows:

0·0976 gave 0·2512 CO_2 and 0·0842 H_2O. C = 70·2; H = 9·5.

$C_9H_{14}O_2$ requires C = 70·1; H = 9·1 per cent.

There is thus no doubt that the bromo acid melting at 132° is the hydrobromide of isolauronolic acid, as that melting at about 100° is the hydrobromide of campholytic acid.

It is now possible to convert any one of the four following acids directly or indirectly into any other in the manner indicated by the arrows in the diagram.

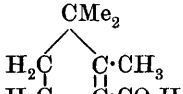
Campholytic acid $\rightleftharpoons$ Bromo-acid, m. p. about 100°

$C_8H_{13}\cdot CO_2H$ $\downarrow$ $\uparrow$ $C_8H_{14}Br\cdot CO_2H$

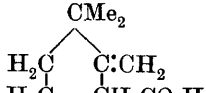
Isolauronolic acid $\rightleftharpoons$ Bromo-acid, m. p. 132°.

Isomerism of Campholytic and Isolauronolic Acids.

Blanc has recently suggested (compare Noyes, *Ber.*, 1900, **33**, 57) that campholytic and isolauronolic acids are structural isomerides, and has assigned to them the following formulæ based on the Perkin-Bouveault formula for camphoric acid :



Isolauronolic acid.



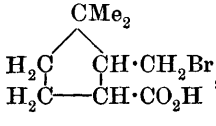
Campholytic acid.

The formula for isolauronolic acid is satisfactory, inasmuch as it readily accounts for its electrolytic formation, its general chemical properties as an $\alpha\beta$-unsaturated acid, and its optical inactivity. The formula for campholytic acid, on the other hand, whilst it accounts simply for the electrolytic production of the acid, must be rejected for the following reasons :

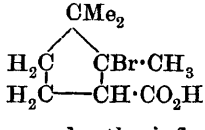
(1) Campholytic acid is not a $\beta\gamma$-acid as the formula indicates, but an $\alpha\beta$-acid, as is proved by the production of isolaurolene, C_8H_{14}, from its hydrobromide, and bromoisolaurolene, $C_8H_{13}Br$, from its dibromide. A $\beta\gamma$-acid under the same conditions would yield a lactone and a bromolactone respectively.

(2) An acid possessing Blanc's formula has an asymmetric carbon atom, and would in all probability be endowed with powerful optical activity, whereas campholytic acid is apparently inactive.

(3) The hydrobromide of an acid having Blanc's formula would be :

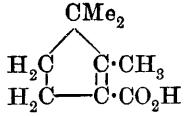


and it is inconceivable that such an acid could be formed from the hydrobromide of isolauronolic acid



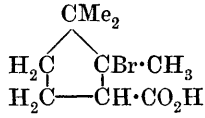
by isomeric transformation under the influence of hydrobromic acid in the cold (this vol., p. 379).

All these difficulties disappear if we consider campholytic and isolauronolic acids to be stereoisomerides having the structural formula:



Campholytic and isolauronolic acids.

Here the acids are both represented as $\alpha\beta$-acids and optically inactive, in accordance with their actual behaviour. The difference between them would merely be caused by the methyl and carboxyl groups being in the one case on the same side of the double bond, and in the other case on different sides. The difference between the stereoisomeric bromides:



would similarly be caused by these two groups being on the same or different sides of the plane of the ring. Thus the isomeric transformation of the acids themselves and of their hydrobromides can be easily explained.

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