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RESOLUTION OF THE $\alpha\delta$-DIHYDROXY-α-METHYL-δ-*ISO*PROPYLADIPIC ACIDS

BY

T. A. HENRY AND H. PAGET

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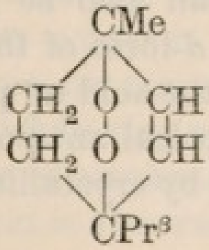
CCXI.—*Resolution of the αδ-Dihydroxy-α-methyl-δ-*iso*propyladipic Acids.*

By Thomas Anderson Henry and Humphrey Paget.

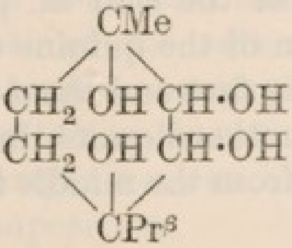
In a previous paper (T., 1921, **119**, 1720), it was shown that the hydrocarbon fraction of chenopodium oil on oxidation with potassium permanganate in acetone yielded considerable quantities of the two αδ-dihydroxy-α-methyl-δ-*iso*propyladipic acids, melting at 189° and 203—204°, and that these were derived from α-terpinene. Both acids proved to be optically inactive, as was to be expected. A third inactive form of the acid, melting at 190—191°, was described by Nelson (*J. Amer. Chem. Soc.*, 1911, **33**, 1411; 1913, **35**, 87) as produced by the oxidation of the erythritol (II) derived from ascaridole (I). In the course of the authors' work on chenopodium oil, considerable quantities of these acids have been obtained, and they have taken the opportunity of investigating them more completely.

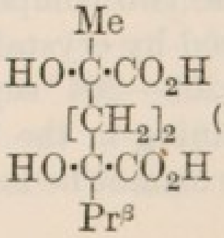
Inspection of the formula of the acid indicates that only two inactive modifications (III and IV) should exist, and re-examination of Nelson's acid shows that it is identical with the acid melting at 203—204°, and not, as Wallach suggested (*Annalen*, 1912, **392**, 67), with that melting at 189°. The known inactive acids are thereby reduced to two.

(I.)



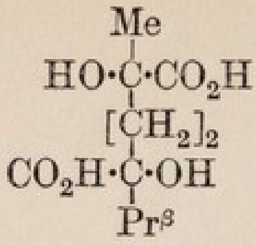
(II.)



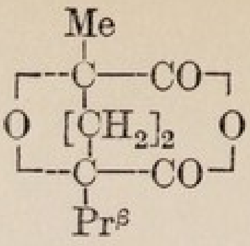


(III.)

(IV.)



$$\begin{array}{c} \text{Me} \\ | \\ \text{HO}\cdot\text{C}\cdot\text{CO}_2\text{H} \\ | \\ [\text{CH}_2]_2 \\ | \\ \text{CO}_2\text{H}\cdot\text{C}\cdot\text{OH} \\ | \\ \text{Pr}^{\beta} \end{array}$$



(V.)

Of these, one melts at 203—204°, is very sparingly soluble in water and other solvents, and loses two molecules of water with great difficulty, yielding Wallach's supposed dilactone, m. p. 62°. The other acid melts at 189°, is readily soluble in water, and yields Wallach's second dilactone, m. p. 74°, with great ease. These differences are characteristic of those which exist between the inactive forms of $\alpha\delta$-substituted adipic acids, such as $\alpha\delta$-dimethyladipic acids (*meso*-form, m. p. 142°, solubility in water 0·56 per cent.; *racemic* form, m. p. 70—72°, solubility in water 6·7 per cent.; Noyes, *J. Amer. Chem. Soc.*, 1910, **32**, 1057), and $\alpha\delta$-dihydroxyadipic acids (*meso*-form, m. p. 174°, less soluble; *racemic* form, m. p. 146°, more soluble; Le Sueur, T., 1908, **93**, 716; 1910, **97**, 173).

It seemed reasonable to assume, therefore, that the acid melting at 203—204° corresponded to the *meso*-form and that melting at 189° to the *racemic* form of these analogous acids, and could be regarded respectively as *anti-* (III), and *para-* (IV) forms; terms which have been revived by Dakin to distinguish the two inactive forms of hydroxyaspartic acid, which are analogous with the acids now dealt with (*J. Biol. Chem.*, 1921, **48**, 273; 1922, **50**, 403).

The facts are, however, not quite so simple. The acid of higher m. p. does not, as Wallach stated, lose two molecules of water when boiled with hydrochloric acid and form the " dilactone," m. p. 62°. This change occurs only on dry distillation under reduced pressure. Further, the supposed " dilactone " is in reality the anhydride (V) of 1 : 4-cineolic acid, and yields the latter acid on hydration. The more fusible acid, on the contrary, readily yields a dilactone, m. p. 74°, when boiled with hydrochloric acid, but only to the extent of 50 per cent. of its weight, and the residual liquor left in the flask now contains the remaining 50 per cent. in the form of the acid melting at 203—204°. Further, this dilactone on hydration yields a new acid, m. p. 198°, intermediate in solubility between the two already described, which reproduces the dilactone, m. p. 74°, in the calculated yield when boiled with hydrochloric acid. Separation of the two components of the acid m. p. 189° can also be partly effected by crystallisation of the quinine salt, the *d*-form of the acid m.p. 203—204° separating first and the *d*-form of the acid m. p. 198° remaining in the final mother-liquors, but the optical antipodes of these cannot be isolated from the middle fractions by crystallisation.

As Wallach had already synthesised the acid melting at 189° (*Annalen*, 1908, **362**, 268) from dimethylacetonylacetone, his experiments were repeated, and yielded not one but all three inactive acids, the relative amounts obtained being acid of m. p. 203—204°; acid of m. p. 189°; acid of m. p. 198° = 3 : 1 : 1. There can be no doubt that the acid melting at 189° is a chemical individual, since it crystallises quite differently from the other two forms, is more soluble than either, and is separable from either by crystallisation. Further, it can be prepared by dissolving the other two forms in hot water, allowing whichever form is in excess to crystallise out, and then concentrating the liquid until crystallisation again begins, when the form, m. p. 189°, invariably separates.

A similar form of αα-dimethylglutaric acid,

$$CO_2H{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}CO_2H,$$

m. p. 105—107°, was described by Bone and Perkin (T., 1896, **69**, 268), which, though not separable into its components by fractional crystallisation from any solvent, could be separated into the ordinary *trans*- and *cis*-forms by crystallisation of the calcium hydrogen salt (compare Auwers, *Ber.*, 1895, **28**, 263), or by warming with acetyl chloride, when the *cis*-form readily yielded an anhydride, whilst the *trans*-form remained unchanged.

It seems clear in view of their physical properties and the difference in their modes of losing water that the acid of m. p. 203—204° is the *anti*-form, and the acid of m. p. 198° the *para*-form, whilst the third acid, m. p. 189°, is a combination of these two. Unlike most of the similar acids in this series, no evidence has been found of interconversion between the *anti*- and *para*-forms.

The *anti* and *para*-acids have both been resolved into their optically active forms, the former by fractional crystallisation of the quinine and cinchonine salts, the second alkaloid being the more convenient agent, and the latter by the use of quinine. The principal facts regarding the two pairs of optically active forms and their salts are summarised in the table opposite.

It will be seen from this table that in the case of the *anti*-acid, *l*-quinine and *d*-cinchonine both separate the dextro-form of the acid first, whilst *d*-quinidine effects virtually no separation, the salts with the *d*- and *l*-forms of the acid being about equally soluble. In the case of the quinine salt, there appears to be no change in the sign of rotation, the salt with the *d*-acid being, as is to be expected, of lower rotation than that of the salt with the *l*-acid. With quinidine, on the contrary, such a change does occur, the salt with the *l*-acid having a higher rotation than that with the *d*-acid. In the case of cinchonine no comparison can be made, as the salt with the *l*-acid is abnormal in composition.

Name.	M. p.	$[\alpha]_D$.	Solubility at 20°. Grams in 100 c.c.
dl-anti-Acid	203—204°	—	1·16 in alcohol; 0·45 in water.
d-anti-Acid :	214	+7·37° (in alcohol)	1·10 in alcohol; 0·50 in water.
sodium salt	—	+5·23	—
neutral quinine salt	231	−127·2	Less soluble.
acid cinchonine ,,	174	+115·2	,, ,,
neutral quinidine ,, *	144	+154·4	More soluble.*
l-anti-Acid :	214	−7·20 (in alcohol)	1·14 in alcohol; 0·41 in water.
sodium salt	—	−5·7	—
neutral quinine salt	225	−135·6	More soluble.
cinchonine † ,,	190	+145·7	,, ,,
neutral quinidine ,,	154	+162·4	Less soluble.*
dl-para-Acid	198	—	4·45 in alcohol; 1·20 in water.
d-para-Acid	206	+9·12 (in alcohol) +9·94 (in water)	4·17 in alcohol. 1·10 in water.
sodium salt	—	−4·03	—
neutral quinine salt	207	−134·5	More soluble.
l-para-Acid	208	−9·6 (in alcohol) −10·9 (in water).	4·09 in alcohol; 1·00 in water.
sodium salt	—	+4·41	—
neutral quinine salt	213	−111·4	Less soluble.

* There is little difference in the solubility of the quinidine salts of the *l*- and *d*-acids.

† The cinchonine salts of the *d*- and *l*-forms are not comparable (see p. 1886).

With the *para*-acid, the opposite state of things occurs as regards the solubility of the quinine salts, the salt of the *l*-acid separating first. Further, there is a change of sign on conversion of the active acids into sodium salts, the sodium salt of the *l*-acid being dextrorotatory, and *vice versa,* and this also seems to occur with the quinine salts, that of the *d*-acid having a higher lævorotation than that of the *l*-acid. Changes of sign on conversion into salts have been noticed before in this series of acids; for example, Le Sueur's *d*-dihydroxyadipic acid gave a lævorotatory ammonium salt (*loc. cit.*). With regard to the relative solubilities of the salts of the optically active forms of acids with alkaloids of the cinchona group, King has shown recently (T., 1922, **121**, 2578), that the stereochemical factor is not the sole determining influence on the solubility of these salts; for example, the least soluble tropate of *l*-quinine and *d*-hydrocinchonine is the salt of the *d*-acid, whilst with *d*-hydroquinidine it is the salt of *dl*-tropic acid, and with *d*-quinidine the salt of the *l*-acid.

EXPERIMENTAL.

Preparation of the Acids.—(*a*) *From α-terpinene.* The preparation and separation of the two forms, m. p. 203—204° and m. p.

189°, from the α-terpinene present in chenopodium oil has been described already (*loc. cit.*). The yield from 1,000 c.c. of the hydrocarbon fraction of the oil, which probably contains about 16 per cent. by volume of α-terpinene, is about 16 grams of the crude crystalline acids, from which, on recrystallisation from boiling water, about 10 grams of the high-melting and about 5 grams of the low-melting form are eventually obtained.

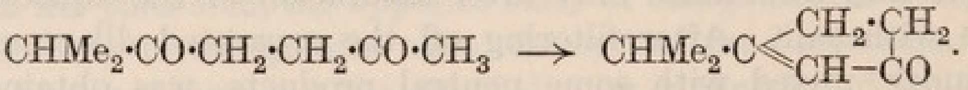
(*b*) *By synthesis from dimethylacetonylacetone.* The dimethylacetonylacetone (b. p. 209—212°/751 mm.) was prepared from methylheptenone made by Verley's method from citral (*Bull. Soc. chim.*, 1897, [iii], **17**, 175). The yield of the diketone, expressed on the citral used, was about 21 per cent.

After preliminary trials, the following method was found to give the best yield of the required acids. Twenty grams of the diketone, cooled to 0°, were mixed with 24 grams of potassium cyanide dissolved in 30 c.c. of water, and, after standing for some time at room temperature, 31·5 c.c. of concentrated hydrochloric acid were added very slowly, the mixture being kept well cooled and shaken, and then left for forty-eight hours at room temperature. On extraction with ether, this yielded 25 grams of viscous, yellow oil, which was at once mixed with twice its volume of concentrated hydrochloric acid, heated during 1 hour at 100°, and then steam-distilled. The dilactone came over slowly as a viscous, yellow oil, which sometimes crystallised at once in the condenser or the receiver and sometimes only after saturation of the aqueous distillate with salt. After filtering off the separated dilactone, the remainder, mixed with some neutral products, was obtained by extracting the distillate with ether. The total yield of dilactone was about 5 per cent. of the weight of diketone taken; it melted at 74°, and the melting point was not changed by recrystallisation from ether (Found: $C = 60{\cdot}40$; $H = 7{\cdot}39$. Calc. for $C_{10}H_{14}O_4$, $C = 60{\cdot}60$; $H = 7{\cdot}07$ per cent.).

The mother-liquor left in the distillation flask, which was apparently not examined by Wallach, was allowed to cool, poured from the considerable quantity of tar formed, and thoroughly extracted with ether, when it yielded about 5 grams of crude crystalline acids, which on recrystallisation from boiling water were separated into the acid of m. p. 203—204° (4 grams), and the acid of m. p. 189° (1 gram), neither of which showed any depression in melting point when mixed with the acids of similar melting point prepared from α-terpinene.

The crystalline dilactone, m. p. 74°, and the mixture of this with neutral products (see above) were separately treated with 2*N*-sodium hydroxide; the former dissolved completely, and on acidification the solution yielded an acid crystallising in rosettes of transparent prisms which melted sharply with effervescence at 198°, and after cooling re-melted at 72—74°, being reconverted into the dilactone. The oily product did not dissolve completely in 2*N*-sodium hydroxide solution even after standing several days, or on heating on the water-bath. The liquid was therefore extracted with ether, and the clear alkaline solution on acidification yielded the same acid melting at 198°. Seven grams of the pure acid were dissolved in 250 c.c. of boiling water (forming a supersaturated solution, which only began to crystallise after some days), and crystallised in six fractions, all of which melted at 198° (Found: C = 51·06; H = 7·67. Calc. for dihydroxymethyl*iso*propyladipic acid, $C_{10}H_{18}O_6$, C = 51·27; H = 7·69 per cent.). Mixed with the acid of m. p. 203—204°, the melting point is depressed to 187—189°, whilst a mixture with the acid of m. p. 189° begins to melt at 189°.

The oily neutral product extracted, with some of the dilactone, from the distillate by ether, after purification with sodium hydrogen sulphite, distilled at 105—130°/10 mm. or 205—215°/760 mm., and on treatment with semicarbazide yielded two substances melting at 189—190° and 174° respectively. These were separated by crystallisation from alcohol; the former, which is the less soluble, crystallised in pearly plates and was identified as the semicarbazone of tanacetophorone (Found: C = 59·29; H = 8·54; N = 22·59. Calc. for $C_9H_{15}ON_3$, C = 59·67; H = 8·29; N = 23·2 per cent.), this being formed, no doubt, from dimethylacetonylacetone by the loss of a molecule of water thus:



$$\mathrm{CHMe_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3} \longrightarrow \mathrm{CHMe_2{\cdot}C}{<}\begin{matrix}\mathrm{CH_2{\cdot}CH_2}\\ \mathrm{CH{-}CO}\end{matrix}.$$

The second semicarbazone, m. p. 174°, crystallised in colourless needles. It was obtainable only in small amount, showed no depression in melting point when mixed with tanacetophorone-semicarbazone, and is possibly the latter with some persistently adherent impurity (Found: C = 58·61; H = 8·48 per cent.).

Separation of the Acid of m. p. 189° *into the Acid of m. p.* 198° *and the Acid of m. p.* 203—204°.—One gram of the acid of m. p. 189°, obtained by the oxidation of α-terpinene, was boiled for forty-five minutes with 20 c.c. of concentrated hydrochloric acid, and the solution diluted with water and steam distilled, yielding 0·44 gram of crystalline dilactone, m. p. 72—74°. From the residual liquor in the flask, 0·53 gram of acid was isolated, which on recrystallisation melted at 204°. The dilactone on hydrolysis by alkali yielded the calculated amount of the acid of m.p. 198°. In a second experiment, from 3·5 grams of the acid of m. p. 189°, 1·6 grams of dilactone, m.p. 72—74°, were obtained.

Conversion of the Acid of m. p. 203—204° *into the Supposed Dilactone, m.p.* 62°.—Wallach stated that this acid was readily converted, by boiling with moderately concentrated hydrochloric acid, into a dilactone, m. p. 62°. 1·2 Grams of the acid were boiled with 30 c.c. of 20 per cent. hydrochloric acid for one hour, and the liquid distilled almost to dryness. The dissolved acid crystallised out during the distillation, and was recovered unchanged. It was then boiled for one hour with 20 c.c. of concentrated hydrochloric acid, and again distilled almost to dryness, with the same result, and eventually 1·14 grams of the acid were recovered unchanged. Repetition of Wallach's dry distillation of the acid was, however, more successful. One gram of the pure acid was distilled under reduced pressure in a small distilling flask, through which a slow stream of carbon dioxide was passed by means of a capillary tube, the flask being heated in a bath of liquid paraffin. Decomposition began at 200°, and heating was continued until evolution of gas stopped. A viscous, yellow oil, amounting to 0·76 gram (90 per cent. of the theoretical), collected in the receiver. On standing on ice, part of the oil crystallised, and this, after recrystallisation from ether, melted at 65° (Found: $C = 59{\cdot}7$; $H = 6{\cdot}5$. Calc. for $C_{10}H_{14}O_4$, $C = 60{\cdot}60$; $H = 7{\cdot}07$ per cent.). The low figure for carbon and the high figure for hydrogen are due to the difficulty of drying such a small quantity of a somewhat volatile substance. On addition of the calculated quantity of 2*N*-sodium hydroxide solution, the product dissolved, forming a clear liquid, which on acidification deposited an oil which crystallised almost at once in fine needles; these, after recrystallisation from hot water, melted constantly at 122°. Admixture with 1 : 4-cineolic acid caused no depression in melting point (Found: $C = 55{\cdot}51$; $H = 7{\cdot}7$. Calc. for 1 : 4-cineolic acid, $C_{10}H_{16}O_5$, $C = 55{\cdot}5$; $H = 7{\cdot}46$ per cent.). The volatile, crystalline product must therefore be the anhydride (V) of this acid. Nelson has already recorded the formation of this substance by the dry distillation of his αδ-dihydroxy-α-methyl-*iso*propyladipic acid, m. p. 190—191° (*loc. cit.*). The formation of this substance by dry distillation confirms the view that the 203—204° acid is the *anti*-form.

Resolution of the anti- *and* para-*Acids.*

A. anti-*Acid, m. p.* 203—204°.—Wallach only obtained this acid by the oxidation of optically active terpinen-4-ol, and he described it as active, but produced no evidence for this. The acid is too sparingly soluble in all ordinary solvents for satisfactory observation in a polarimeter, but a 15 per cent. aqueous solution of the sodium salt showed no optical activity.*

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* Except where otherwise stated, the polarimeter tubes used had $l = 2$ dcm.

To 7·3 grams of the acid, dissolved in 300 c.c. of boiling 96 per cent. alcohol, the calculated quantity of quinine base, dissolved in 100 c.c. of alcohol, was added, and the solution left standing for four days, when it had deposited 14 grams of quinine salt. The latter was then recrystallised from 96 per cent. alcohol until the specific rotation became constant at about $-128°$ and the melting point at 227°. About 10 grams of material of this quality were accumulated by repeatedly working through the middle fractions. The acid regenerated from this, and recrystallised, gave a sodium salt having $[\alpha]_D + 3·53°$, but on repeating the separation it was found that the constancy in melting point and rotation of the quinine salt was only apparent, and with other conditions other results were obtained, sometimes higher and sometimes lower. Recourse was then had to cinchonine, and after various trials it was found that crystallisation of the acid cinchonine salt, $C_{19}H_{22}ON_2,C_{10}H_{18}O_6$, from 96 per cent. alcohol gave much better results, a fraction melting constantly at 174° and having $[\alpha]_D + 116°$ being ready separable. From 23 grams of the crude salt, 7·5 grams of the pure salt of the dextro-acid having $[\alpha]_D + 115·2°$ were obtained ($\alpha_D = + 4·6°$ in alcohol; $c = 2·11$; $l = 1·894$). This salt crystallises in prismatic plates, sparingly soluble in alcohol and scarcely soluble in water. It was suspended in fine powder in hot water and the calculated quantity of 2*N*-soda added, the cinchonine filtered off, washed twice in a mortar with water, and the washings and filtrate concentrated to low bulk under reduced pressure, again filtered, and the clear solution acidified, when it deposited 3·0 grams of well-crystallised acid melting at 214°. This was converted into sodium salt, which had a specific rotation $[\alpha]_D + 5·1°$ ($\alpha + 1·94°$ in water, $c = 19·02$). A second determination gave $[\alpha]_D + 5·36°$ for the same conditions.

The acid regenerated from the sodium salt and recrystallised gave in alcoholic solution $[\alpha]_D^{15°} + 7·37°$ ($c = 0·6$ to $1·25$), but owing to the difficulty of reading such small rotations no great stress is laid on the quantitative value of this result.

The quinine salt made by neutralising the pure *d-anti*-acid with quinine and recrystallising from 96 per cent. alcohol had m. p. 231°, and $[\alpha]_D - 127·2°$ in alcohol ($\alpha - 1·79°$, $c = 0·7454$, $l = 1·894$). The quinidine salt of the *d*-acid, made similarly, crystallises from 30 per cent. alcohol, and has m. p. 144° and $[\alpha]_D + 154·4°$ in alcohol ($\alpha + 15·84°$, $c = 5·417$, $l = 1·894$).

The more soluble cinchonine salt could only be obtained as an oil for some time, but eventually a portion of this was induced to crystallise from a syrupy solution in 10 per cent. alcohol. Yield 5·5 grams = 24 per cent. The acid regenerated from this was converted into the sodium salt, as already described, and gave in successive readings, the acid being recrystallised each time, $[\alpha]_D$ $-5{\cdot}71°$, $-5{\cdot}78°$, $-5{\cdot}62°$ in water ($c = 17{\cdot}94$ to $18{\cdot}03$). The acid itself, regenerated as described in the case of the *d*-acid, melted at 214°, and in alcoholic solution gave as a mean of three determinations $[\alpha]_D -7{\cdot}20°$ ($c = 0{\cdot}76$ to $1{\cdot}42$), but for the reason given in the case of the *d*-acid great accuracy is not claimed for this result.

The pure cinchonine salt of the *l*-acid was made by adding the calculated quantity of base to the acid, dissolved in water, and distilling off the excess of solvent. On cooling, the salt crystallised in colourless, triangular plates, which began to soften at 178° and melted completely at about 190°. This salt is abnormal and appears to have approximately the composition $3C_{19}H_{22}ON_2,2C_{10}H_{18}O_6$. It is soluble in little more than its own weight of 96 per cent. alcohol. $[\alpha]_D + 145{\cdot}7°$ in alcohol ($\alpha + 6{\cdot}96°$, $c = 2{\cdot}521$, $l = 1{\cdot}894$).

The quinine salt, similarly prepared, crystallises from 50 per cent. alcohol in warty masses of colourless needles, m. p. 225°, $[\alpha]_D - 135{\cdot}6°$ in alcohol ($\alpha_D - 2{\cdot}72°$, $c = 1{\cdot}057$, $l = 1{\cdot}894$). The quinidine salt of the *l*-acid, similarly made, crystallises from 30 per cent. alcohol in warty masses of needles closely resembling the quinine salt in appearance. It melts at 154° and has $[\alpha]_D + 162{\cdot}4°$ in alcohol ($\alpha + 17{\cdot}37°$, $c = 5{\cdot}645$, $l = 1{\cdot}894$). The quinidine salts of both the *d*- and the *l*- acid separate from hot solution in dilute alcohol as oils, which slowly crystallise on standing, and are to some extent soluble in water.

para-*Acid, m. p.* 198°.—Five grams of this acid were converted into the neutral quinine salt, and the crude salt recrystallised from 96 per cent. alcohol in the usual manner until a constant product, m. p. 212°, $[\alpha]_D - 111{\cdot}9°$ in alcohol ($\alpha_D - 3{\cdot}18°$, $c = 1{\cdot}420$), was obtained. The yield was 2·5 grams. A repetition of this separation, using 8·3 grams of acid and crystallising from dilute alcohol (30 to 50 per cent.), gave 6·8 grams of pure quinine salt, m. p. 213°, $[\alpha]_D - 111{\cdot}4°$ in alcohol ($\alpha_D - 4{\cdot}62°$, $c = 2{\cdot}074$), but the use of weaker alcohol, involving a higher temperature on concentration, leads to gradual darkening of the solution and makes it more difficult to recover the more soluble quinine salt.

The acid regenerated from the pure less soluble quinine salt melted at 208°, re-solidified on cooling, and then re-melted at 74°, owing to conversion into the dilactone. The sodium salt in aqueous solution gave $[\alpha]_D + 4{\cdot}25°$, $+ 4{\cdot}41°$ ($\alpha + 1{\cdot}49°$, $1{\cdot}62°$; $c = 17{\cdot}54$, $18{\cdot}36$). The free acid had $[\alpha]_D^{21°} - 10{\cdot}96°$ in water ($\alpha - 0{\cdot}22°$, $c = 1{\cdot}004$) and $- 9{\cdot}55°$ in 96 per cent. alcohol ($[\alpha]_D - 0{\cdot}74°$, $c = 4{\cdot}091$, $l = 1{\cdot}894$).

The more soluble quinine salt was difficult to obtain in satisfactory condition, for the reason already stated, but after many crystallisations (1) 8·6 grams of well-crystallised salt, m. p. 207°, $[\alpha]_D$ −129·4° in alcohol ($\alpha - 4{\cdot}99°$, $c = 2{\cdot}035$, $l = 1{\cdot}894$), and (2) 6·5 grams of ultimate residue, partly crystalline, were obtained. Fraction 1 proved to be only partly resolved, since the sodium salt of the acid regenerated from it had $[\alpha]_D - 1{\cdot}69°$. Fraction 2 yielded an acid which melted at 206° and after cooling re-melted at 74°. On conversion into the sodium salt, the latter gave $[\alpha]_D - 3{\cdot}95°$, $-4{\cdot}11°$ in water ($\alpha - 0{\cdot}46°$, $0{\cdot}48°$; $c = 6{\cdot}3$, $l = 1{\cdot}894$), and the acid regenerated from this still melted at 206°, and showed specific rotation $[\alpha]_D + 9{\cdot}03 \ + 9{\cdot}94°$ in water ($\alpha + 0{\cdot}20°$, $0{\cdot}22°$, $c = 1{\cdot}107$), and $[\alpha]_D + 9{\cdot}12°$ in alcohol ($\alpha + 0{\cdot}72°$, $c = 4{\cdot}17$, $l = 1{\cdot}894$). The quinine salt made from the pure acid and recrystallised from dilute alcohol melted at 207° and had $[\alpha]_D - 134{\cdot}5°$ in alcohol ($\alpha - 7{\cdot}60°$, $c = 2{\cdot}98$, $l = 1{\cdot}894$).

Acid, m. p. 189°.—This acid on conversion into the quinine salt and fractional crystallisation of the latter yielded (i) a small fraction which after purification had m. p. 228° and $[\alpha]_D - 130{\cdot}5°$, (ii) a large middle fraction which showed varying melting points on recrystallisation, and (iii) a small ultimate fraction, which could not be obtained well crystallised. The acid regenerated from fraction (i), on recrystallisation from water, proved to give a dextrorotatory sodium salt, and on fractional crystallisation from boiling water was separated into the acid of m. p. 205° and the acid of m. p. 187° in about equal proportions. The acid regenerated from fraction (ii) was largely unchanged acid of melting point 189°, whilst that recovered from fraction (iii) gave a lævorotatory sodium salt, and appeared to consist in part of the dextro-form of the acid m. p. 198°. As shown already (p. 1883), results obtained in other ways proved that the acid melting at 189° is a combination of the *anti*- and *para*-acids, into which it can be separated.

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