34. *The Resolution of Tertiary Hydroxy-carboxylic Acids.*

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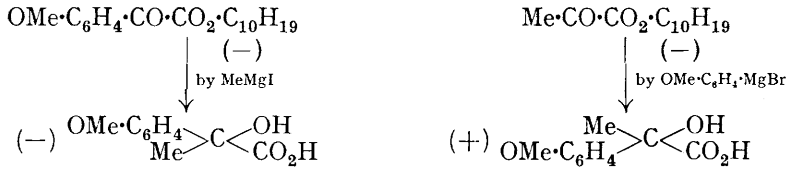
THE only tertiary hydroxy-carboxylic acid to be resolved into its optically active components by means of alkaloids is *r*-atrolactinic acid, which McKenzie and Clough (J., 1910, **97**, 1016) resolved by morphine and by quinine.

For purposes of other investigations it was desired to obtain other optically active acids of the same type, $OH\cdot CRR'\cdot CO_2H$, as atrolactinic acid, but difficulties were encountered at the outset when attempts to resolve four different acids of this type met with no success. This was all the more curious when it was recalled that, in spite of the great success of Pickard and Kenyon in resolving many secondary alcohols, the only tertiary alcohol containing the hydroxyl group attached to the asymmetric carbon atom which has hitherto been resolved is α-terpineol. For the purpose of obtaining (—) and (+)terpineols Fuller and Kenyon (J., 1924, **125**, 2304) crystallised the brucine and the morphine salts of α-terpinyl hydrogen phthalate.

We have, nevertheless, prosecuted our attempts in an unpromising field, and have resolved *r*-phenyl-*p*-tolylglycollic, *r*-*p*-tolylmethylglycollic, and *r*-anisylmethylglycollic acids.

The optically active anisylmethylglycollic acids described by McKenzie and P. D. Ritchie (*Biochem. Z.*, 1932, **250**, 376) were prepared by them, not by the resolution of the *r*-acid, but by asymmetric syntheses, thus :



From these syntheses it was possible to isolate the two acids from the mixtures resulting from the Grignard actions by crystallising from benzene the partially active product in each case, the *r*-acid remaining in the filtrate. These are the only examples where an optically pure compound can be obtained from the product of an asymmetric synthesis when compounds of known constitution are employed. The (—)acid now obtained by resolving the *r*-acid with morphine agreed in m. p. and rotatory power with the (—)acid obtained from (—)menthyl anisoylformate.

EXPERIMENTAL.

r-4-*Methoxybenzilic acid*, prepared by the action of alcoholic potash on 4-methoxybenzil (McKenzie, Luis, Tiffeneau, and Weill, *Bull. Soc. chim.*, 1929, **45**, 414), crystallised from benzene or water in needles, m. p. 148—149° (Found : C, 69·8; H, 5·6. $C_{15}H_{14}O_4$ requires C, 69·7; H, 5·5%). A trace gave an orange coloration with concentrated sulphuric acid.

Attempts to resolve this acid, as well as *r*-methylethylglycollic acid, *r*-phenyl-α-naphthylglycollic acid, and *r*-benzylphenylglycollic acid by means of various alkaloids were unsuccessful, although crystalline alkaloidal salts were available in each case.

Resolution of r-*Phenyl*-p-*tolylglycollic Acid*.—Hydrated quinine (45 g.) was dissolved in a boiling solution of 34 g. of *r*-phenyl-*p*-tolylglycollic acid (McKenzie and Christie, J., 1934, 1070) in ethyl alcohol (1100 c.c.), the amount calculated for quinine trihydrate being 53 g. After 5 hours at the ordinary temperature, the bulky crystals (27 g.) were collected, and recrystallised four times from ethyl alcohol; the homogeneous quinine salt (12 g.) of the (+)acid was then obtained as rosettes of needles. The progress of the resolution was noted by decomposing the filtrates from successive crystallisations by means of dilute sulphuric acid and determining the rotatory power of the acids so obtained. The quinine salt was acidified by dilute sulphuric acid, the organic acid being then extracted with ether.

(+)*Phenyl*-p-*tolylglycollic acid* crystallised from acetone–light petroleum (b. p. 80—100°) in long prisms, m. p. 125—127° (Found : C, 74·8; H, 6·0. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%), whereas the *r*-acid has m. p. 133—134°. A trace gave a cherry-red coloration with concentrated sulphuric acid. In ethyl alcohol : $l = 2$, $c = 5{\cdot}2965$, $\alpha^{20^\circ}_{5461} + 0{\cdot}26^\circ$, $[\alpha]^{20^\circ}_{5461} + 2{\cdot}5^\circ$, the rotatory power being unchanged after the acid had been crystallised.

r-Phenyl-*p*-tolylglycollic acid was reduced by hydriodic acid and phosphorus in the presence of glacial acetic acid. The product was *r*-phenyl-*p*-tolylacetic acid (McKenzie and Widdows, J., 1915, **107**, 702). When (+)phenyl-*p*-tolylglycollic acid was reduced under similar conditions, the product after one crystallisation from dilute acetic acid was *r*-phenyl-*p*-tolylacetic acid, and the filtrate also was optically inactive. This observation has a bearing on Walden inversion where a compound with a hydroxyl group in direct attachment to the asymmetric carbon atom is converted into another where hydrogen is substituted for the hydroxyl group, an aspect which had not been investigated so far.

Ethyl (+)*phenyl*-p-*tolylglycollate*, prepared by esterifying the (+)acid with ethyl alcohol and sulphuric acid, was a mobile oil (Found : C, 75·6; H, 6·5. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%). In acetone : $l = 2$, $c = 4{\cdot}659$, $\alpha^{21^\circ}_{5461} + 0{\cdot}41^\circ$, $[\alpha]^{21^\circ}_{5461} + 4{\cdot}4^\circ$. The oil was distilled under 18 mm., the fraction (b. p. 205—210°) was collected, and found to have the same rotation as that just quoted.

Action of p-*Tolylmagnesium Bromide on Pyruvic Acid.*—The Grignard reagent prepared from 116 g. of *p*-bromotoluene (3 mols.) was added slowly with mechanical stirring to an ethereal solution of 20 g. of freshly-distilled pyruvic acid (1 mol.). A cream-coloured bulky solid separated. After 2½ hours' heating and subsequent decomposition of the additive complex with ice and dilute sulphuric acid, the ethereal layer was removed, the ether expelled, and the product distilled in steam to remove *p*-ditolyl; the residue was extracted with ether. Under diminished pressure the resulting reddish oil solidified gradually, and the solid was crystallised twice from ethyl alcohol–light petroleum (b. p. 60—80°). Yield, 15 g.

r-p-*Tolylmethylglycollic acid* forms needles, m. p. 102—104° (Found : C, 66·6; H, 7·0. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). A trace gave no coloration with concentrated sulphuric acid but when more was added the solution became yellow. This colour reaction is not nearly so delicate as that exhibited either by 4-methoxybenzilic acid or by phenyl-*p*-tolylglycollic acid.

Resolution of r-p-*Tolylmethylglycollic Acid.*—Hydrated quinine (28·8 g.) was dissolved in a boiling solution of the *r*-acid (15 g.) in ethyl alcohol (200 c.c.), the amount calculated for quinine trihydrate being 31·5 g. After 5 hours at the ordinary temperature, the crystals when dried under diminished pressure at 90° amounted to 28 g., and had m. p. 160—184°. These were crystallised repeatedly from ethyl alcohol : the diastereoisomeride of the (−)acid was the more sparingly soluble of the two, but the resolution was slow. The successive crops amounted to 28, 22, 15, 9·3, 5·7, 4·8, 4·3, 3·8, 3·2, and 2·3 g. respectively when dried in a vacuum at 80°, and the corresponding acids recovered from the mother-liquors gave for $[\alpha]_{5461} + 8{\cdot}6^\circ$, $+ 1{\cdot}1^\circ$, $+ 15{\cdot}4^\circ$, $+ 5{\cdot}6^\circ$, $+ 0{\cdot}9^\circ$, $- 15{\cdot}3^\circ$, $- 29{\cdot}5^\circ$, $-42{\cdot}4^\circ$, $- 47{\cdot}8^\circ$ and $- 50^\circ$ in ethyl alcohol. The final crystals (m. p. 202—204°) of the quinine salt of the (−)acid amounted to 2·3 g., and gave after acidification with dilute sulphuric acid and extraction with ether an acid (m. p. 140—142°) with $[\alpha]^{20^\circ}_{5790} - 43{\cdot}4^\circ$ and $[\alpha]^{20^\circ}_{5461} - 50{\cdot}6^\circ$ ($c = 1{\cdot}935$) in ethyl alcohol. This acid was recrystallised from ethyl alcohol–light petroleum (b. p. 80—100°).

(−)p-*Tolylmethylglycollic acid* separated in long prismatic needles, m. p. 140—142° (Found : C, 66·6; H, 6·9. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). In ethyl alcohol : $l = 2$, $c = 1{\cdot}5435$, $\alpha^{20^\circ}_{5790} - 1{\cdot}36^\circ$, $[\alpha]^{20^\circ}_{5790} - 44{\cdot}0^\circ$; $\alpha^{20^\circ}_{5461} - 1{\cdot}58^\circ$, $[\alpha]^{20^\circ}_{5461} - 51{\cdot}2^\circ$.

Action of Anisylmagnesium Bromide on Pyruvic Acid.—The Grignard reagent prepared from 66·5 g. of *p*-bromoanisole (2¾ mols.) was added gradually to a cooled ethereal solution of 11·5 g. of freshly distilled pyruvic acid (1 mol.). After 1 hour's boiling, and decomposition of the additive complex with ice and dilute sulphuric acid, the product from the ethereal layer was distilled in steam to remove dianisyl. By extraction of the residue with ether, 9·6 g. of crude acid were obtained, a further amount (7·5 g.) being got by extracting with ether the acid layer from which the ethereal layer had been removed after the disruption of the additive complex. The united solid was crystallised twice from benzene–acetone. Yield, 10·3 g.

r-Anisylmethylglycollic acid separated in silky needles, m. p. 128—129° (Found : C, 61·1; H, 6·0. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·2%). Bougault (*Bull. Soc. chim.*, 1901, **25**, 854;

Ann. Chim., 1902, **25**, 522, 544) gives m. p. 129—130°. A trace with concentrated sulphuric acid gave a cherry-red coloration somewhat darker than that exhibited by *r*-phenyl-*p*-tolylglycollic acid under similar conditions.

The acid was also prepared by the action of the Grignard reagent from 40 g. of methyl iodide (3 mols.) on an ethereal solution of 17 g. of anisoylformic acid (1 mol.) obtained by oxidising *p*-methoxyacetophenone with alkaline permanganate (McKenzie and P. D. Ritchie, *loc. cit.*). Yield, 13 g.

Both of these methods are more practical than that by the oxidation of 4-methoxyhydratropic acid (Bougault, *loc. cit.*).

When its solution in glacial acetic acid was acted on with hydriodic acid and phosphorus, the product was a compound, m. p. 210—213°, which seemed to be identical with the compound, $C_{20}H_{20}O_6$ (m. p. 215°), described by Bougault (*Compt. rend.*, 1908, **146**, 767, 844) as being formed by the action of mineral acid on 4-methoxyatropic acid.

Resolution of r-*Anisylmethylglycollic Acid.*—42·8 G. of morphine (1 mol.) were dissolved gradually in a solution of 24·9 g. of *r*-anisylmethylglycollic acid (1 mol.) in 1 l. of boiling water. The crystals (A, 33 g.) which had separated over-night in the ice-chest were collected and recrystallised seven times from boiling water, rosettes of prisms of the homogeneous morphine salt (14·9 g.) of the (—)acid being obtained. The acid (5·3 g.) got by decomposing this salt with dilute sulphuric acid and extraction with ether had m. p. 146—147° and gave in ethyl alcohol: $l = 1$, $c = 3{\cdot}997$, $\alpha_{5461}^{19\cdot5^\circ} - 2{\cdot}47^\circ$, $[\alpha]_{5461}^{19\cdot5^\circ} - 61{\cdot}8^\circ$, whereas McKenzie and P. D. Ritchie (*loc. cit.*) give m. p. 146—147° and $[\alpha]_{5461}^{25^\circ} - 61{\cdot}7^\circ$ ($c = 4{\cdot}0645$). The acid underwent partial dehydration when heated at 70° under diminished pressure owing to the formation of 4-methoxyatropic acid, which takes place more readily than does the formation of atropic acid from atrolactinic acid under similar conditions. In the determination of the specific rotatory power it is advisable to conduct the drying at the ordinary temperature under diminished pressure.

The filtrate, from which A had been removed, gradually deposited rectangular crystals (17 g.), which were crystallised twice from water. The resulting crystals (11 g.) were decomposed by dilute sulphuric acid and gave an acid, m. p. 145—146°; in ethyl alcohol $[\alpha]_{5461} + 60^\circ$ ($c = 3{\cdot}946$) This consisted of the almost pure (+)acid, but some 4-methoxyatropic acid was also present, as was shown by the action on potassium permanganate and on bromine water.

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