138. *Investigations on Alkylaconitic Acids.*

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THE influence of a carboxyl group attached to the central carbon atom on the three-carbon system should be manifested by a comparison of the properties of alkylated and dialkylated aconitic and glutaconic acids.

Methods of synthesising the former have been explored, and certain results obtained in connexion with α-methylaconitic acid and some cyanoaconitic esters. Rogerson and Thorpe's method (J., 1906, **89**, 631) gave much better yields when potassium was substituted for sodium and specially dried alcohol was used (compare Hope, J., 1922, **121**, 2216; Kon and Nanji, J., 1931, 560).

As ethyl glutaconate readily gives mono-, di-, and tri-alkyl derivatives (Henrich, *Monatsh.*, 1899, **20**, 539; Thorpe and Wood, J., 1913, **103**, 1752), the alkylation of ethyl aconitate was attempted: the ester, however, underwent self-condensation, yielding a viscous liquid.

The condensation of ethyl chlorofumarate with ethyl sodiomalonate gives ethyl *cyclo*propane-1 : 1 : 2 : 3-tetracarboxylate under ordinary conditions (Ruhemann, J., 1902, **81**, 1212) and the sodium compound of ethyl carbethoxyaconitate,

$$C(ONa)(OEt)\colon CH{\cdot}C(CO_2Et)\colon C(CO_2Et)_2$$

in presence of excess of sodium ethoxide (Bland and Thorpe, P., 1912, **28**, 131). Experiments in which 2, 2·5, or 3 mols. of sodium ethoxide were used with 1 mol. of either ethyl malonate or ethyl cyanoacetate gave hardly a 20% yield of the aconitic ester, and satisfactory results were not obtained by condensing the chlorofumaric ester with ethyl sodiomethylcyanoacetate.

It was thought that a modified extension of Lawrence's method (J., 1897, **71**, 457) might give better yields of substituted citric esters, but the condensation of either oxalacetic ester with ethyl bromopropionate or of methyloxalacetic ester with ethyl bromoacetate in presence of zinc gave equally poor yields of the condensation products.

Finally, the elimination of hydrogen bromide from monobrominated tricarballylic acid was tried, but the use of diethylaniline resulted in the formation of mainly the lactone of diethyl hydrogen α-hydroxytricarballylate and a small amount of aconitic acid. The bromination of substituted tricarballylic acids and their hydrolysis are under investigation.

Cyanoglutaconic esters resemble cyano-monocarboxylic esters in showing three-carbon tautomerism (Kon and Nanji, *loc. cit.*), and it was thought desirable to extend this observation to ethyl α-cyanoaconitate and its methyl derivatives. These esters do not distil without decomposition, and therefore could not be examined by refractometric and iodometric methods. The results of ozonolysis, however, showed that Rogerson and Thorpe's ethyl α-cyanoaconitate (I) (*loc. cit.*) was a mixture of the αβ- and the βγ-isomeride, the latter preponderating. The ester regenerated from its potassio-salt by means of benzoic acid or dry hydrogen chloride was not the

(I.) $CO_2Et{\cdot}CH(CN){\cdot}C(CO_2Et)\colon CH{\cdot}CO_2Et$

(II.) $CO_2Et{\cdot}C(CN)\colon C(CO_2Et){\cdot}CHMe{\cdot}CO_2Et$

(III.) $CO_2Et{\cdot}CH(CN){\cdot}C(CO_2Et)\colon CMe{\cdot}CO_2Et$

(IV.) $CO_2Et{\cdot}CMe(CN){\cdot}C(CO_2Et)\colon CMe{\cdot}CO_2Et$

(V.) $CN{\cdot}CMe\colon C(CO_2Et){\cdot}CHMe{\cdot}CO_2Et$

pure αβ-form (compare Hugh and Kon, J., 1930, 775), a little of the βγ-form also being present. The methylation of ethyl α-cyanoaconitate through its potassio-salt was found, by ozonolysis of the product, to give the methylated ester (II) in the pure αβ-form. Rogerson and Thorpe's isomeric ester (III), like the parent ester (I), proved to be a mixture of the βγ-form with a small quantity of the αβ-form (II). The dimethylated ester, prepared from (II) or (III), has the constitution (IV) assigned to it by Rogerson and Thorpe, for it lost ethyl carbonate on treatment with sodium ethoxide, with the formation of mainly ethyl γ-cyano-β-carbethoxy-α-methyl-Δ^{β}-pentenoate (V), oxidation of which with dilute potassium permanganate solution gave methylmalonic acid as the only isolable product. Thus the behaviour of the cyanoaconitates with regard to three-carbon tautomerism is practically identical with that of the cyanoglutaconates.

α-Methylaconitic anhydride (Rogerson and Thorpe, *loc. cit.*), hydrated under strictly specified conditions (compare Malachowski and Maslowski, *Ber.*, 1928, **61**, 2521), gave an acid, m. p. 105° : this was the *cis*-form, as it reverted to the *trans*-form, m. p. 159°, in contact with hydrochloric acid or when heated. Several attempts were made to prepare a hydroxy-anhydride : on one occasion only, a crystalline solid, m. p. 110°, was obtained in about 9% yield, which had the properties usually associated with the hydroxy-anhydrides of the glutaconic acids and gave the *trans*-acid on hydration with concentrated alkali.

EXPERIMENTAL.

Aconitic acid was prepared from citric acid by Hentschel's method (*J. pr. Chem.*, 1887, **35**, 205).

Attempted Alkylation of Ethyl Aconitate.—The ester (25 g.) was slowly added to dry sodium ethoxide (from 2·3 g. of sodium) suspended in dry ether (200 c.c.), the mixture cooled in ice for 2 hours, methyl iodide (10 c.c.) added in portions, and the whole refluxed for 12 hours. The viscid oil precipitated on acidification boiled at 225—230°/6 mm., and gave a deep red colour with alcoholic ferric chloride (Found : C, 55·6; H, 7·0. $C_{22}H_{32}O_{11}$ requires C, 55·9; H, 6·8%). It (5 g.) was heated with 10% sulphuric acid (50 c.c.) for 12 hours; the acid extracted by ether from the cooled solution crystallised from dilute alcohol in needles, m. p. 116° (Found : C, 53·8; H, 6·2; equiv., 100. $C_9H_{12}O_5$ requires C, 54·0; H, 6·0%; equiv., dibasic, 100). Neither the ester nor the acid gave a solid phenylhydrazone.

Condensation of Ethyl Chlorofumarate with Ethyl Sodiomalonate.—To a well-cooled suspension of ethyl sodiomalonate (11·5 g. of sodium, 40 g. of ethyl malonate, and 175 c.c. of absolute alcohol), ethyl chlorofumarate (52 g.) was gradually added. The mixture was kept in ice for 12 hours, the alcohol removed, and the aqueous solution extracted with ether before and after acidification. The second extract contained ethyl carbethoxyaconitate (15—20%), b. p. 205—207°/16 mm. (Found : C, 54·6; H, 6·7. Calc. for $C_{15}H_{22}O_8$:

C, 54·5; H, 6·6%), which was hydrolysed to aconitic acid, m. p. 190°, by concentrated hydrochloric acid.

Condensation of Ethyl Oxalacetate with Ethyl Bromopropionate.—A mixture of oxalacetic ester (36 g.), ethyl bromopropionate (36 g.), zinc (14 g.), and dry benzene (75 c.c.) was heated on the steam-bath for 2 hours, and again for 4 hours after the vigour of the reaction had abated; the product was then cooled, and decomposed with ice-cold sulphuric acid. *Ethyl α-methylcitrate*, extracted by ether, had b. p. 195°/15 mm. (yield, 5 g.) (Found: C, 53·6; H, 7·8. $C_{13}H_{22}O_7$ requires C, 53·7; H, 7·6%).

Monobromination of Tricarballylic Acid.—A mixture of phosphorus pentachloride (150 g.) and tricarballylic acid (44 g.) was warmed at 50—60° for 2 hours, dry bromine (15 c.c.) added, and after 24 hours the whole was poured into well-cooled absolute ethyl alcohol and heated on the water-bath for 4 hours. Ethyl α-bromotricarballylate, precipitated on dilution with water, extracted in ether, and washed with 10% sodium carbonate solution, was obtained as a colourless liquid, b. p. 210°/10 mm. (Found: Br, 23·0. Calc. for $C_{12}H_{19}O_6Br$: Br, 23·6%) (yield, 80%).

Action of diethylaniline. The bromo-ester (40 g.) was heated with diethylaniline (120 g.) on a sand-bath for 3 hours, and the cooled product poured into excess of dilute hydrochloric acid. The precipitated oil was extracted with ether, washed, dried, recovered, and fractionally distilled. Fraction (1), 5 g., b. p. 165—170°/15 mm., gave aconitic acid, m. p. 190°, on hydrolysis with concentrated hydrochloric acid. Fraction (2), 20 g., b. p. 190—195°/15 mm., and 192°/15 mm. after redistillation (Found: C, 52·0; H, 6·3. Calc. for $C_{10}H_{14}O_6$: C, 52·2; H, 6·1%), was the lactone of diethyl hydrogen α-hydroxytricarballylate.

Ethyl α-Cyanoaconitate (I).—To a cooled solution of potassium (39 g.) in dried alcohol (325 c.c.), ethyl cyanoacetate (113 g.) was added, and then ethyl oxalacetate (188 g. in portions). After the initially formed solid had dissolved, the mixture was kept for 12 hours in ice and for 3 days at room temperature, the alcohol removed in a vacuum, the aqueous solution acidified, and the precipitated oil extracted with ether. Ethyl α-cyanoaconitate had b. p. 201°/10 mm. after redistillation (yield, 65%) (Found: C, 54·9; H, 6·1. Calc. for $C_{13}H_{17}O_6N$: C, 55·1; H, 6·0%).

Oxidation. Through a solution of the ester (10 g.) in ethyl acetate (100 c.c.) ozonised oxygen was passed for 48 hours, the solvent then removed in a vacuum at the ordinary temperature, the ozonide decomposed with water, and the product dissolved in ether, washed with a dilute solution of sodium bicarbonate, dried, and recovered. On distillation under 14 mm., the following fractions were obtained: (1) 60—90°, (2) 90—110°, (3) 110—150°, (4) 160—170°, and residue. Fraction (1), which gave no colour with ferric chloride (the others gave a red colour), contained a small quantity of ethyl glyoxylate (phenylhydrazone, m. p. and mixed m. p. 156°). Fractions (2) and (3), when heated with phenylhydrazine acetate, yielded 3-carbethoxy-1-phenylpyrazolone, m. p. and mixed m. p. 181° (compare Wislicenus, *Annalen*, 1888, **246**, 321). Fraction (4) reacted with semicarbazide acetate, giving 3-*carbethoxy*-1-*carbamyl*-4-*cyanopyrazolone*, which was purified by boiling with alcohol, in which it was sparingly soluble (Found: C, 42·6; H, 3·7. $C_8H_8O_4N_4$ requires C, 42·9; H, 3·5%): a specimen prepared from ethyl oxalocyanoacetate (Bertini, *Gazzetta*, 1901, **31**, i, 586) had the same m. p. 237° (decomp.).

The identified oxidation products of ethyl α-cyanoaconitate were therefore ethyl glyoxylate, ethyl oxalacetate, and ethyl oxalocyanoacetate. The ester regenerated from the potassio-salt (prepared by Kon and Nanji's method) by means of benzoic acid in dry ether or hydrogen chloride in dry petroleum (b. p. 40—60°) gave the same products on oxidation, but a larger proportion of oxalacetic ester, and therefore contained a larger proportion of the αβ-form.

Methylation. This was done by Rogerson and Thorpe's method, potassium being used in place of sodium. The product, ethyl α-cyano-Δ^{α}-butene-αβγ-tricarboxylate (II), b. p. 191°/10 mm., was ozonised, and the product worked up, as in the case of the parent ester. Three fractions were obtained: (1) 120—130°/14 mm. (mostly at 128—129°/14 mm.); (2) 140—150°/14 mm.; (3) above 170°, unchanged ester. Fraction (1) gave a deep reddish-violet colour with ferric chloride and yielded with phenylhydrazine acetate the pyrazolone derivative, m. p. 150°, of methyloxalacetic ester (Wislicenus and Arnold, *Annalen*, 1888, **246**, 331). Fraction (2) did not give a colour with ferric chloride, and gave the phenylhydrazone of ethyl cyanoglyoxylate, m. p. and mixed m. p. 127° (compare Kon and Nanji, *loc. cit.*). The products of oxidation were therefore ethyl cyanoglyoxylate and ethyl methyloxalacetate, indicating the αβ-form for the methylated ester.

Ethyl α-Cyano-γ-methylaconitate (III).—This was prepared, like the parent ester, by condensing methyloxalacetic ester with ethyl cyanoacetate in presence of potassium (yield, 20—25%) (Found: C, 56·4; H, 6·5. Calc. for $C_{14}H_{19}O_6N$: C, 56·5; H, 6·4%).

Oxidation. The ozonised product was worked up as described before. Four fractions were obtained under 14 mm. pressure: (1) up to 70°, (2) 100—140°, (3) 140—160°, (4) above 170°. Fraction (1) gave a deep violet colour with ferric chloride and contained ethyl pyruvate (phenylhydrazone, m. p. and mixed m. p. 119°).

Fraction (2) gave a deep red colour with ferric chloride, and yielded the pyrazolone of methyloxalacetic ester, m. p. 150°, with phenylhydrazine acetate. Fraction (3) gave a red colour with ferric chloride, and gave the carbamyl-pyrazolone, m. p. 237° (decomp.), of ethyl oxalocyanoacetate. The products, therefore, were ethyl pyruvate, ethyl methyloxalacetate, and ethyl oxalocyanoacetate.

Hydration of Methylaconitic Anhydride.—The anhydride (5 g.) was added to ice-cold water (25 c.c.), the solution concentrated in a vacuum, the solid, m. p. 102—104°, obtained dissolved in cold water, and the solvent removed in a vacuum. The cis-*acid* was obtained as a microcrystalline solid, m. p. 105°, evolving gas at 170—175°. It was practically insoluble in ether and benzene (Found: C, 44·5; H, 4·1; equiv., 63. $C_7H_8O_6$ requires C, 44·7; H, 4·2%; equiv., tribasic, 62·7).

Formation of the Hydroxy-anhydride (?) *of α-Methylaconitic Acid.*—This was prepared by Bland and Thorpe's method (J., 1912, **101**, 1494). Finely powdered methylaconitic acid (10 g.) was heated with acetyl chloride (20 c.c.) and absolute chloroform (50 g.) on the water-bath for 8 hours. The undissolved residue (1 g.) was washed with chloroform, dried, and crystallised from ethyl acetate, the *anhydro-acid* (?) being obtained in small needles, m. p. 110°, evolving gas at 140°. It was sparingly soluble in most organic solvents, formed a deep yellow solution in water, and gave a reddish-brown coloration with ferric chloride (Found: C, 49·2; H, 3·6. $C_7H_6O_5$ requires C, 49·4; H, 3·5%).

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