CXLII.—*The Constitution of Guareschi's Cyano-butadiene Acids. An Attempt to Synthesise β-*iso*Propylglutaconic Acid.*

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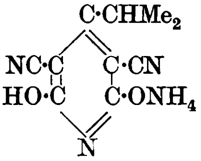
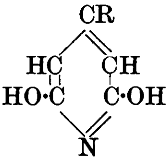
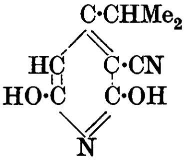
THE simplest method for preparing β-*iso*propylglutaconic acid (III), required for comparison with *cis*-homocaronic acid (J., 1928, 431), would appear to be the hydrolysis of the cyano-acid (II). According to Guareschi (*Mem. Accad. Sci. Torino*, 1907, 57, 281) this cyano-acid is formed when the ammonium salt (I) is digested with sulphuric acid.


(I.)


(IV.)


(V.)

$CN\cdot CH{:}C(CHMe_2)\cdot CH_2\cdot CO_2H$ (II.)

$HO_2C\cdot CH{:}C(CHMe_2)\cdot CH_2\cdot CO_2H$ (III.)

On reviewing the properties of this cyano-acid and a number of related acids described by Guareschi, it appeared to us unlikely that these substances could have the constitution ascribed to them and that in all probability they were the isomeric dihydroxypyridines of the general formula (IV), *i.e.*, the imides of the glutaconic acids.

The properties more especially pointing to this constitution are (i) their high melting points, (ii) their sparing solubility in organic media, (iii) their colour reactions with ferric chloride and with potassium nitrite, and (iv) their tendency to develop a blue colour on keeping : all of these are properties which have been shown by Rogerson and Thorpe (J., 1905, **87**, 1685) to be characteristic of the dihydroxypyridines.

On repeating the condensation of *iso*butaldehyde and ethyl cyanoacetate under the conditions used by Guareschi (*Atti R. Accad. Sci. Torino*, 1902, **38**, 290) we had no difficulty in preparing the ammonium salt (I) in excellent yield. When this salt was hydrolysed with sulphuric acid (60%), and the solution cooled and diluted, a small quantity of a crystalline solid, m. p. 273°, separated which was evidently 2 : 6-*dihydroxy*-3-*cyano*-4-iso*propylpyridine* (V); on removal of the excess of mineral acid with ammonia a substance was obtained which had m. p. 213—214° and was undoubtedly 2 : 6-*dihydroxy*-4-iso*propylpyridine* (IV, $R = CHMe_2$) and not the isomeric acid (II). This was established by the preparation of the *hydrochloride*, the *di*-p-*nitrobenzoyl* derivative, and the *oxime*. We did not obtain a substance of m. p. 177—178°, which according to Guareschi is the m. p. of the cyano-acid. It is probable that Guareschi actually obtained a mixture of (IV) and (V), since in our preliminary experiments we isolated a low-melting substance which crystallised well but was shown by further experiments to be a mixture.

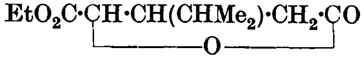
These experiments having shown that Guareschi's *iso*propylcyano-acid was a pyridine derivative, it appeared desirable to prepare the corresponding methylcyano-acid supposed to be formed by the hydrolysis of the condensation product from acetaldehyde and ethyl cyanoacetate (*Atti R. Accad. Sci. Torino*, 1900, **36**, 414). The properties of the cyano-acid resembled very closely those of the 2 : 6-dihydroxy-4-methylpyridine prepared by Rogerson and Thorpe (*loc. cit.*, p. 1689). Repetition of Guareschi's experiments has shown, as was anticipated, the product of the hydrolysis of the ammonium salt to be the dihydroxypyridine. This was characterised by the preparation of the oxime, m. p. 174°, and the dibenzoyl derivative, m. p. 94°. In agreement with Rogerson and Thorpe it has been found that both the hydrated and the anhydrous form of the dihydroxypyridine melt at the same temperature, 193—194°, and not at 199—200° and 225—227°, respectively, as observed by Guareschi.

It is to be concluded that the various cyano-acids described by Guareschi are in reality dihydroxypyridines, and confirmatory evidence of this is afforded by the melting points of the dimethyland methylethyl-dihydroxypyridines and of the isomeric cyano-acids prepared by Rogerson and Thorpe (m. p. 175° and 189°) and by Guareschi (m. p. 175—176° and 191·5—192°) respectively.

In an attempt to prepare the glutaconic acid by the removal of hydrogen bromide from *ethyl α-bromo-β-*iso*propylglutarate* (VI) by diethylaniline, the main product of the reaction was the *lactonic ester* (VII), no trace of either an unsaturated or a cyclic ester being

(VI.) $EtO_2C{\cdot}CHBr{\cdot}CH(CHMe_2){\cdot}CH_2{\cdot}CO_2Et$

(VII.)



$$EtO_2C{\cdot}\underbrace{CH{\cdot}CH(CHMe_2){\cdot}CH_2{\cdot}CO}_{O}$$

apparently formed. This ester has not been described previously, although the lævorotatory form of the lactonic acid was obtained by Semmler (*Ber.*, 1903, **36**, 1749) by the oxidation of phellandrene. The constitution of the synthetic lactone (VII) was established by its oxidation to *iso*propylsuccinic acid. In addition to the lactonic ester, a quantity of an ester with a much lower boiling point was formed by the action of diethylaniline on the bromo-ester. This was found to be ethyl *iso*propylglutarate, simple replacement of the bromine by hydrogen having occurred. Although this reaction is remarkable, it is not without analogy, since Haerdi and Thorpe (J., 1925, **127**, 1242) found that when ethyl α-bromo-β-phenylglutarate was digested with pyridine a similar reaction took place with formation of ethyl β-phenylglutarate. The mechanism of this reaction is not clear, but during the treatment of the bromo-ester with diethylaniline the formation of a volatile oil, probably ethyl bromide, was observed.

It was hoped to prepare ethyl β-hydroxy-β-*iso*propylglutarate (i) by treatment of ethyl acetonedicarboxylate with the appropriate Grignard reagent or (ii) by the condensation of ethyl *iso*butyrylacetate (Bouveault and Bougert, *Bull. Soc. chim.*, 1902, **27**, 1038) with ethyl bromoacetate in the presence of zinc. In both cases, however, the keto-group reacted in its enolic form, so rendering the experiments nugatory. It is possible that the required glutaconic acid could be prepared in poor yield by the method of Rogerson and Thorpe (*loc. cit.*) from ethyl *iso*butyrylacetate and ethyl cyanoacetate, but since the keto-ester can only be prepared with difficulty we have not investigated this reaction.

EXPERIMENTAL.

Ammonium Salt of 2 : 6-*Dihydroxy*-3 : 5-*dicyano*-4-*methylpyridine and* 2 : 6-*Dihydroxy*-4-*methylpyridine*.—The ammonium salt was prepared by Guareschi's method (*Atti R. Accad. Sci. Torino*, 1900, **36**, 454); it crystallised from water in glistening thin prisms

(Found: N, 29·4. Calc.: N, 29·2%). The dihydroxypyridine was obtained when the ammonium salt was hydrolysed with sulphuric acid (60%), and separated from the aqueous solution after removal of the excess of mineral acid with ammonia. It crystallised from hot water, in which it was somewhat readily soluble, in small glistening prisms, m. p. 193—194°, containing one molecule of water of crystallisation, which was lost at 110° without alteration of the melting point. It was not found possible to raise the m. p. to 199—200° as found by Guareschi, but in other respects our substance resembled in all particulars the cyano-acid described by him. It reacted as a monobasic acid, gave with ferric chloride a violet coloration, reduced an ammoniacal silver solution, and in alkaline solution became blue on exposure to the air (Found: H_2O, 12·9; N, 11·3; M, 125·7. Calc.: H_2O, 12·6; N, 11·2%; M, 125). Rogerson and Thorpe found that 2 : 6-dihydroxy-4-methylpyridine had similar properties, and the identity of the two substances was confirmed by the preparation of the oxime, small yellow prisms, decomp. 174—175° (R. and T. give 178°), and the dibenzoyl derivative, m. p. 94°.

Ammonium Salt of 2 : 6-*Dihydroxy*-3 : 5-*dicyano*-4-iso*propylpyridine and* 2 : 6-*Dihydroxy*-4-iso*propylpyridine.*—The ammonium salt, prepared as described by Guareschi (*Atti R. Accad. Sci. Torino*, 1902, **38**, 290), crystallised from hot water, in which it was sparingly soluble, in glistening prisms which did not melt below 295° (Found: N, 25·2. Calc.: N, 25·5%).

Preliminary experiments having shown that on hydrolysis with sulphuric acid (60%) a mixture of products was formed, the following conditions were found most convenient for their separation. A mixture of the ammonium salt (5 g.) and sulphuric acid (60% by weight; 90 c.c.) was boiled under reflux until all evolution of carbon dioxide had ceased (1·5 hours). The cooled product was mixed with water (25 c.c.), and ammonia added until a precipitate just began to form. After remaining in the ice-chest for some hours, the solid, *A* (0·25 g.), was collected, and the filtrate treated with ammonia until it was faintly acid to Congo-red. A voluminous precipitate, *B* (2·8 g.), separated and was collected. The filtrate was evaporated to dryness on the water-bath and the residual salts were extracted with alcohol, which on evaporation gave a third fraction, *C* (0·5 g.).

Fraction *A*, m. p. about 248°, crystallised from water in long glistening needles. 2 : 6-*Dihydroxy*-3-*cyano*-4-iso*propylpyridine* was found to be very sparingly soluble in water, readily soluble in alcohol, but insoluble in the ordinary organic media. From water it crystallised with one molecule of water of crystallisation, which it lost at 110° and then had m. p. 273°. With ferric chloride in aqueous solution it gave a deep purple coloration which became cherry-red on warming. It reduced an ammoniacal silver solution on warming and was readily soluble in alkalis, behaving on titration as a monobasic acid. On keeping, alkaline solutions of the hydroxy-pyridine developed a purple colour (Found : H_2O, 9·4; N, 16·0; *M*, 180·3. $C_9H_{10}O_2N_2,H_2O$ requires H_2O, 9·2%. $C_9H_{10}O_2N_2$ requires N, 15·7%; *M*, 178).

Fraction *B*, m. p. 211°, crystallised from water, in which it was very sparingly soluble, in soft needles, m. p. 213—214°. 2 : 6-*Dihydroxy*-3-iso*propylpyridine* is very sparingly soluble in all the ordinary organic solvents with the exception of methyl and ethyl alcohols. With ferric chloride its aqueous solution gives a purple coloration which disappears on warming. It reduces an ammoniacal silver solution and behaves on titration as a monobasic acid, the alkaline solution becoming purple on keeping (Found : N, 9·0; *M*, 153·5. $C_8H_{11}O_2N$ requires N, 9·2%; *M*, 153). The *hydrochloride* crystallised from concentrated hydrochloric acid in glistening plates (Found : HCl, 18·9. $C_8H_{11}O_2N,HCl$ requires HCl, 19·3%). The benzoyl derivative was a gum, but the *di*-p-*nitrobenzoyl* derivative crystallised from acetic acid in glistening slender needles, m. p. 200—201° (Found : N, 9·5. $C_{22}H_{17}O_8N_3$ requires N, 9·3%). The *oxime* was slowly deposited when an alkaline solution of the pyridine containing an excess of sodium nitrite was treated with acetic acid. It crystallised from alcohol in pale yellow leaflets, m. p. 123—124° (Found : N, 15·2. $C_8H_{10}O_3N_2$ requires N, 15·4%). It dissolved in sodium carbonate, yielding a magenta-red solution.

Fraction *C* melted indefinitely at about 190°. On digestion with a large volume of acetone a very sparingly soluble portion remained undissolved; this crystallised from water in needles, m. p. 265—270°, and was identified as the dihydroxycyanopyridine. The portion soluble in acetone gave after repeated crystallisation from water a further small quantity of the dihydroxypyridine.

Bromination of β-iso*Propylglutaryl Chloride. Ethyl* α-*Bromo*-β-iso*propylglutarate*.—β-*iso*Propylglutaric acid (30 g.) was mixed with phosphorus pentachloride (37 g.) and after the formation of the acid chloride was complete, dry bromine (28·6 g.) was gradually added, the mixture being gently warmed on the water-bath. Absorption of the bromine was complete in 4 hours. The acid chloride was poured into well-cooled alcohol and the next day ice was added. The heavy oil thus precipitated was dissolved in ether, and the ethereal solution well washed with sodium carbonate solution, dried, and evaporated. On fractionation under 28 mm., practically the whole of the residue distilled at 170—180° with slight decomposition (yield, 41 g.). For analysis the *bromo-ester* was redistilled, b. p. 178°/30 mm. (Found : Br, 22·9. $C_{12}H_{21}O_4Br$ requires Br, 25·9%).

*Action of Diethylaniline on Ethyl α-Bromo-*β-iso*propylglutarate.*—The bromo-ester (40 g.) was mixed with freshly distilled diethylaniline (60 g.) and heated at 190—200° for 8 hours. The cooled solution was poured into an excess of dilute hydrochloric acid (1 : 1), the ester extracted with ether, and the ethereal extract well washed with dilute hydrochloric acid to remove diethylaniline, dried and evaporated. On fractionation under 20 mm., the residual oil was readily separated into two main fractions, (*a*) b. p. 150—160° (10 g.) and (*b*) b. p. 165—180° (12 g.). On redistillation, (*a*) boiled very constantly at 154—155°/21 mm., and (*b*) boiled mainly at 170—180°/25 mm. In a second experiment using 52 g. of the bromo-ester from a different preparation an identical result was obtained, the two fractions being respectively 14 and 16 g.

Fraction (*a*), which contained a trace of bromine and therefore was not analysed, was hydrolysed with methyl-alcoholic potassium hydroxide solution; the acid, isolated by means of ether in the usual manner, crystallised almost completely on removal of the solvent. It was purified through the sparingly soluble calcium salt, and after crystallisation from benzene it had m. p. 101—102°. It was identified as β-*iso*propylglutaric acid by the method of mixed m. p., by analysis (Found : C, 55·5; H, 8·1. Calc. : C, 55·1; H, 8·0%), and by the preparation of the semianilide, m. p. 121°. It was observed, contrary to the statement in Beilstein's "Organische Chemie" (II, 703), that the acid is somewhat sparingly soluble in cold benzene but readily soluble in chloroform.

The filtrate from the sparingly soluble calcium salt yielded a small quantity of a liquid acid, which was added to fraction (*b*). Fraction (*b*) was hydrolysed with methyl-alcoholic potassium hydroxide solution, a sparingly soluble potassium salt separating. The acid, isolated by ether, was an oil which showed no tendency to crystallise. On treatment with acetyl chloride a small quantity of an anhydride was formed, which was separated by means of sodium bicarbonate solution and identified as β-*iso*propylglutaric anhydride. The liquid acid, recovered from the sodium bicarbonate solution, was esterified with alcohol and sulphuric acid in the usual manner. The resulting ester had b. p. 178°/26 mm., $n_D^{20°}$ 1·4466, and analysis showed it to be the *ethyl* ester of the *lactone* of dl-*α-hydroxy-*β-iso*propylglutaric acid* (Found : C, 60·3; H, 8·4. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%).

The *lactonic acid* obtained from the ester by hydrolysis was a colourless viscid oil and showed no tendency to crystallise. It was extremely readily soluble in all the ordinary organic solvents with the exception of light petroleum and gave a sparingly soluble copper salt on treatment of its aqueous solution with copper acetate. Its composition was confirmed by titration (Found : M, 171·1, 189. $C_8H_{12}O_4$ requires M, 172. $C_8H_{14}O_5$ requires M, 190). The lactonic acid, which was only slowly attacked by potassium permanganate in alkaline solution, was oxidised by lead peroxide in the presence of sulphuric acid, *dl-iso*propylsuccinic acid being formed. This had m. p. 115—116° after crystallisation from benzene, and the m. p. was not depressed by admixture with an authentic specimen of this acid for which we are indebted to Dr. Henry.

We are grateful to Dr. J. D. A. Johnson for his valuable assistance in connexion with the analytical portion of this work and we desire to express our indebtedness to the Government Grant Committee of the Royal Society for a grant which has covered most of the expenses of this investigation.

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