128. *The Chemistry of the Pyrrocolines. Part VI. The Synthesis of Pyrrocoline-2-carboxylic Acid: A New Route to Pyrrocoline.*

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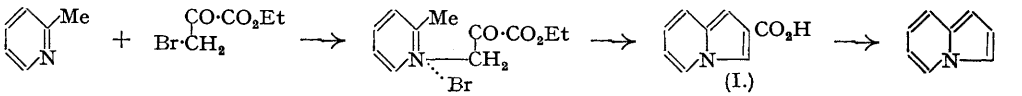
Pyrrocoline-2-carboxylic acid has been synthesised in moderate yield by the action of ethyl bromopyruvate on α-picoline and shown to be identical with the product obtained by Diels and Alder by the hydrolysis and mild decarboxylation of trimethyl pyrrocoline-1 : 2 : 3-tricarboxylate.

Although Tschitschibabin's general method for the synthesis of pyrrocolines is very useful for the preparation of the 2-alkyl and 2-aryl derivatives (Parts I and IV, *J.*, 1946, 1069, 1083) it is of little use for the direct synthesis of pyrrocoline itself. Thus with bromoacetaldehyde and α-picoline yields of not more than 1% could be obtained, and bromoacetal and dibromoparaldehyde were even less effective (Tschitschibabin, *Ber.*, 1927, **60**, 1607). The other known

syntheses of the parent base (Part I, *loc. cit.*) also afford disappointingly low yields, the original method of Scholtz (*Ber.*, 1912, **45** 734), which is the best of these, giving approximately a 10% yield from acetic anhydride and α-picoline after hydrolysis of the 1 : 3-diacetylpyrrocoline first formed.

Since Diels and Alder (*Annalen*, 1932, **498**, 16; 1933, **505**, 103) have shown that pyrrocoline-carboxylic acids are readily decarboxylated, the possibility has been examined of using Tschitschibabin's method for the preparation of *pyrrocoline-2-carboxylic acid* (I) as an indirect synthesis of the parent base.



On mixing equimolecular amounts of ethyl bromopyruvate and α-picoline a vigorous exothermic reaction ensues accompanied by much decomposition, but in boiling alcohol the reaction proceeds smoothly and in this way it has been possible to prepare the required acid in 30% yield after ring closure with aqueous sodium hydrogen carbonate in the usual way. Attempts to isolate the corresponding ethyl ester were unsuccessful, hydrolysis apparently occurring as rapidly as ring closure.

Using bromopyruvic acid with α-picoline, only low yields of pyrrocoline-2-carboxylic acid could be obtained. On heating these two reactants in alcoholic, aqueous, or acetic acid solution there was considerable evolution of gas, and, since Sobin and Bachman (*J. Amer. Chem. Soc.*, 1935, **57**, 2458) have shown that phenylbromopyruvic acid in the presence of pyridine loses carbon dioxide, it is probable that a similar reaction takes place in this case with consequent low yields of the intermediate quaternary bromide. The best results were obtained when the reaction proceeded in alcoholic solution at room temperature.

Pyrrocoline-2-carboxylic acid thus prepared has the same m. p. [240—241° (decomp.)] as the monocarboxylic acid obtained by Diels and Alder (*loc. cit.*) by the hydrolysis and mild decarboxylation of trimethyl pyrrocoline-1 : 2 : 3-tricarboxylate, and since each on treatment with diazomethane gives the same *methyl* ester their identity is established. It would appear from this result that carboxyl groups in the 1- and the 3-position of the pyrrocoline nucleus are as labile as acetyl groups similarly substituted (Part I, *loc. cit.*).

Attempts to obtain pyrrocoline-2-carboxylic acid from 2-methylpyrrocoline by fusion with potassium hydroxide in the same way that 2-methylindole and skatole have been converted to the corresponding acids (Ciamician and Zatti, *Ber.*, 1888, **21**, 1929) were unsuccessful, the 2-methylpyrrocoline being recovered for the most part unchanged.

In the preparation of pyrrocoline-2-carboxylic acid by the method of Diels and Alder an attempt was first made to synthesis the intermediate pyrrocolinetricarboxylic ester by the procedure of Diels and Meyer (*Annalen*, 1934, **513**, 129) who recorded that it could be obtained in moderate yield by the action of pyridine on a methyl-alcoholic solution of dimethyl acetylene-dicarboxylate without cooling. However, it has been possible to isolate only a compound believed to be dimethyl 1-methoxycarbomethoxymethylpyrrocoline-2 : 3-dicarboxylate in small yield by this procedure, the compound which was stated by these workers to be formed when the reaction was carried out at 0°. The required pyrrocolinetricarboxylic ester was therefore prepared by the original method of Diels and Alder (*loc. cit.*) by the oxidation of tetramethyl pyridocoline-1 : 2 : 3 : 4-tetracarboxylate with sodium dichromate in acetic acid solution.

Since Diels and Alder have successfully converted pyrrocoline-2-carboxylic acid into the parent base by heating with calcium oxide, the extension of the general method of Tschitschibabin now described affords a convenient synthesis of pyrrocoline.

Experimental.

(All m. ps. are uncorrected.)

Ethyl bromopyruvate was prepared by a modification of the method of Ward (*J.*, 1923, **123**, 2207). To ethyl pyruvate (126·4 g.) at 50°, bromine (55 c.c.) was added with stirring at such a rate that the temperature remained at 50—60° without external heating (2·5 hours). The cooled resulting yellow liquid was diluted with chloroform (500 c.c.), water (200 c.c.) added, and the mixture stirred with calcium carbonate until effervescence ceased. The separated chloroform layer was washed with a little water and dried. After removal of the solvent the residue was distilled and the fraction, b. p. 98—105°/14 mm., collected (113 g.; 54·5% yield).

Pyrrocoline-2-carboxylic Acid.—A solution of ethyl bromopyruvate (50 g.) and α-picoline (25 c.c.) in dry alcohol (200 c.c.) was heated on the steam-bath for 4 hours, and then kept at room temperature for 3 days. The alcohol was removed under reduced pressure, the residue diluted with water, and the solution extracted with chloroform to remove coloured impurities. Sodium hydrogen carbonate was

added until effervescence ceased, and the liberated α-picoline extracted with ether. To the final brown aqueous solution excess of sodium hydrogen carbonate (20 g.) was added and the mixture heated on the steam-bath for 4 hours. Whilst still warm, the solution was acidified with dilute hydrochloric acid; *pyrrocoline-2-carboxylic acid* then separated as a grey powder (12·2 g.; 29·6% yield). A solution of the crude acid, m. p. 226° (decomp.), in hot alcohol after treatment with charcoal yielded a green solution from which the acid separated as tiny buff-coloured needles when cooled rapidly or as small cubes when cooled slowly, m. p. 240—241° (decomp.) after shrinking and darkening above 215° (Found: C, 66·8; H, 4·2; N, 9·1. $C_9H_7O_2N$ requires C, 67·1; H, 4·4; N, 8·7%).

The same compound was obtained in a less pure state in 13·8% yield by the reaction of bromopyruvic acid (Ward, *loc. cit.*) (10 g.) with α-picoline (6·0 c.c.) in dry alcohol (20 c.c.) at room temperature for 7 days. The m. p. of either specimen was not depressed on admixture with the pyrrocolinecarboxylic acid prepared from trimethyl pyrrocoline-1 : 2 : 3-tricarboxylate.

Methyl Pyrrocoline-2-carboxylate.—A solution of the acid (0·5 g.) in dry dioxan (20 c.c.) was mixed with an ethereal solution of diazomethane in the usual way. After removal of excess of the reagent and the solvents under reduced pressure, the buff-coloured residue separated from aqueous alcohol as colourless tiny platelets of the *ester*, m. p. 97—99° after sintering at 90° (Found: C, 68·2; H, 5·3; N, 7·9. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1; N, 8·0%).

Reaction of Dimethyl Acetylenedicarboxylate with Pyridine in Methyl-alcoholic Solution.—To a solution of dimethyl acetylenedicarboxylate (Moureu and Bongrand, *Ann. Chim. Phys.*, 1920, **14**, 11) (16·5 c.c.) in dry methyl alcohol (45 c.c.), dry pyridine (9 c.c.) was added in four portions. A vigorous reaction set in at first but moderated towards the end of the addition. No solid separated from the resulting red-brown solution after 2 days in the ice-chest. On dilution with water (75 c.c.) a red-brown oil was deposited from which a mass of crystals separated after 1 day. The crude solid (1·27 g.) after being washed with a little methyl alcohol was recrystallised from this solvent; the suspected dimethyl 1-methoxycarbomethoxymethylpyrrocoline-2 : 3-dicarboxylate was thus obtained as colourless needles, m. p. 138—139·5° (*lit.*, m. p. 142—143°), largely depressed on admixture with the trimethyl ester prepared by the method of Diels and Alder (Found: C, 57·2; H, 5·3; N, 4·4. Calc. for $C_{16}H_{17}O_7N$: C, 57·3; H, 5·1; N, 4·2%).

The above suspected methoxy-ester reacted readily with nitric acid in acetic acid solution under the conditions described by Diels and Meyer (*loc. cit.*) to give dimethyl 1-nitropyrrocoline-2 : 3-dicarboxylate, m. p. 160—161° (*lit.*, m. p. 165°) (Found: C, 52·3; H, 3·8; N, 10·4. Calc. for $C_{12}H_{10}O_6N_2$: C, 51·8; H, 3·6; N, 10·1%). After similar treatment trimethyl pyrrocoline-1 : 2 : 3-tricarboxylate was recovered unchanged.

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