142. *Synthetical Experiments relating to Carpaine. Part II.*

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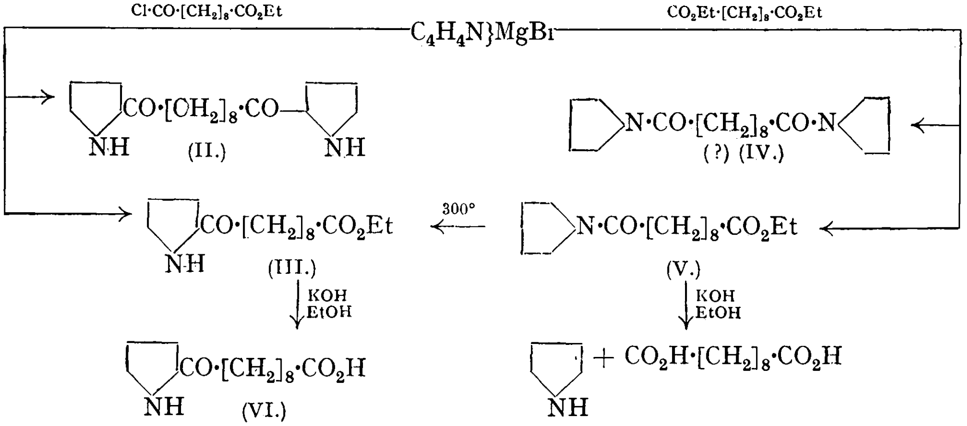
A simple test-case for the applicability of Löffler's *N*-alkylpyrrolidine synthesis (*Ber.*, 1909, **42**, 3427, 3431) to the long-chain aliphatic series has been examined with unpromising results.

N-*Bromo*-11-*methylaminoundecoic acid*, $NMeBr\cdot[CH_2]_{10}\cdot CO_2H$ (I), has been obtained as an oil and found to suffer extensive decomposition when treated with sulphuric acid. We have therefore devoted attention to the interaction of pyrrylmagnesium bromide with ethyl sebacate and with the ester chloride of sebacic acid with the object of isolating C_{14}-substances including a normal carbon chain and an α-substituted terminal pyrrole nucleus. The results are summarised below :



The *ester* (III), or an analogue derived from some other dibasic acid, may subsequently become an intermediate in a synthesis of carpamic acid.

These results are not quite what might have been anticipated, since Tschelinzeff and Terentjeff (*Ber.*, 1914, **47**, 2647, 2652) found that pyrrylmagnesium bromide reacted with ethyl acetate, ethyl propionate, and ethyl butyrate with formation of α-pyrryl alkyl ketones in 50—60% yields. Ethyl carbonate, however, afforded ethyl pyrrole-*N*-carboxylate (Tschelinzeff and Karmanov, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 161, 197).

EXPERIMENTAL.

N-*Bromo*-11-*methylaminoundecoic Acid* (I).—11-Bromoundecoic acid was heated at 100—120° for 5 hours with 33% alcoholic methylamine (10 mols.) as described by Flaschenträger (*Z. physiol. Chem.*, 1930, **192**, 245), but when the alcohol and methylamine were removed by distillation on the steam-bath (finally in a vacuum) and the residue was poured into a large volume of water, a gelatinous precipitate was obtained instead of the crystalline amino-acid. The amino-acid was therefore isolated as its *hydrochloride* by distilling most of the alcohol and methylamine from the reaction mixture, acidifying the remainder with hydrochloric acid, evaporating it to dryness in a vacuum, and extracting the dry residue with boiling acetone. A little methylamine hydrochloride remained undissolved and the filtrate deposited the hydrochloride of the base. This was recrystallised from acetone containing a little water and washed with ether; m. p. 105—105·5° (Found : N, 5·3. $C_{12}H_{25}O_2N,HCl$ requires N, 5·6%. $C_{12}H_{25}O_2N,HCl,H_2O$ requires N, 5·2%). The free amino-acid, liberated by the successive action of silver oxide and hydrogen sulphide, melted at 136—137° as described by Flaschenträger. The yield was 24% and the same yield was obtained when the reaction product was worked up by successive treatment with barium hydroxide, sulphuric acid, silver oxide, and hydrogen sulphide (Flaschenträger reports a yield of 74—76%). Contrary to Flaschenträger's statement, the acid is soluble in dilute aqueous ammonia (also in aqueous methylamine).

An ice-cold suspension of the finely powdered hydrochloride (2·62 g.) in chloroform (20 c.c.) was shaken vigorously with sodium hypobromite solution (2 mols. from 1·6 g. of sodium hydroxide, 15 c.c. of water, and 3·2 g. of bromine). The solid rapidly dissolved and after ½ hour at 0° the chloroform solution was washed with ice-water and dried at 0° over sodium sulphate, and the solvent removed below 30°. A portion of the viscous, light brown oil so obtained was suspended in aqueous potassium iodide, acidified with acetic acid, and titrated with thiosulphate (0·5879 g. required 40·25 c.c. of 0·1*N*-thiosulphate. Found : Br, 27·4. $C_{12}H_{24}O_2NBr$ requires Br, 27·2%). The oil was unstable and in presence of moist solvents rapidly decomposed with regeneration of the amino-acid. Attempts to produce a pyrrolidine by the action of concentrated sulphuric acid at — 15°, 0°, or at room temperature resulted in the liberation of hydrogen bromide and bromine and in carbonisation. A little amino-acid could be recovered from the reaction mixture.

9-Carbethoxynonoyl chloride, $EtO_2C{\cdot}[CH_2]_8{\cdot}COCl$, was prepared as described by Robinson and Robinson (J., 1925, **127**, 177). The yield of product, b. p. 175—178°/19—20 mm. or 139°/1 mm., was 96%.

9-2′-*Pyrroylnonoic Acid* (VI).—Pyrrylmagnesium bromide (prepared from 4·3 g. of pyrrole, 1·54 g. of magnesium, and 7 g. of ethyl bromide in ether) (Oddo, *Gazzetta*, 1909, **39**, 649) was slowly added to an ice-cold solution of 9-carbethoxynonoyl chloride (15·9 g.; 1 mol.) in ether (16 c.c.) in an atmosphere of hydrogen (to prevent rapid aerial oxidation of pyrrylmagnesium bromide). Next day the mixture was heated on the steam-bath for 1 hour. The reaction mixture, which consisted of a thick black tar and an almost colourless, ethereal solution, was shaken with saturated aqueous ammonium chloride and ice until the whole of the black complex had been decomposed and the products passed into the ether. The ethereal solution was washed repeatedly with water and dried over sodium sulphate, the solvent removed, and the residue distilled in a high vacuum ($<$ 1 mm.): (1) Ethyl hydrogen sebacate passed over at 155—175°; (2) a mixture of this ester with ethyl pyrroylnonoate distilled between 175° and 190°; (3) the pyrroylnonoic ester passed over between 190° and 210° and mainly at 190—200°; (4) a small quantity of a solid distilled above 210°. Fractions (2) and (3) were dissolved in ether, repeatedly extracted with dilute sodium carbonate solution and dried, and the solvent evaporated. Recrystallisation of the residue from light petroleum (b. p. 40—60°) by cooling in a freezing mixture afforded long white needles, m. p. 28° (Found: N, 5·1. $C_{16}H_{25}O_3N$ requires N, 5·0%). The yield of this *ethyl* 9-2′-*pyrroylnonoate* (III) varied from 20% to 55% of the theoretical calculated on the pyrrole employed. Saponification of this ester with 0·5*N*-alcoholic potash afforded the corresponding *acid* and very vigorous treatment with the reagent did not remove the side chain. The acid is very readily soluble in acetic acid, acetone, ether and ethyl acetate, slightly less soluble in benzene and chloroform, considerably less so in methyl alcohol, and almost insoluble in light petroleum. It is best recrystallised from 60% alcohol, from which it separates in small, white, clustered needles, m. p. 85—85·5° (Found: C, 66·9; H, 8·8; N, 5·5. $C_{14}H_{21}O_3N$ requires C, 66·9; H, 8·4; N, 5·6%).

Attempts to prepare a semicarbazone of the ester by the usual method failed and resulted in the production of a green solution; on heating, hydrazodicarbonamide was precipitated.

Reduction of the acid in acetic acid solution in the presence of platinum oxide at 2 atmospheres pressure caused the separation of long white needles (after the absorption of *ca.* 2H). These subsequently dissolved and although 6H were absorbed, the product was entirely resinous. Reduction of the ester with sodium and absolute alcohol produced a bright red, sticky resin.

1 : 8-*Di*-2′-*pyrroyloctane* (II).—This is the by-product contained in fraction (4) above. It is produced in larger quantity if the 9-carbethoxynonoyl chloride is added to the pyrrylmagnesium bromide. It separates from hot alcoholic solutions in thin, irregular, rhomboidal plates, m. p. 138° (Found: C, 71·9; H, 8·2; N, 9·6. $C_{18}H_{24}O_2N_2$ requires C, 72·0; H, 8·0; N, 9·3%). It is very difficult to free this *substance* from an impurity which gives the pine-splinter reaction when boiled with concentrated aqueous potassium hydroxide, but the pure substance is recovered unchanged after 4 hours' digestion with 5*N*-alcoholic potash. Hence it would appear to be the diketone, but since (i) the carbethoxynonoyl chloride employed in the preparation had a sharp b. p. and was free from sebacyl chloride, and (ii) it was found that ethyl sebacate reacts with pyrrylmagnesium bromide to yield *N*-substituted pyrroles, it may be formed by rearrangement of *N*-(9-2′-pyrroylnonoyl)pyrrole during the distillation.

N-9-*Carbethoxynonoylpyrrole* (V).—Pyrrylmagnesium bromide (from 3·5 g. of magnesium, 16·3 g. of ethyl bromide, 10 g. of pyrrole, and 95 c.c. of ether) was slowly added (ice-cooling, hydrogen atmosphere) to a solution of ethyl sebacate (48·4 g.; 1·25 mols.) in ether (50 c.c.); the mixture was kept for 4 hours and then heated on the steam-bath for 2 hours. The heavy green layer disappeared when the product was shaken with ice and ammonium chloride. The ethereal solution was washed with water and dried, and the solvent removed. A small quantity of pyrrole was recovered by distillation at 20 mm. and the residue was distilled in a high vacuum ($<$ 1 mm.): (1) Ethyl sebacate (30 g.) distilled at 153—160°, followed by (2) a fraction which mostly passed over at 185—190° and (3) a small fraction (*ca.* 1 g.) which solidified immediately in the receiver. Fraction (2) was recrystallised from boiling light petroleum (b. p. 40—60°), a small insoluble portion being identical with the solid obtained from fraction (3). The long, white prisms so obtained had m. p. 43° (Found: C, 68·8; H, 8·9; N, 5·1. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0; N, 5·0%) (yield, 30% on the pyrrole).

Saponification of the *ester* with 5*N*-alcoholic potash afforded an acid which, after recrystallisation from formic acid, melted at 133°, alone or mixed with sebacic acid.

When the ester was boiled gently in an atmosphere of hydrogen, there was no change after the first hour, but between the second and third hour a transformation occurred (probably suddenly) in which three-quarters of the material resinified. Extraction of the residue with light petroleum furnished ethyl 9-2′-pyrroylnonoate, m. p. 28°, which on saponification afforded 9-2′-pyrroylnonoic acid, m. p. 85—85·5° alone or after admixture with the acid prepared by the direct process. Fraction (**3**) above separated from boiling alcohol in glistening rhombic plates, m. p. 107—107·5°. It yielded pyrrole (intense pine-splinter reaction) when heated with concentrated aqueous potassium hydroxide and so is probably (IV), but it has not been further investigated.

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