141. *Synthetical Experiments relating to Carpaine. Part I. Synthesis of a Basic Long-chain Lactone.*

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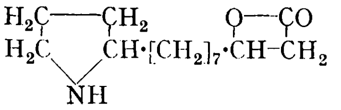
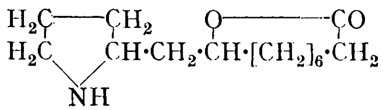
According to Barger, Girardet, and Robinson (*Helv. Chim. Acta*, 1933, **16**, 90), carpaine might be (I) or (II); more recently, formulæ such as (III) have come into consideration.

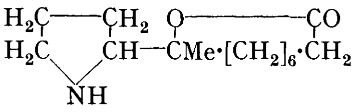
(I.)



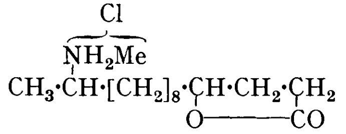
(II.)



(III.)



(IV.)



In any case, carpaine is certainly the lactone of a hydroxyimino-acid (carpamic acid) of the fatty series and it was of interest to prepare such a compound in order to examine its properties.

The starting point was 4-keto-Δ^{13}-tetradecenoic acid, $CH_2{:}CH{\cdot}[CH_2]_8{\cdot}CO{\cdot}[CH_2]_2{\cdot}CO_2H$, which was prepared by the method of G. M. Robinson (J., 1930, 749) and treated with hydrogen bromide in toluene solution with the formation of a homogeneous product. This proved to be the sec.-*bromide*, $CH_3{\cdot}CHBr{\cdot}[CH_2]_8{\cdot}CO{\cdot}[CH_2]_2{\cdot}CO_2H$, because, after replacement of the bromine by hydroxyl and oxidation by means of chromic acid, it afforded 4 : 13-*diketotetradecoic acid*, $CH_3{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO{\cdot}[CH_2]_2{\cdot}CO_2H$. Interaction of the above bromo-acid with methylamine gave 13-methylamino-4-ketotetradecoic acid, which was isolated in the form of a *hydrochloride*, $CH_3{\cdot}CH(NH_2MeCl){\cdot}[CH_2]_8{\cdot}CO{\cdot}[CH_2]_2{\cdot}CO_2H$. On reduction with sodium amalgam, the corresponding *hydroxy-acid* was obtained, and this passed into the *lactone salt* (IV) in hydrochloric acid solution.

One very interesting point of analogy with carpamic acid and carpaine was noted. Carpamic acid and the synthetical hydroxy-acid are tasteless, whereas carpaine and the lactone (IV) are intensely bitter.

Attempts to apply Löffler's *N*-methylpyrrolidine synthesis (*Ber.*, 1909, **42**, 3427, 3431) to the methylamino-acids were unsuccessful.

Experimental.

13-*Bromo*-4-*ketotetradecoic Acid*.—A solution and suspension of ketotetradecenoic acid in twice its weight of dry toluene was saturated with hydrogen bromide at 0°. After a few hours the excess of hydrogen bromide was eliminated by heating on the steam-bath, and the solvent distilled, finally under diminished pressure. The residue crystallised on cooling and separated from light petroleum in voluminous threads, which shrank on drying, m. p. 56° after sintering at 53° (Found : C, 52·9; H, 7·8; Br, 24·2. $C_{14}H_{25}O_3Br$ requires C, 52·3; H, 7·9; Br, 24·9%). The *substance* is freely soluble in acetone or benzene, and readily soluble in hot light petroleum, much more sparingly so in the cold solvent. The yield was almost theoretical and the whole product had f. p. 53·5° and thus appeared to be homogeneous.

4 : 13-*Diketotetradecoic Acid*.—Bromoketotetradecoic acid (6·4 g.) was neutralised by *N*-sodium hydroxide, and the solution mixed with an excess of freshly precipitated silver hydroxide and heated on the steam-bath. After addition of *N*-sodium hydroxide (20 c.c.), the filtered solution was acidified, the precipitated acid taken up in benzene, and the dried solution concentrated; the *hydroxy-acid* precipitated by means of light petroleum crystallised from benzene in small prisms, m. p. 63—64° (Found : C, 65·2; H, 10·3. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%). This acid gives the iodoform reaction. Its constitution was confirmed by oxidation to a diketone.

A mixture of the hydroxy-acid (1 g.), acetic acid (20 c.c.), and chromic anhydride (1 g.) was kept for 2—3 days and then gently heated. The precipitate thrown down on the addition of water was collected, dried, and twice crystallised from benzene, forming microscopic needles,

m. p. 95·5° (Found : C, 65·5; H, 9·4. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%). The *acid* does not reduce ammoniacal silver solutions, but in the presence of sodium hydroxide a silver mirror is obtained. This does not denote an aldehyde, because the hydroxy-acid exhibits the same behaviour.

13-*Methylamino*-4-*ketotetradecoic Acid Hydrochloride*.—A solution of bromoketotetradecoic acid (6·4 g.) in a large excess of alcoholic methylamine (33%) was heated at 100° in a sealed tube for 6 hours and then concentrated to a syrup. In later operations, the details of which are probably unnecessarily complicated, we removed unchanged bromo-acid by extraction from an acid solution, rendered the free amino-acid to ether, and eventually prepared the *hydrochloride*. The solution of this salt was evaporated to dryness on the steam-bath, and the residue crystallised from acetone (Found : C, 58·3; H, 9·7; N, 4·5; Cl, 11·6. $C_{15}H_{29}O_3N,HCl$ requires C, 58·5; H, 9·8; N, 4·6; Cl, 11·5%).

13-*Methylamino*-4-*hydroxytetradecoic Acid*.—Methylaminoketotetradecoic acid hydrochloride was reduced in aqueous solution by means of an excess of 3% sodium amalgam on the steam-bath for 3 hours. The solution was acidified with hydrochloric acid and evaporated to dryness, and the product isolated by extraction of the residue with acetone. The crude substance obtained on removal of the solvent could not be crystallised; it was treated in aqueous solution with freshly precipitated silver carbonate, hydrogen sulphide passed into the filtered solution, and the liquid again filtered and evaporated to dryness. The residue crystallised from alcohol and was then colourless, m. p. 153° (Found : C, 65·8; H, 11·3; N, 5·0. $C_{15}H_{31}O_3N$ requires C, 65·9; H, 11·4; N, 5·1%). This *amino-acid* is readily soluble in water and alcohol, sparingly soluble in acetone and ether, and is tasteless. When it is suspended in water and a few drops of 1% hydrochloric acid, the solution formed is tasteless; in a few seconds a bitter taste becomes apparent and after heating and cooling the solution is intensely bitter; this proves that the hydrochloride of the hydroxy-acid is not bitter.

For the preparation of the substance it suffices to heat 13-bromo-4-ketotetradecoic acid with 33% alcoholic methylamine in a pressure bottle at 100°, acidify the product with hydrobromic acid, remove unchanged acid with ether, neutralise the aqueous solution with sodium hydroxide, and reduce the keto-acid at 100° with 3% sodium amalgam, carbon dioxide being passed through the liquid. The liquid is then neutralised with hydrobromic acid and evaporated, the residue extracted with acetone, and the crude product treated with silver carbonate as already mentioned.

The hydroxy-acid (2·698 g.), dried at 110°, was dissolved in the calculated volume of *N*-hydrochloric acid, and the solution evaporated to dryness. The solid product weighed 2·943 g. (theo. wt., 3·058 g. for simple salt formation and 2·880 g. for lactone formation). When heated with acetic anhydride at 100°, the substance formed an acetyl derivative insoluble in aqueous sodium carbonate and hence was probably the lactone (IV). The salt is intensely bitter.

The *hydrobromide* was soluble in chloroform and on the addition of a few drops of light petroleum separated as an oil that crystallised on keeping at 0°. The colourless plates were hydrated and exhibited no sharp m. p. (Found in material dried at 100° in a high vacuum : C, 53·9; H, 9·1. $C_{15}H_{29}O_2N,HBr$ requires C, 53·6; H, 8·9%).

Attempts to isolate the free lactone failed, as even the mildest methods (such as shaking an aqueous solution with silver carbonate) afforded the hydroxy-acid.

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