CXXXVIII.—*New Derivatives of Aminolauronic Acid.*

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THE following research was undertaken with the view of preparing, by substituting aminolauronic acid for anthranilic acid in the well-known indigotin synthesis, the camphor analogue of indigotin, $C_8H_{14} \begin{smallmatrix} \text{CO-} \\ \text{NH} \end{smallmatrix} \text{C:C} \begin{smallmatrix} \text{CO-} \\ \text{NH} \end{smallmatrix} C_8H_{14}$. The special object of the work was the preparation of a series of optically active compounds corresponding with those obtained as intermediate products in the conversion of anthranilic acid into indigotin. For example, the analogues of indoxyl and indigo-white would be :

respectively, and it was hoped that the polarimetric study of these substances under different conditions would throw some light on the tautomeric changes undergone by compounds of this type.

Unfortunately it was found impossible to effect the desired synthesis on the lines indicated, but in the course of the work several new derivatives of aminolauronic acid have been prepared, which are not without interest and are here described.

Aminolauronic acid (Noyes, *Amer. Chem. J.*, 1896, **16**, 506) was found to undergo condensation with monochloroacetic acid, giving *carboxymethylaminolauronic acid*, $CO_2H \cdot C_8H_{14} \cdot NH \cdot CH_2 \cdot CO_2H$ (m. p.

183—184°), which on fusion lost one molecular proportion of water, and gave a monobasic acid melting at 142—143°. The two possible formulæ for the latter substance are therefore :

Of these alternatives, only a compound corresponding with formula (I) is suitable for the suggested synthesis. The elimination of the carboxyl group was effected by dry distillation of the barium salt of the acid intimately mixed with barium hydroxide. The orange-coloured oily product thus obtained slowly solidified to a dark red wax, which gave analytical figures agreeing with those calculated for $\text{C}_{10}\text{H}_{17}\text{ON}$, and therefore has the constitution

As no derivative corresponding with a nitrosoamine could be obtained from the substance by the action of nitrous acid, its structure is probably that indicated by formula (IV); moreover, on heating the compound with concentrated hydrochloric acid in a sealed tube, no trace of ammonium chloride was formed. It follows that the product obtained on fusing carboxymethylaminolauronic acid must have the constitution represented by formula (II) above, and is therefore *N-anhydrocarboxymethylaminolauronic acid*. The product of the subsequent distillation with barium hydroxide will thus be *N-anhydro-methylaminolauronic acid*.

This result, although it excludes the possible synthesis of "camphor-indigo" on the lines suggested, is not altogether in disagreement with that obtained in the indigotin synthesis from anthranilic acid, as it must be remembered that aminolauronic acid may be regarded as a meta-substitution derivative of a pentamethylene ring, whereas, on the other hand, anthranilic acid is an ortho-derivative of benzene. The essential differences in type are shown below :

Adopting the above skeleton formulæ, the products obtained from each by condensation with monochloroacetic acid are respectively :

and

	Solvent.	$[\alpha]_D$.
Aminolauroic acid hydrochloride.....	Water	+ 26.1°
" "	Alcohol	+ 26.6
Carboxymethylaminolauroic acid	Water	+ 45.7
<i>N</i> -Anhydrocarboxymethylaminolauroic acid	Water	- 22.2
" "	Alcohol	- 11.6

Attempts have also been made to prepare a camphordiamine ($\text{NH}_2 \cdot \text{C}_8\text{H}_{14} \cdot \text{NH}_2$), that is, camphoric acid in which both carboxyl groups have been displaced by amino-groups. A compound of this nature would, presumably, prove available as an active base suitable for use in resolutions, and several attempts have already been made to prepare the substance (Wootton, *Trans.*, 1907, **91**, 1890; Noyes, *Ber.*, 1894, **27**, 918). The latter tried to obtain the compound by the action of ammonia on diethyl camphorate, his intention being to treat the product of the reaction with sodium hypobromite. He found, however, that ammonia was without action on the camphorate even at 150° . Aminolauronic acid appeared to be a more suitable source of the diamine, as one of the necessary amino-groups is already present. Attempts were thus made to esterify aminolauronic acid by standard methods, but without success. However, the benzoyl derivative, which was easily prepared when treated with dry silver oxide and methyl iodide, yielded the corresponding ethereal salt, $\text{CO}_2\text{Me} \cdot \text{C}_8\text{H}_{14} \cdot \text{NHBz}$, as a crystalline solid melting at $88\text{--}89^\circ$. As in the case of diethyl camphorate, it was found that ammonia was without action on this substance, and it thus appears that the alkyloxy-groups in the ethereal camphorates and allied compounds are peculiarly stable towards ammonia.

Another attempt was made to prepare the acid amide of benzoylaminolauroic acid through the medium of the acid chloride. It was found, however, that phosphorus pentachloride simply extracted a molecule of water from the acid, giving *N-anhydrobenzoylaminolauroic*

acid, $C_8H_{14} \begin{smallmatrix} \text{CO} \\ \diagup \\ \text{N} \end{smallmatrix} \text{Bz}$. This ring-formation was again accompanied by a pronounced change in optical activity.

	Solvent	$[\alpha]_D^{15}$.
Benzoylaminolauronic acid	Alcohol	-18.4°
Methylbenzoylaminolauronate	Alcohol	-28.9
N-Anhydrobenzoylaminolauronic acid.....	Alcohol	-69.1

EXPERIMENTAL.

Aminolauronic Acid Hydrochloride.

This compound has already been described by Noyes (*loc. cit.*), but as the following method of preparation seems in many ways an improvement on the original process, it is described in detail.

Finely powdered camphoric anhydride (100 grams) was dissolved with constant shaking in one litre of concentrated ammonia solution. The clear liquid so obtained was freed from excess of ammonia by heating at 20°/15 mm., and then rendered acid by the addition of hydrochloric acid. The precipitated camphoramic acid weighed 100 grams (Auwers and Schnell, *Ber.*, 1893, 26, 1522).

This crude product was converted into aminolauronic acid according to Noyes' directions, sodium hypochlorite being, however, used in place of sodium hypobromite.

Cold solutions of camphoramic acid (1 mol.) and sodium hypochlorite (1 mol.) in sodium hydroxide (3 mols.) were gradually mixed, and the mixture heated for a short time on a water-bath. After cooling, the liquid was acidified with concentrated hydrochloric acid (4 mols.), the solvent removed at 30°/15 mm., and the residue extracted several times with boiling alcohol—preferably in a Soxhlet's apparatus. The alcoholic extract was evaporated to dryness at 25°/15 mm., and the crystalline residue purified by dissolving it in hot water and adding excess of acetone. By this means 70 grams of pure aminolauronic acid hydrochloride (m. p. 303°) were obtained from 100 grams of camphoramic acid.

The specific rotation of the compound was determined both in aqueous and in alcoholic solution :

Solvent.—*Water* : $c = 1.437$, $l = 2$, $\alpha + 0.75^\circ$, $[\alpha]_D^{15} + 26.1^\circ$.
 „ *Alcohol* : $c = 1.335$, $l = 2$, $\alpha + 0.71^\circ$, $[\alpha]_D^{15} + 26.6^\circ$.

Carboxymethylaminolauronic acid, $CO_2H \cdot C_8H_{14} \cdot NH \cdot CH_2 \cdot CO_2H$.

Fifty-five grams of aminolauronic acid hydrochloride (1 mol.) and 26 grams of monochloroacetic acid (1 mol.) were dissolved in 320 c.c. of a 10 per cent. solution of sodium hydroxide (3 mols.), and the mixture

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gently boiled on a glycerol bath for five hours. After cooling and acidifying with hydrochloric acid, the product was precipitated as a crystalline powder, which was purified by recrystallisation from methyl alcohol containing a little water. Yield 50 grams. The compound is readily soluble in water, but sparingly so in organic media.

It crystallises with two molecules of water of crystallisation :

0.3483 lost 0.0442 at 110° . $H_2O = 12.7$.

$C_{11}H_{19}O_4N, 2H_2O$ requires $H_2O = 13.3$ per cent.

Analysis of a specimen dried at 110° gave :

Found, C = 57.5 ; H = 8.43 ; N = 6.07.

$C_{11}H_{19}O_4N$ requires C = 57.6 ; H = 8.30 ; N = 6.01 per cent.

Solvent.—*Water* : $c = 1.445$, $l = 2$, $\alpha + 1.32^{\circ}$, $[\alpha]_D^{18} + 45.7^{\circ}$.

On heating the compound, it fuses with effervescence at about 183° , the melting point being rendered indefinite by conversion into the anhydro-acid now described.

N-Anhydrocarboxymethylaminolauronic Acid,

In order to determine quantitatively the amount of water eliminated by the above fusion, a weighed quantity of carboxymethylaminolauronic acid was heated in a short glass tube at 180 — 190° in a current of carbon dioxide, and the evolved water collected and weighed :

1.1270 lost 0.0882 $H_2O = 7.82$.

$C_{11}H_{19}O_4N$ requires for loss of 1 mol. of water, $H_2O = 7.86$ per cent.

The residue crystallised on cooling in fan-shaped aggregates, which, on recrystallisation from a mixture of benzene and petroleum, melted at 142 — 143° . The compound is readily soluble in water, alcohol ether, acetone, or benzene, sparingly so in petroleum of either low or high boiling point :

Found, C = 62.3 ; H = 8.15.

$C_{11}H_{17}O_3N$ requires C = 62.5 ; H = 8.06 per cent.

Solvent.—*Water* : $c = 1.465$, $l = 2$, $\alpha - 0.65^{\circ}$, $[\alpha]_D^{19} - 22.2^{\circ}$.

„ *Alcohol* : $c = 1.503$, $l = 2$, $\alpha - 0.35^{\circ}$, $[\alpha]_D^{19} - 11.6^{\circ}$.

„ *Benzene* : $c = 1.239$, $l = 2$, $\alpha - 0.55^{\circ}$, $[\alpha]_D^{19} - 22.2^{\circ}$.

N-Anhydromethylaminolauronic acid,

N-Anhydrocarboxymethylaminolauronic acid (1 mol.) was converted into the barium salt by mixing an aqueous solution with excess of

barium hydroxide (3 mols.) and rapid evaporation to dryness. In this way an intimate mixture of the salt with barium hydroxide was obtained, and this was subjected to distillation in a current of nitrogen. During the process the temperature was gradually raised to 300° . A yellowish-red oil was thus obtained, which gradually solidified to a wax. This substance could not be purified by distillation under diminished pressure, but a sample was obtained for analysis by dissolving in anhydrous ether, filtration, and removal of the solvent on a water-bath. The red, oily residue again gradually solidified, exposure to sunlight deepening the red colour very considerably:

Found, C = 71.5; H = 9.90; N = 8.67.

C = 71.6; H = 10.00; N = 8.36.

$C_{10}H_{17}ON$ requires C = 71.8; H = 10.18; N = 8.38 per cent.

The above constitution of the compound was indicated by the fact that it failed to give a nitrosoamine when acted on with nitrous acid under different conditions. Partial reaction seemed to take place, as the carbon-content of the oily product of the reaction was lowered in different experiments to about 64 per cent. Nitrogen estimations showed, however, that nitrosoamine formation had not taken place, and the result recorded above seems therefore due to oxidation. The above constitution was also supported by the fact that, on heating the compound in a sealed tube with concentrated hydrochloric acid for eight hours at $150-160^{\circ}$, no ammonium chloride was detected in the product.

Benzoylaminolauronic acid, $CO_2H \cdot C_8H_{14} \cdot NH \cdot CO \cdot C_6H_5$.

Fifty grams of aminolauronic acid hydrochloride (1 mol.) were dissolved in 300 c.c. of a 10 per cent. solution of sodium hydroxide (3 mols.), and 35 grams of benzoyl chloride (1 mol.) added gradually with constant shaking. When the reaction was complete, the liquid was acidified with hydrochloric acid, the precipitated benzoyl derivative collected, and recrystallised from 80 per cent. alcohol. The compound crystallises in small prisms, melting at 204° . Yield, 60 grams:

Found, C = 69.8; H = 7.59.

$C_{16}H_{21}O_3N$ requires C = 69.8; H = 7.63 per cent.

Solvent.—*Alcohol*: $c = 1.115$, $l = 2$, $\alpha - 0.41^{\circ}$, $[\alpha]_D^{20} - 18.4^{\circ}$.

N-Anhydrobenzoylaminolauronic acid,

With the view of preparing the acid chloride of benzoylaminolauronic acid, 3.5 grams of the latter (1 mol.) were finely powdered, mixed with 20 c.c. of acetyl chloride, and 2.8 grams of phosphorus pentachloride (1 mol.) added. A clear solution was thus obtained. On evaporating off the solvent, an oil remained, which, after distillation at 250°/15 mm., crystallised. Yield, 2.5 grams. On purification by recrystallisation from petroleum of high boiling point, the substance melted at 71—72°. It is readily soluble in alcohol, ether, acetone, or benzene, sparingly so in water or petroleum:

Found, C = 74.7; H = 7.42.

$\text{C}_{16}\text{H}_{19}\text{O}_2\text{N}$ requires C = 74.7; H = 7.40 per cent.

Solvent.—*Alcohol*: $c = 1.476$, $l = 2$, $\alpha = -2.04^\circ$, $[\alpha]_D^{18} = -69.1^\circ$.

Methyl Benzoylaminolauronate, CO₂Me·C₈H₁₄·NH·CO·C₆H₅.

Fifty grams of benzoylaminolauronic acid (1 mol.) were mixed with 110 grams of methyl iodide (4 mols.) and 50 c.c. of pure dry acetone. Ninety grams of dry silver oxide (2 mols.) were added in small quantities from time to time; a vigorous reaction took place, and, after the addition of all the oxide, the mixture was gently boiled for three hours under a condenser. The product was then extracted with boiling ether. The ethereal extract when evaporated to dryness gave a viscid oil, which remained liquid for several months. A specimen dried at 150°/15 mm. crystallised on cooling, and by nucleation the total product was readily obtained in the crystalline state. It was purified by recrystallisation from petroleum of high boiling point. The compound is readily soluble in alcohol, ether, acetone, or benzene, and melts at 88—89°.

Found, C = 70.6; H = 8.06; OMe = 11.3.

$\text{C}_{17}\text{H}_{23}\text{O}_3\text{N}$ requires C = 70.6; H = 7.96; OMe = 10.7 per cent.

Solvent.—*Alcohol*: $c = 1.453$, $l = 2$, $\alpha = -0.84^\circ$, $[\alpha]_D^{18} = -28.9^\circ$.

An alcoholic solution of the substance was boiled for three hours with a 10 per cent. solution of sodium hydroxide. As expected, the product of the hydrolysis proved to be the original benzoylaminolauronic acid melting at 204°.

As mentioned in the theoretical part, a saturated solution of ammonia in alcohol was without action on the above ethereal salt, both at the ordinary temperature and at 130°.

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