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Necrosamine Series. III.* Preparation of 4-(o-Carboxybenzamido-)5-benzylaminoeicosane and its Hydrolysis to 4-Amino-5-hydroxyeicosane

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The reductive alkylation of a mixture of benzylamine and of 4-phthalimido-5-eicosanone (IIa) and 2-methyl-3-phthalimido-4-nonadecanone (IIb) respectively has been described. The acetylated reaction product IVa yielded by hydrolysis 4-amino-5-hydroxyeicosane (Va). Following new compounds were prepared: 4-(o-carboxybenzamido-)5-benzylaminoeicosane (IIIa), m. p. 140—141°; 4-(o-carboxybenzamido-)5-(N-benzyl-N-acetyl-)aminoeicosane (IVa), m. p. 86—87°; 4-amino-5-hydroxyeicosane hydrochloride (Va), m. p. 98—99°; 4-acetylamino-5-acetoxyeicosane, m. p. 84—85°; 2-methyl-3-(o-carboxybenzamido-)4-benzylaminononadecane (IIIb), m. p. 96—98°; 2-methyl-3-(o-carboxybenzamido-)4-(N-benzyl-N-acetyl-)aminononadecane (IVb), m. p. 108—108.5°.

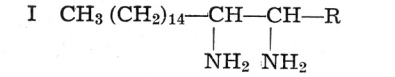
In the endeavor to synthesize racemic necrosamine which appears to be either 4,5-diaminoeicosane (Ia) or 2-methyl-3,4-diaminononadecane (Ib)**, we have investigated the reaction of 4-phthalimido-5-eicosanone (IIa) and of 2-methyl-3-phthalimido-4-nonadecanone (IIb) with benzylamine. The reaction of reductive alkylation seemed to be promising for the introduction of the second amino group into the molecule. As expected the reaction proceeded smoothly but the phthalimido groups were partially cleaved during the reaction furnishing the corresponding phthalamic acids — 4-(o-carboxybenzamido-)5-benzylaminoeicosane (IIIa) and 2-methyl-3-(o-carboxybenzamido-)4-benzylaminononadecane (IIIb). After repeated crystallizations of the reaction mixtures from ethanol, well crystalline IIIa and IIIb were obtained representing probably the less soluble racemates. No efforts have been made to obtain the more soluble racemates in a pure condition. Furthermore all attempts to convert both IIIa and IIIb into the diamines failed and less expected reactions took place. However, IIIa and IIIb could be regarded as derivatives of the diamines in which the basic groups are protected with benzyl- and o-carboxybenzoyl-rests.

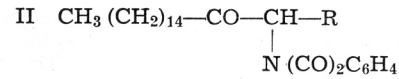
When IIIa was refluxed with acetic anhydride the secondary amino group was acetylated but the phthalimido ring closure was not achieved. The resulting 4-(o-carboxybenzamido-)5-(N-benzyl-N-acetyl-)aminoeicosane (IVa) was

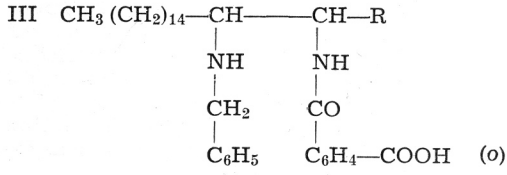
* Paper I and II, see reference[1].

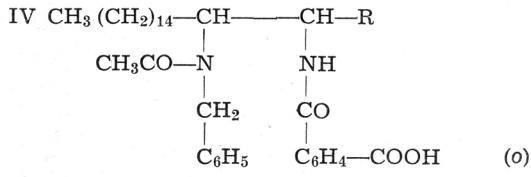
** We described the synthesis of both bases in Paper I and II, where also the references covering the work on necrosamine are listed.

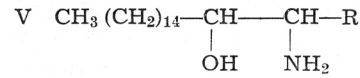
hydrolized by refluxing its ethyl cellosolve solution with 6*N* hydrochloric acid. A nicely crystalline substance, m. p. 98—99°, was obtained to which according to the analytical data, the simplest empirical formula $C_{20}H_{44}ONCl$ was assigned. Evidently, one nitrogen atom was eliminated during the hydrolysis. The substance might possess the structure either of 4-amino-5-hydroxyeicosane hydrochloride (Va) or of 5-amino-4-hydroxyeicosane hydrochloride. In the course of this investigation the structure Va was conclusively established by the catalytic reduction of authentic 4-amino-5-eicosanone hydrobromide in the presence of Adams platinum catalyst. The reaction product when converted into the hydrochloride was found to be identical in every respect with Va obtained by the hydrolysis of IVa.





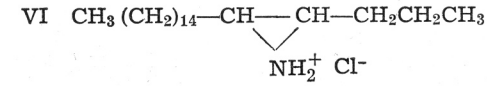






a) R = —$CH_2CH_2CH_3$; b) R = —$CH(CH_3)_2$

As to the mechanism of the reaction IVa → Va it seems reasonable to suppose, that during the hydrolysis phthalic acid was split off with subsequent elimination of benzylamine. In this way the cyclic imine VI might be intermediary formed and converted to Va by hydrolytic cleavage of C_5-N bond. This conclusion is supported by the fact that the reaction mixture contained after hydrolysis both diethoxyethyl phthalate and benzylamine hydrochloride. They could be readily isolated in a pure condition and compared with the authentic samples.



EXPERIMENTAL

The melting points are uncorrected.

4-(o-Carboxybenzamido-)5-benzylaminoeicosane (IIIa)

A solution of 1.5 g. (0.0034 mole) of 4-phthalimido-5-eicosanone (IIa)[1] in 60 ml. of 96% ethanol and 3 ml. of freshly distilled benzylamine was hydrogenated in the presence of 0.1 g. of Adams platinum catalyst[2] at room temperature and at atmospheric pressure. After 8 hrs. 120 ml. of hydrogen was absorbed. In the course of the hydrogen absorbtion the reaction mixture partly crystallized. The crystals were dissolved by warming the suspension and the catalyst was filtered off. The hot filtrate was cooled in the refrigerator and the separated substance collected. There was obtained 0.96 g. (52.4%) colorless crystals, m. p. 124—125°. The mother liquid was steam distilled in order to remove ethanol and the excess of benzylamine. The residue in the distilling flask was extracted with ether, dried with sodium sulphate and the solvent removed. The yellow oil (0.76 g., 40.8%) could not be induced to crystallization. The substance with the m. p. 124—125° was recrystallized four times from absolute ethanol leaving 0.44 g. (23.9%) colorless crystals, m. p. 140—141°.

Anal.: 8.205 mg. subst.: 22.90 mg. CO_2, 7.12 mg. H_2O
8.250 mg. subst.: 23.04 mg. CO_2, 7.19 mg. H_2O
3.480 mg. subst.: 0.155 ml. N_2 (21°, 752 mm)
$C_{35}H_{54}O_3N_2$ (550.80) calc'd: C 76.32; H 9.88; N 5.08%
found: C 76.16; H 9.71; N 5.12%
C 76.21; H 9.75%

4-(o-Carboxybenzamido-) 5-(N-benzyl-N-acetyl-) aminoeicosane (IVa)

Five hundred miligrams (0.9 mMole) of IIIa, pyridine (5 ml.) and acetic anhydride (5 ml.) were heated at 100° for 1.5 hr. The reaction mixture was cooled, poured into ice-water (100 ml.) and the resulting precipitate extracted with ether. The combined ether extracts were washed with water, dried with sodium sulphate and the solvent removed by distillation. The oily residue was crystallized once from acetonitrile. Colorless crystals (300 mg., 56.2%) were obtained; m. p. 86—87°. The melting point did not change after recrystallization from acetonitrile.

Anal. 9.320 mg. subst.: 25.73 mg. CO_2, 8.09 mg. H_2O
7.500 mg. subst.: 0.306 ml. N_2 (25.5°, 751 mm)
$C_{37}H_{56}O_4N_2$ (592.81) calc'd: C 74.96; H 9.51; N 4.72%
found: C 75.34; H 9.71; N 4.61%

4-Amino-5-hydroxyeicosane hydrochloride (Va)

A. To the solution of 370 mg. (0.62 mMole) of IVa in ethyl cellosolve (20 ml.) 6*N* hydrochloric acid (10 ml.) was added and refluxed for 24 hrs. The reaction mixture was left to stand in the refrigerator overnight. The crystalline precipitate was collected and crystallized from acetonitrile. Colorless crystals (120 mg., 55.3%), m. p. 97—98°. Theree crystallizations from a mixture of acetonitrile — absolute ethanol (2 : 1) gave a product with the melting point 98—99°.

Anal. 7.900 mg. subst.: 19.85 mg. CO_2, 8.90 mg. H_2O
5.430 mg. subst.: 0.230 ml. N_2 (23.5°, 753 mm)
$C_{20}H_{44}ONCl$ (350.02) calc'd: C 68.62; H 12.67; N 4.00%
found: C 68.57; H 12.61; N 3.84%

No melting point depression was observed in admixture with an authentic sample of 4-amino-5-hydroxyeicosane hydrochloride (m. p. 98—99°) prepared by the catalytic reduction of 4-amino-5-eicosanone hydrobromide in the presence of Adams platinum catalyst.

The mother liquid which remained after the filtration of the crystals with the m. p. 97—98° was evaporated *in vacuo* to dryness. The yellow oil crystallized after cooling it in the refrigerator. The substance melted at 30° and the melting point corresponded to that of diethoxyethyl phthalate (33°). The substance could not be recrystallized from usual solvents. The mother liquid was made strongly alcaline

by addition of 45% potassium hydroxide solution and steam distilled. After acidification the distillate with dilute hydrobromic acid the aqueous solution was evaporated *in vacuo* to dryness. Colorless leaflets, m. p. 195—196° were obtained, which after crystallization from absolute ethanol-ether (1 : 5) melted at 207—208°. There was no melting point depression in admixture with an authentic sample of benzylamine hydrobromide (m. p. 207—208°).

B. A solution of 4-amino-5-eicosanone hydrobromide[1] (300 mg., 0.77 mMole) in absolute ethanol (50 ml.) was hydrogenated in the presence of Adams platinum catalyst (0.1 g.)[2] at room temperature and at atmospheric pressure. The hydrogen uptake was 25 ml. After removal of the catalyst the solvent was distilled off. The resulting yellow oil crystallized from ethyl acetate. There was obtained 270 mg. (89.1%) colorless crystals, m. p. 105—107°. The substance was shaken with 2*N* sodium hydroxide (100 ml.) and ether. The combined ether extracts were washed with water and dried with sodium sulphate. Dry hydrogen chloride was bubbled in to the ether solution. Colorless crystals precipitated, m. p. 85—87° which were recrystallized from acetonitrile — absolute ethanol (2 : 1); m. p. 98—99°.

Anal. 8.940 mg. subst.: 22.54 mg. CO_2, 10.18 mg. H_2O
$C_{20}H_{44}ONCl$ (350.02) calc'd: C 68.62; H 12.67%
found: C 68.80; H 12.74%

4-Acetylamino-5-acetoxyeicosane

A mixture of Va (55 mg.), pyridine (2 ml.) and acetic anhydride (1 ml.) was heated at 100° for 1 hr. The cooled mixture was then poured into 2*N* sulphuric acid (50 ml.) and extracted with ether. The ether extracts were washed with water, dried with sodium sulphate and the solvent removed by distillation. Two crystallizations of the oily residue from acetonitrile gave colorless crystals, m. p. 84—85°.

Anal. 8.555 mg. subst.: 22.76 mg. CO_2, 9.02 mg. H_2O
$C_{24}H_{47}O_3N$ (397.62) calc'd: C 72.49; H 11.91%
found: C 72.60; H 11.80%

2-Methyl-3-(o-carboxybenzamido-) 4-benzylaminononadecane (IIIb)

The substance was prepared following essentially the same procedure as described for IIIa. Thus, 2-methyl-3-phthalimido-4-nonadecanone (IIb)[1] in 50 ml. of 96% ethanol and 2 ml. of benzylamine when hydrogenated in the presence of Adams platinum catalyst (0.2 g.) gave 0.98 g. (79%) of an oily product which was crystallized from 96% ethanol. Thereby 0.34 g. (27.4%) colorless crystals were obtained, m. p. 95—97°. A sample for analysis was recrystallized from ethanol; m. p. 96—98°.

Anal. 4.435 mg. subst.: 12.32 mg. CO_2, 4.02 mg. H_2O
4.520 mg. subst.: 0.196 ml. N_2 (21.8°, 752 mm)
$C_{35}H_{54}O_3N_2$ (550.80) calc'd: C 76.32; H 9.88; N 5.08%
found: C 75.81; H 10.14; N 4.97%

The alcoholic mother liquid was evaporated *in vacuo* to give 0.54 g. of an oil which could not be induced to crystallization.

2-Methyl-3-(o-carboxybenzamido-)4-(N-benzyl-N-acetyl-)aminononadecane (IVb)

One hundred and ninety miligrams (0.34 mMole) of IIIb, pyridine (2.5 ml.) and acetic anhydride (2.5 ml.) gave in the usual manner 120 mg. (60%) colorless crystals, m. p. 101—102°. Three crystallizations from acetonitrile raised the m. p. to 108—108.5°.

Anal. 5.730 mg. subst.: 15.80 mg. CO_2, 5.02 mg. H_2O
5.885 mg. subst.: 0.244 ml. N_2 (23°, 746 mm)
$C_{37}H_{56}O_4N_2$ (592.81) calc'd: C 74.96; H 9.51; N 4.72%
found: C 75.25; H 9.80; N 4.69%

We are indebted to Mrs. M. Munk-Weinert from our microanalytical laboratory for microanalyses.

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IZVOD

Nekrozamin. III.

Pripravljanje 4-(*o*-karboksi-benzamido-) 5-benzilamino-eikosana i hidroliza u 4-amino-5-hidroksi-eikosan

P. Alaupović i M. Prošteník

Opisana je reduktivna alkilacija smjese benzil-amina i 4-ftalimido-5-eikosanona (IIa), odnosno 2-metil-3-ftalimido-4-nonadekanona (IIb). Nastali produkt III je acetiliran, a acetilni je derivat hidroliziran 6*N* solnom kiselinom u 4-amino-5-hidroksi-eikosan. Pripravljeni su i opisani ovi spojevi: 4-(*o*-karboksi-benzamido-) 5-benzilamino-eikosan (IIIa), t. t. 140—141°; 4-(o-karboksi-benzamido-) 5-(*N*-benzil-*N*-acetil-) amino-eikosan (IVa), t. t. 86—87°; 4-amino-5-hidroksi-eikosan hidroklorid (Va), t. t. 98—99°; 4-acetilamino-5-acetoksi-eikosan, t. t. 84—85°; 2-metil-3-(*o*-karboksi-benzamido-) 4-benzilamino-nonadekan (IIIb), t. t. 96—98°; 2-metil-3-(*o*-karboksi-benzamido-) 4-(*N*-benzil-*N*-acetil-) amino-nonadekan (IVb), t. t. 108—108.5°.

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