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Original Scientific Paper

On the Reaction of 2-Phthalimido-1-octadecanal and 2-Methoxy-1-octadecanal with Nitromethane

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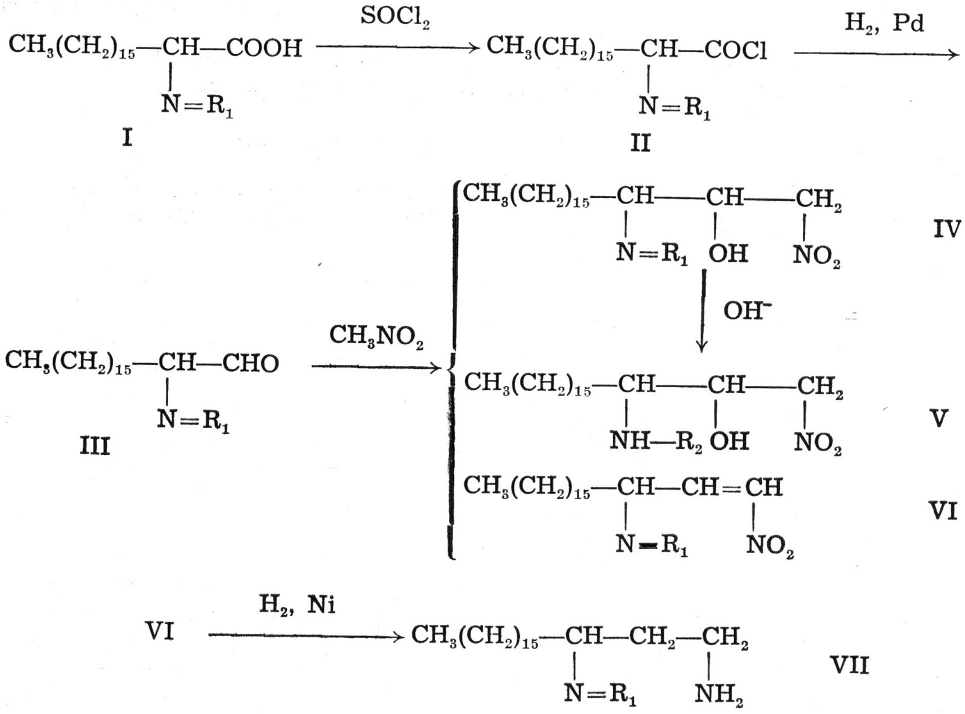
The preparation of 2-phthalimido-1-octadecanal (III) and 2-methoxy-1-octadecanal (XII) is described. Condensation of III with nitromethane in the presence of potassium carbonate yields a mixture of 1-nitro-2-hydroxy-3-phthalimido-nonadecane (IV), 1-nitro-2-hydroxy-3-(o-carboxybenzamido)-nonadecane (V) and 1-nitro-3-phthalimido-1-nonadecene (VI). Similar condensation of XII with nitromethane yields 1-nitro-2-hydroxy-3-methoxynonadecane (XIII). Catalytic reduction of VI and XIII furnishes the corresponding saturated amino compounds (VII and XIV).

The synthesis of certain long-chain aliphatic compounds containing three adjacent asymmetric carbon atoms according to the scheme $C^* + C^* — C^* \rightarrow C^* — C^* — C^*$, two asymmetric carbons being introduced simultaneously, leads to the formation of an inseparable mixture of racemates[1]. Theoretically, the formation of four racemic forms is expected. In the search for a method for the successive introduction of the asymmetric centers in accordance with the scheme $C^* \rightarrow C^* — C^* \rightarrow C^* — C^* — C^*$, two series of reactions, outlined in Chart A and Chart B, were performed. This generalized scheme was supposed to offer the possibility of the stepwise formation and separation of the less complex mixtures of racemates.

The route to compounds given in Chart A began with the reaction of 2-aminooöctadecanoic acid with phthalic anhydride to give 2-phthalimidooöctadecanoic acid (I) in a good yield. The latter was treated with thionyl chloride and the resulting acid chloride II submitted to the Rosenmund reduction under conventional conditions[2]. Since the purification of 2-phthalimido-1-octadecanal (III) did not yield a compound with accurate elemental analysis it was converted for characterization purposes into the 2,4-dinitrophenylhydrazone. Condensation of crude III with nitromethane in the presence of anhydrous potassium carbonate furnished a mixture of at least three compounds (IV, V and VI) which could be separated by fractional crystallization. The structure of the phthalamic acid V was confirmed by the preparation of an authentic sample by partial alkaline hydrolysis of IV. The separation of each IV and V into the racemic pairs (*erythro* and *threo*) was not observed. Catalytic (Raney nickel) hydrogenation in ethanol of the mother liquor which remained after the separation of IV and V gave a product with m.p. 124—125° which may be considered to have the structure VII in view of the mode of preparation, the analytical data and the absence of a hydroxyl band in the infrared at 3600 cm^{-1}. These data support the structure of the nitroalkene VI as well.

CHART A



$$CH_3(CH_2)_{15}-\underset{N=R_1}{\underset{|}{CH}}-COOH \xrightarrow{SOCl_2} CH_3(CH_2)_{15}-\underset{N=R_1}{\underset{|}{CH}}-COCl \xrightarrow{H_2,\ Pd}$$

I II

$$CH_3(CH_2)_{15}-\underset{N=R_1}{\underset{|}{CH}}-CHO \xrightarrow{CH_3NO_2} \begin{cases} CH_3(CH_2)_{15}-\underset{N=R_1}{\underset{|}{CH}}-\underset{OH}{\underset{|}{CH}}-\underset{NO_2}{\underset{|}{CH_2}} & \text{IV} \\ \quad\downarrow OH^- & \\ CH_3(CH_2)_{15}-\underset{NH-R_2}{\underset{|}{CH}}-\underset{OH}{\underset{|}{CH}}-\underset{NO_2}{\underset{|}{CH_2}} & \text{V} \\ CH_3(CH_2)_{15}-\underset{N=R_1}{\underset{|}{CH}}-CH=\underset{NO_2}{\underset{|}{CH}} & \text{VI} \end{cases}$$

III

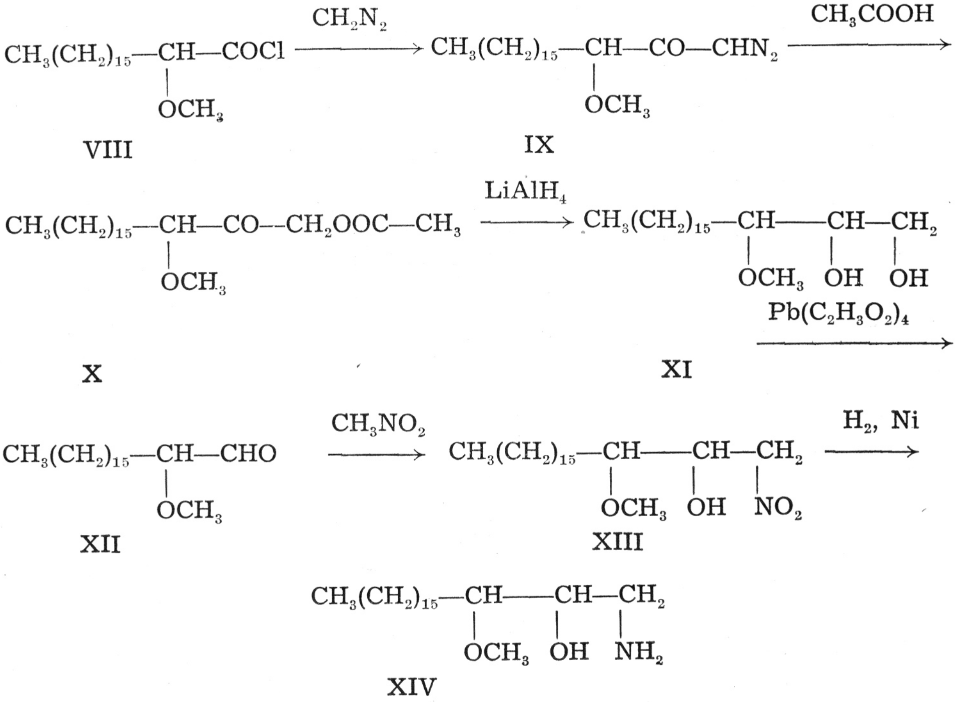
$$\text{VI} \xrightarrow{H_2,\ Ni} CH_3(CH_2)_{15}-\underset{N=R_1}{\underset{|}{CH}}-CH_2-\underset{NH_2}{\underset{|}{CH_2}} \quad \text{VII}$$

$R_1 = (CO)_2C_6H_4$ (*o*) phthaloyl

$R_2 = CO-C_6H_4-COOH$ (*o*)

Another series of reactions (Chart B) was started with 2-methoxyoctadecanoic acid and its chloride VIII. The key intermediate 2-methoxy-1--octadecanal (XII) could be readily prepared in a good yield under mild conditions by applying the Grundmann aldehyde synthesis[3] to VIII. Crude XII was characterized and analyzed as 2,4-dinitrophenylhydrazone. Alkaline condensation of XII with nitromethane gave a mixture of two 1-nitro-2-hydroxy--3-methoxynonadecanes (XIII). The separation of both nitro compounds failed. Catalytic (Raney nickel) hydrogenation in ethanol of XIII yielded a mixture of two isomeric bases (XIV). Both bases were easily separated through the oxalates (I: m.p. 178—180° decomp., II: m.p. 166—168° decomp.) owing to the complete insolubility of the oxalate I in ethanol. The isomeric bases differed markedly in their melting points (I: 80—86°, II: 43—46°) and represented most probably the two possible racemic forms.

CHART B



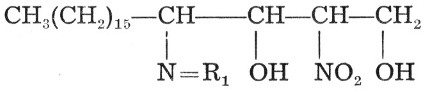
$$\underset{\text{VIII}}{CH_3(CH_2)_{15}\text{—}\underset{\displaystyle OCH_3}{CH}\text{—}COCl} \xrightarrow{CH_2N_2} \underset{\text{IX}}{CH_3(CH_2)_{15}\text{—}\underset{\displaystyle OCH_3}{CH}\text{—}CO\text{—}CHN_2} \xrightarrow{CH_3COOH}$$

$$\underset{\text{X}}{CH_3(CH_2)_{15}\text{—}\underset{\displaystyle OCH_3}{CH}\text{—}CO\text{—}CH_2OOC\text{—}CH_3} \xrightarrow{LiAlH_4} \underset{\text{XI}}{CH_3(CH_2)_{15}\text{—}\underset{\displaystyle OCH_3}{CH}\text{—}\underset{\displaystyle OH}{CH}\text{—}\underset{\displaystyle OH}{CH_2}} \xrightarrow{Pb(C_2H_3O_2)_4}$$

$$\underset{\text{XII}}{CH_3(CH_2)_{15}\text{—}\underset{\displaystyle OCH_3}{CH}\text{—}CHO} \xrightarrow{CH_3NO_2} \underset{\text{XIII}}{CH_3(CH_2)_{15}\text{—}\underset{\displaystyle OCH_3}{CH}\text{—}\underset{\displaystyle OH}{CH}\text{—}\underset{\displaystyle NO_2}{CH_2}} \xrightarrow{H_2,\ Ni}$$

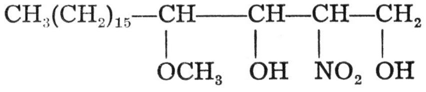
$$\underset{\text{XIV}}{CH_3(CH_2)_{15}\text{—}\underset{\displaystyle OCH_3}{CH}\text{—}\underset{\displaystyle OH}{CH}\text{—}\underset{\displaystyle NH_2}{CH_2}}$$

Many unsuccessful attempts were made to introduce the third asymmetric carbon by condensation of IV and XIII with formaldehyde in endeavour to obtain XV and XVI respectively.



$$CH_3(CH_2)_{15}\text{—}\underset{\displaystyle N{=}R_1}{CH}\text{—}\underset{\displaystyle OH}{CH}\text{—}\underset{\displaystyle NO_2}{CH}\text{—}\underset{\displaystyle OH}{CH_2}$$

XV



$$CH_3(CH_2)_{15}\text{—}\underset{\displaystyle OCH_3}{CH}\text{—}\underset{\displaystyle OH}{CH}\text{—}\underset{\displaystyle NO_2}{CH}\text{—}\underset{\displaystyle OH}{CH_2}$$

XVI

Nevertheless, the experiments reported here open the way to syntheses of a variety of 1,2,3-trisubstituted higher alkanes. The reactions proceed satisfactorily, and the yields in all the steps are acceptable for preparative purposes.

EXPERIMENTAL

All melting points are uncorrected. Infrared absorption spectra were measured on a Perkin-Elmer Model 137 spectrophotometer.

2-Phthalimidoöctadecanoic Acid (I)

A finely ground mixture of 2-aminoöctadecanoic acid[4] (38.4 g., 0.13 mole) and phthalic anhydride (21 g.) was heated with occassional stirring in an oil bath at 150—160° for 3 hrs. The yellow coloured melt was dissolved in light petroleum (50—70°) and allowed to stand in a refrigerator overnight. Thereby, 53 g. (87%)

of colourless crystals were obtained, m.p. 78—82°. Two more crystallizations from light petroleum gave a sample melting at 81—83°.

Anal. $C_{26}H_{39}NO_4$ (429.58) calc'd.: C 72.69; H 9.15; N 3.26%
found: C 72.68; H 9.15; N 3.55%

2-Phthalimidoöctadecanoic Acid Chloride (II)

A solution of I (8.3 g., 0.019 mole) in thionyl chloride (20 ml.) was refluxed for 1 hr. The excess of thionyl chloride was distilled off *in vacuo* and the residue recrystallized from light petroleum (60—80°). Colourless crystals (6.5 g., 76.4%) m.p. 45.5—47.5°.

Anal. $C_{26}H_{38}ClNO_3$ (448.03) calc'd.: C 69.70; H 8.56; N 3.13%
found: C 69.77; H 8.57; N 3.57%

2-Phthalimido-1-octadecanal (III)

The Rosenmund reduction of a sample of II (15 g., 0.034 mole) in xylene (30 ml.) and in the presence of 5% palladium on barium sulphate catalyst (8 g.) gave 11.3 g. (81.5%) of the crude aldehyde, m.p. 59—67°. Consumed was 57.8 ml. of 0.5 *N* NaOH, corresponding to 86.5% HCl. Recrystallization from 95% ethanol yielded a somewhat impure product melting at 63—69°.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized from absolute ethanol; m.p. 90—92.5°.

Anal. $C_{32}H_{43}N_5O_6$ (593.7) calc'd.: C 64.73; H 7.30%
found: C 64.77; H 7.32%

Condensation of 2-Phthalimido-1-octadecanal with Nitromethane

To a cooled solution of III (0.7 g., 1.7 mM) in methanol (6.5 ml.) nitromethane (0.13 g., 1.7 mM) and anhydrous potassium carbonate (60 mg.) were added. The mixture was shaken at rom temperature for 24 hrs. and then acidified cautiously with conc. hydrochloric acid and extracted with ether. The combined extracts were washed with water, dried over sodium sulphate and evaporated to dryness. The crude product (0.8 g.) was recrystallized from a mixture ether — light petroleum (1 : 1) to yield 0.2 g. of colourless crystals, m.p. 90—101° (substance A). Concentration of the mother liquor to a smaller volume gave a second crop of crystals (0.1 g.) melting at 66—81° (substance B).

1-Nitro-2-hydroxy-3-phthalimidononadecane (IV)

The title compound was obtained in a pure condition by several recrystallizations of substance *A* from light petroleum; m.p. 82.5—84.5°.

Anal. $C_{27}H_{42}N_2O_5$ (474.63) calc'd.: C 68.32; H 8.92; N 5.90%
found: C 68.41; H 8.97; N 6.00%

*1-Nitro-2-hydroxy-3-(*o*-carboxybenzamido)-nonadecane* (V)

The compound was obtained by crystallization of substance *B* from ether; m.p. 104—106°.

Anal. $C_{27}H_{44}N_2O_6$ (492.64) calc'd.: C 65.82; H 9.00; N 5.68%
found: C 66.04; H 9.13; N 5.52%

The same compound was prepared by refluxing a solution of IV in 17% methanolic potassium hydroxide for 5 minutes. After cooling and acidification with 2 *N* sulphuric acid, the separated crude product was recrystallized from ether; m.p. 104—106° (found: N 5.65%). The mixed melting point with the foregoing substance was undepressed.

1-Amino-3-phthalimidononadecane (VII)

The mother liquor remaining after the separation of substance *B* was concentrated and cooled overnight. The crystals, m.p. 71—74° from acetonitrile (found: C 78.09; H 10.13; N 4.19%), were discarded. The mother liquor was evaporated to dryness, the sirupy residue dissolved in 95% ethanol and hydrogenated in the presence of Raney nickel catalyst at room temperature and at atmospheric pressure. After removal of the solvent and recrystallization from 95% ethanol the colourless substance VII, m.p. 124—125°, was obtained.

Anal. $C_{27}H_{44}N_2O_2$ (428.64) calc'd.: C 75.65; H 10.35; N 6.54%
found: C 75.89; H 10.14; N 6.78%

The infrared spectrum, taken in nujol, showed a medium absorption at 3200 cm.$^{-1}$, two widely separated bands at 1750 and 1670 cm^{-1}, bands at 1420, 1260, 1160, 1090 and 900 cm.$^{-1}$. There was no band in the hydroxyl region near 3600 cm.$^{-1}$.

1-Diazo-3-methoxy-2-nonadecanone (IX)

2-Methoxyoctadecanoic acid chloride (VIII) was prepared by heating the acid[5] with thionyl chloride at 40—60° for 6 hrs. The excess of thionyl chloride was removed *in vacuo* followed by the azeotropic distillation with benzene. The chloride VII thus obtained (54.3 g., 0.164 mole) was dissolved in dry ether (600 ml.) and the resulting solution was added dropwise at 0° with continuous stirring to the ether solution of diazomethane (prepared from 70 g. of nitrosomethylurea). After standing at room temperature for 3 hrs. ether was evaporated under reduced pressure at 25° to dryness to give the crude, crystalline diazoketone (57.6 g., m.p. 49.5—50°). A sample for analysis was recrystallized three times from ethyl acetate; m.p. 50—52%.

Anal. $C_{20}H_{38}N_2O_2$ (338.52) calc'd.: C 70.96; H 11.32; N 8.28%
found: C 70.57; H 11.32; N 8.27%

1-Acetoxy-3-methoxy-2-nonadecanone (X)

A solution of IX (56.6 g., 0.168 mole, m.p. 49.5—50°) and anhydrous sodium acetate (2.2 g.) in glacial acetic acid (140 ml.) was heated at 70° for 40 min. and then refluxed for 1.5 hrs. The solvent was evaporated *in vacuo,* the oily residue dissolved in light petroleum (50—70°), washed with water and dried. Removal of the solvent yielded 59.4 g. of a red coloured oil which was dissolved in light petroleum (50—70°) and chromatographed over activated alumina. The light petroleum eluates (fractions 4—14) were collected (48.2 g., 81.4%, m.p. 37—40°). A sample for analysis was recrystallized four times from light petroleum, m.p. 45.5—46.5°.

Anal. $C_{22}H_{42}O_4$ (370.56) calc'd.: C 71.30; H 11.42%
found: C 71.62; H 11.32%

1,2-Dihydroxy-3-methoxynonadecane (XI)

A solution of X (44 g., 0.119 mole, m.p. 37—40°) in absolute ether (280 ml.) was added dropwise with stirring in the course of 40 min. to a solution of lithium aluminium hydride (9 g.) in absolute ether (350 ml.). The reaction mixture was left to stand at 0° overnight, the excess of hydride decomposed by successive cautious addition of ethyl acetate and 30% sulphuric acid (300 ml.), the ether layer separated and washed with water to neutral. After removal of the solvent a crystalline, colourless residue remained, which was recrystallized from light petroleum (50—70°). Colourless crystals (33.85 g., 86.9%, m.p. 40—42°). Four additional crystallizations gave a sample for analysis; m.p. 42—44°.

Anal. $C_{20}H_{42}O_3$ (330.54) calc'd.: C 72.67; H 12.81%
found: C 72.01; H 12.89%

2-Methoxy-1-octadecanal (XII)

To a stirred solution of XI (8.6 g., 2.6 mM, m.p. 40—42°) and glacial acetic acid (1.3 ml.) in dry benzene (200 ml.) lead tetraacetate (12.5 g.) was added in small portions at room temperature. The reaction mixture was then heated at 40—45° for 2 hrs. The excess of lead tetraacetate was decomposed by addition of ethylene glycol (10 ml.), the benzene layer was washed with water to remove lead ions and evaporated to dryness *in vacuo*. Thereby, 7.75 g. of a colourless, crystalline residue was obtained. After recrystallization from light petroleum (70—80°) the aldehyde (4.75 g., 61.2%) melted at 30—31%.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized from 95% ethanol; m.p. 102—104.5°.

Anal. $C_{25}H_{42}N_4O_5$ (478.62) calc'd.: C 62.73; H 8.85; N 11.72%
found: C 62.91; H 8.72; N 11.57%

Condensation of 2-Methoxy-1-octadecanal with Nitromethane. 1-Nitro-2-hydoxy-3-methoxynonadecane (XIII)

To a solution of XII (5.95 g., 20 mM) in methanol (10 ml.) nitromethane (2.6 g., 42.6 mM) and anhydrous potassium carbonate (0.45 g.) were added. The mixture was shaken at room temperature for 3 days and then worked up as described above (IV). The crude product was recrystallized from pentane. Colourless crystals (5.1 g., m.p. 40—42.5°), which have not been obtained in pure enough form for correct elemental analysis (low N, high C,H values).

1-Amino-2-hydroxy-3-methoxynonadecane (XIV)

A sample of XIII (1.95 g., 5.42 mM) was dissolved in absolute ethanol (20 ml.) and hydrogenated in the presence of Raney nickel catalyst at room temperature and at atmospheric pressure. The hydrogen uptake was 204 ml. (calc'd. 364 ml.). After removal of the solvent there remained 1.5 g. (84.4%) of a crude, crystalline compound, m.p. 39—42°, which was dissolved in boiling 95% ethanol and treated with an ethanolic solution of oxalic acid. The mixture of the oxalates was precipitated immediately and filtered off from the hot reaction mixture (0.84 g., m.p. 153—160° decomp.). Upon treatment with boiling absolute ethanol (80 ml.) the oxalates could be resolved into an insoluble fraction (0.44 g.) and a soluble one.

The oxalate I, insoluble in ethanol, was recrystallized from glacial acetic acid; m.p. 178—180° (decomp.).

Anal. $C_{21}H_{44}NO_4$ (374.57) calc'd.: C 67.33; H 11.84; N 3.74%
found: C 67.60; H 11.91; N 3.75%

The oxalate II, soluble in ethanol, was obtained upon cooling to 0° the mother liquor remained after the separation of the oxalate I. Colourless substance (0.29 g.), which was recrystallized from 95% ethanol; m.p. 166—168° (decomp.).

Anal. $C_{21}H_{44}NO_4$ (374.57) calc'd.: N 3.74%
found: N 3.86%

The free base I was obtained from the oxalate I (0.75 g.) by treatment with *N* KOH (70 ml.) and extraction with chloroform (300 ml.). Evaporation of the combined chloroform extracts furnished a crystalline substance which was recrystallized three times from ethyl acetate — acetonitrile (1 : 5); m.p. 80—86°.

Anal. $C_{20}H_{43}NO_2$ (329.59) calc'd.: N 4.25%
found: N 4.11%

The free base II was obtained similarly from the oxalate II. After recrystallization from acetonitrile it melted at 43—45°.

Anal. $C_{20}H_{43}NO_2$ (329.59) calc'd.: C 72.89; H 13.15; N 4.25%
found: C 73.34; H 13.22; N 3.92%

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IZVOD

O reakciji 2-ftalimido-1-oktadekanala i 2 metoksi-1-oktadekanala s nitrometanom

J. Pluščec, A. Kisić i M. Proštenik

Opisano je pripremanje 2-ftalimido-1-oktadekanala (III) i 2-metoksi-1-oktadekanala (XII). Kondenzacijom spoja III s nitrometanom uz sudjelovanje bezvodnoga kalijeva karbonata dobiva se smjesa 1-nitro-2-hidroksi-3-ftalimidononadekana (IV), 1-nitro-2-hidroksi-3-(o-karboksibenzamido)-nonadekana (V) i 1-nitro-2-hidroksi-3-metoksinonadekana (XIII). Katalitičkom redukcijom VI i XIII nastaju pripadni zasićeni aminospojevi VII i XIV.

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