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A Facile Synthesis of Dihydrosphingosine

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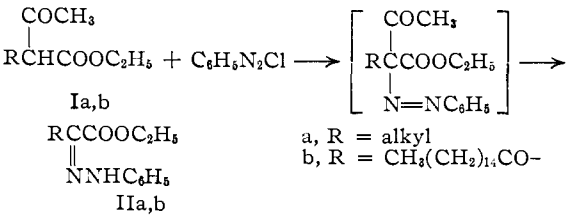
A convenient four-step synthesis of racemic *erythro*-1,3-dihydroxy-2-aminoöctadecane (VI) is described. Ethyl 2,3-dioxoöctadecanoate-2-phenylhydrazone (IIb) is reductively acetylated to the amide III which is reduced by lithium aluminum hydride to N-acetyldihydrospingosine (VII).

In recent years several syntheses of racemic dihydrosphingosine have been published.[1-9] The present investigation was initiated as a preliminary study aimed at the synthesis of natural sphingosine.[10]

The route envisioned for a possible model synthesis involved the phenylhydrazone IIb as key intermediate which was prepared by coupling ethyl palmitoylacetoacetate with benzenediazonium chloride. The reaction of aromatic diazonium salts with α-alkylsubstituted acetoacetic esters (Ia) was first discovered by Japp and Klingemann[11] and is known to proceed according to the scheme

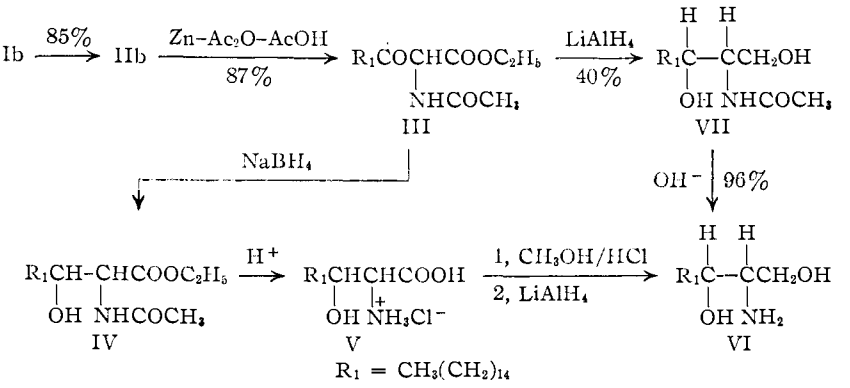


Ia,b

a, R = alkyl
b, R = $CH_3(CH_2)_{14}CO$-

IIa,b

The azo compounds formed in the first phase of the reaction are unstable, and tautomerize to the phenylhydrazones of α-ketoesters IIa after loss of the acetyl group. Similarly, α,α-diacyl-esters (I, R = acyl) give α-phenylhydrazones of α,β-diketoesters.



The course of the latter reaction depends, however, on the competitive behavior of the acyl groups. Thus, Bülow and Hailer[12] correlated the hydrolyzability of the acyl groups with the strength of the corresponding acids, on the basis of the observation that ethyl propionylacetoacetate retained the acetyl group, while the latter was displaced by the "stronger" benzoyl group in the case of ethyl benzoylacetoacetate. In contrast, we found that in the Japp–Klingemann reaction with ethyl palmitoylacetoacetate (Ib) the acetyl group suffered hydrolysis to give the phenylhydrazone IIb.

Exploratory attempts to bring about this reaction were not successful, oily products being obtained which seemed to decompose rapidly on further treatment. Finally it was found that the phenylhydrazone IIb could be obtained in excellent yield when ammonium chloride or acetate had been added to the reaction mixture. This result suggests that the ammonium ion promotes the Japp–Klingemann reaction, possibly by facilitating the hydrolysis of the acetyl group; it finds its parallel in the deacetylation of ethyl benzoylacetoacetate which is best effected by a mixture of ammonia and ammonium chloride.[13,14]

Treatment of the phenylhydrazone IIb with zinc and acetic acid in the presence of acetic anhydride gave ethyl 2-acetamido-3-oxoöctadecanoate (III). Reduction of the keto group with sodium borohydride afforded a mixture of the *erythro* and the *threo* forms of the alcohol IV. Efforts to separate the diastereomers at this stage were not successful. The crude reaction product was, therefore, saponified to the free amino acid which, after esterification with methanol, was reduced with lithium aluminum hydride. Pure *erythro* - dihydrosphingosine was obtained as its tribenzoyl derivative. It is interesting to note that, under the same conditions, the corresponding unsaturated acetamido ester IV (R_1 = 2-hexadecenoyl-) underwent only partial hydrolysis,[10] whereby the ester grouping remained intact.

Alternatively, the keto ester III was reduced selectively with lithium aluminum hydride, and pure *erythro*-N-acetyl-1,3-dihydroxy-2-aminoöctadecane (VII) was obtained in 40% yield after one crystallization. Selective reductions in which the

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amide grouping is retained intact have been reported by several authors. Thus, Felkin[15] found that ethyl 2-acetamido-2-benzyl-3-phenylpropionate was reduced with lithium aluminum hydride to 2-acetamido-2-benzyl-3-phenyl-1-propanol.

Fodor, *et al.*, reported the reduction with lithium borohydride of the keto ester III which they prepared by a different route, and obtained a mixture of both racemates melting over a range of 90–107°.

Since the N-acetyl derivative VII was converted in high yield into the free amino-diol VI, this approach constitutes a convenient four-step synthesis of dihydrosphingosine in an over-all yield of 28%.

Experimental

Ethyl 2,3-Dioxoöctadecanoate-2-phenylhydrazone (IIb).—The exact procedure must be followed as to time, temperature and amounts of reagents and solvents. A partially neutralized solution of benzenediazonium chloride was prepared as follows: aniline (9.3 g.) in hydrochloric acid (sp. gr. 1.19, 33 ml.) and water (110 ml.) was diazotized with sodium nitrite (7.5 g.) dissolved in water (10 ml.). The stirred solution was then treated at −6 to −4° with a solution of sodium carbonate (12 g.) in water (120 ml.).

A solution of ethyl palmitoylacetoacetate[16] (35 g.) in ethanol (2400 ml.) was cooled with stirring to 12–13°, care being taken to avoid crystallization of the ester. After addition of sodium acetate (75 ml., 50%), the diazo solution was added in a thin stream during 2–3 minutes. The temperature was maintained at 10–12°, and during the following 30 minutes acetone (290 ml.) was added in three portions to prevent the separation of an oily product. The last portion was added immediately after addition of ammonium chloride (48 g.). Vigorous stirring was continued until a flocculent precipitate separated (20–40 minutes). The mixture was cooled overnight, filtered, and the product was washed with 70% alcohol, then with water; yield 35 g. (85%). The phenylhydrazone may be recrystallized from alcohol, but the crude product melts sharply at 47–48°, and can be used for the next step without further purification.

Anal. Calcd. for $C_{26}H_{42}N_2O_3$: C, 72.5; H, 9.8; N, 6.5. Found: C, 72.9; H, 9.9; N, 6.9.

Ethyl 2-Acetamido-3-oxoöctadecanoate (III).—A solution of the phenylhydrazone (43 g.) in glacial acetic acid (350 ml.) was added during 30 minutes to a suspension of zinc powder (50 g.) in acetic acid (200 ml.) and acetic anhydride (80 ml.). The temperature was maintained at 18–22° by occasional cooling. Vigorous stirring was continued until the yellow color completely disappeared. The zinc was filtered off with suction, washed with acetic acid, and the colorless filtrate poured into an equal volume of cold water. The solid which separated (33.5 g., 87%) was collected and recrystallized from methanol, giving colorless needles, m.p. 70–71°.

Anal. Calcd. for $C_{22}H_{41}O_4N$: C, 68.9; H, 10.8; N, 3.65. Found: C, 68.8; H, 10.6; N, 3.9.

Ethyl 2-Acetamido-3-hydroxyoctadecanoate (IV).—A solution of the keto ester (20 g.) in methanol (600 ml.) was treated at 20–25° with a solution of sodium borohydride (1 g.) in methanol (30 ml.) which was stabilized by addition of 8 drops of *N* sodium hydroxide solution. The mixture was kept at this temperature for 30 minutes, poured into cold water (600 ml.) and slightly acidified with dilute acetic acid. The separated solid was filtered, dissolved in ether, the ether solution dried and evaporated. The residue was crystallized from 3.5 parts methanol at room temperature (20°) yielding 18.5 g. (92%) of a product melting at 86–89°.

Anal. Calcd. for $C_{22}H_{43}O_4N$: C, 68.53; H, 11.24; N, 3.63. Found: C, 68.78; H, 11.33; N, 3.88.

2-Amino-3-hydroxyoctadecanoic Acid Hydrochloride (*erythro* and *threo*).—A suspension of the hydroxy ester (1 g.) in a mixture of 5% hydrochloric acid (10 ml.) and dioxane (10 ml.) was refluxed for 2 hours. The solution was cooled and cold 6 *N* hydrochloric acid (10 ml.) was added. The filtered product was dried in the desiccator over P_2O_5 and crystallized from ethyl acetate and a little ether, m.p. 140° after sintering at 80°.

Anal. Calcd. for $C_{18}H_{38}O_3NCl$: C, 61.4; H, 10.9; N, 3.99. Found: C, 60.95; H, 10.7; N, 3.97.

erythro-**Tribenzoyl-1,3-dihydroxy-2-aminoöctadecane.**—The hydroxy ester (1.6 g.) was refluxed for 2 hours with 10% hydrochloric acid (10 ml.). After evaporation to dryness, the residue was dissolved in anhydrous methanol (40 ml.) and gaseous hydrogen chloride was bubbled in while the solution was refluxed for 3 hours. The solvent was evaporated, the remainder treated with sodium carbonate solution and extracted with ether. After evaporation of the ether the dried residue (1 g.) was reduced with lithium aluminum hydride (0.5 g.) in ether (30 ml.). On working up, the semi-solid product was benzoylated with an excess of benzoyl chloride in the presence of pyridine to give 0.65 g. of the tribenzoyl derivative of m.p. 142–144°.

erythro-**N-Acetyl-1,3-dihydroxy-2-aminoöctadecane (VII).**—Ethyl 2-acetamido-3-oxoöctadecanoate (10 g.), dissolved in dry tetrahydrofuran (140 ml.), was added during 20 minutes to an ice-cold stirred suspension of lithium aluminum hydride (2 g.) in dry ether (140 ml.). The mixture was refluxed for one hour, cooled and treated with 10% sodium hydroxide solution (10 ml.). The ethereal layer was washed until neutral, dried over sodium sulfate and evaporated. The residue was crystallized once from methanol (65 ml.) at room temperature; yield 3.6 g. (40%), m.p. 122–124° (reported[8] 123–124°).

Anal. Calcd. for $C_{20}H_{41}O_3N$: C, 69.9; H, 12.03; N, 4.08. Found: C, 69.4; H, 11.9; N, 4.15.

erythro-**1,3-Dihydroxy-2-aminoöctadecane.**—The N-acetyl derivative (1.4 g.) was refluxed for 6 hours with a solution of potassium hydroxide (5 g.) in 90% methanol (100 ml.). To the cooled solution water was added and the precipitate (1.2 g., 96%) collected. After one crystallization from petroleum ether and ethyl acetate the product melted at 85–87° and was identical with an authentic specimen.

REHOVOTH, ISRAEL

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