Anal. Calcd. for $C_6H_7BrN_2O_2$: C, 32.89; H, 3.22; Br, 36.48. Found: C, 32.91; H, 3.15; Br, 36.49.

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Studies on Sphingolipids. VIII. Separation of the Diastereoisomeric Dihydrosphingosines. A Simplified Synthesis[1]

DAVID SHAPIRO AND TUVIA SHERADSKY

Daniel Sieff Research Institute,
The Weizmann Institute of Science, Rehovoth, Israel

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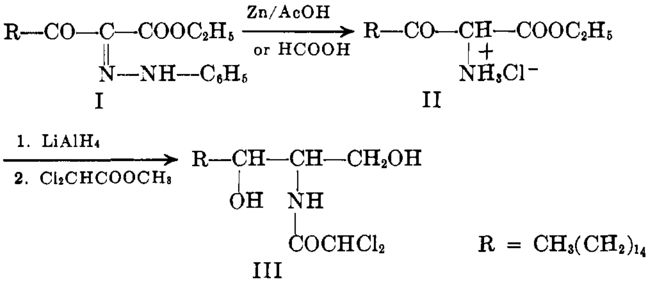
Most syntheses of dihydrosphingosine lead to a mixture of the two possible diastereoisomers,[2-6] whose separation is difficult to achieve. In the course of a recent investigation we observed that pure *erythro*-N-dichloroacetyldihydrosphingosine crystallized from the crude mixture and could thus be separated from its steric counterpart.

In a previous report[7] we described a synthesis of dihydrosphingosine which involved reductive acetylation of the phenylhydrazone I and a selective reduction of the resulting ethyl 2-acetamido-3-oxooctadecanoate with lithium aluminum hydride to give N-acetyldihydrosphingosine. While deacetylation proceeded satisfactorily when run on a relatively small scale, we experienced difficulties with the preparation of larger quantities of dihydrosphingosine, since considerable amounts of the amide resisted hydrolysis even after prolonged reaction.

Reduction of phenylhydrazones of type I with zinc and acetic acid usually is effected in the presence of acetic anhydride with formation of an acetamido group.[7-9] We have found that acetylation can be avoided by employing moist acetic acid, and we were able to isolate the keto ester II as the hydrochloride in 89% yield. The same result was achieved with formic acid at a slightly elevated temperature.



$$\mathrm{R{-}CO{-}\underset{\underset{\displaystyle N{-}NH{-}C_6H_5}{\|}}{C}{-}COOC_2H_5} \xrightarrow[\text{or HCOOH}]{\text{Zn/AcOH}} \mathrm{R{-}CO{-}\underset{\underset{\displaystyle NH_3Cl^-}{|\,+}}{CH}{-}COOC_2H_5}$$

I II

$$\xrightarrow[\text{2. }\mathrm{Cl_2CHCOOCH_3}]{\text{1. }\mathrm{LiAlH_4}} \mathrm{R{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}\underset{\underset{\underset{\underset{\displaystyle COCHCl_2}{|}}{NH}}{|}}{CH}{-}CH_2OH}$$

III $R = CH_3(CH_2)_{14}$

The crude mixture of isomers resulting from the reduction of the hydrochloride II with lithium aluminum hydride was treated directly with methyl dichloroacetate[10] and pure *erythro*-N-dichloroacetyldihydrosphingosine (III) was obtained after one crystallization. Mild alkaline hydrolysis afforded dihydrosphingosine.

The present synthesis offers a convenient method for the preparation of dihydrosphingosine in batches of ten to twenty grams.

Experimental

Ethyl 2-Amino-3-oxooctadecanoate Hydrochloride (II). (A) With Zinc Formic Acid.—To a vigorously stirred suspension of zinc powder (10 g.) in 98% formic acid (100 cc.) the phenylhydrazone I (8.56 g.) was added in portions, the temperature being maintained at 45–50°. After the addition was complete, the mixture was stirred for 20 min., cooled, and the zinc filtered off. The filtrate was poured into cold 2 *N* hydrochloric acid (100 cc.) and the product was filtered, washed with water, and dried. Crystallization from ten volumes of tetrahydrofuran yielded 6.7 g. (89%) of II, m.p. 126–128° (lit.[11] m.p. 114–116°).

Anal. Calcd. for $C_{20}H_{40}NO_3Cl$: C, 63.53; H, 10.64; Cl, 9.39; N, 3.70. Found: C, 63.30; H, 10.47; Cl, 9.27; N, 4.04.

(B) With Zinc-Acetic Acid.—A solution of the phenylhydrazone (8.56 g.) in 97% acetic acid (70 cc.) was added during 30 min. to a stirred suspension of zinc powder (10 g.) in 97% acetic acid (30 cc.), the temperature being maintained at 18–22° by external cooling. After stirring the colorless mixture for 15 min., the zinc was filtered off and the filtrate poured into cold 2 *N* hydrochloric acid (100 cc.). Crystallization from tetrahydrofuran yielded 6.5–6.7 g. of II, m.p. 126–128°.

***erythro*-N-Dichloroacetyldihydrosphingosine (III).**—A solution of the ester hydrochloride II (25 g.) in dry tetrahydrofuran (500 cc.) was added to a cold suspension of lithium aluminum hydride (10 g.) in dry tetrahydrofuran (250 cc.). After stirring at 40° for 1 hr., the mixture was cooled and the excess of lithium aluminum hydride decomposed by ethyl acetate (5 cc.). Sodium potassium tartrate solution (10%, 500 cc.) was then added, followed by 2 *N* sodium hydroxide solution (50 cc.), and saturated sodium chloride solution (100 cc.). The ethereal extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The solid residue (18 g.), melting at 60–70°, was dissolved in methyl dichloroacetate (200 cc.) and the solution heated in a boiling water bath for 2 hr. To the slightly cooled mixture petroleum ether (500 cc.) was added and the precipitated product was crystallized from methanol; yield 12 g. (45%); m.p. 142–144°.

Anal. Calcd. for $C_{20}H_{39}NO_3Cl_2$: C, 58.25; H, 9.53; N, 3.40; Cl, 17.20. Found: C, 58.50; H, 9.44; N, 3.63; Cl, 17.09.

Dihydrosphingosine.—N-Dichloroacetyldihydrosphingosine (4.12 g.) was dissolved with slight warming in methanol (360 cc.), *N* sodium hydroxide solution (40 cc.) was added, and the solution was left overnight at room temperature. *N* Acetic acid (40 cc.) was added and the solution was concentrated *in vacuo* until precipitation set in. Crystallization from chloroform gave 2.45 g. (82%), m.p. 85–86°.

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The Aqueous Chemistry of Peroxychloroacetic Acid

E. KOUBEK AND JOHN O. EDWARDS

Metcalf Research Laboratory, Brown University,
Providence 12, Rhode Island

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There are several reports in the literature concerning the *in situ* preparations of substituted peroxyacetic