A Stereospecific Synthesis of Racemic Dihydrosphingosine

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For a stereospecific synthesis of racemic dihydrosphingosine,[1] a reaction of *trans*-2,3-epoxyoctadecanoic acid[2,3] with benzylamine was carried out. The reaction with ammonia[4] did not give the desired product. The intermediary epoxy acid was obtained from methyl *trans*-2-octadecenoate[3,5] by epoxidation[3] followed by saponification.[6,7] The same *trans*-glycidic acid was also obtained in less satisfactory yield by the Darzens reaction[6] of hexadecanal.[8] In this case, however, *cis*-glycidic acid[2] and a trimer of hexadecanal[9,10] were also formed.

When *trans*-2,3-epoxyoctadecanoic acid was treated with benzylamine in water, *dl-erythro*-2-benzylamino-3-hydroxyoctadecanoic acid was obtained in 68% yield. Liwschitz and co-workers[11] described that benzylamine attacked selectively the α-carbon atom of *trans*-2,3-epoxybutyric acid to give *dl-erythro*-2-benzylamino-3-hydroxybutyric acid quantitatively. On catalytic hydrogenolysis, the product gave *dl-erythro*-2-amino-3-hydroxyoctadecanoic acid,[1a] which showed a positive ninhydrin test, thus showing the α-amino-β-hydroxy acid structure. Kaneko and Inui[12] described that β-hydroxyvaline gave a positive ninhydrin reaction, whereas β-amino-α-hydroxyisovaleric acid did not.

The methyl ester of the benzylaminohydroxy acid gave, on reduction with lithium aluminum hydride, a benzylaminooctadecanediol.[1a,13] from which *dl-erythro*-2-amino-1,3-octadecanediol,[1,8] *i.e.*, racemic dihydrosphingosine, was obtained by catalytic hydrogenolysis.

The N-acetyl derivative of this aminodiol showed no oxidation on treatment with periodate[14] so that the 1,2-diol structure was excluded.

Experimental

***trans*-2,3-Epoxyoctadecanoic Acid.**—Epoxidation[3] of 5.6 g. (0.019 mole) of methyl *trans*-2-octadecenoate was carried out with perbenzoic acid[15] in chloroform and the resulting glycidate together with the unchanged ester were saponified in the usual way.[6,7] Acidification of the products with concentrated sulfuric acid in ether[16] and recrystallization from hexane gave 1.15 g. (20%) of *trans*-2,3-epoxyoctadecanoic acid, m.p. 89–90°, lit. m.p. 87.5°[2] and 84.5°[3]; ν_{max}^{Nujol} 1745, 1718 (carbonyl), 1270, and 890 cm.$^{-1}$ (epoxy).

***trans*-2,3-Epoxyoctadecanoic Acid by the Darzens Reaction.**—To a mixture of 12.0 g. (0.05 mole) of hexadecanal,[8] 7.3 g. (0.06 mole) of ethyl chloroacetate, and 50 ml. of dry toluene was added a solution of 2.4 g. (0.06 g.-atom) of potassium in 60 ml. of *t*-butyl alcohol over a period of 1.5 hr. under a nitrogen atmosphere, while the temperature was maintained below 20° by cooling in an ice bath. After stirring for 6 hr. at room temperature, 300 ml. of ether and 200 ml. of water was added to the reaction mixture. A substance insoluble in both organic solvent and water separated. This was treated with dilute sulfuric acid and extracted with ether. From this ether solution, 4.8 g. of a yellowish white powder, melting at 60–71°, was obtained. By fractional crystallization from ether–hexane, 0.2 g. (1.3%) of *cis*-2,3-epoxyoctadecanoic acid was obtained, m.p. 90.5–91.5°, lit.[2] m.p. 90.5°; ν_{max}^{Nujol} 1720 (carbonyl), 1285, 925, and 835 cm.$^{-1}$ (epoxy).

The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to give a pasty product, which on cooling yielded 0.6 g. (5%) of crystals. These were proved to be trimer of hexadecanal as recrystallized from petroleum ether (b.p. 30–70°), m.p. 72–73°, lit. m.p. 73–74°[9] and 72.5°.[10]

The filtrate from the trimer was distilled under reduced pressure to give 6.1 g. of crude glycidate, b.p. 180–203° (3 mm.). When this glycidate was saponified similarly, 1.3 g. (8.7% based on hexadecanal) of *trans*-2,3-epoxyoctadecanoic acid was obtained, m.p. 90–90.5°.

***dl-erythro*-2-Benzylamino-3-hydroxyoctadecanoic Acid.**—A mixture of 1.30 g. (0.00436 mole) of the *trans*-epoxy acid and 0.93 g. (0.0087 mole) of benzylamine in 10 ml. of water was stirred at room temperature for 1 hr. and then heated at 90–95° for 3 hr. After cooling, the reaction mixture was acidified to pH 4–5 with dilute hydrochloric acid, and the precipitate was collected, washed with water, and dried to give 1.6 g. (90%) of the product, melting at 207–209°. Recrystallization of the product from glacial acetic acid yielded 1.21 g. (68%) of *dl-erythro*-2-benzylamino-3-hydroxyoctadecanoic acid, m.p. 212.5–214°; ν_{max}^{Nujol} 3370 (hydroxy), 3050, 1720, 1612 (amino acid), 750, and 697 cm.$^{-1}$ (monosubstituted benzene).

Anal. Calcd. for $C_{25}H_{43}NO_3$: C, 74.03; H, 10.69. Found: C, 74.30; H, 10.86.

***dl-erythro*-2-Amino-3-hydroxyoctadecanoic Acid.**—A suspension of 0.810 g. (0.002 mole) of the benzylaminohydroxy acid in 50 ml. of glacial acetic acid was shaken at room temperature with 0.5 g. of 10% palladium–carbon under ordinary pressure of hydrogen for 16 hr. The product was recrystallized from glacial acetic acid to afford 0.390 g. (62%) of *dl-erythro*-2-amino-3-hydroxyoctadecanoic acid, m.p. 221–222.5°, lit.[1a] m.p. 217–220°; ν_{max}^{Nujol} 3400 (hydroxy), 1658, and 1590 cm.$^{-1}$ (amino acid). This aminohydroxy acid showed a faint red coloration with ninhydrin.

***dl-erythro*-2-Benzylamino-1,3-octadecanediol.**—To a stirred solution of 0.43 g. of lithium aluminum hydride in 20 ml. of dry ether was added a solution of the methyl ester prepared from 1.215 g. (0.003 mole) of the benzylaminohydroxy acid by Fischer's method and dissolved in 20 ml. of dry ether. After the mixture was refluxed for 4 hr. and excess lithium aluminum hydride was destroyed with careful addition of water, the reaction mixture was made alkaline with 10% sodium hydroxide solution and extracted with ether. From this ether solution, 1.04 g. (89%) of the product, melting at 60–61°, was obtained. Recrystallization of the product from petroleum ether (b.p. 30–70°) gave 0.835 g. (71%) of *dl-erythro*-2-benzylamino-1,3-octadecanediol, m.p. 65–65.5°, lit.[1a] m.p. 62.5–63.5°; ν_{max}^{Nujol} 3320 (N–H), 3020–2750 (hydroxy), 750, and 695 cm.$^{-1}$ (monosubstituted benzene).

***dl-erythro*-2-Amino-1,3-octadecanediol.**—A solution of 0.587 g. (0.0015 mole) of the benzylaminodiol in 30 ml. of ethanol was shaken under hydrogen of atmospheric pressure with 1.0 g. of 10% palladium–carbon for 9 hr. at room temperature. Re-

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crystallization of the product from ether–chloroform gave 0.388 g. (85%) of *dl-erythro*-2-amino-1,3-octadecanediol, m.p. 87–89°, lit.[1a] m.p. 84–86°; ν_{max}^{Nujol} 3310, 1595 (NH_2), ~3000, 1075, and 1015 cm.$^{-1}$ (hydroxy).

When the aminodiol was treated with ethyl acetate, the N-acetyl derivative was obtained, m.p. 125–125.5°, after recrystallization from hexane–ethyl acetate; ν_{max}^{Nujol} 3295 (N–H), ~3100 (hydroxy), 1645, and 1560 cm.$^{-1}$ (amide). This N-acetyl derivative showed negative reaction with the periodate oxidation reagent.[14]

In a usual way, tribenzoyl, m.p. 145.5–146°, lit.[1a] m.p. 144–145°, and triacetyl derivatives of the aminodiol, m.p. 91–92°, lit.[1a] m.p. 90–92°, were prepared in 72 and 69% yields, respectively.

Reactions of Steroidal Δ^4-3-Ketones in the Presence of Phosphorus Trihalides[1]

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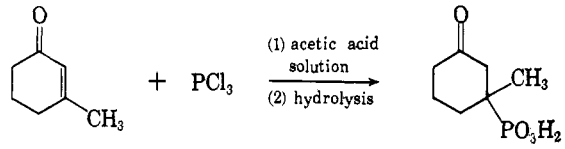
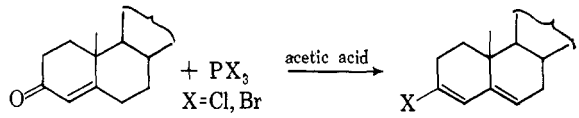
The preparation of steroidal 3-chloro-3,5-dienes from Δ^4-3-ketones has been the subject of two recent publications.[2,3] Oxalyl chloride[2] and phosphorus oxychloride[3] have been found to be effective reagents for causing this transformation. Other acid chlorides which have been used are acetyl chloride,[4] benzoyl chloride,[5] α-chloropropionyl chloride,[6] and phosphorus pentachloride.[7]

Phosphorus trichloride has not been used to effect this conversion. This reagent in fact would not be expected to cause this type of chlorination since the normal mode of reaction of phosphorus trihalides with ketones yields organophosphorus derivatives.[8] Saturated ketones give α-hydroxyphosphonic acids, and α,β-unsaturated ketones undergo Michael-type additions leading to γ-ketophosphonic acids. Thus, 3-methyl-2-cyclohexenone has been reported to react as follows with phosphorus trichloride in acetic acid.[9]



Phosphorus trihalides have been found in the present work, however, to convert steroidal Δ^4-3-ketones in acetic acid solutions to the corresponding 3-halo-3,5-dienes.

When an acetic acid solution of 4-cholesten-3-one and excess phosphorus trichloride is allowed to stand



at room temperature, 3-chloro-3,5-cholestadiene begins to precipitate after 1–2 hr. The conversion appears to be complete after 3–4 hr. The reaction has been extended to the preparation of 3-chloro-3,5-androstadien-17β-ol acetate from testosterone acetate. Phosphorus tribromide reacts equally well to give the previously unreported 3-bromo derivatives. The only other reported bromination of this type involves heating the steroid with α-bromopropionyl bromide.[6]

No similar halogenations of ketones with phosphorus trihalides are known except for the conversion of 1,3-cyclohexanediones to the corresponding 3-chloro-2-cyclohexenones.[10] This reaction is considered to proceed *via* the enol form of the diketone. The enol form of cholestenone or testosterone acetate, however, is probably not present in sufficient concentration to account for the very facile transformation reported here.

An alternate explanation for the ease of this reaction could be that the phosphorus trihalide reacts rapidly with the large excess of acetic acid used to dissolve the steroid. The acetyl chloride thus formed might then be the active halogenating agent. Acetyl chloride has indeed been found in the present investigation to convert cholestenone to the 3-chlorodiene under conditions similar to the phosphorus trichloride method, but this reaction is much slower and gives a lower yield than when the phosphorus reagent is used. The increased rate using phosphorus trihalides is possibly due to a catalytic effect of the phosphorous acid formed concurrently with acetyl chloride.

The influence of solvent is also shown when cholestenone is treated with phosphorus trichloride in acetic anhydride solution, conditions which also nor nally lead to the Michael-type addition. Cholestenone enol acetate results from this reaction. Phosphorus trichloride appears here to have the same function as the acid chloride in the preparation of steroidal enol acetates using acetyl chloride–acetic anhydride mixtures.

Experimental[11]

3-Halo-3,5-dienes. General Procedure.—Solutions of 3–5 g. of the Δ^4-3-ketones, 20–25 ml. of glacial acetic acid, and 2–3 ml. of the phosphorus trihalide were allowed to stand in stoppered flasks at room temperature for about 4 hr. The solutions turned bright yellow upon addition of the phosphorus trihalide, and crystallization of the product usually began after 1 hr. The mixtures were cooled and the crude products were obtained by filtration using sintered-glass funnels. The white, crystalline halodienes were washed with dilute sodium bicarbonate solution, dried, and recrystallized. The compounds as first isolated were pure white, but they decomposed on standing.

3-Chloro-3,5-cholestadiene.—The general procedure was followed using 3.53 g. (9.16 mmoles) of 4-cholesten-3-one, 25 ml. of glacial acetic acid, and 1.5 ml. (2.4 g., 17 mmoles) of phosphorus trichloride. The yield of crude product, m.p. 63–65°, was 3.09 g. (77%). Recrystallization from ether–95% ethanol gave large, colorless prisms, m.p. 65–66°, $[\alpha]^{29}D$ −125° (*c* 1.74, $CHCl_3$), λ_{max} 242 mμ (log ε 4.3); lit.[5,12] m.p. 62–63°, $[\alpha]^{23}D$ −117°, λ_{max} 243 mμ.

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