COMMUNICATIONS

- New or improved synthetic methods
- Key intermediates
- with full experimental and analytical data

Novel Synthesis of 25-Azacoprostane

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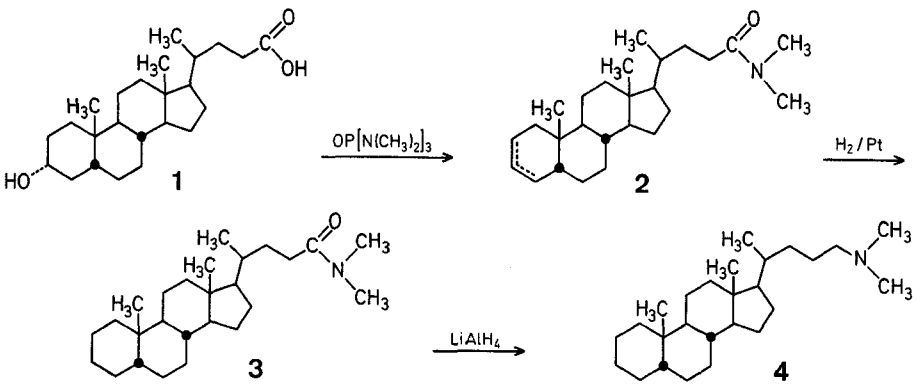
Considerable interest has developed in recent years in azasteroids, which have been found to exhibit many useful biological properties. 25-Azacoprostane **(4)** is an effective inhibitor of molting, metamorphosis, and steroid metabolism in insects[1]. Previous syntheses of **4** have been carried out starting with relatively expensive cholanic acid[2] or more readily available cholic acid[3]. The latter synthesis involved six steps, and proceeded in unspecified yield. In this communication, I wish to report a simple three-step synthesis of **4** from lithocholic acid **(1)**.

Some years ago, it was reported that carboxylic acids could be converted directly to dimethylamides with hexamethylphosphoric triamide (HMPT) at 180–200 °C[4]. Later, it was shown that alcohols can be cleanly dehydrated without rearrangement in refluxing HMPT[5]. When lithocholic acid **(1)** was heated to reflux in HMPT, the unsaturated amide **2** was obtained in 91% crude yield. This reaction is best carried out with a large excess of HMPT at reflux, some solvent being allowed to distill out of the reaction. At lower temperatures, and with lesser amounts of HMPT, intractible materials, probably mixed phosphoric amide/esters, were obtained. Hydrogenation over platinum dioxide in ethanol gave *N,N*-dimethylcholanamide **(3)** contaminated with a single minor impurity. Medium pressure chromatography[6] and crystallization from acetone gave pure **3** in 65% yield. Reduction with lithium aluminum hydride proceeded quantitatively to give pure **4**, after crystallization from ethyl acetate.



25-Azacoprostane (4):

N,N-*Dimethyldehydrocholanamide* **(2**; Mixture of Δ^2 and Δ^3 Isomers): A solution of lithocholic acid (**1**; 15.5 g, 0.041 mol) in HMPT (150 ml) is heated to reflux for 15 min. Then, part of the solvent (~80 ml) is distilled off, the mixture is allowed to cool in a sealed system, diluted with water (500 ml), and extracted with hexane (2 × 200 ml). The hexane solution is extracted with saturated sodium chloride solution (3 × 100 ml), dried with magnesium sulfate, filtered, and stripped on a rotary evaporator to give 14.4 g of crystalline product. [This material shows a strong amide carbonyl band in the I.R. spectrum, with no evidence for hydroxy or carboxy groups. The ^{1}H-N.M.R. spectrum shows complex olefinic proton signals, indicating a mixture of double bond isomers, as well as two sharp signals at $\delta = 3.00$ and 2.96 ppm, characteristic of the dimethylamide group.]

N,N-*Dimethylcholanamide* **(3)**: The entire crude product **2** is dissolved in absolute ethanol (80 ml) and hydrogenated in a Parr apparatus over platinum dioxide overnight. Filtration through Celite® followed by removal of solvent gives the crude amide **3**, which is purified by column chromatography on 40–63 μ silica gel 60[6] (hexane/ethyl acetate 1/1 as eluent). Crystallization of the combined pure fractions from acetone gives pure **3**; yield: 10.2 g (64%, based on **1**); m.p. 125–126 °C.

$C_{24}H_{25}NO$ (387.3501)

M.S. (high resolution): $m/e = 387.3516$ (M^+).

I.R. (Nujol): $\nu = 1644$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.98$ (s, 3H); 2.92 (s, 3H); 0.92 (d, 3H, $J = 6$ Hz); 0.92 (s, 3H); 0.65 ppm (s, 3H).

25-Azacoprostane **(4)**: *N,N*-Dimethylcholanamide (**3**; 9.9 g, 0.0255 mol) is dissolved in ether (500 ml), and lithium aluminum hydride (2.0 g, ~0.055 mol) is added in small batches over 15 min. The solution is heated to reflux for 2 h, then allowed to stand at ambient temperature overnight, and quenched with aqueous sodium sulfate. It is then filtered, the solvent removed in vacuo, and the residue crystallized from ethyl acetate; yield: 9.5 g (~100%); m.p. 64–65 °C (Ref.[1], m.p. 65–66 °C).

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