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Synthesis of 10α-Methoxy-Δ^{8,9}-lysergaldehyde from Elymoclavine

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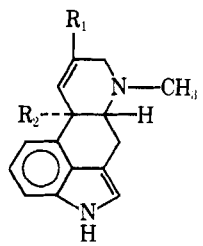
Abstract □ A new synthesis is described for 10α-methoxy-Δ^{8,9}-lysergaldehyde involving the oxidation of elymoclavine with manganese dioxide in methanol. Lysergol and agroclavine provide no reaction under the same conditions.

Keyphrases □ 10α-Methoxy-Δ^{8,9}-lysergaldehyde—synthesized by oxidation of elymoclavine with manganese dioxide in methanol □ Alkaloids, ergot—10α-methoxy-Δ^{8,9}-lysergaldehyde, synthesized by oxidation of elymoclavine with manganese dioxide in methanol □ Elymoclavine—oxidized with manganese dioxide in methanol to 10α-methoxy-Δ^{8,9}-lysergaldehyde

Elymoclavine (I) is well established as an intermediate in the biosynthesis of the lysergic acid-type ergot alkaloids (1). The oxidation of elymoclavine at C-17 is of interest because Δ^{8,9}-lysergaldehyde (II) and/or Δ^{9,10}-lysergaldehyde are possible biosynthetic intermediates and because of the well-known pharmacological properties of the ergot alkaloids. Elymoclavine is easily oxidized to the 8-hydroxy-Δ^{9,10} derivatives penniclavine and isopenniclavine (2), and chanoclavine (6,7-*seco*-elymoclavine) is readily oxidized to chanoclavine aldehyde (3), but the hydroxymethyl group of elymoclavine has proven quite resistant to common oxidants (4, 5).

Lin *et al.* (4) obtained the enol acetate of Δ^{9,10}-lysergaldehyde (6-methyl-8-acetoxymethylene-9-ergolene) by dimethyl sulfoxide–acetic anhydride oxidation of elymoclavine. Mayer and Eich (5) obtained traces of lysergic acid by Oppenauer oxidation of elymoclavine and small yields of dihydrolysergic acid from dihydroelymoclavine. Dihydrolysergaldehyde has been prepared by reduction of lysergic acid derivatives (6).

The manganese dioxide oxidation of 10α-methoxyelymoclavine (III) to 10α-methoxy-Δ^{8,9}-lysergaldehyde (IV) was reported (7). Compound III was obtained by hydride reduction of the 10α-methoxy ester (V) prepared by mercuric acetate oxidation of methyl lysergate in methanol (8). This was the first successful attempt to obtain a lysergaldehyde by oxidation of an elymoclavine derivative.



I: $R_1 = CH_2OH$, $R_2 = H$
II: $R_1 = CHO$, $R_2 = H$
III: $R_1 = CH_2OH$, $R_2 = OCH_3$
IV: $R_1 = CHO$, $R_2 = OCH_3$
V: $R_1 = COOCH_3$, $R_2 = OCH_3$
VI: $R_1 = CH_3$, $R_2 = H$

Previous attempts in this laboratory to prepare lysergaldehydes from elymoclavine also were unsuccessful. However, 10α-methoxy-Δ^{8,9}-lysergaldehyde (IV) can be prepared in good yield by the direct oxidation of elymoclavine with manganese dioxide in methanol.

EXPERIMENTAL[1]

For the preparation of 10α-methoxy-Δ^{8,9}-lysergaldehyde (IV), ely-

[1] Melting points were determined on a Thomas-Hoover Uni-Melt melting-point apparatus and are uncorrected. UV spectra were run on a Beckman model 24 spectrophotometer. IR spectra were run in potassium bromide using a Beckman IR-8 spectrophotometer. NMR spectra were obtained in deuterochloroform on a Jeol C-60H spectrometer with tetramethylsilane as the internal standard. Mass spectra were recorded on an LKB-9000S spectrometer.

moclavine[2] (2.0 g, 7.9 mmoles) in methanol (400 ml) was treated with 20 g of manganese dioxide (9), and the mixture was stirred at room temperature. After 12 hr, the mixture was filtered, the filtrate was evaporated to dryness, and the residue was dissolved in 10 ml of chloroform. TLC on silica gel G with an ethyl acetate–dimethylformamide–ethanol (13:1:1) solvent revealed a major product (R_f 0.77) that was nonfluorescent and gave a green color with Ehrlich's reagent, a small quantity of unreacted elymoclavine (R_f 0.23), and only traces of other Ehrlich-positive compounds.

Purification of the product was accomplished by chromatography on a silica gel (40 g) column with chloroform as the solvent. Recrystallization from chloroform–hexane provided 1.2 g (55% yield) of small white needles, mp 192–194° dec.; UV: λ_{max}(ethanol) 223 (log ϵ 4.58) and 297 (3.73) nm; IR: ν_{max} (KBr) 3170, 2930, 2800, 1680, 1400, 1180, 1070, 900, and 750 cm^{-1}; NMR: δ 2.56 (s, 3H, NCH_3), 3.13 (s, 3H, OCH_3), 6.94–7.44 (m, 4H, indole), 7.67 (s, 1H, 9=CH), 8.33 (s, 1H, NH), and 9.67 (s, 1H, CHO) ppm. The mass spectrum showed a molecular ion at *m/e* 282 (100) and a prominent ion at *m/e* 154 (48) characteristic of ergolines (10).

The product was compared with a reference sample[3] of IV and was identical in all respects (TLC; melting point; and UV, IR, NMR, and mass spectra).

DISCUSSION

Ergoline derivatives including ethers related to IV have been of interest recently as potential prolactin inhibitors (11) and α-adrenergic blocking agents (12). The manganese dioxide oxidation of elymoclavine in methanol provides a convenient one-step synthesis of IV from a readily available starting material.

It was also of interest to obtain some indication of whether manganese dioxide might be useful for the C-17 and/or C-10 oxidation of other ergolines. For this purpose, lysergol, the $\Delta^{9,10}$-isomer of elymoclavine (I), and agroclavine (VI) were treated under the same conditions used for the oxidation of elymoclavine. Lysergol was unchanged under these conditions, which was not surprising since manganese dioxide is most effective for the oxidation of allylic alcohols (13). However, it was interesting that agroclavine was also unreactive since C-10 oxidation of the $\Delta^{8,9}$-ergolenes can be accomplished with various oxidizing agents (1, 2). Additional studies are required to determine the precise utility of manganese dioxide for the C-17 and C-10 oxidation of ergolines.

[2] Isolated from ergot strain SD 58 provided by Dr. James E. Robbers, Department of Medicinal Chemistry and Pharmacognosy, Purdue University, West Lafayette, Ind.

[3] Provided by Dr. E. C. Kornfeld, Eli Lilly Co., Indianapolis, Ind.

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Direct Complexometric Titration of Calcium Phosphates

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Abstract □ Calcium was determined in calcium phosphate samples by dissolving the sample in hydrochloric acid, adding hydroxynaphthol blue indicator and triethanolamine, adjusting the pH to 12.3–12.5 with potassium hydroxide solution, and titrating with standard disodium ethylenediaminetetraacetate solution. Time can be saved and the formation of a precipitate (which dissolves readily during the titration) can be avoided by adding at least 85% of the amount of complexing agent required for titration before adjusting the pH.

Keyphrases □ Calcium—complexometric analysis in dibasic and tribasic calcium phosphates, bulk drug and tablets □ Complexometry—analysis, calcium in dibasic and tribasic calcium phosphates, bulk drug and tablets

Previously, calcium was determined in the presence of phosphate complexometrically by the addition of excess complexing agent and determination of the excess, after separation from phosphate by ion exchange (1), and also after removal of phosphate by formation and extraction of phosphomolybdate (2). All of these efforts are based on the impossibility of a direct complexometric titration of calcium in the presence of equivalent amounts of phosphate. This paper reports a simple, rapid, direct complexometric titration of calcium in the presence of phosphate.

EXPERIMENTAL

All reagents and volumetric solutions were those specified in USP XIX. All experiments were done according to the following general directions, modified as indicated.

General Method—Dissolve a sample expected to contain about 225 mg of calcium, accurately weighed, in 15 ml of hydrochloric acid and 10 ml of water contained in a 100-ml volumetric flask, with the aid of gentle heat if necessary, and cool to room temperature. Dilute to volume with