THERMAL DECOMPOSITION OF DIHYDROERGOCRISTINE METHANESULPHONATE

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Abstract - By thermal decomposition of dihydroergocristine methanesulphonate (1a.CH_3SO_3H) are formed dihydrolysergyldehidrovaline methyl ester (2), dihydrolysergyldehydrovaline azlactone (3c), dihydrolysergic acid (3a), dihydrolysergamide (3b), S-phenylalanyl-S-proline lactam (4a) and S-phenylalanyl-R-proline lactam (4b).

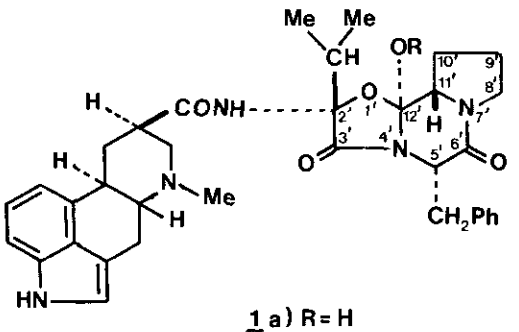
Partially hydrogenated ergot alkaloids are relatively stable compounds and do not isomerize into iso derivatives in solutions. However, their thermal and photochemical stability is limited. Recently, it has been reported that aqueous solution of dihydroergotamine methanesulphonate decomposes by heating at 100°C, where 9,10-dihydrolysergic acid and 9,10-dihydrolysergamide have been isolated as decomposition products.[1]

In this communication we report on the thermal decomposition of dihydroergocristine methanesulphonate (1a.CH_3SO_3H) in the solid state. Dihydroergocristine is one of the constituents of dihydroergotoxine besides dihydroergocornine and dihydroergocryptine obtained by the hydrogenation of the ergotoxine fraction of the Claviceps alkaloids. It is used in the therapy of cerebral arteriosclerosis, arterial hypertension, peripheral angiopathies and postapoplectic conditions, usually in the form of methanesulphonate salts. The thermal instability, frequently observed by the preparation of dihydroergotoxine, stimulated this investigation.

Decomposition of dihydroergocristine methanesulphonate began at 80°C and ended at about 190°C in approximately 30 min. The resulting black tar was dissolved in sodium hydroxide solution and extracted with methylene chloride. The dry residue obtained by evaporation of the solvent was separated by liquid chromatography to give four decomposition products, which were identified with dihydrolysergyldehydrovaline methyl ester (2) (5%), dihydrolysergyldehydrovaline

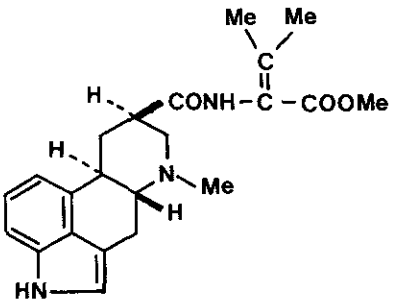
azlactone (3c) (6.9%), 9,10-dihydrolysergamide (3b) (4%), S-phenylalanyl-R-proline lactam (4b) (34%), and S-phenylalanyl-S-proline lactam (4a) (23%).

The work-up of the alkaline aqueous layer gave 9,10-dihydrolysergic acid (3a) (51%). The formation of S-phenylalanyl-R-proline lactam (4b) is due to the easy isomerization of the corresponding S-phenylalanyl-S-proline lactam (4a) in the presence of dilute sodium hydroxide solution at room temperature for a short time, known also for some other diketopiperazines.[2]

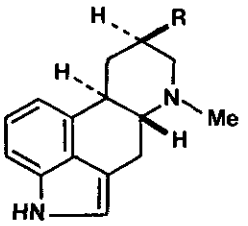


1 a) R = H
b) R = C_2H_5

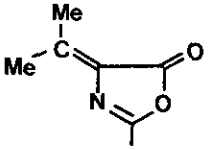
$\triangle$, 190°C

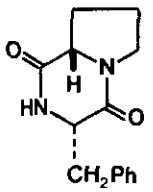


2

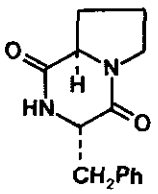


3a) R = COOH
b) R = $CONH_2$
c) R =





4a



4b

EXPERIMENTAL

Preparative Waters Associates LC System 500 equipped with LKB Uvicord II 8300 spectrophotometer and Speedomax 680 recorder, two silica gel Waters Associates prepacked columns no.500 (316 g each, 230-400 mesh) and a mixture of methylene chloride and ethanol (98:2) at 4 atm were used for liquid chromatography separation. IR spectra were recorded on a Perkin-Elmer 457 instrument.

Thermal decomposition of 9,10-dihydroergocristine methanesulphonate (1a.CH_3SO_3H).

9,10-Dihydroergocristine methanesulphonate (1a.CH_3SO_3H) (20 g, 0.028 mole) was heated at 190°C for 30 min. The resulting black tar was dissolved in water (600 ml), made alkaline with sodium hydroxide solution (5% NaOH, 80 ml) and extracted with methylene chloride (6 times, 600 ml each time). The combined extracts were washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent in vacuo gave the dry residue (7.69 g), which represents a mixture of several compounds. Liquid chromatography separation afforded the following decomposition products:

Fraction I. The crude product[3] (0.53 g, 5%) obtained by evaporation of solvent in vacuo, was recrystallized from methanol to give white crystals (0.13 g, 1.3%), mp 235-237°C, ms (M^+) 381, $|\alpha|_D^{20}$ - 122° (c=0.2, pyridine). The compound was identified as dihydrolysergyldehydrovaline methyl ester (2), lit. mp 245-246°C, $|\alpha|_D^{20}$ - 130° (c=0.2, pyridine).[6]

Fraction II. After evaporation of the solvent in vacuo an oily product (3.19 g, 16%) was obtained. It was dissolved in boiling ethyl acetate (70 ml), charcoal (3 g) was added, stirred at room temperature for 15 min and filtered through Celite 545. After cooling diethyl ether (70 ml) was added and after the addition of a few small crystals of S-phenylalanyl-S-proline lactam, in order to induce crystallization, a yellow precipitate (1.84 g, 27%) was formed and collected by filtration. The crude product was dissolved in boiling ethyl acetate (35 ml), filtered, diethyl ether (35 ml) was added to the filtrate after cooling and the mixture left in refrigerator at -15°C overnight. The precipitate was collected by filtration, washed with a mixture of ethyl acetate and diethyl ether (1:1) to give white crystals (1.59 g, 23%), mp 128-132°C, $|\alpha|_D^{20}$ - 80.6° (c=0.2, water). The compound was identified as S-phenylalanyl-S-proline lactam (4a), lit. $|\alpha|_D^{20}$ - 83° (c=0.2, water), lit. mp 133°C,[2] $|\alpha|_D^{20}$ - 84° (c=0.2, water), mp 135°C.[8]

Fraction III. The solid (0.67 g, 6.9%) obtained after evaporation of the solvent in vacuo was crystallized from methanol to give white crystals (0.32 g, 3.3%), mp 236-238°C, ms (M^+) 349, $|\alpha|_D^{20}$ - 104.6 (c=0.35, pyridine). The compound was identified as dihydrolysergyldehydrovaline azlactone (3c), lit. mp 240-241°C, $|\alpha|_D^{20}$ - 107° (c=0.35, pyridine).[6]

Fraction IV. The oily residue (3.34 g, 49%) obtained after evaporation of the solvent in vacuo crystallized by addition of the mixture of methanol and ether (1:1, 50 ml). After further addition of ether (375 ml) white needles (2.32 g, 34%) were obtained, mp 145-146°C, $|\alpha|_D^{20}$ + 90.6° (c=0.2, water). The compound was found identical on the basis of its mp, mixture mp, $|\alpha|_D^{20}$, and ir spectrum with S-phenylalanyl-R-proline lactam, lit. mp 148-150°C, $|\alpha|_D^{20}$ + 92° (c=0.2, water).[2]

Finally, the column was washed with methanol (1000 ml). After evaporation of methanol in vacuo the dark brown residue (280 mg, 4%) was obtained, which gave after recrystallization from methanol white crystals (82 mg, 1%), mp 272-275°C, $|\alpha|_D^{20}$ - 130° (c=0.5, pyridine), identified as 9,10-dihydrolysergamide, lit. mp 276°C, lit. $|\alpha|_D^{20}$ - 131°.[7]

The aqueous layer obtained after extraction with methylene chloride was concentrated in vacuo to 200 ml and saturated with carbon dioxide. White precipitate formed after cooling to room temperature was collected by liftration to give 9,10-dihydrolysergic acid (3.87 g, 51%) identified by comparison of its ir and ms spectra with those of an authentic sample.[7]

REFERENCES AND NOTES

1. H. Auterhoff and A. Walter, Deutsch.Apoth.Ztg., 1975, 115, 1931.
2. H. Ott, A. J. Frey, and A. Hofmann, Tetrahedron, 1963, 19, 1675, and references cited therein.
3. The crude product was contaminated with a trace of 12'-O-ethyldihydroergocristine (1b) detected only by mass spectrometry. The formation of 1b is due most probably to the presence of a trace of ethanol used for crystallization of dihydroergocristine. This is in agreement with the observation that some other ergot alkaloids with a peptide side chain can be easily transformed into 12'-O-alkyl derivatives in the presence of alcohol in acidic media.[4,5]
4. F. Troxler and A. Hofmann, Helv.Chem.Acta, 1957, 40, 2160.
5. H. R. Schneider, P. A. Stadler, P. Stütz, F. Troxler, and J. Seres, Experientia, 1977, 33, 1412.
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7. A. Hofmann, "Die Mutterkornalkaloide", F. Enke Verlag, Stuttgart, 1964, p. 39.
8. The compound was identical with an authentic sample obtained from the Ajinomoto Co. Inc., Tokyo, Japan.

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