A STUDY OF THE HOFMANN DEGRADATION OF ALOPERINE — THE ALKALOID OF SOPHORA ALOPECUROIDES (LEGUMINOSAE)

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It has been established by analysis that aloperine $C_{15}H_{24}N_2$ (I) [1] does not contain a CH_3C group.

Catalytic hydrogenation, which takes place with difficulty in an acid medium on heating, has shown that aloperine (I) has one double bond.

On the basis of these results it may be assumed that it contains four condensed rings.

Like angustifoline [2, 3], aloperine gives a spectrum showing no absorption characteristic for an NH group, but the alkaloid readily gives N-benzoyl- [1], N-acetyl-, and N-methylaloperine. The second nitrogen atom is tertiary.

Depending on the conditions, methylation of aloperine with methyl iodide leads either to the formation mainly of N-methylaloperine (in methyl alcohol) or to the methiodide of N-methylaloperine (in acetone).

The end product of the methylation of both aloperine and its N-methyl derivative is, according to the results of paper chromatography, a mixture of two substances. It has been possible by crystallization to separate it into two methiodides of N-methylaloperine similar in composition but having different constants: a methiodide (II) obtained in major amount, and a methiodide (III).

Mixtures of these two substances give a depression of the melting points and the IR absorption spectra also differ.

The Hofmann degradation of the methiodides (II) and (III) takes place with the formation in both cases of a mixture of decomposition products. The methiodide (III) gives mainly an amorphous substance with R_f 0.31, which crystallizes well in the form of the hydrochloride and the perchlorate. In contrast to that of aloperine, its UV absorption spectrum has an absorption maximum at 240 mμ (log ε 4.25), which shows the presence of conjugated double bonds.

The degradation product of the methiodide (II) was a mixture of substances (R_f 0.6, 0.32 - predominating; 0.2, 0.12 - predominating; 0.03, and a spot at the starting line), which gave no crystalline salts and was not separated.

On performing the second stage of the Hofmann degradation of the methine base of the methiodide (III), the carbonate of a quaternary base which could not be decomposed was formed. The methochloride obtained from it also did not decompose appreciably.

To study Hofmann degradation at the tertiary nitrogen atom, the secondary nitrogen atom of aloperine was previously protected by means of an acetyl group. According to a chromatogram (R_f 0.36, 0.26) the acetyl derivative of aloperine consisted of a mixture of two substances. Recrystallization of the perchlorates of these derivatives gave a small amount of only one of the isomers in the pure state with mp 262-263.5°.

In view of the difficulty of separating the perchlorates, methylation of the mixture of acetylaloperines was carried out, this proceeding very slowly. The resulting mixture of two substances (R_f 0.45 and 0.37) was separated by chromatography on alumina into two methiodides of acetylaloperine-(IV) isolated in the major amount, and (V). A mixture of them gave a depression of the melting point. The IR spectra of both methiodides exhibited characteristic absorption at 1640 cm^{-1}, but in methiodide (V) this band was resolved into a doublet and the valence vibrations of a CH group (3020 cm^{-1} and 3095 cm^{-1}) appeared clearly. The spectra also differed as regards skeletal vibrations.

The Hofmann degradation of the methiodide (IV) led to the splitting out of methyl alcohol. Methylation of the reaction product gave, instead of the initial methiodide (IV), a methiodide which, by IR spectrum, melting point, and R_f, proved to be identical with its isomer (V).

Experimental

Hydrogenation of aloperine. A solution of 10% hydrochloric acid was added to 15 g of aloperine hydrochloride in 50 ml of water to give pH 4, and reduction was carried out in the presence of 1.5 g of platinum at 70-90°. After 12 hr, 1160 ml of hydrogen had been absorbed (calculated 1100 ml). The product consisted of 12.8 g of the crystalline hydrochloride of dihydroaloperine with mp 303-305° (from alcohol), $[\alpha]_D^{20} - 5.7°$ (c 1; methanol); R_f 0.11.

Found: C 52.00; H 9.07; N 8.36; Cl 20.75%. Calculated for $C_{15}H_{28}N_2Cl_2 \cdot 2H_2O$: C 52.44; H 9.39; N 8.16; Cl 20.68.

An aqueous solution of 10 g of the hydrochloride was made alkaline with 25% ammonia to pH 14 and was extracted completely with ether (6. 24 g). This gave dihydroaloperine, which, in contrast to aloperine, did not decolorize a solution of potassium permanganate in sulfuric acid and gave no coloration with tetranitromethane in chloroform. It had mp 84-84. 5° (from acetone), $[\alpha]_D^{20}$ – 16. 5° (c 1; methanol), R_f 0. 11.

Found: C 77. 10; H 11. 04; N 11. 81%. Calculated for $C_{15}H_{26}N_2$: C 76. 85; H 11. 19; N 11. 95%.

Methylation of aloperine with methyl iodide in acetone. A solution of 7. 2 g of aloperine in acetone (1: 10) was boiled with 3. 6 ml of CH_3I for 18 hr. An aqueous solution of the precipitate which deposited (10. 92 g) was treated with ether, made alkaline with 40% caustic soda solution to pH 14, and extracted completely with ether (1. 95 g) and then with chloroform (7. 5 g).

N-Methylaloperine. A solution of 1. 95 g of the oily substances in 25 ml of 10% hydrochloric acid was made alkaline with 25% ammonia and was extracted completely with ether. Mp 97-98° (from ether); R_f 0. 14.

Found: C 77. 91; H 10. 78; N 11. 39%. Calculated for $C_{16}H_{26}N_2$: C 77. 98; H 10. 64; N 11. 37%.

N-Methylaloperine methiodide (II). 7. 5 g of the oily substance was carefully triturated with ether. The solidifying methiodide was washed with 3 ml of acetone (R_f 0. 05 and 0. 1). The methiodide (II) had mp 198-200° (from water), $[\alpha]_D^{20}$ + 117. 6° (c 1; chloroform); R_f 0. 05; on re-passing solvent through the chromatogram, R_f 0. 09.

Found: C 52. 67; H 7. 56; N 7. 15; I 32. 32%. Calculated for $C_{17}H_{29}N_2I$: C 52. 56; H 7. 52; N 7. 21; I 32. 69%.

Methylation of aloperine in methanol. A solution of 6. 4 g of aloperine in 40 ml of methanol was boiled with 3. 2 ml of methyl iodide for 3. 5 hr. The aqueous solution of the reaction products was made alkaline with 25% ammonia and was extracted with ether (5. 43 g) and then with chloroform (0. 83 g).

Methylation of N-methylaloperine with methyl iodide in acetone. A solution of 5. 43 g of N-methylaloperine in acetone (1: 20) was boiled with 2. 8 ml of methyl iodide for 24 hr. From the 5. 07 g of the hydriodide of the methiodide that separated as a precipitate, 2. 54 g of methiodide (R_f 0. 1 and 0. 05) was isolated, and it was recrystallized first from water and then from absolute alcohol.

The methiodide (III) had mp 205-206°, $[\alpha]_D^{20}$ + 85. 6° (c 1; chloroform), R_f 0. 1; on re-passage of the solvent through the chromatogram, R_f 0. 23.

Found: C 52. 17; H 7. 56; N 7. 05; I 33. 41%. Calculated for $C_{17}H_{29}N_2I$: C 52. 56; H 7. 52; N 7. 21; I 32. 69%.

The acetonic solution yielded a further 3. 5 g of methiodide (R_f 0. 05; 0. 1).

Hofmann degradation of aloperine (1st stage). A solution of 1. 1 g of the methiodide (III) in 10 ml of water was shaken with freshly-precipitated silver oxide until the reaction for iodine had disappeared. The filtered aqueous solution was evaporated in vacuum. The residue was heated at 100° for 30 min; the decomposition product was extracted with ether (0. 51 g, R_f 0. 31, 0. 15, 0. 08).

The undecomposed residue was boiled with 60 ml of xylene for 1 hr 30 min. The xylene layer was shaken with 10% sulfuric acid solution. The acid solution was made alkaline with 25% ammonia and extracted with ether (0. 1 g – R_f 0. 31, 0. 15, 0. 08).

The crystalline hydrochloride of the methine base of the methiodide (III) was obtained by the addition of alcoholic hydrochloric acid. Mp 244-245° (from alcohol), $[\alpha]_D^{20}$ + 162. 9° (c 1; methanol), R_f 0. 22.

Found: C 61. 35; H 9. 29 (with oxidizing mixture); N 7. 95; Cl 21. 14%. Calculated for $C_{17}H_{30}N_2Cl_2$: C 61. 22; H 9. 07; N 8. 40; Cl 21. 30%.

The perchlorate of the methine base of the methiodide (III) had mp 219-220°.

Methylation of the methine base of the methiodide (III) with methyl iodide. A solution of 1. 75 g of the base in 25 ml of acetone was boiled with 1 ml of methyl iodide for 30 min, which gave 2. 44 g of methiodide. Mp 222-224° (from alcohol); R_f 0. 21 (slight contamination with R_f 0. 23).

Found: C 53. 24; H 7. 59; N 6. 50; I 31. 99%. Calculated for $C_{18}H_{31}N_2I$: C 53. 78; H 7. 77; N 6. 96; I 31. 55%.

Hofmann degradation of aloperine (2nd stage). An aqueous solution of 1. 7 g of the methiodide of the methine base (III) was shaken with freshly-precipitated silver oxide. The filtered solution was evaporated in vacuum. The crystalline residue (0. 65 g-R_f 0. 22) did not decompose appreciably at 100° or even when it was heated with a gas burner for 5 min or boiled with a 25% alcoholic solution of caustic potash (1 hr 30 min).

When alcoholic hydrochloric acid was added to the crystalline residue, bubbles of CO_2 were evolved.

The hydrochloride of the methochloride had mp 202-210° (from absolute alcohol), $[\alpha]_D^{20}$ + 133. 7° (c 1; methanol), R_f 0. 18 and 0. 11.

Found: C 57.02; H 9.20; N 7.21; Cl 18.52%. Calculated for $C_{18}H_{32}N_2Cl_2 \cdot 1.8\ H_2O$: C 56.80; H 9.46; N 7.36; Cl 18.67%.

Acetylation of aloperine. A mixture of 10 g of aloperine and 40 ml of acetic anhydride was boiled for 10 hr. The reaction mixture was poured into 200 ml of ice water, acidified to pH 2, and treated with 45 g of sodium perchlorate. This gave 6.7 g of crystalline acetylaloperine perchlorate. A further 2.64 g of the base (R_f 0.36 and 0.26) was isolated from the mother liquor.

The acetylaloperine perchlorate had mp 262-263.5° (from 60% alcohol), $[\alpha]_D^{20}$ + 212.8° (c 1; water); R_f 0.56.

Found: C 54.28; H 7.39; N 7.86; Cl 9.54%. Calculated for $C_{17}H_{27}N_2O_5Cl$: C 54.44; H 7.26; N 7.47; Cl 9.47%.

The mixture of perchlorates had mp 244-245°, $[\alpha]_D^{20}$ + 170.25° (c 1; water); R_f 0.56.

Found: C 54.67; H 7.33; N 7.29; Cl 9.41%. Calculated for C 54.44; H 7.26; N 7.47; Cl 9.47.

Methylation of acetylaloperine with methyl iodide. An acetonic solution of 3.96 g of acetylaloperine (R_f 0.36 and 0.26) was boiled with 4 ml of CH_3I for 90 hr. This gave 5.8 g of methiodides (IV) and (V).

Methiodide (IV) had mp 247.5-248.5° [from methanol-ether (3: 1); on a Kofler block], $[\alpha]_D^{20}$ + 181.8° (c 0.8; methanol); R_f 0.37.

Found: C 51.73; H 6.73; N 7.20; I 31.39%. Calculated for $C_{18}H_{29}N_2OI$: C 51.91; H 7.02; N 6.73; I 30.49%.

Chromatography of a mixture of the methiodides (IV) and (V) on Al_2O_3. A solution of 3.1 g of the methiodide in 77.5 ml of a mixture of petroleum ether and chloroform (1: 3) was deposited on 77.5 g of alumina (activity grade I). Elution gave 0.25 g of (V) (R_f 0.45). Then the chloroform content was gradually increased (1: 4; 1: 5; 1: 10) – R_f 0.45 and 0.37.

When the column was washed with mixtures of chloroform and acetone (3: 1; 1: 1; 1: 3), 0.78 g of product was obtained (R_f 0.37, scarcely detectable spot with R_f 0.45).

The methiodide (V) had mp 239.5-240.5° (from methanol; on a Kofler block), $[\alpha]_D^{20}$ + 47.35° (c 0.7; methanol); R_f 0.45.

Found: C 52.11; H 6.77; N 7.07; I 31.54%. Calculated for $C_{18}H_{29}N_2OI$: C 51.91; H 7.02; N 7.73; I 30.49%.

Hofmann degradation at the tertiary nitrogen atom. From 0.4 g of the methiodide (IV) [slightly contaminated with the methiodide (V)], we obtained 0.07 g of an oily substance (R_f 0.3 and a spot at the starting line, decomposing at 100°), and 0.11 g of an oily substance (R_f 0.36 and 0.26: boiling with xylene for 10 min).

Methylation with methyl iodide of the reaction product with R_f 0.36 and 0.26. A mixture of 0.11 g of the product and 0.6 ml of CH_3I was boiled for 14 hr. The resulting methiodide (0.16 g) had mp 239-240.5° (from methanol; on a Kofler block), R_f 0.45. A mixture with the methiode (V) gave no depression of the melting point. The IR spectra coincided. A mixture with the methiodide (IV) gave a depression of the melting point.

Two-phase ascending paper chromatography for 16 hr at room temperature was carried out in an n-butanol – 5% acetic acid (1: 1) system. IR spectra (in paraffin oil) were taken on a UR-10 recording spectrophotometer, and UV spectra (in alcohol) on an SF-4 spectrophotometer.

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