ALKALOIDS OF A NEW TYPE FROM *Sophora alopecuroides* L.

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UDC 547—94

Aloperine, $C_{15}H_{24}N_2$ (I), was first isolated by A. P. Orekhov, N. F. Proskurnina, and R. A. Konovalova in 1935 from the herbage and seeds of *Sophora alopecuroides* L. [1]. The alkaloid contains a double bond which is not an enamine double bond, since it is hydrogenated in the presence of platinum oxide but is not reduced by sodium tetrahydroborate. The C^{13} NMR spectrum confirmed the presence of a double carbon—carbon bond and also showed the presence of five carbon atoms adjacent to nitrogen atoms. In the IR spectrum of aloperine taken in the solid state and in chloroform solution there are no frequencies characteristic for mobile hydrogen atoms. A direct chemical determination by the Zerewitinoff method did not reveal any such hydrogen atoms, either. However, the alkaloid readily forms a series of well-characterized derivatives at a nitrogen atom (N-methyl, N-acetyl, and N-benzoyl derivatives) indicating the secondary nature of one of the nitrogen atoms.

High-resolution mass spectra have shown that the nature of the fragmentation of aloperine differs from that of known types of quinolizidine alkaloids of *Sophora*.

It has been shown that in the first place the cleavage of one heterocyclic ring takes place with the elimination of the nitrogen atom present in it in the form of fragments with the compositions CH_3N, C_2H_5N, and C_3H_8N. Because of this, the majority of the fragments contain one nitrogen atom. The splitting off of the CH_3N fragment confirms the secondary nature of one of the nitrogen atoms eliminated. It has been established by a mass-spectrometric study of derivatives of aloperine at a nitrogen atom that the first step is the splitting off of the radical attached to the nitrogen, and then decomposition takes place by the pathways characteristic for aloperine itself.

From the same plant we have recently isolated a new liquid base, $C_{18}H_{28}N_2$ (II) with R_f 0.98 (for aloperine R_f 0.64) the mass spectrum of which showed peaks of the ions M^+ (272) and M − 41 (231); the latter is formed as the result of the loss of a C_3H_5 fragment. The other peaks were the same as in the spectrum of aloperine. The NMR spectrum of this compound confirmed the presence of an allyl group in it. The replacement the allyl group of the mobile hydrogen atom attached to nitrogen showed the identity of compound (II) with a sample of N-allylaloperine obtained by the action of allyl bromide on aloperine. In this way the presence of the same skeleton in the two bases was demonstrated.

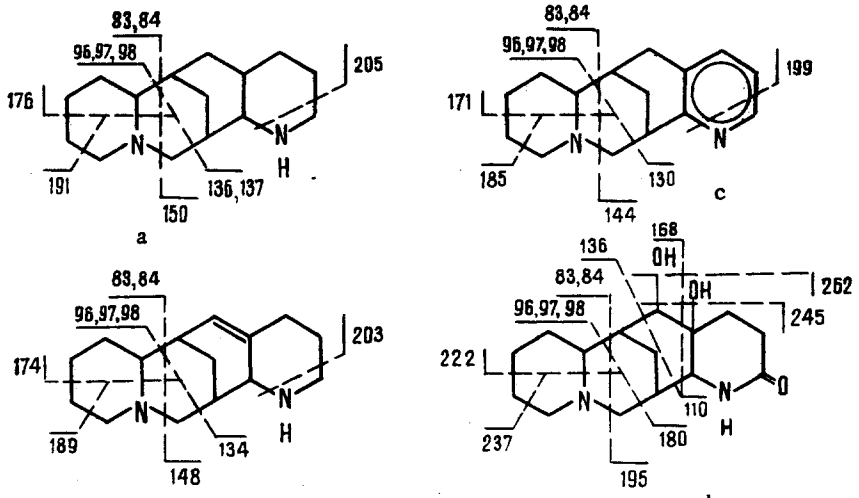
The secondary—tertiary nature of the double bond follows from the NMR spectra of (I) (δ 5.27 ppm, 1 H; J = 6.5 Hz) and of (II) (δ 5.50 ppm, 1 H; J = 6.5 Hz). The mild dehydrogenation of aloperine with sulfur gave a tetradehydro derivative (III), $C_{15}H_{20}N_2$, and oxidation with potassium permanganate gave a dihydroxylactam (IV), $C_{15}H_{24}N_2O_3$. The NMR spectrum of (III) showed three signals of the α, β, and γ protons of a pyridine ring, determining the position of the nitrogen atom in ring D. At the same time, no other aromatic or olefinic protons were observed in the spectrum. Thus, the aromatization of ring D was accompanied by the migration of the double bond, which shows the immediate proximity of the double bond to ring D undergoing aromatization.

All-Union Scientific-Research Institute of Medicinal Plants. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 30-37, January-February, 1975. Original article submitted August 23, 1973.

TABLE 1. Characteristics of the NMR Spectrum of Aloperine and Its Tetradehydro Derivative (given

Name	H_7	H_{17}	H_{11}	H_{13e}	H_{13a}	H_{10a}	H_{10e}	H_{15e}	Other signals
Aloperine	δ 1,79	δ 5,40 $J_{7,17} = 6,4$	δ 3,11 $J_{9,11} = 6,3$	δ 3,08 $^2J_{13} = 12,0$	δ 2,66 $J_{13,14a} = 9,0$ $^2J_{13} = 12,0$	δ 2,45 $J_{10,9} = 3,4$ $J_{10,10'} = 12,0$	δ 2,86 $J_{10,9} = 5,2$	δ 2,26 $^2J_{15} = 13,5$ $J_{15,13e} = 2,2$ $J_{15,14e} = 2,2$	
Tetradehydro-aloperine	δ 1,75	$H_{17e} = 2,98$ $^2J = 17,0$ $J_{17,7} = 7,0$ $H_{17a} = 2,65$ $J_{17a,7} < 2$			$H_{13} = 8,11$	δ 2,35 $^3J_9 = 2,3$ $^4J = 2,7$	δ 3,22 $^2J = 10,6$ $J_{9,10e} = 3,5$	δ 7,12	H_{14} 6,84 H_9 2,96

The presence of a quinolizidine ring and also the extra-quinolizidine position of the double bond were found from the mass spectrum of the oxidation product (IV), which was obtained under conditions excluding the destruction of the skeleton or the isomerization of the double bond. In the mass spectrum of this compound we observed fragments characteristic for a quinolizidine nucleus with m/e 136, 137, and 150, and also hydroxyl-containing fragments with m/e 168 and 195 which could be explained only by the participation of a nonquinolizidine nucleus in the oxidation. Additional information on the position of the double bond can be obtained from an analysis of the mass spectra of dihydroaloperine and of the tetradehydro derivative from the shifts of the ions with m/e 134 and 148 of aloperine by two and four mass units, respectively. On the other hand, the peak of the tropylium ion with m/e 91 (C_7H_7) in aloperine and its derivatives shows the presence of a carbocyclic ring (absent from other *Sophora* alkaloids). (See the probable scheme of the fragmentation of aloperine.)



Scheme of the fragmentation of aloperine and its derivatives under the action of electron impact: a) 16,17-dihydroaloperine (aloperane); b) aloperine; c) tetradehydroaloperine (11,12,13,14,15,16-hexadehydroaloperane); d) 16,17-dihydroxyaloperan-13-one.

The production of the pyridine derivative (III) as the main dehydrogenation product* confirms the presence of steric factors in ring C preventing the dehydrogenation of the latter without the cleavage of a carbon–carbon bond.

Fundamental information on the skeleton of aloperine was obtained from the NMR spectrum of the base itself and of its derivatives (Figs. 1-3). Analysis of the signals in the NMR spectrum of allylaloperine at 1.10 ppm (quartet, $J_{8,7}$ = 3.1 Hz; ^2J = 12.0 Hz) and also at 1.95 and 1.76 ppm (the structures of which were determined by means of the INDOR method) show the presence in the molecule of the fragment —CH—CH_2—CH—. Such a fragment is present in the sparteine alkaloids, and also in the tetracyclic system of

*It has been shown experimentally that other dehydrogenation products result from the destruction of the aloperine skeleton formed as the result of the cleavage of, apparently, ring B or C.

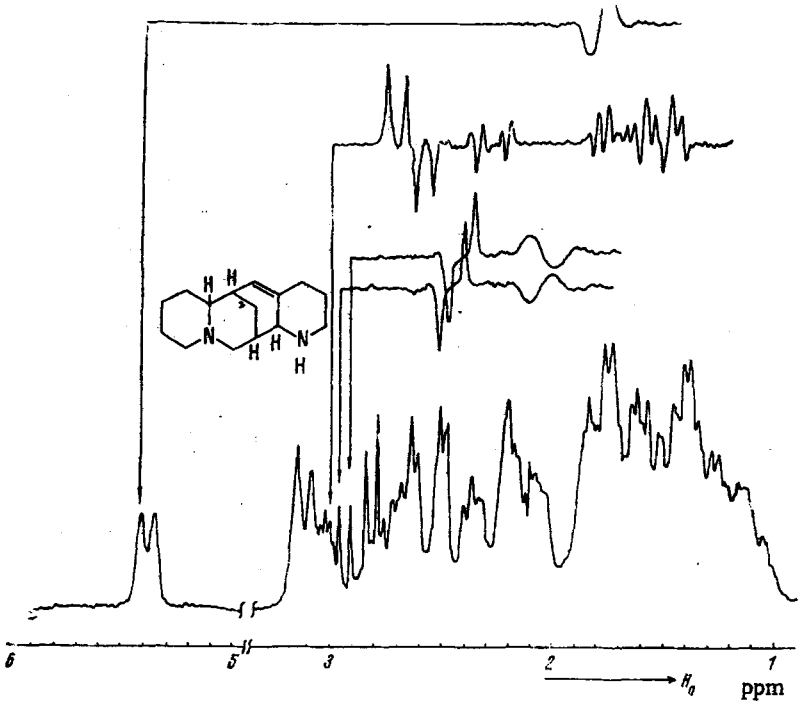


Fig. 1. ^1H NMR spectra and INDOR spectra of aloperine.

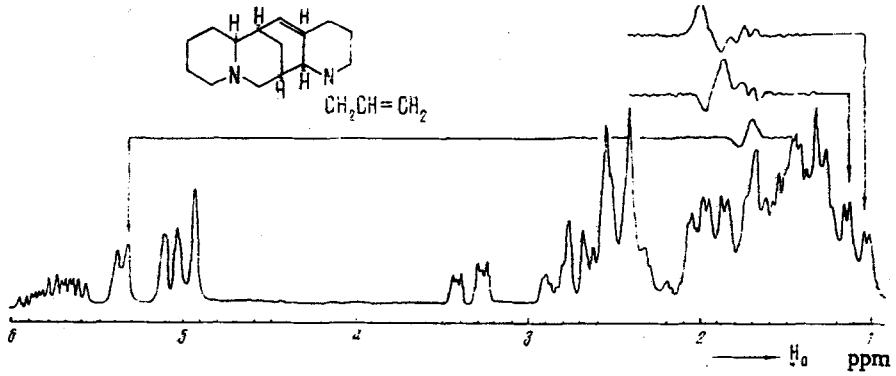


Fig. 2. ^1H NMR spectra and INDOR spectra of allylaloperine.

the alkaloids of *Ormosia* [2-5], the latter also containing a secondary amino group. Other features of the NMR spectrum are also in favor of a structure of a skeleton of aloperine and allylaloperine of the same type as that of the *Ormosia* alkaloids. A doublet at δ 3.11 ppm, $J_{9,11}$ = 6.3 Hz, relates to the H_{11} proton in the α position to the nitrogen atom. The presence of a N–CH_2CH– fragment is confirmed by the existence of two quartets (H_{10e} 2.86 ppm, $J_{10,9}$ = 5.2 Hz; H_{10a} = 2.45 ppm, $J_{10,9}$ = 3.4 Hz; $J_{10,10'}$ = 12 Hz). One of the methine protons is vicinal to an olefinic proton. This follows from the fact that one of the INDOR signals obtained on the lines of the quartet at 1.10 ppm and on the olefinic doublet is present at the same position of the spectrum (1.76 ppm) and has the same width in each case. The signal of this proton consists of a quartet, which shows the presence of another methine proton (H_6).

The presence of weak Bohlmann absorption bands in the IR spectrum of the base and the absence of them in the N-methyl, N-acetyl, and N-benzoyl derivatives of aloperine, and also the results of Hofmann degradation show the cis linkage of rings A/B.

The Hofmann degradation of aloperine and its N-acetyl derivative [6] stops at the stage

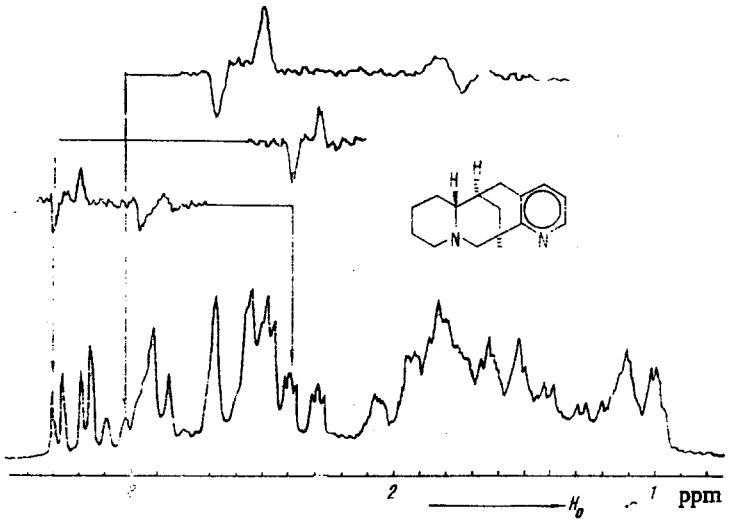
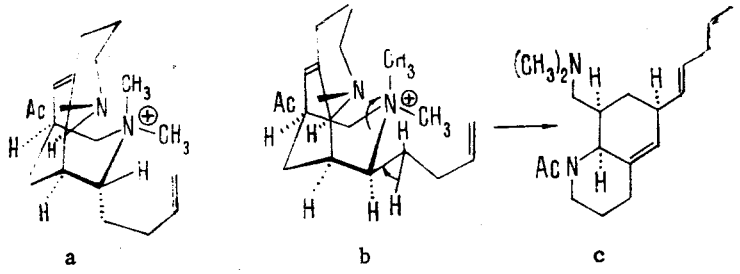


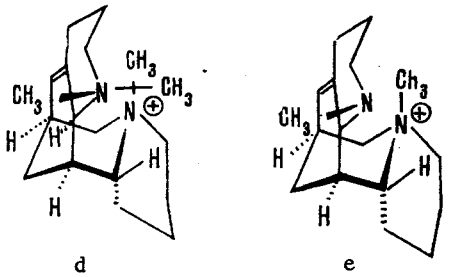
Fig. 3. ^1H NMR spectra and INDOR spectra of tetradehydroaloperine.

of the formation of a methine derivative because of the absence from the methiodide of the methine base (a) of the four anticoplanar centers that are necessary for elimination leading to the opening of ring B to take place. In the case of the transoid isomer of the structure (b) such decomposition should take place readily with the formation of a bicyclic derivative (c).



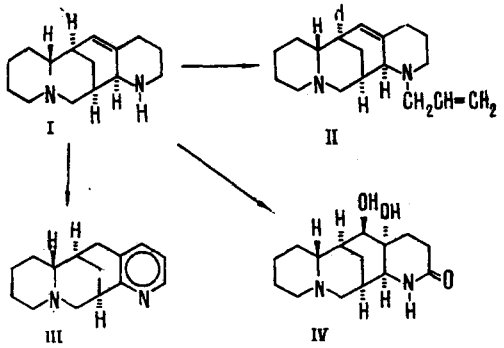
a b c

The formation of a dimethiodide of N-methylaloperine (d) is difficult because of the steric hindrance arising as a consequence of the proximity of the nitrogen atoms to one another in the methiodide of the N-methyl derivative (e), which is the final product of the interaction of aloperine with methyl iodide and does not undergo further methylation. Consequently, only one ring undergoes degradation subsequently.



d e

Thus, aloperine and allylaloperine have structures (I) and (II), respectively.



EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument in chloroform solution and in paraffin oil, the mass spectra on a Varian CH-8 instrument at 30-35°C with an energy of the ionizing electrons of 70 eV, and the NMR spectra on a Varian HA-100 instrument ($CDCl_3$, 20°C, 0 — HMDS). The high-resolution mass spectra were taken on a Varian MAT 311 instrument at a temperature of 160°C with an energy of ionization of the electrons of 70 eV in combination with a Spectrosystem 100/81 MS. The ^{13}C NMR spectra were taken on a Brüker Spectrosystem WH—90 instrument; D_2O and C_6D_6. The melting points were determined on a Kofler block. Chromatographic separation was performed in columns of alumina of activity grade IV in a ratio of 1:50. Chromatographic monitoring was performed in a thin layer of alumina of activity grade IV in the petroleum ether—ether (1:1) + 5% of methanol system. The spots were revealed in iodine vapor. The analyses of all the compounds corresponded to the calculated figures.

The aloperine was isolated by a method described previously [7] from the fractions of the strong bases soluble in petroleum ether, followed by purification on a column of alumina. mp 70-71°C (from petroleum ether and acetone), $[\alpha]_D^{20}$ + 82.1° (c 0.854; ethanol), M^+ 232. Dihydrochloride, $C_{15}H_{24}N_2 \cdot 2HCl$, mp 265°C (from ethanol). Monohydrochloride, $C_{15}H_{24}N_2 \cdot HCl$, mp 208°C (from ether).

The fraction of strong bases insoluble in petroleum ether was chromatographed on alumina, and a benzene eluate yielded 0.00014% of liquid allylaloperine with R_f 0.98 having the composition $C_{18}H_{28}N_2$ (M^+ 272).

Acetylaloperine. A solution of 0.2 g of aloperine in 3 ml of chloroform was treated with 1 ml of acetic anhydride and was boiled under reflux for 4 h, and then the solvent was distilled off with the addition of benzene twice. The residue was chromatographed on alumina. Elution was performed with a mixture of benzene and 10% of chloroform. This gave a liquid base with the composition $C_{17}H_{26}N_2O$. R_f 0.75, M^+ 274, NMR spectrum (CCl_4): 1.91 ppm (N—$COCH_3$); 5.50 ppm, 1 H; J = 6.5 Hz (C=C<u>H</u>—CH).

Methylation of Aloperine. A solution of 0.82 g of aloperine in 8 ml of acetone was treated with 0.4 ml of methyl iodide and the mixture was boiled under reflux for 4 h. The precipitate that deposited was boiled with ethanol and the hydriodide of the N_1 methiodide of N_{12}-methylaloperine, $C_{17}H_{30}I_2N_2$ was isolated with mp 275-276°C. The ethanolic mother solution was evaporated, the residue was dissolved in water, the solution was made alkaline with 40% caustic soda solution, and the free N-methylaloperine was extracted with ether. After drying with sodium sulfate, the distillation of the solvent yielded a compound with the composition $C_{16}H_{26}N_2$, mp 94-95°C (from ether), M^+ 246, R_f 0.87.

IR spectrum: 2800 cm^{-1} (N—CH_3), 1450-1475 cm^{-1} (double bond); NMR spectrum (CCl_4): 2.08 ppm (N—CH_3); (CF_3COOH): two singlets at 2.56 ppm and 2.60 ppm (N—CH_3).

Oxidation of Aloperine. With stirring, an acetone solution of potassium permanganate (calculated amount) was gradually added to a solution of 2 g of aloperine in 30 ml of anhydrous acetone, and then the precipitate of manganese dioxide was separated off, the acetone solution was evaporated, and the 1.35 g of residue was extracted with ether; evaporation of the ethereal extract gave 0.06 g of a crystalline compound with mp 182-183°C (from acetone), $C_{15}H_{24}O_3N_2$. M^+ 280. IR spectrum (in $CHCl_3$): 1603 cm^{-1} (lactam carbonyl), 3590 and 3630 cm^{-1} (hydroxyl).

Dehydrogenation of Aloperine. Tetradehydroaloperine. A mixture of 0.46 g of free aloperine and 0.13 g of sulfur was heated in a metal bath. At 135°C the evolution of hydrogen sulfide began, and the reaction was complete after 10 min. The reaction products were dissolved in benzene and passed through a column of alumina. The benzene eluate yielded a liquid base with the composition $C_{15}H_{20}N_2$, R_f 0.98 (M^+ 228).

Allylaloperine (from Aloperine). To a solution of 0.2 g of aloperine in 3 ml of acetone was added 0.2 ml of allyl bromide. After a few minutes, shaking led to the precipitation of crystals of allylaloperine hydrobromide, and these were filtered off and recrystallized from ethanol; $C_{18}H_{28}N_2 \cdot HBr$, mp 235-237°C.

The free base was a liquid with R_f 0.98 (M^+ 272). In its chromatographic mobility and spectral characteristics, the substance was identical with the base isolated from the plant.

SUMMARY

The structures of aloperine and allylaloperine (from *Sophora alopecuroides* L.) — alkaloids of a new structural type for the genus *Sophora* — have been established by chemical and spectral methods. A number of parameters, NMR spectra, and mass spectra characterizing this class of compounds has been obtained. The partial synthesis of allylaloperine has been performed.

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