ALKALOIDS OF UNGERNIA SEVERTZOVII (RG1) B. FED.

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Ungernia severtzovii grows in large amounts in the mountain regions of Uzbekistan, being distributed in places as a landscape plant.

From the leaves of this plant gathered in Karzhantau we have isolated nine alkaloids: lycorine, galanthamine, hippeastrine, tazettine, ungminorine, pancratine, dl-narwedine, d-narwedine, and l-narwedine [1-4]. The first five bases were identified with known samples obtained from various types of Ungernia, and pancratine by a mixed melting point with hemanthidine given to us by W. Döpke of the German Democratic Republic (Berlin).

The alkaloid isolated by treating the total ethereal extract with acetone had a melting point, composition, and analytical formula coinciding with that of narwedine [5], but its salts and derivatives melted at higher temperatures than the corresponding derivatives of narwedine. The alkaloid was optically inactive. Consequently, we assumed that this alkaloid is racemic narwedine. Its reduction with lithium aluminum hydride in ether gave racemic epigalanthamine [6] and l-galanthamine identical with galanthamine from U. victoris [1]. When the alkaloid was reduced again with lithium aluminum hydride in tetrahydrofuran, racemic epigalanthamine and d-galanthamine were formed.

The production of galanthamine and epigalanthamine shows that the alkaloid isolated is racemic narwedine. Natural narwedine racemizes readily in alkali during its isolation from plants. Racemization takes place with rupture of the oxygen bridge and the formation of a symmetrical dienone [7]. It is possible that the narwedine racemized completely in our case also. To isolate optically active narwedine, we extracted fresh leaves with chloroform, and obtained narwedine with $[\alpha]_D$ +310°; on the other hand, where the alkaloids were extracted from the dry leaves with ether, narwedine with $[\alpha]_D$ $-34.7°$ was isolated.

From the roots and bulbs of U. severtzovii, growing in Burchmulla, we isolated in addition to the known alkaloids, an alkaloid with mp 173-174° and $[\alpha]_D$ +163° (chloroform), not reported in the literature, to which we have given the name unsevine [8]. Its composition has been established as $C_{18}H_{21}O_5$ and its analytical formula is $C_{14}H_{12}(=N-CH_3)(CH_2O_2)(OCH_3)(OH)(-O-)(=)$. The UV spectrum of unsevine determined in ethanol has two maxima, indicating the presence of a benzene ring with substituents in the alkaloid.

During oxidation of unsevine (I) with 16 atoms of oxygen (potassium permanganate) hydrastic acid is obtained. Consequently, the benzene ring of the alkaloid carries only a methylenedioxy group.

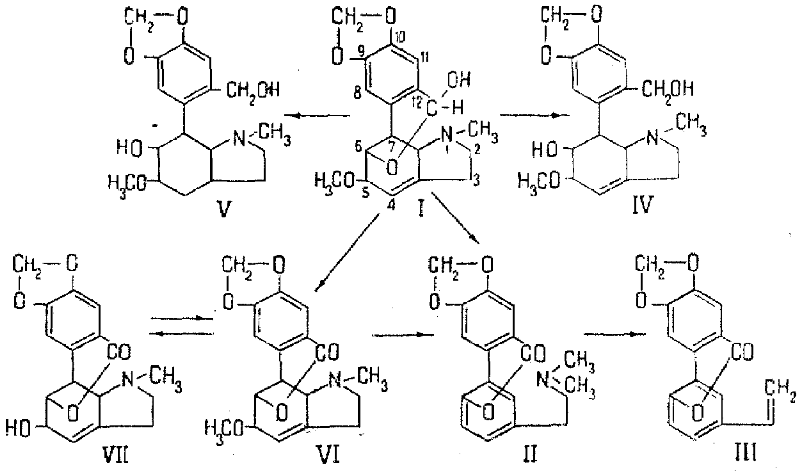
On carrying out the Hoffmann degradation of this base with silver oxide, an optically inactive des-N-methylunsevine (II), identical with des-N-methylungerine, was isolated in the first stage. The methiodide of des-N-methylunsevine and the nitrogen-free substance (III) also correspond precisely to ungerine derivatives.

Evidently the B nucleus of unsevine was aromatized with the elimination of the methoxy group in the form of methyl alcohol. However, the appearance of a δ-lactone ring apparently shows that, in addition to the latter, unsevine contains a hemiacetal group, which is oxidized by silver oxide to a lactone group.

To confirm these suppositions, unsevine was reduced with lithium aluminum hydride and also with an Adams' catalyst. In the first case, dihydrounsevine (IV) of composition $C_{18}H_{23}O_5N$ was obtained; in this, in contrast to unsevine, there is a second hydroxyl group, but the methoxy and methylenedioxy groups and the double bond are retained. The catalytic hydrogenation of unsevine gave tetrahydrounsevine (V), $C_{18}H_{25}O_5N$, with two hydroxyl groups, a methoxyl, and a methylenedioxy group.

Alkaloids with a hemiacetal group of the lycorenine type behave in a similar manner, this group opening up upon reduction with the formation of a second hydroxyl group [9].

Dihydrounsevine is identical with tetrahydroungerine, which is formed on the reduction of ungerine with lithium aluminum hydride. Tetrahydrounsevine is identical with d-hexahydroungerine, the product of the catalytic hydrogenation of ungerine with subsequent reduction with lithium aluminum hydride [10]. The mechanism of the conversions of unsevine are as follows:



Unsevine differs from ungerine (VI) only by the fact that the latter has a δ-lactone ring and unsevine a hemiacetal group. To confirm this, unsevine was oxidized with chromic acid. The oxounsevine obtained was identical with ungerine.

Date of collection	Plant organ	Total alkaloids	Lycorine	Pancratine	Galanthamine	Narwedine	Hippeastrine	Ungminorine	Tazettine	Ungerine	Unsevine
		% of the weight of the dry plant									
Karzhantau											
10 April, 1962	Leaves	0.75	0.46	0.12	0.01	0.005	0.008	0.005	0.004	—	—
19 April	Bulbs	1,32	0,38	0,12	0.033	0.01	—	0.74	0.005	—	—
23 March	Roots	2.15	0.8	0,022	—	—	—	0.48	0.006	—	—
1 September	Bulbs	1.52	0.65	0.14	0.052	0.004	—	0.065	0.063	—	—
1 September	Roots	2.64	1.1	0.41	0.042	0,007	—	0.18	0.02	—	—
Gal'vasai											
11 June, 1964	Leaves	0,82	0.27	0.08	—	0.018	—	—	—	—	—
	Bulbs	1.4	0.20	0.15	0.11	0,038	—	—	—	—	—
	Roots	2.2	0.20	0.13	—	0.013	—	—	0.03	—	—
Burchmulla											
13 April, 1960	Leaves	0.29	0.04	—	—	—	0.0001	—	0.016	0.043	—
10 May-10 June	Bulbs	0.9	0.15	—	0.05	—	—	—	0.017	0.089	0,025
13 April, 1960	Roots	1.44	0.11	—	—	—	—	—	0.33	—	0.016
5-10 June	Roots	2.36	0.65	—	—	—	—	—	0.52	—	0.041
Zarkent											
10 March, 1962	Bulbs	0.79	0.067	—	—	—	0.02	0.25	—	—	—
14 April, 1962	Bulbs	0.66	0.165	—	—	—	—	0.04	0.03	0.01	—
	Leaves	0.306	0.02	—	—	—	0.03	0.01	0.0008	—	—
	Roots	1.38	0.25	—	—	—	—	0.72	0.11	—	—

To investigate the possibility of oxidizing the hemiacetal to a lactone, unsevine was oxidized with silver oxide, which gave ungerine. Consequently, in this case, in addition to the Hofmann degradation, oxidation of a secondary alcohol group to a lactone group takes place.

Oxounsevine or ungerine differs from **hippeastrine** (VII) by having a methoxyl group in place of a hydroxyl group. The methylation of hippeastrine with methyl p-toluenesulfonate gave ungerine, and the saponification of ungerine with hydrochloric acid gave hippeastrine [11]. This conversion establishes the relationship of the three alkaloids unsevine, ungerine, and hippeastrine.

On studying U. severtzovii from Gal'vasai, Karzhantau, Burchmulla, and Zarkent (western spurs of the Tyan'-Shan), we confirmed the assertion that the total alkaloids and their qualitative composition vary in plants of one and the same species in relation to their growth site [12](table). Thus, only lycorine and tazettine were found in almost all the organs of the plants from the above-mentioned growth sites. The maximum amount of lycorine was found in the roots of plants collected in the late vegetation season in Karzhantau, and the smallest amount of tazettine in the roots of plants of the late vegetation season from Burchmulla. Pancratine and narwedine were isolated from *U. severtzovii* growing in Karzhantau and Gal'vasai, and ungerine was found in *U. severtzovii* from Zarkent and Burchmulla. Hippeastrine and ungminorine were found in plants from Karzhantau and Zarkent.

On studying the dynamics of alkaloid accumulation in *U. severtzovii* from Karzhantau, it was found that as the leaves grew the total amount of alkaloids in them decreased, and naturally shrivelled leaves contained no alkaloids. The total alkaloids in the bulbs were greater than in the leaves at all vegetation periods. During the growth of the plant, the alkaloid content of the bulbs fell slightly, but it rose at the end of the vegetation period. In the roots, the total amount of alkaloids was greater than in the leaves and bulbs at all vegetation periods, and its increase ran parallel with the growth of the plant. In the fruiting period, alkaloids appeared in the seeds (0.83% of the weight of the dry seeds).

On the basis of the results obtained with *U. severtzovii* collected in Karzhantau, it is possible to trace the probable interconversion of ungminorine and lycorine: in the later vegetation period, the lycorine content of the bulbs and roots increases and that of ungminorine falls. And, conversely, in the period of leaf development, the amount of ungminorine in the bulbs and roots increases while that of lycorine decreases correspondingly.

Experimental

Extraction of the leaves of U. severtzovii. Eighty-nine kilograms of the dried and finely comminuted leaves of *U. severtzovii* collected on 10th April 1962 in Karzhantau were wetted with ammonia and were extracted with chloroform; the alkaloids were extracted with 10% sulfuric acid. When the acid solution was made alkaline with concentrated ammonia, lycorine (375 g) was precipitated. After the removal of the lycorine, the alkaline solution was shaken first with ether and then with chloroform. When the ethereal solution was concentrated, precipitate A was deposited (120.15 g). The total yield from the ethereal extract was 180.9 g and from the chloroform extract 52 g. The total yield of combined alkaloids was 728.05 g.

Pancratine. 120.15 g of precipitate A was boiled several times with methanol; 48.5 g of lycorine remained undissolved. On cooling, the methanol solution deposited pancratine, mp 185-187° (from methanol).

Found, %: C 64.3, 64.4; H 6.46, 6.51; N 4.18, 4.15. Calculated for $C_{17}H_{19}O_5N$, %: C 64.35; H 6.04; N 4.4.

Separation of the total alkaloids from the ethereal extract. Treatment of 180.9 g of the total alkaloids from the ethereal extract with acetone isolated 4 g of a microcrystalline residue B. The acetone solution yielded 8.17 g of a hydrobromide with mp 264-265°. The base from the hydrobromide was identical with hippeastrine. The total amount of alkaloids of the ethereal extract isolated from the acetone mother liquor was again dissolved in acetone. The hydrobromide of galanthamine (11.6 g) with mp 255-256° was obtained. The mother liquor, after the evaporation of the acetone and basification with ammonia, was shaken with ether. The latter was then evaporated and the total alkaloids extracted by ether (12.98 g) were suspended in 250 ml of benzene and transferred to a column of alumina (360 g). The alkaloids were eluted from the column first with benzene and then with ethyl acetate, in fractions of 150 ml. Twenty-six benzene and seven ethyl acetate fractions were collected. The alkaloids were extracted from each fraction with 10% sulfuric acid, the acid solution was made alkaline with ammonia and then extracted with ether. The 2nd-7th benzene fractions gave an additional amount of 1.61 g of residue B, the 20th-23rd benzene fractions gave 0.13 g of tazettine, and the 4th and 5th ethyl acetate fractions gave 0.45 g of ungminorine.

Racemic narwedine. 5.61 g of residue B was recrystallized first from acetone (1:25) and then from methanol (1:20): mp 186-187°, $[\alpha]_D^{20}$ ±0° (c 2.356; chloroform).

UV spectrum: $\lambda_{max}^{ethanol}$ 262 mμ (lg ε 3.821), $\lambda_{max}^{ethanol}$ 250 mμ (lg ε 3.66); IR spectrum: 1685, 1445, 1510, 1595, 1270, 1055, 935 cm^{-1}.

Found, %; C 71.5, 71.4; H 6.78, 6.85; N 5.0, 5.22; OCH_3 10.9, 10.5; N—CH_3 4.3, 3.3; mol. wt. 283.7, 282.45 (potentiometric). Calculated for $C_{17}H_{19}O_3N$, %: C 71.55; H 6.71; N 4.9; OCH_3 10.88; N—CH_3 5.27, mol. wt. 285.

The hydrobromide of dl-narwedine had mp 255-256° (from ethanol).
The nitrate of dl-narwedine melted at 244-245° (from ethanol).
The picrate of dl-narwedine had mp 192-193° (from 70% ethanol).
The methiodide of dl-narwedine had mp 265-266° (from methanol).

Reduction of dl-narwedine with lithium aluminum hydride. A reaction mixture consisting of 0.27 g of dl-narwedine, 300 ml of absolute ether, and an ethereal solution of lithium aluminum hydride was boiled for 4 hr, after which damp ether and water were added to it. The separated ethereal fraction was dried with potassium carbonate and evaporated to dryness. Treatment of the dry residue with acetone gave 0.1 g of a residue with mp 185-186° (from methanol), $[\alpha]_D^{16} \pm 0°$ (c 0.243; chloroform). The alkaloid gave a depression of the melting point with the initial narwedine. Its IR spectrum exhibited absorption bands characteristic of a hydroxyl group, and the absorption band for a carbonyl group was absent.

The acetone solution, after the removal of the epigalanthamine, was evaporated to dryness, and the residue was recrystallized three times from ether. Mp 125-126°, $[\alpha]_D^{16} -104°$ (c 0.239; chloroform). The substance obtained gave no depression of the melting point with galanthamine isolated from *U. victoris*.

The reduction of dl-narwedine was repeated with lithium aluminum hydride in tetrahydrofuran. The reaction products were worked up as in the first case. This gave racemic epigalanthamine and an alkaloid with mp 125-126°, $[\alpha]_D^{21} +93.4°$ (c 0.536; chloroform), which gave a depression of the melting point with natural galanthamine, although its IR and UV spectra were identical with those of natural galanthamine.

Ethereal extraction of the leaves of U. severtzovii. Fifteen kilograms of the dried and comminuted leaves was wetted with ammonia and extracted with ether. The ethereal extract was worked up by the usual method. When the ethereal extract of the total alkaloids was concentrated, 19 g of pancratine was deposited. Acetone treatment of the total ethereal extract gave 2.38 g of a crystalline fraction. The remaining mixture was separated by the method described above. The total weight of alkaloids was 117.36 g.

l-Narwedine. The 2.38 g of residue had mp 184-185° (from benzene) and $[\alpha]_D^{16} -34.7°$ (c 2.51; chloroform). The alkaloid gave no depression of the melting point with racemic narwedine.

d-Narwedine. 2.5 kg of fresh finely-cut leaves of *U. severtzovii* was mixed with 8% ammonia. The alkaloids were extracted with chloroform. The chloroform extract was treated in the usual way. When the ethereal extract of the combined alkaloids were concentrated, a mixture of lycorine and pancratine (1.13 g) was deposited. After the remaining combined alkaloids had been dried and treated with acetone, narwedine (0.3 g) was isolated with mp 185-186° (from acetone), $[\alpha]_D^{16} +310°$ (c 0.485; chloroform). The total weight of alkaloids was 3.34 g.

Alkaloids of the roots of U. severtzovii from Burchmulla. 5.58 kilograms of dried and comminuted roots was extracted with chloroform in the usual way. When the acid solution was made alkaline, 12.76 g of lycorine was precipitated.

The total ethereal extract, concentrated to 1.5 liter, was separated into phenolic and nonphenolic fractions. The phenolic fraction gave 18.14 g of tazettine. When the nonphenolic fraction was concentrated, an additional 0.4 g of tazettine was obtained from it. After this, the combined alkaloids were dried and were dissolved in the butanolic fraction of the butan-1-ol–acetic acid–water (100 : 5 : 100) system and transferred to a cellulose powder column. The combined alkaloids were eluted with the same butanolic solution. The eluates were collected in 150-ml fractions and were treated as described above. The 3rd-6th fractions gave 0.91 g of a crystalline residue. The total alkaloids amounted to 80.88 g.

Unsevine. The residue (0.91 g) had mp 173-174° [from acetone (1:25)] and $[\alpha]_D^{20} +163°$ (c 2.5; chloroform). The alkaloid was readily soluble in chloroform and sparingly soluble in ether, acetone, ethanol, benzene, and petroleum ether. With concentrated sulfuric acid it gave a yellow coloration disappearing after a day. On paper chromatography in the butan-1-ol–acetic acid–water (100:5:100) system, it gave one spot R_f 0.59.

UV spectrum: $\lambda_{max}^{ethanol}$ 238, 288 mμ (lg ε 3.76, 3.64); IR spectrum: 3690, 2832, 1620, 1440, 1365, 1250, 1040 335 cm^{-1}. Found, %: C 65.4, 65.5; H 6.5, 6.5; N 4.36, 4.56; OCH_3 9.88; N—CH_3 3.35, H_{act} mol. wt. 328.6, 362.2 (nonaqueous titration). Calculated for $C_{18}H_{21}O_5N$, %: C 65.22; H 6.39; N 4.23; OCH_3 9.37; N-CH_3 9.88, H_{act} 0.33; mol. wt. 331.

Unsevine oxalate, mp 195-196° (from ethanol).

Unsevine methiodide, mp 249-250° (from ethanol), $[\alpha]_D^{20} +145.8°$ (c 1.563; water).

Des-N-methylunsevine was obtained by treating 2 g of unsevine methiodide with silver oxide with subsequent heating under vacuum of the dried reaction product; mp 155-156° (from acetone), $[\alpha]_D^{16} \pm 0°$.

UV spectrum: $\lambda_{max}^{ethanol}$ 254, 308 mμ (lg ε 4.50; 4.02); IR spectrum: 1720, 1625, 1590, 1513, 1490, 1040, 935 cm^{-1}. Found, %: C 69.1; H 5.73; N—CH_3 4.48. Calculated for $C_{18}H_{17}O_4N$, %: C 69.43; H 5.5; N—CH_3 4.87

Des-N-methylunsevine methiodide was obtained by boiling the des-base with methyl iodide in methanol, mp 270-271°.

The nitrogen-free derivative of unsevine was formed by boiling the methiodide of the des-base in 30% caustic potash solution, mp 184-185°. IR spectrum: 1720, 1630, 1595, 1513, 1490, 1040, 935 cm^{-1}. Found, %: C 72.10; H 3.99. Calculated for $C_{16}H_{10}O_4$, %: C 72.17; H 3.78.

Tetrahydrounsevine. Two grams of unsevine was dissolved in 10% hydrochloric acid and reduced by Adams' catalyst. 310 ml of hydrogen was absorbed, which corresponds to four hydrogen atoms per molecule of unsevine. The acid solution was made alkaline and extracted with ether, and the dry residue from the evaporation of the ether had mp 186-187° (from acetone), $[\alpha]_D^{17}$ +33.9° (c 0.602; ethanol), $[\alpha]_D^{17}$ +41° (c 0.723; chloroform). IR spectrum: 3330, 1510, 1360, 1240, 1040, 935 cm^{-1}. Found, %: C 64.48, 64.58; H 7.72, 6.75; N 4.01, 3.92; N—CH_3 5.9. Calculated for $C_{18}H_{25}O_5N$, %: C 64.45; H 7.51; N 4.17; N—CH_3 8.6

Dihydrounsevine. A reaction mixture consisting of 1 g of unsevine, 500 ml of absolute ether, and 100 ml of an ethereal solution of lithium aluminum hydride was boiled for 6 hr. After the addition of ether and water, the ethereal layer was concentrated to small bulk; this gave 0.57 g of a crystalline precipitate, mp 154-155° (from a mixture of ether and acetone), $[\alpha]_D^{17}$ 56.1° (c 0.998; chloroform). Found, %: C 64.5, 64.6; H 7.17, 7.2; N 4.25, 4.4. Calculated for $C_{18}H_{23}O_5N$, %: C 64.85; H 6.95; N 4.2.

Conversion of unsevine into ungerine. 1. A solution of 0.75 g of unsevine in 20% sulfuric acid was treated with 0.33 g of potassium dichromate, and the solution was heated for 15 min. after which it was made alkaline and was extracted with ether. The concentrated ethereal solution gave a hydrochloride with mp 269-270° (from 70% ethanol). The base isolated from the hydrochloride (0.2 g) with mp 132-133° was identical with ungerine obtained previously from the same plant.

2. The silver oxide obtained from 0.16 g of silver nitrate was added to a solution of 0.2 g of unsevine in acetone. The acetone solution was stirred for 2 hr and was then evaporated to small bulk, after which 0.15 g of the initial unsevine was separated off. The acetone mother liquor yielded a hydrobromide identical with ungerine.

Summary

1. *Ungernia severtzovii* has yielded lycorine, hippeastrine, l-narwedine, d-narwedine, dl-narwedine, ungerwine, unsevine, galanthamine, tazettine, pancratine, and ungminorine; l-narwedine and unsevine have been obtained from the plant for the first time.

2. Unsevine has the structure of 9, 10-methylenedioxy-5-methoxy-12-hydroxy-N-methylbenzopyranoindole with a double bond between C_{3a} and C_4.

3. Interconversions of unsevine, ungerine, and hippeastrine have been effected.

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