BULGARSENINE AND RETROISOSENINE, ALKALOIDS FROM *Senecio nemorensis* L., VAR. *bulgaricus* (VEL.) STOJ. *et* STEF.*

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The isolation of nemorensine (*I*) and of two new alkaloids bulgarsenine and retroisosenine from *Senecio nemorensis* L., var. *bulgaricus* (VEL.) STOJ. et STEF. has been described. The two new alkaloids are assigned the structures *VIII* and *V* on the basis of chemical reactions, the ^{1}H-NMR and mass spectral data.

In one of earlier papers[1], we described the isolation and identification of alkaloids from three different varieties of *Senecio nemorensis*. A new alkaloid nemorensine was found which was assigned structure *I* with a thirteen-membered ring. Since it is an alkaloid containing a dicarboxylic acid of a new type, we undertook to study a larger quantity of *S. nemorensis* L., var. *bulgaricus* (VEL.) STOJ. et STEF. for the alkaloids contained therein and their structure. From this plant material, a crude mixture of alkaloids (1·66% per dry weight) was obtained. Thin-layer chromatography showed that it consisted of seven alkaloids. Three of them could be isolated in pure state, *i.e.* the already earlier known[1] nemorensine (*I*) and two new alkaloids which were named retroisosenine and bulgarsenine.

On the basis of high resolution mass spectrometry, retroisosenine is assigned the empirical formula $C_{18}H_{25}NO_5$. Intense peaks in the mass spectrum at *m/e* 120, 119, and 80 ($C_8H_{10}N$, C_8H_9N, and C_5H_6N) qualify[2] it as a pyrrolizidine alkaloid with a base having one additional double bond. This conclusion is further supported by the fragmentation pattern of retroisosenine (Scheme 1). The molecular ion gives chiefly the ion *m/e* 119 (loss of dibasic acid $C_{10}H_{16}O_5$) and *m/e* 291 (loss of CO_2, typical for all macrocyclic retronecine alkaloids). Two decomposition pathways of the latter ion have some diagnostic value: the loss of C_2H_3O leading to the *m/e* 248

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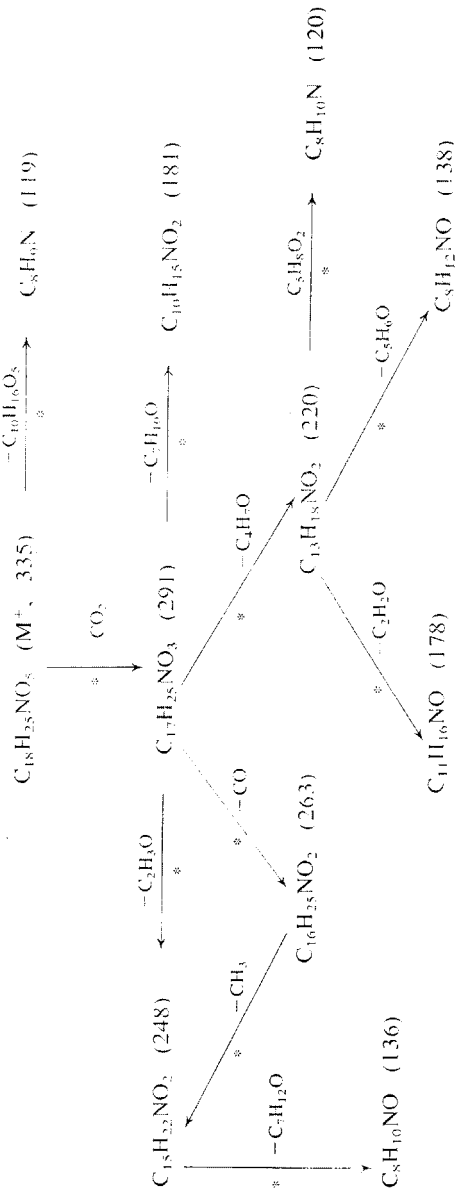


Scheme 1
Fragmentation Pattern of Retroisosenine (V)

ion and the elimination of C_4H_7O yielding the ion m/e 220. Their interpretation suggests that $C_{(2)}$ is bonded to oxygen and that $C_{(3)}$ is probably substituted by a methyl group. The UV (ref.[3]) and IR spectra of retroisosenine show that it probably consists of an unsaturated necine and a saturated acid. The absence of a coupling between the signals of two protons in the olefinic region of the ^{1}H-NMR spectrum (Table I) (5·89 and 5·42 p.p.m.) excludes a disubstituted double bond. The AB system (5·10 and 4·16 p.p.m.) with J_{AB} = 11·3 Hz, which is assigned to two geminal $C_{(9')}$ protons, locates the double bond between $C_{(1')}$ and $C_{(2')}$. Therefore, the most downfield lying broad singlet at 5·89 p.p.m. is ascribed to $H_{(2')}$. The irradiation of this signal sharpens both $H_{(9'u)}$ and $H_{(9'd)}$ doublets and removes some couplings in the 4·35 p.p.m., 3·95 and 3·42 p.p.m. multiplets. The doublet (J = 16 Hz) at 3·95 p.p.m. is assigned to $H_{(3'd)}$ on the basis of a large geminal coupling. Its counterpart $H_{(3'u)}$ appears at 3·42 p.p.m. The second low field lying signal is assigned to $H_{(7')}$ on the basis of chemical shift considerations. It is coupled to the 4·35 p.p.m. multiplet and to some aliphatic protons. Its linewidth indicates a mixed *exo-endo* conformation of the pyrrolizidine moiety[4]. The proton whose multiplet appears at 4·35 p.p.m. is coupled both to $H_{(2')}$ and $H_{(7')}$ and, therefore, it can be assigned to $H_{(8')}$ which is the only proton satisfying these data. The remaining multiplet at 3·29 p.p.m. is probably due to one $H_{(5')}$ proton. Thus, all the ^{1}H-NMR signals above 3 p.p.m. can be readily interpreted in terms of the retronecine structure (*II*).

The formula of the acyl is obtained by subtraction of the elemental composition of retronecine from the molecular formula. It contains two carboxyls, eight carbons, fourteen hydrogens and one oxygen atom. Since there is no OH band in the IR spectrum, the oxygen atom must form an oxygen bridge as in the case of nemorensine[1] (*I*). The acid portion of the molecule must accommodate one secondary (0·92 p.p.m., J = 6·4 Hz) and two tertiary (1·40 and 1·46 p.p.m.) methyl groups. The above requirements are met by nemorensic acid (*III*), or its diastereoisomer. The 2·61 p.p.m two-proton singlet might then represent an isolated CH_2 group. Alkaline hydrolysis yielded an oily base, identical according to ^{1}H-NMR, MS, and mixed melting point of the hydrochloride with retronecine. The ^{1}H-NMR spectrum of the acid contains two singlets of tertiary methyls at 1·30 and 1·40 p.p.m., a doublet (J = 6·6 Hz) of a secondary methyl at 1·00 p.p.m. and signals of five aliphatic hydrogens. They consist of an AB system assigned to an isolated methylene group and the BCD part of an A_3BCD system involving the secondary methyl. All structural features mentioned above resemble the earlier described nemorensic acid (*IIIa*) but the actual values of chemical shifts are different. Reaction with diazomethane afforded a dimethyl ester $C_{12}H_{20}O_5$ whose mass spectrum was nearly identical with that of dimethyl nemorensinate (*IIIb*). The fragmentation pattern (Scheme 2) supports the structure of substituted tetrahydrofurane. Main competing fragmentations are the loss of $COOCH_3$ and CH_2COOCH_3 from the two α-positions to oxygen. These ions and the products of their decompositions are responsible for the most intense

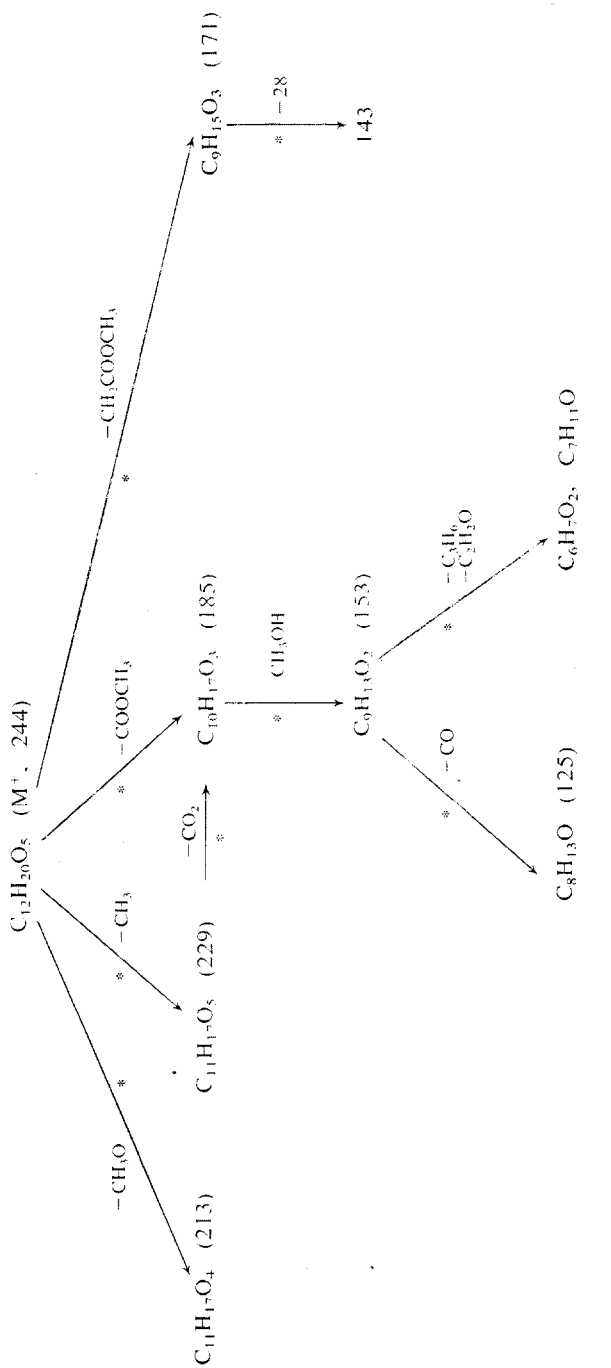
TABLE I

^{1}H-NMR Spectral Data

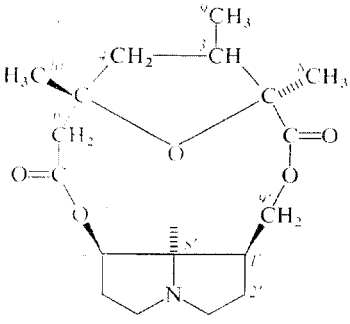
Acidic part Compound	$H_{(3)}$	$H_{(4)}$	$H_{(6)}$	$H_{(8)}$	$H_{(9)}$	$H_{(10)}$
IIIa	2·62 m	1·58 t (12·0) 2·26 dd (12·0, 6·0)	2·49 s (2 H)	1·25 s	1·09 d (6·4)	1·39 s
IIIb[a]	2·66 m	1·52 t (12·0) 2·39 dd (12·0, 6·5)	2·54 d (12·5) 2·63 d (12·5)	1·27 s	1·06 d (6·8)	1·41 s
IVa	2·32 m (12·0, 6·0, 6·6)	1·81 t (12·0) 2·05 dd (12·0, 6·0)	2·62 d (15·0) 2·87 d (15·0)	1·30 s	1·00 d (6·6)	1·40 s
IVb[b]	2·35 m	1·85 t (12·0) 2·09 dd (12·0, 5·0)	2·76 d (15·0) 3·01 d (15·0)	1·46 s	0·96 d (6·5)	1·34 s
V	—	—	2·61 s (2 H)	1·46 s	0·92 d (6·4)	1·40 s
VIII[c]	—	—	5·65 m	1·27 s	1·00 d (6·2)	1·87 d (1·3)

Necine part Compound	$H_{(2')}$	$H_{(3')}$	$H_{(5')}$	$H_{(7')}$	$H_{(8')}$	$H_{(9')}$
V	5·89 m	3·95 d (16·0) 3·42 m	3·29 m (1 H)	5·42 m	4·35 m	5·10 d (11·3) 4·16 d (11·3)
VIII	—	—	—	5·49 m	3·31 dd (4·4 6·8)	4·00 dd (10·8, 2·9) 4·40 t (10·8)

[a] 3·64, 3·70 (2 × $COOCH_3$); [b] 3·66, 3·67 (2 × $COOCH_3$); [c] 3·61 s (OH).



SCHEME 2
Fragmentation Pattern of *IIIb* and *IVb*



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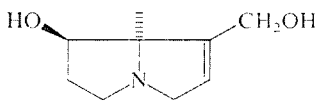
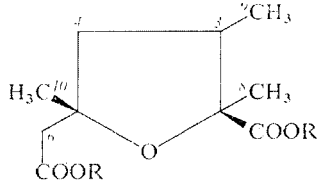
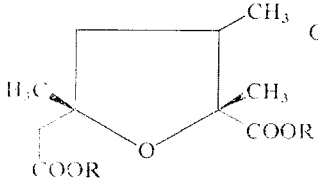


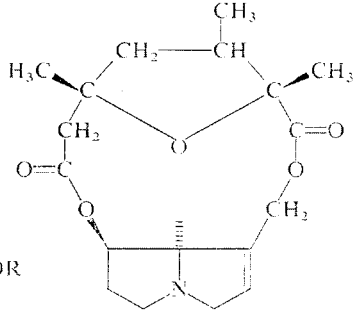
II



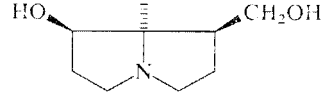
IIIa, R = H
IIIb, R = CH_3



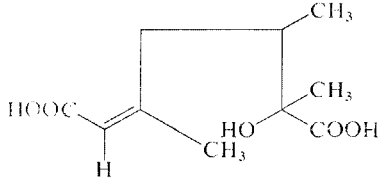
IVa, R = H
IVb, R = CH_3



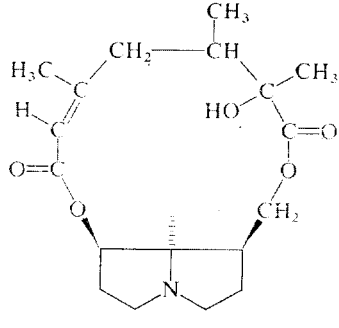
V



VI



VII

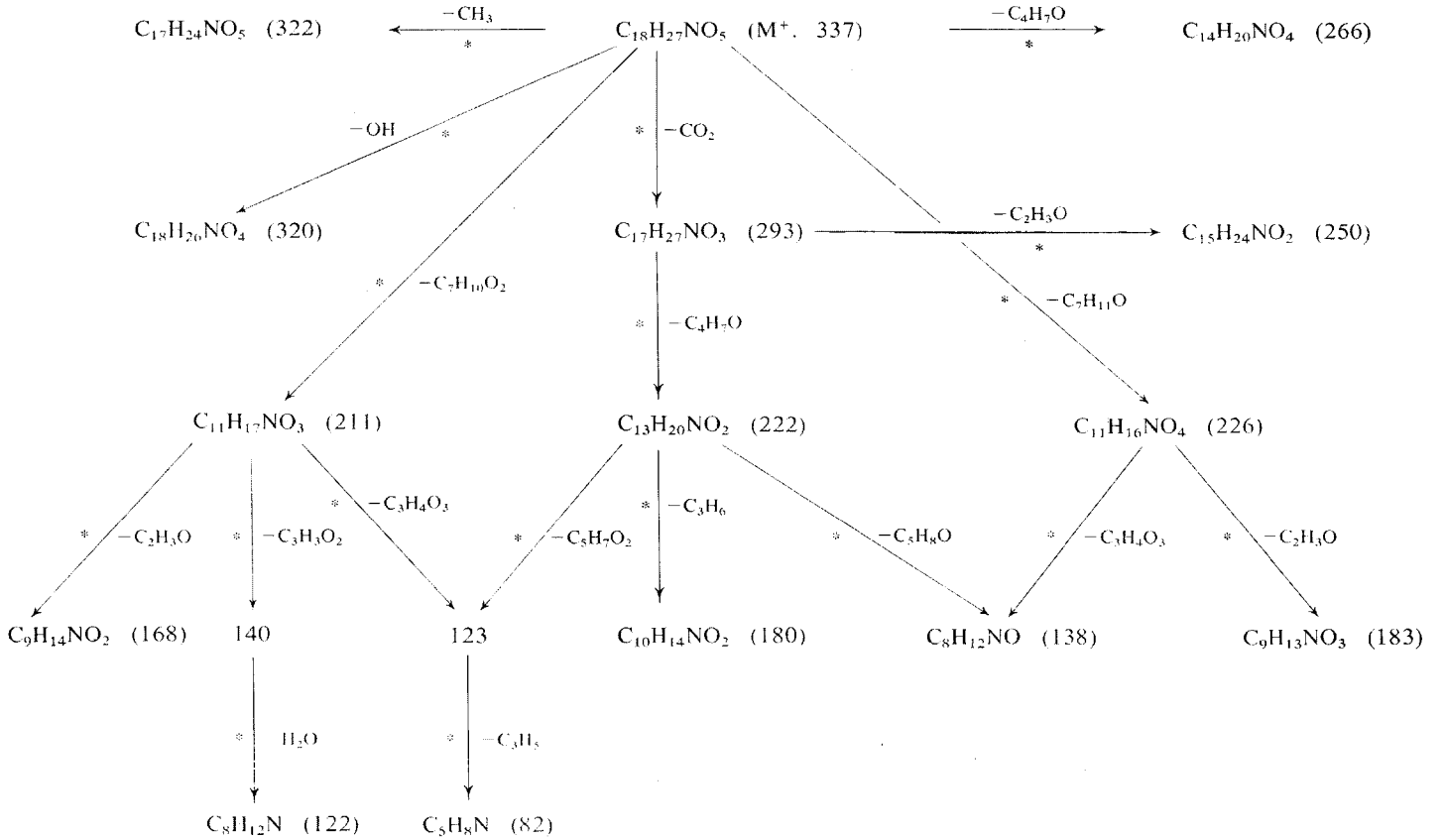


VIII

peaks in the mass spectrum. The ^{1}H-NMR spectrum of *IVb* also indicates the isomerism with dimethyl nemorensinate (*IIIb*) (Table I). The $C_{(10)}$ methyl can be determined by its long-range coupling to one member of the AB system of the $H_{(6)}$ protons. The problem of relative stereochemistry is then solved using the shielding

effect of the $COOCH_3$ group on the methyl protons. Assuming a downfield shift of methyl *cis*-oriented with respect to this group (a similar but somewhat smaller effect can be expected for the CH_2COOCH_3 group), the structure *IIIb* with *trans*-$-COOCH_3$ and CH_2COOCH_3 was assigned to dimethyl nemorensinate. In this compound, the $C_{(9)}$ and $C_{(10)}$ methyls resonate at a lower magnetic field and the $C_{(6)}$ protons exhibit a smaller magnetic nonequivalence. Thus, the acidic portion of retroisosenine is *cis*-nemorensic acid (*IVa*) and the structure of retroisosenine is represented by the formula *V*.

The empirical formula of bulgarsenine is $C_{18}H_{27}NO_5$ (from the high-resolution mass spectrum). The peaks at *m/e* 123, 122 and 82 indicate[5,6] that it is an alkaloid of pyrrolizidine type with a saturated base, esterified by a C_{10} dicarboxylic acid forming a macroring. According to the UV[3] and the IR spectra, bulgarsenine consists of a saturated base and of an α,β-unsaturated acid. The interpretation of the ^{1}H-NMR spectrum of bulgarsenine is also based on the presence of a saturated base in the molecule. Consequently, one of the two most downfield lying signals in the ^{1}H-NMR spectrum (Table I) must be due to $H_{(7')}$. Since the multiplet at 5·65 p.p.m. is responsible for the 1·3 Hz splitting of the olefinic methyl signal at 1·87 p.p.m., the corresponding proton must be located in the acidic moiety. The other multiplet at 5·49 p.p.m. belongs to $H_{(7')}$. This proton is coupled to the proton at 3·31 p.p.m. (J = 4·8 Hz), which can be assigned to $H_{(8')}$, and to some protons at 1·94–2·60 p.p.m. The assignment of two quartets at 4·40 and 4·00 p.p.m. with mutual coupling $J = J_{gem}$ = 10·8 Hz to the protons of the primary alcoholic group at $C_{(9')}$ is straightforward. The width of the $H_{(7')}$ multiplet indicates a mixed *exo-endo* conformation of the pyrrolizidine ring[4]. The size of $J_{7',8'}$ and $J_{1',8'}$ (4·8 and 6·8 Hz) shows[1] that the base is platynecine or its diastereoisomer. This opinion is supported by the isolation of platynecine (*VI*) as a hydrolytic product of bulgarsenine. By subtracting the empirical formula of the base from the whole molecule, we obtain the formula $C_{10}H_{14}O_5$ for the acyl. It must accommodate (^{1}H-NMR, UV and IR spectra) one CH_3CH group, CH_3—C, OH, olefinic CH_3, one olefinic proton, and two COO groups. One C and two H's remain unassigned, they probably form a CH_2 group. The 1·3 Hz coupling between the olefinic proton and the methyl excludes their geminal arrangement. They must be either *cis* or *trans* (that question cannot be resolved using a J value alone since the ranges are 0·8–1·4 Hz for the *cis* and 1·2–1·5 Hz for the *trans* coupling[7]). However, the observed NOE clearly indicate the *cis*-arrangement. The magnitude of the couplings of the olefinic proton require its allylic position to the aliphatic chain attached to the double bond. The chemical shift of the olefinic methyl indicates its *trans* position relative to the carboxyl. Thus, the formula of the esterifying acid of bulgarsenine is probably the same as that of the unsaturated acid *VII* isolated[1] from *S. nemorensis* L., var. *subdecurrens*. Further arguments can be extracted from the fragmentation pattern of bulgarsenine (Scheme 3). The prevailing fragmentations of the molecular ion are leading to the ions *m/e* 211



SCHEME 3

Fragmentation Pattern of Bulgarsenine (*VIII*)

and 226. They involve the loss of a seven-carbon moiety containing the double bond and are followed by loss of $C_3H_4O_3$, $C_3H_3O_2$ and C_2H_3O. The same loss is observed from the *m/e* 293 ($M-CO_2$) ion. Therefore the CH_3 and OH groups can be placed at $C_{(2)}$. Expulsion of C_4H_7O from the M^+ ion and from the ion $M-CO_2$ indicates the location of the secondary methyl at $C_{(3)}$. A detailed examination of the Scheme[3] allows to write the double bond between $C_{(5)}$ and $C_{(6)}$. The observed fragmentation is somewhat exceptional among the pyrrolizidine alkaloids because of the usually dominating decomposition through the M—CO_2 ion.

In view of the fact that bulgarsenine (*VIII*) contains (^{1}H-NMR, UV and IR spectra) an unsaturated acid, whereas on hydrolysis it affords nemorensic acid (*IIIa*), it must easily come on hydrolysis to stereospecific addition of the hydroxyl group at $C_{(2)}$ to a double bond in the position 5, 6 under formation of the tetrahydrofurane ring. This was already observed earlier[8] in the alkaloid erucifoline.

A characteristic feature of the three alkaloids isolated from four varieties of *S. nemorensis* L. is the presence of dicarboxylic acids of a new type, which leads to the formation of a thirteen-membered macrocycle. Thus, the plant *S. nemorensis* differs from the other plants of the genus *Senecio*. After a comparison of the other substances contained therein, this might be of importance for the chemotaxonomy.

EXPERIMENTAL

The melting points have been determined on the Kofler block and are uncorrected. The UV spectra were measured on a Unicam SP-700 in 95% ethanol, the IR spectra on an instrument UR 20 (Zeiss, Jena) in chloroform or nujol, the ^{1}H-NMR spectra on a Varian T-60 and on a Tesla BS 487 tetramethylsilane as an internal standard, the chemical shifts are expressed in δ-values. The CD spectra were measured on a Roussel-Jouan dichrograph model 185 in ethanol, the mass spectra on a Varian MAT 311 instrument. Thin-layer chromatography was carried out on silica gel G in the solvent systems S_1 (benzene–ethyl acetate–diethylamine, 7 : 2 : 1) and S_2 (tetrachloromethane–isobutyl alcohol–methanol–20% ammonium, 40 : 15 : 15 : 4), detection with Dragendorff reagent. Column chromatography was carried out on silica gel G 100/160 (Lachema). The solutions of all the substances in organic solvents were dried over anhydrous sodium sulphate.

Isolation of Alkaloids

The dry, powdered leaves of *S. nemorensis* L., var. *bulgaricus* (VEL.) STOJ. et STEF. (3000 g), collected at the end of July 1971 on the mountain Vitosha (Bulgaria), were repeatedly extracted with a tenfold quantity of 4% sulphuric acid at 55—60°C in the presence of zinc powder (10% of plant weight). The acidic extract was filtered, ammonium added up to pH 5—6, and again filtered under vacuum. The filtrate was made alkaline to pH 10·5 and extracted several times with chloroform up to a negative test with silicotungstic acid. After drying and evaporation, the combined chloroform extracts gave a viscous brown mass (50 g, 1·66% per dry material) of hR_F 56, 48, 34, 26, 21, 15 and 5 (S_2).

Separation and Purification of Alkaloids

The mixture (10 g) of alkaloids was chromatographed on silica gel (300 g, tube 35 mm i.d.), collection of 25 ml fractions, solvent system chloroform–methanol, 3 : 2. According to the results of thin-layer chromatography, the fractions 38—106 (portion A), 122—524 (portion B) and 525 to 809 (portion C) were combined and each portion rechromatographed.

The portion A (0·18 g) contained two alkaloids of hR_F 56 and 48 (S_2) of which the alkaloid of hR_F 48 was predominant. This mixture was chromatographed on silica gel (25 g, tube 10 mm i.d.) with the solvent system S_2, collection of 1 ml fractions. The fractions containing the alkaloid of hR_F 48 were collected and repeatedly chromatographed to obtain an alkaloid of hR_F 48, contaminated with ballast substances. It was diluted in 5% hydrochloric acid, filtered, made alkaline and extracted with ether. After evaporation of ether, the residue was converted to a tartrate, from which the pure retroisosenine (*V*) hR_F 48 (S_2) or 61 (S_1) was obtained; m.p. 127°C, $[\alpha]_D^{24}$ +118° ± 2° (*c* 0·69 in chloroform), UV: λ_{max} 220 nm (log ε 3·44), IR ($CHCl_3$): ν_{max} 1734 cm^{-1} (ester), no absorption of hydroxyl groups. MS (*m/e*, relative intensity, elemental composition): 335 (0·5, $C_{18}H_{25}NO_5$), 291 (2·6, $C_{17}H_{25}NO_3$). 263 (1·0, $C_{16}H_{25}NO_2$), 248 (4·3, $C_{15}H_{22}NO_2$), 220 (23, $C_{13}H_{18}NO_2$), 181 (6·0, $C_{10}H_{15}NO_2$), 178 (7·8, $C_{11}H_{16}NO$), 138 (40·2, $C_8H_{12}NO$), 136 (59·8, $C_8H_{10}NO$), 121 (41·4), 120 (87·3, $C_8H_{10}N$), 119 (100, C_8H_9N), 95 (24·1), 94 (21·8), 93 (34·5, C_6H_7N), 80 (12·6, C_5H_6N), 43 (27·6). According to thin-layer chromatography and IR spectra, retroisosenine (*V*) is identical with the alkaloid SN-A, isolated[1], from *S. nemorensis*, var. *subdecurrens*. The total amount of isolated retroisosenine (*V*) was 0·3 g (0·01% per dry plant).

The portion B (3·5 g) contained (thin-layer chromatography) the main alkaloid of hR_F 34 (S_2) and traces of four other alkaloids of hR_F 26, 21, 15 and 5 (S_2). The mixture was dissolved in 5% hydrochloric acid, filtered, made alkaline with ammonia, and repeatedly extracted with ether. After removal of the solvent, the residue was converted to a tartrate from which the pure bulgarsenine (*VIII*) of hR_F 34 (S_2) or 55 (S_1) was obtained; m.p. 115°C, $[\alpha]_D^{24}$ −54° ± 2° (*c* 0·78 in chloroform), UV: λ_{max} 222 nm (log ε 3·93), IR ($CHCl_3$): ν_{max} 1654 cm^{-1} (C=C), 1720 cm^{-1} (ester), 3525 and 3623 cm^{-1} (OH group). MS (*m/e*, relative intensity, composition): 337 (2·6, $C_{18}H_{27}NO_5$), 322 (0·8, $C_{17}H_{14}NO_5$), 320 (0·8, $C_{18}H_{26}NO_4$), 293 ($C_{17}H_{27}NO_3$), 266 (1·3, $C_{14}H_{20}NO_4$), 250 (0·3, $C_{15}H_{24}NO_2$), 238 (1·2), 226 (3·9, $C_{11}H_{16}NO_4$), 222 (2·2, $C_{13}H_{20}NO_2$), 211 (29·9, $C_{11}H_{17}NO_3$), 180 (19·6, $C_{10}H_{14}NO_2$), 168 (2·9, $C_9H_{14}NO_2$), 156 (11·3), 140 (97·9, $C_8H_{14}NO$), 138 (61·9, $C_8H_{12}NO$), 123 (46·4, $C_8H_{13}N$), 122 (78·4, $C_8H_{12}N$), 96 (38·1), 95 (20·6), 82 (100, C_5H_8N), 55 (24·7), 43 (30·9), 41 (22·7). Thin-layer chromatography showed that bulgarsenine (*VIII*) is identical with the alkaloid SN—B which was detected[1] in *S. nemorensis* L., var. *subdecurrens*. The total amount of isolated bulgarsenine (*VIII*) was 13·5 g (0·45% per dry plant).

The portion C (0·3 g) contained five alkaloids. The mixture was subjected to column chromatography on silica gel (50 g, tube 20 mm i.d.) with the solvent system S_2, collection of 1 ml fractions. From the fractions 17—40, an alkaloid of hR_F 26 (S_2) was obtained which after purification via a tartrate was identified as nemorensine[1] (*I*), m.p. 132°C. The total amount of isolated nemorensine (*I*) was 10 mg (0·0003% per dry plant material).

Alkaline Hydrolysis of Retroisosenine (*V*)

A solution of retroisosenine (143 mg) and potassium hydroxide (150 mg) in methanol (6 ml) was refluxed for 6 h. The mixture was evaporated in vacuum, and the residue extracted 5× with hot chloroform. After evaporation, the yield was 56 mg of an oily base the ^{1}H-NMR spectrum of which was identical with that of retronecine[9] (*II*). Its hydrochloride was prepared with ethanolic hydrogen chloride to give 16 mg of crystals of m.p. 159—161°C which on the basis

of the mixed melting point are identical with authentic retronecine hydrochloride. After extraction with chloroform, the residue was dissolved in water, acidified with 1M sulphuric acid, and extracted 5× with ether to afford oily *cis*-nemorensic acid (*IVa*), $[\alpha]_D^{24}$ +49° ± 4° (*c* 0·76 in ethanol).

For spectral measurements, the dimethyl ester *IVb* was prepared with diazomethane. The oily product was assigned the empirical formula $C_{12}H_{20}O_5$. MS (*m/e*, relative intensity, composition): 244 (0·1, $C_{12}H_{20}O_5$), 229 (1·0, $C_{11}H_{17}O_5$), 213 (2·4, $C_{11}H_{17}O_4$), 185 (100, $C_{10}H_{17}O_3$), 171 (12·5, $C_9H_{15}O_3$), 153 (55·0, $C_9H_{13}O_2$), 125 (41·3, $C_8H_{13}O$), 111 (16·3, $C_6H_7O_2 + C_7H_{11}O$), 109 (12·5), 107 (11·3), 43 (60·6).

Alkaline Hydrolysis of Bulgarsenine (*VIII*)

A solution of bulgarsenine (815 mg) and potassium hydroxide (800 mg) in methanol (20 ml) was refluxed for 3 h. The mixture was evaporated in vacuum and the residue extracted 5× with hot chloroform. After evaporation, the chloroform extract gave 525 mg of an oil the ^{1}H-NMR spectrum of which was identical with that of platynecine[10] (*VI*). The oily base was treated with ethanolic hydrogen chloride to give a hydrochloride which could not be brought to crystallization. It was dissolved in water, filtered over a column of Amberlite IRA RO1 in the OH^- cycle, the filtrate was evaporated in vacuum and crystallized from acetone to afford 260 mg of crystals of m.p. 145–147°C, $[\alpha]_D^{24}$ −57° ± 2° (*c* 0·54 in chloroform). Platynecine (*VI*) is reported[11] to have m.p. 147–148°C, $[\alpha]_D^{20}$ −60·3° (chloroform). After extraction with chloroform, the residue was worked-up as in the case of retroisosenine to give needles (241 mg) of m.p. 173–177°C (ethyl acetate) which, on the basis of the mixed melting point, the IR, ^{1}H-NMR, mass and CD spectra (212 nm, $\Delta\varepsilon = +1{\cdot}51$), are identical with nemorensic acid[1] (*IIIa*).

Acid Hydrolysis of Bulgarsenine (*VIII*)

A solution of the alkaloid (251 mg) in 15% sulphuric acid (7 ml) was refluxed for 4 h, cooled, diluted with water 1 : 1, and extracted 6× with ether. After evaporation of ether, crystallization from ethyl acetate gave needles (80 mg) of m.p. 168–173°C which, on the basis of the IR, ^{1}H-NMR, mass and CD spectra, are identical with those of nemorensic acid[1] (*IIIa*).

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