SUMMARY

A new cycloartane glycoside, cycloorbicoside A, has been isolated from the epigeal part of the plant *Astragalus orbiculatus* Ledeb.; it has the structure of (23R,24S)-16β,23:16α,24-diepoxycycloartane-3β,7β,25-triol 3-O-β-D-xylopyranoside.

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ABSOLUTE CONFIGURATION AND CONFORMATIONAL FEATURES OF ALKALOIDS OF THE NITRAMINE GROUP AND THEIR DERIVATIVES

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The absolute configurations of the asymmetric centers in the natural alkaloids nitramine (6R,7eS), isonitramine (6S,7eS), and sibirine (6R,7eR) have been established by the circular dichroism method using the octant rule.

On the basis of the results of x-ray structural analysis (XSA) of crystalline salts the conformations of the cations of nitramine and isonitramine have been found previously [1, 2]. Since the use of the program did not permit antipodes to be distinguished, the suggested diastereomerism of nitramine (I) and isonitramine (II) at the C(7) asymmetric center proved to be erroneous. Later by a comparison of the optical properties of the oxidation products of the two alkaloids we showed that (I) and (II) differed by the configuration of the C(6) spiro carbon atom [3]. In the present paper we give information on the study of the stereochemistry of the molecules of (I) and (II) and their N-methyl derivatives, and also of sibirine [4] by the circular dichroism (CD) method.

The nitramine and isonitramine molecules are fairly mobile. However, in solutions they exist predominantly in conformations fixed by an intramolecular hydrogen bond [1] which is characteristic, in particular, for γ-amino alcohols. Nitramine is conformationally more mobile than isonitramine, and therefore the sign of its specific rotation changed on passing from chloroform ($[\alpha]_D$ + 16°) to methanol ($[\alpha]_D$ − 8°). The conformation of isonitramine is more stable in relation to a change of solvent: $[\alpha]_D$ − 30° ($CHCl_3$) and $[\alpha]_D$ − 37° (CH_3OH).

The oxidation of the hydroxy groups in (I) and (II) to carbonyl groups gave dehydronitramine (III) and dehydroisonitramine (IV) each with one asymmetric center at the C(6) spiro atom. In the CD spectra of compounds (III) and (IV) there were Cotton effects (CEs) in the 300 nm due to the n → π* transition of the carbonyl chromophore with were equal in intensity ($\Delta\varepsilon$ = 0.60) and opposite in sign (Fig. 1, curves 6 and 1, respectively). Similar results were obtained for the specific rotation: $[\alpha]_D$ III −46° (chloroform), $[\alpha]_D$ IV +44° (chloroform). On

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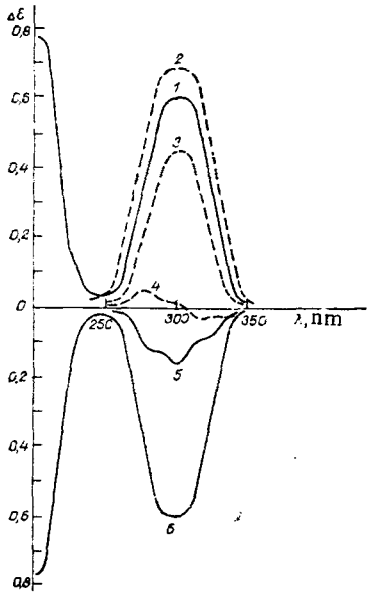


Fig. 1

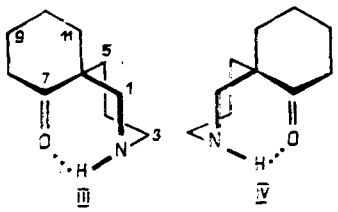


Fig. 2

Fig. 1. CD spectra in $CHCl_3$: 1) dehydroisonitramine; 2) immediately after oxidation; 3) 2 h later; 4) a day later; 5) ten days later; 6) dehydronitramine.

Fig. 2. Conformations of dehydronitramine (III) and of dehydroisonitramine (IV).

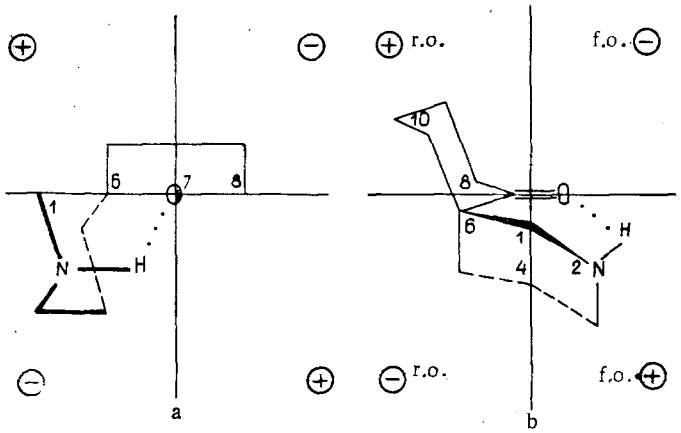


Fig. 3. Projection of the dehydroisonitramine (IV) molecule on the rear (a) and left (b) octants (r.o. — rear octants; f.o. — front octants.

this basis, it was concluded that the spiro atoms in the dehydro derivatives (III) and (IV) and, accordingly, in the initial bases, had different absolute configurations.

The results of XSA and NMR spectroscopy showed that the two rings in nitramine and also those in isonitramine had the chair conformation [1]. From the IR spectra we determined the presence of a strong intramolecular hydrogen bond (shift of the absorption band of active hydrogen into the 3200-3235 cm^{-1} region), which was present both in the bases and in the oxidation products. Figure 2 shows two possible stereoisomers at the spiro atom (III) and (IV) in conformations stabilized by intramolecular hydrogen bonds.

Let us consider octant diagrams for one of the isomers; for example, for structure (IV). The bulk of the molecule is located in the left front and rear octants. Consequently, in Fig. 3, in addition to projections of the rear octants (a) a lateral projection of the left front and rear octants (b) has been illustrated. It can be seen from the diagrams given that

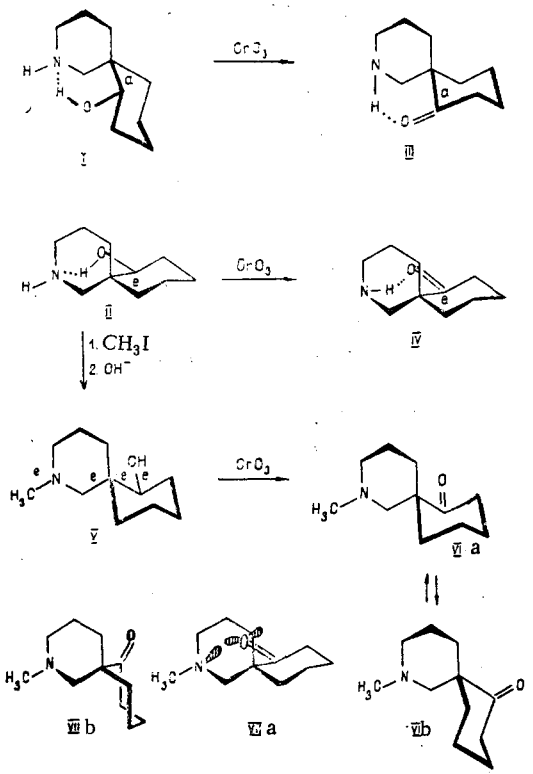
the C(8)—C(7), C(7)—C(6), and C(6)—C(1) bonds lie in the horizontal nodal plane, and, consequently, make a zero contribution to the optical activity. Determining the magnitude and sign of the CE are the nitrogen atom and the ring formed by the hydrogen bond. This part of the molecule falls into the front left lower positive octant and, consequently structure (IV) must correspond to a positive CE, which agrees with the CD spectrum of dehydroisonitramine and the S-configuration of the spiro atom. On considering the corresponding octant diagrams for structure (III) it was established that the spiro center in dehydronitramine has the R-configuration.

When a chloroform solution of (IV) was acidified, the amplitude of the CE increased, and then it slowly decreased and after ten days the sign of the CE changed (Fig. 1, curves 2-5). Apparently, initially a hydrogen chloride molecule plays the role of substituent at the nitrogen atom, but subsequently, in the process of salt formation, a passage takes place to a conformation without a hydrogen bond, as has been demonstrated for the crystalline hydrochloride of (II) by the XSA method [1].

From Dreiding models it can be seen that the oxidation of isonitramine is not accompanied by an appreciable change in the conformation of the molecule ((II) → (IV), see scheme), while in the case of nitramine the appearance of a hydrogen bond between the proton of the amino group and a free electron pair of the carbonyl oxygen requires a change in the conformation of the carbocycle ((I) → (III), see scheme).

In view of the CD and XSA results and on the basis of conformations fixed by an intramolecular hydrogen bond, we suggest the S-configuration for the asymmetric C(7) atom in each of the bases (I) and (II).

The methylation of isonitramine with methyl iodide gave N-methylisonitramine ((II) → (V), see scheme). The conformation (V) is probably the structure with the lowest energy, since it contains the maximum number of equatorial bonds. The production of this conformation from (II) with the cleavage of the hydrogen bond is apparently preferential. The oxidation of (V) with chromium trioxide gave N-methyldehydroisonitramine (VI) having a weak ($\Delta\varepsilon \sim 0.1$) positive CE in the 300 nm region of the CD spectrum. It must apparently be considered that in chloroform solution compound (VI) exists in the form of two conformers (VIa) and (VIb) in approximately equal amounts (scheme), and the sign of the CE is due to the larger contribution of the (VIb) conformation. This is illustrated in Fig. 4, which gives the octant diagrams of the two conformers.



Scheme of the transformations of nitramine (I) and isonitramine (II).

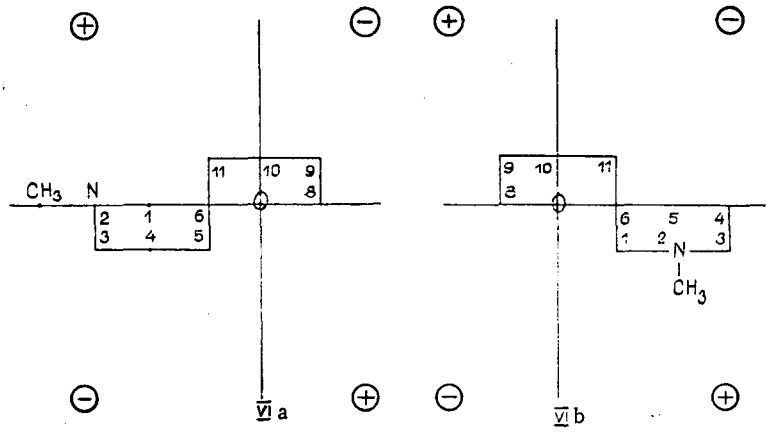


Fig. 4. Octant diagrams of the conformers (VIa) and (VIb) of the product of the oxidation of N-methylisonitramine (rear octants).

There are numerous indications that the methyl groups in N-methylpiperidines are oriented equatorially for preference [5, 6]. In the case that we are considering of the alkaloids of the nitramine group, the spiro system exerts steric hindrance to the axial orientation of the N-methyl group, and therefore conformations with an axial methyl group will not be discussed here. The existence of another two forms (VIIa) and (VIIb) (scheme) which are the invertomers of conformers (VIa) and (VIb) respectively at the piperidine ring and in which the C(6)—C(7) bond has the axial orientation is theoretically possible. However, the stability of structure (VIIa) raises doubts because of the strong electrostatic repulsion of the axial electron pair of the nitrogen atom and an electron pair of the carbonyl oxygen present in it. So far as concerns the (VIIb) conformation, a consideration of octant diagrams shows that it can lead to a negligibly small CE caused by only one carbon atom, C(4) and, therefore, has no appreciable influence on the total magnitude of the Cotton effect.

As has been established previously [4], N-methylisonitramine is the antipode of the natural alkaloid sibirine. In actual fact, dehydrosibirine and N-methyldehydronitramine obtained similarly showed negative Cotton effects in the 300 nm region of their CD spectra with intensities of the same order of magnitude and, are therefore, enantiomers of N-methyldehydroisonitramine.

EXPERIMENTAL

CD spectra were recorded on a JASCO-20 spectropolarimeter. The concentration of the solutions was 2 mg/ml, with cell thicknesses of 1.0, 0.5, and 0.1 cm. Chloroform and methanol were used as solvents. The signs of the CEs for the dehydro derivatives did not change on passing from chloroform to methanol solutions. For acidification, a drop of an ethanolic solution of HCl was added to 3 ml of a chloroform solution. The oxidation and methylation reactions were performed by the procedures described in [1]. The presence of an intramolecular hydrogen bond was determined from the IR spectra taken in chloroform (I-V) and in carbon tetrachloride (I-IV) on a UR-20 instrument.

SUMMARY

Using the octant rule and circular dichroism spectra, the absolute configurations of the asymmetric centers of the following alkaloids have been established: (+)-nitramine — 6R,7eS; (—)-isonitramine — 6S,7eS; and (—)-sibirine — 6R,7eR. The conformational features of the bases and of their N-methyl derivatives have been discussed.

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ALKALOIDS OF *Nitraria schoberi*.

RING-CHAIN TAUTOMERISM OF THE HYDROLYSIS PRODUCT OF NITRARAMINE

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The chemical properties of nitraramine have been studied. The possibility has been shown of the existence of the hydrolysis product in three tautomeric forms: amino-aldehyde, carbinolamine, and semiacetal. The NMR spectra of nitraramine and its derivatives (N-acetylnitraramine, dihydronitraramine) have been analyzed and this has permitted spatial structures to be suggested for these compounds.

The structure of the alkaloid nitraramine has been established previously [1] on the basis of results of x-ray structural analysis of a crystalline salt; it has the original structures (I). In the present paper we give the results of a study of the ^1H and ^{13}C NMR spectra and also of the behavior of the nitraramine molecule in acetylation, hydrolysis, and hydrogenation reactions.

The ^{13}C NMR spectrum of (I) taken under the conditions of complete and partial suppression of C—H interactions had the following signals (ppm): 82.2 (doubet, C-17), 75.9 (d, C-7), 66.4 (d, C-1), 50.4 (triplet, C-15) 45.3 (t, C-3), 38.8 and 37.9 (doublets, C-12 and C-11), 32.3 (singlet, C-6), 30.5 (t), 28.4 (t), 25.1 (t), 24.0 (t), 21.9 (t), 15.3 (t), and 14.5 (t). In the assignment of the signals mentioned, the comparative characteristics of the spectra of the related alkaloids nitramine, isonitramine [2], and nitrabirine [3], the molecule of each of which also contains a 2-azaspiro[5.5]undecane system, were also taken into consideration. Thus, the value of the chemical shift of the doublet from C-7 at 75.9 ppm in the spectrum of (I) is within the range found for the three bases mentioned above: 77.0, 79.8, and 74.7 ppm, respectively.

The triplet at 45.3 ppm was assigned to the C-3 atom; the position of the analogous signal in the spectrum of nitramine is 46.7 ppm and in that of isonitramine 47.3 ppm. The signal of the carbon atom in the first positions was somewhat descreened through the presence of a second nitrogen atom linked to it (in the spectrum of nitramine, 52.0 ppm, and in that of isonitramine 60.3 ppm). The signal of the spiro carbon atom at 32.3 ppm in the spectrum of nitraramine, conversely, is screened by the 2,6-oxazabicyclo[2.2.2]octane system as compared with the analogous signals for nitramine (36.1 ppm) and for isonitramine (36.2 ppm).

In the PMR spectrum of nitraramine [1], a broadened one-proton signal ($W_{1/2}$ = 6.3 Hz) at 4.37 ppm must be assigned to an equatorial H-7 proton geminal to an ether oxygen. Its strong descreening ($\Delta\delta$ ~ 0.85 ppm) as compared with the signal of the analogous carbinol protons in the spectra of nitramine and isonitramine [2] is apparently connected with the influence of the lone pair of electrons of the N(2) nitrogen atom (see formula I in the scheme). Descreening of a similar nature has been reported in nitrabirine [3]. Furthermore, in the spectrum of (I) a 1-H doublet (^3J = 2.5 Hz) at 4.01 ppm is due to the H-17 proton (axial-equatorial interaction in relation to the lower pyridine ring with the H-12 proton). The axial H-1 proton gives a narrow singlet at 3.28 ppm. The equatorial hydrogens of the C-3 and C-15 methylene groups resonate in the form of a broadened doublet (a doublet with split components) at 3.03 ppm (2 H, ^2J = —12 Hz). The axial protons geminal to them give a multiplet at 2.64 ppm (broadened triplet, 2 H, $^2J = {}^3J$ = 12 Hz).

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