STRUCTURES OF NITRAMINE AND ISONITRAMINE — ALKALOIDS OF A NEW TYPE FROM PLANTS OF THE GENUS *Nitraria*

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The proof of the structures of two isomeric alkaloids — nitramine and isonitramine — from two species of plants of the genus *Nitraria* is given. Their diastereoisomerism with respect to the C_7 asymmetric atom has been established. This is the first time that alkaloids with the structure of 2-azaspiro[5,5]undecan-7-ol have been found.

The alkaloid nitramine (I) was isolated from *Nitraria schoberi*. The catalytic dehydrogenation of (I) led to the formation of 8-methylquinoline. On the basis of the information available, the structure of 8-methyldecahydroquinolin-7-ol was put forward for (I) [1].

Isonitramine (II) was later isolated from *Nitraria sibirica* [2]. As was found, compounds (I) and (II) had the same composition ($C_{10}H_{19}NO$) and skeleton, but they differed by the stereochemistry of their molecules [2]. The chemical transformations of (II) did not contradict the structure of (I) put forward previously. However, it was impossible on the basis of a decahydroquinoline structure to make a satisfactory assignment of the signals in the PMR spectra of (I) and (II), and this has induced us to perform additional experiments.

An investigation of the ^{13}C NMR spectra of the bases (I) and (II) has shown the absence of methyl groups from their molecules and the presence in each of of them of a quaternary spiro carbon atom, a single methine group to which a hydroxyl is attached, and also eight methylene groups, two of which are linked to a nitrogen atom. Below we give the chemical shifts (ppm) of carbon atoms (I) and (II) (the symbols for the multiplicities of the signals are given in parentheses: t — triplet; d — doublet; s — singlet in a spectrum obtained under the conditions of incomplete decoupling from protons):

Substance	C-1(*t*)	C-3(*t*)	C-6(*s*)	C-7(*d*)	C-4 5, 8—11 (*t*...*t*)
I	52,0	46,7	36,1	77,0	37,4; 36,3; 32,0; 23,9; 28,2; 21,1
II	60,3	47,3	36,2	79,8	36,3; 29,8; 28,7; 24,3; 23,1; 20,4

It follows from the facts given that the azacyclic and carbocyclic rings form a spirobicyclic system, and the nitrogen atom is present in the α position to the spiro center.

The PMR spectra of (I) and (II) (Table 1) each have two doublets of axial and equatorial protons of an isolated methylene group with ^2J = 11.9 Hz, which shows the position of the methylene group under consideration between the nitrogen atom and the spiro center. It is known that on passing from NH to NCH_3 derivatives in piperidines [3], α-equatorial protons are screened by an amount (∿ 0.25 ppm) averaging one third of that of α-axial protons (∿ 0.76 ppm). In the spectra of N-Me (I) and N-Me (II) a screening of H_{1e} by an average of 0.32 ppm is observed and the H_{1a} signals are displaced into the methylene hump, which confirms the assignment made. The axial proton at C_3 has the form of a triplet the components of which are additionally split (Table 1).

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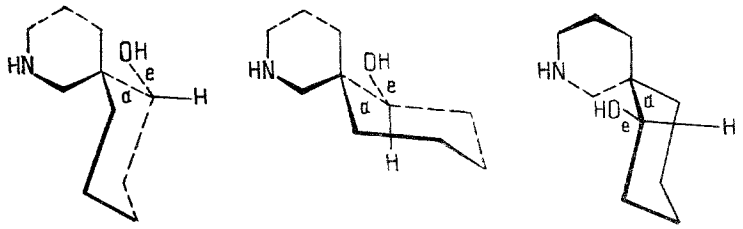
TABLE 1. Parameters of the PMR Spectra of Nitramine and Isonitramine and Their Derivatives (ppm, Hz)

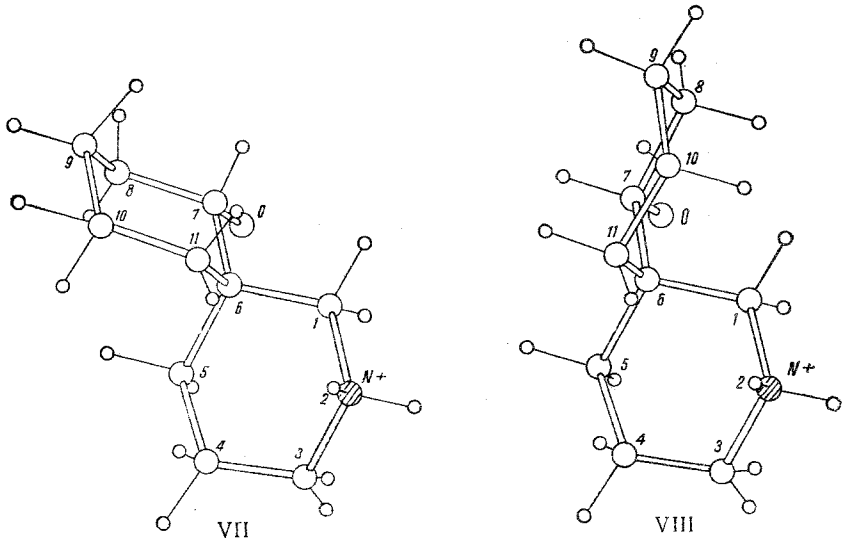
Substance	H_{1a}	H_{1e}	H_{3a}	H_{3e}	H_{7a}	O-H	N-H
Nitramine (I)	2,37 d* $^2J=-11.9$	3.34 d $^2J=-11.9$	2,58 (d.t) $^2J=-11.4$ $^3J=11.4; 3.3$	2,95 m	3.48 d.d $^3J=9,1; 4,2$	3,98 (br.s)	3,98 br.s
Isonitramine (II)	2,44 d $^2J=-11.4$	2,88 d $^2J=-11.4$	2,54 (d.t) $^2J=-11.4$ $^3J=11,4; 3.5$	2.92 m	3,57 d.d $^3J=11,0; 3.5$	3,87 (br.s)	3.87 br.s
N-methyl-(I)		3.07 d $^2J=-11.7$		2,67 m	3.42 d.d $^3J=9.3; 4.1$	5,43 (br.s)	
N-methyl(II)		2.51 t.d $^2J=-11.7$ $^4J=1,6; 1,6$		2,73 m	3,54 d.d $^3J=9.3; 4.1$	5,39 (br.s)	
7-Oxonitramine (III)	2.33 d $^2J=-13.4$	3.13 d.d $J=2,0$ $^2J=-13,4$	2,56 m	2,89 m			2.1 br.s
7-Oxoisonitramine (IV)	2,33 d $^2J=-13,4$	3,13 d.d $J=2,0$ $^2J=-13,4$	2 58 m	2,90 m			3.56 br.s

*d) doublet; d.d) doublet of doublets; d.t) doublet of triplets; br.s) broadened singlet; m) multiplet; br.m) broadened multiplet (missing in Russian original — Consultants Bureau); i.d) triplet of doublets.



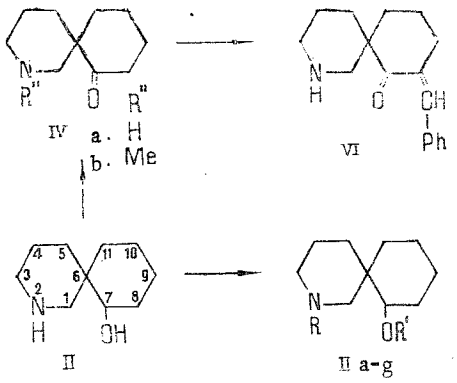
II IIh

Fig. 1



VII VIII

Fig. 2. Structures of the cations of nitramine (VII) and of isonitramine (VIII).



	R	R'
a	Ac	H
b	Ac	Ac
c	Me	Ac
d	Me	T
e	H·HCl	H
f	Me·Me	H
g	Me	H

In the IR spectra of the products of the oxidation of nitramine (III) and of isonitramine (IV) (see scheme; transformations of nitramine analogous), there is a strong absorption band at 1700 cm^{-1} (KBr) showing the probable location of the carbonyl group in a six-membered (and not in a five-membered) ring.

Compounds (II) and (IV) form monobenzylidene derivatives (V and VI), which shows the location of the hydroxy groups in (I) and (II) at the α carbon atoms in relation to the spiro-center atom. The region of appearance and the nature of the splitting of the signal from the proton geminal to the OH group in the PMR spectrum of (I) and that of (II) (Table 1) confirm this conclusion, and also indicate the equatorial orientation of the substituent in the structure of each alkaloid.

Experiments using the multifrequency resonance procedure have enabled it to be established that the only methine proton in the molecule of (I) and in that of (II) and the protons located at C_3 do not interact vicinally with the same methylene group. This unambiguously shows that the hydroxy group is present in the cyclohexane ring.

Thus, from the facts given above the most probable chemical structure of nitramine and of isonitramine follows as 2-azaspiro[5,5]undecan-7-ol.

Analysis of the IR spectra of (I) and (II) at various concentrations in chloroform showed the existence of a strong intramolecular hydrogen bond in the solutions of each alkaloid. [(I) 3200 cm^{-1}; (II) 3235 cm^{-1}].

Consequently, nitramine and isonitramine may be stereoisomeric either at C_6 [(I) and (IIg)] or at C_7 [(I) and (II), Fig. 1].

The results of an x-ray structural investigation of nitramine nitrate (VII) and isonitramine hydrochloride (VIII) confirmed the structures based on chemical and spectral characteristics and permitted the conformations of the cations to be determined (Fig. 2). Both the cyclohexanol ring with the equatorially oriented hydroxy group and the piperidine ring in each compound have the chair configuration. The C_6-C_7 bond in (VII) and (VIII) is equatorial. The alkaloids differ by the configuration of the C_7 asymmetric center.

Returning to the conformations of the bases in solution, it must be mentioned that, apparently, nitramine and isonitramine have the preferred conformations (I) and (II), respectively, with axial C_6-C_7 bonds (see Fig. 1).

The absolute configurations of the alkaloids are being studied.

Thus, nitramine and isonitramine each have the structure of 2-azaspiro[5,5]undecan-7-ol and are diastereomers at the C_7 asymmetric atom. This is the first time that alkaloids of this type have been found [4]. Alkaloids closest in structure to (I) and (II) — histrionicotoxin and dihydroisohistrionicotoxin, from the skin of the tree frog *Dentrobotes histrionicus* — have a 1-azaspiro[5,5]undecane skeleton [5].

EXPERIMENTAL

^{13}C spectra were recorded on a CFT-20 instrument (in $CDCl_3$; 0 — TMS); PMR spectra on a JNM-4H-100 spectrometer (0 — HMDS; δ scale); IR spectra on a UR-20 spectrophotometer; and mass spectra on an MKh-1303 instrument with a system for the direct introduction of the sample into the ion source. The homogeneity of the substances was established in a thin layer of silica gel-gypsum in the benzene—methanol (4 : 1), chloroform—methanol (1 : 1), and chloroform—methanol — ammonia (40 : 10 : 1) systems.

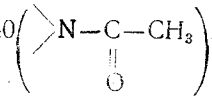
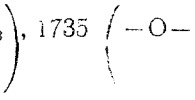
The x-ray structural study was performed on a Syntex four-circle automatic diffractometer. Crystals of salts of (I) and (II) are rhombic. Space groups $P2_12_12_1$, $z = 4$ [(I): $a = 8.682$, $b = 10.260$, $c = 13.069$. (II): $a = 8.031$, $b = 7.122$, $c = 20.81$]. The structures were interpreted by the direct method from 891 (I) and 874 (2) reflections with $|F|^2 \geqslant 2\sigma$ measured on the diffractometer (λ, CuK_α) and refined to $R = 0.073$ (I) and 0.066 (II).

Extraction of the Alkaloids. The air-dry comminuted epigeal part of *N. sibirica* (40 kg) was moistened with 8% ammonia solution and the bases were extracted with chloroform. The concentrated chloroform extract was treated with 10% sulfuric acid, the acid solution was washed with ether and was then made alkaline with concentrated ammonia solution, and the bases were extracted successively with ether and chloroform. This gave 66.9 g of ether-extracted and 33.3 g of chloroform-extracted alkaloids — 0.25% of the weight of the dry plant.

Isonitramine. A benzene solution of the repurified total ether-soluble material was separated according to basicity by means of citrate-formate buffer solutions into fractions with pH 8, 7, 6, 5, and 4. When the fraction with pH 8 was treated with ether, isonitramine precipitated in the form of white needles, mp 101-103°C (sublimation); $[\alpha]_D^{25} - 30°$ (c 1.36; chloroform).

Isonitramine Hydrochloride. An acetone solution of 50 mg of the base was treated dropwise with an ethanolic solution of HCl to pH 4. On standing, the crystalline hydrochloride precipitated. The crystals were separated off and dissolved in acetone—ethanol (3 : 2). The single crystals formed on evaporation of the solvent were used for the x-ray structural analysis.

O,N-Diacetylisonitramine. A solution of 50 mg of isonitramine in 2.5 ml of acetic anhydride was treated with 75 mg of p-toluenesulfonic acid. The mixture was heated at 100°C for

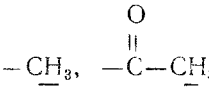
2 h, cooled with ice, and heated with a solution of sodium carbonate, and the O,N-diacetyl derivative was extracted with ether. After the solvent had been distilled off, 55 mg of an oily product was obtained. ν_{max} (cm^{-1}): 1640 (), 1735 (). M^+ 252.

N-Methylisonitramine. A solution of 75 mg of (II) in 2 ml of ethanol was treated with 1.25 ml of methyl iodide. The mixture was heated at 90°C, and the reaction was monitored by chromatography. After 2 h, heating was stopped and the solvent and excess of the reagent were evaporated off. The dry residue was treated with ice water, the mixture was made alkaline with 5% caustic soda solution, and the product was extracted with ether. This gave 75 mg of oily N-methylisonitramine with M^+ 183.

Isonitramine Methiodide. A mixture of 25 mg of (II), 0.7 ml of acetone, and 0.25 ml of methyl iodide was boiled for 15 min and evaporated to dryness, and the product was separated as in the preceding experiment. A mixture of 20 g of the resulting N-Me-(II) was treated with 0.7 ml of acetone and 0.23 ml of methyl iodide and the mixture was again boiled for 15 min. The white crystals of methiodide that formed were separated off. Yield 20 mg, mp 188-189°C.

7-Oxoisonitramine (IV). A mixture of 30 mg of (II), 55 mg of chromium trioxide, and 1.5 ml of acetic acid was kept at room temperature for three days (chromatographic monitoring). The solvent was driven off in vacuum. The dry residue was treated with 1 ml of water, the mixture was made alkaline with 5% caustic soda solution, and the product was extracted with ether, giving 20 mg of oily (IV). M^+ 167, ν_{max} 1700 cm^{-1} (KBr).

N-Methyl-7-oxoisonitramine. A mixture of 42 mg of N-Me-(II), 85 mg of chromium trioxide, and 2 ml of acetic acid was left at room temperature for three days. The product was isolated as described in the preceding experiment with a yield of 22 mg in the form of an oil with M^+ 181; δ 2.17 (N—$\underline{CH_3}$); ν_{max} 1712 cm^{-1} (film).

O-Acetyl-N-methylisonitramine. A solution of 30 mg of N-Me-(II) in 1.7 ml of acetic anhydride was treated with 50 mg of p-toluenesulfonic acid. The mixture was heated at 100°C for 2 h, cooled with ice, and treated with a solution of sodium carbonate, and the product was extracted with ether. After the solvent had been distilled off, 30 mg of an oily product was obtained. M^+ 225; δ 2.14, 2.03 ppm (), ν_{max} 1735 cm^{-1} (film).

Condensation of 7-Oxoisonitramine with Benzaldehyde in an Acid Medium. Monobenzylidene Derivative of 7-Oxoisonitramine. A mixture of 30 mg of the ketone (IV), 0.2 ml of freshly-purified benzaldehyde, and 0.2 ml of acetic anhydride was saturated with dry hydrogen chloride for 3 h. Then the reaction mixture was shaken in a shaking machine for 2 days. After alkalination with 5% caustic soda solution, the products were extracted with ether. The resulting mixture was separated on a column of alumina with elution by chloroform. This yielded 13 mg of the monobenzylidene derivative (IV). Mass spectrum, m/z: 255 (M^+), 238, 226, 212, 211, 200, 167.

N-Methyl-O-tosylisonitramine. A solution of 92 mg of N-Me-(II) in 4 ml of freshly distilled pyridine cooled in the freezing chamber of a refrigerator was treated with 160 mg of p-toluenesulfonyl chloride. The dissolved mixture was covered with paraffin oil and left in the refrigerator for a day and was then kept at room temperature for another day. Since 30-40% of the initial substance still had not reacted (chromatographic monitoring), the reaction mixture was heated in the water bath with stirring for 1 h. The solvent was evaporated off, the residue was dissolved in 10% H_2SO_4, the solution was decomposed with 10% NaOH, and the products were extracted with ether. They were separated from the starting material by chromatography on a column of silica gel with elution by chloroform. This gave 40 mg of the oily O-TS ester of N-Me-(II). PMR (ppm): 7.76 and 7.26 (TS—H), 4.62 (C_7—H), 2.38 (TS—Me), and 2.1 (N—Me). This experiment was performed in order to dehydrate the N-Me-(II). No satisfactory results were obtained in an experiment on dehydration with thionyl chloride, either.

Nitramine. Single crystals of nitramine nitrate [1] for X-ray structural investigation were obtained by the slow evaporation of a solution of the salt in ethanol.

N-Methylnitramine. A solution of 74 mg of (I) in 1 ml of ethanol was treated with 1 ml of methyl iodide. The mixture was heated for 2 h at 90°C and the product was extracted as described for N-Me-(II); the yield of N-Me-(I) was 52 mg.

7-Oxonitramine (III). A mixture of 40 mg of (I), 75 mg of chromium trioxide, and 2 ml of acetic acid was left at room temperature for 3 days. The oxidation product was extracted as described for (IV). This gave 25 mg of (III) [1].

N-Methyl-7-oxonitramine. A mixture of 23 mg of N-Me-(I), 50 mg of chromium trioxide, and 1 ml of acetic acid were left at room temperature for 3 days. Then it was worked up as in the preceding experiment, giving 12 mg of N-Me-(III), ν_{max} 1710 cm^{-1}.

SUMMARY

The structures of nitramine and isonitramine — alkaloids from two species of plants of the genus *Nitraria* — have been established. They are diastereomers of one another at the asymmetric C_7 atom. Their preferred conformations in solutions have been determined.

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