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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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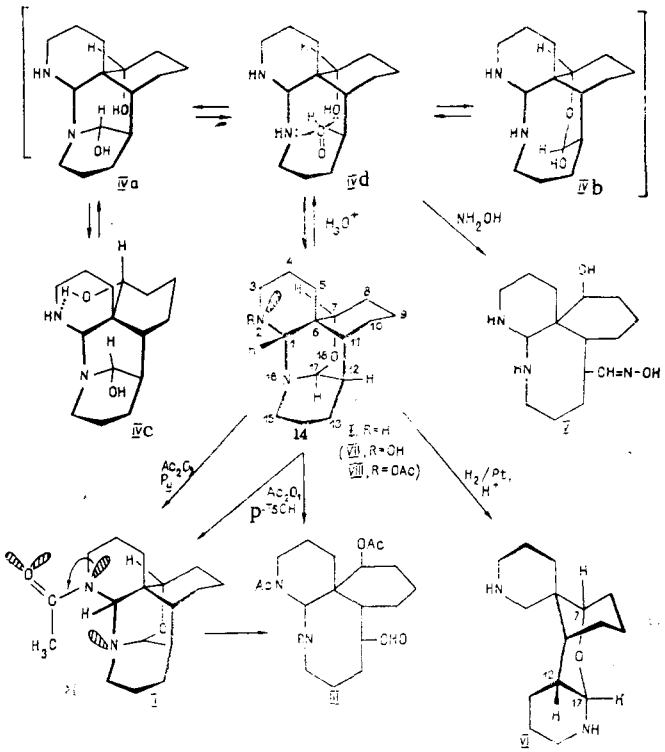

Scheme of the transformations of nitraramine (I).

The NMR spectrum of N-acetylnitraramine shows the descreening of the signal of the equatorial proton at C-3 (4.80 ppm, broadened doublet, 1 H, ^2J = –12.5 Hz) somewhat greater than that observed in N-acylpiperidines [4]. This fact is apparently explained by the predominance of rotamer (II) (see scheme): the opposite positions of the carbonyl and methyl groups are prevented by the nonbonding electron pair of the N(16) nitrogen. Conformation (II) also explains the relatively downfield position of the signal of the protons of the CH_3CO group (2.36 ppm, s, 3 H), which is under the descreening influence of this electron pair. The singlet of the hydrogen at C-1 also undergoes a downfield shift and fuses with the signal of the proton at C-17 (4.07 ppm, br.s, 2 H). The broadened 1-proton singlet at 3.94 ppm ($W_{1/2}$ = 6.3 Hz) must be assigned to the proton at C-7. The upfield shift of this signal as compared with the spectrum of the initial base ($\Delta\delta$ 0.43 ppm) is due to the displacement of the lone electron pair of the N(2) nitrogen in order to neutralize the positive charge localized on the carbon atom of the carbonyl group.

When nitraramine was acetylated with acetic anhydride in the presence of p-toluenesulfonic acid, in addition to the main product (II) a small amount of a N,O-di- or -triacetyl product (III, R = H or Ac, see scheme) was formed the IR spectrum of which in the carbonyl region contained a group of bands difficult to interpret (see the Experimental part). Compound (III) was also formed under similar conditions from (II). It is known that under the action of acetic anhydride in the presence of hydrogen ions an acetal gives an aldehyde and an ester [5]. Since a 1,3-tetrahydrooxazine (the atoms 1–6–7–18–17–16 in structure (I)) can be regarded as a cyclic O,N-acetal, a change must be expected just in this part of the nitraramine molecule on acetylation in an acid medium. Although the acetyl group located at N(2) provides serious steric hindrance to the introduction of another such substituent into the N(16) position, a very small amount of the O,N,N-triacetyl aldehyde derivative ((III), R = Ac) is nevertheless formed, apparently, since in the mass spectrum of the product there is a weak peak of an ion with m/z 392 corresponding to it. The tautomeric form of the N,O,O-triacetyl derivative is not excluded, either.

For a detailed understanding of the process taking place, we studied the hydrolysis of nitraramine. It must be mentioned that (I) is stable in 10-40% sulfuric acid at room temperature and on heating to 80°C for 10 h. However, when the time was lengthened (100 days at 30°C) or the temperature was raised (boiling) it was possible to isolate the expected product of the addition of one molecule of water (IV, see scheme). The possibility of the existence of (IV) in the tautomeric form (IVd), together with (IVa) and (IVb) was confirmed by the prep-

aration of the oxime (V) by a standard procedure. The IR spectrum of (IV) (film) contained absorption bands of associated active hydrogen (3300 cm^{-1}) and also of a carbonyl group (1666 cm^{-1}). Such a low region of frequencies, which is not typical for a saturated aldehyde, is obviously due to the very strong double transannular interaction of the nonbinding electron pairs of the N(16) nitrogen and the O(18) oxygen with the partial positive charge localized on the carbonyl carbon atom. A similar "amide type" of transannular neutralization has been described in the cases of other alkaloids (protopine, vomicine, and some others) and of simpler compounds containing 8-10-membered azacarbonyl rings with tertiary nitrogen atoms [6].

In compound (IV) there is the possibility of realization of two types of tautomerism. On the one hand, (IVd) is the amino aldehyde form of the α-carbinolamine (IVa). At the same time, (IVd) can be regarded as a δ-hydroxy aldehyde that is present in tautomeric equilibrium with the semiacetal (IVb). It must be mentioned that both extreme forms (IVa) and (IVb) (scheme) are sterically hindered to a considerable degree. This apparently explains the possibility of recording the presence of the aldehyde tautomer (IVd) in the IR spectrum of a film of the substance. However, the band of carbonyl absorption has a low intensity (of the order of 40%), and when the spectrum was recorded in absolute chloroform it broadened and decreased in intensity. The predominance in chloroform solutions of the less polar forms (IVa) and (IVb) was confirmed by the PMR spectrum of the hydrolysis product (see the Experimental part), in which no signal of an aldehyde proton was observed. The weakest signal in the spectrum was a one-proton broadened singlet at 4.82 ppm. The region of its appearance enabled this to be assigned to the semiacetal proton in (IVb), while the half-width indicated that the conformation of the pyran ring was distorted from boat to envelope through the withdrawal of the anomeric carbon atom from the N(16) nitrogen. The signal at 4.46 ppm corresponds to the equatorial proton at C-7. Signals due to the presence of the carbinolamine form (IVa) or, more accurately, to its conformer (IVc) were also observed in the spectrum. A narrow multiplet at 4.16 ppm and a broad one in the 3.30 ppm region were caused by protons geminal to hydroxy groups — H-17 and H-7, respectively ((IVc), see scheme). A singlet at 3.58 ppm having a small satellite at its base, corresponds to the H-1 proton in structures (IVa-c).

In conclusion, let us dwell on the hydrogenation of nitraramine over a platinum catalyst in acetic acid [1]. Analysis of the PMR spectrum of teh dihydro product (VI) shows that it was formed by the reductive cleavage of the C(1)—N(16) bond, as takes place in similar structures of *Ormosia* alkaloids under comparable conditions [7]. Thus, the singlet from C(1)—H resonating in the spectrum of (I) at 3.28 ppm does not appear in the spectrum of (VI). The signal from C(17)—H remains unchanged (4.01 ppm, d, 1 H, ^3J = 2.5 Hz) and the signal from C(7)—H (3.65 ppm, br.s, 1 H, $W_{1/2}$ = 6.5 Hz) is strongly screened in comparison with the spectrum of (I) (Δδ 0.72 ppm). The latter fact indicates that the hydrogenolysis of the bond mentioned was accompanied by a change in the conformation of the molecule as a whole in such a way that N(2) and C(7)—H were at the greatest possible distance from one another ((VI), see scheme).

The Experimental part of this paper also describes the reactions of the mutual transition (I) ⇄ (VII) and of the acetylation (VII) → (VIII) (see scheme) permitting a chemical correlation to be made of the structure of the natural alkaloid nitraroxine (VII) with the structure of nitraramine [8]. It has been shown that (VII) is a hydroxylamine derivative of (I).

EXPERIMENTAL

^1H NMR spectra were recorded on JNM-4H-100 and Tesla BS-567A/100 MHz instruments (0 — HMDS, δ scale). The ^{13}C NMR spectrum was obtained on a Bruker AM-300 instrument (0 — TMS). Deuterochloroform was used as solvent. IR spectra were taken on a UR-20 instrument under the conditions described in the text. Mass spectra were obtained on a MKh-1310 spectrometer.

Type KSK silica gel was used for thin-layer and column chromatography. The solvent systems are given in the descriptions of the experiments.

Acetylation of Nitraramine. A mixture of 0.038 g of nitraramine, 0.080 g of p-toluene sulfonic acid, and 5 ml of freshly purified acetic anhydride was heated in the boiling water bath for 2.5 h. The ice-cooled reaction mixture was treated with ammonia solution, and the products were extracted with chloroform. After the solvent had been driven off, 0.041 g of a mixture was obtained which was separated on a column of silica gel (8 × 350 mm, particle size 100-200 μ). On elution with benzene—methanol (4:1) the first fractions yielded 0.008 g of the amorphous substance (III). ν_{max}: 1745, 1710, 1698, 1665-1635 cm^{-1}.

Acetylation of N-Acetylnitraramine. To 0.040 g of (II) obtained as described in [1] were added 0.115 g of p-toluenesulfonic acid and 4.3 ml of acetic anhydride. The mixture was heated for three hours, and, after cooling, ammonia solution was added and the products were extracted successively with ether and with chloroform. The extracts were washed with dilute aqueous sodium carbonate solution and were then dried over anhydrous sodium sulfate. After the solvent had been distilled off, 0.017 g of ether-extracted material and 0.023 g of chloroform-extracted material were obtained. The ether-extracted material was chromatographed on a column of silica gel by the procedure described above, giving 0.009 g of (III).

Hydrolysis of Nitraramine. A mixture of 0.123 g of nitraramine and 6 ml of 15% sulfuric acid was boiled under reflux for 10 h. After being left to stand at room temperature for 18 h, the reaction solution was neutralized with 5% KOH solution and the products were immediately extracted with chloroform. Drying over anhydrous sodium sulfate and elimination of the extractant yielded 0.121 g of a mixture of products which was transferred to a column of silica gel (10.8 g, particle size 50-90 μ) and was eluted with the chloroform—methanol—ammonia (104:104:8) system. Fractions with a volume of 4-6 ml were collected. From fractions 3 and 4 was isolated 0.004 g of a substance identical with the natural alkaloid nitraroxine (VII) [8]. Mass spectrum, m/z: 264 (M^+), 248, 247, 219, 204, 190, 176, and others. Combined fractions 5-9 yielded 0.057 g of the initial nitraramine. The oily fractions 11-14 solidified on standing in the form of a vitreous mass. A total of 0.018 g of (IV) was isolated; mass spectrum, m/z: 266 (M^+), 248 $(M - H_2O)^+$, 237 $(M - CHO)^+$, and others. IR spectrum (cm^{-1}), ν_{max}: 3300 (active hydrogen), 2935, 2860 (saturated C—H bonds), 1666 (C=O) and others. PMR spectrum, ppm: 4.82 (br.s, 1 H, $W_{1/2}$ = 4 Hz), 4.46 (br.s, 1 H, $W_{1/2}$ = 6.5 Hz), 4.16 (multiplet, 1 H, $W_{1/2}$ = 7 Hz), 3.58 (s, 1 H), 3.27 (m, 1 H, $W_{1/2}$ = 20 Hz), 3.02 (multiplet of doublets, 2 H, ^2J = —12.0 Hz), 2.80-1.00 ("methylene hump").

Condensation of the Hydrolysis Product with Hydroxylamine. To 0.012 g of product (IV) were added 0.005 g of hydroxylamine hydrochloride and 1 ml of water, followed by a solution of 0.009 g of sodium carbonate in 0.5 ml of water over 5 min. In this process and for another 1 h the reaction mixture was stirred by a magnetic stirrer at room temperature. On the next morning, the solution was diluted twofold with water and, after it had been made alkaline with potash solution, the product was exhaustively extracted with chloroform. After drying over anhydrous sodium sulfate and distillation of the solvent, 0.006 g of the oxime (V) was obtained with M^+ 281.

Oxidation of Nitraramine. Nitraroxine (VII). A mixture of 0.039 g of nitraramine and 2 ml of 5% hydrogen peroxide was left at room temperature for 16 h. The resulting mixture of products was separated on a column of silica gel with elution by the benzene—methanol (8:3) system, giving 0.016 g of (VII), M^+ 264.

Reduction of Nitraroxine. Nitraramine (I). A solution of 0.018 g of nitraroxine in 5 ml of absolute ethanol was heated to the boil under reflux with stirring by a magnetic stirrer. Over 15 min, 0.20 g of metallic sodium cut into pieces was added with the heating switched off. Then the heating and stirring were continued until the sodium had dissolved completely (30 min). During this process, the reaction mixture became turbid. The cooled solution was treated with 5 ml of water and evaporated to half-volume, and then 1 ml of 5% caustic potash solution was added and the reaction product was extracted successively with petroleum ether (40-70°C) and chloroform. The two fractions were repurified by the method customary for bases. After drying and elimination of the solvents, 0.008 g of petroleum-ether and 0.0046 g of chloroform fractions were obtained. The first consisted of a mixture of two substances, while the chloroform extract was pure nitraramine (M^+ 248, IR spectrum).

Acetylation of Nitraroxine. In a round-bottomed flask, 1 ml of freshly purified acetic anhydride and 0.5 ml of pyridine were added to 0.011 g of nitraroxine. After the mixture had been left to stand at room temperature for 6 days, the pyridine and the excess of the reagent were driven off in vacuum and the oily residue was passed through a column of silica gel with elution by benzene. This gave 0.007 g of O-acetylnitraroxine (VIII), M^+ 306, ν_{max}, 1747 cm^{-1}.

SUMMARY

A detailed analysis has been made of the ^{13}C NMR spectrum of nitraramine and also of the PMR spectra of nitraramine, N-acetylnitraramine, and dihydronitraramine, which has permitted suggestions to be put forward on the spatial structures of these compounds. It has been shown that the unusually strong descreening of the α-equatorial proton of N-acetylnitraramine is due to hindered rotation about the N—CO bone.

The chemical properties of nitraramine have been studied. The possibility has been established of the existence of the product of its hydrolysis in three tautomeric forms: an amino aldehyde chain form and two cyclic forms — α-carbinolamine and semiacetal.

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ALKALOIDS OF THE ROOTS OF THE *Haplophyllum obtusifolium*

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The roots of the *Haplophyllum obtusifolium* Ledeb. have yielded robustine, dictamnine, skimmianine, γ-fagarine, and evoxine and the new alkaloid haplobine for which on the basis of spectral characteristics and a passage to the main alkaloid haplopine (7-hydroxy-4,8-dimethoxyfuranoquinoline) the structure of 7-(3'-chloromethylbut-2'-enyloxy)-4,8-dimethoxyfuranoquinoline has been established.

The isolation from the epigeal part of the *Haplophyllum obtusifolium* Ledeb. collected in the environs of Mt. Nukus of evoxine, haplopine, acetylhaplatine, skimmianine, evodine, and methylevoxine has been reported previously [1]. The present paper is devoted to a study of the alkaloids of the roots of *H. obtusifolium* from the same growth site.

The roots were extracted with methanol. The evaporated extract was separated in the usual way into basic and neutral fractions. Chromatography of the basic fractions yielded robustine, dictamnine, base (I), skimmianine, γ-fagarine, and evoxine.

Base (I) had mp 151-153°C. Its mass spectrum permitted the assumption that its molecule contained a chlorine atom, since in the region of the molecular ion there were two peaks, with m/z 347 (19%) and 349 (6.2%) differing by two units and with an intensity ratio of 3:1, which is characteristic for chlorine-containing compounds [2]. The spectrum also contained the peaks of the M − 35 ion (m/z 312) formed as the result of the cleavage of a C—Cl bond.

The presence of a chlorine atom was confirmed by the Beilstein test and Stepanov's qualitative reaction [3]. Base (I) is new and we have called it haplobine.

The UV spectrum of (I) coincided with that of furanoquinoline alkaloids with alkoxy substituents in positions 4, 7, and 8, for which maxima at 250, 320, and 335 nm and a deep minimum in the 280 nm region are characteristic [4]. The IR spectrum had absorption bands at 3115 and 3145 cm^{-1} (unsubstituted furan ring). There was no absorption due to active hydrogen.

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