SYNTHESIS AND X-RAY DIFFRACTION AND QUANTUM-CHEMICAL ANALYSIS OF 1-ALLYL-3-FORMYLPYRIDINIUM BROMIDE THIOSEMICARBAZONE

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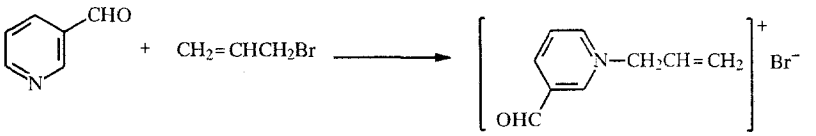
Successive alkylation of 3-pyridinecarboxaldehyde with allyl bromide and reaction of 1-allyl-3-formylpyridinium bromide with thiosemicarbazide gave 1-allyl-3-formylpyridinium bromide semicarbazone. X-ray diffraction analysis and quantum-chemical calculations with optimization of geometry were conducted on the semicarbazone synthesized. It was shown that quaternization of the nitrogen atom did not have any effect on the planarity of the heterocycle and the cationic charge was mainly localized on the thiosemicarbazone group, in which intramolecular hydrogen bonding is absent, despite the small interatomic separation of N...H–N.

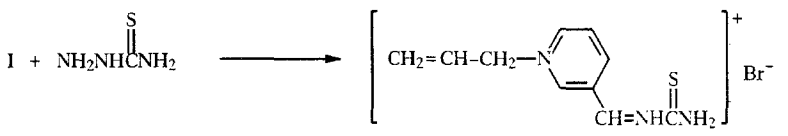
The continued interest in pyridine derivatives is due to the wide range of their biological effect [1, 2]. The biological activity of these compounds is governed to a considerable degree by the role of pyridine bases in vital processes [vitamins PP, B_6, homarine, trigonelline, nicotinamide adenine dinucleotide (NAD^+), etc.].

The present study is concerned with the synthesis of N-allyl-3-formylpyridinium bromide (I) and its thiosemicarbazone (II) as well as an analysis of the structural and electronic characteristics of the latter compound. The pyridinium residue of compound II is similar in nature to that in the nicotinic acid coenzyme NAD^+ [3] and in the hormone 1-methylpyridinium 3-carboxylate (trigonelline), a cell division regulator [4]. Its salt-like nature is responsible for compound II being soluble in water, and the thiosemicarbazone section of the molecule imparts strong complexing properties. According to the results of x-ray diffraction analysis of pyridinecarboxaldehyde derivatives, a minimum of six functional groups in the molecule can participate in hydrogen bonding: $-NH_2$, $-NH-$, $=N-$, $=C=S$, the heteroatom of the ring, and CH_α in the heterocycle. The π-electron system of the heterocycle can also participate in complex formation.

1-Allyl-3-formylpyridinium bromide thiosemicarbazone was synthesized by the following route:



I



II

It is also feasible to obtain compound II by a variant of this route, in which the pyridinecarboxaldehyde thiosemicarbazone is synthesized at the first stage and then undergoes quaternization. However, it is clear from the x-ray

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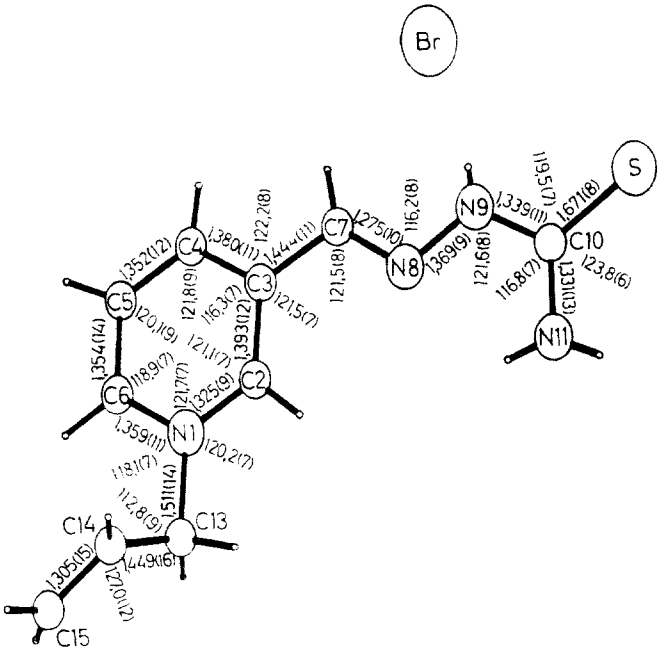

Fig. 1. General molecular form of II.

TABLE 1. Torsion Angles in Compound II

Angle	τ, deg	Angle	τ, deg
$C_{(3)}$—$C_{(2)}$—$N_{(1)}$—$C_{(6)}$	-0,7(13)	$C_{(4)}$—$C_{(3)}$—$C_{(2)}$—$N_{(1)}$	-0.0(12)
$C_{(3)}$—$C_{(2)}$—$N_{(1)}$—$C_{(13)}$	-179,1(9)	$C_{(4)}$—$C_{(3)}$—$C_{(2)}$—$N_{(1)}$	-177,8(9)
$C_{(5)}$—$C_{(6)}$—$N_{(1)}$—$C_{(2)}$	0,9(14)	$C_{(5)}$—$C_{(4)}$—$C_{(2)}$—$C_{(2)}$	0.6(12)
$C_{(5)}$—$C_{(6)}$—$N_{(1)}$—$C_{(13)}$	179,3(9)	$C_{(5)}$—$C_{(4)}$—$C_{(3)}$—$C_{(7)}$	178.3(10)
$C_{(14)}$—$C_{(13)}$—$N_{(1)}$—$C_{(2)}$	126,0(9)	$N_{(8)}$—$C_{(7)}$—$C_{(3)}$—$C_{(2)}$	8.5(15)
$C_{(14)}$—$C_{(13)}$—$N_{(1)}$—$C_{(6)}$	-52,5(12)	$N_{(8)}$—$C_{(7)}$—$C_{(3)}$—$C_{(4)}$	-169.2(10)
$C_{(10)}$—$N_{(9)}$—$N_{(8)}$—$C_{(7)}$	-177,3(10)	$C_{(6)}$—$C_{(5)}$—$C_{(4)}$—$C_{(3)}$	-0.4(13)
$C_{(3)}$—$C_{(7)}$—$N_{(8)}$—$N_{(9)}$	178,8(9)	$N_{(1)}$—$C_{(6)}$—$C_{(5)}$—$C_{(4)}$	-0.4(12)
S—$C_{(10)}$—$N_{(9)}$—$N_{(8)}$	176,7(8)	$C_{(15)}$—$C_{(14)}$—$C_{(13)}$—$N_{(1)}$	121.1(14)
$N_{(11)}$—$C_{(10)}$—$N_{(9)}$—$N_{(8)}$	-5,0(16)		

diffraction data of azomethine derivatives of pyridinecarboxaldehydes [5-7, 9, 10] that the nitrogen atom of the pyridine ring in these compounds is already partially quaternized through intermolecular N...H−N interactions which inhibit its quaternization by allyl bromide. The first alternative is therefore preferable.

The bond lengths and bond angles of 1-allyl-3-formylpyridinium bromide thiosemicarbazone are given in Fig. 1 and the torsion angles are listed in Table 1.

The results of the x-ray diffraction analysis of compound II indicate that quaternization of the pyridine nitrogen atom has virtually no effect on the planarity of the ring. It is clear from the values of the endocyclic bond angles in the heterocycle that there is some degree of ring stretching along a line connecting the $C_{(3)}$ and $C_{(6)}$ atoms and the angles at the nitrogen atom and $C_{(4)}$ have increased. Similar changes occur in the ring in cinchomeronic acid on protonation of the nitrogen atom [11].

The allyl residue of the cation has an almost perpendicular configuration relative to the pyridine ring, forming an angle of 93.1(6)° with it. All the nonhydrogen atoms of the allyl group — $C_{(13)}$, $C_{(14)}$, and $C_{(15)}$ — are on the same side of the heterocycle. The atoms of the substituent at the 3-position of the pyridine ring lie on the other side of the plane of the ring, and the angle with the median plane formed by the $C_{(7)}$, $N_{(8)}$, $N_{(9)}$, $C_{(10)}$, and $N_{(11)}$ atoms is only 9.0(3)°. The bond lengths and bond angles in the cation are normal in magnitude and match those of 4-formylpyridine thiosemicarbazone within the limits of experimental error [5]. The hydrogen atoms on the $N_{(11)}$ nitrogen atom are coordinated with the bromide anion and hence do

TABLE 2. Immediate Environment of Br^- Anion

Atom X	$Br^-...X$ (Å)	Symmetry operation	Atom X	$Br^-...X$ (Å)	Symmetry operation
$H_{(11,2)}$	2,784	$x, 0,5 - y, 0,5 + z$	$H_{(9)}$	3,004	x, y, z
$H_{(11,1)}$	2,870	$2 - x, -0,5 + y, 0,5 - z$	$H_{(4)}$	3,078	$2 - x, -y, 1 - z$
$H_{(2)}$	2,880	$2 - x, -0,5 + y, 0,5 - z$	$H_{(15,2)}$	3,087	$-1 + x, y, z$
$H_{(6)}$	2,982	$-1 + x, y, z$	$H_{(7)}$	3,135	x, y, z

TABLE 3. Cartesian Coordinates of the Atoms in the Cation of Molecule II in a Free State

Atom	x	y	z	Atom	x	y	z
$N_{(1)}$	0,0000	0,0000	0,0000	$C_{(15)}$	-3,0098	-1,5708	-0,9730
$C_{(2)}$	1,3250	0,0000	0,0000	$H_{(2)}$	1,8248	-0,8834	0,0000
$C_{(3)}$	2,0445	1,1927	0,0000	$H_{(4)}$	1,7837	3,2482	0,0000
$C_{(4)}$	1,3010	2,3553	0,0000	$H_{(5)}$	-0,5705	3,2083	0,0000
$C_{(5)}$	-0,0508	2,3364	0,0000	$H_{(6)}$	-1,7282	1,1344	0,0000
$C_{(6)}$	-0,7134	1,1557	0,0000	$H_{(7)}$	3,9821	2,0897	0,0040
$C_{(7)}$	3,4884	1,2028	0,0041	$H_{(9)}$	5,9354	1,1885	0,0301
$N_{(8)}$	4,1622	0,1204	0,0142	$H_{(11,1)}$	4,9283	-1,9717	-0,0536
$N_{(9)}$	5,5243	0,2564	0,0283	$H_{(11,2)}$	6,3019	-2,6386	0,0641
$C_{(10)}$	6,3351	-0,8074	0,0896	$H_{(13,1)}$	-0,0648	-2,0197	-0,0839
$N_{(11)}$	5,7592	-2,0054	0,0221	$H_{(13,2)}$	-1,0700	-1,2965	0,9507
$S_{(12)}$	7,9844	-0,5781	0,2287	$H_{(14)}$	-1,4737	-1,5472	-2,0377
$C_{(13)}$	-0,7600	-1,3059	0,0000	$H_{(15,1)}$	-3,4600	-1,6610	-0,0846
$C_{(14)}$	-1,7211	-1,3962	-1,0806	$H_{(15,2)}$	-3,6063	-1,6224	-1,7739

not participate in the C=S...H−N−H intermolecular interaction with the sulfur atom that is characteristic of 4-formylpyridine thiosemicarbazone [5]. Because of quaternization of the ring nitrogen, the $N_{(9)}-H...N_{(1)}$ hydrogen bond that is characteristic of 4-formylpyridine thiosemicarbazone [5] is not formed.

In order to establish the distribution of positive charge on the cation, the closest contacts of the anion (Br^-) to the cation atoms were calculated. Eight of these contacts with symmetry operations for coordinate transform of the corresponding atoms are given in Table 2. The numbering of the hydrogen atoms corresponds to that of the adjacent nonhydrogen atoms. If there is more than one hydrogen atom attached to a nonhydrogen atom, the number of the H atom is specified after the comma.

It follows from the information given in Table 2 that the Br^- anion lies closer to the thiosemicarbazone group. This suggests that it is there that the positive charge of the cation is mainly localized.

In order to make a more detailed study of the electronic structure of the cation, quantum-chemical calculations were carried out on it and its radical using a molecular orbital method based on the x-ray diffraction data. The calculations were carried out using self-consistent field theory with the MNDO approximation [12] on an sp basis set of Slater AOs with partial optimization of geometry. The Cartesian coordinates of the atoms, as determined by geometry optimization, are given in Table 3.

The calculations indicate that the cation of molecule II is even flatter in the free state than in the crystalline state. In effect it is only the vinyl group of the allyl substituent that projects from the plane of the conjugated system. The N−H bond lengths have approximately normal values (they differ significantly in the x-ray diffraction data because of errors in the H atom coordinates). On the whole the geometry of the cation as determined by theoretical calculation is similar to that in the crystal obtained by x-ray diffraction analysis.

Despite the very short interatomic distance of $N_{(11)}-H...N_{(8)}$ (2.658 Å), the quantum-chemical calculation suggests that there is no intramolecular hydrogen bonding in the thiosemicarbazone residue of the molecule (the maximum bond order of H...N is equal to 0.0159).

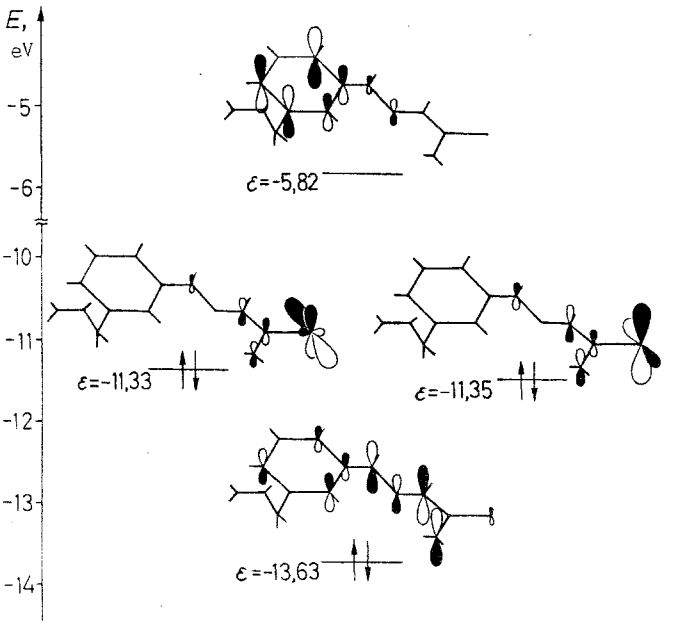

Fig. 2. HOMO and LUMO orbital structures.

TABLE 4. Effective Atomic Charges in Cation II

Atom	Charge	Atom	Charge	Atom	Charge
$N_{(1)}$	-0,1425	$N_{(11)}$	-0,2490	$H_{(7)}$	0,0791
$C_{(2)}$	0,1629	$S_{(12)}$	-0,3738	$H_{(9)}$	0,2382
$C_{(3)}$	-0.0593	$C_{(13)}$	0,2569	$H_{(11,1)}$	0,1750
$C_{(4)}$	0.0927	$C_{(14)}$	-0,2484	$H_{(11,2)}$	0,2070
$C_{(5)}$	-0,0702	$C_{(15)}$	0,0964	$H_{(13,1)}$	0,0352
$C_{(6)}$	0,1355	$H_{(2)}$	0,1234	$H_{(13,2)}$	0,0367
$C_{(7)}$	-0,0002	$H_{(4)}$	0,0976	$H_{(14)}$	0,0829
$N_{(8)}$	-0,0620	$H_{(5)}$	0,1131	$H_{(15,1)}$	0,0425
$N_{(9)}$	-0,2603	$H_{(6)}$	0,1210	$H_{(15,2)}$	0,0638
$C_{(10)}$	0,3052				

The complete effective atomic charges calculated using Mulliken's analysis of population density [13] are presented in Table 4. It is clear from Table 4 that the distribution of atomic charges is consistent with the conclusion drawn from the x-ray diffraction analysis that the positive charge is mainly located on the thiosemicarbazone group.

The orbital structures of the highest occupied MOs (HOMOs) and lowest unoccupied MOs (LUMOs) are given in Fig. 2. In the electronic structure of the cation there is a coincidental degeneracy of the two HOMOs, which are mainly located on the thiosemicarbazone group. This corresponds to the classical structural formula of the cation with a positive charge on the heterocycle. The LUMO, on the other hand, is mainly located on the heterocycle. The structure of the HOMOs and LUMOs suggests that the heterocycle remains the site for attack by nucleophilic reagents as well as for reduction reactions, the most probable center for attack being the $C_{(4)}$ atom. Calculations on the free radical also indicate that the unpaired electron is located on the $C_{(4)}$ and $C_{(6)}$ atoms. It can be deduced from this that in the free radical the dipole moment vector $\bar{\mu} = -10.076\bar{i} - 1.893\bar{j} - 0.694\bar{k}$ (the system of coordinates being the same as for the cation, Table 3) has the substantial absolute value of 10.275 D and is directed toward the heterocycle from the thiosemicarbazone part of the molecule. The calculated electron affinity for the cation is 6.34 eV.

The results obtained for 1-allyl-3-formylpyridinium bromide thiosemicarbazone may prove useful for the analysis of certain biochemical processes involving NAD^+ (for example, reduction processes).

TABLE 5. Atomic Coordinates ($\times 10^4$, $\times 10^3$ for H) with Standard Deviations for Compound II

Atom	x	y	z	Atom	x	y	z
Br	7861(1)	554(1)	3858(1)	$H_{(2)}$	1287(9)	344(12)	258(6)
S	6958(2)	2217(4)	1189(2)	$H_{(4)}$	1228(9)	162(12)	461(5)
$N_{(1)}$	14396(6)	3270(9)	3427(4)	$H_{(5)}$	1465(11)	160(14)	521(7)
$N_{(8)}$	10453(6)	2613(10)	2501(4)	$H_{(6)}$	1587(10)	269(13)	441(6)
$N_{(9)}$	9146(7)	2381(14)	2255(5)	$H_{(7)}$	1062(9)	172(12)	364(6)
$N_{(11)}$	9253(8)	3216(14)	943(5)	$H_{(9)}$	890(12)	230(18)	250(8)
$C_{(2)}$	13134(7)	3174(11)	3129(5)	$H_{(11,1)}$	997(10)	340(13)	118(6)
$C_{(3)}$	12304(7)	2448(12)	3592(5)	$H_{(11,2)}$	886(8)	341(11)	48(5)
$C_{(4)}$	12871(9)	1844(14)	4368(5)	$H_{(13,1)}$	1466(11)	457(15)	240(7)
$C_{(5)}$	14159(8)	1965(13)	4665(6)	$H_{(13,2)}$	1565(14)	312(19)	276(9)
$C_{(6)}$	14934(8)	2685(12)	4197(6)	$H_{(14)}$	1578(10)	635(13)	347(6)
$C_{(7)}$	10934(8)	2285(13)	3261(5)	$H_{(15,1)}$	1773(8)	634(11)	382(5)
$C_{(10)}$	8541(7)	2620(12)	1464(5)	$H_{(15,2)}$	1781(11)	437(15)	356(7)
$C_{(13)}$	15276(10)	4086(17)	2919(7)				
$C_{(14)}$	16065(10)	5401(13)	3369(7)				
$C_{(15)}$	17327(11)	5479(20)	3540(10)				

EXPERIMENTAL

The results of C, H, and N analysis for compounds I and II correspond to the calculated values.

1-Allyl-3-formylpyridinium Bromide (I). To a solution of 2.68 g (0.025 mole) of 3-pyridinecarboxaldehyde in 25 ml of hexane was added a solution of 3.03 g (0.025 mole) of allyl bromide in 25 ml of hexane. The mixture was agitated at 60°C under a reflux condenser for 3 h and then for a further 1.5 h at room temperature. Xylene (5 ml) was then added and the mixture was left overnight. The solution was decanted, and the precipitate that had formed was washed with ether, filtered off, and dried under vacuum to give I. $C_9H_{10}BrNO$, mp 100°C. Yield 4.5 g (79%).

1-Allyl-3-formylpyridinium Bromide Thiosemicarbazone (II). To 2.85 g (0.0125 mole) of compound I in 10 ml of ethanol was added 1.14 g (0.0125 g) thiosemicarbazide in 10 ml of water. The reaction mixture was refluxed for 1 h. The precipitate which separated out on cooling was filtered off and dried under vacuum to give II. $C_{10}H_{13}BrN_4S$, mp 218°C (with decomp.). Yield 2.89 g (77%).

X-Ray Diffraction Analysis of Compound II. The light yellow monocrystals of compound II $[C_{10}H_{13}N_4S]^+Br^-$ which were grown from 50% aqueous ethanol belong to a monoclinic class and they have the following crystallographic parameters: a = 10.540(2), b = 8.002(3), c = 16.376(3) Å, β = 101.43(1)°, V = 1353.8(6) Å^3, M = 301.2, d_{calc} = 1.48 g/cm^3, Z = 4, space group $P2_1/c$.

The intensities of 2579 reflections were recorded on an automatic Syntex $P2_1$ diffractometer (MoKα radiation, graphite monochromator, $\theta/2\theta$ scanning up to $2\theta_{max}$ = 53°). The 2160 independent reflections with $I \geq 2\sigma_1$ were used for the calculations. The structure was interpreted directly using the program SHELXS-86 [14] and refined by a full-matrix least-squares method without taking into account absorption in an anisotropic approximation for the nonhydrogen atoms and an isotropic approximation for the hydrogen atoms to a final value of R = 0.0742.

At the final stage of refinement the different synthesis of electron density was determined, in which the primary peak of residual electron density with a height of 1 e/Å^3 was situated 1.03 Å from the anion atom (Br^-).

The final values of the atomic coordinates are given in Table 5.

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