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TAUTOMERISM OF 1-METHYL-5-AMINO-2,3-DIHYDRO-1,2,4-TRIAZOLIUM–1-ALKYLIDENE (OR ARYLIDENE)-2-METHYLAMINOGUANIDINIUM IODIDE

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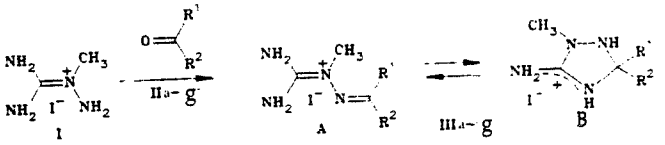
^{1}H and ^{13}C NMR spectroscopy has been used to examine the structures of the products of the condensation of aldehydes and ketones with 1-methyl-1-aminoguanidinium iodide, which in some instances in solution are involved in a ring–chain tautomeric equilibrium between 1-methyl-5-amino-2,3-dihydro-1,2,4-triazolium iodide and 1-alkylidene(or arylidene)-2-methylaminoguanidinium iodide.

It is known that the introduction of substituents into the 2-position of semi- and thiosemicarbazones [1, 2] and of 1-alkylidene(and arylidene)amidrazones [3], and to an even greater extent the protonation of these compounds, facilitate their cyclization to 1,2,4-triazolines and 1,3,4-thiadiazolines, respectively. In this connection salts of 2-alkylguanylhydrazones have not been studied, the only compounds of this type having been reported being the nitrate [4], chloride and sulfate [4, 5], picrate [4], and iodide [6] of benzylidene-1-methyl-1-aminoguanidine, these having been used to identify 1-methyl-1-aminoguanidine. However, no information is available on the fine structure of these compounds.

We here present information on the structures of 2-methylguanylhydrazonium salts obtained by condensing 1-methyl-1-aminoguanidinium iodide (I) with aldehydes and ketones (IIa-g).



II, III a–e R^1=H, f,g R^1=CH_3; e,f R^2=CH_3, b R^2=C_6H_5, c R^2=4-$CH_3OC_6H_4$; d R^2=4-$O_2NC_6H_4$; e R^2=C_6H_5CH=CH; g R^2=C_2H_5

The guanylhydrazonium iodides (IIIa-g) are obtained in near-quantitative yields following prolonged standing of the reactants at 20°C, but with p-nitrobenzaldehyde (IId) prolonged boiling of the reaction mixture was necessary. With branched-chain ketones (pinacoline, acetophenone), however, condensation failed to take place.

In assigning structures of the compounds (III), which may exist in solution either in the straight-chain (A) or the cyclic (B) forms or a mixture of the two, we made use of previously developed structural criteria [3]. In the PMR spectra, the signals for the R^1 and R^2 substituents in the cyclic form B should occur at higher field than in the linear tautomer A, and when R^1 = R^2, these substituents are equivalent. In the ^{13}C NMR spectra of the cyclic form B a signal for the sp^3-hybridized atom $C_{(3)}$ should occur, resonating in the range 70-80 ppm [3], whereas in the linear form A the C=N signal should lie at much lower field.

From the results obtained (Tables 1 and 2), it may be concluded that: the arylidene compounds (IIIb-d) exist in solution in DMSO and DMF as the linear tautomers, irrespective of the nature of the para-substituent, together with the cinnamaldehyde derivative (IIIe),

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TABLE 1. Properties of (IIIa-g) and (V)

Compound	mp, °C*	Form	Amount %	PMR spectrum, δ, ppm (J, Hz)†			
				N–CH₃	R¹	R²	NH
IIIa	103—108	A	93	3,40	7,65 q (5)	1,99 d (5)	7,83
		B	7	2,79	5,46 q (5)	1,53 d (5)	7,98; 8,17 (2NH); 9,08 (NH_2)
IIIb	278—280 [G]	A	100	3,57	8,40	7,3—7,5 m; 7,9—8,1 m	8,40
IIIc	263—265	A	100	3,67	8,45	4,02 (OCH_3); 7,25; 8,23 d (8, H arom)	8,05
IIId	254—256	A	100	3,66	8,62	8,55	8,36
IIIe	251—253	A	100	3,67	7,44	7,34 d (7, α-H); 8,28 d (7, β-H); 7,5—7,9m (H arom)	8,05
IIIf	Oil	A	37	3,42	2,34	2,43	8,38
		B	63	3,44	1,66		6,55; 8,87 (2NH); 7,54 (NH_2)
IIIg	Oil	A	53	3,35	2,24; 2,35 ‡	1,15 t; 2,77 q (8); 1,18 t; 2,92 q (8)	8,98; 8,30; 7,51; 6,45
		B	47		1,59	1,16 t; 1,92 q (8)	
V	133—136	A	7	3,30	2,46	2,18 (CH_3); 3,98 (CH_2)	9,16
		C (trans)	61	3,33	2,20	2,06 (CH_3); 5,59 (CH)	7,75 ($2NH_2$); 11,15 (NH)
		C (cis)	32	3,38	2,37	2,21 (CH_3); 5,42 (CH)	7,81 ($2NH_2$); 11,15 (NH)

*(IIIb, c, e) and (V) were crystallized from methanol, and (III) were purified by reprecipitation from the chloroform solution with ether (IIIa, f, g) or from the solution in DMF with ethyl acetate (IIId).

†The spectra of (IIIa-b) and (V) were obtained in DMF-D_7, internal standard HMDS, and of (IIIc-g) in DMSO-D_6, external standard HMDS.

‡Signals for stereoisomers of form A.

TABLE 2. ^{13}C NMR Spectra of (IIIa-g), (V)

Compound	Form	^{13}C NMR spectra, δ, ppm				
		NCH_3	$H_2NC{=}N$ (5-C)	$R^1R^2C{=}N$ (3-C)	R^1	R^2
IIIa	A	34,5	171,4	146,5	—	14,5
	B	32,1	157,8	67,9	—	18,6
IIIb	A	35,1	156,8	145,5	—	128,5; 128,8; 130,8; 132,0
IIIc	A	32,3	161,1	155,7	—	55,6 (OCH_3); 113,9; 114,1; 125,9; 129,9
IIId	A	32,3	156,3	148,3	—	123,9; 129,2; 139,8
IIIe	A	32,2	155,8	146,2	—	140,7; 135,5 (CH=CH); 129,0; 124,8; 127,1
IIIf	A	37,1	171,3	155,0	15,2	21,8
	B	34,4	156,7	75,4		25,1
IIIg	A	36,0	171,4	155,3	29,6	31,4 (CH_3)*
	B	34,4	156,5	77,9	22,6	31,3 (CH_3)*
V	A	39,6	176,0	157,0	30,2	18,5 (CH_3); 51,0 (CH_2); 204,3 (C=O)
	C (trans)	37,9	157,9	155,9	28,5	14,5 (CH_3); 94,9 (C=C); 195,2 (C=O)
	C (cis)	39,0	159,9	158,8	30,5	15,9 (CH_3); 99,5 (C=C); 197,0 (C=O)

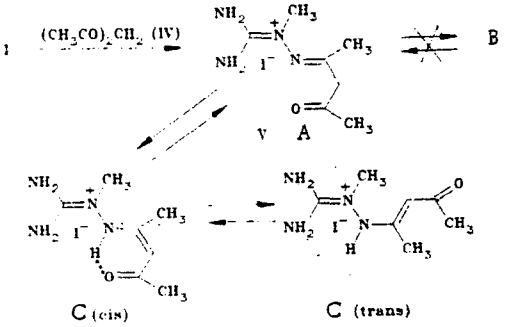
*The signals for the CH_2 groups were not localized.

as a result of stabilization by conjugation. The 2-ethylideneguanylhydrazonium salt (IIIa) occurs to a small extent (7%) as the cyclic tautomer B, this proportion increasing considerably in the case of the acetone and ethyl methyl ketone derivatives (IIIf, g), in which the cyclic form becomes predominant.

From the nature of the changes in the PMR spectra of the latter compounds with time, it may be concluded that in the crystal they, like the other compounds (III) obtained, have the linear structure A. This behavior, as would be expected, is similar to that seen in the 1-alkylidene(arylidene)-2-alkylacetamidrazone salts [3].

It was of interest to determine the structure of the condensation product of 1-methyl-1-aminoguanidinium iodide with acetylacetone (IV). As we have recently found, the product of the reaction of acetylacetone with aminoguanidinium nitrate is 1-guanyl-3,5-dimethyl-5-hydroxypyrazolinium nitrate [7], but with $N_{(2)}$-substituted aminoguanidines cyclization to the pyrazoline ring is precluded, although as noted above there is a tendency to cyclize to the triazoline ring. However, (V), in contrast to (III), shows no tendency to cyclize to isomer B.

In the case of (V), as in other 1,1-disubstituted hydrazones of dicarbonyl compounds [8], there is a tendency to undergo conversion into the enehydrazine tautomer. In solution in DMSO-D_6, (V) is present to only 7% as the hydrazone form A, as shown by the ^1H and ^{13}C NMR spectra (Tables 1 and 2). The remainder consists of two isomeric enehydrazines, cis- (with an intramolecular hydrogen bond) and trans- (without such a bond). Assignment of the stereoisomeric forms was made on the basis of the data given in [8].



The ring-chain tautomerism A ⇄ B observed in guanylhydrazones must be taken into account in future syntheses in this series, and in biological activity—structure studies, since the guanylhydrazones include a substantial number of compounds with physiological activity of widely differing types.

EXPERIMENTAL

PMR spectra were obtained on a Tesla BS-497 (100 MHz) spectrometer, and ^{13}C NMR spectra on a CFT-20 instrument (20 MHz), with full suppression of proton—carbon coupling. Internal standard HMDS. The quantitative measurement of the amounts of the tautomeric forms was carried out from the PMR spectra using two measurements with tenfold electron integration of suitable indicator signals. The error in the determinations was ±3%.

1-Methyl-1-aminoguanidinium Iodide (I). Thiourea methiodide (0.1 mole) was treated in methanol at 0°C with an equimolar amount of methylhydrazine in 100 ml of methanol. After 1 day, the methanol was removed, and (I) recrystallized from propan-2-ol, mp 73-75°C. PMR spectrum (DMSO-D_6): 3.55 (NCH_3), 5.48 (NH_2), 7.40 ppm ($2NH_2$).

Compounds (III) and (V). A mixture of 0.05 mole of (I) and 0.05 mole of the carbonyl component (II) in 20 ml of methanol was kept for 2 weeks at 20°C [in the case of aldehyde (IId), the mixture was boiled for 10 h]. The solvent was removed under reduced pressure, and the residue recrystallized from an appropriate solvent.

The properties of (IIIa-g) and (V) are given in Tables 1 and 2.

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TRANSFER OF OXYGEN FROM NICOTINIC ACID N-OXIDE TO PYRIDINE

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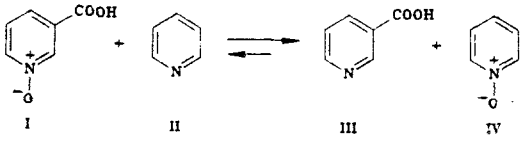
Reversible transfer of oxygen from nicotinic acid N-oxide to pyridine has been observed in a sealed ampul at 190-260°C.

Deoxygenation is an important reaction of heterocyclic N-oxides. The reduction of N-oxides is usually carried out with phosphorus(III) compounds or with hydrogen in the presence of a catalyst [1]. Some N-oxides lose their oxygen on heating with oxidants, for example a mixture of sulfuric acid and selenium dioxide [2]. The N-oxides of pyridine, quinoline, and their derivatives are also known to decompose on heating with the liberation of oxygen and the formation of the corresponding bases [3-5], enabling these oxides to be used as oxidants [6, 7].

We have now found that it is possible to oxidize nitrogenous heterocycles with N-oxides in a closed system, as exemplified by the reaction between nicotinic acid N-oxide and pyridine:



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It has been shown that prolonged boiling of a mixture of these compounds, either without a solvent or in the presence of acetic acid or acetic anhydride, results in quantitative deoxygenation of the nicotinic acid N-oxide without the formation of pyridine N-oxide. In order to reduce the duration of deoxygenation and prevent the loss from the reaction mixture of the oxygen formed, the reactants were heated at higher temperatures in sealed ampuls. When the reaction was carried out with equimolar amounts of the reactants, reaction was 90% complete at 170-180°C. When a threefold excess of pyridine was used, the conversion was quantitative. Increasing the temperature considerably shortened the reaction time. The reverse transfer of oxygen from pyridine N-oxide to nicotinic acid is also possible in principle, but even when a fivefold excess of pyridine N-oxide was used, the reaction occurred to the extent of 25% only. By using acetic acid as solvent, it is possible to shorten the reaction time by a factor of nearly two, the position of the equilibrium remaining unchanged (Table 1). In this reaction, the equilibrium is strongly shifted toward the formation of the N-oxide of the more basic heterocycle, namely pyridine. This is in accordance with the known fact that the formation of the N-oxides of pyridines with electron-acceptor substituents, which reduce the basicity of the nitrogen, requires more severe conditions [8].

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