ACYL DERIVATIVES OF 3-AMINO-1,2,4-TRIAZOLE

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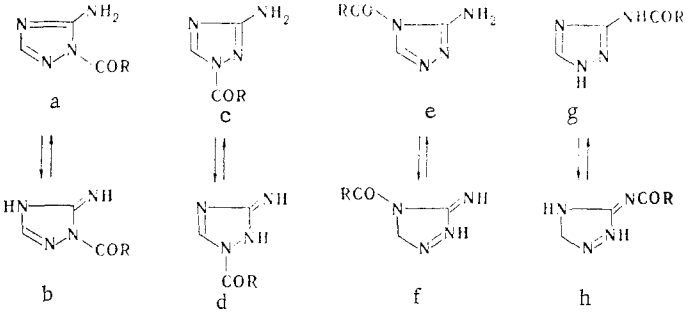
Only 3-acylamino-1,2,4-triazoles were isolated in the acylation of 3-amino-1,2,4-triazole with acid chlorides that contain strong electron acceptor substituents. Acylation takes place in the 2 position when aliphatic and aromatic acid chlorides are used as the acylating agents. The action of methoxy- and ethoxyformyl chlorides leads to the formation of 1- and 2-alkoxycarbonyl-3-amino-1,2,4-triazoles. When N-acyl-3-amino-1,2,4-triazoles are heated, they undergo intermolecular trans-aminoacylation to 3-acylamino-1,2,4-triazoles, which exist in the solid phase in the form of amido and imido tautomers. Under the conditions of mass-spectroscopic analysis the percentage of the imido form increases as the electron-acceptor capacity of the substituent increases.

Despite the fact that a significant number of studies have been devoted to the acylation of 3-amino-1,2,4-triazole, the site of incorporation of the acyl group has not yet been ascertained [1-6]. It has been reported that 4-acyl-3-amino-1,2,4-triazoles are formed with aromatic acid chlorides [2-4], while ethoxyformyl chloride acylates aminotriazole in the 1 and 2 positions [6].

The aim of the present research was to establish the structures of the products of acylation of 3-amino-1,2,4-triazole with carboxylic acid chlorides and to study their isomerization to 3-acylamino-1,2,4-triazoles.

The available literature data [1-6] provided a basis for the expectation that the acyl group would be incorporated in the 1,2,4-triazole ring to give structures of the *a*, c, and e types or their tautomers (structures of the b, d, and f types).



We established that the structures of the acylation products are determined by the nature of R in the acylating agent. If the acylating agents are chlorides of strong organic acids (R = C_3F_7, CCl_3, and CHF_2), the only reaction product is the 3-acylamino-1,2,4-triazole (VII-IX, Table 1). In this case the initially formed N-acyl-3-amino-1,2,4-triazoles probably undergo intermolecular transacylation (see below). In all of the remaining investigated cases the acylation of 3-amino-1,2,4-triazole takes place at the ring nitrogen atoms to give compounds of the *a* type (R = alkyl, C_6H_5) or a mixture of isomers of the *a* and c types (according to the PMR data; R = C_2H_5O, CH_3O). The nature of the solvent has a substantial effect on the ratio of the *a* and c isomers. Thus the ratio of the *a* and c isomers is 9:1 for V

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TABLE 1. Acyl Derivatives of 3-Amino-1,2,4-triazole

Compound	R	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
Ia	CH_3	148	38,7	4,9	44,4	$C_4H_6N_4O$	38,1	4,8	44,4	71
IIa	C_2H_5	147	43,4	6,1	40,1	$C_5H_8N_4O$	42,8	5,8	40,0	45
IIIa	C_3H_7	93	46,8	6,4	37,7	$C_6H_{10}N_4O$	46,7	6,5	36,3	78
IVa	C_6H_5	190	57,8	4,6	29,5	$C_9H_8N_4O$	57,4	4,3	29,8	64
Va+Vc	OCH_3	148	33,8	4,1	40,3	$C_4H_6N_4O_2$	33,8	4,3	39,4	43
VIa+VIc	OC_2H_5	111	39,0	5,4	35,6	$C_5H_8N_4O_2$	38,5	5,2	35,9	46
VIIg[a]	CCl_3	292[b]	20,4	1,7	24,5	$C_4H_3Cl_3N_4O$[c]	20,9	1,3	24,4	88
VIIIg[d]	CHF_2	246—247[b]	30,1	2,3	35,0	$C_4H_4F_2N_4O$[e]	29,6	2,5	34,6	74
IXg[f]	C_3F_7	222[b]	26,0	1,8	20,1	$C_6H_3F_7N_4O$g	25,7	1,1	20,0	68
Xa	CH_3	133—135	53,3	6,9	31,1	$C_{16}H_{26}N_8O_2$	53,0	7,2	30,9	78
XIb	C_6H_5	194	63,9	6,6	22,5	$C_{26}H_{30}N_8O_2$	64,2	6,2	23,0	72

[a]PMR spectrum (here and below for 5% solutions in d_6-DMSO), δ: 8.38 (5-H) and 12.08 ppm (NH). [b]Sublimation. [c]Found: Cl 46.2%. Calculated: Cl 46.4%. [d]PMR spectrum, δ: 8.17 (5-H), 9.74 (NH), and 3.90 ppm (CHF_2, $^2J_{HF}$ = 53 Hz). [e]Found: F 23.1%. Calculated: F 23.4%. [f] PMR spectrum, δ: 8.44 (5-H) and 10.29 ppm (NH). [g]Found: F 46.7%. Calculated: F 47.5%.

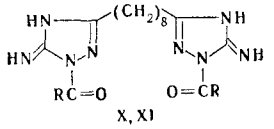
(Table 1) in the case of acylation in acetonitrile, as compared with 1:1 in dimethylformamide (DMF); the *a*:c ratio if 1.5:1 for VI (Table 1) in the case of acylation in DMF.

The IR spectra of the c isomers of V and VI contain characteristic bands of stretching vibrations of a carbonyl group, and the PMR spectra contain characteristic proton signals (Table 2). The $\nu_{C=O}$ bands in the IR spectra of I-IV and V and VI (the *a* isomers) in both the solid state and in solution in chloroform are found at 1690-1760 cm^{-1}. The decrease in the $\nu_{C=O}$ values as compared with the corresponding 1-acyl-1,2,4-triazoles and the small difference in the spectra of the examined compounds in solutions and in the crystalline state constitute evidence for the existence in 1-acyl-5-amino-1,2,4-triazoles of an intramolecular hydrogen bond between the N—H proton and the oxygen atom of the carbonyl group. The difference in the experimentally observed $\nu_{NH_2}^{s}$ frequencies and the values calculated from the formula

$$\nu_{NH_2}^{s} = 345.58 + 0.876\nu_{NH_2}^{as} \text{ [7]}$$

serves as an additional confirmation of this interaction. As demonstrated in Table 2, two bands (or one intense band, which is evidently an overall band) are present in the IR spectra of crystalline I-VI (KBr pellets) at 1630-1670 cm^{-1}. The appearance of a second band is probably due to the stretching vibrations of the C=N group of imino tautomer b. The presence of a broad band at 2800-3300 cm^{-1}, which is associated with the stretching vibrations of associated heteroring NH groups, can also be explained by the existence of tautomer b.

The acylation of 1,8-bis(5-amino-1,2,4-triazol-3-yl)octane proceeds in the same way as the acylation of 3-amino-1,2,4-triazole. The absence of a band of stretching vibrations of a free NH_2 group at 3300-3400 cm^{-1} in the IR spectrum of XI (Table 2) vis-à-vis the presence of a broad band of associated NH groups at 2600-3200 cm^{-1} makes it possible to assign the structure of an imino form to it:



X, XI

X R = CH_3; XI R = C_6H_5

When N-acyl-3-amino-1,2,4-triazoles I-VI are heated in the fused state, they undergo isomerization to 3-acylamino-1,2,4-triazoles. The mechanism of this rearrangement has not yet been studied, but it has been assumed that it is an intramolecular process [1-4, 6, 8]. However, prolonged heating of dilute solutions of VI in diethylene glycol dimethyl ether at 150°C does not lead to isomerization. Isomerization at an appreciable rate (30% isomerization takes place in 1 h) is observed in more concentrated solutions (20%) in the same solvent even at 125°C. However, the reaction is complete after 72 min in the fused state

TABLE 2. IR and PMR Spectra of N-Acyl-3-amino-1,2,4-triazoles

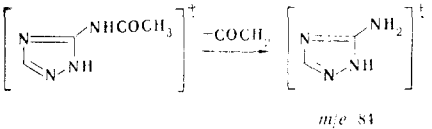
Compound	δ, ppm[a]			Characteristic bands (cm^{-1}) in the IR spectra					
				KBr pellets			chloroform		
	=CH	NH_2	R	$\nu_{C=O}$	σ_{NH_2}	ν_{NH_2}	$\nu_{C=O}$	σ_{NH_2}	ν_{NH_2}
I	7,50	7,43	2,51	1734 s	1642 s	3415 s 3292 m 3210 s 3125 m	1728 s	1626 s	3513 s 3392 s
II	7,49	7,85	—	1722 s	1657 s	3427 s 3305 m 3215 m 3130 m	1721 s	1625 s	3515 s 3399 s
III	7,50	7,49	2,90 1,65 0,93	1726 s	1645 s 1630 sh	3479 s 3285 m 3210 s 3120 m	1721 s	1625 s	3512 s 3394 s
IV	7,59	7,80	7,20	1703 s	1663 s 1643 m	3115 s 3300 m 3217 m 3121 s	1695 s	1622 s	3502 s 3392 s
V	8,68 b 7,52	5,70 7,36	4,02 4,02	1780 sh[b] 1742 s	1670 s 1652 s	3424 s 3310 m 3230 m 3140 m	1782 m 1753 s	1628 s	3512 s 3398 s
VI	8,70 b 7,49	5,94 7,26	4,30 1,24 4,33 1,24	1770 sh[b] 1745 s	1632 vs	3473 s 3300 s 3240 m 3175 w	1773 m 1747 s	1630 s	3513 s 3398 s
X	—	—	—	1723	—	3415 3220 3330 3130			
XI	—	—	—	1680		2600 3200			

[a]For 5% solutions in d_6-DMSO. [b]For the c isomer.

at 128°C. Thus it may be assumed that the conversion of 1-acyl-5-amino-1,2,4-triazoles to 3-acylamino-1,2,4-triazoles is an intermolecular trans-aminoacylation process.

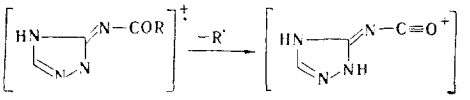
It has been pointed out that the introduction of an electron-acceptor substituent in the acyl fragment has a substantial effect on the shift of the tautomeric equilibrium of acylated amino heterocycles by increasing the probability of the existence of imido form h [9-13].

We investigated the amide—imide equilibrium of 3-acylamino-1,2,4-triazoles I-IV and VI-IX by mass spectrometry and IR spectroscopy. It has been previously demonstrated that the amido form undergoes fragmentation under electron-impact conditions with the splitting out of a cation radical of the heterocyclic amine, whereas cleavage of the C—C bond in the acyl group occurs in the case of the imido compounds [12]. In the case of an amido structure (g) one should expect the appearance of an ion with m/e 84, the subsequent fragmentation of which gives a spectrum identical to the spectrum of the starting 3-amino-1,2,4-triazole, in the mass spectra of the investigated compounds:



m/e 84

A fragment ion with m/w 111 should appear in the spectra in the case of the imido structure:



The mass spectra of the investigated compounds contain ion peaks with m/e 84 and 111, which correspond to fragmentation of both the amido and imido forms of the 3-acylamino-1,2,4-triazole. A comparison of the intensities of both peaks shows that I-IV, VI, and VIII exist primarily in amido form g in the gas phase (Table 3). The percentage of imido form h increases

TABLE 3. IR and Mass Spectra of 3-Acylamino-1,2,4-Triazoles I-IV, VI-IXg ⇄ I-IV, VI-IXh

Compound	R	Intensities of the ion peaks, %[a]		$\nu_{C=O}$, cm^{-1}	X (R)	σ*
		m/e 84	*m/e* 111			
I	CH_3	92	5	1689 1624	1,81	0,0
II	C_2H_5	—	—	1689 1606	1,76	−0,1
III	C_3H_7	64	13	1687 1604	1,75	−0,115
IV	C_6H_5	26	2	1664 1594	1,07	0,6
VI	OC_2H_5	100	18	1714 1638	2,57	1,366
VII	CCl_3	29	100	1720 1605	2,44	2,65
VIII	CHF_2	80	33	1713 1605	2,56	2,05
IX	C_3F_7	18	76	1730 1612	—	3,04

[a]Relative to the maximum peak in the spectrum.

as the electron-acceptor capacity of substituent R increases. The highest concentration of the g form under the conditions of mass-spectrometric analysis is observed for 3-perfluorobutyrylamino-1,2,4-triazole (IX, Table 3), the intensity of the peak with m/e 111 in the mass spectrum of which is 76%, whereas the intensity of the peak with m/e 84 is 18%. The low-intensity peak of the ions with m/e 84 in the spectra of 3-perfluorobutyrylamino- and 3-trichloroacetamido-1,2,4-triazoles indicates the presence of 3-amino-1,2,4-triazole, which is formed by hydrolysis of the investigated samples. The IR spectra also provide evidence for the simultaneous presence of the g and h forms in the investigated compounds. The IR spectrum of a compound with a fixed imido structure, viz., 1,4-dimethyl-5-acetimido-1,2,4-triazoline, in the region of the stretching vibrations of a carbonyl group contains one intense band at 1590 cm^{-1}. Two intense bands at 1660-1730 and 1590-1640 cm^{-1} appear in the spectra of the remaining compounds. The long-wave band is associated with $\nu_{C=O}$ vibrations in the imido form, while the short-wave band is associated with $\nu_{C=O}$ vibrations in the amido form. Its frequency is 20-70 cm^{-1} higher than in the spectra of amides of the corresponding carboxylic acids [14]. This constitutes evidence for a definite electron-acceptor effect of the 1,2,4-triazole ring on the carbonyl group in 3-acylamino-1,2,4-triazoles. However, this effect is displayed to a considerably smaller extent than in the case of 1-acyl-1,2,4-triazoles. The band at 1550 cm^{-1} corresponds to the C=N stretching vibrations in the C=N—COR fragment and also constitutes evidence for the existence of the imido form.

The high intensity of the short-wave $\nu_{C=O}$ band in the IR spectra of 3-perfluorobutyrylamino- and 3-trichloroacetamido-1,2,4-triazoles, which attest to a rather high percentage of the g form, is in contradiction with the mass-spectrometric data. However, this contradiction vanishes in the case of a study of the IR spectra in the gas phase. The band at 1605 cm^{-1} in the spectra of 3-trichloroacetamido-1,2,4-triazole in the gas phase is intense, while the band at 1720 cm^{-1} is weak. Thus 3-acylamino-1,2,4-triazole with an electron-acceptor R substituent in the acyl group exists primarily in imido form h according to the data from the IR and mass spectra in the gas phase. At the same time, in the crystalline state the contribution of the g form increases, probably as a result of intermolecular interaction. The IR spectra at 1600-1700 cm^{-1} of 3-acetamido-1,2,4-triazole in both the crystalline and gaseous states are virtually identical and characterize the presence of both the g and h forms. Its conversion to amido form g, which is recorded in the mass spectrum, is apparently realized by excitation of the molecular ion immediately prior to fragmentation, while the imido form of 3-perfluorobutyrylamino-1,2,4-triazole is formed as it passes into the gaseous phase.

The absorption at 2600-3100 cm^{-1} in the IR spectra is associated with the stretching vibrations of the N—H groups of the 1,2,4-triazole ring, which form strong intermolecular associates [15]. The band at 3270-3300 cm^{-1} in the spectra of I-IV and VI (Table 2) corre-

sponds to the stretching vibrations of the N–H bonds of the amide grouping. An increase in the acidity of the amide hydrogen atom under the influence of an electronegative substituent in 3-difluoroacetamido-, 3-trichloroacetamido-, and 3-perfluorobutyrylamino-1,2,4-triazoles leads to the formation of intermolecular hydrogen bonds that are spectroscopically comparable to endocyclic NH bonds.

Intramolecular interaction between substituent R and the carbonyl group is manifested in a change in the $\nu_{C=O}$ vibrational frequencies of the amido form. A linear dependence exists between the $\nu_{C=O}$ values and the X(R) substituent constants, which make it possible to take into account its inductive, resonance, and steric effects [10]. The regression equation has the form

$$\nu_{C=O} = 1626 + 35.3\,X(R);\ r = 0.98,\ s = 4$$

The correlation coefficient is increased if VII is excluded from this dependence. As in 1-acyl-1,2,4-triazoles [17], the angle of rotation of the acyl group relative to the plane of the heteroring in VII apparently differs from the corresponding angle in the remaining acylaminotriazoles. In this case the regression equation takes on the form

$$\nu_{C=O} = 1629 + 32.8\,X(R);\ r = 0.998,\ s = 0.9$$

Since the spectroscopic X(R) substituent constants in VI-VIII are close, whereas the composition of the tautomeric mixture in the gas phase for these compounds is different, it may be assumed that the shift in the tautomeric equilibrium is determined by the inductive effect of substituent R.

EXPERIMENTAL

The N-acyl-3-amino- and 3-acylamino-1,2,4-triazoles (I-IX, Table 1) were obtained by the method in [6]. The bis(1-acyl-5-amino-1,2,4-triazol-3-yl)octanes (X and XI, Table 1) were obtained by the method in [18] with a mixture of acetonitrile and γ-collidine as the solvent.

The IR spectra of KBr pellets and solutions (0.008 mole/liter) of the compounds in chloroform were recorded with a UR-20 spectrometer. The spectra of I and VII in the gas phase (Table 3) were obtained by vaporization of the compounds in a cuvette chamber at a temperature above the melting point. The PMR spectra of solutions of the compounds in $(CD_3)_2SO$ were obtained with a Tesla BS-487-C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with an MKh-1303 mass spectrometer with direct introduction of the samples into the source.

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