1,4,5,6-TETRAHYDRO-1,2,4-TRIAZIN-6-ONES AND 3-AMINO-1-IMIDAZOLIN-4-ONES FROM 2-AMINOACYLHYDRAZINES

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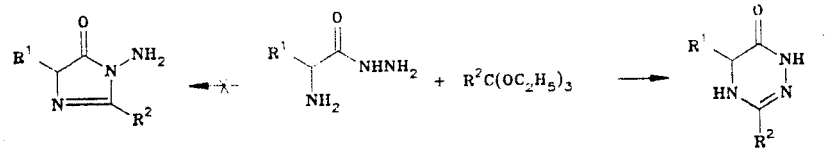
The 2-aminoacylhydrazines form 1,4,5,6-tetrahydro-1,2,4-triazin-6-ones with orthoesters and iminoesters. Benzylidene and isopropylidene derivatives of the 2-aminoacylhydrazines give the corresponding derivatives of 3-amino-1-imidazolin-4-ones with the same reagents.

In connection with the study of the reactivity of 2-aminoacylhydrazines having some nucleophilic centers and the capacity to form different types of heterocyclic compounds, we turned to the investigation of the reactions of 2-aminoacylhydrazines and their derivatives with orthoesters and iminoesters. The formation of both the six-membered triazines (III) and the five-membered imidazolines (IV) could be expected in these reactions. It was found that the sole products of the reactions of the 2-aminoacylhydrazines (I) with the orthoesters (II) are the tetrahydrotriazines (III) (cf. Table 1), isolated with yields of 60-70%.

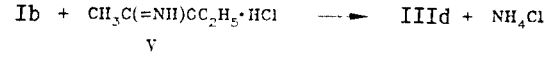


IV Ia-c IIa,b IIIa-e

Ia R^1=H; b R^1=CH_3; c R^1=$CH_2C_6H_5$; IIa R^2=H; b R^2=CH_3; IIIa R^1=R^2=H; b R^1=CH_3, R^2=H; c R^1=$CH_2C_6H_5$, R^2=H; d R^1=H, R^2=CH_3, e R^1=R^2=CH_3

It should be noted that triethyl orthoacetate (IIb) reacts significantly more readily with 2-aminoacylhydrazines than does triethyl orthoformate (IIa). When the reagents are boiled in ethanol without a catalyst, the reaction is completed after 5-6 h in the first case, and after 10-13 h in the second case. The application of catalytic amounts of sulfuric acid allows the reaction time to be reduced to 1-2 h.

The reaction of 2-aminopropionylhydrazine (Ib) with ethyl iminoacetate (V) leads to the analogous result with the simple mixing of the solutions of the reagents in ethanol in the cold.



Ib + V → IIId + NH_4Cl

The absence of significant amounts of any substances besides the triazines (III) among the reaction products is confirmed by the PMR spectra of the reaction mixtures. The PMR spectra of the 3-aminoimidazolidin-4-ones [saturated analogs of the imidazolines (IV)] [1] and the imidazoline (VII) (cf. below) have the characteristic feature of the distant spin—spin coupling (J = 1-2 Hz) between the proton at the position 5 and the protons of the substituent at the position 2 of the ring. Such splitting is absent from the spectra of the triazines (III). The second fact testifying in favor of the triazine structure of the compounds (III) is the band of the stretching vibrations of the carbonyl group in the region of 1650-1680 cm^{-1}, which is also characteristic of hydrogenated analogs of the triazines (III) [2]. For the imidazolines (IV), the appearance of this band should be expected at about 1710 cm^{-1} [1]. Finally, the triazines (IIIa), (IIId), and (IIIe) do not react with acetone and 4-methoxybenzaldehyde, even under fairly drastic conditions, whereas the imidazolines (IV) should form the corresponding hydrazones readily.

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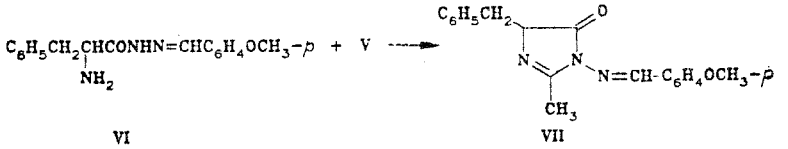
TABLE 1. Physicochemical Characteristics of the Triazines (IIIa-e)

Compound	Emprical formula	mp, °C (methanol)	PMR spectrum (CD_3OD), δ, ppm (SSCC, J, Hz)			IR spectrum (mineral oil), ν, cm^{-1}		Yield, %
			5-H	R^1	R^2 (s)	C=O	C=N	
IIIa	$C_3H_5N_3O$	183	3,93 (s)		6,94	1670	1632	62
IIIb	$C_4H_7N_3O$	133	4,13 (q, J=6,5)	1,38 (d, J=6,5)	6,95	1670	1635	62
IIIc	$C_{10}H_{11}N_3O$	143	4,30 (t, J=5,0)	3,00 (d, J=5,0) 7,30 (m)	6,80	1670	1633	66
IIId	$C_4H_7N_3O$	161	3,86 (s)		1,85	1680	1635	60
IIIe	$C_5H_9N_3O$	75	4,10 (q, J=6,5)	1,35 (d, J=6,5)	1,92	1650	1635	75

The formation of the triazines seems unexpected to some extent since the close analogs of the 2-aminoacylhydrazines — the carbohydrazide and thiocarbohydrazide — give five-membered N-aminotriazolines with orthoesters and iminoesters [3-5]. The formation of six-membered rings was also not noted in the reaction of 2-aminoacylhydrazines with carbonyl compounds [1]. In all probability, the reaction of 2-aminoacylhydrazines with orthoesters commences with the attack of either the "amine" or of the β-hydrazide nitrogen atom at the carbon atom of the orthoester with subsequent cyclization. In the first case, the formation of both a five-membered and a six-membered ring is possible, but the formation of the imidazolines (IV) should be expected since five-membered rings are formed more rapidly than six-membered rings. In the second alternative, the cyclization may only lead to the six-membered triazine. It is possible that it is precisely this route which is realized in the reactions of 2-aminoacylhydrazines with orthoesters.

With the object of studying the possible formation of derivatives of 3-amino-1-imidazolin-4-ones, we investigated the reaction of two β-N-substituted 2-aminoacylhydrazines with orthoesters and iminoesters. The reaction of the hydrazone (VI) with ethyl iminoacetate gave a low yield of the expected imidazoline (VII).

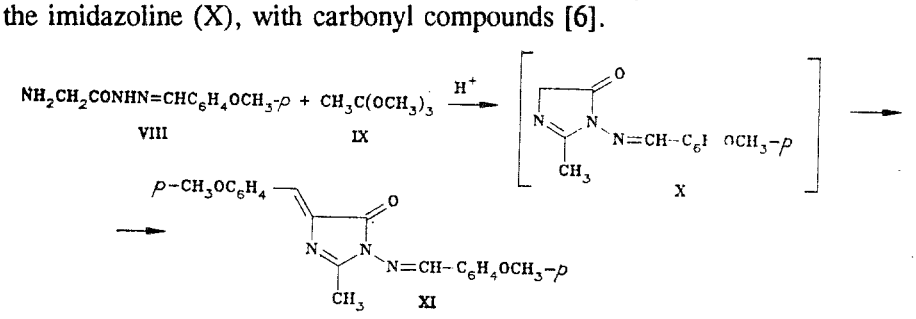


VI VII

The spectral properties of this compound differ strongly from those of the triazines (III). In the IR spectrum of the imidazoline (VII), the absorption band of the carbonyl group is situated, as expected, at 1712 cm^{-1}. In the PMR spectrum, attention is drawn to the relatively high (1.8 Hz) SSCC for $2\text{-}CH_3$—5-H.

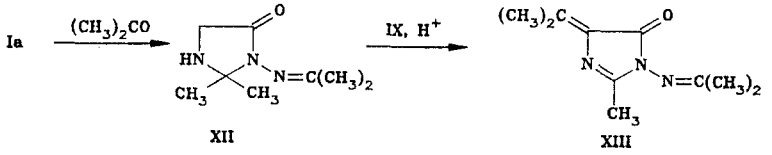
The product of the reaction of the hydrazone (VIII) with trimethyl orthoacetate (IX) was unexpectedly shown to be the 5-arylidenimidazoline (XI), the structure of which was confirmed by the PMR spectrum.

This reaction probably occurs with the initial formation of the imidazoline (X) with the active methylene group in the α-position to the C=O and N=C bonds. In all probability, the transfer (most preferably intermolecular) of the benzylidene fragment proceeds from the nitrogen atom to the nucleophilic carbon atom under the conditions of the reaction. Processes of such a type proceed readily in the interaction of azlactones, which are close analogs of the imidazoline (X), with carbonyl compounds [6].



VIII IX X XI

In connection with the formation of the imidazoline (XI), we studied the possibility of the synthesis of such types of compounds by some more convenient route from the product of the condensation of 2-aminoacetylhydrazine with 2 moles of the carbonyl compound and the orthoester. The compound (XII), which is formed by he treatment of the hydrazine (Ia) with excess acetone, was described by Curtius [7], who assigned the linear iminohydrazone structure to it. However, the PMR and ^{13}C NMR spectra indicate the cyclic structure of the compound (XII).



The imidazolidine (XII) and trimethyl orthoacetate give the imidazoline (XIII), the structure of which was established by the methods of PMR and ^{13}C NMR spectroscopy and by mass spectrometry. The reaction probably proceeds via the stage of the hydrolytic cleavage of the initial imidazolidine (XII).

The imidazolidine (XII) does not react at all with triethyl orthoformate. This fact, as well as the difference in the reactivity of the orthoacetate and the orthoformate toward aminoacylhydrazines, gives a possible indication that the orthoacetate reacts, at least partially, cleaving a molecule of the alcohol and forming the reactive ketene dialkylacetal. The last readily enters into further conversion. Such a path is not possible for the orthoformate; this determines its lower activity in the reactions under consideration.

EXPERIMENTAL

The NMR spectra were obtained on the Bruker AC-200 spectrometer (200 MHz) and the Varian EM-360 spectrometer (60 MHz). The IR spectra were recorded on the UR-20 spectrometer. The mass spectrum was obtained using the LKB-2091 chromato-mass spectrometer.

1,4,5,6-Tetrahydro-1,2,4-triazin-6-ones (IIIa-e). The solution containing 0.1 mole of the 2-aminoacylhydrazine, 0.1 mole of the orthoester, and 1 drop of concentrated H_2SO_4 in 100 ml of ethanol was boiled for 1-2 h. The ethanol was distilled off in a vacuum, and the residue was recrystallized from methanol.

3,5-Dimethyl-1,4,5,6-tetrahydro-1,2,4-triazin-6-one (IIIe). The solutions of 2.0 g (0.02 mole) of 2-aminopropionylhydrazine (Ib) in 15 ml of ethanol and 2.5 g (0.02 mole) of ethyl iminoacetate hydrochloride (V) in 20 ml of ethanol were mixed. The residue of ammonium chloride was filtered off after 8 h; the filtrate was concentrated in vacuo, and the residue was recrystallized from methanol. The yield was 49%.

4-Methoxybenzaldehyde 2-Aminoacetylhydrazone (VIII), ($C_{10}H_{13}N_3O_2$). To the solution of 1.8 g (0.02 mole) of aminoacetylhydrazine (Ia) in 25 ml of ethanol were added 2.7 g (0.02 mole) of 4-methoxybenzaldehyde. After 30 min, the ethanol was evaporated in vacuo. The hydrazone (VIII) was reprecipitated by ether from methanol. It had mp 148°C. The PMR spectrum (CD_3OD) for the form A was as follows: 3.37 (2H s, CH_2), 3.81 (3H, s, OCH_3), 7.00 (2H, d, J = 9.0 Hz, ArH), 7.76 (2H, d, J = 9.0 Hz, ArH), and 8.12 ppm (1H, s, CH=N). The spectrum for the form B was as follows: 3.78 (2H, s, CH_2), 3.81 (3H, s, OCH_3), 7.00 (2H, d, J = 90 Hz, ArH), 7.64 (2H, d, J = 9.0 Hz, ArH), and 7.91 ppm (1H, s, CH=N). The ratio of the forms A:B was ≈5:4. The yield was 73%.

4-Methoxybenzaldehyde2-Amino-3-phenylpropionylhydrazone (VI), ($C_{17}H_{19}N_3O_2$). This compound was obtained analogously. The yield was 61%. The mp was 55°C (from chloroform).

5-Benzyl-2-methyl-3-(4-methoxybenzylidenamino)-1-imidazolin-4-one(VII),($C_{19}H_{19}N_3O_2$). Thesolutions of 3.3 g (6 mmoles) of the hydrazone (VI) in 10 ml of ethanol and 0.74 g (6 mmoles) of ethyl iminoacetate hydrochloride in 10 ml of ethanol were mixed. The residue of ammonium chloride was filtered off after 6 h. The solvent was evaporated in vacuo, and the residue was recrystallized from ethanol. The mp was 134°C. The PMR spectrum ($CDCl_3$) was as follows: 2.23 (3H, d, J = 1.8 Hz, 2-CH_3), 3.03 (1H, m, J = 14.0, 4.8 Hz), 3.25 (1H, m, J = 14.0, 7.2 Hz, CH_2), 3.80 (3H, s, OCH_3), 4.25 (1H, m, J = 1.8, 4.8, 7.2 Hz, 5-H), 6.92 (2H, d, J = 9.0 Hz, ArH), 7.68 (2H, d, J = 9.0 Hz, ArH), 7.24 (5H, m, C_6H_5), and 9.46 ppm (1H, s, CH=N). The yield was 32%.

2-Methyl-5-(4-methoxybenzylidene)-4-(4-methoxybenzylidenamino)-1-imidazolin-4-one (XI), ($C_{20}H_{19}N_3O_3$). The solution containing 2.3 g (11 mmoles) of the hydrazone (VIII), 1.4 g (12 mmoles) of trimethyl orthoacetate, and 1 drop of concentrated H_2SO_4 in 15 ml of methanol was boiled for 2 h. The reaction mixture was then cooled to 0°C, and the yellow crystals of the imidazoline (XI) were filtered off. The yield was 1.1 g (55%). The mp was 185°C. The PMR spectrum ($CDCl_3$) was as follows: 2.50 (3H, s, 2-CH_3), 3.83 (6H, s, OCH_3), 6.92 (2H, d, J = 9.0 Hz, Ar—C=N), 7.73 (2H, d, J = 9.0 Hz, Ar—C=N), 6.92 (2H, d, J = 9.0 Hz, Arc-C=C), 8.14 (2H, d, J = 9.0 Hz, Ar—C=C), 7.07 (1H, s, CH=C), and 9.68 ppm (1H, s, CH=N). The yield was 1.1 g (55%).

3-Isopropylidenamino-2,2-dimethylimidazolidin-4-one (XII). To the solution of 5.4 g (60 mmoles) of aminoacetylhydrazine in 20 ml of ethanol is added the solution of 11.6 g (200 mmoles) of acetone in 20 ml of benzene. After 2 h, the solvent was evaporated in vacuo; the residue was recrystallized from the 1:5 mixture of benzene—hexane. The yield of 5.6 g (57%) of the imidazolidine (XII) was obtained; it had mp 85°C. According to the data of [7], mp 79°C. The PMR spectrum (CCl_4) was as follows: 1.40 (6H, S, 2-CH_3), 1.95 (3H, s, =C—CH_3), 2.05 (3H, s, =C—CH_3), and 3.54 ppm (2H, s, CH_2). The ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD) was as follows: 18.4, 22.3, 23.5 (CH_3), 45.3 (CH_2), 77.8 (N—C—N), 168.4, and 174.4 ppm (C=N, C=O).

5-Isopropyliden-3-isopropylidenamino-2-methyl-1-imidazolin-4-one (XIII), ($C_{10}H_{15}N_3O$). The solution containing 4.2 g (25 mmoles) of the imidazolidine (XII), 3.0 g (25 mmoles) of trimethyl orthoacetate, and 1 drop of concentrated H_2SO_4 in 25 ml of methanol was boiled for 3 h. The methanol was evaporated; the residue was distilled in vacuo and recrystallized from methanol. The yield of 3.3 g (69%) of the imidazoline (XIII) was obtained. It had bp 133°C (2 mm Hg stem) and mp 29°C. The PMR spectrum ($CDCl_3$) was as follows: 1.94 (3H, s), 2.20 (6H, s), 2.22 (3H, s), and 2.36 ppm (3H, s). The ^{13}C NMR spectrum ($CDCl_3$) was as follows: 14.5, 18.9, 20.9, 21.5, 24.8 (CH_3), 134.4, 148.3, 155.9, 161.9, and 175.7 ppm (=C). The mass spectrum (m/z; I_{rel}, %) was as follows: 194 (10, M + 1), 193 (85, $M^{+}\cdot$), 137 (50, M — [$NC(CH_3)_2$]), 110 (5), 68 (36, [$(CH_3)_2CCN$]), 67 (10), 57 (27), 56 (100) $(CH_3)_2CN$, 43 (17), 42 (33), 41 (12), m* 88.5 (137 → 110), and 33.9 (137 → 68).

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