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THE MECHANISM OF PYRAZOLINE FORMATION. I. 1-AMIDINOPYRAZOLINES.

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The reaction of hydroxylamine with substituted Mannich bases (I), forms isoxazolines. This reaction which proceeds through intermediary oximes of the β-substituted ketones (I), involves oxime anchimerism (1). A formally similar reaction (2) is the condensation of substituted hydrazines (II) with ketones (I) to form pyrazolines (IV) (Figure 1). We have now found that this reaction does not involve hydrazine anchimerism. The first step instead is an elimination reaction of the bases (I) to yield vinyl ketones (V) which then undergoes hydrazone formation (VI), followed by hydrazine intramolecular addition to yield compounds (IV). This appears to us to constitute the general pattern of such pyrazoline synthesis irrespective of the nature of the hydrazine used.

In our present study we used aminoguanidine nitrate (IIIA, Ar' $C(=NH_2^+)$-NH_2 NO_3^-) as substituted hydrazine for work-up reasons and also because of our past interest (3) in the stability of 1-amidinopyrazolines (IV, Ar' = $C(=NH_2^+)NH_2X^-$). One of the first general discoveries we made in our study of the condensation of (IIA) with representative Mannich bases (I, Ar = p-BrC_6H_4, C_6H_5 or β-$C_{10}H_7$) was that the products from such condensations depended upon the acidity of the reaction medium. At pH 2-3 aminoguanidine nitrate reacted with the appropriate Mannich base (in aqueous ethanol with refluxing for three hours) to yield the new guanyl hydrazone dinitrates (VII) in good yields. In weaker acidic media (pH 5-6) (preferably with the Mannich bases as methiodides) another reaction occurred. Thus when β-dimethylamino-ethyl-p-bromophenyl ketone (I, Ar = p-BrC_6H_4) methiodide was refluxed with a slight excess of aminoguanidine nitrate in aqueous ethanol for two hours, the product was the bis-ketohydrazine (VIII, Ar = p-BrC_6H_4). Similar reactions occurred with the other Mannich bases used also (Table 1).

Finally, when the Mannich bases (I), as free bases were refluxed in 95% ethanol for two hours, they yielded the 1-amidinopyrazolines (IX) in good yields (Table 1). The pH of the reaction solution increased almost

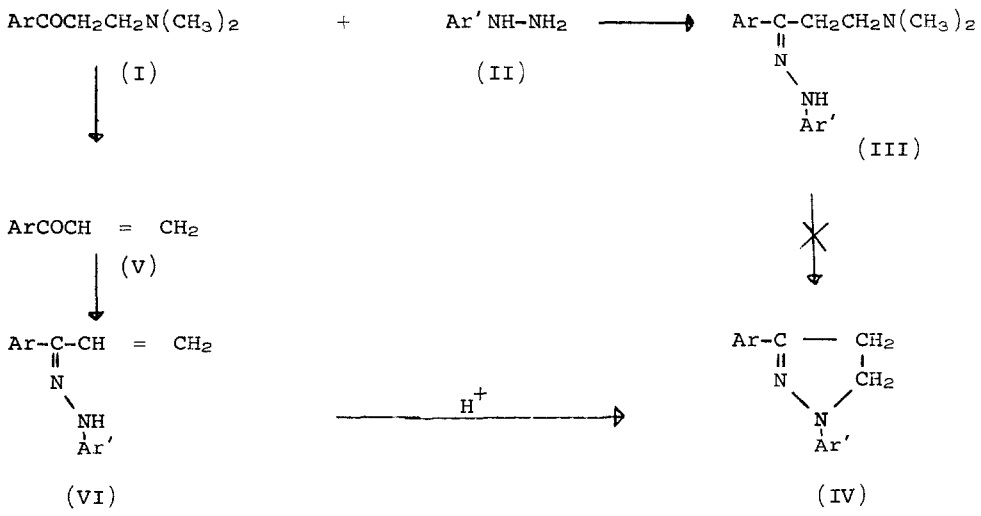
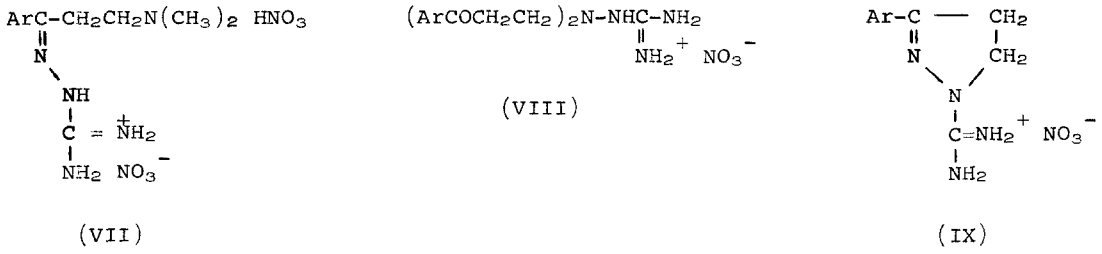


Figure 1.



immediately on refluxing from 6 to 10. A resinous mixture of byproducts was also obtained which was shown by t.l.c. to be due to the decomposition of the Mannich base alone.

We expected the hydrazones (VII) to be the precursors to the guanylpyrazolines (IX). However, we failed to convert compounds (VI) to compounds (IX) under a variety of conditions [e.g. by refluxing for 2 hours in aqueous ethanol containing 1 equivalent of diethylamine i.e. under conditions where the 1-amidinopyrazolines (IX) are easily formed from aminoguanidine nitrate and the Mannich bases]. We then probed further the mechanism of 1-amidinopyrazoline formation using as model compounds (for work-up reasons) the

Table 1 - Product Data

Substrate	Pyrazolines (IX)		Hydrazones (VII)		Bis-ketohydrazines (VIII)	
Ar=	m.p.(°C.)	Yield (%)	m.p.(°C.)	Yield (%)	m.p.(°C.)	Yield (%)
C_6H_5	238-239	49	178-181	66	205-207	51
p-BrC_6H_4	228-230	58	182-184	62	196-197	55
β-$C_{10}H_7$	241-243	41	184-186	63	213-215	47

appropriate p-bromophenyl derivatives (Figure 2). The p-bromophenyl guanylhydrazone nitrate (X) was converted via its free base (m.p. 119-121°) to its methiodide (XI), m.p. 306-308°. Heating this compound in an excess of 1.5N NaOH for 30 minutes at 70° yielded the vinylguanylhydrazone (XII), m.p. 166-169°. The n.m.r. data obtained for compound (XII) included a quartet centred

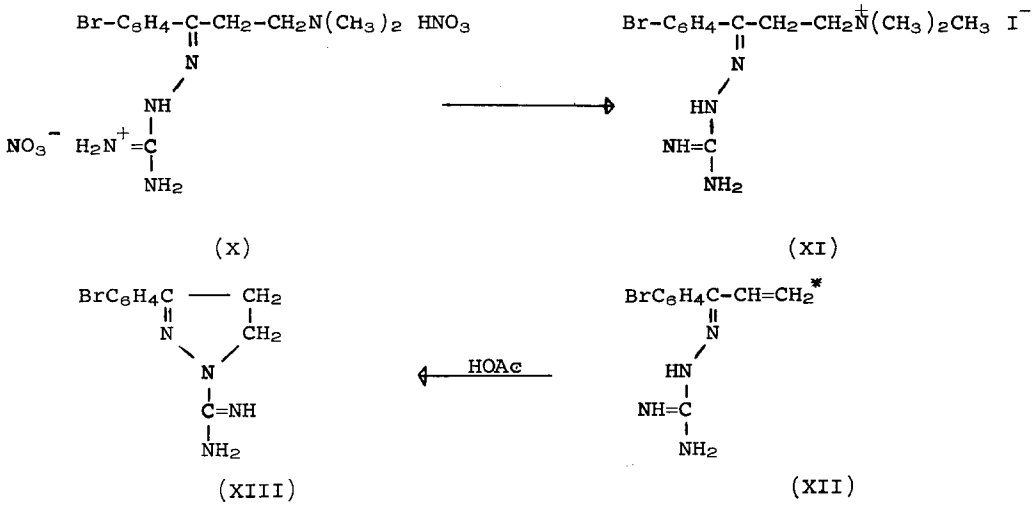


Figure 2.

at τ = 3.4 which we ascribe to the (starred) methylene protons and on the basis of which we tentatively assign (4) hydrazone (XII) [and hence also hydrazones (XI) and (X)] a configuration in which the guanyl group is anti to the vinyl moiety. Refluxing compound (XII) in acetic acid for 2 hours

afforded the 1-amidinopyrazoline (XIII), isolated either as its nitrate, or picrate, m.p. 276-278°, in 91% yield. On the other hand, refluxing the vinylhydrazone (XII) in aqueous ethanolic dimethylamine for 2 hours afforded no pyrazoline, the hydrazone (X) being regenerated instead in 84% yield (isolated as the dinitrate). In striking contrast to this result, reaction of p-bromophenyl vinyl ketone (V, Ar = p-BrC_6H_4) with one equivalent of aminoguanidine nitrate in the presence of either one equivalent of trimethylamine, dimethylamine or NaOH, afforded the 1-amidinopyrazoline (XIII) (nitrate) in 61% yield. This latter reaction most probably involves first the formation of the syn-isomer of hydrazone (XII), which then readily cyclises.

Our mechanism studies thus suggest that the formation of 1-amidinopyrazolines from aminoguanidine nitrate and the aryl Mannich bases used involves the following stages: a. formation of the appropriate aryl vinyl ketone, b. its reaction with the substituted hydrazine to form a syn vinyl hydrazone, c. the facile cyclisation of such a hydrazone. Under acidic conditions, due to dipole-dipole interactions, the aminoguanidine and Mannich base salts yield hydrazones with an anti configuration (in our sense). These exhibit no hydrazine anchimerism and can only be converted to pyrazolines by first elimination to an anti vinyl hydrazone, followed by its (geometric) isomerisation and ultimate cyclisation in acetic acid.

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(2) Cf. T. L. Jacobs, in R. C. Elderfields Heterocyclic Compounds, Wiley, New York, 1967, Vol. 5, p. 107 et. seq.

(3) See e.g. F. L. Scott and M. T. Scott, Chimia (Switzerland), 12, 148 (1958).

(4) Compare P. Bravo, G. Gaudiano and A. Umani-Ronchi, Gazz. 97 1664 (1967), and G. Gaudiano, P. P. Ponti and E. A. Umani-Ronchi, Gazz. 98 47 (1968).