HYDRAZINOLYSIS OF SOME AZOLOPYRAZINES

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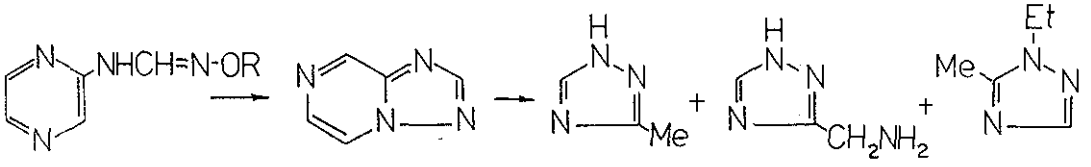
The reaction of hydrazine hydrate with some azolopyrazines (2, 6 and 8) was investigated. From the reaction mixture derivatives of 1,2,4-triazole or imidazole were isolated and identified. The mechanism of these transformations is outlined and discussed.

Recently, we have shown that s-triazolo(1,5-a)pyrazines undergo abnormal substitution and that under the influence of aqueous sodium hydroxide s-triazolo(1,5-a)pyrazine (2) is decomposed into 3-aminomethyl-1,2,4-triazole and glycolic acid.[1] Moreover, hydrazinolysis of s-triazolo(1,5-b)pyridazine also proceeded with the rupture of the azine part of the molecule to give 3-(pyrazolyl-5')-1,2,4-triazole.[2] In view of these findings it seemed worthwhile to investigate more in detail the reactivity of azolopyrazines towards hydrazine.

As model compounds s-triazolo(1,5-a)pyrazine[2] (2), s-triazolo(4,3-a)-pyrazine[3] (6) and imidazo(1,2-a)-pyrazine (8) were investigated. The later compound was prepared from 2-aminopyrazine and bromoacetaldehyde in ethanolic solution at room temperature for 48 hr. Upon neutralisation and evaporation of the solvent the product (8) was extracted with chloroform and crystallized from chloroform and petrolether (41 % yield), mp 92°. The nmr (DMSO-d_6) spectrum revealed signals at τ = 2.18 (d, H_2), 1.85 (d, H_3), 1.37 (dd, H_5), 2.12 (d, H_6), 0.95 (d, H_8); $J_{2,3}$ = 1.0, $J_{5,6}$ = 4.5 and $J_{5,8}$ = 1.5 Hz. Although the synthesis of s-triazolo(1,5-a)pyrazine (2) was described earlier,[2] we have now found that cyclization of the corresponding hydroxyiminomethyleneaminopyrazine (1a) could be performed preferentially via the intermediate O-acetyl derivative (1b), mp about 130° with conversion into (2), nmr (DMSO-d_6) τ = 1.25 (s, H_3), 1.50 (s, H_5, H_6), 1.5 (d, NHCH), -0.4 (broad, NHCH). Compound 1b when heated in water under reflux for 2 hr afforded the bicycle (2) in 73 % yield.

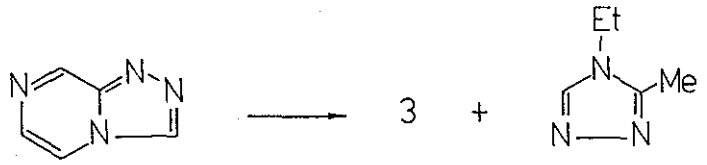
s-Triazolo(1,5-a)pyrazine (2) when heated with excess of 98 % hydrazine hydrate under reflux for 113 hr was transformed into a mixture of triazoles. Upon separation these were identified as 3-methyl-1,2,4-triazole (3), mp 95° [lit.[4] gives mp 94-95°; nmr spectrum ($CDCl_3$): τ = 2.05 (s, H_5), 7.53 (s, Me), 0.70 (broad, NH)], and 3-aminomethyl-1,2,4-triazole (4) (as hydrochloride, mp 256-258°, see also lit.[5,6]). The nmr (DMSO-d_6) spectrum of the later revealed signals at τ = 1.60 (s, H_5), 5.95 (s, CH_2), -1.0 (broad, NH, NH_2). From a nmr examination of a probe, taken during the reaction, it could be established that also 1-ethyl-5-methyl-1,2,4-triazole (5) was formed in a small amount. Its nmr (H_2O) spectrum exhibited signals at τ = 2.05 (s, H_3), 7.50 (s, 5-Me), 8.60 (t, $CH_2\underline{CH}_3$), 5.90 (q, $\underline{CH}_2CH_3$); J_{Et} = 7.2 Hz.

A similar experiment with s-triazolo(4,3-a)pyrazine (6) afforded a mixture of 3 and 1-ethyl-2-methyl-1,2,4-triazole (7). The compounds were separated by gas chromatography and the nmr ($CDCl_3$) spectrum of the later revealed signals at τ = 1.85 (s, H_5), 7.55 (s, Me), 8.60 (t, $CH_2\underline{CH}_3$), 6.07 (q, $\underline{CH}_2CH_3$); J_{Et} = 7.2 Hz. Finally, hydrazinolysis of imidazo(1,2-a)pyrazine (8) afforded after 40 hr an oily mixture of 2-methylimidazole[7] (9) and 1-ethyl-2-methylimidazole[8] (10) in a ratio of 5:4. Nmr spectrum of 9 ($CDCl_3$) revealed τ = 3.10 (s, H_4 and H_5), 7.63 (s, Me), 4.07 (broad, NH), and that of 10 ($CDCl_3$) showed signals at τ = 3.14 (s, H_4 and H_5), 7.63 (s, Me), 8.62 (t, $CH_2\underline{CH}_3$); J_{Et} = 7.5 Hz.

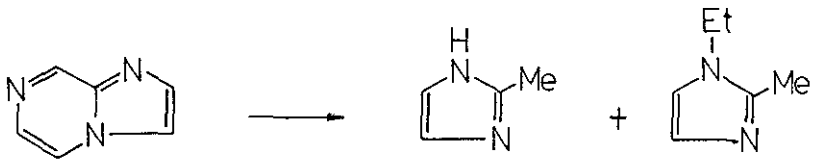


1a, R=H
1b, R=COMe

2 3 4 5

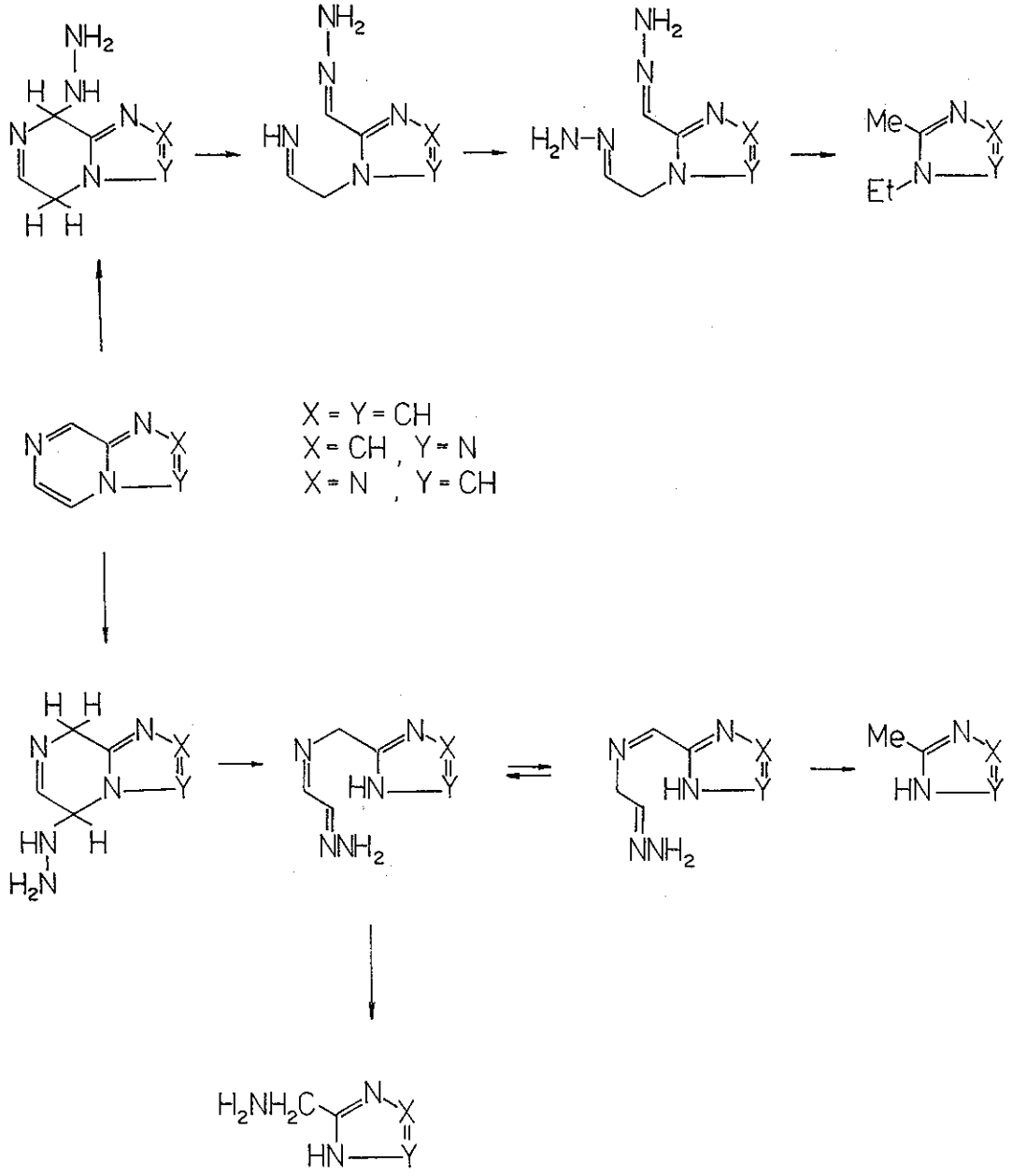


6 7



8 9 10

The formation of the above mentioned azoles can be explained in terms of two pathways. We can envisage the attack of hydrazine to the investigated systems in a similar manner as observed for the nucleophilic displacement of 5-halo s-triazolo(1, 5-a)pyrazines where either a 5- or 8- substituted derivative was formed.[1] Thus the attack of hydrazine nucleophile can occur at any of the 5- or 8-electron deficient centers and the reaction sequence is outlined in the scheme:


X = Y = CH
X = CH , Y = N
X = N , Y = CH

The products are formed mainly by an initial nucleophilic addition of hydrazine to position 8 with consequent cleavage and reduction of a Wolff-Kishner type.[9] In an analogous way, addition of hydrazine to position 5 of the azolopyrazines gives compound 4 which could be detected only among the decomposition products of s-triazolo(1,5-a)pyrazine.

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