REACTION OF HYDRAZINE WITH β-AMINOCROTONONITRILE: SYNTHESIS OF 2,7-DIMETHYL-5-AMINOPYRAZOLO[1,5-a]PYRIMIDINE

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Condensation of hydrazine with β-aminocrotononitrile at room temperature gives β-(3-methyl-5-amino-1-pyrazolyl)crotononitrile, thermal rearrangement of which produces 2,7-dimethyl-5-aminopyrazolo[1,5-a]pyrimidine in excellent yield. Consequently, the various reactions of hydrazine with β-aminocrotononitrile can readily be rationalised.

The reactions of hydrazine with β-aminocrotononitrile were first studied in 1895 by Meyer,1 who reported that three isomeric products of molecular formula C₈H₁₀N₄ could be obtained, depending on the reaction conditions employed. Structures 1 and 2 were

![Structures 1 and 2](attachment:image)

assigned to two of these products and 1 was later shown to be
correct by Kurtz et al. No structure was postulated by Meyer for the third, somewhat unstable isomer, as attempts to repeat the preparation failed and resulted only in the formation of \( \text{I} \). About ten years ago Takamizawa et al. claimed that structure \( \text{I} \) was incorrect, and that the product obtained from acid catalysed cyclisation of \( \text{I} \) was in fact the isomeric compound \( \text{II} \). Recently, Alcade et al. have published details of a comprehensive and sophisticated spectroscopic study of all three products described by Meyer; their results confirm that structure \( \text{I} \) is correct, show that structure \( \text{II} \) is almost certainly correct, and prove that the third isomer reported by Meyer is the azine \( \text{III} \).

The reactions of hydrazine with 6-aminocrotononitrile were investigated in detail in these laboratories some years ago, and we now describe briefly one aspect of that work. Using a spectroscopic approach similar to that of Alcade et al., structures \( \text{I} \) and \( \text{IV} \) for two of the Meyer products were readily confirmed. In our opinion, however, absolute distinction between the two isomers \( \text{I} \) and \( \text{II} \) on purely spectroscopic grounds could not be made entirely unambiguously. Hence both compounds were synthesised as follows. Reaction of hydrazine with 6-aminocrotononitrile at room temperature gave the azine \( \text{IV} \) as a colourless, crystalline solid,
mp 99-102°, which cyclised smoothly to 3, mp 201-202°, when heated under reflux in either acetic or aqueous hydrochloric acid. The properties of 3 and 4 thus prepared are fully consistent with those reported by Alcade et al. When 4 was heated neat in a test tube over a low flame, however, it melted at about 100° and, when heating was continued, a vigorous exothermic reaction set in at about 250°; the product of this reaction, formed in excellent yield, was the hitherto unknown fourth isomer of molecular formula C₈H₁₀N₄, the pyrazolo[1,5-a]pyrimidine 2, mp 185-186°. Thermal rearrangement of 1 similarly gave 2 in excellent yield.

As anticipated, the spectral properties (ir, uv, nmr, mass) of 2 and 3 are almost identical, although as predicted by Alcade et al. there is indeed a four bond coupling of 1.0 Hz in the nmr spectrum of 2 between the 6-proton and the 7-methyl group, but no discernable coupling between the 5-methyl group and the 6-proton in 3. Unambiguous proof that the thermal rearrangement of 1 and 4 gives 2 was obtained by single crystal X-ray analysis of the 5-N-acetyl derivative of 2, the details of which have been published elsewhere. ²

The above results therefore not only completely confirm the structural assignments made by Alcade et al. for compounds 1, 3 and 4 but clarify the long-confused situation with respect to the nature of the reactions of hydrazine with 8-aminocrotononitrile and the products thus formed; the various transformations are summarised in the Scheme. Moreover, formation of 2 and 3 under the conditions described above is interesting in mechanistic terms. Compound 2 can be regarded as the "expected" product of
cyclisation of 1, yet is formed only by thermal cyclisation of either 1 or 4. The "unexpected" isomer 3, on the other hand, is obtained from 1 or 4 by treatment with hot acid and is presumably formed via a ring-opening/ring reclosure sequence.

Experimental

2,2-Dimethyl-5-aminopyrazolo[1,5-a]pyrimidine 2. Hydrazine hydrate (5.0 g, 0.1 mol) was added to a solution of β-aminocrotononitrile (8.2 g, 0.1 mol) in acetic acid (10 ml) and the mixture shaken. A colourless, voluminous solid precipitated almost immediately;
the mixture was allowed to stand at room temperature for 5 min, after which the solid was collected by filtration, washed with cold water (2 x 20 ml), dried by suction, and recrystallised from a chloroform-petroleum ether (bp 40-60°C) mixture. This gave 6.5 g (67%) of the pure azine \( \frac{A}{4} \) as colourless crystals, mp 99-102°C.

Anal. calcd for \( C_8H_{10}N_4 \): C, 59.24; H, 6.21; N, 34.54. Found: C, 59.48; H, 6.17; N, 34.81.

The azine thus prepared (4 g) was melted in a test tube over a small flame; heating was continued to about 250°C, when a vigorous exothermic reaction commenced. The tube was removed from the heat and the contents allowed to boil for a few minutes. The liquid crystallised on cooling, and the solid was purified by vacuum sublimation (130°C/0.1 mm) followed by recrystallisation from a chloroform-petroleum ether (bp 60-80°C) mixture. This gave 3.5 g (87%) of pure \( \frac{2}{2} \) as very pale yellow needles, mp 185-186°C.

Anal. calcd for \( C_8H_{10}N_4 \): C, 59.24; H, 6.21; N, 34.54. Found: C, 59.02; H, 6.24; N, 34.51.

IR (Nujol): 3340 and 3140 (N-H), 1660 cm\(^{-1}\) (C=N); nmr (\( CDCl_3 \)): \( \delta \) 2.42 (d, 3H, \( ^4J_{2,3} = 0.5 \) Hz, 2-CH\(_3\)), 2.60 (d, 3H, \( ^4J_{6,7} = 1.0 \) Hz, 7-CH\(_3\)), 5.85 (d, 1H, \( ^4J_{6,7} = 1.0 \) Hz, 6-H), 5.92 (d, 1H, \( ^4J_{2,3} = 0.5 \) Hz, 3-H); uv (\( C_2H_5OH \)): \( \lambda_{max} \) 245, 275, 285 308 (sh) nm (log \( \epsilon \) 4.57, 3.39, 3.36, 3.05).

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References


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