

Fused Pyrazolopyrimidines. I.

Pyrazolo[4,3-*e*]-*v*-triazolo[1,5-*a*]pyrimidine. A New Heterocyclic System

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5-Azido-4-cyano-1-phenylpyrazole reacts with benzylocyanide in the presence of sodium methoxide to give the title ring system.

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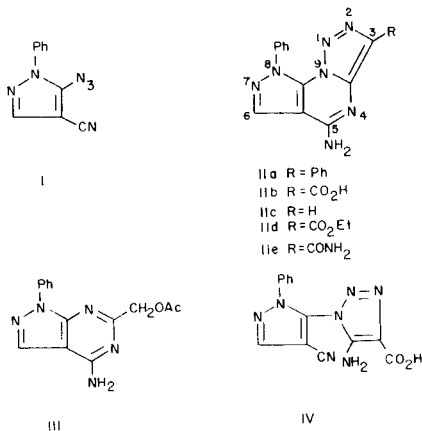
A few heterocyclic systems containing a 1,2,4-triazole ring fused to a pyrazolopyrimidine are described in the literature (1), but there is no mention of a *v*-triazole fused pyrazolopyrimidine ring system. Appropriately substituted azidopyrazoles could possibly react with acetonitriles leading to such a ring system and as such we explored the feasibility of this reaction.

When 5-azido-4-cyano-1-phenylpyrazole (I) was heated with benzylocyanide in the presence of sodium methoxide, 5-amino-3,8-diphenyl-8*H*-pyrazolo[4,3-*e*]-*v*-triazolo[1,5-*a*]pyrimidine (IIa) was obtained in 94% yield. The structure of IIa was confirmed from its elemental analysis, and infrared and proton magnetic resonance spectra. In the infrared spectrum of IIa the characteristic absorptions due to the nitrile and the azide groups of I (2230 and 2130 cm^{-1} , respectively) were absent, while two absorption peaks at 3400 and 3290 cm^{-1} indicated the presence of an amino group. In the proton magnetic resonance spectrum, two multiplets between δ 7.20-7.80 and δ 8.10-8.50, due to the ten aromatic protons of the two phenyl groups were observed, while a singlet at δ 8.60 of the pyrazole ring together with another broad signal at δ 9.55, due to the two protons of the amino group, confirmed the structure IIa. Furthermore in the mass spectrum of IIa, a molecular ion peak was found at m/e 327, which also gave support to the structure IIa. The compound IIa is the first example of a new ring system, 8*H*-pyrazolo[4,3-*e*]-*v*-triazolo[1,5-*a*]pyrimidine.

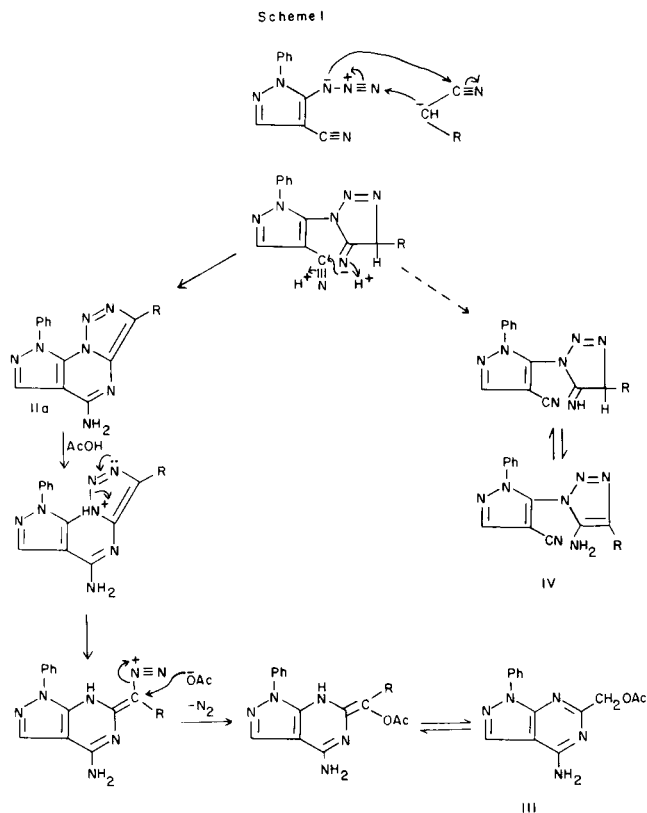
Attempts to obtain other derivatives of this new ring system, by employing other acetonitriles, were not successful and the reaction led to the formation of a pyrazolo[3,4-*d*]pyrimidine or a 1-(pyrazol-5'-yl)-*v*-triazole. Thus the reaction between I and cyanoacetic acid gave 89% yield of 6-acetoxymethyl-4-amino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (III). The expected IIb or its decarboxylation product IIc were not isolated from this reaction. The structure of III followed from its elemental analysis, the infrared spectrum (the absence of the azide and the nitrile absorption bands of I, the appearance of an amino group absorption bands at 3450 and 3330 cm^{-1} , and another absorption band at 1749 cm^{-1} due to the carbonyl of the acetoxy group), and the proton magnetic resonance spectrum which showed a multiplet for the five aromatic protons between δ 7.20-8.30, a one proton singlet at δ 8.32 for the pyrazole ring proton, a three proton singlet at δ 2.18 and a two proton singlet at δ 5.07 pertaining to an acetoxy group. The mass spectrum of this product also confirmed the structure III (molecular ion peak at m/e 283). In another attempt to isolate II*d*, we replaced cyanoacetic acid by ethyl cyanoacetate in this reaction, but again III was the only isolable product.

In another reaction however, using cyanoacetamide, neither the expected II*e* nor the pyrazolopyrimidine (III) could be obtained. Instead, a different product was obtained in 69% yield. This product was identified as 5-amino-1-(4'-cyano-1'-phenylpyrazol-5'-yl)-*v*-triazole-4-carboxylic acid (IV). The infrared spectrum of IV showed a strong absorption band at 2120 cm^{-1} and broad absorption bands between 3450-2800 and 1700-1660 cm^{-1} , due to the amino and the carboxyl groups, while the proton magnetic resonance spectrum displayed the following signals: a multiplet for five aromatic protons between δ 7.20-8.30, a one proton singlet at δ 8.29 for the pyrazole ring proton and broad signal for two amino protons at δ 8.89. The mass spectrum of IV showed a molecular ion peak corresponding to m/e 295.

Based on the fact that different products are obtained in the reaction of I with substituted acetonitriles, it seems that in the reaction of benzylocyanide, cyanoacetic acid and ethyl cyanoacetate, the ring system II is formed. However,



the isolation procedures employed lead to the decarboxylation of IIb and IIc with the concomitant ring openings. The acetoxy group of III comes from the participation of acetic acid employed during the work up and has been proposed in a similar reaction (2). In the reaction of I with cyanoacetamide, the amino group of the triazole ring fails to condense with the cyano group of the pyrazole to give IIe, the amide being hydrolyzed to the acid during the reaction. A mechanistic scheme to account for all the products obtained during different reactions may be summarized in Scheme I



We are proceeding with these investigations to establish conditions for the synthesis of IIb-IIe, as well as other derivatives of the new ring system, and to study the reactivity of the compounds.

EXPERIMENTAL

The pmr spectra were taken on a 60 MHz Hitachi Perkin-Elmer model R-20B using tetramethylsilane as an internal reference. Infrared absorption spectra were measured on a Perkin-Elmer model 180, samples were

examined as potassium bromide pellets. The melting points were observed on a Fisher-Johns apparatus and are uncorrected.

5-Amino-3,8-diphenyl-8H-pyrazolo[4,3-e]-v-triazolo[1,5-a]pyrimidine (IIa).

A mixture of 0.21 g. of I [obtained from 5-bromo-4-cyano-1-phenylpyrazole and sodium azide (3)], 0.11 g. of benzyl cyanide and 0.24 g. of sodium methoxide in 8 ml. of anhydrous methanol was stirred at room temperature for 0.5 hours. The solvent was evaporated and ice water was added to the residue. The solid was collected by filtration, washed with water and dried to give 0.30 g. (94%) of IIa, m.p. 205-206° (acetic acid); pmr (DMSO-*d*₆, 70°): δ 7.20-7.80 and 8.10-8.50 (2m, aromatic), 8.60 (s, H-6), 9.55 (br, NH₂); ir: 3400 and 3290 (NH₂), 3110, 1670, 1620, 1600, 1560, 1500, 1400, 1240, 975, 880, 770, 760, 690 cm⁻¹; ms: m/e 327 (M⁺).

Anal. Calcd. for C₁₈H₁₃N₇: C, 66.04; H, 4.00; N, 29.95. Found: C, 66.20; H, 4.19; N, 29.75.

6-Acetoxyethyl-4-amino-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (III).

A mixture of 0.21 g. of I, 0.11 g. of ethyl cyanoacetate and 0.3 g. of sodium ethoxide in 10 ml. of anhydrous ethanol was heated under reflux for 2.5 hours. The solvent was removed and 15 ml. of 50% acetic acid added to the residue. The mixture was stirred for 3 hours at room temperature and the solid was collected by filtration, washed with water and dried giving 0.25 g. (89%) of III, m.p. 217-218° (acetic acid); pmr (DMSO-*d*₆): δ 2.18 (s, CH₃), 5.07 (s, -O-CH₂-C=N), 7.20-8.30 (m, aromatic and NH₂), 8.32 (s, H-3); ir: 3450 and 3330 (NH₂), 3240, 3000, 1749 (C=O), 1665, 1591, 1570, 1510, 1400, 1380, 1235, 965, 850, 790, 760, 720, 690; ms: m/e 283 (M⁺).

Anal. Calcd. for C₁₄H₁₃N₅O₂: C, 59.36; H, 4.63; N, 24.72. Found: C, 59.15; H, 4.78; N, 24.56.

Using cyanoacetic acid in place of ethyl cyanoacetate in the above reaction, III was obtained in comparable yield.

5-Amino-1-(4'-cyano-1'-phenylpyrazol-5'-yl)-v-triazole-4-carboxylic Acid (IV).

A mixture of 0.21 g. of I, 0.08 g. of cyanoacetamide and 0.24 g. of sodium methoxide in 8 ml. of anhydrous methanol was heated under reflux for 15 minutes and then stirred at the room temperature for 24 hours. The solvent was evaporated and the residue treated with 15 ml. of 50% acetic acid. The solid was collected by filtration, washed with water and dried to yield 0.20 g. (69%) of IV, m.p. 224-225° (acetic acid); pmr (DMSO-*d*₆): δ 7.20-8.20 (m, aromatic), 8.29 (s, H-3'), 8.90 (br, NH₂); ir: 3450-2800 (NH₂ and CO₂H), 2120 (C≡N), 1700-1600 (C=N), 1600, 1590, 1560, 1500, 1465, 1400, 1240, 980, 790, 750, 685 cm⁻¹; ms: m/e 295 (M⁺).

Anal. Calcd. for C₁₃H₉N₇O₂: C, 52.70; H, 3.71; N, 36.50. Found: C, 52.40; H, 3.53; N, 36.45.

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