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Studies on 5-Aminopyrazole Derivatives
Synthesis of Some New Fused Pyrazole Derivatives

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5-Amino-4-cyano-3-phenylpyrazole (**1**) reacts with acrylonitrile or ethyl acrylate to yield 4-cyano-3-phenyl-4,5,6,7-tetrahydro-5-oxopyrazolo-[1,5—*a*]-pyrimidine (**2**). With urea, thiourea and ethyl acetoacetate **1** gives the pyrazolopyrimidine derivatives **6a**, **6b**, and **7** respectively. On the other hand, compound **1** reacted with benzoylisothiocyanate to give the corresponding thiourea derivative **4**. Diazotized **1** was coupled with malononitrile and ethyl cyanoacetate to yield the pyrazolopyrimidine derivatives **10** and **11**, respectively, whereas on coupling with α-chloro acetoacetic ester and with acetylacetone the hydrazones **12** and **13** were obtained.

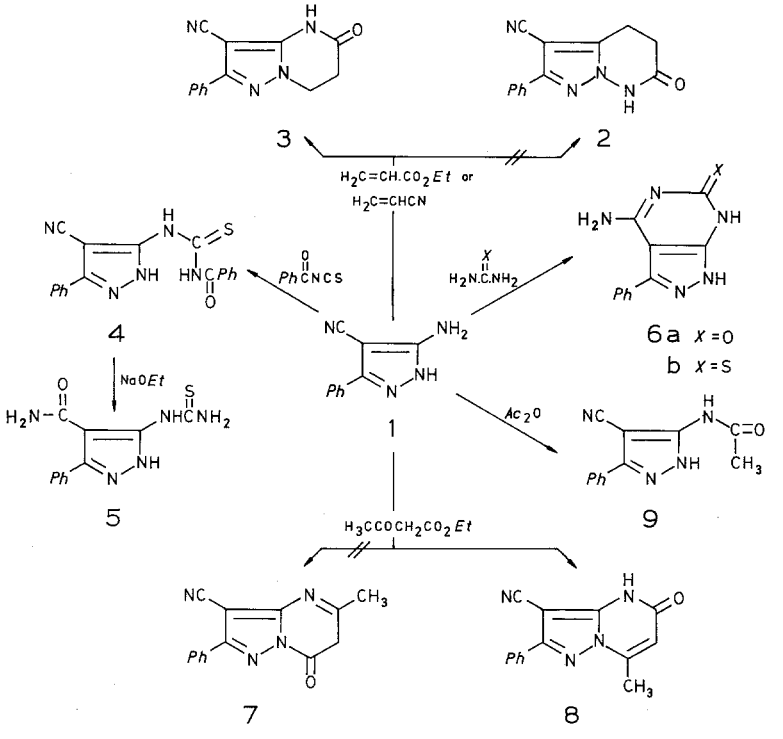
(Keywords: Enaminonitriles; Fused Pyrazoles)

Untersuchungen an 5-Aminopyrazolderivaten.
Synthese von verschiedenen neuen kondensierten Pyrazolderivaten

Die Reaktion von 5-Amino-4-cyano-3-phenylpyrazol (**1**) mit Acrylnitril oder Ethylacrylate ergibt 4-Cyano-3-phenyl-4,5,6,7-tetrahydro-5-oxopyrazolo-[1,5—*a*]-pyrimidin (**2**). Die Reaktion von **1** mit Harnstoff, Thioharnstoff und Ethyl acetoacetat ergibt die Pyrazolopyrimidinderivate **6a**, **6b** und **7**. Andererseits entsteht das Thioharnstoffderivat **4** durch die Reaktion von **1** mit Benzoylisothiocyanat. Diazotiertes **1** koppelt mit Malononitril und Ethylcyanoacetat zu den Pyrazolopyrimidinen **10** und **11**, die Kopplung mit α-chloroacetoacetic ester und Acetylaceton ergibt jedoch die Hydrazone **12** und **13**.

Fused pyrazoles are biologically interesting compounds[1—3]. Diverse biological activities have been reported in the last fifty years for these derivatives. These ranges from *CNS* regulants[4] to antischistosomisal activities[5]. Our group has contributed to efforts of preparing new fused

pyrazoles of promising biological activities[6,7]. The newly reported antischistosomisal activity of pyrazolopyrimidines has renewed our interest in this class of compounds as schistosomiasis is one of the most acute problems in our country. In the present paper we report the synthesis of several new fused pyrazoles utilising 5-amino-4-cyano-3-phenylpyrazole (**1**) as starting material. Although compound **1** is known



in literature[6], our newly reported synthesis[8] was utilized for its preparation since it is more convenient. It has been found that **1** reacts with acrylonitrile to yield a product which may be formulated as **2** or isomeric **3**. The same compound could be obtained from the reaction of **1** with ethyl acrylate. Although structure **3** seemed more likely based on analogy to the well established behaviour of 5-aminopyrazoles toward activated double bond systems[9] an independent structure proof seemed mandatory as the relative reactivities of ring and exocyclic amino functions proved to be dependent on the nature of substituents on the pyrazole ring and the applied reaction conditions. ^{1}H-NMR however,

provided an evidence in favour of structure **3** as it revealed a triplet at δ 2.8 ppm for CH_2 protons and a multiplet at 4.2 ppm for other CH_2 protons. It should be noted that the two protons here are more effected by ring current and are thus deshielded and better resolved. If the reaction product was **2** a reverse pattern should have been observed as the high field methylene signal should be coupled with the NH proton and the lower field methylene signal should appear as a symetrical triplet (only coupled with other methylene protons).

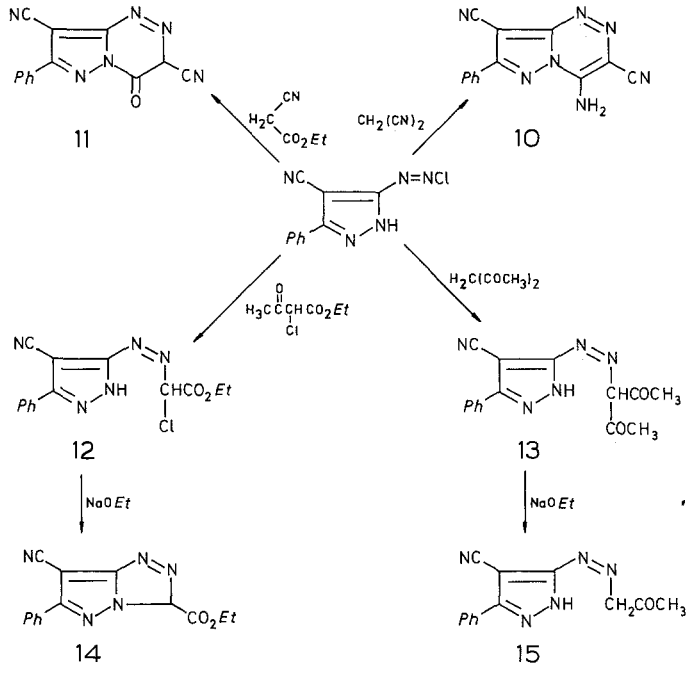
Similar to the literature reports[7] **1** reacted with benzoylisothiocyanate to yield the benzoylthiourea derivative **4**. Attempted cyclization of the latter into a pyrazolo[4,3—*d*]pyrimidine derivative afforded the carboxamidopyrazol-5-yl-urea derivative **5**. Pyrazolo [4,3—*d*]pyrimidine derivative **6** could be obtained via fusion of **1** with urea and thiourea.

1 was also condensed with ethylacetoacetate to yield a product which may be formulated as **7** or isomeric **8**. Structure **8** was assigned for the reaction product based on the IR spectrum which revealed a ring CO at 1 660 cm^{-1}. If this compound were isomeric **8**, the ring CO should have been observed at higher frequency. This method of discriminating both isomers has been previously reported by *Elnagdi* et al.[10].

1 also reacted with acetic anhydride to yield the acetyl derivative **10**. Attempts to effect cyclization of **10** into pyrazolooxazine derivative or into pyrazolopyrimidine derivative were unsuccessful. The molecule proved to be highly stable under conditions reported for cyclization of 4-cyano-5-acetamidopyrazoles[11].

5-Aminopyrazoles have been reported to diazotize readily to yield the corresponding diazonium salts. The later could be utilized for the synthesis of a variety of pyrazolotriazine derivatives. Reactions of this type have been recently reviewed by one of us[12], however, the behaviour of 5-amino-4-cyanopyrazole derivatives have never been investigated. Now it has been found that **1** reacts with sodium nitrite in presence of hydrochloric acid to yield the corresponding diazonium salt. The latter could not be isolated in a free state, however it could be trapped via reaction with different coupling components. Thus, diazotized **1** coupled with malonitrile to yield the enaminopyrazolo[1,5—*c*]-*as*-triazine derivative **10** and with ethylcyanoacetate to yield the 7-oxo-pyrazolo[1,5—*c*]-*as*-triazine derivative **11**. Coupling with α-chloro-ethylacetoacetate and with acetylacetone afforded the corresponding hydrazones **12** and **13**, respectively. Whereas **12** was readily cyclized on treatment with sodium ethoxide into the corresponding **14**, acyl group cleavage occured on the attempted cyclization of **13** and compound **15** was isolated.

The formation of **15** under this condition might be assumed to proceed via a sequence similar to that described[13] for acyl group cleavage in the *Jap-Clingman* reactions and similar reactions.



Experimental

All melting points are uncorrected. IR spectra were recorded on a Beckmann spectrophotometer (KBr). NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer in *DMSO* using *TMS* as internal standard and chemical shifts are expressed as δ ppm.

4-Cyano-7-phenyl-4,5,6,7-tetrahydro-5-oxopyrazolo[1,5—a]pyrimidine (**2**)

To a solution of **1** (1.8 g) in pyridine (30 ml) was added acrylonitrile (0.5 ml). The reaction mixture was refluxed for 6 h. The solvent was then removed *in vacuo* and the oily residue was dissolved in ethanol. The solid product formed was collected by filtration and crystallized from ethanol. **3** formed colourless crystals, m.p. 260°; yield 65%; IR: 1 690 cm^{-1} (ring CO), 2 230 cm^{-1} (CN). ^{1}H-NMR: 2.8 (t, 2 H, CH_2), 4.2 (m, 2 H, CH_2), 7.4–8.1 (m, 6 H, ph, NH). $C_{13}H_{10}N_4O$. Found C 65.9, H 4.2, N 23.2%. Calcd. C 65.5, H 4.2, N 23.5%.

3 was also formed on reaction of **1** with ethylacrylate under the above experimental conditions. **3** was identified by m.p. and mixed m.p.

1-Benzoyl-3-(4-cyano-3-phenyl-5-yl)thiourea (**4**)

To a solution of benzoylisothiocyanate in acetone (prepared from 0.12 g of NH_4SCN and 0.1 mol of benzoyl chloride)[14] **1** was added. The reaction mixture was refluxed for 3 h and then the solvent evaporated. The remaining product was then triturated with water and the so formed solid product was collected by filtration. **4** formed yellow crystals from dioxan; m.p. 190°; yield 70%. IR: 1680 cm^{-1} (benzoyl CO), 2240 cm^{-1} (CN) and 3250 cm^{-1} (NH). $C_{18}H_{13}N_5OS$. Found C 62.2, H 3.5, S 9.0%. Calcd. C 61.9, H 3.9, S 9.2%.

4-Carboxamido-3-phenylpyrazol-5-yl-thiourea (**5**)

To an ethanolic sodium ethoxide solution (prepared from 0.59 g of sodium metal and 30 ml ethanol) was added **4** (1.5 g); the reaction mixture was refluxed for 3 h and then evaporated *in vacuo*. The residue was dissolved in water and acidified with HCl. The solid that separated was collected by filtration and crystallized from dioxan. **5** formed colourless crystals; m.p. 260°; yield 65%. IR: 1650 cm^{-1} (CO), 3200 cm^{-1} (NH). $C_{11}H_{11}N_5OS$. Found C 50.3, H 4.3, S 12,6%. Calcd. C 50.5, H 4.2, S 12.2%.

Pyrazolo[4,3—d]pyrimidines **6a, b**

A mixture of **1** (0.01 mol) and either urea or thiourea (0.01 mol) was heated in an oil bath at 150° for 2 h, then the reaction mixture was triturated with ethanol. The solid product formed was collected by filtration.

6a formed colourless crystals from dioxan; m.p. > 300°; yield 70%. IR: 1630 cm^{-1} (CO), 3000–3500 cm^{-1} (NH_2). $C_{11}H_9N_5O$. Found C 58.7, H 3.7, N 30.5%. Calcd. C 58.4, H 3.9, N 30.8%.

6b formed colourless crystals from dilute ethanol m.p. 255°; yield 73%. IR: 1630 cm^{-1} (CO), 3150–3500 cm^{-1} (NH).

^{1}H-NMR: 6.9 (s, 2H, NH_2), 7.5 (m, 6H, ph, NH), 13.5 (s, 1H, NH). $C_{11}H_9N_5S$. Found C 54.7, H 3.8, S 13.0%. Calcd. C 54.3, H 3.7, S 13.1%.

3-Cyano-4,5-dihydro-7-methyl-2-phenyl-5-oxopyrazolo[1,5—a]-pyrimidine (**8**)

A mixture of **1** (2.0 g) and ethylacetoacetate (2 ml) was heated at 160° (bath temperature) for 8 h. The reaction mixture was cooled, triturated with ethanol, and the resulting solid product was collected by filtration and crystallized from *DMF*. **8** formed colourless crystals; m.p. > 330°; yield 60%. IR: 1640 (C=C), 1670 (ring CO), 2230 (conj. CN), 2500–3150 (OH dimer). $C_{14}H_{16}NO$. Found C 67.2, H 4.1, N 6.3%. Calcd. C 67.5, H 4.4, N 6.5%.

5-Etamido-4-cyano-3-phenylpyrazole (**9**)

A solution of **1** (2 g) in acetic anhydride (30 ml) was refluxed for 4 h. The excess acetic anhydride was evaporated *in vacuo*. The reaction mixture was cooled and the resulting solid product was filtered off and crystallized from alcohol. **9** formed brownish crystals; m.p. 210°; yield 70%. IR: 1700 (CO), 2220 (CN). $C_{12}H_{10}N_4O$. Found C 63.8, H 4.4, N 24.8%. Calcd. C 63.7, H 4.4, N 24.9%.

Reaction of Diazotized **1** *with Active Methylene Reagents*

A solution of diazotized **1** (prepared from 0.1 mol of **1** and the appropriate quantities of conc. HCl and sodium nitrite as has been previously described[15]) was added to a solution of the active methylene reagents (0.1 mol) in ethanol

(150 ml) and sodium acetate (13 g). The reaction mixture was stirred at room temperature for 2 h and the solid product formed was collected by filtration.

10 formed yellow crystals from dioxan, m.p. > 300°; yield 80%. IR: 1650 (CO), 2220 (CN), 3040–3200 (NH_2). $C_{13}H_7N_7$. Found C 59.7, H 2.7, N 37.3%. Calcd. C 60.0, H 2.3, N 37.5%.

11 formed red crystals from dilute ethanol; m.p. 172°; yield 75%. IR: 1700 (CO), 2220 (CN). $C_{13}H_6N_6O$. Found C 59.7, H 2.3, N 31.7%. Calcd. C 59.5, H 2.3, N 32.0%.

12 formed buff crystals from methanol; m.p. 185°; yield 80%. IR: 1700 (CO), 2200 (CN). $C_{14}H_{12}N_5O_2Cl$. Found C 53.1, H 3.8, N 21.8%. Calcd. C 52.9, H 3.7, N 22.0%.

13 formed yellow crystals from dilute ethanol; m.p. 220°; yield 70%. IR: 1670 (CO), 2220 (CN). $C_{15}H_{13}N_5O_2$. Found C 61.2, H 4.3, N 23.7%. Calcd. C 61.0, H 4.4, N 23.7%.

Action of Sodium Ethoxide on Compounds **12** *and* **13**

A solution of either **12** or **13** was refluxed in ethanolic sodium ethoxide for 2 h and the same procedure described for the preparation of **5** was followed. The products were identified as **14** and **15**, respectively.

14 formed yellow crystals from dilute ethanol; m.p. 204°; yield 60%. IR: 1675 (CO), 2220 (CN). $C_{14}H_{11}N_5O_2$. Found C 59.7, H 4.0, N 24.7%. Calcd. C 59.7, H 3.9, N 24.9%.

15 formed brown crystals from dioxan; m.p. > 300°; yield 65%. IR: 1720 (CO), 2250 (CN). $C_{13}H_{11}N_5O$. Found C 62.0, H 4.3, N 27.2%. Calcd. C 61.7, H 4.3, N 27.6%.

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