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REACTIONS WITH β-CYANOETHYLHYDRAZINE—I

A ROUTE FOR THE PREPARATION OF PYRAZOLO[1.5-a]PYRIMIDINES AND PYRROLO[1.2-b]PYRRAZOLES

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Abstract—Malononitrile (1) reacts with β-cyanoethylhydrazine (2) to yield 5-amino-4-cyano-1-β-cyanoethyl-3-cyanomethyl-pyrazole (3). Treatment of 3 with 1% NaOH solution results in the formation of 3-cyano-2-cyanomethyl-4,5,6,7-tetrahydropyrazolo[1.5-a] pyrimine (6). On the other hand, when 3 was refluxed with acetic acid-hydrochloric acid mixture, the pyrido{3:4:3':4']pyrazolo[1.5-a] pyrimidine (10) was formed.

1,2-Dihydro-5-hydroxy-3-phenylazopyrazolo[1.5-a] pyrimidine (16) was obtained by cyclization of 3,5-diamino-1-(β-cyanoethyl)-4-phenylazopyrazole (18), which, in turn, was obtained by the action of 2 on phenylazomalononitrile (17).

Ethoxymethylenemalononitrile (20) reacts with 2 to yield 3-amino-4-cyano-1-(β-cyanoethyl)-pyrazole (21). Compound 21 was readily cyclized into the pyrrolo[1.2-b]pyrazole derivative 25 by the action of either 3% NaOH solution or conc sulphuric acid.

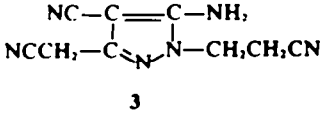
Pyrazolo[1.5-a]pyrimidines have become of considerable interest during the last decade.[1-12] Many of these compounds have proved to be active anticancer,[5-10] antipyritic and anti-infalammatory agents,[8-12] Most of the syntheses reported in the literature involve the reaction of 3-aminopyrazoles with a 1,3-bifunctical reagent. In-continuation of previous work on the synthesis of pyrazolo[1.5 - a]pyrimidines[3,4] a new route for the synthesis of this class of compounds, via the reaction of malononitrile and its derivatives with β-cyanoethylhydrazine, is reported in this paper. Thus, treatment of malononitrile (1) with β-cyanoethylhydrazine (2), in ethanol solution, resulted in the formation of a product of molecular formula $C_9H_8N_6$.

$CH_2(CN)_2$ (1) $\quad$ $NCCH_2CH_2NH.NH_2$ (2)

The IR spectrum of the product showed absorption corresponding to amino, unconjugated and conjugated cyano groups. Three structures are possible for this product (*cf* 3–5). Structure 5 was eliminated since the reaction product was readily converted into 3-cyano - 2 - cyanomethyl - 4,5,6,7-tetrahydropyrazolo[1.5-a]pyrimidine - 5-one (6) on treatment with 1% NaOH solution. Compound 6 was also obtained by the action of ethyl acrylate on 5-amino - 4 - cyano - 3-cyanomethylpyrazole (7). Moreover, 3 was also obtained by the action of acrylonitrile on 7.

Structure 3 was preferred over the possible isomeric 4 since its UV spectrum is similar to that reported for 7 and its 1-phenyl derivatives[13,14] and different from that of the pyrazolopyrimidine derivative (6).

The formation of 3 from 1 and 2 may proceed via



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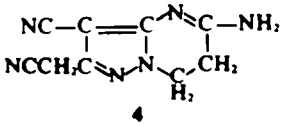

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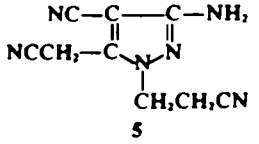

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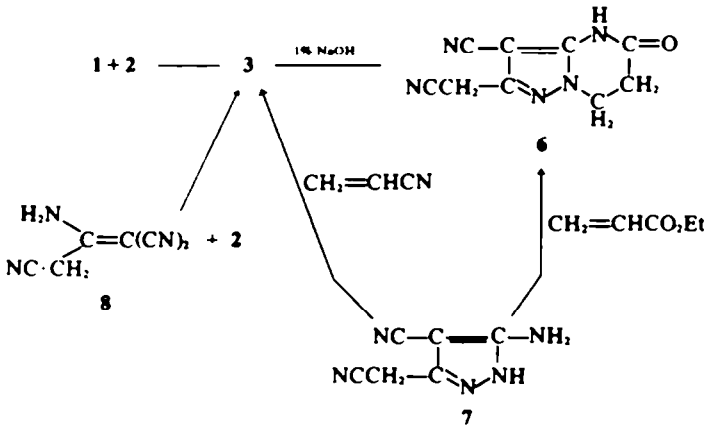


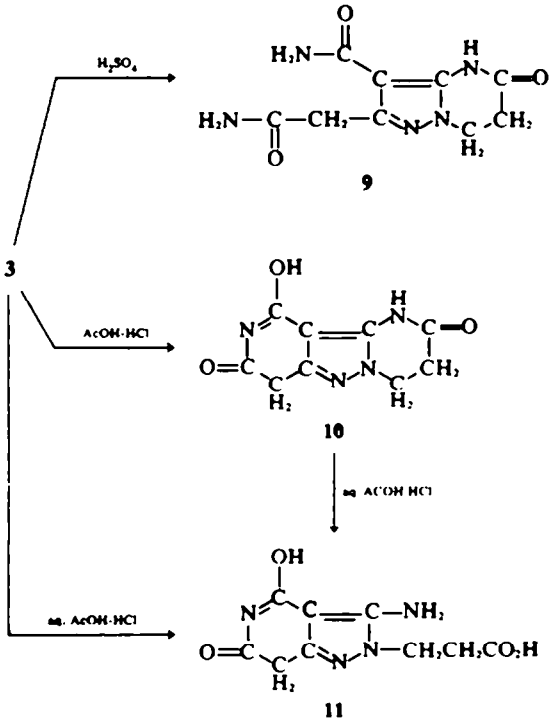
malononitrile dimer [1,1,3 - tricyano-2- aminopropene (**8**)]. This finds support from the fact that **3** is also formed, in a better yield, by the interaction of **2** and **8**. This is comparable to the reaction of **1** with hydrazines.[13,14]

Compounds **3** could be cyclized under different conditions to form different polycyclic compounds. Thus, when **3** was treated with conc sulphuric acid it was converted to the diamide **9**. On the other hand, the pyrido [3:4:3′:4′]pyrazolo[1.5 - a]pyrimidine derivative (**10**) was formed upon treatment of **3** with acetic acid-hydrochloric acid mixture. However, when **3** was refluxed for a long period with aqueous acetic acid and hydrochloric acid, 3 - amino-2β - carboxyethyl-4 - hydroxy-6,7 - dihydropyrazolo[3.4 - c]pyridine-6 - one (**11** or possible tautomers) was formed. Compound **11** was also formed by the action of the same reagent on **10**. Structures proposed for compounds **9**–**11** were inferred from their analytical and IR data.

Compound **10** was found to condense readily with benzaldehyde to yield the benzylidene derivative **12**, which was also obtained by the cyclization of 3-amino - 7 - benzylidene-2 - β- carboxyethyl-4 - hydroxy-6,7 - dihydropyrazolo[3.4 - c]pyridine-5 - one (**13**) by the action of acetic acid. Compound **13**, in turn, was obtained by the action of benzaldehyde on **11**. Compound **10** also coupled with benzenediazonium chloride to yield the corresponding phenylazo derivative **14** (or possible tautomers).

In a previous investigation[4] it has been shown that 3-amino-4 - phenylazo-2 - pyrazolin-5 - one (**15**) reacts with ethyl acrylate to yield the pyrazolopyramidine derivative **16**. The structure proposed for this compound (**16**) was mainly based on spectral data. Now, compound **16** has been synthesised as follows: Phenylazomalono-nitrile (**17**) was treated with **2** at 120° in the absence of a solvent to yield 1-β- cyanoethyl-3,5 - diamino-4 - phenylazopyrazole (**18**). Compound **18** was found to be identical with the product previously obtained by the action of acrylonitrile on 3,5-diamino-4 - phenylazopyrazole (**19**). Treatment of **18** with acetic acid-hydrochloric acid mixture affects cyclization and hydrolysis of the amino group to yield **16**.

The behaviour of ethoxymethylenemalononitrile (**20**) toward the action of **2** was also investigated as a possible route for the preparation of pyrazolo[1.5 - a]pyrimidines. When **20** was treated with **2** a crystalline product, mp 200°, with molecular formula of $C_7H_7N_5$, was formed. The IR spectrum of the product showed bands corresponding to amino, unconjugated cyano, and conjugated cyano groups. There are two possible isomeric structures for this product (*cf* **21** and **22**). It has been reported[15] that **21** reacts with hydrazine hydrate to yield, in addition



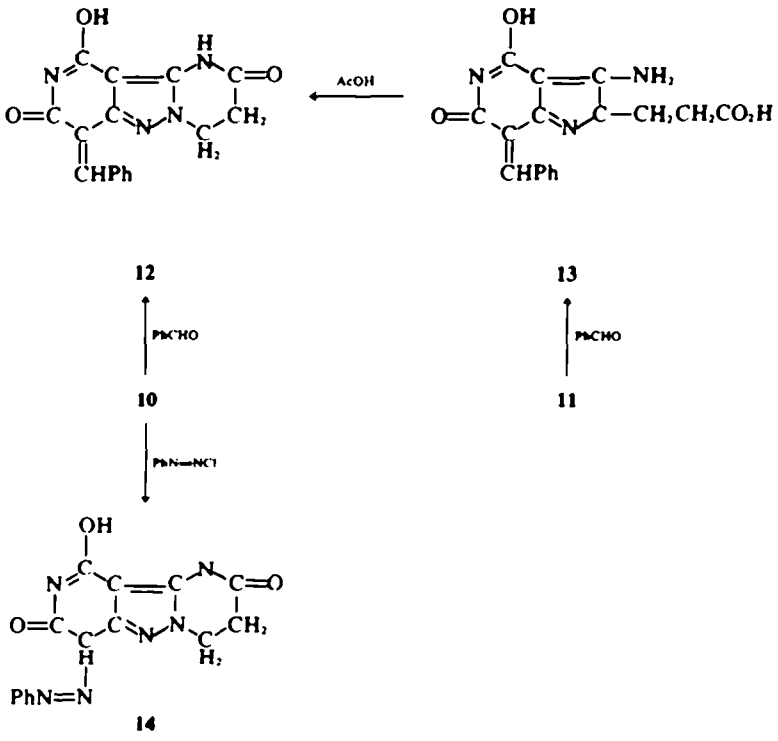
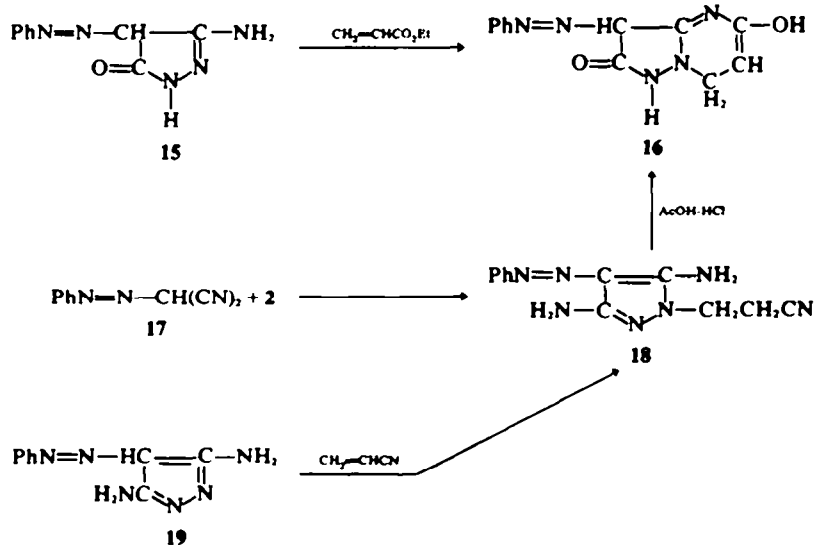
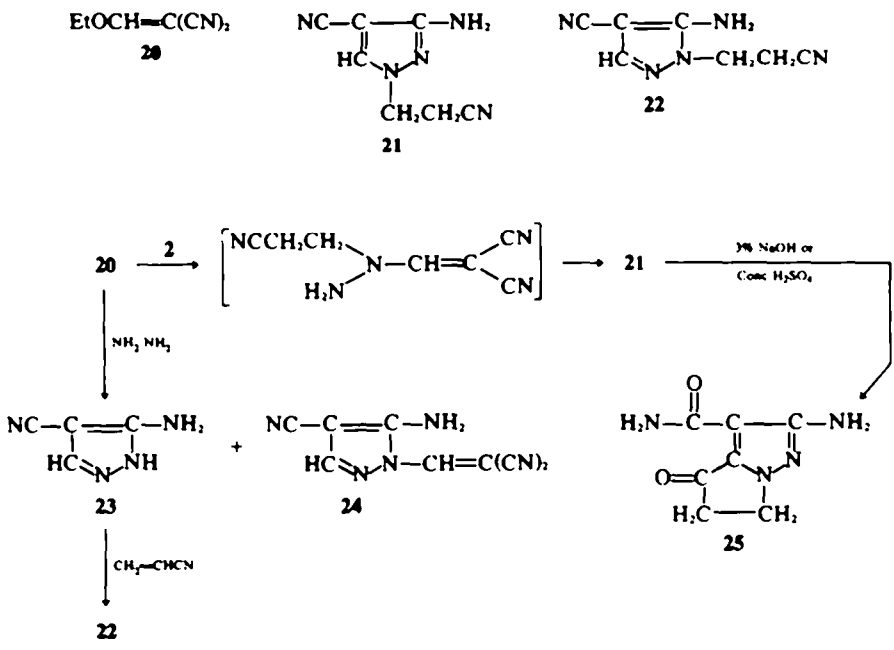


CHART I.

to 3-amino-4 - cyanopyrazole (**23**), 5-amino-4 - cyano-1 - methylene - malononitrileopyrazole (**24**). The formation of the latter product may lead to the conclusion that the first step in the reaction of **20** with hydrazines involves condensation of the hydrazine with the ethoxymethylene moiety in **20** followed by addition of the other hydrazine moiety to the cyano group. Taking into consideration the relative basisities of the N atoms in **2**, it is expected that the reaction of **2** with **20** would involve firstly condensation of the more basic NH with the ethoxymethylene group in **20**, followed by cyclization via the addition of the NH_2 to the cyano group. This sequence, so illustrated, would lead to compound **21** rather than to **22**. However, an independent chemical evidence for this structure proposal





seemed to be mandatory. To establish the structure of the product of the reaction of **2** with **20** (m.p. 200°), compound **23** was treated with acrylonitrile to give a product which can be assigned structure **22**, in analogy to the well established structure for the reaction of **7** with acrylonitrile as described above. Since the product of the reaction of **20** with **2** was not identical with **22**, it most likely has structure **21**.

When **21** was treated with conc sulphuric acid, or with 3% NaOH solution, followed by acidification, it was converted into **25**, the structure of which was derived from analytical data, IR spectra and the absence of a singlet around δ2·2 for ring CH in its NHR spectrum. The ease with which **21** was cyclised into **25** can be rationalized in terms of increased reactivity of the ring CH, induced by the presence of the adjacent cyano group, (*cf* Ref 17).

It is interesting to report here that the cyclization of **21** into **25** constitutes a new way for the preparation of the biologically active[17-19] pyrrolo[1.2 - b]pyrazole ring system. Only resently[20] has the synthesis of the alkaloid "Whitasomnine" (a pyrrolo[1.2 - b]pyrazole derivative) been reported. Further work on this matter is being carried out to explore the synthetic potentialities of compound **25**.

EXPERIMENTAL

All m. ps were determined on a micro hot stage and are uncorrected. The IR spectra were recorded with a Hitachi Grating Infrared Spectrometer Model EPI–G3. UV spectra were measured, in water, with a Hitachi 124 spectrophotometer.

5-Amino-4 - cyano-1-β - cyanoethyl-3 - cyanomethyl-pyrazole (**3**):

(1) *From the reaction of* **2** *with* **1**. A mixture of **2** (25 ml) and **1** (33 g) in EtOH (200 ml) was refluxed for 1 h. The mixture was then left to cool gradually to room temp. The solvent was removed *in vacuo* and the remaining oily product was dissolved in hot water. The solid product, obtained on standing, was collected by filteration and crystallized from water.

Compound **3**, colourless crystals, m.p. 161°; yield 17·8 g. IR: 3380, 3320 (NH_2 vibration); 2940, 2920, 2900 (3 CH_2); 2240 (unconjugated cyano); 2200 (conjugated cyano) and 1660 cm^{-1} (NH_2 deformation). (Found: C, 54·29; H, 4·15; N, 41·77. Calcd for $C_8H_8N_6$: C, 53·99; H, 4·03; N, 41·98)%; UV: no maxima above 220 nm.

(2) *From* **7** *and acrylonitrile*. A soln of **7** (2·0 g) in pyridine (80 ml) and water (20 ml) was treated with acrylonitrile (1·0 ml) and the mixture was refluxed for 4 h. The solvent was then removed *in vacuo* and the remaining residue was dissolved in hot water. The solid product, obtained on standing, was collected by filtration and proved (m.p. and mixed m.p.) to be **3**, yield 2·0 g.

(3) *From* **8** *and* **1**. A soln of **8** (20 g) in EtOH (200 ml) was treated with **2** (25 ml). The mixture was treated as described under **1** and the reaction product (25 g) was identified as **3**. Identity was carried out by m.p. and mixed m.p. determination and by IR.

3-Cyano-2-cyanomethyl - 4,5,6,7 - tetrahydropyrazolo[1.5 - a]*pyrimidin - 5-one* (**6**)

(1) *From* **3**. Compound **3** (2·0 g) was treated with 1% NaOHaq (100 ml) and the mixture was heated to boiling and the resulting soln was kept at room temp for 3 h. The mixture was neutralized with HCl and then the solvent was removed *in vacuo*. The resulting solid product was dissolved in little hot water and left to cool. The crystals, so formed, were collected by filtration and recrystallized from water.

Compound **6**, colourless crystals, m.p. 225°; yield 1·1 g;

IR: 3200, 3050 (NH); 2970, 2920, 2895 (3 CH_2); 2240 (unconjugated cyano), 2205 (conjugated cyano) and 1680 cm^{-1} (CO); UV max λ 248 nm. (Found: C, 53·63; H, 3·63; N, 34·64. Calcd for $C_6H_7N_3O$: C, 53·73; H, 3·51; N, 34·81%).

(2) *From* **7** *and ethyl acrylate.* To a soln of **7** (2·0 g) in pyridine (60 ml) and water (10 ml) ethyl acrylate (2·0 ml) was added and the mixture was refluxed for 10 h. The solvent was removed *in vacuo* and the resulting oily product was dissolved in hot water and left to cool. The solid product, so formed, was identified (mp and mixed mp) as **6**, yield 1.2 g.

2-*Acetamido*-3 - *carboxamido* - 4,5,6,7 - *tetrahydropyrazolo*[1.5 - a]*pyrimidine* (**9**)

A mixture of **3** (3·0 g) with conc H_2SO_4 (2·0 ml) was kept at room temp for 1 h. The mixture was then diluted with water (20 ml), neutralized with dil NH_4OH aq and evaporated *in vacuo* to nearly ⅓ of its volume. The solid product, obtained on cooling the mixture, was collected by filtration and crystallized from water.

Compound **9** formed colourless crystals mp 300°; yield 2·2 g; IR: 3397, 3320, 3200 (NH_2 vibrations); 1705, 1670–1660 (CO); 1650–1630 cm^{-1} (NH_2 deformations).

5-*Hydroxy*-2,3,6,7,8,9-*hexahydropyrido*[3:4:3':4']*pyrazolo*[1,5 - a]*pyrimidin* - 3,7-*dione* (**10**)

To a mixture of AcOH acid (30 ml) and HCl (8·0 ml), 3·0 g of **3** was added and the mixture was refluxed for 3 h. The solvent was removed *in vacuo* and the residue was treated with a little cold water. The solid product, which separated on standing, was collected by filtration and crystallized from AcOH.

Compound **10** formed yellowish white crystals m.p. 300°; yield 2·7 g; IR: 3590 (OH); 3378, 3170, 3050 (NH group) and 1745–1690 cm^{-1} (CO groups). (Found: C, 48·94; H, 3·82; N, 24·87. Clacd for $C_9H_8N_4O_3$: C, 49·09; H, 3·66; N, 24·45%).

3-*Amino*-2-β *carboxyethyl*-4 *hydroxy*-6,7 *dihydropyrazolo*[3.4 - c]*pyridin*-6 - *one* (**11**)

To a mixture of AcOH (40 ml), water (20 ml) and HCl (10 ml; 37·5) 2·0 g of **3** was added, the mixture was refluxed for 16 h. The solvent was then removed *in vacuo* and the remaining solid product was boiled with water (100 ml) and filtered quickly while hot. The insoluble part (1·0 g) was crystallized from AcOH and identified (IR) as **10**.

On cooling the filtrate, white crystals were separated and these were collected and recrystallized from water to yield 0·9 g of **11** m.p. 300°; IR: 3580 (OH): 3370, 3190, 3050 (NH_2 vibration); 1720, 1715–1705, 1680 (CO groups) and 1620 cm^{-1} (NH_2 deformation). (Found: C, 45·52; H, 4·19; N, 23·71. Calcd for $C_9H_{10}N_4O_4$: C, 45·38; H, 4·23; N, 23·52%).

Compound **11** was also formed on treatment of **10** with aqueous AcOH and HCl mixture under the experimental conditions described above.

2-*Benzylidene*-5 - *hydroxy* - 2,3,7,8,9 - *hexahydropyrido*[3:4:3':4']*pyrazolo*[1.5 - a]*pyrimidine* - 3,7-*dione* (**12**)

A suspension of **10** in AcOH (40 ml) was treated with benzaldehyde (1·0 ml) and KOAC (4·0 g) and the mixture was refluxed for 3 h. The mixture was then cooled and diluted with water. The solid product, formed on a standing, was collected by filtration and crystallized from ACOH to yield 1·0 g of **12**, yellow crystals m.p. 300. (Found: C, 61·94; H, 3·94; N, 18·00. Calcd for $C_{16}H_{12}N_4O_3$: C, 62·33; H, 3·92; N, 18·18%); IR: 3190, 3055 (NH_2); 1715–1690 cm^{-1} (CO groups).

3-*Amino*-7 - *benzylidene*-2-β - *carboxyethyl*-4 - *hydroxy*-6,7 - *dihydropyrazolo*[3,4 - c]*pyridine*-6-*one* (**13**)

A suspension of **11** (2·0 g) in EtOH (60 ml) was treated with benzaldehyde (1·0 ml) and two drops of piperidine. The mixture was refluxed for 16 h and then left to cool at room temp. The crystals, separated on cooling, were filtered off and recrystallized from dimethylformamide:

Compound **13** formed yellow crystals, m.p. > 300°, yield 1·0 g; IR: 3370, 3225, 3050 (NH_2 vibration); 1720, 1700–1685 (CO groups) and 1640 (NH_2 deformation) cm^{-1}. (Found: C, 58·74; H, 4·33; N, 17·36. Calcd for $C_{16}H_{14}N_4O_4$: C, 58·89; H, 4·32; N; 17·17%).

When compound **13** was refluxed in AcOH for 3 h it was quantitatively converted into **12** (identity was carried out by IR spectra).

5-*Hydroxy*-2 - *phenylazo* - 2,3,6,7,8,9 - *hexahydropyrido*[3:4:3':4']*pyrazolo*[1.5 - a]*pyrimidin* - 3,7-*dione* (**14**)

To a soln of **10** (3·0 g) in dioxane (80 ml) was added 10% K_2CO_3aq (80 ml). The mixture was cooled to 0° and gradually treated with a soln of benzene–diazonium chloride prepared from 1 ml of aniline). The mixture was left in a refrigerator for 10 h and then diluted with water. The solid product, so formed, was collected by filtration and was crystallized from dimethylformamide to yield 2·2 g of **14**, golden yellow crystals m.p. > 300°; IR: 35600, 3500 (OH); 3180, 3040 (NH); 1710–1665 (CO) and 1610 cm^{-1} (C═N). (Found: C, 55·46; H, 4·08; N, 26·171. Calcd. for $C_{14}H_{12}N_6O_3$: C, 55·55; H, 3·73; N, 25·92%).

3,5-*Diamino*-1-(β - *cyanoethyl*)-4 - *phenylazopyrazole* (**18**)

A mixture of **18** (2·0 g) and (β-cyanoethylhydrazine (1·0 ml) was heated at 120° (bath temp) for 3 h. The mixture was then allowed to cool and dissolved in EtOH. The crystals separated out on cooling were recrystallized form EtOH and identified' (m.p. and mixed mp) as XVIII, yield, 2·0 g.

1,2-*Dihydro*-5 - *hydroxy*-3 - *phenylazopyrazolo*[1.5 - a]*pyrimidin*-2 - *one* (**16**)

To a suspension of **18** (2·0 g) in AcOH (30 ml), 27·5% HCl (2 ml) was added and the mixture was refluxed for 3 h. The solid product was collected by filtration while the soln was still hot and crystallized from dimethylformamide and proved to be **16**' by IR, yield, 1·8 g.

3-*Amino*-4-*cyano*-1-β - *cyanoethylpyrazole* (**21**)

To a sol of **20** (10 g) in EtOH (100 ml), 10 ml of **2** was added. The mixtrue was heated under reflux for 2 h. The solvent was then removed *in vacuo* and the remaining solid product was crystallized from water.

Compound **21** formed colourless crystals, m.p. 200° (dec) yield 1475 g; IR: 3395, 3338, 3180 (NH_2 vibration); 2970, 2920 (CH_2), 2230 (unconjugated cyano); 2205 (conjugated cyano) and 1640 cm^{-1} (NH_2 deformation). (Found: C, 51·91; H, 4·39; N, 43·27. Calcd for $C_5H_7N_5$: C, 52·16; H; 4·39; N, 43·46%).

5-*Amino*-4 - *cyano*-1-β - *cyanoethylpyrazole* (**22**)

To a sol of **20** (13 g) in pyridine (100 ml) and water (50 ml), acrylonitrile (6 ml) was added. The mixture was

then treated woth one drop of conc KOHaq and the remaining oily product was dissolved in hot EtOH. On cooling, white crystals were separated and these were collected and recrystallized from EtOH to yield 13 g of **22**, mp 131°; IR: 3390, 3340, 3180 (NH_2 vibration); 2980, 2925 ($2\,CH_2$); 2235 (unconjugated cyano); 2210 (conjugated cyano) and 1630 cm^{-1} (NH_2 deformation). (Found: C, 51·98: H, 4·39; N, 43·29. Calcd for $C_7H_7N_3$: C, 52·16; H, 4·39; N, 43·46%).

2-Amino-3 - carboxamido-5,6 - dihydropyrrolo[1.2 - b]pyrazol-4 - one (**25**)

(1) *By the action of dilute sodium hydroxide solution on* **21**. A mixture of **21** (3 g) and 3% NaOHaq (100 ml) was refluxed until no more ammonia odour could be detected (3 h). The mixture was then left to cool; neutralized with dil HCl and evaporated *in vacuo*. The remaining solid product was rinsed with a little water and collected by filtration to yield 2·4 g of **25** which was recrystallized from water.

Compound **25** formed colourless crystals mp 294°; IR: 3390, 3320, 3170, 3080 (NH_2 vibrations); 1695, 1670 (CO vibrations); 1620 cm^{-1} (NH_2 deformation). (Found: C, 46·06; H, 5·51; N, 31·28. Calcd for $C_7H_{10}N_4O_2$: C, 46·15; H, 5·52; N, 30·96%).

(2) *By the action of concentrated sulphuric acid on* **21**. A mixture of **21** (3 g) and conc 98% H_2SO_4 (2 ml) was kept at room temp for 2 h. The mixture was then diluted with water (20 ml) and neutralized by the gradual addition of dil NH_4OHaq. The mixture was then evaporated *in-vacuo* and the remaining solid product was dissolved in the least amount of hot water and left to cool. The crystals, separated on standing, were collected and identified (m.p. and mixed m.p.) as **25**, yield 2·3 g.

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