

REACTIONS WITH β -CYANOETHYLHYDRAZINE—II

SYNTHESIS OF SOME 4,5,6,7-TETRAHYDROPYRAZOLO[1,5-a]PYRIMIDINE DERIVATIVES

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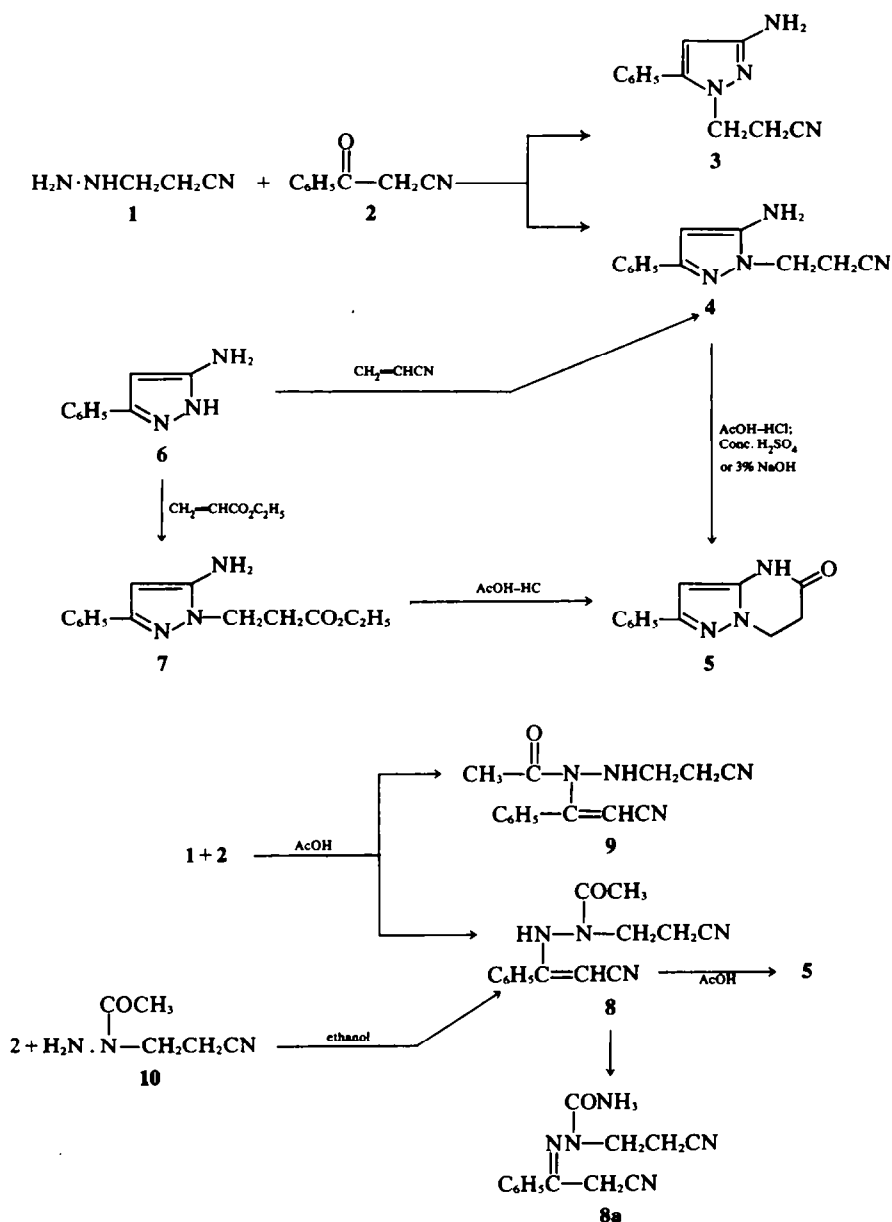
Abstract— β -Cyanoethylhydrazine 1 reacts with benzoylacetonitrile 2 in refluxing ethanol to yield 5-amino-1- β -cyanoethyl-3-phenylpyrazole 4; in acetic acid acetyl- β -cyanoethylhydrazone 8 was obtained. Compounds 4 and 8 were readily cyclized into 2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-5-one 5 by acetic acid-hydrochloric acid. 3-p-Chlorophenylazo-2-phenyl-4,5,6,4-tetrahydropyrazolo[1,5-a]pyrimidin-5-one 15 was synthesized by the action of 1 on the p-chlorophenylazo derivative of 2 and cyclization of the resulting aminopyrazole 12 by concentrated sulphuric acid. The arylidene derivative of benzoylacetonitrile 16 reacts with 1 in acetic acid to yield the correspondings β -cyanoethylhydrazones 17. Cyclization of 17 with acetic acid-hydrochloric acid led to the formation of the pyrazolo (1,2-b) pyrazole derivative 19. On the other hand, the 1- β -carboxyethylpyrazole derivative 20 was obtained by the action of 3% aqueous NaOH.

Pyrazolo[1,5-a]pyrimidines have recently become of increasing importance owing to the reported antitumour,¹⁻³ anti-inflammatory and antipyretic activity of many of its derivatives.^{4,5} Recently a new route for the synthesis of this class of compounds, via the reaction of malononitrile and its derivatives with β -cyanoethylhydrazine, has been reported by one of us.⁶ In continuation of this work the reaction of benzoylacetonitrile, and its derivatives with β -cyanoethylhydrazine 1 was investigated as a possible route for the synthesis of pyrazolo[1,5-a]pyrimidines. In this manner, when benzoylacetonitrile 2 was treated with 1, in refluxing ethanol, a product of molecular formula $C_{12}H_{12}N_4$ was obtained. The IR spectrum of the product revealed the presence of an unconjugated cyano and amino groups. Two structures were possible for this product, 3 and 4. Structure 3 was eliminated since the reaction product was readily cyclized into 2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-5-one 5 on treatment with 3% NaOH solution, concentrated sulphuric acid or acetic acid-hydrochloric acid mixture. Structure of compound 5 was established by its synthesis via cyclization of ethyl 5-amino-1- β -carboxyethyl-3-phenylpyrazole 7 by the action of acetic acid-hydrochloric acid mixture. Compound 7, in turn, was obtained by the action of ethyl acrylate on 3-phenyl-5-aminopyrazole 6. Further evidence for structure 4, proposed for the reaction product of 1 and 2 was obtained by its synthesis via the action of acrylonitrile on 6. That cyanoethylation of 6 has involved ring N-1 and not the amino group or ring N-2 is assumed by analogy with the

reported behaviour of aminopyrazoles toward activated double bond systems.⁶⁻¹¹

When the reaction of 1 with 2 was conducted in acetic acid, a product of molecular formula $C_{14}H_{14}N_4O$ was obtained. When this compound was refluxed for two hours with acetic acid, it was converted almost quantitatively into 5. The IR spectrum of $C_{14}H_{14}N_4O$ indicated the presence of NH, unconjugated and conjugated cyano groups and the amide group. Two structures seemed possible for this product, 8 and 9. The formation of this acetylhydrazone may be assumed to take place via acylation of 1, by the action of acetic acid, followed by condensation with the carbonyl group in 2. From consideration of the behaviour of 1 on acylation¹² the product of reaction of 1 and 2 in acetic acid (molecular formula $C_{14}H_{14}N_4O$) seemed most likely to be 8. However, independent chemical proof seemed necessary. To establish structure 8, 2 was treated with 1-acetyl-1- β -cyanoethylhydrazine 10 in ethanol and the product obtained was identical with the reaction product of 1 and 2 in acetic acid thus establishing structure 8 for this product. Structure 8 was preferred for this product based on its IR data, rather than the tautomeric 8a.

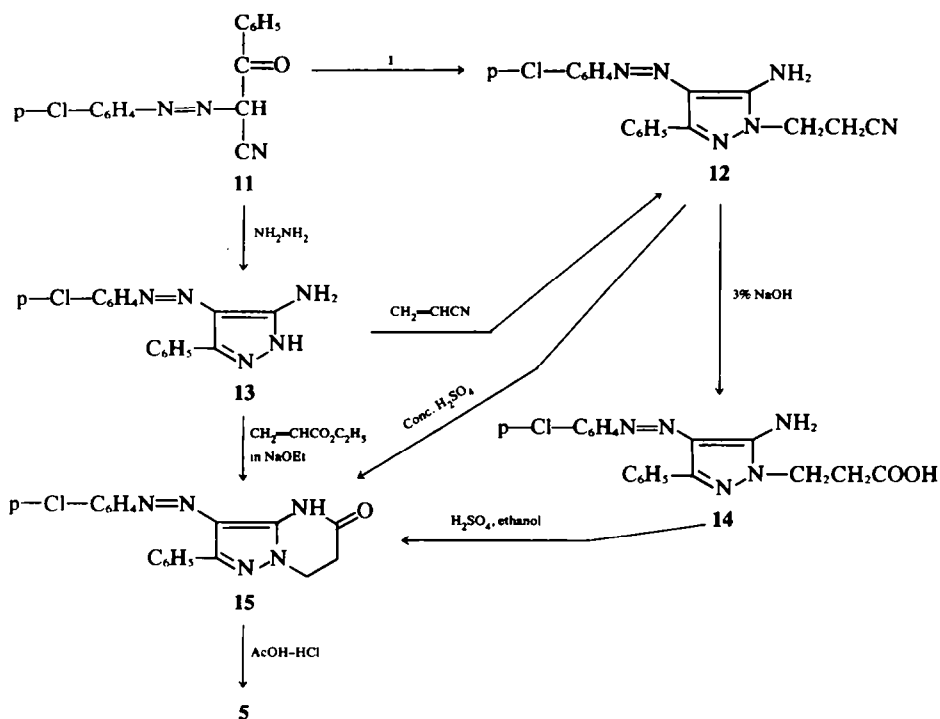
When 2,3-diketo-3-phenylpropionitrile 2-p-chlorophenylhydrazone 11 was treated with 1,5-amino-1- β -cyanoethyl-4-p-chlorophenylazopyrazole 12 was formed, synthesised via the action of acrylonitrile on 5-amino-4-p-chlorophenylazo-3-phenyl-pyrazole 13. Attempted cyclization of 12 into a pyrazolo[1,5-a]pyrimidine, by the action of 3% NaOH solution, as for cyclization of 4 into 5, gave 5-amino-1- β -carboxyethyl-



4-p-chloro-phenylazopyrazole 14. However, when 12 was treated with acetic acid-hydrochloric acid mixture or with concentrated sulphuric acid, it gave 5-ketopyrazolo[1,5-a]pyrimidine derivative 15, also obtained by cyclization of 14 by the action of hot ethanol and conc. H_2SO_4 . Structure proposed for 15 was established by its synthesis via the action of ethyl acrylate on 12 in refluxing ethanolic sodium ethoxide solution. Moreover, when 15 was refluxed for a long time with aqueous acetic acid-hydrochloric acid mixture it was converted to 5.

The behaviour of arylidenebenzoylacetonitrile 16 with 1 was also investigated as a possible route for the synthesis

of pyrazolo[1,5-a]pyrimidines. Whereas scission of the double bond in 16 was reported to take place by the action of hydrazines in basic media, the formation of 3,5-diaryl-3-pyrazolines was reported to take place in acid media.¹³⁻¹⁶ Intermediate phenylhydrazone (17; $\text{Ar} = \text{C}_6\text{H}_4\text{NO}_2\text{-p}$) was isolated in the reaction of (16; $\text{Ar} = \text{C}_6\text{H}_4\text{NO}_2\text{-p}$) with phenylhydrazine.¹⁴ When (16; $\text{Ar} = \text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$) was treated with 1 in acetic acid, 17 or the possible isomeric 3-pyrazoline 18 was obtained. Structure 17 was preferred over 18 for the reaction since it was coloured and showed UV absorption which was closely similar to that of (17; $\text{Ar} = \text{C}_6\text{H}_4\text{NO}_2\text{-p}$). The latter shows two maxima at 386



and 318 nm. The isomeric 3-pyrazoline structure **18** would be colourless having UV absorption similar to that reported for 3-pyrazolines.^{18,19} Attempts to cyclize **17** into isomeric 3-pyrazoline or into 5-amino-4-*p*-dimethylaminobenzylidene-3-phenylpyrazole have led to the formation of the pyrazolo[1,2-*a*]pyrazole derivative **19** or the carboxylic acid **20** depending on the reaction conditions. Thus, when **17** was treated with acetic acid-hydrochloric acid mixture compound **19** was obtained, whilst treatment of **17** with 3% NaOH solution has led to the formation of **20**. Compound **20** was recovered unchanged after being refluxed for 30 hours with acetic acid, indicating that cyclization of **17** into **19** does not proceed via intermediate formation of **20** but most likely via cyclization into **18** followed by addition of ring N-2 electron pair to the cyano group and hydrolysis of the intermediate ketimine (cf. Scheme 1). Structure assignment for compounds **19** and **20** were based on analytical and IR data.

EXPERIMENTAL

All melting points are uncorrected; IR spectra were recorded in KBr on a Perkin-Elmer 337 spectrophotometer; UV spectra were measured in ethanol, on a Beckman DK-2 spectrophotometer.

5-Amino-1- β -cyanoethyl-3-phenylpyrazole **4**

From **1** and **2**. A suspension of **2** (14.4 g) in EtOH (150 ml) was treated with 10 ml of **1**. The reaction mixture was refluxed for three hours. The solvent was then removed on a water-bath and the remaining oily product was then treated with water and dilute hydrochloric acid. The resulting solid product was filtered off and crystallized from EtOH-H₂O mixture to yield 20 g of **4**; colourless crystals m.p., 142°; IR: 3375, 3320, 3185 cm^{-1} (NH vibrations); 2255 cm^{-1} (unconjugated cyano) and 1655 cm^{-1} (NH₂ deforma-

tion). Found: C, 67.91; H, 6.12; N, 26.31. Calc for $\text{C}_{12}\text{H}_{12}\text{N}_4$: C, 67.90; H, 5.70; N, 26.40%.

From 5-amino-3-phenylpyrazole **6** and acrylonitrile. A solution of **6** (2.0 g) in pyridine (40 ml) and water (10 ml) was treated with acrylonitrile (1.0 ml) and the reaction mixture was refluxed for four hours. The solvent was then removed by vacuo and the remaining residue was dissolved in hot 50% aqueous ethanol. The solid product, obtained on standing, was collected by filtration and proved (m.p. and mixed m.p.) to be **4**; yield 2.0 g.

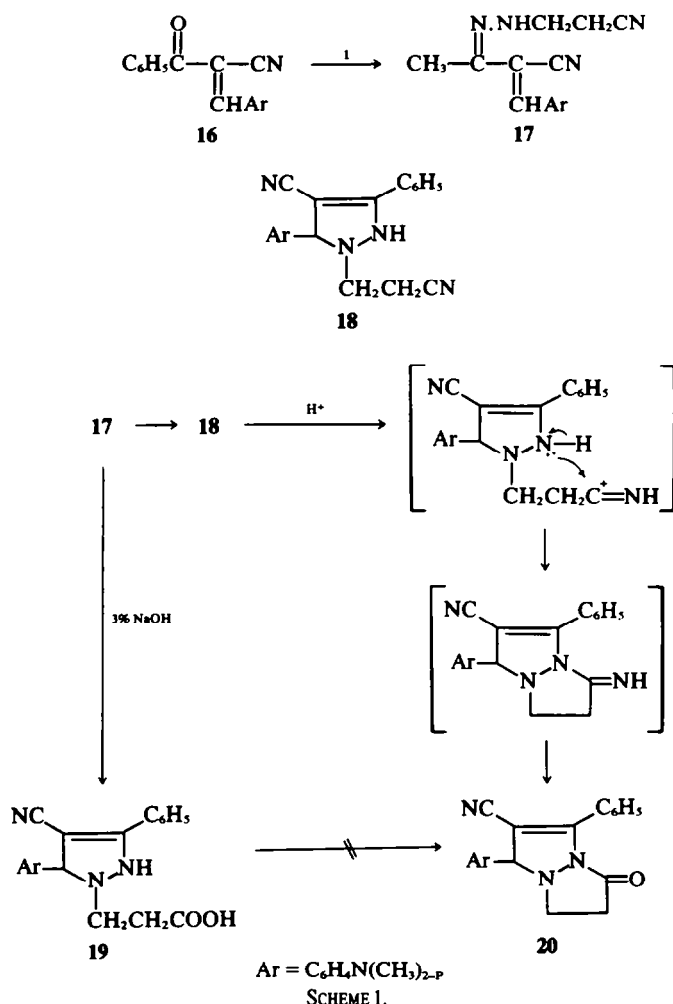
4,5,6,7-Tetrahydro-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-one (**5**)

From **4** and acetic acid-hydrochloric acid mixture. A suspension of **4** (2.0 g) in AcOH (30 ml) was treated with 5 ml of concentrated HCl (37.5%). The reaction mixture was refluxed for two hours. The solvent was removed by vacuo and the remaining solid product was treated with little water and left to stand. The product, so formed, was collected by filtration and crystallized from water to yield 1.5 g of **5**; mp 248°; IR: 3190, 3120 cm^{-1} (NH); 3060, 3040 cm^{-1} (2CH₂); 1700 cm^{-1} (ring CO group). Found: C, 67.60; H, 5.32; N, 19.61. Calc. for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}$: C, 67.59; H, 5.20; N, 19.71%.

From **4** and concentrated sulphuric acid. A mixture of **4** (3.0 g) and H₂SO₄ (2.0 ml; 98%) was kept at room temperature for two hours. The reaction mixture was diluted with 20 ml. of water and left to stand. The solid product was collected by filtration and identified (by IR and by m.p. and mixed m.p.) as **5** (yield 2.7 g).

By the action of dilute sodium hydroxide on **4**. A mixture of **4** (3.0 g) and NaOH solution (100 ml; 3%) was refluxed until no more ammonia odour could be detected (3 h). The reaction mixture was then left to cool; neutralized with dilute hydrochloric acid and left to stand at room temperature. The solid product, formed on standing, was filtered off and identified (m.p. and mixed m.p.) as **5**.

From 5-amino-1- β -ethoxycarbonyl-3-phenylpyrazole **7**. A suspension of 2.0 g of **7** (see below) in AcOH (20 ml) was treated with 3 ml of HCl (37.5%) and the reaction mixture was refluxed for 3 h. The solvent was then removed by vacuo. The remaining solid



product was treated in the manner described before and the product (1.8 g) was identified (m.p. and mixed m.p.) as 5.

From 2-phenyl-3-ketopropionitrile 3-acetyl- β -cyanoethyl-hydrazone 8. A solution of 2.0 g 8 (see below) in 30 ml acetic acid was treated with 5 ml of water. The reaction mixture was refluxed for 3 h. The solvent was removed by vacuo and the remaining solid was treated as described above and identified (m.p. and mixed m.p. and by IR) as 5 (yield 1.8 g).

5-Amino-1- β -ethoxycarbonyl-3-phenylpyrazole 7. A solution of 6 (2.0 g) in pyridine (40 ml) and water (10 ml) was treated with ethyl acrylate (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 ethanol. The solid product, obtained on cooling, was collected by filtration and recrystallized from ethanol to yield 2.0 g of 7; m.p. 94°; IR: 3360; 3300 cm^{-1} (NH_2 vibration); 1715 cm^{-1} (ester CO) and 1640 cm^{-1} (NH_2 deformation). Found: C, 65.00; H, 6.60; N, 16.12. Calc. for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2$; C, 64.84; H, 6.61; N, 16.21%.

3-Phenyl-3-ketopropionitrile-3-acetyl- β -cyanoethyl-hydrazone 8:

From 2 and 1 in acetic acid. A solution of 14.5 g of 2 in acetic acid (100 ml) was treated with 1 (10 ml). The reaction mixture was refluxed for 30 min and then poured onto ice cold water. The solid product, separated on standing, was filtered off and crystallized

from ethanol to yield 15 g of 8; m.p. 131°; IR: 3260 cm^{-1} (NH); 2230 and 2200 cm^{-1} (unconjugated and conjugated cyano) and 1670 cm^{-1} (acyl CO). Found: C, 66.30; H, 5.88; N, 21.82. Calc. for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}$; C, 66.12; H, 5.55; N, 22.04%.

From 2 and acetyl-1- β -cyanomethylhydrazine 10. A solution of 2 (14.5 g) in ethanol (150 ml) was treated with 10 (14.0 g). The reaction mixture was refluxed for 3 h. The solvent was then removed in vacuo and the resulting solid product was treated with water, collected by filtration, crystallized and identified (m.p. and mixed m.p.) as 8.

5-Amino-1- β -cyanoethyl-4-*p*-chlorophenylazo-3-phenylpyrazole 12:

From 2-*p*-chlorophenylhydrazone-3-keto-3-phenylproionitrile 11 and 1. A suspension of 11 (18.5 g) in ethanol (200 ml) was treated with 1 (10 ml). The reaction mixture was refluxed for 10 h. The solvent was removed in vacuo and the remaining oily product was triturated with ethanol and left to cool. The crystals, separated on standing were collected by filtration and crystallized from ethanol to yield 23 g of 12; mp 209°; IR: 3380 and 3280 cm^{-1} (NH_2 vibrations); 2260 cm^{-1} (unconjugated cyano) and 1620 cm^{-1} (NH_2 deformation). Found: C, 68.50; H, 4.70; N, 26.60; Cl, 11.00. Calc. for $\text{C}_{14}\text{H}_{13}\text{ClN}_4$; C, 68.56; H, 4.75; N, 26.65; Cl, 11.26%.

From 5-amino-4-*p*-chlorophenylazo-3-phenylpyrazole 13 and

acrylonitrile. The experimental procedure described for the cyano-ethylation of 6 was adopted, but 20 h reflux were necessary for complete reaction. The solid product, obtained on treatment of the reaction mixture in a manner similar to that described before, was identified (m.p. and mixed m.p.) as 12 (yield 60%).

5-Amino-1- β -carboxyethyl-4-*p*-chlorophenylazo-3-phenyl-phenylpyrazole 14. A mixture of 12 (100 g) and ethanolic-aqueous sodium hydroxide solution (120 ml; 50% ethanolic solution containing 4.0 g of NaOH) was refluxed until no more ammonia odour was detected (6 h). The reaction mixture was allowed to cool and neutralized by the addition of acetic acid. The solid product, separated on dilution of the reaction mixture was collected by filtration and recrystallized from ethanol to yield 9.0 g of 14; m.p. 129°; IR: 3420, 3320 cm^{-1} (NH_2 vibration); 2800 cm^{-1} (OH dimer); 1700 cm^{-1} (carboxyl CO) and 1635 cm^{-1} (NH_2 deformation). Found: C, 58.27; H, 4.22; N, 18.76; Cl, 9.40. Calc. for $\text{C}_{18}\text{H}_{16}\text{ClN}_5\text{O}_2$: C, 58.14; H, 4.30; N, 18.84; Cl, 9.54%.

3-*p*-Chlorophenylazo-2-phenyl-4,5,6,6-tetrahydropyrazolo[1,5-*a*]pyrimidin-5-one 15

From 12 and acetic acid-hydrochloric acid mixture. The experimental procedure described previously for the cyclization of 4 into 5 by the same reagent was used and the resulting solid product was collected by filtration and crystallized from ethanol to yield 15; yellow crystals; mp 285°; yield 78%; IR: 3270, 3045 cm^{-1} (NH vibration), 2940, 2920 cm^{-1} (2CH_2) and 1700 cm^{-1} (ring CO). Found: C, 61.29; H, 4.06; N, 20.21; Cl, 9.80. Calc. for $\text{C}_{18}\text{H}_{14}\text{ClN}_4\text{O}$: C, 61.46; H, 3.98; N, 19.91; Cl, 10.09%.

From 13 and concentrated sulphuric acid. The experimental conditions used for cyclization of 4 into 5 by the action of the same reagent were adopted and the product was identified (m.p. and mixed m.p. and by IR) as 15 (yield 80%).

From 14 and ethanol-concentrated sulphuric acid mixture. A suspension of 14 (2.0 g) in ethanol (50 ml; 99%) was treated with 3 ml of conc. H_2SO_4 . The reaction mixture was refluxed for 15 h. The solvent was removed in vacuo and the remaining product was triturated with water, collected by filtration and crystallized from ethanol. The crystals, so formed, were identified as 14 (yield 1.2 g).

From 13 and ethyl acrylate. To a sodium ethoxide solution (prepared from 3.0 g of sodium metal and 150 ml of absolute ethanol) 5.0 ml of ethyl acrylate and 10.0 g of 13 were added. The reaction mixture was refluxed for 25 h. The solvent was then removed in vacuo and the remaining solid product was dissolved in little water and then acidified with concentrated hydrochloric acid. The solid product, so formed, was filtered off and identified (m.p. and mixed m.p.) as 15 (yield 70%).

Action of acetic acid-hydrochloric acid mixture on 15. A suspension of 15 (10.0 g) in acetic acid (80 ml) was treated with hydrochloric acid (10 ml; 37.5%). The reaction mixture is then treated with 30 ml of water and refluxed for 30 h. The solvent was removed in vacuo and the reaction product was identified (m.p. and mixed m.p. and by IR) as 5 (yield 5 g).

(*p*-Dimethylamino)benzylidene benzoylacetonitrile β -cyano-ethylhydrazone 17. To a solution of 16 (0.2 mole) in acetic acid (150 ml) 0.2 mole of 1 was added. The reaction mixture was refluxed for two hours, left to cool, and diluted with water. The solid product, obtained on standing, was collected by filtration and crystallized from ethanol. Compound 17 formed colourless

crystals m.p. 184°C; yield 58%. IR: 3420, 3400 cm^{-1} (NH vibration); 2850, 2900 cm^{-1} (CH_2); 2245 cm^{-1} (unconjugated cyano) and 2270 cm^{-1} (conjugated cyano). UV: 322 and 386 nm. Found: C, 73.20; H, 5.85; N, 20.09. Calc. for $\text{C}_{21}\text{H}_{21}\text{N}_5$: C, 73.44; H, 6.16; N, 20.39%.

2-Cyano-1-*p*-dimethylamino-5,6-dihydro-3-phenylpyrazolo[1,2-*a*]pyrazole 19. 17 was treated with acetic acid-hydrochloric acid mixture using the same experimental procedure described previously for cyclization of 4 to 5 by the same reagent. The product obtained was crystallized from ethanol. Compound 19 formed colourless crystals m.p. 188°C; yield 80% IR: 3040–2950 cm^{-1} (CH_2 and CH_3); 2230 cm^{-1} (conjugated cyano) and 1710 cm^{-1} (ring CO). Found: C, 73.11; H, 5.67; N, 16.10. Calc. for $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}$: C, 73.23; H, 5.86; N, 16.27%.

4-Cyano-1-carboxyethyl-5-*p*-dimethylaminophenyl-3-phenyl-3-pyrazoline 19. 17 was treated with 3% sodium hydroxide using experimental procedure similar to that described previously for the reaction of 4 or 12 with the same reagent. The reaction product was crystallized from ethanol-water mixture to yield 19; colourless crystals, m.p. 250°; yield 60% IR: 3320 cm^{-1} (NH); 2850, 2820 (OH dimer); 2230 cm^{-1} (conjugated cyano) and 1670 cm^{-1} (CO). Found: C, 69.80; H, 6.00; N, 15.30. Calc. for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_2$: C, 69.59; H, 6.12; N, 15.46%. Compound 19 was recovered almost unchanged after being refluxed with acetic acid for 20 h.

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