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CHEMICAL BEHAVIOUR OF 2-AMINO-4-H-PYRAN

2-Amino-3,5-dicyano-4,6-diphenyl-4-H-pyran (**III**) was synthesized via the action of malononitrile on α -cyanoketone **I**. Compound **III** reacted with acetic anhydride to yield the pyrano-pyrimidine derivative **VI**. 3,5-Dicyano-2,4,6-triphenyl-pyridine (**X**) was the only isolable product on treatment of **III** with formamide. On the other hand, the pyrano-[2,3:5',6']-pyrazolo [1,5-a] pyrimidine derivative **XII** could be obtained when **III** was treated with 5-amino-3-methyl-4-phenylpyrazole.

1 — INTRODUCTION

In previous work[1], we have reported that α -cyanoketone **I** reacted with malononitrile to yield the Michael type adduct **II**.

However, QUINTEIRO *et al*[2,3] have reported later that **I** reacted with malononitrile under almost the same conditions to yield the isomeric 2-amino-3,5-dicyano-4,6-diphenyl-4-H-pyran (**III**). In order to establish whether structure **II** or isomeric **III** was formed on reaction of **I** with malononitrile and also because of interest in the chemistry of cyclic β -enamines[4,5], it occurred to us of value to investigate the chemical behaviour of this reaction product. Thus, it has been found that **I** reacts with malononitrile to yield an adduct, the $^1\text{H-n.m.r.}$, i.r. and analytical data for which indicated that it has the cyclic structure **III**.

Compound **III** reacted with acetic anhydride to yield a product for which structure **IV**, **V** or **VI** seemed possible (cf. Chart 1). The cyclic structure **IV** could be excluded based on i.r. spectrum which revealed only one cyano band at 2220 cm^{-1} . If this product has structure **IV** it would exhibit another absorption band in the range observed for the enamine **III**. The benzoxazine structure **V** was

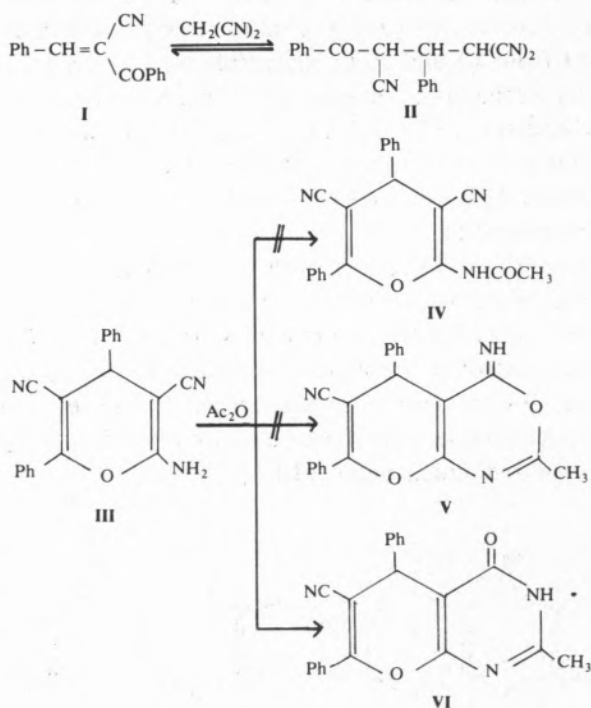


Chart 1

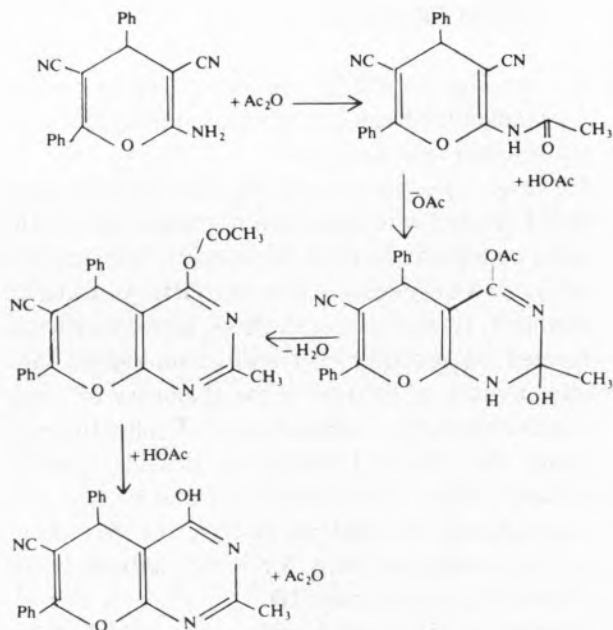
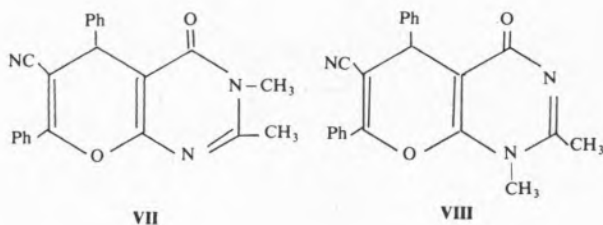


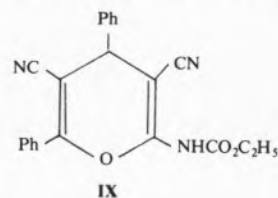
Chart 2

also eliminated based on the stability of the reaction product towards reagents reported to effect ready cleavage of benzoxazine rings[6,7]. Thus, the reaction product was recovered unaffected after treatment with aniline at 160° C or on heating with ethanolic hydrochloric acid. Structure **VI** was thus established for the reaction product. The formation of **VI** from **III** and acetic anhydride may proceed via the mechanism demonstrated in chart 2. However, conversion of **IV** which may form **VI** via oxazine **V** and its rearrangement or intermediate formation of amide derivative and elimination of water can not be overlooked.

Compound **VI** reacted with methyl iodide to yield the *N*-methyl derivative. Two possible isomeric structures for this compound were suggested (Cf. structures **VII** and **VIII**). Structure **VII** was established for the reaction product based on IR spectrum which revealed absorbance at much lower frequency than that anticipatable **VIII**[8].



Compound **III** reacted with ethoxycarbonyl isothiocyanate to yield the ethoxycarbonylamino derivative **IX**. The formation of **IX** from this reaction finds parallelism to the reported acylation of amines on treatment with the same reagents[9,10].



In contrast to the reported formation of fused pyrimidines on treatment of heterocyclic β -enamino esters with formamide, **III** reacted with formamide to yield 3,5-dicyano-2,4,6-triphenylpyridine **X**. The formation of this product may be assumed to proceed via decomposition of **III** to yield **I** by a reversal of the Michael addition.

Compound **I** then undergoes ylidenic bond cleavage by the effect of the media to yield benzoylacetonitrile which then condenses with **I** to yield a Knoevenagel type condensation product. The later reacts with formamide to yield the end product as shown in chart 3. This mechanism finds parallelism to the reported reaction of α,β -unsaturated ketones with benzoylacetonitrile in presence of acetamide to yield cyanopyridine derivatives[11].

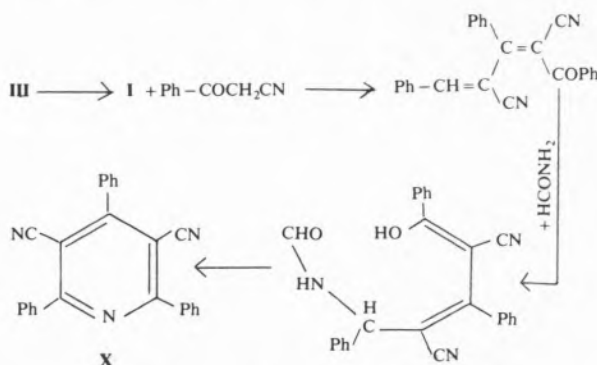


Chart 3

Similar to the reported behaviour of cyclic β -enamino nitriles towards the action of 5-amino-4-phenylpyrazole (**XI**)[4,5], compound **III** reacted with 3-methyl-4-phenyl-5-aminopyrazole (**XIa**) to yield the pyrano-[2,3:5',6']-pyrazolo[1,5-a] pyrimidine derivative **XII**. However, when **III** was treated with **XIb**, a product of molecular formula

$C_{25}H_{16}N_4$ was obtained. The same product was obtained on treatment of α -cyanoketone **II** with the same reagent under the same conditions. Structure **XIII** was thus suggested for this reaction product. The formation of **XIII** from **III** and **XIb** may be assumed to proceed via decomposition of **III** under the reaction conditions to yield **I** and **II**. The aminopyrazole adds to the activated double bond of **I** followed by cyclization via elimination of water. However, it seems quite possible that **I** first condenses with the exocyclic amino function in **XIb** to yield the Schiff base which then cyclizes via addition to the double bond (Cf. chart 4). The different chemical behaviour of compound **XIa** and **XIb** towards compound **III** can be rationalised in terms of the pronounced difference in basicity (pK_a s, 4.2 and 5.2 for **XIa** and **XIb** respectively)[12]. However, other factors (*c. a.* the thermodynamic control) can not be ruled out. This subject is now under investigation.

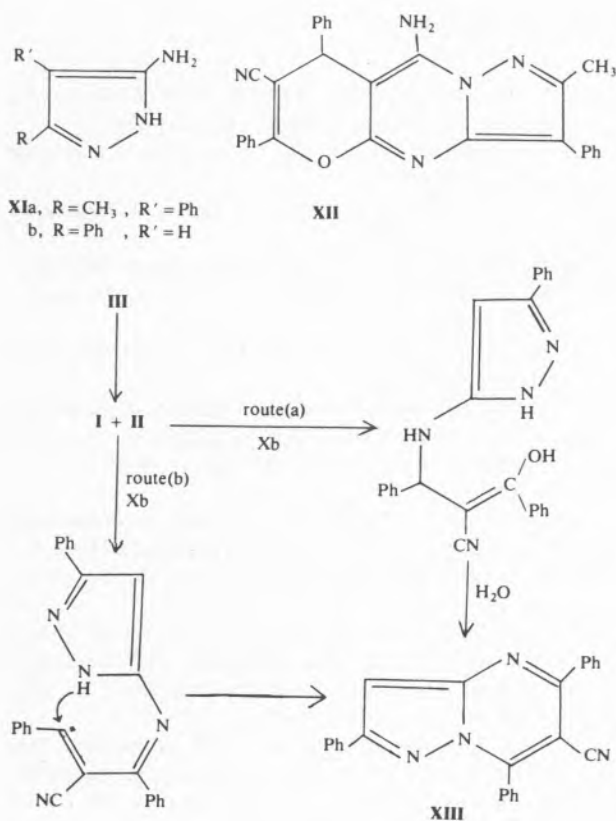


Chart 4

2 — EXPERIMENTAL

All melting points are uncorrected. i.r. spectra were measured (KBr) on a Pye-Unicam SP 1000. ^1H -n.m.r. were measured in DMSO on a Varian A 60 MHz using TMS as internal standard and chemical shifts are expressed as δ ppm.

2-Amino-3,5-dicyano-4,6-diphenyl-4-H-pyran (**III**)

To a solution of 6.6 g (0.1 mole) malononitrile in absolute ethanol (100 ml), α -cyanoketone (0.1 mole) and 1 ml of piperidine was added. The reaction mixture was boiled for 8 hours, then evaporated in vacuo. The remaining product was triturated with water and the resulting solid product was collected by filtration.

Compound **III** formed colourless crystals from ethanol, m.p. 168°C , yield 50%, i.r.: 1670 cm^{-1} (NH_2), 2220 and 2210 cm^{-1} (two conj. cyano groups), $3460, 3360\text{ cm}^{-1}$ (NH_2), ^1H -n.m.r., 4.66 (s, 1H, pyran 4H), 6.22 (s, 2H, NH_2) and 7.33 ~ 7.90 (m, 10H, aromatic CH).

$\text{C}_{19}\text{H}_{13}\text{N}_3\text{O}$ Calcd.: C, 76.2; H, 4.4; N, 14.0%; Found: C, 76.3; H, 4.3; N, 14.1%.

3-Cyano-2,4-diphenyl-6-methyl-4,5-dihydropyrano [2,3-d] pyrimidine (**VI**)

A solution of **III** (5 g) in acetic anhydride (50 ml) was heated under reflux for 4 hours, the solvent was then concentrated to quarter its original volume and left to cool, the solid product that separated on standing was collected by filtration. Compound **VI** formed colourless crystals from dioxane, m.p. 285°C , yield 49%, i.r.: $1660\text{--}1670\text{ cm}^{-1}$ (CO), 2220 cm^{-1} (conj. CN), $2500\text{--}3300\text{ cm}^{-1}$ (conjugately shielded NH), ^1H -n.m.r., 2.11 (s, 3H, CH_3), 4.66 (s, 1H, pyran 4H), 7.3–7.9 (m, 10H, aromatic CH) and 12.5 (s, 1H, NH).

$\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_2$ Calcd.: C, 73.9; H, 4.4; N, 12.3%; Found: C, 73.5; H, 4.5; N, 12.0%.

3-Cyano-6,7-dimethyl-2,4-diphenyl-4,5-dihydropyrano [2,3-d] pyrimidine (**VII**)

To a solution of 3.4 g of **VI** (0.01 mole) in acetone (100 ml), 3 g of potassium carbonate and 2.1 g of methyl iodide (0.015 mole) were added. The reaction mixture was refluxed for 3 hours, evaporated

till near dryness and then poured onto water. The resulting solid product was collected by filtration and washed well with water. Compound **VII** formed colourless crystals from ethanol-dioxane mixture, m.p. 238° C, yield 65%, i.r.: 1640 cm⁻¹ (C=C), 1665 cm⁻¹ (CO), 2950 cm⁻¹ (CH₃).

C₂₂H₁₇N₃O₂ Calcd.: C, 74.4; H, 4.8; N, 11.8%; Found: C, 74.1; H, 5.0; N, 12.2%.

3,5-Dicyano-4,6-diphenyl-2-ethoxycarbonylamino-4-H-pyran (**IX**)

To a solution of ethoxycarbonyl isothiocyanate (prepared from 0.1 mole of NH₄SCN and the appropriate quantity of ethylchloroformate as has been previously described[13] in 50 ml of dry dioxane. Compound **III** (3 g) was added, the reaction mixture was heated for 10 hours, evaporated under vacuo and the reaction product was collected by filtration.

Compound **IX** formed yellow crystals from dioxane, m.p. 160° C, yield 54%, i.r.: 1670 cm⁻¹ (CO), 2200, 2220 cm⁻¹ (two conj. cyano groups), 2980, 2940 and 2860 cm⁻¹ (CH, CH₂ and CH₃), 3200 and 3400 cm⁻¹ (NH).

C₂₂H₁₇N₃O₃ Calcd.: C, 71.1; H, 4.6; N, 11.3%; Found: C, 70.9; H, 4.4; N, 10.9%.

3,5-Dicyano-2,4,6-triphenylpyridine (**X**)

A solution of **III** (3 g) in formamide (20 ml) was heated under reflux for one hour. The reaction mixture was cooled, diluted with water and the solid product that separated was filtered.

Compound **X** formed pale yellow crystals from dilute dioxane, m.p. 214° C, yield 80%, i.r.: 2220 cm⁻¹ (CN).

C₂₅H₁₅N₃ Calcd.: C, 84.0; H, 4.2; N, 11.7%; Found: C, 83.6; H, 4.4; N, 12.0%.

5-Amino-3-cyano-8-methyl-2,4,7-triphenyl-4-H-pyran-[2,3:5',6']-pyrazolo [1,5-a] pyrimidine (**XII**)

To a solution of **III** (0.1 mole) in pyridine was added **XIa** (0.1 mole) and the reaction mixture was heated under reflux for 10 hours. The resulting solution was then evaporated, triturated with dilute HCl and the resulting solid was filtered.

Compound **XII** formed brownish red crystals from dioxane, m.p. > 300° C, yield 52%, i.r.: 1620 cm⁻¹ (C=C), 1640 cm⁻¹ (NH₂), 2240 cm⁻¹ (CN), 3360, 3490 cm⁻¹ (NH₂).

C₂₉H₂₁N₅O Calcd.: C, 76.5; H, 4.6; N, 15.4%; Found: C, 76.2; H, 4.8; N, 15.4%.

6-Cyano-2,5,7-triphenyl-4,5-dihydropyrazolo [1,5-a] pyrimidine (**XIII**)

Compound **XIII** was obtained on reaction of **III** and **XIb** following the same procedure for the synthesis of **XII**.

Compound **XIII** formed yellow crystals from ethanol, m.p. 265° C, yield 51%, i.r.: 2240 cm⁻¹ (CN).

C₂₅H₁₆N₄ Calcd.: C, 80.6; H, 4.3; N, 15.1%; Found: C, 80.5; H, 4.3; N, 15.0%.

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