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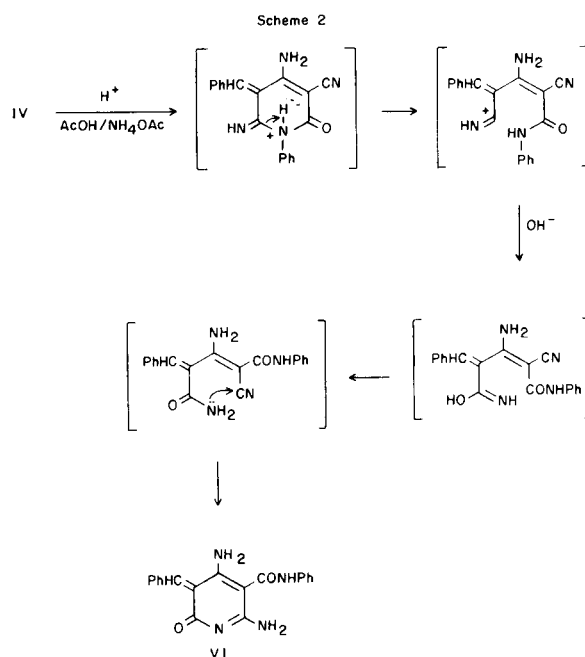
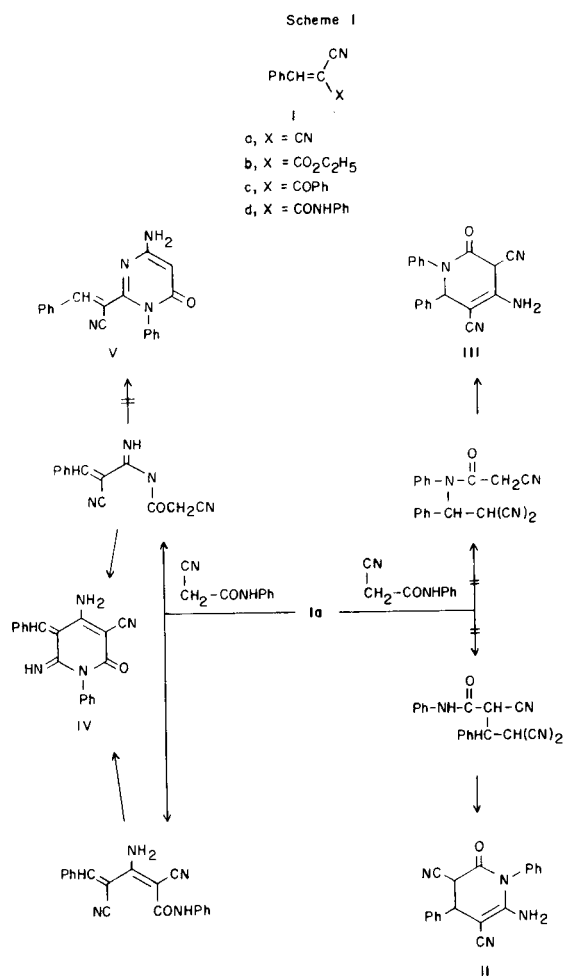
The reaction of substituted cinnamitrile derivatives with cyanoacetanilide and with ethyl acetoacetate produced several new polyfunctional pyridine and pyran derivatives. Evidence for assigned structure of the reaction products and the possible mechanisms of their formation is presented.

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In the last decade we have been involved in a program to explore the synthetic potential, scope and limitations for using  $\alpha,\beta$ -unsaturated nitrile derivatives in heterocyclic synthesis [1,2]. Several new approaches for the synthesis of five, six and fused heterocyclic derivatives were achieved during this work [3-6]. As a part of this program the reaction of the cinnamitrile derivatives Ia-c with cyanoacetanilide and with ethyl acetoacetate was investigated. Thus, it has been found that Ia reacts with cyanoacet-

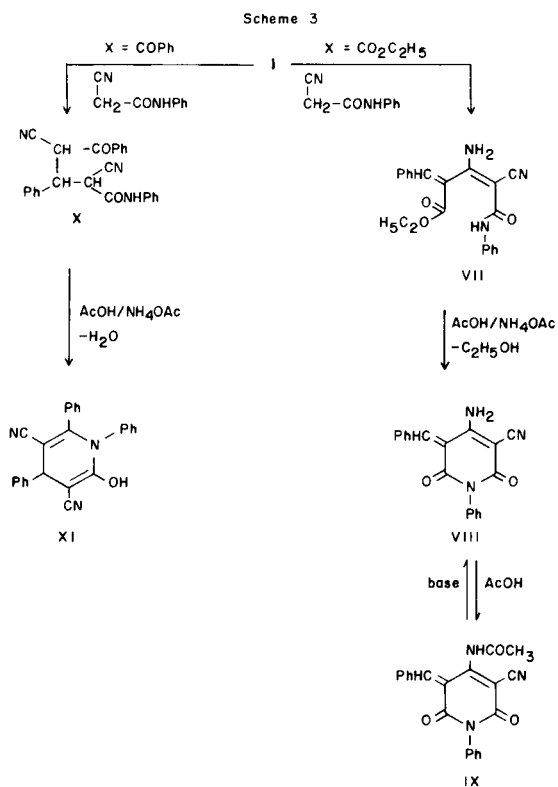
anilide to yield a 1:1 adduct. (*cf.* structures II-V, Scheme 1). Although structures II and III seemed more likely, based on analogy to the well established behaviour of Ia toward active methylene reagents [7], both structures were ruled out on the basis of  $^1\text{H-nmr}$  which revealed the absence of any proton resonance between  $\delta$  4-7 ppm for a pyridine 4-H proton in II and 2-H in III. The  $^1\text{H-nmr}$  also ruled out structure V as it revealed the absence of pyrimidine-H resonance. Thus, structure IV was considered for the reaction product. The formation of IV from the reaction of Ia and cyanoacetanilide may be assumed to proceed *via* addition of the amide nitrogen to the cyano group in Ia and subsequent cyclisation to IV. Alternately, addition of the methylene group to the cyano group in Ia followed by cyclisation *via* addition of the amide nitrogen to the other cyano group would also lead to the formation of IV.

When IV was heated with acetic acid in the presence of

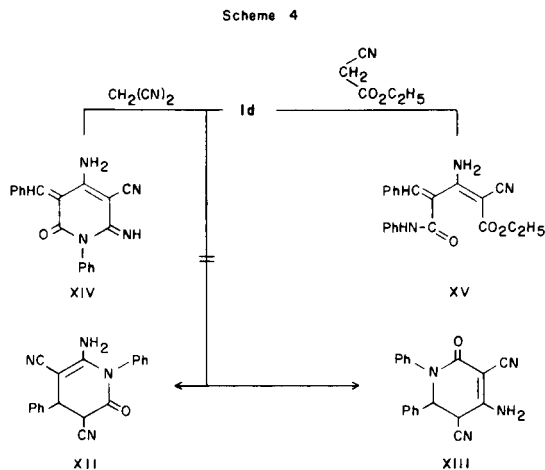


aqueous ammonium acetate solution it rearranged to the amide VI. The formation of VI is assumed to proceed *via* acid catalysed ring opening of IV and recyclisation (*cf.* Scheme 2).

Compound Ib reacted with cyanoacetanilide in ethanol and in presence of triethylamine to yield the acyclic adduct VII. The latter cyclised into VIII on reflux in acetic acid for five hours. Long reflux of VII in the same medium afforded unstable acetyl derivative IX which was readily



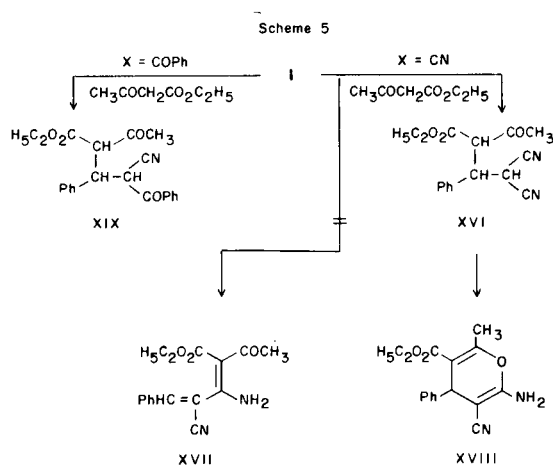
converted into VIII on treatment in basic medium. Compound Ic reacted with cyanoacetanilide to yield the acyclic derivative X. The latter afforded the pyridine derivative XI on reflux in acetic acid. The reaction is assumed to pro-



ceed here *via* our previously reported reaction sequence of activated nitriles with active methylene reagents (*cf.* Scheme 3).

Compound Id reacted with malononitrile to yield also a 1:1 adduct isomeric with IV. Again <sup>1</sup>H-nmr revealed the absence of resonance for pyridine ring protons in the range  $\delta$  5-7 ppm, thus excluding structures XII or isomeric XIII. Consequently, structure XIV was considered for this product. Similarly Id reacted with ethyl cyanoacetate to yield the ester XV (*cf.* Scheme 4).

Compound Ia was allowed to react with ethyl acetoacetate to yield a 1:1 adduct. Several isomeric structures were considered. The <sup>1</sup>H-nmr and ir were utilised to establish structure XVIII for this product. Thus, nmr revealed, in addition to the ethyl ester protons, methyl protons (singlet at  $\delta$  3.3), a pyran 4-H proton at  $\delta$  4.4, amino protons at  $\delta$  6.8 and aromatic protons at  $\delta$  7.1-7.5 ppm. These data exclude other possibilities (*cf.* structure XVII, Scheme 5). On the other hand, the reaction of Ic with the same reagent afforded the acyclic adduct XIX whose structure was established based on <sup>1</sup>H-nmr (*cf.* Experimental, Table 3).



These results when combined with our previous findings indicate that the reaction of Ia-c with suitable active methylene reagents can be utilised as an excellent route for synthesis of several, otherwise difficultly accessible, heterocyclic derivatives. However, several exceptions to this generalisation were observed. Thus, caution should be used before suggesting structures for reaction products of similar reactions based on analogy to our results. Although we are not now in a position to define the factors that determine the course of the reactions, we believe that the reactions are kinetically controlled. Thus whereas reversible addition of the methylene group to the double bond or the functional groups may simultaneously occur, the rate of formation of end product is the controlling step. In the reaction under consideration, the rate of formation of the isolated products is much faster than the

Table 1  
Physical Data and Elemental Analyses

Compound	Crystallization Solvent	mp (°C)	Yield (%)	Molecular formula (Molecular wt)	Found Analysis (%)		
					C	H	N
IV	EtOH	> 300	70	C <sub>19</sub> H <sub>14</sub> N <sub>4</sub> O (314.33)	72.5	4.3	17.8
					72.60	4.49	17.83
VI	AcOH	> 300	60	C <sub>19</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> (332.35)	68.9	4.6	17.2
					68.66	4.85	16.86
VII	EtOH	286	70	C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> (361.39)	70.0	5.6	11.6
					69.79	5.30	11.63
VIII	AcOH	254	75	C <sub>19</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> (315.32)	72.6	4.6	13.5
					72.37	4.16	13.33
IX	AcOH	235	60	C <sub>21</sub> N <sub>15</sub> N <sub>3</sub> O <sub>3</sub> (357.35)	70.2	4.6	12.0
					70.58	4.23	11.76
X	EtOH	199	80	C <sub>25</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> (393.43)	76.6	5.0	11.0
					76.32	4.87	10.68
XI	AcOH	242	80	C <sub>25</sub> H <sub>17</sub> N <sub>3</sub> O (375.41)	79.9	4.5	11.5
					79.98	4.56	11.19
XIV	EtOH	280	70	C <sub>19</sub> H <sub>14</sub> N <sub>4</sub> O (314.33)	72.2	4.4	17.5
					72.60	4.49	17.83
XV	EtOH	239	70	C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> (361.39)	69.8	5.6	11.2
					69.79	5.30	11.63
XVIII	EtOH	197	60	C <sub>16</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> (284.30)	67.6	5.4	9.6
					67.59	5.67	9.85
XIX	EtOH	218	65	C <sub>22</sub> H <sub>21</sub> NO <sub>4</sub> (363.40)	72.5	6.0	4.2
					72.71	5.82	3.85

Table 2

## IR Data

Compound	IR (cm <sup>-1</sup> ), selected bands
IV	3450, 3330 (NH <sub>2</sub> ), 3200-2700 (chelated NH), 2200 (CN), 1680-1660 (CO and C=N) and 1630-1600 (μ NH <sub>2</sub> and C=C)
VI	3450, 3330, 3200 (NH <sub>2</sub> and NH), 1670-1680 (ring and exocyclic CO) and 1630-1605 (μ NH <sub>2</sub> and C=C)
VII	3400-2700 (NH <sub>2</sub> and chelated NH), 2220 (CN), 1700-1660 (CO groups) and 1650-1630 (μ NH <sub>2</sub> and C=C)
VIII	3500-3000 (NH <sub>2</sub> ), 2220 (CN), 1680-1660 (two ring CO) and 1630-1605 (C=C and C=N)
IX	3300 (NH), 2220 (CN), 1710 (acetyl CO), 1680-1660 (ring CO) and 1630 (C=C and C=N)
X	3440-3400 (NH), 2220 (CN) and 1680 (CO)
XI	3470, 3420 (OH), 2215 and 2195 (two CN bands) and 1640 (C=C)
XIV	3450, 3380 (NH <sub>2</sub> and NH), 2230 (CN), 1700-1670 (CO and C=N) and 1650-1610 (μδ NH <sub>2</sub> and C=C)
XV	3380-3200 (NH <sub>2</sub> and NH), 2230 (CN), 1725 (ester CO), 1670 (amide CO)
XVIII	3400, 3340, 3270, 3200 (NH <sub>2</sub> ), 2200 (CN), 1690 (ester CO) and 1640 (C=C)
XIX	2220 (CN), 1740 (ester CO) and 1715 (CO)

rate of formation of other possible products. Other factors controlling these reactions are now under investigation.

Table 3

<sup>1</sup>H-NMR Data

Compound	<sup>1</sup> H-N δ ppm
IV	3.33 (S, 3H, NH <sub>2</sub> and NH), 7.3-7.9 (m, 11H, 2 C <sub>6</sub> H <sub>5</sub> and CH)
VIII	3.33 (br, 2H, NH <sub>2</sub> ), 7.0-7.8 (m, 11H, 2 C <sub>6</sub> H <sub>5</sub> and CH)
XIV	3.5 (br, 3H, NH <sub>2</sub> and NH), 7.0-7.8 (m, 11H, 2 C <sub>6</sub> H <sub>5</sub> and CH)
XV	1.2 (t, 3H, CH <sub>3</sub> ), 2.9 (q, 2H, CH <sub>2</sub> ), 3.9 (br, S, 3H, NH <sub>2</sub> and NH), 6.9-7.8 (m, 11H, 2 C <sub>6</sub> H <sub>5</sub> and CH)
XVIII	1.1 (t, 3H, CH <sub>3</sub> ), 3.3 (S, 3H, CH <sub>3</sub> ), 4.0 (q, 2H, CH <sub>2</sub> ), 4.4 (S, 1H, pyran 4-H), 6.8 (S, 2H, NH <sub>2</sub> ) and 7.1-7.5 (m, 5H, C <sub>6</sub> H <sub>5</sub> )
XIX	1.1 (t, 3H, CH <sub>3</sub> ), 2.5 (S, 3H, CH <sub>3</sub> ), 3.4 (m, 3H, 3CH), 4.1 (q, 2H, CH <sub>2</sub> ) and 7.2-7.8 (m, 10H, 2 C <sub>6</sub> H <sub>5</sub> )

## EXPERIMENTAL

All melting points are uncorrected. IR spectra were obtained (potassium bromide) on a pye Unicam Sp-1000 spectrophotometer or a Shimadzu IR 408. The <sup>1</sup>H-nmr were measured on a Varian EM-390-90 MHz in DMSO using TMS as internal standard and chemical shifts are expressed as δ ppm. Analytical data were obtained from the analytical data unit at Cairo University. Compounds Ia-d were prepared following literature procedures [8-10].

The Reaction of Ia-c with Cyanoacetamide and With Ethyl Acetoacetate. General Procedure.

To a suspension of either Ia-Ic (0.01 mole) in ethanol (30 ml) and cy-

anoacetanilide or ethyl acetoacetate (0.01 mole) and one ml of triethylamine was added. The reaction mixture was refluxed for six hours then cooled and poured onto water. The solid product, so formed, was collected by filtration and crystallised from the proper solvent (*cf.* Table 1).

Reaction of IV, VII and X With Acetic Acid-Ammonium Acetate Mixture. General Procedure.

To a solution of either IV, VII or X (0.01 mole) in acetic acid (30 ml), ammonium acetate (0.03 mole) was added. The reaction mixture was refluxed for six hours. The solid product, so formed, was collected by filtration and crystallised from the proper solvent (*cf.* Table 1).

Reaction of VIII With Acetic Acid.

A solution of VIII (0.01 mole; 3.03 g) in acetic acid (20 ml) was refluxed for 12 hours. The solvent was then evaporated to half its original volume. The solid product, so formed, was collected by filtration and crystallised from the proper solvent (*cf.* Table 1).

Reaction of Id With Malononitrile and Ethyl Cyanoacetate.

A solution of Id (0.01 mole, 2.5 g) in ethanol (30 ml), malononitrile or ethyl cyanoacetate (0.01 mole) and 1 ml of triethylamine was refluxed for five hours, then cooled and poured into water. The solid product, so formed, was collected by filtration and crystallised from the proper solvent (*cf.* Table 1).

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