REACTIONS OF SIX-MEMBERED HETEROCYCLIC β-ENAMINONITRILES WITH ELECTROPHILIC REAGENTS

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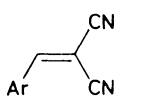
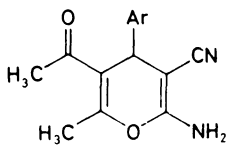
The nitriles *I* reacted with acetylacetone and with ethyl acetoacetate to afford 2-amino-3-cyano-4*H*-pyran derivatives. They reacted further to yield pyranopyridine derivatives. The reaction of *V* with acetylacetone afforded the pyridinethione *VIII*. This afforded, reacting with aromatic aldehydes or with cinnamonitriles quinoline derivatives *XVII*.

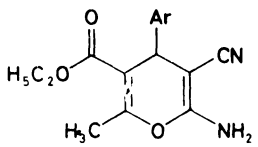
Cyclic β-enaminonitriles are versatile reagents and their chemistry has received considerable attention[1-3]. The chemical reactivity of cyclic β-enaminonitriles has been well explored[1]. However little has been reported, so far, on the chemistry of six member cyclic enaminonitriles. Recently we have reported several syntheses of cyclic six member heterocyclic β-enaminonitrile derivatives and some of our results on their chemical behaviour[2-6].



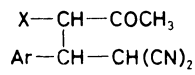
I	Ar
a	C_6H_5
b	*p*-$CH_3OC_6H_4$
c	*p*-ClC_6H_4
d	2-thienyl



II	Ar
a	C_6H_5
b	*p*-$CH_3OC_6H_4$



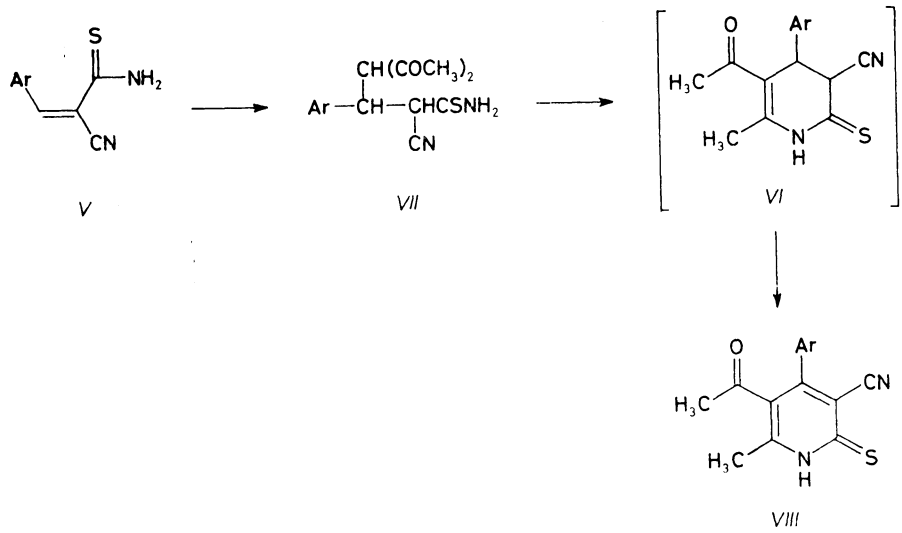
III	Ar
c	*p*-$CH_3OC_6H_4$
b	*p*-ClC_6H_4



IV

The pyran derivatives *IIa*, *IIb* were prepared via refluxing *Ia*, *Ib* with acetylacetone.

The formation of *IIa*, *IIb* from *Ia*, *Ib* and acetylacetone is assumed to proceed via addition of the methylene moiety of acetylacetone to the activated double bond in *I*. This is then followed by cyclization into the final product. Formation of pyrans on addition of acetylacetone to activated double bonds has been reported earlier by us, as well as by other groups[7,8]. Similar to acetylacetone, *Ib*, *Ic* reacted with ethyl acetoacetate to yield pyrans *IIIa*. *IIIb*. The pyran structures *II* and *III* were supported by IR and ^{1}H NMR. The IR spectrum revealed in each case bands at 3 400 to 3 310 cm^{-1} and 3 400–3 100 cm^{-1} for amino groups. Also conjugated CN bands at 2 210, 2 220 cm^{-1} were observed. ^{1}H NMR revealed pattern that can be intelligibly interpreted only for the pyran structure. Thus, pyran H-4 appeared at 4 to 4·5 ppm. If reaction products were acyclic Michael adducts *IV*, one would expect existence of two doublets in this region. In contrast to the observed formation of thiopyrans on reacting methylene reagents with ylidene cyanothioacetamide, product of the condensation via water and hydrogen elimination was formed on reaction *Va*, *Vb* with acetylacetone. These were formulated as the pyridinethiones *VIIIa*, *VIIIb*. Compounds *VIII* are assumed to be formed via acyclic Michael adducts *VII* which give *VI* as an intermediate, oxidized into *VIII* (Scheme 1). Compounds *IIa*, *IIb*

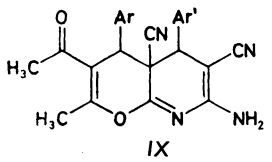


In formulae *V* – *VIII*: *a*, Ar = *p*-$CH_3OC_6H_4$; *b*, Ar = *p*-ClC_6H_4

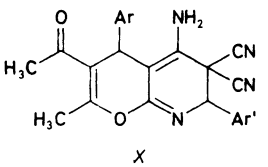
SCHEME 1

reacted with another molecule of *Ia*, *Ib* to yield adducts. These can be formulated as *IX* or isomeric *X*. Structure *X* was preferred over the possible *IX* based on ^{1}H NMR

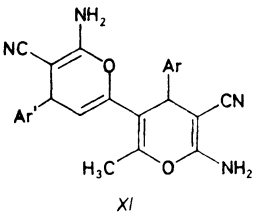
which revealed that the methyl at C-2 appeared as a doublet and in addition to signal for pyran H-4, other multiplet at δ 5·2 ppm. This is assigned to the pyrano-pyridine *X*. If the reaction products were *IX* it would be difficult to explain the



IX



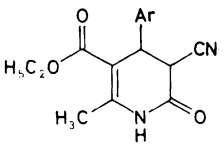
X



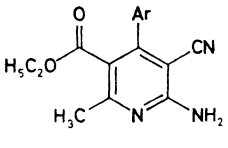
XI

In formulae *IX*–*XI*: *a*, Ar = C_6H_5, Ar' = C_6H_5; *b*, Ar = C_6H_5, Ar' = *p*-$CH_3OC_6H_4$; *c*, Ar = *p*-$CH_3OC_6H_4$, Ar' = C_6H_5; *d*, Ar = Ar' = *p*-$CH_3OC_6H_4$

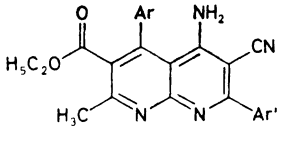
proton multiplicity and the signal at δ 5·2 ppm. Moreover, one would expect this signal to appear at higher field (δ 4·5 ppm). The behaviour of *IIa*, *IIb* towards *I* is thus different from that of the five member cyclic β-enaminonitriles toward electrophilic reagents, where C-β of these compounds have been shown to be the most reactive[1]. In an earlier report we have assigned structure *XI* to products of reaction of *I* with *II* (ref.[7]), contradicting a report by Martin et al.[8]. We are now convinced, based on presented evidence, that structure *X*, proposed by Martin et al.[8] is the correct one.



XII

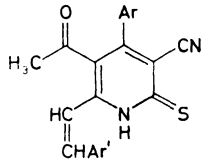


XIII

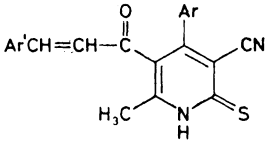


XIVa, Ar' = C_6H_5
XIVb, Ar' = *p*-$CH_3OC_6H_4$

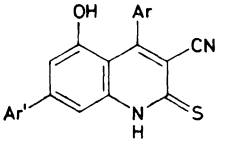
In formulae *XII*–*XIV*: *a*, Ar = *p*-$CH_3OC_6H_4$; *b*, Ar = *p*-$CH_3OC_6H_4$



XV



XVI



XVII

In formulae *XV*–*XVII*: *a*, Ar = *p*-$CH_3OC_6H_4$, Ar' = C_6H_5; *b*, Ar = *p*-$CH_3OC_6H_4$, Ar' = 2-thienyl; *c*, Ar = *p*-ClC_6H_4, Ar' = C_6H_5; *d*, Ar = *p*-ClC_6H_4, Ar' = 2-thienyl

Compound *III* rearranged on treatment with acetic acid in the presence of ammonium acetate to yield mixture of two products. These were formulated as pyridone *XII* and pyridine *XIII*, as indicated from ^{1}H NMR data.

Similarly to the behaviour of the enaminonitrile moiety in *II*, the enaminonitrile moiety in *XIII* also reacted with ylidenemalononitrile. Products of the addition and hydrogen cyanide elimination were isolated. These were formulated as *XIVa*, *XIVb* and are assumed to be formed by addition of the amino function in *XIII* to the double bond in *I*. This is followed by cyclization and hydrogen cyanide elimination.

The pyridine derivative *VIIIa* reacted with benzylidenemalononitrile to yield a product of the molecular formula $C_{23}H_{18}N_2O_2S$. The same product was obtained via reacting of *VIIIa* with benzaldehyde. Thus, the ylidene structure *XV*, *XVI* were considered. Structure *XVI* was excluded, based on ^{1}H NMR which revealed acetyl CH_3. When *XV* was refluxed in acetic acid it cyclized into *XVII*.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr with a Pye Unicam SP-1100 Spectrophotometer. ^{1}H NMR spectra were measured on a Varian EM-390 Spectrometer with hexadeuterodimethyl sulfoxide as solvent, using TMS as internal standard, and chemical shifts are expressed in ppm. Microanalyses were performed by the microanalytical unit at Cairo University. Compounds *Ia*—*Id* and *Va*, *Vb* were prepared as described in literature[9-11].

5-Acetyl-4-aryl-2-amino-4*H*-6-methylpyran-3-carbonitriles (*II*)

A solution of each of *Ia*, *Ib* (0·01 mol) and acetylacetone (0·01 mol) in 20 ml ethanol containing few drops of piperidine was refluxed for 3 h, then poured onto ice cold water. The formed solid product was collected by filtration and crystallized from aqueous ethanol (see Tables I, II and III).

Ethyl 2-Amino-3-cyano-4-aryl-4*H*-6-methylpyran-5-carboxylates (*III*)

To a solution of each of *Ia*, *Ib* (0·01 mol) in 20 ml ethanol containing few drops of piperidine (0·1 ml), ethyl acetoacetate (0·01 mol) was added. The reaction mixture was refluxed for 3 h, cooled, allowed to stand, the solid product was collected by filtration and crystallized from ethanol (see Tables I, II and III).

5-Acetyl-1,2-dihydro-4-aryl-6-methyl-2-thioxopyridine-3-carbonitriles (*VIIIa*, *VIIIb*)

To a suspension of sodium metal (0·2 g) in dioxane (20 ml), acetyl acetone (0·01 mol) was added and the mixture was refluxed for 5 min. Then 0·01 mol of *Va*, *Vb* was added. The reaction mixture was refluxed for 2 h and cooled. The solid products were collected by filtration and crystallized from the proper solvent (see Tables I, II and III).

3-Acetyl-5-amino-4,7-diaryl-2-methylpyrano[2,3-*b*]pyridine-6,6-dicarbonitrile (*Xa*, *Xb*)

A solution of *Ia*, *Ib* (0·01 mol) in ethanol (20 ml) was treated with *IIa*, *IIb* and a catalytic amount

TABLE I

Analytical data of heterocyclic compounds *IIa*—*XVIIa*

Compound	M.p., °C	Yield %	Formula (M.w.)	Calculated/Found			
				% C	% H	% N	% S
IIa	158	38	$C_{15}H_{14}N_2O_2$ (254·3)	70·85 70·9	5·55 5·6	11·02 10·7	— —
IIb	175—177	33	$C_{16}H_{16}N_2O_3$ (284·3)	67·59 67·6	5·67 6·0	9·85 9·3	— —
IIIa	129—130	85	$C_{17}H_{18}N_2O_4$ (314·3)	64·96 65·0	5·77 5·7	8·91 9·0	— —
IIIb	160—161	81	$C_{16}H_{15}ClN_2O$ (318·8)	60·29 59·9	4·74 4·8	8·79 8·6	— —
VIIIa	220	63	$C_{16}H_{14}N_2O_2S$ (298·4)	64·41 65·0	4·73 5·0	9·39 8·6	10·75 10·1
VIIIb	273—275	63	$C_{15}H_{11}ClN_2OS$ (302·7)	59·50 59·5	3·66 3·8	9·25 9·4	10·59 10·8
Xa	220	40	$C_{25}H_{15}N_4O_2$ (407·4)	73·7 74·0	4·7 5·0	13·75 14·0	— —
Xb	195—197	40	$C_{26}H_{21}N_4O_3$ (437·5)	71·38 71·4	4·84 4·9	12·81 12·5	— —
Xc	203—205	52	$C_{26}H_{21}N_4O_3$ (437·5)	71·38 71·5	4·84 4·9	12·81 12·4	— —
Xd	198—199	52	$C_{27}H_{23}N_4O_4$ (467·5)	69·38 69·7	4·46 4·7	11·98 11·5	— —
XIIa	121—122	51	$C_{17}H_{18}N_2O_4$ (314·3)	64·46 64·4	5·77 5·6	8·91 8·7	— —
XIIb	130—131	70	$C_{16}H_{15}ClN_2O_3$ (318·8)	60·29 60·4	4·74 4·7	8·79 8·6	— —
XIIIa	168—169	55	$C_{17}H_{17}N_3O_3$ (311·3)	65·58 64·9	5·50 5·3	13·50 13·2	— —
XIIIb	216—217	37	$C_{16}H_{14}ClO_2N_3$ (315·8)	60·86 60·4	4·47 4·5	13·31 13·1	— —
XIVa	198—200	20	$C_{26}H_{23}N_4O_3$ (439·5)	71·06 71·3	5·27 5·4	12·75 12·5	— —
XIVb	203—204	20	$C_{27}H_{24}N_4O_4$ (468·5)	69·22 69·0	5·16 5·0	11·96 11·2	— —
XVa	188	70	$C_{23}H_{18}N_2O_2S$ (386·5)	71·48 71·2	4·69 5·0	7·25 6·5	8·30 7·8

TABLE I
(*Continued*)

Compound	M.p., °C	Yield %	Formula (M.w.)	Calculated/Found			
				% C	% H	% N	% S
XVb	175	75	$C_{21}H_{16}N_2O_2S_2$ (392·5)	64·26 64·6	4·1 4·5	7·14 6·8	16·34 15·9
XVc	185	78	$C_{22}H_{15}ClN_2OS$ (390·9)	67·60 68·0	3·87 3·5	7·17 6·8	8·20 7·9
XVd	165	70	$C_{20}H_{13}ClN_2OS_2$ (364·4)	65·81 65·1	3·52 3·5	7·61 8·0	17·49 17·6
XVIIa	165	60	$C_{23}H_{14}N_2O_2S$ (382·4)	72·23 71·9	3·69 3·3	7·32 6·9	8·38 7·9

TABLE II
Selected IR data for compounds listed in Table I

Compound	$\tilde{\nu}$, cm^{-1}
IIa	3 420 (NH); 2 225 (CN); 1 700 (CO)
IIb	3 410 (NH_2); 2 220 (CN); 1 700 (CO)
IIIa	3 400—3 100 (NH_2); 2 220 (CN); 1 720 (CO)
IIIb	3 400—3 100 (NH_2); 2 220 (CN); 1 720 (CO)
VIIIa	3 200 (NH); 2 240 (CN); 1 700 (CO)
VIIIb	3 200 (NH); 2 240 (CN); 1 700 (CO)
Xa	3 425 (NH_2); 2 210 (CN); 1 650 (CO)
Xb	3 380 (NH_2); 2 210 (CN); 1 610 (CO)
Xc	3 360 (NH_2); 2 210 (CN); 1 610 (CO)
Xd	3 460 (NH_2); 2 215 (CN); 1 620 (CO)
XIIa	3 300 (NH_2); 2 235 (CN); 1 720 (CO)
XIIb	3 300 (NH_2); 2 235 (CN); 1 720 (CO)
XIIIa	3 460—3 360 (NH_2); 2 220 (CN); 1 725 (CO)
XIIIb	3 410—3 200 (NH_2); 2 220 (CN); 1 730 (CO)
XIVa	3 220 (NH_2); 2 240 (CN); 1 730 (CO)
XIVb	2 240 (CN); 1 740 (CO)
XVa	2 940, 2 885 (CH_3); 2 225 (CN); 1 705 (CO)
XVb	2 950, 1 875 (CH_3); 2 225 (CN); 1 705 (CO)
XVc	2 930, 2 860 (CH_3); 2 225 (CN); 1 710 (CO)
XVd	2 940 (CH_3); 2 225 (CN); 1 705 (CO)
XVIIa	3 400 (NH); 2 220 (CN)

TABLE III

^{1}H NMR data for compounds listed in Table I

Compound	δ, ppm
IIa	2·0 s, 3 H (CH_3); 2·5 s, 3 H ($COCH_3$); 4·3 s, 1 H (H-4); 7·1—7·6 m, 6 H (aromatic protons + NH_2)
IIb	2·0 s, 3 H (CH_3); 2·6 s, 3 H ($COCH_3$); 3·9 s, 3 H (OCH_3); 4·3 s, 1 H (H-4); 7·1—7·6 m, 6 H (aromatic protons + NH_2)
IIIa	1·2 t, 3 H (CH_3); 3·6 s, 3 H (CH_3); 3·8 s, 3 H (OCH_3); 4·2 q, 2 H (CH_2); 4·1 s, 1 H (H-4); 6·9 s, 2 H (NH_2); 7·2—7·6 m, 4 H (aromatic protons)
IIIb	1·2 t, 3 H (CH_3); 2·4 s, 3 H (CH_3); 4·2 q, 2 H (CH_2); 4·8 s, 1 H (H-4); 6·9 s, 2 H (NH_2); 7·2—7·6 m, 4 H (aromatic protons)
VIIIa	1·78 s, 3 H (CH_3); 2·5 s, 3 H (OCH_3); 6·83—7·24 m, 3 H (aromatic protons); 7·34 s, 1 H (NH)
VIIIb	2·2 s, 3 H (CH_3); 2·64 s, 3 H (CH_3); 7·35—7·64 m, 4 H (aromatic protons)
Xb	2·2 d, 3 H (CH_3); 3·9 s, 3 H (OCH_3); 4·4 s, 1 H (H-4); 5·2 m, 1 H (H-7); 7·0 m (aromatic protons + NH_2)
Xc	2·2 d, 3 H (CH_3); 4·5 s, 3 H (OCH_3); 4·4 s, 1 H (H-4); 5·2 m, 1 H (H-7); 7·2 m (aromatic protons + NH_2)
XIIb	1·25 t, 3 H (CH_3); 2·35 s, 3 H (CH_3); 3·9—4·25 q, 3 H (CH_2 and H-4); 4·35 d, 1 H (H-3); 7·0—7·4 m, 4 H (aromatic protons); 8·3 s, 1 H (NH)
XIIIa	1·1 t, 3 H (CH_3); 2·2 d, 3 H (CH_3); 3·65—4·4 m, 7 H (CH_2, CH_3 and NH_2); 6·7—7·25 m, 4 H (aromatic protons), 8·1 s, 1 H (NH)
XIIIb	1·0 t, 3 H (CH_3); 2·5 s, 3 H (CH_3); 3·9 q, 2 H (CH_2); 5·4 s, 2 H (NH_2); 7·25—7·6 m, 5 H (aromatic protons + NH)
XIVa	2·07 t, 3 H (CH_3); 2·3 s, 3 H (CH_3); 3·7 m, 5 H (OCH_3 and CH_2); 7·0 m, 1 H (aromatic protons + NH_2)
XIVb	2·08 t, 3 H (CH_3); 2·6 s, 3 H (CH_3); 4·8 q, 8 H (2 CH_3 and CH_2); 7·0 m, 10 H (aromatic protons + NH_2)
XVa	3·6 s, 3 H (OCH_3); 4·6 s, 3 H ($COCH_3$); 7·0—7·5 m, 11 H (aromatic protons and 2-styryl protons)
XVb	2·6 s, 3 H ($COCH_3$); 4·0 s, 3 H (OCH_3); 6·8 m, 9 H (aromatic and ethylene protons
XVc	2·5 s, 3 H ($COCH_3$); 7·4—8·0 m, 11 H (aromatic protons and styryl protons)
XVd	2·5 s, 3 H ($COCH_3$); 7·3 m, 9 H (aromatic and ethylene protons)
XVIIIa	3·7 s, 3 H (OCH_3); 7·0 m, 13 H (aromatic protons + NH); 8·0 s, 1 H (OH)

of piperidine. The reaction mixture was refluxed for 3 h and left to cool. The formed solid product was filtered off and crystallized from benzene–petroleum ether 60—80, (see Tables I, II and III).

Reaction of *IIIa*, *IIIb* with Acetic Acid and Ammonium Acetate (*XIIa*, *XIIb*) and (*XIIIa*, *XIIIb*)

To a solution of *IIIb*, *IIIc* (0·01 mol) in acetic acid (20 ml), 1 g of ammonium acetate was added. The reaction mixture was refluxed for 8 h, left to cool and then triturated with water. The solid product was collected by filtration and crystallized from ethanol. The solid product is a mixture of an ethanol soluble and ethanol insoluble product, reaction products are listed in Tables I, II and III.

Ethyl 5-Amino-6-cyano-4,7-diaryl-2-methylpyrido[2,3-*b*]pyridine-3-carboxylates (*XIVa*, *XIVb*)

A solution of *Ia*, *Ib* (0·01 mol) in ethanol (20 ml) was treated with *XIIIa*, *XIIIb* and a catalytic amount of piperidine. The reaction mixture was refluxed for 3 h and left to cool. The solid product was filtered off and crystallized from ethanol (see Tables I, II and III).

5-Acetyl-1,2-dihydro-4-aryl-6-styryl-2-thioxopyridine-3-carbonitriles (*XVa*, *XVb*)

A solution of *Ia*, *Id* (0·01 mol) in ethanol (20 ml) was treated with *VIIIb*, *VIIIc* and few drops of piperidine. The reaction mixture was refluxed for 3 h and then left to cool. The formed solid product was filtered off and crystallized from aqueous ethanol (see Tables I, II and III).

1,2-Dihydro-5-hydroxy-4-p-methoxyphenyl-7-phenyl-2-thioxoquinoline-3-carbonitrile (*XVIIa*)

A solution of *XVa*, in acetic acid (20 ml) was refluxed for 2 h, left to cool and then triturated with water. The solid product was collected by filtration and crystallized from aqueous ethanol to give *XVIIa* (see Tables I, II and III).

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