NITRILES IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESES OF BENZO[*b*]PYRANS, NAPHTHO[1,2-*b*]PYRANS, NAPHTHO[2,1-*b*]-PYRANS, PYRANO[3,2-*h*]QUINOLINES AND PYRANO[3,2-*c*]QUINOLINES

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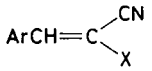
Benzo[*b*]pyrans, naphtho[1,2-*b*]pyrans, naphtho[2,1-*b*]pyrans, pyrano[3,2-*h*]quinolines, and pyrano[3,2-*c*]quinolines were synthesized by the reaction of cinnamonitriles with phenols, naphthols, 8-hydroxyquinoline, and 1-methyl-4-hydroxy-2-quinolone.

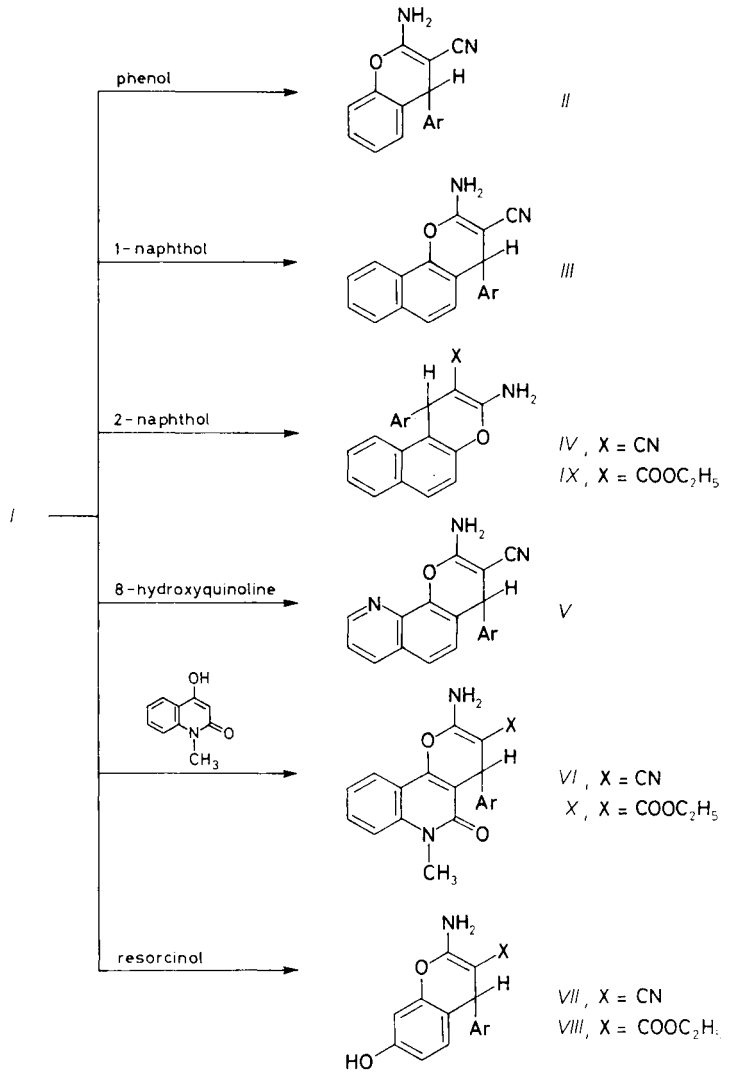
The reaction of acrylonitrile with substituted phenols has been reported[1] to enable the synthesis of C-cyanoethylated derivatives. Although this C—C bond forming reaction seems to be interesting, allowing alkylation of aromatics with α,β-unsaturated nitriles, only one report[2] on utilization of this reaction has appeared. Schmidt and Junek[2] have reported formation of fused pyrano derivatives via cyclocondensation reaction from ethoxymethylene malononitrile reacting with 4-hydroxy-2-pyridinone and 4-hydroxy-2-quinolone in the presence of sodium ethoxide.

With respect to our interest in exploring synthetic potentialities of α,β-unsaturated nitriles[3,4], we report here on utilization of reactions of the cinnamonitriles *Ia–d* with anions of phenols, naphthols, and hydroxy π-deficient heterocycles which lead to the formation of ^4H-pyrans in high yields. Thus, it has been found that cinnamonitrile derivatives *Ia,b* react with phenol in the presence of a catalytic amount of piperidine to yield 1 : 1 adducts. ^{1}H NMR spectra revealed, in addition to aromatic protons, one proton singlet at $\delta = 4{\cdot}84$ ppm and two D_2O-exchangable proton signals at 6·8 ppm for the amino group. Based on these data, two isomeric benzopyran structures have been considered. Thus, the α,β-unsaturated moiety in *I* may react with phenol C-2 to yield acyclic Michael adduct which can then cyclizate via the addition of the hydroxy function to the cyano group, possessing ^4H-benzopyran derivatives *IIa,b*. Alternately, ^2H-benzopyrans may be formed via the attack of phenolic oxygen at the electron-deficient double bond in *I* leading to an isomeric Michael adduct which then cyclizates via a further attack of the phenolic C-2 at the cyano function.

However, the probability of such cyclization seems to be extremely low. Thus, an acyclic product of the reaction of *Ia–d* with phenols via the latter demonstrated



Ia, Ar = C_6H_5; X = CN *Ic*, Ar = C_6H_5; X = $COOC_2H_5$
Ib, Ar = 4-CH_3O—C_6H_4; X = CN *Id*, Ar = 4-CH_3O—C_6H_4; X = $COOC_2H_5$



In formulae *II–X*: *a*, Ar = C_6H_5 *b*, Ar = 4-CH_3O—C_6H_4

TABLE I

Analytical data of the synthesized compounds

Compound[a]	M.p., °C (yield, %)	Formula (mol. wt.)	Calculated/found			$\tilde{\nu}$(KBr), cm^{-1} (selected bands)
			% C	% H	% N	
IIa	210 (80)	$C_{16}H_{12}N_2O$ (248·3)	77·40 77·30	4·87 4·60	11·28 11·20	3 460, 3 320, 3 260 (NH_2); 2 200 (CN)
IIb	175 (85)	$C_{17}H_{14}N_2O_2$ (278·3)	73·37 73·50	5·07 5·30	10·07 10·20	3 480, 3 320, 3 240 (NH_2); 2 210 (CN)
IIIa	210 (85)	$C_{20}H_{14}N_2O$ (298·3)	80·52 80·46	4·73 4·58	9·39 9·51	3 460, 3 320, 3 200 (NH_2); 2 200 (CN)
IIIb	182 (80)	$C_{21}H_{16}N_2O_2$ (328·4)	76·81 76·62	4·91 4·79	8·53 8·40	3 480, 3 340, 3 220 (NH_2); 2 200 (CN)
IVa	278 (90)	$C_{20}H_{14}N_2O$ (298·3)	80·52 80·37	4·73 4·60	9·39 9·51	3 440, 3 360, 3 200 (NH_2); 2 190 (CN)
IVb	192 (85)	$C_{21}H_{16}N_2O_2$ (328·4)	76·81 76·65	4·91 5·12	8·53 8·71	3 460, 3 340—3 200 (NH_2); 2 200 (CN)
Va	270 (80)	$C_{19}H_{13}N_3O$ (299·3)	76·24 76·51	4·38 4·00	14·04 14·18	3 480, 3 340, 3 200 (NH_2); 2 200 (CN)
Vb	220 (80)	$C_{20}H_{15}N_3O_2$ (329·4)	72·94 73·15	4·59 4·81	12·76 12·82	3 480, 3 340, 3 210 (NH_2); 2 210 (CN)
VIa	300 (90)	$C_{20}H_{15}N_3O_2$ (329·4)	72·94 72·75	4·59 4·38	12·76 12·93	3 420, 3 360, 3 220 (NH_2); 2 210 (CN); 1 680 (CO)
VIb	258 (90)	$C_{21}H_{17}N_3O_3$ (359·4)	70·18 70·32	4·77 4·93	11·69 11·75	3 410, 3 330, 3 210 (NH_2); 2 210 (CN); 1 680 (CO)
VIIa	225 (90)	$C_{16}H_{12}N_2O_2$ (264·3)	72·72 72·93	4·58 4·61	10·60 10·72	3 520, 3 440—3 340, 3 220 (OH, NH_2); 2 200 (CN)
VIIb	214 (85)	$C_{17}H_{14}N_2O_3$ (294·3)	69·38 69·52	4·79 4·85	9·18 9·11	3 520, 3 420, 3 350 (OH, NH_2); 2 210 (CN)
VIIIa	218 (70)	$C_{18}H_{17}NO_4$ (311·3)	69·44 69·47	5·50 5·63	4·50 4·62	3 480, 3 320—3 150 (OH, NH_2); 1 680 (CO ester)
VIIIb	178 (72)	$C_{19}H_{19}NO_5$ (341·4)	66·85 66·91	5·61 5·65	4·10 4·23	3 500, 3 420—3 200 (OH, NH_2); 1 680 (CO ester)
IXa	195 (72)	$C_{22}H_{19}NO_3$ (345·4)	76·50 76·28	5·55 5·74	4·06 4·18	3 480, 3 360 (NH_2); 1 700 (CO ester)
IXb	168 (65)	$C_{23}H_{21}NO_4$ (375·4)	73·58 73·81	5·64 5·68	3·73 3·79	3 460, 3 320 (NH_2); 1 700 (CO ester)
Xa	238 (85)	$C_{22}H_{20}N_2O_4$ (376·4)	70·19 70·32	5·36 5·59	7·44 7·63	3 400, 3 300 (NH_2); 1 710 (CO ester); 1 680 (CO)
Xb	234 (80)	$C_{23}H_{22}N_2O_5$ (406·4)	67·87 67·81	5·46 5·69	6·89 6·72	3 410, 3 310 (NH_2); 1 700 (CO ester); 1 680 (CO)

[a] Crystallization solvent for compounds *IIa*—*Vb* is ethanol–dimethylformamide and for compounds *VIa*—*Xb* dioxane.

sequence would be expected in contrast to experimental evidences which indicate the formation of a pyran derivative. Moreover, the ^2H-pyran form could be also ruled out based on ^{1}H NMR which exhibited a signal at $\delta = 4{\cdot}5-5{\cdot}0$ ppm for one proton linked to sp^3 carbon. Signals at similar positions have been noted by us for ^4H-pyrans and ^4H-thiopyrans of similar structures[5,6]. If ^2H-pyrans are the products of the reaction of *Ia, b* with phenols, one would expect this signal to appear at lower δ values.

Similarly to the behaviour of phenols, *Ia, b* reacted with 1-, 2-naphthols, 8-hydroxyquinoline and 1-methyl-4-hydroxy-2-quinolone to yield pyran derivatives *III – VI*.

The reaction of *Ia, b* with resorcinol created 1 : 1 adducts. Based on spectral data, these were considered to represent ^4H-pyrans. Although either resorcinol C-2 or C-4 may attack the double bond in *I*, only products resulting from the attack at C-4 were formed. Resorcinol C-4 is known to be the most nucleophilic centre. Thus, the structure *VII* has been suggested for these products.

Compounds *Ic, d* reacted with resorcinol, 2-naphthol and with 1-methyl-4-hydroxy--2-quinolone to yield pyrano derivatives *VIII*, *IX* and *X*, respectively. However, under the same conditions, phenol, 1-naphthol and 8-hydroxyquinoline failed to

TABLE II

^{1}H NMR data of some prepared compounds

Compound	^{1}H NMR, δ ppm
IIa	4·84 s, 1 H (pyran 4-H); 6·8 brs 2 H (NH_2, D_2O-exchangeable); 7·25—7·66 m, 9 H (ArH)
IIIa	4·75 s, 1 H (pyran 4-H); 6·6 brs, 2 H (NH_2, D_2O-exchangeable); 6·95—8·2 m, 11 H (ArH)
IVa	5·35 s, 1 H (pyran 4-H); 6·9 brs, 2 H (NH_2, D_2O-exchangeable); 7·2—8·10 m, 11 H (ArH)
VIb	3·5 s, 3 H (CH_3); 3·7 s, 3 H (CH_3); 4·5 s, 1 H (pyran 4-H); 6·85 brs, 2 H (NH_2, D_2O-exchangeable); 7·1—8·0 m, 8 H (ArH)
VIIa	4·84 s, 1 H (pyran 4-H); 6·8 brs, 2 H (NH_2, D_2O-exchangeable); 7·2—7·66 m, 9 H, (ArH + OH)
VIIIa	1·2 t, 3 H (CH_3); 3·4 q, 2 H (CH_2); 4·9 s, 1 H (pyran 4-H); 6·8 brs, (2 H, NH_2, D_2O-exchangeable); 7·0—7·6 m, 9 H (ArH + OH)
IXa	1·2 t, 3 H (CH_3); 3·2 q, 2 H (CH_2); 5·2 s, 1 H (pyran 4-H); 6·8 brs (2 H, NH_2, D_2O-exchangeable); 7·1—8·0 m, 11 H (ArH)
Xb	1·1 t, 3 H (CH_3); 3·5 s, 3 H (CH_3); 3·65 s, 3 H (CH_3); 4·0 q, 2 H (CH_2); 4·8 s, 1 H (pyran 4-H); 6·75 brs, 2 H (NH_2, D_2O-exchangeable); 7·1—8·1 m, 8 H (ArH)

react. Structures *VIII*, *IX*, and *X* were established based on the IR spectra of these reaction products which revealed the absence of a cyano-group absorption. In addition, ^4H-pyran signals could be detected by ^{1}H NMR. It is interesting to note that the signals of pyrans H-4 in *IV* and *IX* are deshielded by about 0·5 ppm as compared to that in other products. This low field shift is due to the aromatic π-electron over which the pyran H-4 is located in the most stable conformation.

Although addition of ketomethyl carbanions to cinnamonitriles has been extensively utilized for the synthesis of ^4H-pyrans[7–9], to our knowledge this is the first reported reaction of phenols, naphthols and hydroxy π-deficient heterocycles with cinnamonitriles.

EXPERIMENTAL

All the melting points are uncorrected. IR spectra were obtained (KBr) on a Pye-Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian A-90 spectrometer. Analytical data were obtained from the analytical department of Cairo University.

Reaction of *Ia–d* with Phenols, Naphthols, 8-Hydroxyquinoline and 1-Methyl-4-hydroxy-2-quinolone

A solution of *I* (0·01 mol) in ethanol (30 ml) was treated with the appropriate hydroxy compound (0·01 mol) and piperidine (0·5 ml). The reaction mixture was heated until complete precipitation (reaction time: 15 min for *Ia,b* and 120 min for *Ic,d*). The solid product formed was collected by filtration and recrystallized from a suitable solvent. For the analytical data see Tables I and II.

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