KINETIC AND SPECTRAL STUDIES ON 5-PHENOXY-2-FURALDEHYDES AND THEIR CONDENSATION PRODUCTS*

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The base-catalyzed reaction of 5-(4- or 3-phenoxy)-2-furaldehydes (X = 4-OCH_3, 4-CH_3,4-Cl, 4-NO_2, 3-NO_2, 4-Br, 4-$COOC_2H_5$, 3-$NHCOCH_3$, 4-SCH_3) with malonodinitrile in ethanol gave the corresponding condensation products. The course of the reaction has been monitored kinetically. The kinetics of the nucleophilic substitution reaction at the position 5 of the furan ring of the obtained 2-cyano-3-(5-X-phenoxy-2-furyl)acrylonitriles with secondary cyclic amines (piperidine, morpholine, pyrrolidine) has been studied. The effect of X across the oxygen bridge upon the reaction site is discussed from the point of view of kinetics of the reaction. ^1H-NMR spectra of the starting aldehydes and of the formed condensation products have been measured.

It is known[1,2] that under basic conditions 5-substituted 2-furaldehydes react with malonodinitrile to give condensation products. Owing to the electron deficiency at the position 5 of the furan ring, resulting from the effect of the strongly electron-withdrawing $-CH=C(CN)_2$ group, the thus formed furfurylidenemalonodinitriles are good substrates for nucleophilic reactions. We have previously studied nucleophilic substitution reactions of 5-arylthio-[3,4], 5-arylsulphonyl-[3,4], heteroarylthio-[4], 5-methylthio-[5], 5-methylsulphonyl-[5], 5-bromo-[6], and 5-nitro-2-furfurylidenmalonodinitriles[6] with secondary cyclic amines (piperidine, morpholine, pyrrolidine) and found that the rate of the S_N reaction largely depends upon the nucleophility of the reagent. The attack of the nucleophile was found to be the rate-determining step, *i.e.* the reaction follows the addition-elimination mechanism. A similar nucleophilic substitution in the aromatic series was studied by Brunskill and coworkers[7] who performed substitution reactions of 4-halogenobenzylidenemalonodinitriles with secondary amines.

The present work describes reactions of 5-phenoxy-2-furaldehydes with malonodinitrile to give the corresponding 2-cyano-3-(5-X-phenoxy-2-furyl)acrylonitriles. Compounds *Ia*–*IIi* (Table I, yellow or orange materials) were obtained by allowing to react in ethanol and at room temperature compound *I* with malonodinitrile in the

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presence of a catalytic amount of sodium ethoxide. The reaction was monitored kinetically. When studying this Knoevenagel condensation reaction Patai[8] found that an important factor in the reaction is the dissociation of the C—H bond in the methylene component of the dinitrile. With strong bases, the carbanion is formed immediately and this step does not affect the overall reaction rate. It follows from our findings, as well as from those of the previous authors[8], that the reaction is of 1st order with respect to the methylenic component which, after the carbanion had been formed, commences the reaction. The addition of the carbanion is then the slowest, rate determining step of the process. The reaction was performed in the presence of a catalytic amount of piperidine and under the conditions of a pseudounimolecular reaction, *i.e.* with an excess of the dinitrile. The process was followed spectrophotometrically in the range of the last absorption maximum of the product (~380 nm).

TABLE I

The Synthesized 2-Cyano-3-(5-X-phenoxy-2-furyl)acrylonitriles *IIa*—*IIi*

Compound	Formula (m.w.)	M.p., °C yield, %	Calculated/Found, % C	H	N	other	λ_{max}, nm log ε			$\nu(C\equiv N)$, cm^{-1}
IIa	$C_{15}H_{10}N_2O_3$	112	68·71	3·84	10·67	—	223	281	391	2 235
	(262·2)	87·6	68·60	3·75	10·50		3·96	3·18	4·36	
IIb	$C_{15}H_{10}N_2O_2$	115—116	71·97	4·02	11·19	—	225	269s	388	2 234
	(250·3)	87·5	71·80	4·07	11·35		3·91	3·30	4·49	
IIc	$C_{14}H_7ClN_2O_2$	145	62·12	2·61	10·35	13·09[a]	218	272s	382	2 234
	(270·7)	85	62·20	2·58	10·20	13·19	4·08	3·27	4·51	
IId	$C_{14}H_7N_3O_4$	144—145	59·79	2·51	14·94	—	211	258	373	2 236
	(281·2)	80	59·60	2·45	14·87		4·19	3·92	4·45	
IIe	$C_{14}H_7N_3O_4$	118—120	59·79	2·51	14·94	—	—	245	377	2 236
	(281·2)	85	59·80	2·55	14·90			4·13	4·49	
IIf	$C_{14}H_7BrN_2O_2$	142	53·35	2·24	8·89	25·33[b]	219	275	382	2 234
	(315·1)	82·2	53·00	2·05	8·82	25·02	4·20	3·30	4·59	
IIg	$C_{17}H_{12}N_2O_4$	148—150	66·22	3·92	9·08	—	226	253	380	2 234
	(308·3)	84·5	66·10	3·90	9·02		4·16	4·14	4·45	
IIh	$C_{16}H_{11}N_3O_3$	120—121	65·52	3·78	14·32	—	205	240	384	2 235
	(293·3)	80·5	65·38	3·70	14·25		4·44	4·27	4·51	
IIi	$C_{15}H_{10}N_2O_2S$	101—102	63·82	3·57	9·92	11·34[c]	206	257	388	2 235
	(282·3)	85·6	63·68	3·48	9·90	11·19	4·29	4·33	4·50	

[a] % Cl, [b] % Br, [c] % S; s — shoulder.

The rate constants were calculated according to the first-order kinetic equation, the applied procedure being justified by the observed linear dependence log ΔE *vs* time. The k_2 values were obtained by dividing k_{obs} by the concentration of the methylenic component. It can be seen from k_2 values (Table II) that the reaction rate depends upon the electron defficiency at the carboxylic carbon atom of the aldehyde, the reaction site being affected by the substituents in the *para* or *meta* position of the phenoxy residue. It follows from the data in Table II that electron-donating and electron-withdrawing substituents invariably decrease and increase, respectively, the condensation rate. The correlability of log k with σ constants of the substituents ($\varrho = 0.55$, $r = 0.97$) is in agreement with these conclusions. The rate constants found

TABLE II

Kinetic Data for the Reaction of 5-(X-Phenoxy)-2-furaldehydes with Malonodinitrile in Ethanol; 25° ± 0·2°C

Compound	k_2[a]	σ	Compound	k_2[a]	σ
Ia	0·77 ± 0·005	−0·27	*If*	1·73 ± 0·002	+0·232
Ib	0·81 ± 0·010	−0·17	*Ig*	1·85 ± 0·018	+0·450
Ic	1·72 ± 0·002	+0·227	*Ih*	1·50 ± 0·005	+0·21
Id	2·64 ± 0·008	+0·778	*Ii*	0·95 ± 0·002	0
Ie	2·72 ± 0·023	+0·710			

[a] $l\ mol^{-1}\ s^{-1}$.

TABLE III

The Rate Constants ($k_2\ 10^{-3}\ l\ mol^{-1}\ s^{-1}$) for the Reactions of *IIa*—*IIi* with Secondary Amines in Methanol, $t = 25 \pm 0.2$°C

Compound	Pyrrolidine	Piperidine	Morpholine
IIa	7·718 ± 0·015	3·33 ± 0·015	1·074 ± 0·018
IIb	8·37 ± 0·031	3·49 ± 0·01	1·176 ± 0·03
IIc	9·96 ± 0·025	4·50 ± 0·015	1·54 ± 0·025
IId	13·82 ± 0·025	5·75 ± 0·048	2·27 ± 0·028
IIe	12·91 ± 0·010	5·16 ± 0·003	2·117 ± 0·015
IIf	9·05 ± 0·018	4·608 ± 0·010	1·45 ± 0·008
IIg	10·74 ± 0·030	4·714 ± 0·020	1·380 ± 0·012
IIh	8·52 ± 0·005	4·20 ± 0·025	1·252 ± 0·015
IIi	8·75 ± 0·012	4·126 ± 0·012	1·301 ± 0·010

for the phenoxy derivatives are somewhat smaller, compared with those in the series[1] of 5-(4-X-phenylthio)-2-furaldehydes.

The prepared 2-cyano-3-(5-X-phenoxy-2-furyl)acrylonitriles *IIa*–*IIi* react with secondary cyclic amines to give 5-amino derivatives. Piperidine, morpholine and pyrrolidine have been used in these nucleophilic substitution reactions and 5-piperidino-, 5-morpholino-, and 5-pyrrolidino-2-furfurylidenemalonodinitriles were obtained. Their structure was confirmed by common analytical methods and mass spectrometry[4]. The reaction was monitored kinetically in methanolic solutions of secondary cyclic amines (large excess of the amine) under the conditions of pseudo-unimolecular reaction, according to the absorption maximum of the formed 5-amino-derivative (at 470, 472 and 467 nm for piperidine, pyrrolidine and morpholine, rerespectively). It can be seen from the calculated rate constants (Table III) that the rate of these S_N reactions decreases with the decrease of the nucleophility of the reagent, *i.e.* the reaction carried out with pyrrolidine is the fastest one and the smallest k_2 was determined for the reaction involving morpholine. In addition, the reaction rate depends largely upon the electron defficiency at the carbon atom 5 of the furan ring, effected not only by the electron-withdrawing substituent at the position 2 and the hetero atom in the ring but, to a certain extent, also by the character of the substituent X on the benzene ring: while electron-donating substituents decrease the reaction rate, the presence of electron-withdrawing substituents results in a shift of k_2 to higher values. From these phenomena follows also a good correlation of, $\log k_2$ and σ constants of the substituents, with $\varrho = 0{\cdot}22$ and $r = 0{\cdot}97$ for the reaction with piperidine, $\varrho = 0{\cdot}23$ and $r = 0{\cdot}95$ for the reaction with pyrrolidine and $\varrho = 0{\cdot}28$ and $r = 0{\cdot}94$ for the one with morpholine.

A comparison of the rate constants for variously substituted 2-furfurylidenemalonodinitriles (Table IV) shows that the S_N reaction on the furan ring is also affected by other factors, such as the character of the leaving group (mainly its electron-with-

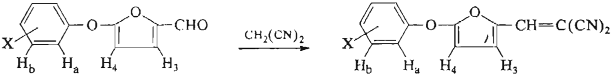
TABLE IV

The k_2 Values for the S_N Reaction of 5-X-2-Furfurylidenemalonodinitrile with Piperidine in Methanol; 25° ± 0·2°C

X	CH_3SO_2	CH_3S	NO_2	Br	$C_6H_5SO_2$	C_6H_5O	C_6H_5S
$k_2 \cdot 10^{3a}$	10 731	657·0	26·0	20·63	11·36	3·905	3·00
Ref.	9	9	6	6	3	[b]	3

[a] $l\ mol^{-1}\ s^{-1}$; [b] this work.

drawness, *cf.* C_6H_5S and NO_2), and steric interactions of the leaving group and the nucleophile (*cf.* k_2 for $C_6H_5SO_2$ and CH_3SO_2).



Ia, X = 4-OCH_3
Ib, X = 4-CH_3
Ic, X = 4-Cl
Id, X = 4-NO_2
Ie, X = 3-NO_2

If, X = 4-Br
Ig, X = $COOC_2H_5$
Ih, X = 3-$NHCOCH_3$
Ii, X = 4-SCH_3

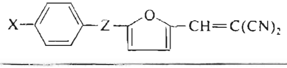
SCHEME 1

A replacement of the phenoxy group for a methoxy group in 2-cyano-3-(5-X-phenoxy-2-furyl)acrylonitriles makes it possible to introduce a methoxy group directly to the furan ring. The structure of the product was confirmed by elemental analysis and UV, IR and ^{1}H-NMR spectroscopy. Interestingly, the soft base sodium methoxide is capable of pushing out the phenolate anion.

The electron spectra of 2-cyano-3-(5-X-phenoxy-2-furyl)acrylonitriles show three absorption bands; the last of them, extending itself to the visible region (~380 nm), results from the electron stretching across the whole conjugated system (*cf.* ref.[9-11] for the corresponding aldehydes showing the second absorption band at 293–308 nm). No significant difference in the position of the absorption maxima is evident from the comparison with UV spectra of analogous condensation products of 2-cyano-

TABLE V

The λ_{max} Values (nm) for the Last Absorption Maximum of Substances



X[a]	H	CH_3	CH_3O	Cl	Br	NO_2
I	402	411	430	403	406	402
II	394	395	407	385	395	370
III	—	388	391	382	382	373

[a] Z = —(*I*), Z = S(*II*), Z = O(*III*).

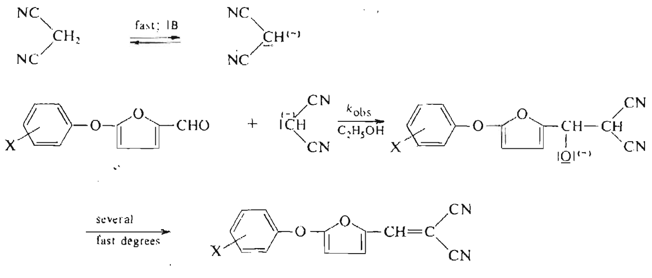
-3-(5-X-phenylthio-2-furyl)acrylonitriles[1]. On the other hand, similar condensation products of 2-cyano-3-(5-X-phenyl-2-furyl)acrylonitriles[12], compounds not containing an —S— or an —O— bridge, show a bathochromic shift of the K-band to the visible region of the spectrum (Table V).

TABLE VI

Chemical Shifts (δ, ppm) for Compounds *Ia*—*Ii* and *IIa*—*IIi*

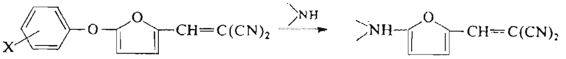
Compound	—CH=[a]	H_3[b]	H_4	H_a[c]	H_b	Other signals
Ia	9·34	7·17	5·43	6·99	7·10	3·79(CH_3)
Ib	9·35	7·19	5·49	7·04	7·24	2·32(CH_3)
Ic	9·38	7·19	5·60	7·11	7·35	—
Id	9·45	7·29	5·91	7·20	8·22	—
Ie	9·41	7·31	5·85	(7·50—8·25)[d]		—
If	9·39	7·21	5·61	7·05	7·50	—
Ig	9·40	7·29	7·53	7·18	8·08	1·35(CH_3) 4·33(CH_2)
Ih	9·35	7·22	5·62	(6·75—7·62)[d]		2·12(CH_3) 8·06(NH)
Ii	9·36	7·18	5·54	7·09	7·27	2·45(CH_3)
IIa	7·24	7·31	5·54	6·93	7·15	3·76(CH_3)
IIb	7·24	7·31	5·55	7·09	7·90	2·35(CH_3)
IIc	7·27	7·33	5·68	7·17	7·40	—
IId	7·34	7·36	5·92	7·25	8·27	—
IIe	7·31	7·35	5·88	(7·50—8·25)[d]		—
IIf	7·27	7·33	5·69	7·10	7·54	—
IIg	7·31	7·36	5·79	7·25	8·12	1·40(CH_3) 4·40(CH_2)
IIh[e]	7·97	7·46	5·89	(6·87—7·75)[d]		1·98(CH_3)
IIi	7·25	7·32	5·62	7·08	7·35	2·50(CH_3)

[a] Olefinic proton for *IIa*—*IIi*, aldehydo proton for *Ia*—*Ii*; [b] $J_{3,4} = 3\cdot9$ Hz for *IIa*—*IIi*, $J_{3,4} = 3\cdot6$ Hz for *Ia*—*Ii*; [c] $J_{a,b} = 8\cdot6$ Hz—9·0 Hz; [d] multiplet of aromatic protons; [e] measured in hexadeuteriodimethyl sulphoxide.



SCHEME 2

The IR spectral data for *IIa*–*IIi* (Table I) show that the substituents at the position 4 on the benzene ring have virtually no effect upon the position of $\nu_{(C\equiv N)}$. The higher wave-number values observed with 2-cyano-3-(5-X-phenoxy-2-furyl)acrylonitriles, as compared *e.g.* with 3-(5-aryl-2-furyl)acrylonitriles[11,12] result from mutual deactivation effect of the two cyano groups linked to the same carbon atom. The position of $\nu_{(C\equiv N)}$ in the spectra of *IIa*–*IIi* does not differ significantly from that of similar 2-cyano-3-(5-X-phenylthio-2-furyl)acrylonitriles[1].



SCHEME 3

The ^{1}H-NMR data (Table VI) for the starting 2-furaldehydes *Ia*–*Ii* and for the prepared *IIa*–*IIi* confirm the structure of the substances. The transfer of effects of *para* and *ortho* substituents on the phenyl ring across the oxygen bridge upon furan, aldehydo and olefinic protons has also been investigated. The chemical shifts of aldehydo and olefinic protons are only slightly affected. The most affected proton was found to be H_4 at the furan ring: as a result of *p*-*π* conjugation an upfield shift of the H_4 signal was observed. A good linear correlation of chemical shifts for H_4 with Hammett σ constants has been found (*IIa*–*IIi*: $\varrho = 2.679$ and $r = 0.995$; *Ia*–*Ii*: $\varrho = 2.223$ and $r = 0.990$).

EXPERIMENTAL

Electron absorption spectra (200—800 nm) for solutions (1—5 . 10^{-5}M) in methanol were measured with a Specord UV VIS (Zeiss) spectrometer using 10 mm cells. The IR spectra

(3 600—600 cm^{-1}) for 0·03M chloroform solutions were measured in NaCl cells (0·26 mm thickness) with a UR 20 (Zeiss) instrument. The ^{1}H-NMR spectra (80 MHz) for solutions in deuteriochloroform were measured with a Tesla BS 487C spectrometer using tetramethylsilane as the internal standard. The used 5-(4-X-phenoxy)-2-furaldehydes were prepared[11] from sodium phenolates and 5-bromo-2-furaldehyde.

2-Cyano-3-(5-X-phenoxy-2-furyl)acrylonitriles

A solution of malonodinitrile (0·66 g, 0·01 mol) in ethanol (10 ml) was added to a solution of the respective 5-phenoxy-2-furaldehyde (0·01 ml) in ethanol (20 ml). One drop of ethanolic sodium ethoxide was added and the mixture was stirred at room temperature for 2—3 h. The material that had separated during this time was filtered off and recrystallized from ethanol.

2-Cyano-3-(5-methoxy-2-furyl)acrylonitrile

The respective 2-cyano-3-(5-X-phenoxy-2-furyl)acrylonitrile (0·01 mol) was dissolved in ethanol and solid sodium methoxide (0·01 mol) was added. The mixture was stirred at room temperature for 2 h, left overnight and the separated material was recrystallized from ethanol. M.p. 170 to 171°C, yield 45%. For $C_9H_6N_2O_2$ (174·1) calculated: 62·08% C, 3·44% H, 16·07% N; found: 61·95% C, 3·40% H, 15·95% N. ^{1}H-NMR (δ, ppm): 4·14 (s, 3 H, CH_3), 7·49 (d, 1 H, H_3), 5·91 (d, 1 H, H_4), 7·64 (s, 1 H, —CH=), $J_{3,4}$ = 3·9 Hz.

Kinetics of the Condensation Reaction with Malonodinitrile

The reaction mixture contained: methanolic piperidine (0·2 ml, $c = 5 \cdot 10^{-2}$M), methanolic dinitrile (0·1 ml, $c = 1 \cdot 10^{-3}$M), methanolic aldehyde (0·3—0·5 ml, $c = 3$—$5 \cdot 10^{-5}$M). The volume was adjusted with methanol to 10 ml and the reaction rate was monitored at 25° ± 0·2°C by reading the increments of the K-band (~380 nm) of the formed product.

Kinetics of the Nucleophilic Substitution with Secondary Amines

The reaction mixture contained: methanolic secondary amine (piperidine, morpholine, pyrrolidine, 5 ml, $c = 2{\cdot}5 \cdot 10^{-2}$M), methanolic *IIa—IIi* (0·3 ml, $c = 3 \cdot 10^{-5}$M), and methanol (4·7 ml). The absorption maximum of the formed 5-piperidino-, 5-morpholino-, and 5-pyrrolidino-2-furfurylidenemalonodinitrile in the reaction mixture was read against a blank, not containing he aldehyde.

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