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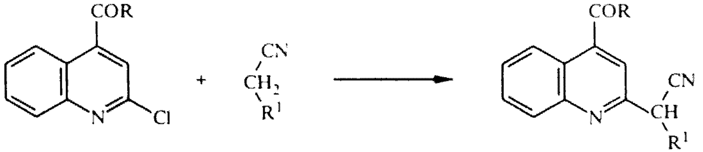
SYNTHESIS AND PROPERTIES OF (4-CARBAMOYLQUINOL-2-YL)CYANOACETIC ACIDS

A. I. Mikhalev, M. E. Konshin, and M. I. Vakhrin

Reaction of 2-chlorocinchoninic acid amides with malonodinitrile or cyanoacetic ester and potassium carbonate in refluxing DMF gives (4-carbamoylquinol-2-yl)malonodinitriles and -cyanoacetic esters respectively. Using UV and PMR spectroscopy it was shown that they exist in the ylidene form, being stabilized in the latter case by a chelate type intramolecular hydrogen bond.

Quinol-2-ylcyanoacetic acids are of interest as subjects for the study of tautomeric conversions [1] and as potentially biologically active materials.

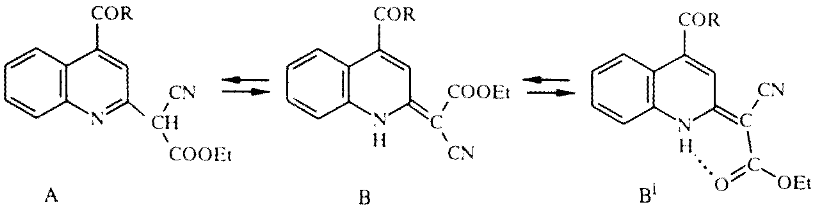
The aim of this study was the synthesis and investigation of the properties of (4-carbamoylquinol-2-yl)cyanoacetic acids. Such materials are usually obtained by reaction of haloquinolines with the sodium derivatives of active methylene compounds [2, 3]. By reaction of 2-chlorocinchoninic acid amides with malonodinitrile or cyanoacetic ester and anhydrous potassium carbonate in refluxing DMF we were able to prepare (4-carbamoylquinol-2-yl)cyanoacetic acid derivatives Ia-g (Table 1) in 72-90% yields.



Ia-g

I a R – morpholino, R^1 – CN; b R – NHC_4H_9, R^1 – CN; c R – NHC_3H_7, R^1 – $COOC_2H_5$;
d R – NHC_3H_7-*i*, R^1 – $COOC_2H_5$; e R – morpholino, R^1 – $COOC_2H_5$; f R – NHC_5H_{11}-*i*,
R^1 – $COOC_2H_5$; g R – NHC_6H_{11}-*c*, R^1 – $COOC_2H_5$

The structures of Ia-g and their tautomeric conversions were identified by UV, IR, and PMR spectroscopy (Table 1, 2). On the basis of [2, 4] we have proposed that Ia-g show a [1,3]-sigmatropic tautomerism of the type A → B. Moreover, the ylidene tautomer can exist in the chelated B′ and nonchelated B forms.



A B B¹

The UV spectra of Ia,e are similar to those of quinol-2-ylcyanoacetic ester and quinol-2-ylmalonodinitrile [2]. They have a broad, long wavelength band at 410-420 nm which corresponds to the ylidene tautomer form according to [2].

A change from nonpolar solvent (CCl_4) to polar ($CHCl_3$ or ethanol) causes a hypsochromic shift of the long wavelength band.

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TABLE 1. Parameters for Compounds Synthesized

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm					Yield, %
			solvent	NH, s, quinoline	NH, t, amide	ArH, m	$COOC_2H_5$	
Ia	$C_{17}H_{14}N_4O_2$	251...253	DMSO-D_6	12,67		7,0...7,9		74
Ib	$C_{17}H_{16}N_4O$	296...298	DMSO-D_6	12,65	8,93	7,0...7,87		75
			$CDCl_3$	12,43	8,17	7,2...7,7		
Ic	$C_{18}H_{19}N_3O_3$	214...216	DMSO-D_6	13,27	8,90	6,9...7,67	4,2 q (CH_2), 1,2 t (CH_3)	82
			$CDCl_3$	13,27	8,0	6,9...7,7	4,0 q (CH_2), 1,27 t (CH_3)	
Id	$C_{18}H_{19}N_3O_3$	218...220	DMSO-D_6	13,25	9,0	7,17...7,8	4,27 q (CH_2), 1,2 t (CH_3)	86
Ie	$C_{19}H_{19}N_3O_4$	156...157	DMSO-D_6	13,2		7,2...8,0	4,23 q (CH_2), 1,2 t (CH_3)	88
			$CDCl_3$	13,33		7,2...8,1	4,33 q (CH_2), 1,27 t (CH_3)	
If	$C_{20}H_{23}N_3O_3$	148...150	DMSO-D_6	13,23	8,93	7,13...7,83	4,23 q (CH_2), 1,2 t (CH_3)	72
Ig	$C_{21}H_{22}N_3O_3$	228...230	DMSO-D_6	13,25	8,83	7,1...8,0	4,17 q (CH_2), 1,3 t (CH_3)	90
			$CDCl_3$	13,27	8,1	6,8...7,8	4,0 q (CH_2), 1,23 t (CH_3)	

TABLE 2. UV and IR Spectra of Ia-g

Compound	UV spectra		IR spectra, ν cm^{-1}			
	solvent	λ_{max}, nm (log ε)	amide CO	ester CO	CN	amide NH
Ia	Ethanol	290 (4,25), 410 (3,88)	1658		2192, 2212	
	conc. H_2SO_4	252 (4,41), 290 (4,40), 340 (3,94				
	0.1 N NaOH	285 (4,16), 300 (4,15)				
Ib			1678		2192, 2212	3280
Ic			1660	1642	2208	3276
Id			1660	1642	2208	3280
Ie	Ethanol	236 (4,51), 290 (4,40), 410 (4,05)	1670	1642	2205	
	0.1 N NaOH	236 (4,55), 284 (4,11), 300 (4,11), 387 (3,65)				
	0.1 N HCl	236 (4,46), 288 (4,3), 400 (3,94)				
	CCl_4	296 (4,21), 420 (3,38)				
	$CHCl_3$	242 (4,10), 292 (4,34), 415 (3,98)				
	conc. H_2SO_4	252 (4,65), 336 (4,43)				
If			1660	1645	2204	3268
Ig			1660	1643	2205	3296

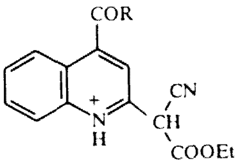
The PMR spectra of Ic-g in DMSO-D_6 and $CDCl_3$ have signals at 13.2-13.8 ppm which are typical of a chelated ring proton. Hence the PMR and UV spectra show that Ic-g in $CHCl_3$ or CCl_4 exist as the ylidene B' tautomer with a chelated intramolecular hydrogen bond. The ylidene structure for Ic-g is also confirmed by the UV spectra of the malonodinitrile Ia which has a maximum at 410 nm, since azine malonodinitriles are known to exist exclusively in the ylidene form [1].

The UV spectra of Ie in 0.1 N solutions of HCl and NaOH in ethanol are both similar to the spectra of Ia and show maxima at 400 and 387 nm respectively. Hence one can assume that Ie and Ia have similar structures in HCl and NaOH solutions and exist as the nonchelated ylidene tautomer B.

TABLE 3. Elemental Analytical Data for Ia-g

Compound	Found, %			Calculated, %		
	C	H	N	C	H	N
Ia	56,60	4,57	18,33	56,65	4,61	18,29
Ib	69,80	5,46	19,12	69,84	5,52	19,17
Ic	66,39	5,84	12,87	66,44	5,89	12,92
Id	66,50	5,93	12,98	66,44	5,89	12,92
Ie	64,51	5,49	11,84	64,58	5,42	11,89
If	67,92	6,51	11,83	67,97	6,56	11,90
Ig	69,17	6,13	11,58	69,21	6,09	11,53

In concentrated sulfuric acid the long wavelength band in Ia,e disappears and is replaced by a maximum at 336 nm. This is similar to the behavior of 2-pyridylcyanoacetic ester in concentrated acids [4] and is associated with the formation of aromatic protonated forms. For Ie-g this form can be assigned the structure C. It is possible that, in concentrated sulfuric acid, protonation of the amide or ester function occurs [5] so excluding the formation of the intramolecular hydrogen bond.



C

In contrast to Ie, compound Ia is only partly protonated in concentrated sulfuric acid and has maxima both at 430 nm and at 405 nm,* associated with the lower basicity of the latter.

EXPERIMENTAL

IR Spectra were taken on a UR-20 instrument in Vaseline oil. PMR Spectra were recorded on an RY-2310 instrument (60 MHz) with HMDS internal standard and DMSO-D$_6$ or CDCl$_3$ solvent. UV Spectra were recorded on an SF-16 instrument for $2 \cdot 10^{-5}$ molar solutions. The compound parameters are given in Tables 1-3.

Elemental analytical data for C, H, and N agreed with that calculated.

(4-Carbamoylquinol-2-yl)malonodinitriles Ia,b. A mixture of the corresponding 2-chlorocinchoninic acid amide [6] (0.01 mole), malonodinitrile (0.7 g, 0.01 mole), and anhydrous potassium carbonate (1.4 g, 0.01 mole) in DMF (10 ml) was heated at 150°C for 3 h, cooled, diluted with water, and neutralized with acetic acid. The precipitate was filtered and crystallized from dioxane.

(4-Carbamoylquinol-2-yl)cyanoacetic Esters Ic-g. A mixture of the corresponding 2-chlorocinchoninic acid amide (0.01 mole), the ethyl ester of cyanoacetic acid (1.1 g, 0.01 mole), and anhydrous potassium carbonate (1.4 g, 0.01 mole) was heated at 150°C for 6 h, cooled, and neutralized with acetic acid. The precipitate was filtered off and crystallized from alcohol.

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*Table 2 says 290 and 340 nm for Ia — Translator.

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