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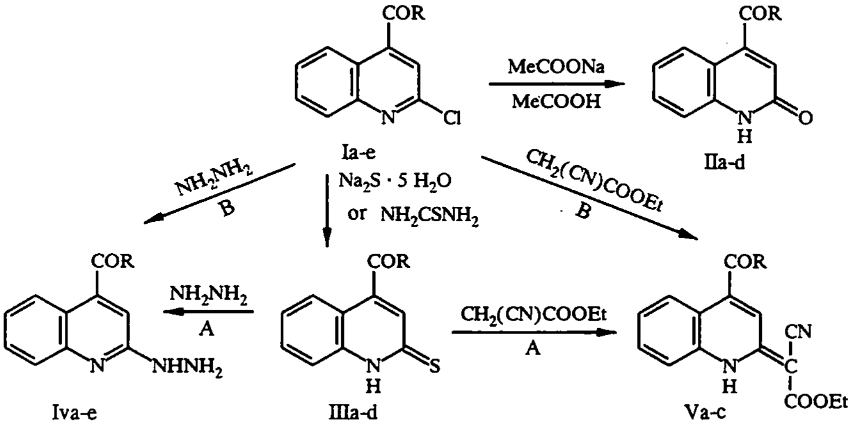
SYNTHESIS AND CONVERSIONS OF 2-SUBSTITUTED CINCHONINIC ACID AMIDES

A. I. Mikhalev, M. E. Kon'shin, and M. I. Vakhrin

Amides of 2-oxo- or 2-thiocinchoninic acid have been obtained by the reaction of substituted amides of 2-chlorocinchoninic acid with sodium acetate or sodium sulfide. The reaction of 2-thiocinchoninic acid amides with hydrazine hydrate or ethyl cyanoacetate leads to derivatives of 2-hydrazinocinchoninic acid or (4-carbamoyl-2-quinolyl)cyanoacetic ester respectively, which were also obtained from 2-chlorocinchoninic acid amides.

In studies previously reported by us it was shown that substituted amides of 2-chlorocinchoninic acid may be used as starting materials for obtaining biologically active amides of 2-hydrazino- and 2-arylaminocinchoninic acids [1, 2].

The present work was undertaken with the aim of finding conditions for converting 2-chlorocinchoninic acid amides into 2-oxo- and 2-thiocinchoninic acid amides and studying certain nucleophilic reactions for replacing sulfur in the latter.



I—V a R = C_3H_7NH; b R = *i*-C_3H_7NH; c R = morpholino; d R = 2-ClC_6H_4NH;
e R = 2-$CH_3C_6H_4NH$

The investigations showed that substituted amides of 2-oxocinchoninic acid (IIa-d) (Table 1) are formed in good yield from amides (I) when using acetate anion as a strong nucleophile. The reaction is probably catalyzed by acetic acid due to protonation of the quinoline ring.

When heating amides (I) with sodium sulfide in DMF or with thiourea, substituted amides of 2-thiocinchoninic acid (IIIa-d) are formed. In the latter case it is probable that after nucleophilic replacement of chlorine by a residue of thiourea the intermediate compound is decomposed with the formation of the 2-thio derivative.

The signals at 12.20-12.83 ppm in the PMR spectra of these compounds were assigned to the NH group proton of the quinoline nucleus on the basis of literature data [3] on the oxo and thione structure of quinoline derivatives of types (II) and (III).

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TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	PMR spectrum, δ, ppm				Yield, %, method A (B)
		C	H	N		NH quinoline	NH amide	ArH, NH, m	NH_2 br. s	
1	2	3	4	5	6	7	8	9	10	11
IIa	$C_{13}H_{14}N_2O_2$	67.81 67,92	6.13 6,25	12.17 12,22	291...292	11,20	8,77	6,43...7,83		76
IIb	$C_{13}H_{14}N_2O_2$	67.81 67,90	6.13 6,08	12.17 12,04	222...223	11,93	8,60	6,45...7,80		80
IIc	$C_{14}H_{14}N_2O_3$	65.10 65,17	5.46 5,53	10.85 10,77	206...207	11,95		6,40...7,73		78
IId	$C_{16}H_{11}Cl_2N_2O_2$	61.06 61,14	3.52 3,42	8.90 8,73	318...320	11,90	8,70	6,50...7,80		72
IIIa	$C_{13}H_{14}N_2O$	63.39 63,30	5.73 5,65	11.37 11,43	278...280	12,83	8,78	7,10...8,20		71
IIIb	$C_{14}H_{14}N_2O$	65.09 65,15	5.46 5,52	10.85 10,90	120...121	12,80		7,20...8,35		67
IIIc	$C_{16}H_{11}ClN_2O$	61.06 61,11	3.52 3,60	8.90 8,96	188...190	12,80	8,80	7,23...8,00		78
IIId	$C_{17}H_{14}N_2O$	69.36 69,27	4.79 4,72	9.52 9,47	268...270	12,82	8,75	7,27...8,00		83
IVa	$C_{13}H_{15}N_4O$	64.18 64,28	6.22 6,31	23.03 23,12	180...181		8,60	7,25...7,80	6,77	(81)

TABLE 1 (continued)

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	PMR spectrum, δ, ppm				Yield, %, method A (B)
		C	H	N		NH quinoline	NH amide*	ArH, NH, m	NH_2 br. s	
1	2	3	4	5	6	7	8	9	10	11
IVb	$C_{13}H_{15}N_4O$	64,18 64,23	6,22 6,15	23,03 23,15	184...185		8,60	7,27...7,83	6,83	70 (85)
IVc	$C_{16}H_{13}ClN_4O$	61,44 61,37	4,19 4,10	17,92 17,86	187...188		8,50	7,23...8,00	7,17	63 (78)
IVd	$C_{18}H_{18}N_4O$	70,56 70,44	5,92 5,85	18,29 18,21	174...175		8,27	7,28...8,00	7,10	65 (83)
IVe	$C_{18}H_{18}N_4O$	70,56 70,46	5,92 6,06	18,29 18,23	189...190		8,30	7,30...7,80	7,15	(87)
Va †	$C_{21}H_{16}ClN_3O$	69,71 69,64	4,46 4,38	11,62 11,57	228...230	13,27	10,77	7,33...8,10		58 (80)
Vb †	$C_{22}H_{19}N_3O_3$	70,76 70,82	5,13 5,20	11,25 11,33	236...237	13,23	10,60	7,27...8,10		63 (82)
Vc †	$C_{23}H_{21}N_3O_3$	71,30 71,21	5,46 5,38	10,85 10,93	238...240	13,33	10,50	7,20...8,10		(84)

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*The signals of protons of substituents at the amide group are not given in Table 1.

†Signals of protons of the $COOC_2H_5$ group: (Va) 4.31 q (CH_2), 1.23 t (CH_3); (Vb) 4.27 q (CH_2), 1.27 t (CH_3); (Vc) 4.23 q (CH_2), 1.2 t (CH_3).

On boiling with hydrazine hydrate the 2-thiocinchoninic acid amides were converted into 2-hydrazinocinchoninic acid amides (IVb-d), and on reaction with ethyl cyanoacetate into derivatives of (4-carbamoyl-2-quinolyl)-cyanoacetic ester (Va, b). Compounds (IV) and (V) were also synthesized from amides (I) to confirm their structure and also to compare alternative methods of synthesis. The results obtained indicate that both methods may be used successfully for preparative purposes.

EXPERIMENTAL

The IR spectra were recorded on a UR 20 instrument in Nujol. The PMR spectra were obtained on a RYa 2310 instrument (60 MHz), internal standard was HMDS, and solvent DMSO-D_6. The characteristics of the compounds obtained are given in Table 1.

Substituted Amides of 2-Oxocinchoninic Acid (IIa-d). A mixture of the appropriate 2-chlorocinchoninic acid amide [4] (0.01 mole) and sodium acetate (1.2 g, 0.015 mole) in conc. AcOH was boiled for 1 h, cooled, diluted with water, the precipitate was filtered off, and recrystallized from DMF. IR spectra of compounds (IIa-d): 1640-1660 (CO amide); 3200-3285 cm^{-1} (NH).

Substituted Amides of 2-Thiocinchoninic Acid (IIIa-d). A mixture of the appropriate 2-chlorocinchoninic acid amide (0.01 mole) and hydrated sodium sulfide (2.5 g, 0.015 mole) in DMF (10 ml) was heated at 150°C for 2 h, cooled, and diluted with water. Contaminants were filtered off, hydrochloric acid was added to the filtrate, and the precipitated solid recrystallized from dioxan. IR spectra of compounds (IIIa-d): 1640-1670 (CO amide); 3200-3290 cm^{-1} (NH).

2-Thiocinchoninic Acid o-Tolylamide (IIId). A mixture of 2-chlorocinchoninic acid o-tolylamide (2.97 g, 0.01 mole) and thiourea (0.76 g, 0.01 mole) in DMF (10 ml) was heated for 5 h, cooled, diluted with 10% aqueous sodium hydroxide solution, and filtered from contaminants. The reaction product was precipitated with dilute hydrochloric acid, and recrystallized from dioxan. Yield was 1.8 g (60%), mp 268-269°C.

Substituted Amides of 2-Hydrazinocinchoninic Acid (IVb-d). A. A solution of the appropriate 2-thio-cinchoninic acid amide (0.01 mole) in 60% aqueous hydrazine hydrate solution (10 ml) and dioxan (10 ml) was boiled for 1 h, cooled, and diluted with water. The precipitated solid was recrystallized from dioxan.

B. A solution of the appropriate 2-thiocinchoninic acid amide (0.01 mole) in 60% aqueous hydrazine hydrate solution (10 ml) and dioxan (10 ml) was boiled for 2 h, and cooled. The precipitated solid was filtered off and recrystallized from dioxan. Compounds (IVa-e) were obtained. Mixed melting points with samples obtained under conditions of the previous experiment gave no depression of melting point.

Derivatives of (4-Carbamoyl-2-quinolyl)cyanoacetic Ester (Va, b). A. A mixture of the appropriate amide (IIIc, d) (0.01 mole), ethyl cyanoacetate (1.1 g, 0.01 mole), and anhydrous potassium carbonate (1.4 g, 0.01 mole) in DMF (10 ml) was heated at 120°C for 2 h, cooled, diluted with water, and neutralized with acetic acid. The precipitate was recrystallized from dioxan. IR spectra of compounds (Va, b): 1640-1670 (CO amide); 2204-2208 ($C\equiv N$); 3200-3285 cm^{-1} (NH).

B. A mixture of the appropriate amide (Id-f) (0.01 mole), ethyl cyanoacetate (1.1 g, 0.01 mole), and anhydrous potassium carbonate (1.4 g, 0.01 mole) in DMF (10 ml) was heated at 150°C for 6 h, cooled, diluted with water, and neutralized with acetic acid. The precipitated solid was filtered off and crystallized from dioxan. Compounds (Va-c) were obtained. Mixed melting points with samples of (Va, b) obtained under the conditions of the previous experiment showed their identity.

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