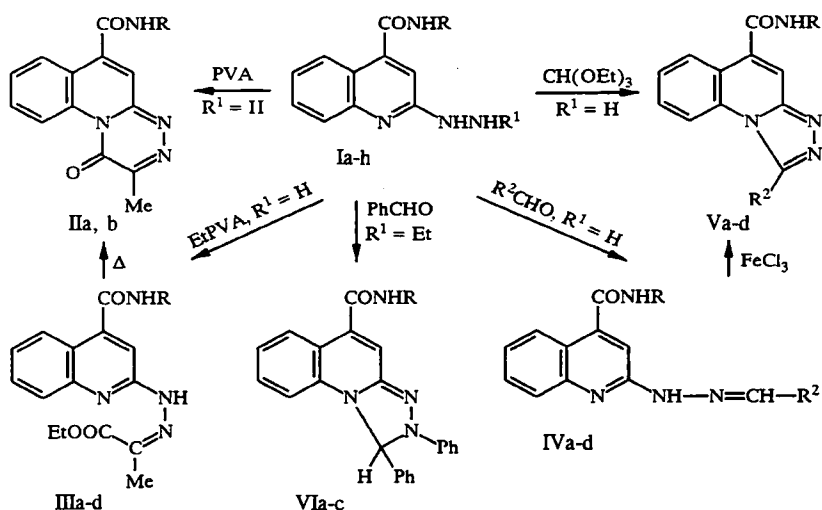


SYNTHESIS OF 2-SUBSTITUTED CINCHONINIC ACID AMIDES AND THEIR CYCLIZATION INTO 1,2,4-TRIAZOLO[4,3-*a*]- QUINOLINE-9- AND 1,2,4-TRIAZINO[4,3-*a*]QUINOLINE-10- CARBOXYLIC ACID AMIDES

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*Substituted amides of 2-hydrazino- and 2-ethylhydrazinocinchoninic acids react with pyruvic acid and its ethyl ester to give amides of 3-methyl-4-oxo-1,2,4-triazolo[4,3-*a*]quinoline-10-carboxylic acid. On reaction with aromatic aldehydes they are converted into amides of 2-ethyl-3-phenyl-2,3-dihydro-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid, or, in the case of unsubstituted hydrazines, into amides of 2-arylidenehydrazinocinchoninic acid, which was oxidized to substituted 1,2,4-triazolo[4,3-*a*]quinolines.*

We showed in previous studies [1, 2] that amides of 2-hydrazinocinchoninic acid and their N-acyl derivatives may be used as starting materials for the synthesis of biologically active amides of 1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid. In the present work the reaction of substituted amides of 2-hydrazino- and 2-ethylhydrazinocinchoninic acids with pyruvic acid, its ethyl ester, and with formic acid have been studied and also with aldehydes leading to condensed heterocycles containing a cinchoninic acid fragment.



Ia R = *n*-Pr, R¹ = H; Ib R = *i*-Pr, R¹ = H; Ic R = 2-MeC₆H₄, R¹ = H; Id R = 2,5-Me₂C₆H₃, R¹ = H;
Ie R = 2,6-Me₂C₆H₃, R¹ = H; If R = *n*-Pr, R¹ = Et; Ig R = *i*-Pr, R¹ = Et; Ih R = 2,5-Me₂C₆H₃,
R¹ = Et; IIa R = *n*-Pr; IIb R = *i*-Pr; IIIa R = *n*-Pr; IIIb R = *i*-Pr; IIIc R = 2,5-Me₂C₆H₃;
IIId R = 2,6-Me₂C₆H₃; IVa R = *i*-C₃H₇, R² = 2-FC₆H₄; IVb R = *i*-Pr, R² = 4-ClC₆H₄; IVc R = *i*-Pr,
R² = Ph; IVd R = 2-MeC₆H₄, R² = Ph; Va R = *i*-Pr, R² = H; Vb R = *i*-Pr, R² = H; Vc R = *i*-Pr,
R² = Ph; Vd R = 2-MeC₆H₄, R² = Ph; VIa R = *n*-Pr; VIb R = *i*-Pr; VIc R = 2,5-Me₂C₆H₃

TABLE 1. Characteristics of the Compounds Synthesized

Com- pound	Empirical formula	Found, % Calculated, %			mp, °C	PMR spectra, δ ppm				Yield, %
		C	H	N		quinoline NH	amide , NH	ArH, m [†]	other protons	
1	2	3	4	5	6	7	8	9	10	11
I f	C ₁₅ H ₂₀ N ₄ O	66.00 66.15	7.32 7.40	20.43 20.57	139...140	8.87	10.7	7.6...8.7	4.17 q (CH ₂), 1.2 t (CH ₃)	76
I g	C ₁₅ H ₂₀ N ₄ O	66.03 66.15	7.52 7.40	20.67 20.57	145...146	8.80	10.8	7.6...8.3	4.13 q (CH ₂), 1.3 t (CH ₃)	80
I h	C ₂₀ H ₂₂ N ₄ O	71.94 71.83	6.78 6.63	16.88 16.76	164...165	8.85	10.8	7.6...8.3	4.15 q (CH ₂), 1.2 t (CH ₃)	85
II a	C ₁₆ H ₁₆ N ₄ O ₂	64.70 64.85	5.52 5.44	18.86 18.91	230...231		8.7	7.4...8.0	2.13 s (CH ₃)	69
II b	C ₁₆ H ₁₆ N ₄ O ₂	64.94 64.85	5.57 5.44	18.83 18.91	227...228		8.7	7.6...7.8	2.1 s (CH ₃)	75
III a	C ₁₈ H ₂₂ N ₄ O ₃	64.22 63.14	6.54 6.48	16.46 16.37	194...195	10.93	8.8	7.2...8.0	4.23 q (CH ₂), 2.13 s (CH ₃), 1.2 t (CH ₃)	81
III b	C ₁₈ H ₂₂ N ₄ O ₃	63.25 63.14	6.33 6.48	16.44 16.37	215...217	11.0	8.8	7.2...8.0	4.2 q (CH ₂), 2.2 s (CH ₃), 1.2 t (CH ₃)	78
III c	C ₂₃ H ₂₄ N ₄ O ₃	68.20 68.30	5.85 5.98	13.77 13.86	187...188	10.17	8.2	6.8...7.8	4.27 q (CH ₂), 2.3 s (CH ₃), 1.2 t (CH ₃)	84
III d	C ₂₃ H ₂₄ N ₄ O ₃	68.21 68.30	6.13 5.98	13.70 13.86	221...222	10.33	8.2	6.9...7.9	4.27 q (CH ₂), 2.1 s (CH ₃), 1.27 t (CH ₃)	87
IV a	C ₂₀ H ₁₉ FN ₄ O	68.64 68.55	4.58 4.47	16.12 15.99	263...265	11.73	8.8	7.0...8.1	8.4 s (-CH-)	82

TABLE 1 (continued)

Com- pound	Empirical formula	Found, % Calculated, %			mp, °C	PMR spectra, δ ppm				Yield, %
		C	H	N		quinoline NH	amide NH	ArH, m [†]	other protons	
1	2	3	4	5	6	7	8	9	10	11
IVb	C ₂₀ H ₁₉ ClN ₄ O	65.35 65.48	5.10 5.22	15.16 15.27	260...262	11.67	8.8	7.1...7.9	8.2 s (-CH-)	80
IVc	C ₂₀ H ₂₀ N ₄ O	72.77 72.87	6.13 6.07	16.73 16.86	288...290	11.50	8.8	7.2...7.9	8.27 s (-CH-)	86
IVd	C ₂₄ H ₂₀ N ₄ O	75.61 75.77	5.38 5.30	14.81 14.73	268...270	10.47	8.3	6.9...7.8	8.1 s (-CH-)	90
Va	C ₁₄ H ₁₇ N ₄ O	65.46 65.35	6.78 6.66	21.85 21.78	232...233		8.7	7.7...8.2	10.1 s (1H, 3-H)	89
Vb	C ₁₄ H ₁₇ N ₄ O	65.27 65.35	6.51 6.66	21.62 21.78	260...262		8.8	7.5...8.5	10.1 s (1H, 3-H)	93
Vc	C ₂₀ H ₁₉ N ₄ O	72.55 72.48	5.86 5.78	16.80 16.91	242...243		8.6	7.6...8.2		70
Vd	C ₂₄ H ₁₈ N ₄ O	76.03 76.17	4.68 4.80	14.70 14.81	230...232		8.2	7.3...8.0		75
VIa	C ₂₂ H ₂₄ N ₄ O	73.22 73.30	3.85 3.94	15.40 15.55	149...150		10.2	7.6...8.1	7.1 (1H, 3-H)	67
VIb	C ₂₂ H ₂₄ N ₄ O	73.18 73.30	3.80 3.94	15.43 15.55	140...142		10.1	7.7...8.1	7.3 (1H, 3-H)	72
VIc	C ₂₇ H ₂₆ N ₄ O	76.03 76.15	6.10 6.20	13.38 13.26	160...161		10.3	7.1...8.2	6.77 (1H, 3-H)	65

*Signals for protons in amide group substituents are not given in Table 1.

[†]Signals for ArH and NH protons for compounds (If, h).

It was established that 3-methyl-4-oxo-1,2,4-triazino[4,3-*a*]quinoline-10-carboxylic acid amides (IIa, b) were formed on heating compounds (Ia, b) with pyruvic acid (Table 1).

2-(1-Ethoxycarbonylethylidenehydrazino)cinchoninic acid amides (IIIa-d) were obtained on using ethyl pyruvate in place of the acid in the reaction with amides (I). In difference to their analogs with a free carboxyl group, these compounds did not cyclize under these conditions into triazinoquinoline derivatives. This is probably due to the catalytic effect of protons formed on dissociation of the free carboxyl group. Compounds (IIIa, b) underwent an intramolecular cyclization on thermolysis to give the corresponding 1,2,4-triazino[4,3-*a*]quinoline derivatives (IIa, b).

Compounds (Ib, c) containing a free hydrazino group react with aromatic aldehydes giving the corresponding hydrazones (IVa-d), which were converted on oxidation with ferric chloride into amides of 3-phenyl-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid (Vc, d). The analogous compounds (Va, b) without a substituent at position 3 were also obtained on heating amides (Ia, b) with formic acid or ethyl orthoformate. Probably the cyclization of 2-hydrazinocinchoninic acid amides proceeds through the intermediate acyl derivative and in the case of the ortho ester through the ethoxymethylenehydrazino derivative.

The 2-(β -ethylhydrazino) derivatives (If-h) were converted on reaction with benzaldehyde into 3-substituted 2-ethyl-2,3-dihydro-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid amides (VIa-c), i.e., stabilization of the intermediate O,N-hemiacetal was achieved by cyclization.

The structures of the compounds obtained were confirmed by data of IR and PMR spectra (see Table 1 and Experimental section).

EXPERIMENTAL

The IR spectra were taken on a UR 20 instrument in Nujol. The PMR spectra were obtained on an RYa 2310 (60 MHz) instrument, internal standard was HMDS, and solvent DMSO- D_6 . The characteristics of compounds are given in Table 1. Compound (Ic) is reported in [1] and compounds (Ia, b, d, e) in [4].

Substituted Amides of 2-Ethylhydrazinocinchoninic Acid (If-g). A solution of the appropriate 2-chlorocinchoninic acid amide [3] (0.01 mole) and ethylhydrazine (0.6 g, 0.01 mole) (or hydrazine) in dioxan (10 ml) was boiled for 2 h, cooled, the precipitated solid was separated, and recrystallized from dioxan.

Substituted Amides of 2-(1-Ethoxycarbonylethylidenehydrazino)cinchoninic Acid (IIIa-d). A solution of the appropriate amide (I) (0.01 mole) and ethyl pyruvate (1.16 g, 0.01 mole) in dioxan (10 ml) was boiled for 2 h, cooled, and diluted with water. The solid was filtered off and recrystallized from dioxan.

Substituted Amides of 3-Methyl-4-oxo-1,2,4-triazino[4,3-*a*]quinoline-10-carboxylic Acid (IIa, b). A. A mixture of amide (Ia, b) (0.01 mole) and pyruvic acid (0.88 g, 0.01 mole) in dioxan (10 ml) was boiled for 1 h, cooled, and poured into water. The solid was filtered off and recrystallized from DMF. IR spectra of compounds (IIa, b): 1640-1660 (CO), 3200-3300 cm^{-1} (NH).

B. A solution of amide (IIIa, b) (0.01 mole) in ethyleneglycol (10 ml) was heated for 5 h at 160°C, cooled, and diluted with water. The solid was filtered off and recrystallized from DMF. Compounds (IIa, b) were obtained. A mixed melting point with samples of (IIa, b) obtained under the conditions of experiment A proved their identity.

Substituted Amides of 2-(β -Arylidenehydrazino)cinchoninic Acid (IVa-d). Benzaldehyde (1.06 g, 0.01 mole) was added to a solution of amide (Ib, c) (0.01 mole) in dioxan (10 ml) and 50% acetic acid (5 ml) and the mixture boiled for 1 h, cooled, and diluted with water. The solid was filtered off and recrystallized from dioxan.

Substituted Amides of 1,2,4-Triazolo[4,3-*a*]quinoline-9-carboxylic Acid (Va-d). A. A solution of amide (Ia, b) (0.01 mole) and ethyl orthoformate (1.5 g, 0.01 mole) in dioxan (10 ml) was boiled for 1 h, cooled, and diluted with water. The solid was recrystallized from DMF. IR spectra of compounds (Va, b): 1625-1630 (CO amide), 3200-3300 cm^{-1} (NH).

B. A mixture of amide (IVc, d) (0.01 mole) and iron(III) chloride (2.4 g, 0.015 mole) in DMF (10 ml) was boiled for 2 h, cooled, and poured into water. The solid was filtered off and recrystallized from DMF. Compounds (Vc, d) were obtained.

1,2,4-Triazolo[4,3-*a*]quinoline-9-carboxylic Acid Isopropylamide (Vb). A solution of 2-hydrazinocinchoninic acid isopropylamide (2.44 g, 0.01 mole) in formic acid (10 ml) was boiled for 1 h, cooled, diluted with water, and neutralized with sodium carbonate solution. The solid was filtered off and recrystallized from DMF. Compound (Vb) (1.8 g, 70%) was obtained having mp 259-260°C. A mixed melting point with a sample of (Vb) obtained under the conditions of the previous experiment gave no depression of melting point.

Substituted Amides of 2-Ethyl-3-phenyl-2,3-dihydro-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid (VIa-c). Benzaldehyde (1.06 g, 0.01 mole) was added to a mixture of amide (If-h) (0.01 mole) in dioxan (10 ml) and 50% acetic acid (5 ml). The reaction mixture was boiled for 1 h, cooled, poured into water, and neutralized with sodium carbonate solution. The solid was filtered off and recrystallized from dioxan. IR spectra of compounds (VIa-c): 1625-1640 (CO amide), 3200-3300 cm^{-1} (NH).

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