Reaction of N-Oxide Ib with TCE. This reaction was carried out for the first 24 h with cooling of the mixture to 4°C, then at room temperature. The CTC was not recrystallized, as it was unstable.

Reaction of N-Oxide II with TCE. This reaction was carried out in a 1:1 mixture of dioxane and benzene; the CTC was recrystallized from a 1:2 mixture of dioxane and benzene.

Interaction of CTC of N-Oxide Ic (with TCE) with Acetylenedicarboxylic Ester. To a solution of 0.156 g (1.1 mmoles) of the diester in 6 ml of absolute chloroform, 0.188 g (~1 mmole) of the CTC was added. The solution was mixed by means of a magnetic stirrer for 6 h at room temperature. The course of the reaction was followed by means of TLC (chloroform—ethanol, 20:1). The solution was evaporated under vacuum to a volume of 0.5 ml, and the mixture was separated in a column with 4 g of silica gel. By elution with a 20:1 mixture of chloroform and ethanol, the following fractions were obtained: dark yellow oil (products of polymerization of the acetylenedicarboxylic ester and decomposition of the TCE) 0.086 g (not identified); betaine IVc 0.107 g (38%) as a yellow powder, mp 201-202°C. Identical to known preparation obtained by interaction of N-oxide Ic with acetylenedicarboxylic ester.

Decomposition of CTC of N-Oxide If (with TCE) by Hydrobromic Acid. To a 0.250-g sample (~1 mmole) of the CTC in 5 ml of dioxane, 0.22 ml (~2 mmoles) of concentrated HBr was added. The colorless residue of the hydrobromide of the N-oxide If was separated by centrifuging, washed with 2 ml of dioxane and then with ether (2 × 2 ml), and recrystallized from acetone. Obtained 0.204 g (76%) of the salt, mp 146-148°C. Identical to a known salt obtained by the interaction of the N-oxide If with HBr.

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SYNTHESIS OF SUBSTITUTED 2-HYDRAZINO- AND 2-(β-ACYLHYDRAZINO)-CINCHONINIC ACID AMIDES AND THEIR CYCLIZATION TO 1,2,4-TRIAZOLO[4,3-*a*]QUINOLINE-9-CARBOXYLIC ACID AMIDES

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UDC 547.832

The reaction of substituted 2-chlorocinchoninic acid amides with hydrazine hydrate or acylhydrazines gave 2-hydrazino- and 2-(β-acylhydrazino)cinchoninic acid amides. The latter were also obtained by acylation of the 2-hydrazino derivatives. It is shown that 1,2,4-triazolo[4,3-a]quinoline-9-carboxylic acid amides are formed when 2-hydrazinocinchoninic acid amides are refluxed with formic or acetic acid.

2-Hydrazinocinchoninic acid amides have not been previously investigated. At the same time, they are of interest as starting compounds for obtaining condensed heterocycles containing a quinoline fragment and as potentially biologically active substances [1].

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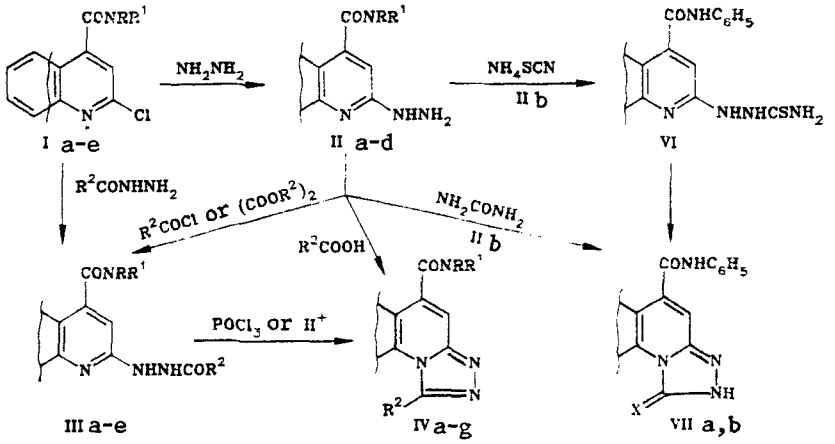
The present research was undertaken to synthesize 2-hydrazino- and 2-(β-acylhydrazino)cinchoninic acid amides and study the possibility of converting them to amide derivatives of 1,2,4-triazolo[4,3-*a*]quinoline. To achieve these ends we studied the reaction of 2-chlorocinchoninic acid amides I with hydrazine hydrate and acylhydrazines.



Ia R=H, R¹=CH₃; b R=H, R¹=*t*-C₄H₉; c R=H, R¹=C₆H₅; d R=R¹=C₂H₅; e RR¹= =piperidyl; IIa R=H, R¹=*t*-C₄H₉; b R=H, R¹=C₆H₅; c R=R¹=C₂H₅; d RR¹=piperidyl; ; IIIa R=H, R¹=CH₃, R²=C₆H₅; b R=H, R¹=*t*-C₄H₉, R²=C₆H₅; c RR¹= piperidyl, R²=C₆H₅; d R=H, R¹=C₆H₅, R²=CH₃; e R=H, R¹=C₆H₅, R²=COOC₂H₅; IV a R=R¹= =C₂H₅, R²=H; b R=R²=H, R¹=*t*-C₄H₉; c R=H, R¹=C₆H₅, R²=CH₃; d RR¹=piperidyl, R²=CH₃; e R=H, R¹=CH₃, R²=C₆H₅; f RR¹=piperidyl, R²=C₆H₅; g R=H, R¹=C₆H₅, R²=COOC₂H₅; VII a X=S, b X=O

It was established that amides Ib-e react with hydrazine hydrate on refluxing in ethanol to give 2-hydrazinocinchoninic acid amides IIa-d in 66-82% yields (Table 1). Hydrazinolysis of the amido group does not occur under these conditions.

2-(β-Acetylhydrazino)cinchoninic acid anilide (IIId) is obtained in the reaction of IIb with acetyl chloride, while 2-(β-ethoxalylhydrazino)cinchoninic acid anilide (IIIe) is obtained when IIb is heated with diethyl oxalate in ethanol.

2-(β-Benzoylhydrazino)cinchoninic acid amides IIIa-c are obtained in good yields in the reaction of amides Ia, b, e with benzoylhydrazine in refluxing DMF. To confirm the structures of IIIb, c we carried out the reaction of amides IIa, d with benzoyl chloride. The IIIb, c obtained by the two methods were identical.

Acylation of the hydrazino function with simultaneous heterocyclization at the nitrogen atom of the quinoline ring occurs when amides IIa-d are refluxed in excess formic or acetic acid to give 1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid amides IVa-d.

It should be noted that we did not observe the formation of 1,2,4-triazolo[4,3-*a*]quinoline derivatives either in the synthesis of III or in an attempt at their thermal cyclization. However, amides IVe, f were obtained when IIIa, c were heated in glacial acetic acid. Under similar conditions IIId, e were converted to 3-methyl-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid amides IVc, g. These examples and those presented above constitute evidence that the cyclization of 2-(β-acylhydrazino)quinolines to IV is an acid-catalyzed process.

It was shown that IIIa, c, e undergo cyclization to 3-phenyl-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid amides IVe-g when they are refluxed in phosphorus oxychloride. 3-Phenyl-9-cyano-1,2,4-triazolo[4,3-*a*]quinoline (V) is obtained when IIIb, which contains a tert-butyl group (a good leaving group), undergoes cyclization under these conditions.

In the case of IIb it was shown that heating it with ammonium thiocyanate in ethanol gives a mixture of 2-(β-thiocarbamoylhydrazino)cinchoninic acid amide (VI) and 3-thio-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid amide (VIIa). Compound VI was also obtained by heating amide Ic with thiosemicarbazide in ethanol. In the latter case we also noted the formation of a small amount of VIIa, the presence of which was proved by TLC. In both reactions the initially formed VI evidently undergoes thermal cyclization to VIIa.

2-Oxo-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid anilide (VIIb) is formed when IIb is refluxed with urea in ethylene glycol.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in d_6-DMSO were obtained with an RYa-2310 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard.

TABLE 1. Characteristics of the Synthesized II-VII

Compound	Empirical formula	mp, °C*	IR spectra, ν, cm^{-1}		PMR spectra, ppm	Yield, %
			N—H	C=O		
IIa	$C_{14}H_{18}N_4O$	219...221	3260, 3400, 3490	1645	1,45 (9H, s, *t*-Bu); 7,92 (8H, m, Ar, NH, NH_2)	78
IIb	$C_{16}H_{14}N_4O$	225...227	3340, 3185, 3235	1655	7,28 (13H, m, Ar, NH, NH_2); 10,62 (1H, s, NH)	82
IIc	$C_{14}H_{18}N_4O$	156...158	3220, 3325	1630	1,02 (6H, t, $2CH_3$); 3,15 (4H, q, $2CH_2$); 5,78 (2H, d, NH_2); 7,18 (6H, m, Ar, NH)	66
IId	$C_{15}H_{18}N_4O$	193...195	3335, 3430	1615	1,55 (6H, m, $3CH_2$); 3,35 (4H, t, $2CH_2$); 7,08 (8H, m, Ar, NH, NH_2)	82
IIIa	$C_{18}H_{16}N_4O_2$	262...264	3130, 3245, 3345	1610, 1635	3,22 (3H, d, CH_3); 7,92 (11H, m, Ar, NH); 9,22 (1H, d, NH); 9,95 (1H, d, NH)	73
IIIb	$C_{21}H_{22}N_4O_2$	263...264	3220, 3295, 3380	1630, 1670	1,38 (9H, s, *t*-Bu); 7,52 (11H, m, Ar, NH); 8,93 (1H, d, NH); 10,35 (1H, d, NH)	60 (67)**
IIIc	$C_{22}H_{22}N_4O_2$	233...234	3155, 3240	1610, 1645	1,55 (6H, m, $3CH_2$); 3,22 (4H, t, $2CH_2$); 7,38 (10H, m, Ar); 9,08 (1H, d, NH); 10,48 (1H, d, NH)	56 (61)**
IIId	$C_{18}H_{16}N_4O_2$	245...247	3130, 3245, 3290	1640, 1650	2,02 (3H, s, CH_3); 7,28 (10H, m, Ar); 8,88 (1H, d, NH); 9,82 (1H, d, NH); 10,62 (1H, s, NH)	78
IIIe	$C_{20}H_{18}N_4O_4$	203...205	3345, 3440, 3510	1625, 1670, 1715	1,35 (3H, t, CH_3); 4,28 (2H, q, CH_2); 7,38 (12H, m, Ar, NH, NH); 10,72 (1H, s, NH)	67
IVa	$C_{15}H_{16}N_4O$	165...166	—	1630	1,13 (6H, t, $2CH_3$); 3,30 (4H, q, $2CH_2$); 7,52 (5H, m, Ar); 9,92 (1H, s, CH)	32
IVb	$C_{15}H_{16}N_4O$	197...199	3220	1630	1,42 (9H, s, *t*-Bu); 7,65 (5H, m, Ar); 8,22 (1H, s, NH); 9,75 (1H, s, CH)	59
IVc	$C_{18}H_{14}N_4O$	314...316	3180	1650	3,05 (3H, s, CH_3); 7,72 (10H, m, Ar); 10,68 (1H, s, NH)	95
IVd	$C_{17}H_{18}N_4O$	230...232	—	1630	1,55 (6H, m, $3CH_2$); 3,15 (3H, s, CH_3); 3,52 (4H, t, $2CH_2$); 7,75 (5H, m, Ar)	79
IVe	$C_{18}H_{14}N_4O$	255...257	3335	1650	2,83 (3H, d, CH_3); 7,45 (10H, m, Ar); 8,58 (1H, q, NH)	63 (66)***
IVf	$C_{22}H_{20}N_4O$	246...248	—	1640	1,55 (6H, m, $3CH_2$); 3,41 (4H, t, $2CH_2$); 7,45 (10H, m, Ar)	45 (43)***
IVg	$C_{20}H_{16}N_4O_3$	224...226	3240	1650, 1715	1,38 (3H, t, CH_3); 4,32 (2H, q, CH_2); 7,42 (10H, m, Ar); 10,72 (1H, s, NH)	65 (78)***
V	$C_{17}H_{10}N_4$	252...254	—	2050 (C≡N)	7,75 (10H, m, Ar)	42
VI	$C_{17}H_{15}N_5OS$	193...195	3175, 3195, 3285	1660	5,58 (2H, br.s, NH_2); 7,35 (12H, m, Ar, 2NH); 10,75 (1H, s, NH)	48
VIIa	$C_{17}H_{12}N_4OS$	325...327	3265, 3360	1625	7,35 (11H, m, Ar, NH); 10,58 (1H, s, NH)	7
VIIb	$C_{17}H_{12}N_4O_2$	332...334	3185, 3340	1680, 1715	7,38 (11H, m, Ar, NH); 10,62 (1H, s, NH)	58

*The compounds were recrystallized: IIa-d, IIIe, IVg, and VI from acetonitrile, IVe,f and V from ethanol, IVa, b from isopropyl alcohol, IIIa-c from n-butanol, IIId from dioxane, VIIa, b from DMF, and IVc, d from DMF—water (2:1).

**The yields of IIIb, c obtained by the reaction of amides IIa, d with benzoyl chloride are indicated in parentheses.

***The yields of IVe-g obtained by cyclization of amides IIIa, c, e by the action of phosphorus oxychloride are indicated in parentheses.

The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates in an ethyl acetate—benzene (1:1) system.

The characteristics of the compounds obtained are presented in Table 1. The results of elementary analysis for C, H, and N were in agreement with the calculated values.

2-Chlorocinchoninic Acid Anilide (Ic). A 2.1-g (2 mmole) sample of phosphorus pentachloride was added to 1.89 g (1 mmole) of 2-oxocinchoninic acid, and the mixture was heated cautiously at 100°C until a homogeneous mass was obtained and hydrogen chloride evolution ceased. The resulting phosphorus oxychloride was removed by vacuum distillation (using a water aspirator), and the residue was dissolved in 50 ml of benzene. The benzene solution was treated with 3 ml of triethylamine and 0.93 g (10 mmole) of aniline, and the mixture was heated on a water bath for 1 h. The benzene and volatile substances were removed by distillation, and the residue was treated with 40% sodium carbonate solution, washed with water, and crystallized from acetonitrile to give 2.46 g (87%) of anilide Ic with mp 206-208°C.

2-Hydrazinocinchoninic Acid Amides IIa-d. A mixture of 1 mmole of the corresponding 2-chlorocinchoninic acid amide Ib-e [2, 3], 10 ml of a 60% aqueous solution of hydrazine hydrate, and 5 ml of ethanol was refluxed for 2 h, after which it was cooled, and the precipitate was recrystallized.

2-(β-Benzoylhydrazino)cinchoninic Acid Amides IIIa-c. A. A solution of 10 mmole of the corresponding amide Ia, b, e [2] and 1.3 g (12 mmole) of benzoylhydrazine in 15 ml of DMF was refluxed for 1 h, after which it was cooled and poured into water. The aqueous mixture was neutralized with 40% sodium carbonate solution, and the precipitate was recrystallized.

B. A solution of 10 mmole of the corresponding amide IIa,d and 1.7 g (12 mmole) of benzoyl chloride in 10 ml of dioxane was refluxed for 1 h, after which it was poured into water, and the aqueous mixture was worked up as described above.

2-(β-Acetylhydrazino)cinchoninic Acid Amide (IIId). A 0.9-g (12 mmole) sample of acetyl chloride was added gradually dropwise with cooling to 2.78 g (10 mmole) of anilide IIb in 20 ml of dioxane, after which 100 ml of water was added, the aqueous mixture was neutralized with 40% sodium carbonate solution, and the precipitate was recrystallized.

2-(β-Ethoxalylhydrazino)cinchoninic Acid Anilide (IIIe). A mixture of 2.78 g (10 mmole) of amide IIb, 2.2 g (15 mmole) of diethyl oxalate, and 15 ml of ethanol was refluxed for 1 h, after which it was cooled, and the precipitate was recrystallized.

3-R-1,2,4-Triazolo[4,3-*a*]quinoline-9-carboxylic Acid Amides IVa-f and 3-Carbethoxy-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid Anilide (IVg). A solution of 10 mmole of the corresponding amide IIa-f (amide IIIe for anilide IVg) in 10 ml of acetic acid (formic acid for amides IIa, c) was refluxed for 1 h, cooled, and poured into 100 ml of water. The aqueous mixture was neutralized with 40% sodium carbonate solution, and the precipitate was removed by filtration and recrystallized from the appropriate solvent.

3-Phenyl-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid Amides IVe,f, 3-Carbethoxy-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid Anilide (IVg), and 3-Phenyl-9-cyano-1,2,4-triazolo[4,3-*a*]quinoline (V). A 10-ml sample of phosphorus oxychloride was added to 10 mmole of amides IIIa, c (amide IIIe for anilide IVg, and amide IIIb for amide V), and the mixture was heated on a water bath for 1 h. The reaction mass was then worked up as in the preceding experiment. No melting-point depressions were observed for mixtures of these products with the IVe-g samples obtained under the conditions of the preceding experiment.

Cyclization of 2-(β-Acetylhydrazino)cinchoninic Acid Anilide. A solution of 3.2 g (10 mmole) of anilide IIId in 10 ml of acetic acid was refluxed for 1 h, after which it was cooled and poured into 100 ml of water. The aqueous mixture was neutralized with 40% sodium carbonate solution, and the precipitate was removed by filtration and crystallized from DMF—water (2:1) to give 2.82 g (82%) of IVc with mp 314-316°C. No melting-point depression was observed for a mixture of this product with a sample of IVc obtained under the conditions of the experiment described above, which demonstrated that they were identical.

Reaction of 2-Hydrazinocinchoninic Acid Anilide with Ammonium Thiocyanate. A mixture of 2.78 g (10 mmole) of amide IIb, 1.52 g (20 mmole) of ammonium thiocyanate, and 15 ml of ethanol was refluxed for 8 h, after which it was cooled. The resulting precipitate was recrystallized to give 0.2 g of 3-thio-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid anilide (VIIa). The mother liquor was poured into water, and the precipitate was recrystallized to give 1.6 g of 2-(β-thiocarbamoylhydrazino)cinchoninic acid anilide (VI).

2-(β-Thiocarbamoylhydrazino)cinchoninic Acid Anilide (VI). A mixture of 2.83 g (10 mmole) of anilide Ic, 0.91 g (1 mmole) of thiosemicarbazide, and 20 ml of ethanol was refluxed for 6 h. The small amount of substance that precipitated after the reaction mass was cooled (amide VIIa according to TLC data) was removed by filtration. The mother liquor was poured into water, and the aqueous mixture was neutralized with 40% sodium carbonate solution. Recrystallization of the precipitate gave 2.1 g (62%) of anilide VI.

3-Oxo-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid Anilide (VIIb). A mixture of 2.78 g (10 mmole) of anilide IIc, 0.72 g (12 mmole) of urea, and 30 ml of ethylene glycol was refluxed, after which it was cooled, and the resulting precipitate was recrystallized.

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PYRIDO[2,3-d]PYRIMIDINES

3.* SYNTHESIS AND PROPERTIES OF 7-CHLORO- AND 6-NITRO-7-CHLOROPYRIDO[2,3-d]PYRIMIDINE-2,4,5-TRIONES

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7-Chloropyridopyrimidine was obtained by diazotization of 1,3-dimethyl-7-amino-8H-pyrido[2,3-d]pyrimidine-2,4,5-trione in HCl, and its nitration and reactions with nucleophilic reagents were studied. An imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine derivative was synthesized.

Pyrido[2,3-d]pyrimidine derivatives have a broad spectrum of biological properties, including the manifestation of anticancer [2], diuretic [3], and antifolic [4] activity.

The aim of the present research was to develop methods for obtaining 7-chloro- and 6-nitro-7-chloropyrido[2,3-d]pyrimidine-2,4,5-triones, investigate their reactions with nucleophilic agents, and study their biological activity.

The reaction of 1,3-dimethyl-7-amino-8H-pyrido[2,3-d]pyrimidine-2,4,5-trione (I) with sodium nitrite in 35% HCl at 0-5°C leads to 7-chloropyridopyrimidine II. Compound II is nitrated by a blend in concentrated H_2SO_4 at 80°C to give 6-nitro derivative III.

7-Chloropyridopyrimidines II and III react with nucleophilic agents such as amines, sodium azide, and sodium butoxide to give the corresponding 7-substituted pyrido[2,3-d]pyrimidines IV and V (Table 1).

Refluxing II and III in dry DMF leads to 7-dimethylamino derivatives IVb and Vd (see [5, 6]).

Absorption bands of an NH group attached to the $C_{(7)}$ atom (3300-3375 cm^{-1}) and of an 8-NH group at 3100 cm^{-1} are present in the IR spectra of IVa and Va-c. Signals of an NH proton attached to the $C_{(7)}$ atom at 8.45-9.11 ppm and of an 8-NH proton at 10.5-12.5 ppm are present in the PMR spectra (Table 2).

Refluxing 6-nitro-7-butylamino derivative Vb with thionyl chloride in the presence of a catalytic amount of DMF gave 5-chloro derivative VI, the IR spectrum of which contains bands of stretching vibrations of the carbonyl groups of a pyrimidine ring at 1667 and 1702 cm^{-1} and of an NH bond at 3385 cm^{-1}; a signal of an NH proton attached to the $C_{(7)}$ atom is observed in the PMR spectrum at 6.75 ppm, while a signal of a proton attached to the $N_{(8)}$ atom at 10-15 ppm is absent.

The reaction of Vc with $SOCl_2$ at 20°C leads to 7-(2-chloroethyl)aminopyridopyrimidine Ve (26%) and derivative VII (59%). Derivative VII was obtained in quantitative yield when Vc was refluxed with thionyl chloride in chloroform or when it was heated at 140°C with polyphosphoric acid. Signals of labile protons of the NH group attached to the $C_{(7)}$ atom at 9.06 ppm and of the 8-NH group at 14.43 ppm are observed in the PMR spectrum of Ve. The band of $N_{(8)}$—H vibrations at 3100 cm^{-1} is absent in the IR spectrum of VII, and an intense band at 3333 cm^{-1}, which is characteristic for $C_{(7)}$—NH vibrations, is observed.

*See [1] for Communication 2.

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