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SYNTHESIS OF 1,2,4-TRIAZOLO[4,3-*a*]QUINOLINE-9-, 1,2,3,4-TETRAZOLO[4,3-*a*]QUINOLINE-9 AND 1,2,4-TRIAZINO[4,3-*a*]QUINOLINE-10-CARBOXYLIC ACIDS FROM 2-CHLORO- AND 2-HYDRAZINOCINCHONINIC ACIDS

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Treatment of 2-chlorocinchoninic acid with hydrazine gives 2-hydrazinocinchoninic acid and with aroylhydrazines to give 1,2,4-triazolo[4,3-a]quinoline-9-carboxylic acids. These are also prepared by the action of benzoyl chloride or the carboxylic acid on 2-hydrazinocinchoninic acid. With pyruvic acid the latter gives 3-methyl-4-oxo-1,2,4-triazino[4,3-a]quinoline-10-carboxylic acid and with nitrous acid gives 1,2,3,4-tetrazolo[4,3-a]quinoline-9-carboxylic acid.

In a previous report [1] we have described 2-hydrazino- and 2-(β-acylhydrazino)cinchoninic acid amides and shown that they can be converted to 1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid amides.

The aim of the present study was to synthesize analogs with a free carboxyl group. To do so we studied the reaction of 2-chlorocinchoninic acid with hydrazine and acylhydrazines and of 2-hydrazinocinchoninic acid with benzoyl chloride, carboxylic acids, and nitrous acid.

It has been shown that 2-chlorocinchoninic acid (I) reacts with hydrazine hydrate upon heating in ethanol for 3 h to form 2-hydrazinocinchoninic acid (II, Table 1) (see scheme below).

Carrying out the reaction in DMF gives the 1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acid (IIIa). The same compound, and its $C_{(3)}$ (IIIb) derivative, are also formed by heating acid II with formic or acetic acids.

In contrast to the 2-chlorocinchoninic acid amides [1], heating acid I with aroylhydrazines leads not to 2-aroylhydrazinocinchoninic acids but to 3-aryl-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic acids (IIIc, d). Compound IIIc is also formed by reaction of acid II with benzoyl chloride.

Heating acid II with diethyloxalate in DMF gives IV.

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TABLE 1. Physical Constants for II-VI

Compound	Empirical formula	mp, °C	IR spectrum, ν_{COOH}, cm^{-1}	PMR spectrum, δ, ppm	Yield, %*
II	$C_{10}H_9N_3O_2$	304...306	1710**	4,38 (d, 2H, NH_2); 7,32 (m, 7H, Ar, NH); 9,72 (s. 1H, COOH)	60
IIIa	$C_{11}H_7N_3O_2$	308...309	1710	7,48 (m, 5H, Ar); 10,02 (s 1H, COOH); 10,58 (s, 1H, CH)	52
IIIb	$C_{12}H_9N_3O_2$	308...310	1700	2,95 (s, 3H, CH_3); 7,98 (m, 5H, Ar)	42
IIIc	$C_{17}H_{11}N_3O_2$	264...266	1700	7,55 (m 10H, Ar); 8,05 (s 1H, COOH)	35
IIId	$C_{17}H_{11}N_3O_3$	282...284	1710	4,28 (s, 1H, OH); 7,28 (m 9H, Ar); 8,15 (s. 1H, COOH)	34
IV	$C_{22}H_{12}N_6O_4$	305...306	1700	7,98 m., 10H, Ar); 10,02 (s 2H, CCOH)	45
V	$C_{13}H_9N_3O_3$	298...300	1650 (CO), 1700	2,15 (s, 3H, CH_3); 7,68 (m 5H, Ar); 8,35 s, 1H, COOH)	53
VI	$C_{10}H_6N_4O_2$	267...269	1710	8,05 (m, 5H, Ar); 8,48 (s, 1H, COOH)	66

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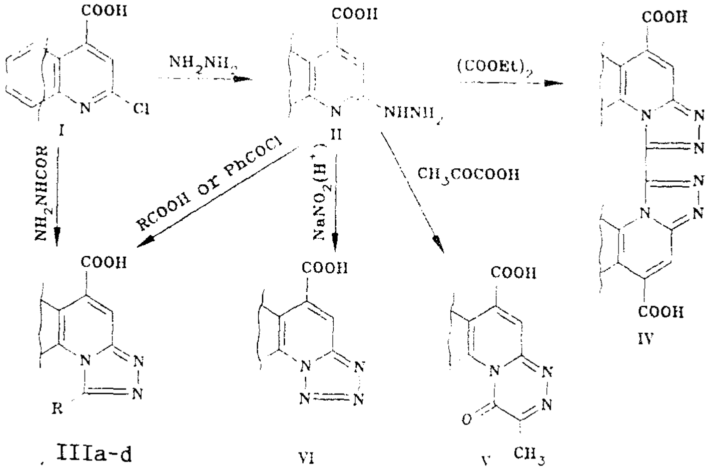
*For IIIa the yield refers to reaction of acid I with hydrazine hydrate in DMF, for IIIc to acid I with benzoylhydrazine.

**ν_{NH} at 3220, 3270, 3420 cm^{-1}.



IIIa R=H, b R=CH_3, c R=C_6H_5, d R=m-HOC_6H_4

Evidently the intermediates in the reaction of I with aroylhydrazines and acid II with acylating agents are the 2-(β-acylhydrazino)cinchoninic acids, cyclization of which is assisted by the presence of the carboxyl group in these compounds. This is in agreement with earlier proposals concerning acid catalyzed cyclization.

We have proposed that pyruvic acid will react with the hydrazine function through the carbonyl and not the carboxyl group with subsequent cyclization of the intermediate hydrazone via the carboxyl and the heterocyclic nitrogen. Indeed, the product of the reaction was 3-methyl-4-oxo-1,2,4-triazino[4,3-*a*]quinoline-10-carboxylic acid (V).

Treatment of acid II with nitrous acid gives 1,2,3,4-tetrazolo[4,3-*a*]quinoline-9-carboxylic acid (VI).

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in Vaseline mull and PMR spectra on an RY-2310 (60 MHz) instrument using HMDS internal standard and DMSO-d_6 solvent.

The reaction course and product purity was monitored on Silufol UV-254 plates in the solvent system butanol—acetic acid—water (1:1:1).

The physical constants for the compounds prepared are given in Table 1.

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

2-Hydrazinocinchoninic Acid (II). A mixture of 2-chlorocinchoninic acid (I, 2.1 g, 0.01 mole), 60% aqueous hydrazine hydrate (10 ml), and ethanol (5 ml) was refluxed for 3 h, poured into water (100 ml), and neutralized to pH 7 with 20% HCl. The precipitated crystalline solid was filtered off and crystallized from aqueous DMF.

1,2,4-Triazolo[4,3-*a*]quinoline-9-carboxylic Acid (IIIa). A. A solution of I (2.1 g, 0.01 mole) and 60% hdyrazine hydrate (10 ml) in 10 ml DMF was refluxed for 1 h, poured into water (100 ml), acidified with 20% HCl, and the solid filtered off and crystallized from aqueous DMF.

B. A solution of II (2.0 g, 0.01 mole) in formic acid (10 ml) was refluxed for 1 h, poured into water and the solid filtered off and recrystallized from aqueous DMF. The yield of IIIa was 1.1 g (50%) with mp 307-309°C. A sample mixed with IIIa obtained by method **A** showed no depression of melting point.

3-Methyl-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid (IIIb). Glacial acetic acid (10 ml) was added to II (2.0 g, 0.01 mole), refluxed for 1 h, poured into water (100 ml), and the solid filtered off and crystallized from DMF.

3-Aryl-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid (IIIc, d). A mixture of I (2.1 g, 0.01 mole) and the corresponding aroylhydrazine (0.015 mole) was heated for 1 h and poured into water (100 ml). The solid was filtered off and crystallized from dioxane—water (4:1).

3-Phenyl-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid (IIIc). A solution of II (2.0 g, 0.01 mole) and benzoyl chloride (1.7 g, 0.012 mole) in dioxane (10 ml) was refluxed for 1 h and poured into water (100 ml). Using the method above gave IIIc (1.2 g, 41%) with mp 264-266°C. Mixing a sample with one prepared as above gave no depression of melting point.

3-(1,2,4-Triazolo[4,3-*a*]-9-carboxy-3-quinolyl)-1,2,4-triazolo[4,3-*a*]quinoline-9-carboxylic Acid (IV). Diethyloxalate (2.9 g, 0.02 mole) was added to a solution of II (2.0 g, 0.01 mole) in DMF (10 ml) and refluxed for 5 h. The product was poured into water (100 ml) and acidified with 20% HCl. The solid was filtered off and crystallized from aqueous DMF.

3-Methyl-4-oxo-1,2,4-triazino[4,3-*a*]quinoline-10-carboxylic Acid (V). A mixture of II (2.0 g, 0.01 mole) and pyruvic acid (1.3 g, 0.015 mole) in ethanol (10 ml) was refluxed for 1 h. The product was cooled and the solid filtered off and recrystallized from aqueous DMF.

1,2,3,4-Tetrazolo[4,3-*a*]quinoline-9-carboxylic Acid (VI). A solution of sodium nitrite (2.1 g, 0.03 mole) in water (3 ml) was added dropwise with cooling to a solution of II (2.0 g, 0.01 mole) in glacial acetic acid (10 ml). After standing for 2 h at room temperature the solid was filtered off and recrystallized from aqueous DMF.

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