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SYNTHESIS OF 6-NITRO-8-CHLORO-2,3-DIHYDRO-4(1H)-QUINOLONE

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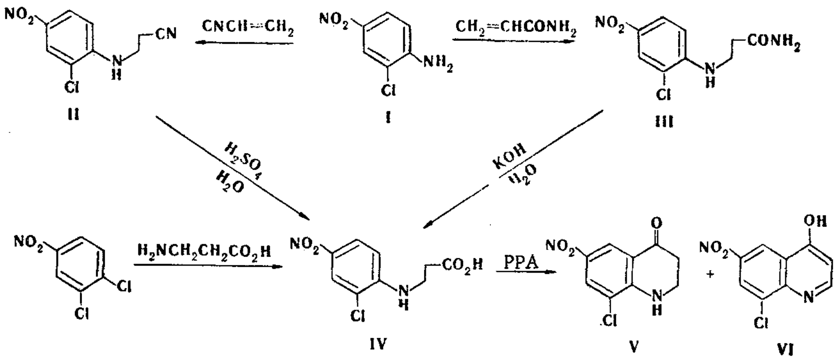
6-Nitro-8-chloro-2,3-dihydro-4(1H)-quinolone and its dehydrogenation product – 6-nitro-8-chloro-4-hydroxyquinoline – were isolated in the cyclization of N-(2-chloro-4-nitrophenyl-β-alanine in polyphosphoric acid.

In a continuation of our search for antiparasitic preparations in the dihydro-4-quinolone series [1, 2] we have synthesized the previously unknown 6-nitro-8-chloro-2,3-dihydro-4(1H)-quinolone (V) via the following scheme:



Cyanoethylation and carbamoylethylation of 2-chloro-4-nitroaniline (I) gave the nitrile (II) and amide (III) of N-(2-chloro-4-nitrophenyl)-β-alanine, which were saponified to N-(2-chloro-4-nitrophenyl)-β-alanine (IV). The latter was also obtained by reaction of 3,4-dichloronitrobenzene with β-alanine. The cyclization of alanine IV in polyphosphoric acid (PPa) gives, in addition to 2,3-dihydro-4-quinolone (V), 4-hydroxy-6-nitro-8-chloroquinoline (VI), the amount of which increases when heating is prolonged. Similar aromatization was also observed in the case of the cyclization of N-(o-nitrophenyl)-β-alanine [3], which led to the formation of 8-nitro-2,3-dihydro-4(1H)-quinolone and 8-chloro-4-quinolone. This process involves reduction of the nitro group, since the presence of a primary amino group was established in crude V by a qualitative test (diazotization and coupling with β-naphthol). This is confirmed by the formation of aminoquinolines in the dehydrogenation of tetrahydroquinolines [4].

Bands at 1673 (C=O), 3328 (NH), and 1330 cm^{-1} (NO_2) are observed in the IR spectrum of solid quinolone V. The band at 1350 cm^{-1} (NO_2) is retained in the spectrum of hydroxyquinoline VI, and a broad intense band at 3450 cm^{-1}, which should be assigned to the OH group, appears. This shows that the tautomeric equilibrium for VI in the crystalline state is shifted to favor the enol form. Compound VI evidently has a ketone form in solutions, including solutions in acetic acid, since V and VI form 2,4-dinitrophenylhydrazones. The UV spectra of alcohol solutions of quinolones V and VI contain three maxima that are close to the maxima of their chlorine-free analogs [5].

The PMR spectrum of V contains signals of methylene groups, and signals of protons attached to a conjugated double bond are observed in the spectrum of VI.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				R_f (ethanol)	Yield, %
		C	H	Cl	N		C	H	Cl	N		
II	131—132	48,2	3,6	15,5	18,9	$C_9H_8ClN_3O_2$	47,9	3,6	15,7	18,6	0,72	75
III	148—149	44,1	4,3	14,3	17,3	$C_9H_{10}ClN_3O_3$	44,4	4,1	14,5	17,3	0,65	86
IV	139—141	43,9	3,2	14,5	11,5	$C_9H_9ClN_2O_4$	44,2	3,7	14,5	11,5	0,56	67,4
V	194—196	47,9	2,9	15,6	12,5	$C_9H_7ClN_2O_3$	47,7	3,1	15,7	12,4	0,76	35,3
VI	312—314	48,0	2,6	—	12,3	$C_9H_5ClN_2O_3$	48,1	2,1	—	12,5	0,4	3—4

EXPERIMENTAL

The IR spectra of KBr pellets or chloroform solutions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in CD_3COOD were recorded with Tesla B-487C and Bruker WH-60 spectrometers with tetramethylsilane as the internal standard. The UV spectra of methanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. Thin-layer chromatography (TLC) was carried out on Silufol-254 plates in ethanol.

N-(2-Chloro-4-nitrophenyl)-β-alanine Nitrile (II). A mixture of 43 g (0.25 mole), of 2-chloro-4-nitroaniline, 200 ml of dioxane, 100 ml of acrylonitrile, and 25 ml of Triton B was allowed to stand at room temfor 48 h, after which 1 liter of water was added, and the mixture was heated to 80°C. It was then cooled, and the precipitated product was removed by filtration and crystallized from acetic acid to give a light-yellow powder. IR spectrum: 1330 (NO_2), 2262 (C≡N), 3428 and 3362 (NH), and 3434 cm^{-1} (NH, solution in $CHCl_3$). UV spectrum, λ_{max} (log ε): 227 (3.79) and 368 nm (4.20).

N-(2-Chloro-4-nitrophenyl-β-alanine Amide (III). A solution of 71 g (1.0 mole) of acrylamide in 200 ml of dioxane and 50 ml of Triton B were added to a solution of 86 g (0.5 mole) of 2-chloro-4-nitroaniline in 200 ml of dioxane, and the mixture was heated with stirring on a boiling-water bath for 6 h. The solvent was then removed by distillation to half the original volume, and the residue was poured into 1.5 liters of water. The resulting precipitate was removed by filtration, washed with water, dried, and crystallized from acetic acid to give a light-yellow powder. IR spectrum: 1335 (NO_2), 1670 (amide I), 1602 (amide II), 3295 and 3229 (amide NH), and 3462 cm^{-1} (amine NH). UV spectrum, λ_{max} (log ε): 227 (3.91) and 370 nm (4.29).

N-(2-Chloro-4-nitrophenyl)-β-alanine (IV). A) A mixture of 10 g (41.2 mmole) of III and 125 ml of 10% KOH was heated at 85°C with stirring in the course of 5 h until ammonia evolution ceased. It was then treated with charcoal and filtered, and the filtrate was acidified to pH 2-3. The precipitate was removed by filtration, washed with water, dried, and crystallized from chloroform to give light-yellow crystals. IR spectrum: 1330 (NO_2), 1712 (CO in COOH), 2500-3100 (OH in COOH), and 3419 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 227 (3.87) and 377 nm (4.27).

B) A mixture of 4.5 g (30 mmole) of II and 45 ml of 80% sulfuric acid was heated with stirring at 60°C for 5 h, after which it was cooled and treated with 100 ml of water, and the resulting precipitate was removed by filtration, washed with water, dried, and crystallized from chloroform to give the product in 33.2% yield.

C) A mixture of 19.2 g (0.1 mole) of 3,4-dichloronitrobenzene, 11.1 g (125 mmole) of β-alanine, 20.7 g (0.15 mole) of potassium carbonate, and 200 ml of dimethylformamide (DMF) was refluxed with stirring for 10 h, after which the DMF was removed by distillation, and 500 ml of water was added to the residue. The aqueous mixture was acidified to pH 2-3, and the precipitate was removed by filtration, washed with water, dried, and crystallized from chloroform. No melting-point depression was observed for a mixture of samples of IV obtained by methods A and B. Their IR spectra were also identical. The product was obtained in 76.2% yield.

6-Nitro-8-chloro-2,3-dihydro-4(1H)-quinolone (V). A mixture of 31 g of orthophosphoric acid and 31 g of P_2O_5 was heated with stirring at 150°C for 1 h, after which the resulting polyphosphoric acid (PPA) was cooled to 105°C, 12.25 g (0.05 mole) of IV was sprinkled into it, and the mixture was maintained at this temperature for 2 h. It was then cooled to 50°C and poured over 500 g of ice. The precipitate that formed on standing was removed by filtration, washed with water, and heated with 10% sodium carbonate solution. The solid was removed by filtration and crystallized from alcohol to give orange crystals. PMR spectrum: 2.74 (CO–CH_2, m, 2H), 3.77 (N–CH_2, m, 2H), 8.24 (H_{arom}, d, J = 2.5 Hz, 1H), and 8.54 ppm (H_{arom}, d, J = 2.5 Hz, 1H). UV spectrum, λ_{max} (log ε): 363.5 (4.25), 250 (4.01), and 233 nm (4.18). The 2,4-dinitrophenylhydrazone of V was obtained as bright-orange crystals with mp 315-317°C. Found: N 20.8%. $C_{15}H_{11}ClN_6O_6$. Calculated: N 20.7%.

6-Nitro-8-chloro-4-hydroxyquinoline (VI). Repeated crystallization of the precipitates obtained by evaporation of the alcohol mother liquors after separation of cyclization product V gave light-brown crystals of VI. PMR spectrum: 6.67 (H_α, d, J = 7.5 Hz, 1H), 7.05 (H_β, d, J = 7.5 Hz, 1H), 8.23 (H_{arom}, d, J = 2.5 Hz, 1H), and 8.52 ppm (H_{arom}, d, J = 2.5 Hz, 1H). UV spectrum, λ_{max} (log ε): 332 (4.78), 317 (4.83), and 250 (4.04). The 2,4-dinitrophenylhydrazone of VI was obtained as bright-red crystals with mp 325-327°C (from ethanol). Found: N 20.8%. $C_{15}H_9ClN_6O_6$. Calculated: N 20.8%. Compound V was obtained in 8% yield, and VI was obtained in 14.5% yield in the case of more prolonged cyclization of IV (20 h).

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CONDENSATION REACTIONS BASED ON 3-FORMYLINDAZOLE

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The chemical properties of 3-formylindazole were studied in the case of nucleophilic addition reactions (Knoevenagel, Rodionov, and crotonic condensations). The possibility of the preparation of Schiff bases in the unsubstituted 3-formylindazole series was investigated. 3-Indazolylacrylic and β-(3-indazolyl)-β-aminopropionic acids, the products of crotonic condensation, and azomethines were synthesized.

Despite the interest currently being displayed in the chemistry of indazole, up until now very little data on the chemical behavior of 3-formylindazole have been available.

The chemical properties of 1-methyl-3-formylindazole have been studied [1], and the increased reactivity of the formyl group with respect to nucleophilic reagents and the impossibility of carrying out similar reactions with 3-formylindazole [2] have been noted. In this connection, it seemed of interest to study the chemical properties of unsubstituted 3-formylindazole under the conditions of nucleophilic addition reactions (the Knoevenagel and Rodionov reactions and crotonic condensation). In addition, the possibility of the preparation of Schiff bases in the unsubstituted 3-formylindazole series was studied.

We have established that unsubstituted 3-formylindazole also quite readily undergoes condensation with malonic acid in the presence of pyridine and catalytic amounts of piperidine (a modified Knoevenagel reaction).

In the PMR spectrum of 3-indazolylacrylic acid (I) the protons of the ethylene group form an AB system (7.39 and 6.79 ppm) with a spin–spin coupling constant (SSCC) of 16 Hz; this confirms the trans configuration of the compound.*

When we carried out the condensation of 3-formylindazole with malonic acid in the presence of an alcohol solution of ammonia (the Rodionov reaction), we isolated β-(3-indazolyl)-β-aminopropionic acid (II) in 25% yield. The β-amino acid was obtained in somewhat higher yield (33%) by means of the Johnson modification.

The IR spectral data show that the β-amino acid obtained exists in the form of a dipolar ion, as evidenced by the presence of an amino acid I band at 1640 cm^{-1} and an amino acid II band at 1550 cm^{-1} due to the sym-

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* See display at top of next page after Table 1.

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