NITRATION OF PYRAZOLO[4,3-b]QUINOLINONES

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The nitration of 1-methyl-4H-pyrazolo[4,3-b]quinolin-9-one and some of its derivatives with nitric acid in sulfuric acid and acetic anhydride was studied. It was established that the number and site of incorporation of the nitro groups depends on the nature of the attacking agent, the reaction conditions, and the substituents present in the molecule.

Electrophilic substitution in the pyrazolo[4,3-b]quinolinone series has not been previously studied. In a continuation of our investigation of this class of compounds [1], in the present research we desired to observe the behavior of 1-methyl-4H-pyrazolo[4,3-b] quinolin-9-one (I) and some of its derivatives in electrophilic substitution reactions in the case of nitration.

It is known that acridone undergoes electrophilic substitution quite readily to give, in particular, tetranitroacridone in the case of nitration with a nitrating mixture under rather mild conditions [2].

We have established that in the nitration of pyrazolo-quinolinone I the number and the site and order of incorporation of nitro groups depend on the nature of the nitrating agent, the reaction conditions, and the substituents present in the molecule. Thus the action of an equimolar amount of nitric acid in sulfuric acid on I at −5°C gives 1-methyl-7-nitro-4H-pyrazolo[4,3-b]-quinolin-9-one (II) (87% yield), which according to data from the PMR spectrum and thin-layer chromatography (TLC), does not contain other isomers, in contrast to acridone, in the nitration of which under similar conditions up to 30% of the 4-nitro isomer is formed along with the principal product 2-nitroacridone [3].

The structure of II was confirmed by the PMR spectrum, in which, in addition to singlets of protons of a methyl group and a proton in the 3 position, one observes three groups of signals of protons of the benzene ring with δ 7.56, 8.30, and 8.92 ppm (the protons in the 5, 6, and 8 positions) and spin-spin coupling constants (SSCC) J = 2 and 9 Hz, which are characteristic for meta and ortho orientations of the protons in the benzene ring [4], and also by alternative synthesis of II by cyclization of 1-methyl-4-(4-nitrophenylamino)pyrazole-5-carboxylic acid [1] in polyphosphoric acid (PPA).

The nitration of I with nitric acid in acetic anhydride gives, in addition to nitropyrazoloquinolinone II, the isomeric 1-methyl-5-nitro-4H-pyrazolo[4,3-b]quinolin-9-one (III) (according to the PMR spectral data, the isomer ratio was 2:1). This composition of the reaction products constitutes evidence that the specific "ortho effect" that is peculiar to acetyl nitrate in its action on strongly activated aromatic systems [5] is manifested to only a slight extent in the case of I. This is evidently associated with a decrease in the basicity of the $N_{(4)}$ atom of the heteroring, which is in "rigid" conjugation with the benzene and pyrazole parts of the molecule.

Compound III, which was isolated from the mixture by fractional crystallization, was found to be identical to the product obtained by cyclization of 1-methyl-4-(2-nitrophenylamino)pyrazole-5-carboxylic acid [1] in PPA.

The absence of a 3-nitro isomer among the products of nitration of pyrazoloquinolinone I constitutes evidence that the 3 position of the heteroring is the least reactive position in electrophilic substitution reactions. This is explained by the specific characteristics of the distribution of the electron density in the N-substituted pyrazole ring, which leads

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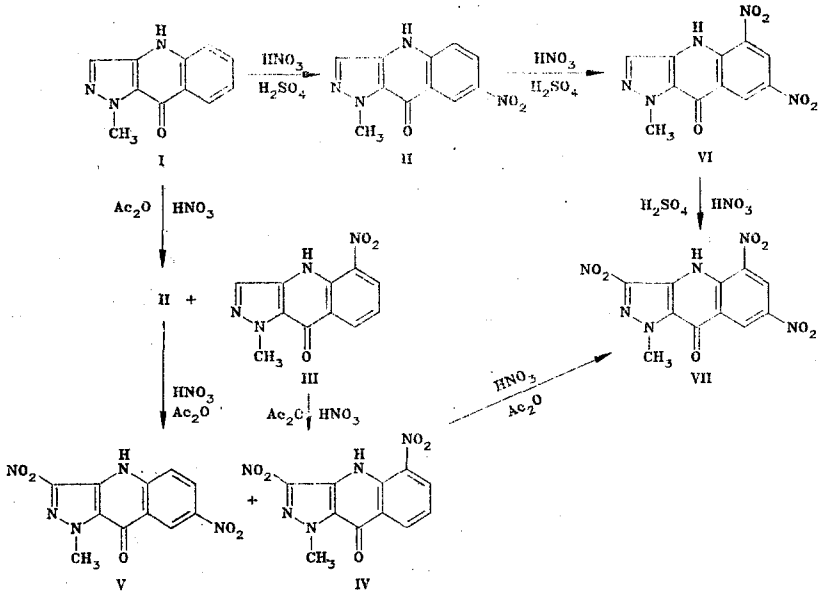
to surplus π-electron density in the 4 position, a deficiency of π-electron density in the 3 position, and a low degree of double-bond character of the $C_{(4)}$–$C_{(3)}$ bond in the pyrazole fragment [6]; this imposes limitations on the effect of the electron-donor grouping of the quinoline ring on the $C_{(3)}$ atom. The electrophilicity of this atom increases in sulfuric acid as a result of protonation of the adjacent $N_{(2)}$ atom.

Mononitropyrazoloquinolinones II and III are quite reactive compounds and form dinitro-substituted derivatives upon nitration with excess nitric acid at 5-10°C; the site of incorporation of the second nitro group depends chiefly on the composition of the nitrating mixture. One might have expected that the introduction of an electron-acceptor substituent into the benzene ring of the heterocycle would, as a result of partial deactivation of the free position in this fragment, in which nitration is possible, lead to the production of primarily 3-nitro derivatives. The latter assumption proved to be valid only in the case of nitration in acetic anhydride, in which pyrazoloquinolinones undergo reaction in the form of the free bases. Thus in the case of treatment of I with more than a twofold excess of nitric acid in acetic anhydride the 5- and 7-mononitro-substituted III and II that are formed in the first step are further nitrated only in the 3 position to give the corresponding 3,5- and 3,7-dinitropyrazoloquinolinones IV and V, the amounts of which are determined by the ratio of the mononitro products formed in the first step (2:1 according to the PMR spectral data).

A different pattern is observed in the nitration of I with a twofold quantity of nitric acid in sulfuric acid; the only dinitro compound that we isolated as a result of the reaction was 1-methyl-5,7-dinitro-4H-pyrazolo[4,3-b]quinolin-9-one (VI), which, according to the PMR spectral data, contains a small amount of admixed II. These results are due to the fact that the pyrazoloquinolinones undergo the reaction in the form of the conjugate acids.

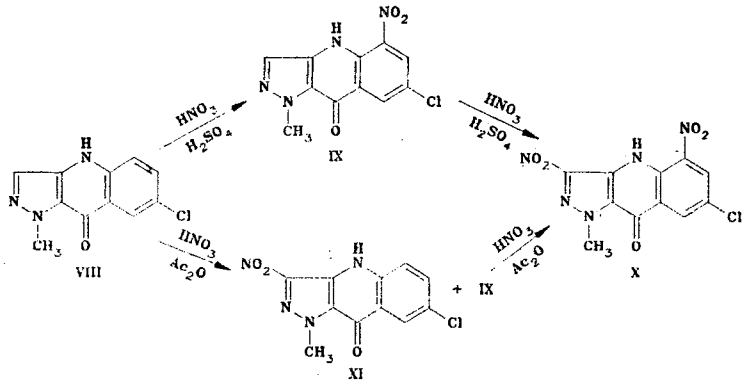


The nitration of 5,7-dinitro derivative VI or unsubstituted pyrazolquinolinone I with excess nitric acid in sulfuric acid at 40-45°C gives the same compound, the PMR spectrum of which makes it possible to assign the 3,5,7-trinitropyrazolo[4,3-b]quinolin-9-one (VII) structure to it. Compound VII is also formed by the action of excess nitric acid in acetic anhydride on I at 20°C. It is possible that in the case of nitration in sulfuric acid dinitropyrazoloquinolinone VI participates in the reaction in the form of the neutral molecule, which promotes electrophilic attack of the 3 position. Similar examples are known in the nitration of some dinitroindazoles [7].

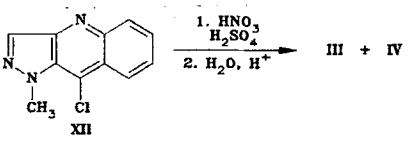
The nitration of 1-methyl-7-chloro-4H-pyrazolo[4,3-b]-quinolin-9-one (VIII) with a nitrating mixture at 0°C leads exclusively to 5-nitro derivative IX, which in the presence of excess nitrating agent is subsequently converted to 1-methyl-3,5-dinitro-7-chloro-4H-pyrazolo[4,3-b]quinolin-9-one (X), in the PMR spectrum of which two doublets with δ 8.60 and 8.76 ppm and J = 2 Hz (protons in the 8 and 6 positions) are observed along with a singlet of protons of a methyl group at 4.42 ppm.

A complex mixture containing the starting compound and mono- and dinitro products is formed by the action of an equimolar amount of nitric acid in acetic anhydride on 7-chloropyrazoloquinolinone VIII. A comparison of the PMR spectra of the reaction products (after separation of the starting compound) and IX and X, isolated in pure form, made it possible to establish the presence among the products of 5-nitro derivative IX and 3,5-dinitro-substituted X, as well as 1-methyl-3-nitro-7-chloro-pyrazolo[4,3-b]quinolin-9-one (XI), in a ratio of 1:2:2. We were unable to isolate XI in individual form.

According to the PMR spectrum, the nitration of VIII with excess nitric acid in the presence of acetic anhydride gives a mixture of dinitro product X and 3-nitro-substituted XI. 5-Nitro-7-chloropyrazoloquinolinone IX was not present in the reaction products; this is explained, in our opinion, by the difference in the rates of nitration of the 3- and 5-mononitro derivatives to dinitro compound X. In 3-nitropyrazoloquinolinone XI the nitro group adjacent to the $N_{(4)}$ atom evidently excludes the possibility of specific "ortho nitration" by acetyl nitrate in the 5 position, whereas the formation of X from 5-nitro-substituted IX, which takes place through a step involving the addition of protonated acetyl nitrate to the $N_{(2)}$ atom of pyrazole [8] with subsequent attack of the 3 position, does not depend on the analogous deactivating effect on the part of the nitro group in the 5 position.



A study of the nitration of 1-methyl-9-chloropyrazolo[4,3-b]-quinoline (XII) showed that this compound differs significantly from pyrazoloquinolinone I with respect to its reactivity and orientation in electrophilic substitution. Compound XII was isolated unchanged when it was treated with a mixture of nitric acid and acetic anhydride at 20°C for 2 days. In the reaction of an equimolar amount of nitric acid in sulfuric acid we isolated a mixture of mono- and dinitro-disubstituted compounds in 74% yield based on the converted pyrazoloquinoline XII (the conversion did not exceed 40%); because of their facile hydrolyzability, we isolated and identified these products in the form of the pyrazoloquinolines. According to the PMR spectra data, the mixture obtained after hydrolysis consisted of 5-nitro and 3,5-dinitro compounds III and IV in a ratio of 1:1. The only final product is dinitropyrazoloquinolinone IV in the nitration of XII under the same conditions with excess nitric acid. Thus, with respect to its behavior in nitration, pyrazoloquinoline is closer to quinoline, which gives 5-nitroquinoline (along with the 8-nitro isomer) upon nitration [9], then to acridine, which is nitrated primarily in the 2 position to give 2-nitroacridine [10].



A comparison of these data with the results of nitration in sulfuric acid of pyrazoloquinolinone I and 4-quinolone, from which only 6-nitroquinolone is obtained [11], and acridone evidently provides evidence that the π-electron system of the protonated pyrazole ring condensed with a quinolone or quinoline ring behaves quite autonomously and in the case of nitration has virtually no effect on the orientation of substitution in the benzene part of the 1-methyl-4H-pyrazolo[4,3-b]quinolin-9-one and 1-methyl-9-chloropyrazolo[4,3-b]quinoline molecules.

TABLE 1. Nitro-Substituted 1-Methyl-4H-pyrazolo[4,3-b]-quinolin-9-ones II-VII, IX, and X

Compound	mp, deg C*	PMR spectrum, δ, ppm			Found, %			Empirical formula	Calculated, %		
		CH_3	3-H	benzene ring protons	C	H	N		C	H	N
II	314—316	4,23	7,81	7,56 (1H, д, 5-H), 8,30 (1H, m, 6-H), 8,92 (1H, д, 8-H)	53,8	3,0	22,7	$C_{11}H_8N_4O_3$	54,1	3,3	23,0
III	277—279	4,27	7,96	7,36 (1H, m, 7-H), 8,66 (2H, m, 6-H+8-H)	54,2	3,2	23,3	$C_{11}H_8N_4O_3$	54,1	3,3	23,0
IV	282—284	4,44	—	7,66 (1H, m, 8-H), 8,76 (2H, m, 6-H+7-H)	45,4	2,0	24,4	$C_{11}H_7N_5O_5$	45,7	2,4	24,2
V	312—314	4,37	—	8,12 (1H, m, 5-H), 8,44 (1H, m, 6-H), 8,92 (1H, , 8-H)	45,9	2,2	24,5	$C_{11}H_7N_5O_5$	45,7	2,4	24,2
VI	269—271	4,26	8,00	9,14 (1H, m, 8-H), 9,25 (1H, m, 6-H)	45,2	2,8	24,0	$C_{11}H_7N_5O_5$	45,7	2,4	24,2
VII	290—292	4,41	—	9,29 (2H, m, 6-H+8-H)	39,7	1,8	24,8	$C_{11}H_6N_6O_7$	39,5	1,8	25,1
IX	257—258	4,28	7,97	8,58 (2H, m, 6-H+8-H)	47,8	2,4	20,3	$C_{11}H_7ClN_4O_3$	47,5	2,5	20,1
X	285—286	4,42	—	8,60 (1H, m, 8-H), 8,76 (1H, , 6-H)†	40,4	1,8	21,5	$C_{11}H_6ClN_5O_5$	40,9	1,9	21,7

*The compounds were crystallized: II, V-VII, and X from dimethylformamide (DMF), IV and IX from dimethyl sulfoxide—H_2O (1:1), and III from DMF—H_2O (1:1).
†The spectrum of a solution in N-methylpyrrolidone was recorded.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Tesla BS-497 spectrometer (100 MHz) with hexamethyldisiloxane as the standard. Chromatographic monitoring of the individuality of the compounds obtained was accomplished on Silufol UV-254 plates by elution with benzene—ethanol (5:1).

Pyrazoloquinolines I, VIII, and XII were obtained by the method in [1]. The characteristics of II-VII, IX, and X are presented in Table 1.

1-Methyl-7-nitro-4H-pyrazolo[4,3-b]quinolin-9-one (II). A) A 1-g (5 mmole) sample of pyrazoloquinolinone I was dissolved in 10 ml of concentrated H_2SO_4, the solution was cooled to —10°C, and a nitrating mixture consisting of 0.25 ml of nitric acid (sp.gr. 1.52) and 10 ml of concentrated H_2SO_4 was added at —10°C to —5°C. The reaction mixture was maintained at —5°C for 30 min, after which it was poured over ice. The aqueous mixture was worked up to give 1.06 g of product.

B) A 1.3-g (5 mmole) sample of 1-methyl-4-(4-nitrophenylamino)pyrazole-5-carboxylic acid was added to 25 g of heated (to 70°C) polyphosphoric acid (PPA), after which the mixture was stirred at 120-125°C for 4 h and then diluted with 100 ml of water. The aqueous mixture was neutralized with sodium carbonate solution, and the precipitate was removed by filtration and washed with water to give 0.71 g (60%) of product.

Pyrazoloquinolinone III. This compound was similarly obtained in 71% yield from 1-methyl-4-(2-nitrophenylamino)pyrazole-5-carboxylic acid.

Nitration of Pyrazoloquinolinone I in Acetic Anhydride. A 1-g (5 mmole) sample of I was suspended in 10 ml of glacial acetic acid, the suspension was cooled to 0°C, and a solution of 0.3 ml of nitric acid (sp. gr. 1.52) in 25 ml of acetic anhydride was added with vigorous stirring. The reaction mixture was maintained at 0°C for 1 h, after which it was poured over ice. Fractional Crystallization of the precipitate (1.1 g), which, according to the PMR spectral data, consisted of a mixture of mononitro-substituted II and III, from DMF gave 0.3 g of III and 0.52 g of 7-nitro derivative II.

1-Methyl-5,7-dinitro-4H-pyrazolo[4,3-b]quinolin-9-one (VI). A solution of 0.7 ml of concentrated HNO_3 in 10 ml of H_2SO_4 was added at 5°C to a solution of 5 mmole of pyrazoloquinolinone I in 10 ml of concentrated H_2SO_4, after which the reaction mixture was maintained at 5-10°C for 2 h and poured over ice. Workup gave 1.0 g (70%) of product. According to the PMR spectra data, the product contained admixed 7-mononitro derivative II.

Dinitropyrazoloquinolinones IV and V. A 5-mmole sample of I was dissolved in 10 ml of glacial acetic acid at 5°C, and the solution was cooled to 0°C and added with stirring to a

nitrating mixture consisting of 1 ml of nitric acid (sp. gr. 1.52) and 25 ml of acetic anhydride. The reaction mixture was maintained at 0°C for 4 h and poured over ice. Workup gave 1.2 g (85%) of a mixture of IV and V (according to the PMR spectra data, the isomer ratio was 2:1). The precipitate was recrystallized twice from DMF to give 0.6 g of V.

1-Methyl-3,5,7-trinitro-4H-pyrazolo[4,3-b]quinolin-9-one (VII). A) A nitrating mixture consisting of 2 ml of HNO_3 (sp. gr. 1.52) and 10 ml of sulfuric acid was added at 5°C to a solution of 5 mmole of I in 10 ml of sulfuric acid (sp. gr. 1.84), and the reaction mixture was maintained at 40-45°C for 3 h. It was then cooled and poured over ice, and the aqueous mixture was worked up to give 1.14 g (70%) of product.

B) This compound was similarly obtained in 78% yield by nitration of 5,7-dinitro derivative VI with a nitrating mixture at 50°C for 2 h.

C) A 5-mmole sample of pyrazoloquinolinone I was added at 10°C to a nitrating mixture consisting of 4 ml of nitric acid and 30 ml of acetic anhydride, after which the reaction mixture was maintained at 20°C for 8 h and poured over ice. Workup gave the product in 64% yield.

1-Methyl-5-nitro-7-chloro-4H-pyrazolo[4,3-b]quinolin-9-one (IX). This compound was obtained by nitration of 7-chloropyrazoloquinolinone VIII with a nitrating mixture as in the case of II. The reaction mixture was maintained at 0°C for 1 h, after which it was poured over ice. Workup gave the product in 91% yield.

1-Methyl-3,5-dinitro-7-chloro-4H-pyrazolo[4,3-b]quinolin-9-one (X). A 1.16-g (5 mmole) of sample of VIII was dissolved in 10 ml of concentrated H_2SO_4, the solution was cooled to 0°C, and 1 ml of nitric acid (sp. gr. 1.52) in 20 ml of sulfuric acid was added with stirring. The mixture was maintained at 10°C for 4 h, after which it was poured over ice. Workup gave 1.45 g (90%) of product.

Nitration of 1-Methyl-7-chloro-4H-pyrazolo[4,3-b]quinolin-9-one (VIII) in Acetic Anhydride. A) Nitration with an equimolar amount of nitric acid. A solution of 0.25 ml of HNO_3 (sp. gr. 1.52) in 25 ml of acetic anhydride was added at 0°C to a solution of 1.16 g (5 mmole) of VII in 10 ml of acetic acid, after which the reaction mixture was maintained at 5°C for 3 h and poured over ice. The precipitate was removed by filtration and treated on the filter with 30 ml of 5% HCl to remove the starting VIII. The yield of nitration products was 0.8 g. According to the PMR spectral data, 3- (XI) and 5-mononitro-substituted (IX) compounds and 3,5-dinitro compound X were obtained in a ratio of 2:1:2.

B) Nitration with excess nitric acid. This reaction was carried out as in the preceding experiment with a nitrating mixture consisting of 1 ml of HNO_3 and 25 ml of acetic anhydride and maintenance of the reaction mixture at 5°C for 4 h. The reaction products were 3-nitropyrazoloquinolinone X and 3,5-dinitro-substituted X in a ratio of 1:2.

Nitration of 1-Methyl-9-chloropyrazolo[4,3-b]quinoline (XII). A) Nitration with an equimolar amount of nitric acid. A solution of 0.25 ml of HNO_3 in 10 ml of sulfuric acid was added to a solution of 1.0 g (5 mmole) of XII in 10 ml of sulfuric acid, after which the reaction mixture was maintained at 50-55°C for 6 h, cooled, and poured over ice. The precipitate was removed by filtration and washed with 5% HCl to give 0.4 g of product (neutralization of the mother liquor with sodium carbonate solution gave 0.6 g of starting XII). The precipitate was suspended in 10 ml of 5% HCl, and the suspension was refluxed for 30 min. It was then neutralized with sodium carbonate solution, and the precipitate was separated. According to the PMR spectral data, the precipitate consisted of pyrazoloquinolinones III and IV in a ratio of 1:1.

B) Nitration with excess nitric acid. This reaction was carried out as in the preceding experiment. The nitrating mixture consisted of 1 ml of HNO_3 and 10 ml of sulfuric acid, and the reaction mixture was maintained at 60-70°C for 3 h. As a result of the reaction and subsequent hydrolysis, dinitro derivative IV was isolated in 54% yield.

C) A solution of 0.5 ml of nitric acid in 20 ml of acetic anhydride was added to a solution of 5 mmole of XII in 10 ml of acetic acid, after which the mixture was maintained at 20°C for 2 days and poured over ice. The aqueous mixture was neutralized with sodium carbonate solution to give 0.88 g of starting XII.

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SYNTHESES BASED ON DIMETHYLPYRAZOLES.

8.* REACTION OF 3,4- AND 4,5-DIAMINOPYRAZOLES WITH 4-NITRONAPHTHALIC ANHYDRIDE

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Mono- and diacylation products were obtained in the reaction of 3,4-diamino-1,5-dimethylpyrazole with 4-nitronaphthalic anhydride in acetic acid; the monoacylation products do not undergo cyclization even in polyphosphoric acid (PPA). The reaction of 4,5-diamino-1-methylpyrazole under similar conditions gives 2-(5-amino1-1-methyl-4-pyrazolyl)-7-nitrobenzo[d,e]isoquinoline-1,3-(1H,3H)dione, during heating of which in polyphosphoric acid ethyl ester only mono- and diethylation at the amino group occurs.

We have previously synthesized 4-amino-5-carbamoyl-1-methylpyrazole and have shown that it reacts with naphthalic anhydride in the same way as anthranilic acid amide to give 1-methyl-1H-pyrazolo[3,4-5',6']pyrimidino[1,2-a]benzo[d,e]isoquinoline-5,13-(5H, 13H) dione [1]. 4-Amino-N-pyrazolylnaphthalimides have intense luminescence, and the photostabilities of daytime fluorescent pigments obtained from them exceed the photostabilities of pigments that contain 4-amino-N-phenylnaphthalimide [2]. Naphthoylene-benzimidazoles, which are effective luminophores, are formed in the reaction of o-phenylenediamine with substituted naphthalic anhydrides [3]. These are the reasons that we became interested in a study of the possibility of the synthesis of pyrazole analogs of naphthoylenebenzimidazole from 3,4-diamino-1,5-dimethylpyrazole (I) and 4,5-diamino-1-methylpyrazole (II).

The reduction of 1,5-dimethyl-3,4-dinitropyrazole (III) [4] and 5-amino-1-methyl-4-nitropyrazole (IV) [5] with hydrazine hydrate on Raney nickel was used to synthesize, respectively, o-diamino-pyrazoles I and II, which are resistance to the action of air oxygen and were isolated in the form of hydrochlorides. Immediately prior to the reaction aqueous

*See [1] for communication 7.

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