RESEARCH ON 1,4-NAPHTHOQUINONE AND QUINOLINE-5,8-QUINONE

VI.* ISOMERIC ACYLAMINO CHLORO AND AMINO CHLORO DERIVATIVES OF QUINOLINE-5,8-QUINONE

O. S. Klimovich, B. G. Boldyrev, and V. T. Kolesnikov

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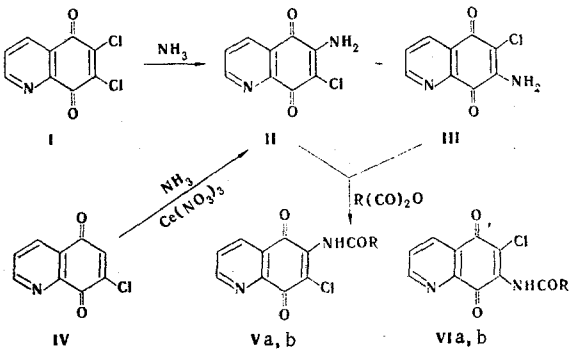
A mixture of isomeric amino chloro derivatives, the structures of which were confirmed by alternative syntheses, is formed in the amination of 6,7-dichloroquinoline-5,8-quinone.

6-Propionylamino-7-aminoquinoline-5,8-quinone and other acylamino derivatives of quinoline-5,8-quinones have been described [2] as substances that have antitubercular activity, but the structures of these compounds have not been proved, inasmuch as the formation of a mixture of isomeric amino chloro derivatives is possible in the amination of 6,7-dichloroquinoline-5,8-quinone (I).



I II III IV Va, b VIa, b

V, VI a $R=CH_3$; b $R=C_2H_5$

In fact, in the amination of I we obtained a product that gives two spots on its chromatogram and is a mixture of two isomers — II and III. We were unable to separate them by repeated crystallization; only a negligible amount of one of them was isolated. This substance is not isomer II, inasmuch as the authentic product with this structure, which we obtained by the addition of ammonia to 7-chloroquinoline-5,8-quinone (IV), has a different melting point.

It was natural to assume that the acylamino derivatives described in [3] and obtained from the product of amination of 6,7-dichloroquinoline-5,8-quinone also are not individual substances. A mixture of amino chloro derivatives (II and III) of quinoline-5,8-quinone gives a mixture of Va and VIa on acylation with acetic anhydride; Va was identical to the product of acylation of authentic 6-amino-7-chloroquinoline-5,8-quinone, and VIa is 7-acetamido-6-chloroquinoline-5,8-quinone. The isomeric acetamidochloroquinoline-5,8-quinones (Va and VIa) were then deacylated to give, respectively, 6-amino-7-chloroquinoline-5,8-quinone and its 6-chloro-7-amino isomer. The first isomer is identical to the product obtained by addition of ammonia to 7-chloroquinoline-5,8-quinone (IV).

*See [1] for communication V.

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TABLE 1

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
II	316 (nitrobenzene)	$C_9H_5ClN_2O_2$	51,6	2,6	16,9	13,5	51,8	2,4	17,0	13,4	19
Va	244 (chlorobenzene, ethanol)	$C_{11}H_7ClN_2O_3$	52,6	3,2	14,1	11,2	52,7	2,8	14,1	11,2	52
Vb	204 (m-xylene, chlorobenzene)	$C_{12}H_9ClN_2O_3$	54,8	3,6	13,5	10,5	54,4	3,4	13,4	10,5	47
III	333 (nitrobenzene)	$C_9H_5ClN_2O_2$	52,1	2,5	16,9	13,5	51,8	2,4	17,0	13,4	42
VIa	224 (ethanol)	$C_{11}H_7ClN_2O_3$	52,7	2,6	14,2	11,2	52,7	2,8	14,1	11,1	16
VIb	206 (chlorobenzene, ethanol)	$C_{12}H_9ClN_2O_3$	54,5	3,3	13,5	10,5	54,5	3,4	13,4	10,6	30

A mixture of propionylamino chloro derivatives of quinoline-5,8-quinone, from which individual isomeric products were isolated by fractional crystallization, was similarly obtained from a mixture of II and III. 6-Propionylamino-7-chloroquinoline-5,8-quinone (Vb) was identified by a mixed melting-point determination with the genuine product obtained by acylation of 6-amino-7-chloroquinoline-5,8-quinone.

EXPERIMENTAL

Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates (with elution by ethyl acetate or glacial acetic acid).

7-Chloro- and 6,7-dichloroquinoline-5,8-quinones were obtained by the methods in [4, 5].

6-Amino-7-chloroquinoline-5,8-quinone (II). A) A suspension of 10 g (52 mmole) of 7-chloroquinoline-5,8-quinone (IV) and 1.5 g of anhydrous cerium nitrate in 200 ml of absolute alcohol saturated with dry ammonia was stirred at room temperature for 4 h, after which the solid material was removed by filtration, washed with water, and treated successively with a saturated ferric chloride solution and water. The black precipitate was extracted with boiling chlorobenzene to give a red amine, which was crystallized twice from nitrobenzene (Table 1). The product was soluble in ordinary organic solvents but insoluble in dimethylformamide (DMF).

B) Dry hydrogen chloride was bubbled for 20 min at 5° through a suspension of 1.5 g of 6-acetamido-7-chloroquinoline-5,8-quinone (Va) in 30 ml of absolute alcohol, after which the mixture was heated up to the boiling point and refluxed for 4 h. It was then cooled, and the precipitate was removed by filtration, washed with alcohol, crystallized from nitrobenzene, and washed successively with hot alcohol and ether to give 1.0 g (80%) of a product that did not depress the melting point of the product obtained by method A.

Amination of 6,7-Dichloroquinoline-5,8-quinone. Concentrated ammonium hydroxide (50 ml) was added to a boiling suspension of 50.0 g of I in 500 ml of alcohol, and gaseous ammonia was bubbled through the mixture for 2 h, after which it was allowed to stand at the same temperature. It was then cooled, and the resulting precipitate was removed by filtration, washed with hot water, dried, and crystallized from nitrobenzene. The yield of a mixture of isomers II and III was 42.0 g (92%).

6-Acetamido-7-chloro- (Va) and 6-Chloro-7-acetamidoquinoline-5,8-quinones (VIa). A) A 25-g sample of a mixture of II and III was added in small portions to a mixture of 100 ml of acetic anhydride and 10 ml of H_2SO_4 (sp. gr. 1.84) in such a way that the temperature did not rise above 35°. The mixture was then cooled and allowed to stand at 20-25° for 1 h, after which it was poured into 200 ml of cooled 25% sodium acetate solution. The resulting precipitate was removed by filtration and crystallized from alcohol and chlorobenzene. The yield of the mixture of Va and VIa was 12.8 g (43%).

A 1.5-g sample of the mixture of Va and VIa was subjected to fractional crystallization from alcohol; 0.23 g of VIa and 0.98 g of Va were isolated. No melting-point depression was observed for a mixture of the latter with an authentic sample obtained by acylation of II.

B) A 2.0-g sample of II was added in small portions with stirring at 25° to a mixture of 20 ml of acetic anhydride and 0.4 ml of H_2SO_4 (sp. gr. 1.84), after which it was allowed to stand for 2 h. It was then poured into 100 ml of a 25% sodium acetate solution cooled to 5°, and the yellow precipitate was removed by filtration, washed with water, dried, and crystallized from chlorobenzene and alcohol.

6-Propionylamino-7-chloro- (Vb) and 6-Chloro-7-propionylaminoquinoline-5,8-quinone (VIb). These compounds were similarly obtained from a mixture of isomers II and III. Fractional crystallization of 2.5 g of the mixture of Vb and VIb from alcohol yielded 0.75 g of VIb and 1.05 g of Vb; no melting-point depression was observed for a mixture of the latter with an authentic sample.

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RESEARCH ON UNSATURATED AZOLE DERIVATIVES

IV.* ALKYLATION OF INDAZOLE WITH PROPARGYL BROMIDE

P. V. Tkachenko, I. I. Popov,
A. M. Simonov, and Yu. V. Medvedev

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The alkylation of indazole with propargyl bromide and 2,3-dibromo-1-propene was investigated. It is shown that the ratio of the resulting isomeric 1- and 2-propargyl indazoles is determined by the reaction conditions. 1-(2'-Propynyl)indazole is readily isomerized in the presence of potassium hydroxide to 1-propadienylindazole.

It is well known that the alkylation of indazoles gives isomeric 1- and 2-alkyl derivatives, the ratio of which depends on the indazole compound and the synthetic conditions [2]. However, the reaction of indazole with unsaturated alkyl halides has not been studied, and only the synthesis of 1-allylindazole has been described [3]. Continuing our research on the synthesis of propargyl-substitited azoles [4, 5], we studied the reaction of indazole with propargyl bromide.

We found that indazole (I) readily reacts with propargyl bromide in liquid ammonia in the presence of sodium amide to give 1- and 2-propargylindazoles II and III in a ratio of 13:3, respectively. Alkylation of the sodium salt of indazole by refluxing it with propargyl bromide in toluene is accompanied by resinification. The ratio of isomers II and III in this case is 5:2. Replacement of the toluene by benzene or tetrahydrofuran (THF) reduces resinification, but it lowers the yields of the reaction products; the ratio of the isomers also changes to favor the formation of isomer II. Refluxing the silver salt of indazole with propargyl bromide in toluene gives a mixture of isomers II and III in a ratio of 6:5. Indazole reacts extremely smoothly with propargyl bromide on refluxing in a neutral medium (ethanol or butanol). In this case exclusively isomer III is formed. Structures II and III were assigned to the isomers obtained in this study on the basis of a comparison of their UV spectra with the spectra of 1-methyl- and 2-methylindazole [6].

The reaction of I with 2,3-dibromo-1-propene in alcoholic alkali gives only 1-(β-bromoallyl)indazole (IV), the dehydrobromination of which with sodium amide in liquid ammonia gives II.

Like 1-propargylbenzimidazole, II is readily isomerized by the action of potassium hydroxide in THF at 0°C to 1-propadienylindazole V, which can also be obtained under these conditions from IV. The IR spectrum of V contains ν_{as} bands at 1960 (−C=C=C−) and 890 cm^{-1} (>C=CH_2 out-of-plane deformation vibrations), which are characteristic for terminal allenes [7].

1-(β-Ethoxyallyl)indazole (VI) is formed in the dehydrobromination of IV in alcoholic potassium hydroxide. The reaction evidently proceeds through the intermediate formation of allene V, the nucleophilic addition of alcohol to which also leads to VI (see [5]). This conclusion is confirmed by the conversion of II and V to VI by the action of alcoholic potassium hydroxide.

*See [1] for communication III.

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