INTRODUCTION OF SUBSTITUENTS IN THE PYRIDINE PROTON OF 7-AZAINDOLINE*

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Electrophilic substitution (nitration, bromination, and chlorination) of 4-methyl-6-chloro-7-azaindoline (and its N-acetyl derivative) takes place in the 5 position. 4-Methyl-5-amino-7-azaindoline, 4-methyl-5-nitro-7-azaindoline, and 1-acetyl-4-methyl-5-amino-6-chloro-7-azaindoline were obtained by reduction of 1-acetyl-4-methyl-5-nitro-6-chloro-7-azaindoline under various conditions. A method was developed for the preparation of a new three-ring system — 1,2,3-oxadiazolo[5,4-b]-pyrrolo[2,3-e]pyridine.

In contrast to the thoroughly investigated electrophilic substitution processes of 7-azaindoles involving the 3 position [2, 3], not enough study has been devoted to analogous reactions for azaindoline molecules, in which attack at 3-C is impossible. There is only a communication [4] regarding the nitration of unsubstituted 7-azaindoline at the nitrogen atom of the pyrroline ring with subsequent rearrangement at higher temperatures to 5-nitro-7-aza-indoline. It might have been expected that the methyl group and the chlorine atom in 4-methyl-6-chloro-7-azaindoline (I) [5] facilitate electrophilic substitution in the pyridine portion of the molecule and open up new possibilities for the preparation of 5-substituted 7-azaindoles which are of considerable interest from the point of view of the heretofore unknown 7-aza analog of serotonin.

In fact, I was brominated with dioxane dibromide readily at room temperature, and 4-methyl-5-bromo-6-chloro-7-azaindoline (II) was obtained in 82% as the hydrobromide. In the synthesized dihalo derivative II the liabilities of the chlorine atom in the α position and of the bromine atom in the β position relative to the pyridine nitrogen atom proved to be extremely close. No reaction occurred up to 160° on treatment of II with potassium methoxide, whereas at 190° the compound underwent 58% substitution by the methoxy group (according to the results of potentiometric titration of the halogen atoms in the reaction mixture, which was carried out by argentometric titration with a silver indicator electrode), and the ratio of ionic bromine to ionic chlorine was 3:1.

The chlorination of I also proceeded readily, but the process did not terminate with electrophilic substitution of the hydrogen in the 5 position. Even under mild conditions (at 2° with an equimolar amount of chlorine), the yield of 4-methyl-5,6-dichloro-7-azaindoline (III) was ∿30%, and we observed the formation of a previously uninvestigated substance, which, according to the results of elementary analysis, contains four chlorine atoms.

In contrast to the nitration of unsubstituted 7-azaindoline, which is described in [4], the nitration of I proceeds ambiguously — 1- and 5-nitro derivatives are formed. The ratios of the two isomers vary over a wide range, depending on the reaction conditions. Thus, for example, at 0° the yield of 1-nitro-4-methyl-6-chloro-7-azaindoline (IV) was 24% and the yield 4-methyl-5-nitro-6-chloro-7-azaindoline (V) was 35% (∿40% of I was recovered). Raising the nitration temperature to 25° lowers the yield of the mixture of nitro derivatives to 14%, and the ratio of the 1-nitro (IV) and 5-nitro (V) isomers in this case is 2:1. At 30° the yield of the mixture of nitro derivatives is 6%, and the ratio of IV and V is 6:1. Thus, despite the data in [4], an increase in the percentage of the 1-nitro derivative (IV) in the mixture was observed as the temperature rose, and the rearrangement of 1-nitro derivative IV

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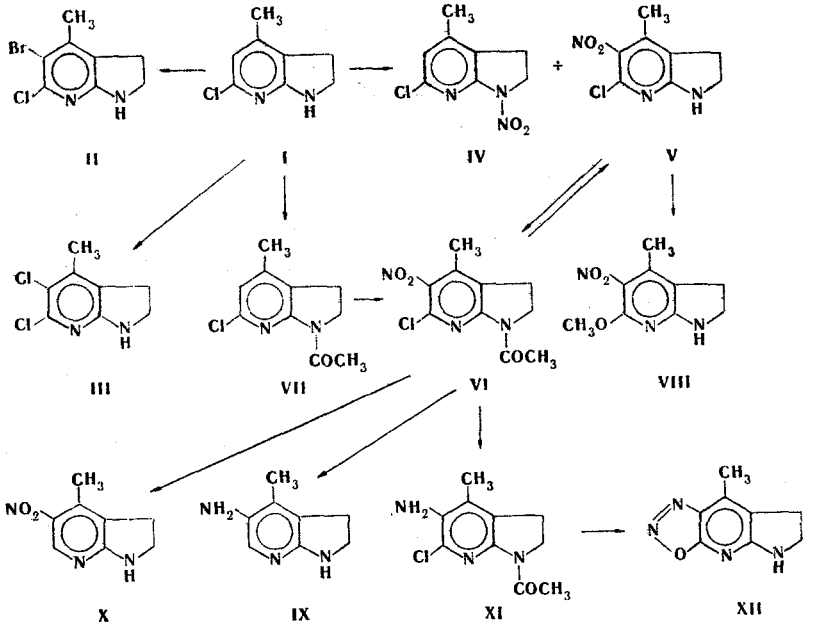
to the 5-nitro isomer was found to be difficult. An increase in the nitration temperature to 40° leads to more pronounced oxidative processes that are accompanied by destruction of the azaindoline molecules.



Acetylation of the mixture of 1- and 5-nitro isomers (IV and V) with acetic anhydride made it possible to obtain 1-acetyl-4-methyl-5-nitro-6-chloro-7-azaindoline (VI) in practically quantitative yield based on 5-nitro isomer V. Compound VI was also obtained in 55% yield by nitration of 1-acetyl-4-methyl-6-chloro-7-azaindoline (VII). As expected, the introduction of an electron-acceptor N-acetyl group hindered electrophilic substitution in the 5 position. At 0°, where compound I undergoes 58% nitration to give a mixture of IV and V, VII is recovered quantitatively. We were able to nitrate VII only at 20°. 1-Acetyl-4-methyl-7-azaindoline, which does not contain a halogen atom in the 6 position, does not undergo nitration under these conditions and is recovered unchanged.

As we have previously noted [6], a chlorine atom in the 6 position of the azaindoline molecule is replaced by a methoxy group under sufficiently severe conditions — at 190° (the analogous reaction in the 6-chloro-7-azaindole series occurs only at 300°). The introduction of a strong electron-acceptor nitro group in the ortho position relative to the chlorine atom considerably increases the tendency of the halogen atom to undergo nucleophilic substitution reactions. Thus, for example, the conversion of chloro derivative V to 4-methyl-5-nitro-6-methoxy-7-azaindoline (VIII) under the influence of potassium methoxide is realized at the boiling point of methanol. Depending on the character of the reagent used and the reaction conditions, the reduction of VI leads to different products. 4-Methyl-5-amino-7-azaindoline (IX) is formed in the reaction of VI with stannous chloride in acidic media. 4-Methyl-5-nitro-7-azaindoline (X) was isolated in 35% yield from the mixture of reaction products from the reaction with sodium in liquid ammonia. In the catalytic reduction of VI with palladium on carbon in an alcohol medium we were able to selectively reduce the nitro group to an amino group while retaining the halogen atom and the N-acetyl residue. The chlorine atom in the 6 position in 1-acetyl-4-methyl-5-amino-6-chloro-7-azaindoline (XI) is readily replaced by a hydroxy group by diazotization with sodium nitrite in aqueous medium and subsequent alkalization, during which one observes simultaneous closing of a 1,2,3-oxadiazole ring. This reaction is a preparative method for the synthesis of a new three-ring system — 1,2,3-oxadiazolopyrrolopyridine — the first representative of which is 4-methyl-5,6-dihydro-1,2,3-oxadiazolo[5,4-b]pyrrolo[2,3-e]pyridine (XII).

EXPERIMENTAL

The IT spectra of mineral oil suspension of the compounds were recorded with a Perkin—Elmer 457 spectrometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at 50 eV. Gas—liquid chromatography (GLC) was carried out with a Pye-Unicam 104 chromatograph with a flame-ionization detector; the 2.1 by 4 mm column was filled with 10% SE-30 silicone elastomer on silanized

diatomaceous earth (100-200 mesh), the nitrogen flow rate was 29 ml/min, and the temperature was 250°. Retention times: I 2.6 min, IV 7.2 min, V 8.4 min, VI 10.1 min, and X 5.8 min.

4-Methyl-5-bromo-6-chloro-7-azaindoline (II). A solution of dioxane dibromide, obtained from 3.15 g (20 mmole) of bromine and 30 ml of dioxane, was added with stirring at 20° to a solution of 3 g (18 mmole) of 4-methyl-6-chloro-7-azaindoline (I) in 100 ml of dioxane, and the mixture was stirred at 20° for 1 h. The hydrobromide of II was removed by filtration and washed with dioxane to give 4.81 g (82%) of a product with mp 232-233°. The base was prepared as follows. Ammonium hydroxide (25%) was added to a solution of the hydrobromide of II in hot methanol, the mixture was cooled, and the precipitated II was removed by filtration to give colorless crystals with mp 190-191°. The base was soluble in hot chloroform, benzene ethyl acetate, and alcohols but insoluble in heptane and water. Found: C 39.1; H 3.0; Br 32.0; Cl 14.0; N 11.0%. $C_8H_8BrClN_2$. Calculated: C 38.8; H 3.3; Br 32.3; Cl 14.3; N 11.3%.

4-Methyl-5,6-dichloro-7-azaindoline (III). A 16.5-ml sample of carbon tetrachloride containing 0.36 g (5 mmole) of chlorine was added at 2° to a suspension of 0.84 g (5 mmole) of 4-methyl-6-chloro-7-azaindoline (I) in 25 ml of carbon tetrachloride, after which the mixture was allowed to stant at 2° for 15 h. The solvent was then removed by distillation, and the residue was washed with ether and dissolved in chloroform. The solution was washed with 25% potassium carbonate solution, and the chloroform was removed by distillation to give 0.29 g (29%) of III with mp 174-175° (from benzene). The product was soluble in chloroform, alcohols, ethyl acetate, acetone, and hot benzene. Found: C 47.7; H 3.8; Cl 34.0; N 13.4%. $C_8H_8Cl_2N_2$. Calculated: C 47.3; H 4.0; Cl 34.9; N 13.8%. PMR spectrum (in C_5D_5N), δ: 2.02 s (CH_3), 2.75 and 3.57 t (CH_2CH_2N); the singlet of the proton attached to C_5 observed in the spectrum of I at 6.34 ppm was absent.

Nitration of 4-Methyl-6-chloro-7-azaindoline (I). A 1-g (6 mmole) sample of 4-methyl-6-chloro-7-azaindoline (I) was added in portions in the course of 15 min at 0° to 15 ml of nitric acid (sp. gr. 1.5). After 1 h, the mixture was poured over ice, and the aqueous mixture was made alkaline. The precipitate was removed by filtration, washed with water, and dried to give 1.16 g of a mixture of substances containing, according to GLC data, 0.41 g (41%) I, 0.3 g (24%) 1-nitro-4-methyl-7-azaindoline (IV), and 0.44 g (35%) 4-methyl-5-nitro-6-chloro-7-azaindoline (V). Successive recrystallization from ethyl acetate and alcohol gave 0.5 g of isomeric nitro derivatives IV and V. Found: C 44.9; H 3.8; Cl 16.3; N 19.8%. $C_8H_8ClN_3O_2$. Calculated: C 45.0; H 3.8; Cl 16.6; N 19.7%.

A 0.4-g sample of the mixture of isomeric nitro derivatives IV and V (in a ratio 4:5 according to GLC data) was refluxed for 6 h with 2 ml of acetic anhydride, after which the mixture was vacuum evaporated. Water (2 ml) was added to the residue, and the mixture was extracted with ether. When the ether extract was allowed to stand, 0.17 g (95%) of 1-acetyl-4-methyl-5-nitro-6-chloro-7-azaindoline (VI), with mp 179-180°, precipitated from it. The product was soluble in chloroform, hot acetone, slightly soluble in ether, and insoluble in heptane and water. Found: C 47.0; H 4.0; Cl 13.5; N 16.2%. $C_{10}H_{10}ClN_3O_3$. Calculated: C 47.0; H 4.0; Cl 13.8; N 16.4%.

4-Methyl-5-nitro-6-chloro-7-azaindoline (V). A 0.14-g (0.5 mmole) sample of 1-acetyl-4-methyl-5-nitro-6-chloro-7-azaindoline (VI) was refluxed for 45 min with 10 ml of 8% hydrochloric acid, after which the mixture was cooled, and the precipitate was removed by filtration to give 0.09 g (75%) of yellow crystals with mp 196-197°. The product was soluble in hot chloroform, methanol, ethyl acetate and acetone, slightly soluble in alcohol, water, and ether, and insoluble in heptane. Found: C 45.3; H 3.9; Cl 16.3; N 19.7%. $C_8H_8ClN_3O_2$. Calculated: C 45.0; H 3.8; Cl 16.6; N 19.7%. PMR spectrum (in $CDCl_3$), δ: 2.06 s (CH_3), 2.92 and 3.66 ppm t (CH_2CH_2N). Signals of protons in the aromatic region were absent.

1-Acetyl-4-methyl-6-chloro-7-azaindoline (VII). A 14-g (83 mmole) sample of 4-methyl-6-chloro-7-azaindoline (I) was refluxed for 6 h with 300 ml of acetic anhydride. At the end of the reaction, the acetic anhydride was removed by vacuum distillation, and the residue was washed with ether to give 16.8 g (96%) of colorless crystals of VII with mp 156-157°. The product was soluble in chloroform, acetone, hot ethyl acetate, and alcohol, slightly soluble in ether, and insoluble in water. Found: C 56.8; H 5.1; Cl 16.7; N 13.1%. $C_{10}H_{11}ClNO$. Calculated: C 57.0; H 5.3; Cl 16.8; N 13.3%. PMR spectrum (in C_5D_5N), δ: 1.98 and 2.65 s (CH_3, $OCCH_3$), 2.60 and 3.98 t (CH_2CH_2N), 6.71 ppm s (C_5—H).

1-Acetyl-4-methyl-5-nitro-6-chloro-7-azaindoline (VI). A total of 46 ml of nitric acid (sp. gr. 1.5) was added dropwise with stirring to 15.33 g (73 mmole) of 1-acetyl-4-methyl-6-

chloro-7-azaindoline (VII) in 300 ml of acetic anhydride while maintaining the temperature at 20°. After 2 h, the mixture was poured over ice, and the resulting precipitate was removed by filtration, washed with water, dried, and recrystallized from ethyl acetate to give 10.2 g (55%) of yellow crystals with mp 179-180°. No melting-point depression was observed for a mixture of this product with a sample of VI obtained by acetylation of 4-methyl-5-nitro-6-chloro-7-azaindoline (V). The IR spectra of the two samples were identical. PMR spectrum (in C_5D_5N), δ: 2.03 and 2.58 s (CH_3, $OCCH_3$), 2.71 and 4.07 ppm t (CH_2CH_2N).

4-Methyl-5-nitro-6-methoxy-7-azaindoline (VIII). A suspension of 0.48 g (2 mmole) of 4-methyl-5-nitro-6-chloro-7-azaindoline (V) in 15 ml of methanol was added to a methanol solution of potassium methoxide obtained from 0.23 g (6 mmole) of potassium and 15 ml of methanol, and the mixture was refluxed for 10 h, after which the methanol was removed by distillation. Water (5 ml) was added to the residue, and the mixture was extracted with ether. The solvent was removed by distillation to give 0.36 g (77%) of yellow crystals of VIII with mp 154-155° (from ethyl acetate). The product was soluble in chloroform, benzene, alcohol and hot acetone and insoluble in petroleum ether. Found: C 52.0; H 5.5; N 20.3%. $C_9H_{11}N_3O_3$. Calculated: C 51.7; H 5.3; N 20.1%.

4-Methyl-5-amino-7-azaindoline (IX). Concentrated hydrochloric acid [6 ml (66 mmole)] was added with stirring to a mixture of 2.5 g (10 mmole) of 1-acetyl-4-methyl-5-nitro-6-chloro-7-azaindoline (VI) and 10 g (44 mmole) of stannous chloride in 120 ml of glacial acetic acid. When the mixture was heated, it initially became homogeneous, but a precipitate formed at 70° and subsequently dissolved when the mixture was refluxed. The solution was refluxed for 2.5 h, after which it was cooled to 5°, and the precipitate was removed by filtration and dissolved in chloroform. The chloroform solution was treated with 20% sodium hydroxide solution, dried, and evaporated to give 0.7 g (47%) of IX with mp 132-134° (from ethyl acetate). The product was soluble in chloroform, hot acetone, and ethyl acetate. Found: C 64.4; H 7.3; N 28.5%. $C_8H_{11}N_3$. Calculated: C 64.4; H 7.4; N 28.2%; M 149 (mass spectroscopically).

Reaction of 1-Acetyl-4-methyl-5-nitro-6-chloro-7-azaindoline (VI) with Sodium in Liquid Ammonia. A suspension of 2.56 g (10 mmole) of 1-acetyl-4-methyl-5-nitro-6-chloro-7-azaindoline (VI) in 170 ml of toluene was added in the course of 30 min to a solution prepared from 2.8 g of sodium and 400 ml of liquid ammonia, after which the mixture was stirred for 2 h, during which the ammonia gradually evaporated. The ammonia was removed, and 6 ml of methanol and 50 ml of water were added successively with stirring. The toluene layer was separated, and the aqueous layer was washed five times with 20-ml portions of benzene, made alkaline with 50% potassium carbonate solution, and extracted with butanol. Removal of the solvents from the toluene–benzene solution gave 0.06 g of X with mp 224-225° (from alcohol). This product was soluble in chloroform, butanol, and hot methanol and ethanol and slightly soluble in acetone, ethyl acetate, and ether. Found: C 54.0; H 5.2; N 23.1%. $C_8H_9N_3O_2$. Calculated: C 53.6; H 5.1; N 23.4%; M 179 (mass spectroscopically). Evaporation of the butanol extract gave 1.3 g of a product containing, according to the GLC data 0.57 g of X. The overall yield of X was 0.63 g (35%).

1-Acetyl-4-methyl-5-amino-6-chloro-7-azaindoline (XI). A solution of 2 g (8 mmole) of 1-acetyl-4-methyl-5-nitro-6-chloro-7-azaindoline (VI) in 300 ml of alcohol was shaken with hydrogen at room temperature in the presence of 2 g of Pd/C. At the end of the hydrogenation, the catalyst was removed by filtration and washed successively with alcohol and chloroform. The solvents were removed by distillation to give 0.91 g (52%) of XI with mp 250-251° (from alcohol). Found: C 53.3; H 5.2; Cl 15.4; N 19.0%. $C_{10}H_{12}ClN_3O$. Calculated: C 53.2; H 5.4; Cl 15.7; N 18.6%. IR spectrum: 3470 and 3360 (NH_2); 1645 cm^{-1} (amide CO).

4-Methyl-5,6-dihydro-1,2,3-oxadiazolo[4,5-b]pyrrolo[2,3-e]pyridine (XII). A 0.39-g (6 mmole) sample of sodium nitrite was added in portions at 3° to a suspension of 1.12 g (5 mmole) of 1-acetyl-4-methyl-5-amino-7-azaindoline (XI) in 40 ml of glacial acetic acid. After 3 h at this temperature, the mixture was heated on a water bath for 1 h, after which it was cooled, made alkaline with sodium carbonate, washed with ether, and extracted repeatedly with hot chloroform. The chloroform was removed by distillation to give 0.59 g (55%) of dark-red crystals with mp 158-160° (dec., from ethanol). Found: C 55.0; H 4.7; N 31.9%. $C_{10}H_{11}N_5O$. Calculated: C 55.3; H 5.1; N 32.2%. The IT spectrum contained absorption bands at 2080 and 1658 cm^{-1} characteristic for the 1,2,3-oxadiazole system. Molecular weight 176 (by mass spectrometry). PMR spectrum (in CD_3OD), δ: 2.16 singlet (CH_3), 2.95 and 3.72 ppm, (CH_2CH_2N).

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DIQUINOLYLS

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A convenient method was developed for the synthesis of diquinolyls by recombination of quinoline anion radicals formed by reaction of quinolines with active metals. A series of diquinolyls, their homologs, and partially hydrogenated derivatives were obtained.

Heteroaromatic anion radicals obtained by one-electron reduction of aromatic heterocycles *in situ* readily hetarylate organic compounds [1] or recombine to give bisheteroaromatic systems [2]. This is the basis of the well-known syntheses of dipyridyls, but diquinolyls have not been obtained by this method because of low yields and the formation of difficult-to-separate mixtures of isomers [2]. 2,2'-Diquinolyl (cuproin), which is widely used in industry as an extracting agent for monovalent copper ions, is currently obtained in ~60% yields by decarboxylation of 2,2'-dicinchoninic acid, which in turn is usually synthesized in 50% yield from isatin and 3-chloro-2-butanone [3]. Thus the overall yield of 2,2'-diquinolyl in this two-step synthesis, which has been adopted industrially, does not exceed 30%. It seemed of interest to attempt to develop a direct method for the preparation of cuproin and other diquinolyls and their homologs in high yields directly from quinoline, quinaldine, and lepidine, which are the components of quinoline bases of coal tar and have not yet found qualified application despite the considerable resources available [4].

It was found that the reaction of quinoline with metal in an inert gas atmosphere gives isomers of partially hydrogenated diquinolyls, the oxidation of which with nitrobenzene leads to a mixture of diquinolyls, the composition of which depends on the nature of the metal used. In particular, we were able to obtain, in one step almost pure 2,2'-diquinolyl in 50% yield when we heated quinoline with aluminum dust, activated by mercuric chloride, in nitrobenzene solution [5]. Quinoline homologs react similarly with aluminum dust. A mixture of 4,4'- and 2,2'-diquinolyls in a ratio of 4:1 is formed when zinc dust is used; mixtures of approximately equal amounts of 2,3'-, 2,2'-, and 4,4'-diquinolyls are obtained, as a rule, in the presence of other metals, and the remaining isomers are formed in vanishingly small amounts, which we detected only by chromatography. Carrying out the reaction in inert solvents in a nitrogen atmosphere makes it possible to also obtain various partially hydrogenated diquinolyls.

To ascertain the possibilities of the proposed method for the synthesis of diquinolyls and to establish the nature of the reactions occurring during it, we preparatively obtained and characterized all the types of compounds formed in this process. However, we did not attempt to isolate the intermediates in all cases, since the partially hydrogenated diquinolyls are oxidized to give diquinolyls III, VI, VIII, and XI when the reaction is carried out

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