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METHYLATION OF 3-ARYLAZOINDAZOLES

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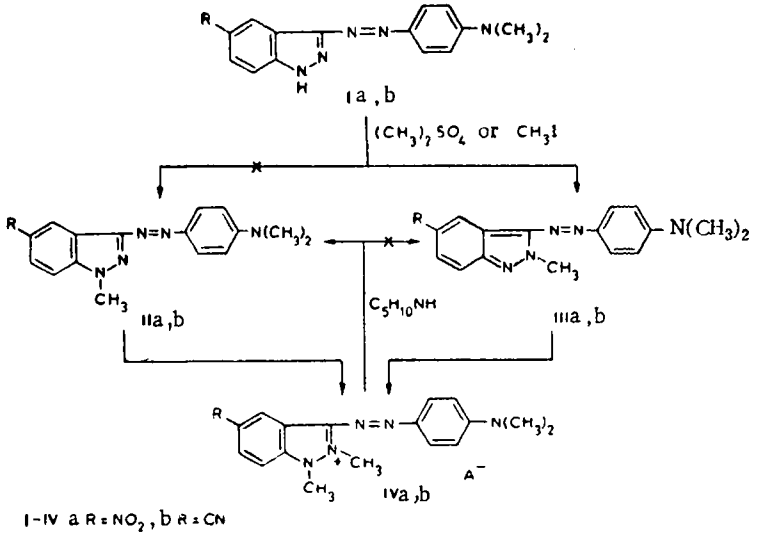
Alkylation of 3-arylazoindazoles represents a possible route to salts of 1,2-dialkyl-3-arylazoindazoles, which are used as cationic dyes. This route is effective if the 3-aminoindazole precursor is available, which is converted into the 3-arylazoindazole by diazotization and azo coupling with an aromatic amine. Although salts of 1,2-dialkyl-3-arylazo-5-nitroindazole have found practical application as dyes, and 3-amino-5-nitroindazole is formed in high yield by the reaction of 5-nitro-2-chlorobenzonitrile with hydrazine hydrate [1], the synthesis of dyes via 3-arylazo-5-nitroindazoles has not been described. They are generally produced by a multistage synthesis of 1,2-dialkyl-5-nitroindazole-3-hydrazones with subsequent oxidative coupling [2, 3].

We have studied the alkylation of 3-arylazo-5-nitroindazoles and of the previously unknown 3-arylazo-5-cyanoindazoles, for example the methylation of 3-(4-dimethylaminophenylazo) derivatives (Ia, b). For identification of the reaction products 1- and 2-methyl-3-arylazoindazoles were synthesized by the alternative route via diazotization of the corresponding N-methyl-3-aminoindazoles and azo coupling with N,N-dimethylaniline.



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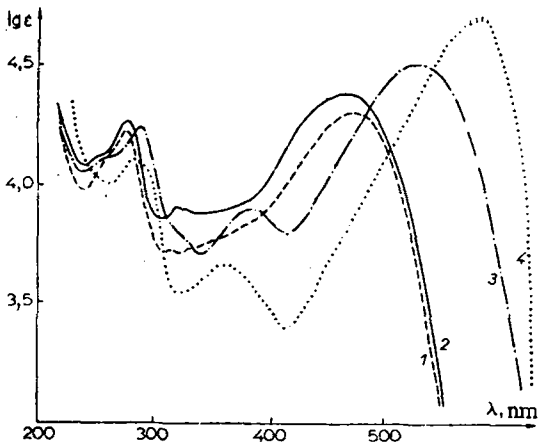
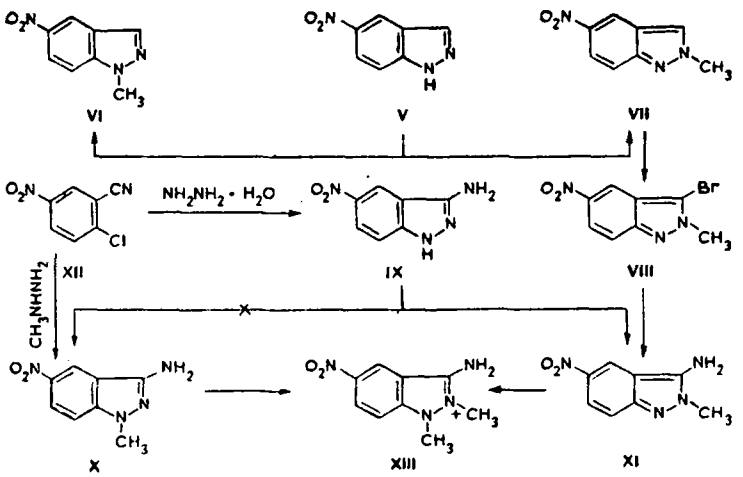


Fig. 1. Electronic spectra in ethanol: 1) 3-(4-dimethylaminophenylazo)-5-nitroindazole (Ia); 2) 1-methyl-3-(4-dimethylaminophenylazo)-5-nitroindazole (IIa); 3) 2-methyl-3-(4-dimethylaminophenylazo)-5-nitroindazole (IIIa); 4) 1,2-dimethyl-3-(4-dimethylaminophenylazo)-5-nitroindazole iodide (IVa).

In order to characterize the effect of the 3-arylazo group, methylation of 3-arylazo-5-nitroindazole (Ia) and of 5-nitroindazole (V) was also carried out. Here we encountered contradictory data in the literature regarding the structure of the isomeric N-methyl-5-nitroindazoles. In some published reports [4-6] the structure of 2-methyl-5-nitroindazole (VII) was ascribed to the higher-melting isomer (mp 163°C), whereas in other reports [7, 8] it was ascribed to the lower-melting isomer (mp 129°). In order to establish the structure we converted the low-melting isomer into the 3-bromo compound (VIII) [7] and by subsequent ammonolysis into the amine, which proved to be identical to 2-methyl-3-amino-5-nitroindazole (XI), the structure of which has been proved by an independent route [1]: by synthesis of 1-methyl-3-amino-5-nitroindazole (X) by reaction of 5-nitro-2-chlorobenzonitrile (XII) with methylhydrazine. Hence the 2-methyl derivative (VII) is the lower melting of the products of methylation of 5-nitroindazole and the data given in [4-6] needs to be corrected. When 5-nitroindazole is methylated with methyl iodide in dimethyl sulfoxide at 70°, together with 17% of the quaternary salt there is isolated 50% of the 2-methyl-substituted compound VII and 10% of the 1-methyl-substituted compound VI, and not the contrary as indicated in [6]. When the anion of 5-nitroindazole is methylated [8] with methyl iodide in methanol in the presence of potassium hydroxide a mixture of the 1-methyl compound VI and the 2-methyl compound VII is formed in the ratio 47:53. Thus methylation of both the nonionized and the anionic form of 5-nitroindazole results in a mixture of the two isomers with a large preponderance of the 2-methyl isomer in the first case.



Under the same conditions by methylation of the anion of 3-arylazo-5-nitroindazole we have obtained a mixture of the 1-methyl-substituted compound IIa and the 2-methyl compound

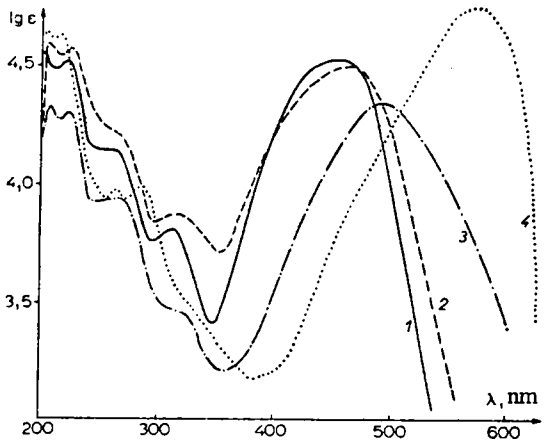


Fig. 2. Electronic spectra in ethanol: 1) 3-(4-dimethylaminophenylazo)-5-cyanoindazole (Ib); 2) 1-methyl-3-(4-dimethylaminophenylazo)-5-cyanoindazole (IIb); 3) 2-methyl-3-(4-dimethylaminophenylazo)-5-cyanoindazole (IIIb); 4) 1,2-dimethyl-3-(4-dimethylaminophenylazo)-5-cyanoindazole iodide (IVb).

IIIa in the ratio 40:60 (yield 68%), and by methylation of the nonionized compound Ia, 10% of the 2-methyl compound IIIa, 4% of the quaternary salt IVa, and 70% of the starting substance. By methylation of the azo compound Ia under strictly controlled conditions at 110-115° in a medium of dimethyl sulfide complete conversion to the quaternary salt IVa was achieved, and checking by thin-layer chromatography (TLC) showed that only the 2-methyl compound IIIa and not the 1-methyl compound IIa was formed. In the same way quaternization of 3-arylazo-5-cyanoindazole Ib occurred via the stage of solely the 2-methyl compound IIIb. The preparation of the indazole salts IVa, b in good yield indicates that a preparative route to cationic dyes via the 3-arylazo-5-nitro and 3-arylazo-5-cyano-indazoles can be realized.

From the results given above it follows that introduction of 3-arylazo groups into the 5-nitroindazole molecule directs methylation of the nonionized form exclusively to position 2, at the same time slowing down the reaction. The assumption that the absence of the 1-methyl-substituted compounds II is caused by their more rapid conversion to the quaternary salt IV, is improbable since it is known [9] that the rate constant for quaternization of 1-methylindazole is one third that of 2-methylindazole. The high preference for position 2 compared to position 1 can be explained by the existence of the azo compounds I in the 1H-form and by the nucleophilic contribution of the azo group to methylation of the adjacent position.

The existence of the azo compounds I in the 1H-form is indicated by comparing their electronic spectra with the spectra of the 1- and 2-methyl-substituted compounds. As seen from Figs. 1 and 2, the spectra of 3-arylazoindazoles I are closely similar to the spectra of the 1-methyl-substituted compounds II, but differ from the spectra of the 2-methyl compounds III, which are shifted to longer wavelengths. Since the electron density in the indazole molecule at the pyridine nitrogen atom is greater than on the pyrrole nitrogen [10], in the 1H-form the pyridine nitrogen atom in position 2 during alkylation will readily undergo electrophilic attack. The predominance of the 1H-tautomer in solution evidently explains the preferred alkylation at position 2 of indazole and its nitro-substituted compounds in the nonionized form [6]. A factor giving rise to alkylation of 3-arylazoindazoles exclusively in position 2 can be the participation of the unshared electron pairs of the nitrogen atoms of the azo group in the formation of the transition state. A similar cooperation, which is a particular case of the effect of the participation of neighboring groups [11], we have noted previously on the part of the peri-disposed carbonyl oxygen atom in the N-alkylation [12] and quaternization [13] of the anthraquinonetriazoles.

From what has been stated it can be expected that introduction into position 3 of the indazole of other substitutents possessing a heteroatom with an unshared electron pair will also lead to the formation of only the 2-alkyl-substituted compounds. This assumption was confirmed by the methylation of 3-amino-5-nitroindazole IX, from which in the absence of

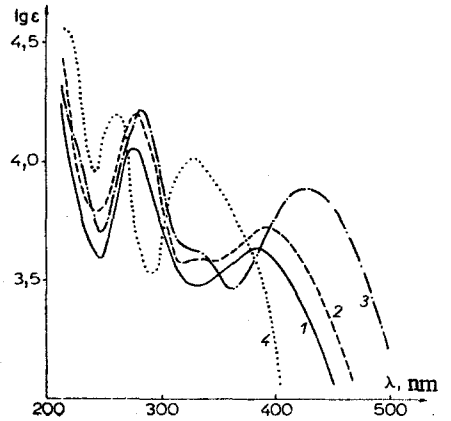


Fig. 3. Electronic spectra in ethanol: 1) 3-amino-5-nitroindazole (IX); 2) 1-methyl-3-amino-5-nitroindazole (X); 3) 2-methyl-3-amino-5-nitroindazole (XI); 4) 1,2-dimethyl-3-amino-5-nitroindazole iodide (XIII).

bases the 2-methyl isomer XI was isolated in 46% yield [1]. By repeating the experiment in [1] we showed by means of TLC that the 1-methyl isomer was absent throughout the reaction.

Comparison of the electronic spectra of 3-amino-5-nitroindazole IX and its N-methyl-substituted compounds X, XI indicates that here the nonalkylated compound exists in the 1H-form in solution: the spectra of compounds IX and X coincide, but the spectrum of the 2-methyl-substituted compound XI is bathochromically shifted (Fig. 3). In contrast to the conversion of 3-arylazo-5-nitroindazoles to the dye IVa (Fig. 1), quaternization of 3-amino-5-nitroindazoles to the indazole salt XIII (Fig. 3) gives rise to not a bathochromic but a hypsochromic shift of the long-wave band, which is the intramolecular charge-transfer (IACT) band. The reason for this difference lies probably in the fact that the increase in the electron-acceptor ability of the heterocyclic ring as a result of quaternization in the case of the 3-(4-dimethylaminophenylazo)indazoles, where the donor center — the dialkylamino group — is separated from the heterocyclic bond system, has an effect mainly in the excited state facilitating IACT, whereas in the case of the 3-aminoindazoles where the amino group is directly joined to the heterocyclic ring it is now apparent in the ground state increasing its polarity and making IACT more difficult during photoexcitation.

The 1,2-dimethyl-3-arylazo-5-nitroindazole salt IVa when reacted with a base (piperdine) loses a methyl group from position 2, and is converted into the 1-methyl-substituted compound IIa. By thermal treatment in an inert solvent both monomethyl compounds — IIa and IIIa — are formed. Demethylation only from position 2 through base action can serve to indicate the existence of the dye IV in the benzenoid form, in which the positive change in the heterocyclic ring is concentrated on the nitrogen atom at position 2, for which reason the methyl group linked to it undergoes nucleophilic attack. Such a benzenoid structure is more suitable than an o-quinonoid structure for a positive charge on the nitrogen atom in position 1 since it provides interaction with the electron-donor dimethylamino group by the shortest conjugation chain and compensates for the electron-acceptor effect of the substituent, present at position 5, due to the unshared electron pair of the nitrogen atom in position 1.

EXPERIMENTAL

Electronic spectra were measured on a Specord UV-vis spectrophotometer; IR spectra were measured on a UR-20 instrument using KBr disks. Melting points were determined on a micro hot-stage in sealed capillaries. For TLC on Silufol the eluants applied were: a mixture of dichloroethane—ethanol 5:1 (A) and diethyl ether (B).

3-(4-Dimethylaminophenylazo)indazoles (Ia, b). 3-Amino-5-nitro- or -5-cyanoindazole (0.03 mole) was dissolved in 110 ml of 64% hydrochloric acid with heating, then cooled to 2° and 6 ml (0.03 ml) of a 5 N sodium nitrite solution added. After 30 min a solution of 4.00 g (0.033 mole) of N,N-dimethylaniline in 10 ml of 10% hydrochloric acid was added, heated 1 h at 70° and on cooling a precipitate of the azo compound separated, yield 87-94%.

In the same way from 1-methyl-3-amino-5-nitroindazole [1] and 1-methyl-3-amino-5-cyanoindazole were obtained the azo compounds IIa, b (Table 1).

TABLE 1. 3-(4-Dimethylaminophenylazo)indazoles

Compound	mp, °C* (dec.)	R_f on Silufol		λ_{max}, nm (log ε), in ethanol	Found, %			Empirical formula	Calculated, %		
		A			C	H	N		C	H	N
Ia	261	0,67	0,81	468 (4,38)	57,8	4,6	27,2	$C_{15}H_{14}N_6O_2$	58,0	4,5	27,1
IIa	254	0,94	0,82	475 (4,30)	58,9	4,7	25,8	$C_{16}H_{16}N_6O_2$	59,2	4,9	25,9
IIIa	225	0,94	0,90	530 (4,52)	59,0	4,8	25,8	$C_{16}H_{16}N_6O_2$	59,2	4,9	25,9
IVa	200	0,18	0,0	581 (4,68)	42,1	4,1	17,2	$C_{17}H_{19}IN_6O_2 \cdot H_2O$	42,1	4,4	17,3
Ib	294	0.49	0,83	461 (4,52)	66,0	4,7	29,1	$C_{16}H_{14}N_6$	66,2	4,7	28,9
IIb	245	0,92	0,91	470	67,0	5,2	27,4	$C_{17}H_{16}N_6$	67,1	5,3	27,6
IIIb	235	0,91	0,89	512 (4,33)	66,8	5,3	27,5	$C_{17}H_{16}N_6$	67,1	5,3	27,6
IVb	221	0,18	0,0	579 (4,76)	48,2	4,1	18,7	$C_{18}H_{19}IN_6$	48,4	4,2	18,8

*Compounds Ia, b were recrystallized from ethanol, IIa, b from nitromethane, IIIa, b from a mixture of chloroform–petroleum ether, IVa, b from propanol.

2-Methyl-3-(4-dimethylaminophenylazo)5-nitroindazole (IIIa). To a solution of 0.80 g (4 mmole) 2-methyl-3-amino-5-nitroindazole [1] in 21 ml of 85% phosphoric acid at 0° was added 0.28 g (4 mmole) of sodium nitrite, stirred 3 h at 0-5° and a solution of 0.49 g (4 mmole) N,N-dimethylaniline in a mixture of 25 ml 0.2 N hydrochloric acid and 25 ml acetone was run in, stirred 3 h at 0-5° and 100 ml water added. The precipitate of the azo compound IIIa was separated, and washed with water. Yield 33% (Table 1).

1,2-Dimethyl-3-(4-dimethylaminophenylazo)-5-nitro- and -5-cyanoindazole Iodides (IVa, b). A solution of 5 mmole of the azo compound Ia or Ib in 6.2 ml (62 mmole) of dimethyl sulfate was heated 40 min at 110-115°, 20 ml of water was added, heated at boiling 1 h, a further 50 ml of water and 10 ml (19 mmole) of a 30% solution of potassium iodide was run in. The precipitate of the iodide IVa or IVb was separated and recrystallized from aqueous propanol, yields 64 and 73%, respectively.

Methylation of 3-(4-Dimethylphenylazo)-5-nitroindazole (Ia). A) A solution of 0.78 g (2.5 mmole) of the azo compound Ia and 1.06 g (7.5 mmole) methyl iodide in 8 ml dimethyl sulfoxide was heated 5 h at 70° and diluted with water. The precipitate was separated, dried and dissolved in chloroform and chromatographed on a column of silica gel. The red-violet band of the 2-methyl compound IIIa, 0.08 g (10%), and the orange band of the original azo compound (Ia), 0.55 g (70%), were eluted with chloroform, and then the blue band of the iodide IVa, 0.5 g (4%), with acetic acid. A check by TLC on Silufol during the reaction did not reveal the presence of the 1-methyl compound IIa.

B) A solution of 0.78 g (2.5 mmole) of the azo compound Ia, 0.42 g (7.5 mmole) of potassium hydroxide, and 1.06 g (7.5 mmole) of methyl iodide in 10 ml of methanol was heated at boiling 1 h and then diluted with water. The precipitate was filtered off and chromatographed on a column of silica gel, giving by elution with chloroform 0.55 g (68%) of a mixture of the methyl compounds IIa and IIIa in the ratio 2:3 (determined spectrophotometrically), and then 0.03 g (4%) of the starting compound Ia.

Methylation of 3-Amino-5-nitroindazole (IX). A solution of 0.89 g (5 mmole) compound IX and 0.76 g (6 mmole) freshly distilled dimethyl sulfate in 10 ml of nitrobenzene was heated 1 h at 150° and a test sample removed for TLC on Silufol. As calibrants were used the starting amine IX, its 1- and 2-methyl derivatives X, XI prepared by the method in [1], with R_f values, respectively of 0.66, 0.79, and 0.16. The presence of the 1-methyl derivative X was not detected. After treatment according to [1], 40% of the 2-methyl derivative XI was isolated.

2-Methyl-3-amino-5-nitroindazole (XI). This was also prepared from 2-methyl-3-bromo-5-nitroindazole (VIII) [7] by heating the latter in an ethanolic solution of ammonia for 20 h at 120° in a sealed tube. From the IR spectrum and the R_f by TLC on Silufol the substance proved to be identical to the compound synthesized by methylation of 3-amino-5-nitroindazole (IX).

Demethylation of 1,2-Dimethyl-3-(4-dimethylaminophenylazo)-5-nitroindazole Iodide (IVa). A) A solution of 0.20 g (0.4 mmole) of the iodide IVa in a mixture of 5 ml piperidine and 5 ml ethanol was heated at boiling 4 h and poured into 2 N hydrochloric acid. The precipitate

was filtered off and washed with water, giving 60% of the 1-methyl compound IIa. A check by means of TLC on Silufol during the reaction did not reveal the presence of the 2-methyl compound IIIa.

B) A solution of 0.20 g (0.4 mmole) of the iodide IVa in 50 ml of tetrachloroethane was heated at boiling for 4 h, about 40 ml of the solvent distilled off, 20 ml of petroleum ether added, and the solid filtered off giving 52% of compound IIa. By evaporation of the filtrate 22% of 2-methyl compound IIIa was obtained.

3-Amino-5-cyanoindazole. A mixture of 20.70 g (0.1 mole) of 4-bromoisophthalodinitrile, 12.5 ml (0.2 mole) 78% hydrazine hydrate, and 300 ml of ethanol was heated at boiling for 15 h. The solvent was distilled off and the precipitate dissolved in 210 ml of 2 N hydrochloric acid while boiling. The solution was filtered hot and on cooling 230 ml of a 27% solution of sodium acetate was added. The precipitate was separated and recrystallized from water, yield 6.85 g (43%), as colorless needles mp 226° (dec). IR spectrum: 2230 (CN), 3225, 3350 cm^{-1} (NH_2). Found: C 60.6; H 3.7; N 35.2%. $C_8H_6N_4$. Calculated: C 60.7; H 3.8; N 35.4%.

3-Amino-1-methyl-5-cyanoindazole. This was prepared in the same way as described above using methylhydrazine, yield 52%. Colorless needles, mp 162° (dec.), from aqueous ethanol. IR spectrum: 2221 (CN), 3228, 3346 cm^{-1} (NH_2). Found: C 62.6; H 4.5; N 32.3%. $C_9H_8N_4$. Calculated: C 62.8; H 4.7; N 32.5%.

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