SYNTHESIS OF AZOXINDOLES

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UDC 547.751.07

Heating N-substituted 2-methyl-3-phenyl-5-nitroindoles in methanol with excess base yields the corresponding azoxindoles. Under the same conditions 2-methyl-5-nitroindole is converted to bis(2-methyl-5-nitroindol-3-yl)methane. Reaction of 1,2-dimethyl-3-formyl-5-nitroindole with benzyl cyanide gives 1,2-dimethyl-3-(β-cyano-β-phenyl)vinyl-5-nitroindole.

It is known that nitrobenzenes can condense with benzyl cyanides in the presence of base to form a variety of compounds. These include 4-arylcyanomethylenecyclohexa-2,5-dienone oximes, 1-p-nitrophenyl-1-phenylacetonitrile, 1-phenyl-1-p-hydroxylaminophenylacetonitrile, and substituted anthranils [1–4].

Recently it has been shown that 5-nitrobenzimidazoles also take part in this reaction to form imidazo[4,5-e]benzisoxazoles (anthraniles) [5].

In this work we have attempted to use 5-nitroindoles Ia–c in the same type of condensation. Heating 1,2-dimethyl-3-phenyl-5-nitroindole (Ia) with benzyl cyanide in methanol in the presence of excess potassium hydroxide gives a product whose IR spectrum shows the absence of CN and NO_2 absorption bands. According to mass spectrometry, the molecular weight of the product is 480 and the PMR spectrum ($CDCl_3$) (Table 1) shows a double set of closely positioned signals for all protons, thus pointing to a structure of near symmetry. These data suggest that the benzyl cyanide does not take part in the reaction. Instead, there occurs an oxidative-reductive process, characteristic of nitrobenzenes [6] in alcoholic basic media, leading to 1,1',2,2'-tetramethyl-3,3'-diphenylazoxindole (IIa). In fact, it was found that the same compound is formed in essentially the same yield by heating nitroindole Ia in methanolic base without addition of the benzyl cyanide.

The reactions of 1-ethyl (Ib) and 1-benzyl-2-methyl-3-phenyl-5-nitroindole (Ic) occur similarly to give the corresponding azoxindoles IIb,c. A necessary condition for the reaction is the use of an alcoholic solvent, in this case methanol. The reaction does not occur in acetone or dimethylsulfoxide (equally neither does the condensation with benzyl cyanide) and virtually all starting material is recovered. The process is extremely sensitive to the structure of the starting material, thus no analogous reaction occurs with the N-unsubstituted 2-methyl-3-phenyl-5-nitroindole (Id), starting material being recovered. Evidently in the presence of excess base Id is ionized and the excess electron density on the NO_2 group significantly lowers its oxidative properties. The anthranyl cyclization did not succeed either for 2-methyl-5-nitroindole (III). Both with and without benzyl cyanide the reaction took another pathway and yielded bis(2-methyl-5-nitroindol-3-yl)methane (IV).*

In this case, ionization of the indole N–H bond directs the reaction to the 3-position of the molecule because of the increased electron density at indole C_3. The notable effect of NH ionization on this process is evidenced by the fact that IV is not formed from 1,2-dimethyl-5-nitroindole.

We have attempted to introduce into position 3 of the molecule electron-acceptor substituents like the formyl group. In this instance neither the anthranyl cyclization nor azoxy derivative formation is observed, but a Knoevenagel reaction takes place between 1,2-dimethyl-3-formyl-5-nitroindole (V) and benzyl cyanide to form 1,2-dimethyl-3-(β-cyano-β-phenyl)vinyl-5-nitroindole (VI).

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*Compound IV obtained before [7]. In our case, it is obtained by condensation of two molecules of III with formaldehyde produced by oxidation of methanol with the nitroindole.

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TABLE 1. Constants for the Synthesized Compounds

Compound	Empirical formula	mp, °C (from ethanol)	PMR Spectrum ($CDCl_3$), δ, ppm*	Yield, %
IIa	$C_{32}H_{28}N_4O$	280...283** (decomp.)	2,50 and 2,51 (s, 2-, 2'-CH_3); 3,78 and 3,79 (s 1-, 1'-CH_3); 8,85 and 8,61 (d, $J_1 \approx 1{,}7 \ldots 2{,}1$ Hz, 4-, 4'-H); 8,22 and 8,13 (q $J_1 \approx 1{,}7 \ldots 2{,}1$ Hz, $J_2 = 9$ Hz); 7,31...7,50 (7-, 7'-H)	64
IIb	$C_{34}H_{32}N_4O$	254...256	2,50 and 2,51 (s, 2-, 2'-CH_3); 1,43 (t, 1-, 1'-CH_3); 4,23 (q, CH_3CH_2); 8,84 and 8,60 (d $J_1 \approx 1{,}7 \ldots 2{,}1$ Hz, 4-, 4'-H); 8,24 and 8,13 (q $J_1 \approx 1{,}7 \ldots 2{,}1$ Hz, $J_2 \approx 9$ Hz, 6-, 6'-H); 7,35...7,55 (7-, 7'-H)	65
IIc	$C_{44}H_{36}N_4O$	275...277	2,44 and 2,43 (s, 2-, 2'-CH_3); 5,41 and 5,42 (s, 1-, 1'-CH_2Ph); 8,87 and 8,63 (d, $J_1 \approx 2{,}0 \ldots 2{,}7$ Hz, 4-, 4'-H); 8,17 and 8,04 (q $J = 2{,}0 \ldots 2{,}7$ Hz, 6-, 6'-H); 7,00...7,58 (7-, 7'-H)	67
IV	$C_{19}H_{16}N_4O_4$	350...354 (decomp.)	2,49 (s 2-, 2'-CH_3); 8,17 (d, $J \approx 2{,}3$ Hz 4-, 4'-H); 7,86 (q $J_1 \approx 2{,}3$ Hz, $J_2 \approx 9{,}0$ Hz, 6-, 6'-H); 7,37 (d $J_1 \approx 9$ Hz, 7-, 7'-H); 4,16 (s, $-CH_2-$)	25
VI	$C_{19}H_{15}N_3O_2$	156...158		72

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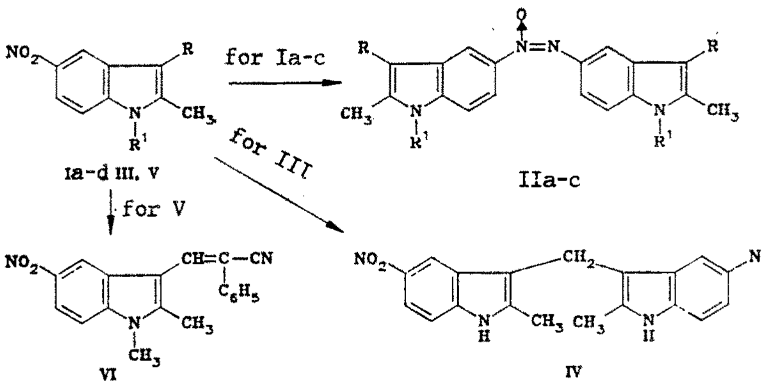
*PMR spectrum of IV recorded in DMSO-d_6.

**From a mixture of ethanol–DMF (2:1).



I a-d II a-c R=C_6H_5, a R^1=CH_3, b R^1=C_2H_5, c R^1=$CH_2C_6H_5$, d R^1=H; III R=R^1=H;
V R^1=CH_3, R=CHO

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer 457 instrument in Vaseline mull and PMR spectra on a Varian XL-200 spectrometer with TMS internal standard. Melting points were determined on a Boetius apparatus.

Physical constants and yields for the compounds synthesized are given in Table 1. Elemental analytical data correspond to that calculated.

Compounds Ia–c were obtained by [8] and aldehyde V by [9].

5,5'-Azoxyindoles (IIa–c). A. A mixture of nitroindole Ia–c (0.025 mole), potassium hydroxide (0.1 mole), and benzyl cyanide (0.075 mole) in methanol (300 ml) was refluxed for 12 h. After cooling, the precipitate was filtered, washed with water, and dried.

B. A mixture of nitroindole Ia–c (0.005 mole), potassium hydroxide (0.02 mole), and methanol (50 ml) was refluxed for 12 h. The product was again cooled, filtered, washed with water, and dried.

Mixed samples from methods A and B did not show a melting point depression. The yields of IIa–c from both methods were identical.

Bis(2-methyl-5-nitroindol-3-yl)methane (IV). A mixture of 2-methyl-5-nitroindole (3.52 g, 0.02 mole), sodium hydroxide (4 g, 0.1 mole), and benzyl cyanide (8.7 g, 0.075 mole) was refluxed in methanol (200 ml) for 5 h. The solvent was evaporated in vacuo and the residue treated with water. The product was filtered, washed with water, and dried.

1,2-Dimethyl-3-(β-cyano-β-phenyl)vinyl-5-nitroindole (VI). A mixture of aldehyde V (1.08 g, 0.005 mole), sodium hydroxide (8 g, 0.2 mole), and benzyl cyanide (0.59 g, 0.005 mole) was refluxed in methanol (80 ml) for 3 h. The solvent was evaporated in vacuo, the residue treated with water, and the solid filtered, washed with water to neutrality, and dried.

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REACTION OF 2,3,3-TRIMETHYL-3H-INDOLE HYDROCHLORIDE WITH METHACRYLIC AND CROTONIC AMIDES

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UDC 547.398.1'753'853.5:
543.422.25:541.63

Reaction of 2,3,3-trimethyl- and 2,3,3,5-tetramethyl-3H-indole hydrochlorides with methacrylic and crotonic amides gives 3- and 4-methyl-1,2,3,4,10,10a-hexahydropyrimido[1,2-a]indol-2-ones. With perchloric acid these are converted to 1-carbamoylpropyl-3H-indolium perchlorates. The syntheses of 10a-(4-dimethylaminostyryl)- and 10a-[(4-dimethylaminophenyl)butadienyl]-3,10,10-trimethylpyrimido[1,2-a]indol-2-ones have been studied.

Reaction of 2,3,3-trimethyl-3H-indole salts with acrylamide in proton containing solvents and workup of the mixture with bases leads to formation of 1,2,3,4,10,10*a*-hexahydropyrimido[1,2-*a*]indol-2-one [1]. Their styryl derivatives have been proposed as color-forming materials in data recording [2, 3].

In our work, we have studied the products of the reaction of 2,3,3-trimethyl- and 2,3,3,5-tetramethyl-3H-indole hydrochlorides with methacrylic and crotonic amides.

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