ELECTROPHILIC SUBSTITUTION REACTIONS OF ALKYLATED 2-AMINOINDOLE DERIVATIVES

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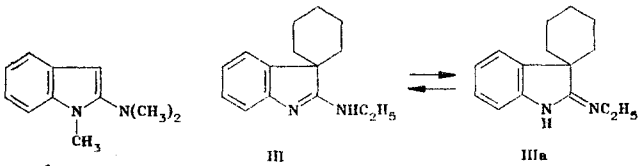
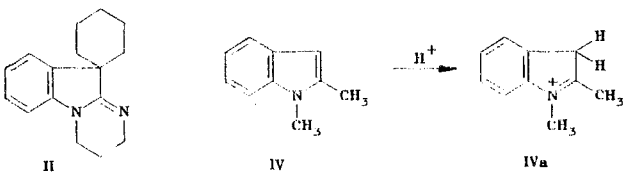
Bromination, nitration, and acylation of 1-methyl-2-dimethylaminoindole under mild conditions proceed to give the 3-substituted reaction products. In acidic media, in which the parent indole exists in the form of an amidinium cation, substitution occurs in the 5-position of the benzene ring. Aminoindoles, which are capable of existing only in the iminoindoline or aminoindolenine forms, always give products derived from substitution at the para position relative to the nitrogen atom, regardless of the reaction conditions.

The literature concerning the electrophilic substitution reactions of 2-aminoindoles is very complete with respect to acylation [1] and alkylation [2] of both the nitrogen atom and the β-carbon atom. There are no examples concerning substitution within the benzene ring. It is known, however, that, depending on the acidity of the reaction medium, 1,2-dimethylindole is brominated and nitrated in different positions: In concentrated sulfuric acid, for instance, substitution occurs at the 5-position (para-orientation of the immonium group in the protonated indole IVa [3]), whereas the basic indole form IV is nitrated [4] and brominated [5] in the 3-position.

We have investigated various types of electrophilic substitution reactions, namely bromination, nitration, and acylation, for three model compounds I-III, below.





The model compounds I and II are constrained to exist in the indole and iminoindoline forms, respectively, while compound III can exist in tautomeric forms.

We have found that aminoindole I is readily brominated at −20°C at the 3-position using elemental bromine in $CHCl_3$. The crystalline hydrobromide V is deposited from the reaction mixture after only several minutes reaction time; this compound undergoes very rapid resinification either upon attempted conversion to its basic form (upon treatment with base or pyridine), or upon exposure to air during standing (apparently as a result of polycondensation and gum-forming reactions).

In the PMR spectrum of compound V in CF_3COOH the signal due to the 3-H proton, which is located adjacent to the bromine atom, has been shifted downfield by 2 ppm (relative to that found in the indole I in CF_3COOH). Just as is observed in the spectrum of the indole I, the dimethylamino group gives rise to two broadened singlet signals as a consequence of restricted rotation about the C—N multiple bond.

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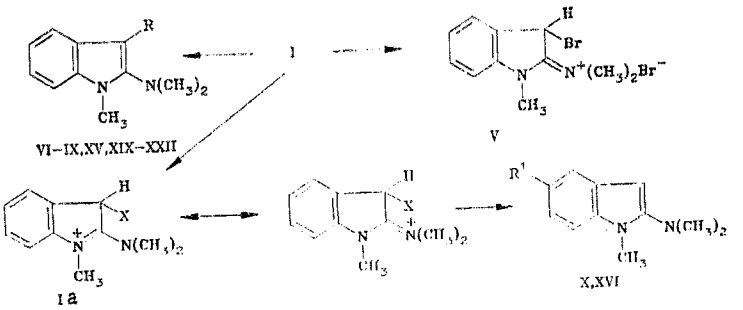

VI—IX R=Acyl; XV R=NO_2; XIX—XXII R=Alk; X R^1=CH_3CO; XVI R^1=NO_2

Acylation of the aminoindole I using chloroanhydrides in the presence of pyridine or triethylamine also occurs much more readily than for free indole [6], and gives the 3-acylated derivatives VI-IX (see Table 1). The relatively low value of the carbonyl group stretching frequency in compounds VI-IX (1650 cm^{-1}) may be ascribed to the electron donating effect of the enediamine system [7]; the PMR spectra of these compounds are characterized by a downfield shift of the 4-H proton signal by about 0.6-0.8 ppm, relative to the signal due to the residual aromatic protons, which is consistent with the spectral properties of 3-acylindoles [8].

Friedel—Crafts type acylation of the aminoindole I results in the formation not of the 3-substituted product, but rather the 5-substituted derivative X. The introduction of a substituent in the benzene ring was verified by the splitting pattern of the aromatic protons. The PMR spectrum (Table 1) also exhibits a signal due to the 3-H proton in the 5.9-ppm region.*

The acylation of 1,2-dimethylindole using a CH_3COCl—$AlCl_3$ complex is also known to occur at the 5-position [9]. It can be assumed, therefore, that the cation Ia, analogous to the cation IVa, is formed and takes part in the reaction, thus guaranteeing the attack of the electrophilic reagent at the 5-position. This was confirmed by studying the electrophilic substitution reactions of the model compounds II and III, in which attack occurs at the 8-position (corresponding to the 5-position in indoles), regardless of the reaction conditions (acidity of the medium) employed. Compounds II and III cannot exist in the indole form, and the orientation of the benzene ring is based on the presence of amino-, imino-, or immonium groups in the para position (see Table 2†).

The conventional nitrating agents (KNO_3—H_2SO_4, HNO_3—H_2SO_4, and HNO_3—CH_3COOH) used in the reactions of indoles were found to be unsuitable for the reactions of the easily oxidized aminoindoles, and only complex mixtures of unidentified products were formed in these reactions. Nitration of the indole I was best accomplished using a nonoxidizing reagent, such as nitronium fluoroborate or N-nitropyridinium fluoroborate [11]. The latter reagent reacted with indole I at —20°C to give the expected 3-substituted product XV. Nitration of the same indole with nitronium fluoroborate in acidic medium (CF_3COOH) gave a 76% yield of the 5-nitro isomer XVI, uncontaminated with other isomeric impurities. Hydrolysis of compound XVI leads to 5-nitro-1-methyloxyindole [12], as described in the literature; this is good evidence for the structure of the aminoindole XVI. The aminoindoles II and III, which are less prone to oxidation [13], could be easily nitrated using a mixture of nitric and acetic acids to give the 8-substituted products (compounds XVII and XVIII).

It has been demonstrated, therefore, that in its basic (indole) form 2-aminoindole I is brominated, nitrated, and acylated at the 3-position, just as is 1,2-dimethylindole. These reactions proceed very rapidly, which is consistent with the high nucleophilicity of the β-carbon atoms in these molecules (the electron-donating effect of the 2-amino group). When the nitration or acylation reactions are carried out in acidic solutions, where the cation Ia is formed, substitution occurs at the 5-position. The aminoindoles II and III, which cannot exist in the indole form, always give benzene ring substitution products corresponding to replacement at the para position relative to the cyclic nitrogen atom.

*According to PMR analysis, the unpurified reaction product contains very small (insignificant) amounts of the 3,5-diacetyl derivative.

†The structure of compound XI was verified by an independent synthesis according to [10].

TABLE 1. Derivatives of 1-Methyl-2-dimethylaminoindole I

Compound	R*	mp, °C	PMR spectrum, δ, ppm		Found, %		Molecular formula	Calc., %		Yield, %
			3-R	Ar	C	H(N)		C	H(N)	
VI	$COCH_3$	—	2,58 (3H, s)	7,1—7,2 (3H, m, 5-H—7-H); 7,7—7,86 (1H, m, 4-H)	72,8	7,8	$C_{13}H_{16}N_2O$	72,2	7,4	69
VII	$COCH_2Cl$	76	4,65 (2H, s)	7,18—7,24 (3H, m, 5-H—7-H); 7,8—7,9 (1H, m, 4-H)	62,5	6,4	$C_{13}H_{15}ClN_2O$	62,3	6,0	62
VIII	$COCH=CH_2$	—	5,75 (1H, d, d, J_1=2,5 Hz, J_2=12 Hz); 6,35 (1H, d, J_3=18 Hz); 7,2 (1H, d, d)	7,17—7,3 (3H, m, 5-H—7-H); 7,9—8,05 (1H, m, 4-H)	—	—	—	—	—	12
IX	$COCH_2COOEt$	—	1,28 (3H, t, Et, J=8 Hz); 4,0 (2H, s, CH_2); 4,2 (2H, q, Et)	7,18—7,24 (3H, m, 5-H—7-H); 7,84—8,0 (1H, m, 4-H)	59,3	7,1	$C_{16}H_{20}N_2O_3 \cdot HCl$	59,2	6,5	51
X	H	116	5,92 (1H, s)	7,18 (1H, d, 7-H, J=8,5Hz); 7,77 (1H, d, d, 6-H); 8,1 (1H, d, 4-H, J=1,8Hz)	72,0	7,5	$C_{13}H_{16}N_2O$	72,2	7,4	53
XV	NO_2	261	—	7,04—7,32 (3H, m, 5-H—7-H); 7,52—7,64 (1H, m, 4-H)	60,5	6,2	$C_{11}H_{13}N_3O_2$	60,3	5,9	32
XVI	H	160	5,97 (1H, s)	7,15 (1H, d, 7-H, J=9Hz); 7,98 (1H, d, d, 6-H); 8,3 (1H, d, 4-H, J=2,5 Hz)	60,4	6,2	$C_{11}H_{13}N_3O_2$	60,3	5,9	76
XIX	CH_2COOEt	—	1,22 (3H, t, Et, J=8 Hz); 3,75 (2H, s, CH_2); 4,1 (2H, q, Et)	7,04—7,22 (3H, m, 5-H—7-H) 7,44—7,56 (1H, m, 4-H)	69,4	7,9	$C_{15}H_{20}N_2O_2$	69,2	7,7	40
XX	$CH(CH_3)COOEt$	—	1,3 (3H, t, Et, J=8 Hz); 1,67 (3H, d, CH_3, J=8 Hz); 4,15 (1H, q, CH); 4,2 (2H, q, Et)	7,0—7,2 (3H, m, 5-H—7-H) 7,55—7,65 (1H, m, 4-H)		(9,8)	$C_{16}H_{22}N_2O_2$		(10,2)	20
XXI	$CH_2C_6H_5$	—	4,1 (2H, s, CH_2)	6,9—7,3 (9-H, m)	—	—	—	—	—	22
XXII	$CH_2C_6H_4NO_2$-p	—	4,2 (2H, s, CH_2); 7,2—7,4, 7,9—8,1 (4H, m, A_2B_2)	7,0—7,4 (4H, m, 4-H—7-H)	69,5	6,0	$C_{18}H_{19}N_3O_2$	69,9	6,1	48

* VI—IX, XV, XIX—XXII R^1=H; X R^1=CH_3CO; XVI R^1=NO_2.

TABLE 2. Derivatives of the Iminoindoline II (XI, XII, XVII) and the Aminoindolenine III (XIII, XIV, XVIII)

Compound	8-R (5-R)	mp, °C	PMR spectrum (aromatic protons), δ, ppm	Found, %		Molecular formula	Calc., %		Yield, %
				C	H		C	H	
XI	Br	—	6,72 (1H, d, 6-H, J=8 Hz); 7,36 (1H, d, d, 7-H); 7,68 (1H, d, 9-H, J=2 Hz)	45,7	4,5	$C_{16}H_{19}BrN_2 \cdot HClO_4$	45,9	4,8	90
XII	$COCH_3$	—	6,65 (1H, d, 6-H, J=8 Hz); 7,9 (1H, d, d, 7-H); 8,14 (1H, d, 9-H, J=2 Hz)	67,6	7,2	$C_{18}H_{22}N_2O \cdot HCl$	68,0	7,2	75
XVII	NO_2	—	6,55 (1H, d, 6-H, J=8 Hz); 7,16 (1H, d, d 7-H); 7,46 (1H, d, 9-H, J=2 Hz)	60,0	6,4	$C_{16}H_{19}N_3O_2 \cdot HCl$	59,9	6,2	75
XIII	(Br)	220	7,1 (1H, d, 7-H, J=8,5 Hz); 7,3 (1H, d, d 6-H); 7,6 (1H, d, 4-H, J=2,2 Hz)	58,8	6,2	$C_{15}H_{19}BrN_2$	58,6	6,2	74
XIV	($COCH_3$)	205	7,25 (1H, d, 7-H, J=8,5 Hz); 7,86 (1H, d, d, 6-H); 8,14 (1H, d, 4-H, J=2,2 Hz)	66,4	7,5	$C_{17}H_{22}N_2O \cdot HCl$	66,5	7,5	63
XVIII	(NO_2)	212	7,05 (1H, d, 7-H, J=9 Hz); 8,05 (1H, d, d, 6-H); 8,18 (1H, d, 4-H, J=2,5 Hz)	66,2	7,4	$C_{15}H_{19}N_3O_2$	65,9	7,0	56

We were unable to achieve the alkylation of indole I using methyl iodide as the alkylating agent. More reactive alkyl halides, such as $BrCH_2COOC_2H_5$, $BrCH(CH_3)COOC_2H_5$, $ClCH_2C_6H_5$, or $p\text{-}ClCH_2C_6H_4NO_2$, react with this indole to give oily 3-alkyl derivatives (compounds XIX-XXII, respectively), in 20-50% yields. The PMR spectra of these substances are missing the signal due to the 3-H proton, and new signals due to the newly introduced alkyl substituents are found (see Table 1). The principal side reaction appears to be attack of the alkyl halide at the exocyclic nitrogen atom, since 1-methyloxyindole can be identified in the product mixture (after decomposition with water).

EXPERIMENTAL

PMR spectra were obtained on a Tesla BS-497 spectrometer for solutions in $CDCl_3$ or CF_3COOH using TMS as the internal standard. In all of the experiments the extent of the reaction was monitored by PMR spectroscopy of the reaction mixture, and the purified products were all analyzed in this way as well. The extent of reaction and purify of the final products were also assessed by TLC on Silufol using benzene–methyl ethyl ketone (4:1) as the eluent system, or on aluminum oxide using benzene–methanol (10:1) as the eluting system. The compounds were purified by column chromatography on Silpearl grade silica gel.

3-Bromo-1-methyl-2-dimethylaminoindole Hydrobromide (V). A solution containing 174 mg (1 mmole) of aminoindole I in 5 ml of dry chloroform at −20°C was treated with 0.051 ml (1 mmole) of bromine. The reaction mixture was maintained several hours at 0°C, and the resulting precipitate was removed by filtration, washed with chloroform, and dried under vacuum. Yield 235 mg (70%), mp 61°C (dec.). PMR spectrum (in CF_3COOH): 3.65, 3.76 [6H, s, $N(CH_3)_2$], 3.82 (3H, s, NCH_3), 6.21 (1H, s, 3-H), 6.9-7.4 ppm (4H, m, Ar).

Indoles II and III were brominated in a similar manner at 20°C, although in the latter case a twofold excess of bromine was used. The indole bases XI and XIII (cf. Table 2) were prepared by the reaction of aqueous base on the hydrobromides.

1-Methyl-2-dimethylamino-3-acetylindole (VI). A solution of 0.3 g (1.7 mmole) of indole I and 0.135 ml (1.7 mmole) of pyridine in 5 ml of absolute methylene chloride was treated with small portions of a solution of 0.12 ml (1.7 mmole) of acetyl chloride in 3 ml of methylene chloride; the mixture was cooled to −10°C and continuously stirred during this time. The reaction mixture was maintained at room temperature for 20 min, washed with water and 5% hydrochloric acid solution, and the organic layer was dried and solvent evaporated to give a residue, which was purified on a column of SiO_2 (benzene–methyl ethyl ketone, 4:1).

The 3-acylindoles VII-IX (see Table 1) were prepared in an analogous manner.

1-Methyl-2-dimethylamino-3-carboethoxymethylindole (XIX). A mixture of 0.3 g (1.7 mmole) of indole I, 0.57 ml (5.2 mmole) of ethyl bromoacetate, and 0.42 ml (5.2 mmole) of pyridine was refluxed for 15-20 h in nitromethane under an argon atmosphere. The nitromethane was distilled off, 20 ml of water was added, and the mixture was extracted with chloroform. The residue after solvent evaporation was subjected to column chromatography on SiO_2 with benzene, and the material with R_f equal to 0.2 was collected.

The alkyl derivatives XX-XXII were obtained in an analogous manner.

Friedel–Crafts Acylation of Indoles I-III. A solution of indole I-III in dichloroethane was treated with a three- to fivefold excess of $AlCl_3$ at 0°C; the mixture was stirred for 20 min at room temperature, and then cooled again to 0°C as a three- to fivefold excess of CH_2COCl was added. The mixture was then heated at reflux for 10-20 h. The mixture was decomposed with ice, neutralized with cooling with aqueous base to a very strongly basic pH (until the aluminum hydroxide had dissolved), and the organic layer was separated; the aqueous layer was extracted with chloroform. The residue remaining after solvent evaporation and workup was recrystallized from benzene–hexane (1:1) (the acyl derivative XII was isolated in the form of its hydrochloride).

3-Nitro-1-methyl-2-dimethylaminoindole (XV). A solution of 230 mg (1.72 mmole) of nitronium fluoroborate in 5 ml of absolute acetonitrile at 0°C was treated with 0.275 ml (3.4 mmole) of pyridine, the mixture was cooled to −20°C and a solution of 300 mg (1.72 mmole) of indole I in 3 ml of acetonitrile was added; the mixture was shaken several times and then, after 5-10 sec (as the solution began to darken), was poured onto 30 ml of ice water. The crystalline dark red precipitate (300 mg) was removed by filtration, dried *in vacuo*, and subjected to column chromatography using benzene–methyl ethyl ketone–methanol (10:5:1); the

fraction with R_f equal to 0.3 was collected. The nitroindole XV was obtained in 120 mg (32%) yield after solvent evaporation.

5-Nitro-1-methyl-2-dimethylaminoindole (XVI). A solution of 450 mg (3 mmole) of nitronium fluoroborate in 3 ml of trifluoroacetic acid was treated at 0°C with a solution of 350 mg (2 mmole) of indole I in 3 ml of CF_3COOH; the mixture was stirred for 30 min at room temperature, poured onto ice water, and neutralized with cooling with aqueous base to pH 8-9. The resulting precipitate was removed by filtration, dried, and recrystallized from benzene–hexane (2:1). Yield 330 mg (76%) of indole XVI (yellow crystals).

Nitration of Indoles II and III. The appropriate indole was heated for 5 h at 50-70°C with a 20% solution of nitric acid in acetic acid. The reaction mixture was neutralized with cooling with aqueous based to pH 8-9, and the residue remaining after workup was recrystallized from benzene–hexane (2:1). The yields and properties of the products (compounds XVII and XVIII) are reported in Table 2.

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