ELECTROPHILIC SUBSTITUTION IN THE BENZENE RING OF INDOLE COMPOUNDS (REVIEW)

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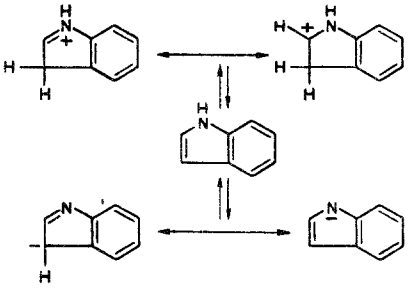
Data on the orientation of electrophilic substitution reactions (nitration, halogenation, acylation, and sulfonation) in the benzene ring of indoles are systematized. The effect of protonation on the direction of substitution is examined. The effects of a pyrrole ring and a substituent in the benzene ring on the orientation reactions are compared.

Electrophilic substitution in the indole molecule has been studied quite extensively. A particularly large number of studies, which have been correlated in review papers and individual chapters of monographs (for example, see [1, 2]), have been devoted to substitution in the pyrrole part of the molecule. The studies dealing with substitution in the benzene ring of indole have not yet been systematized. Particular attention in the present review was directed to the reactions on indoles containing unsubstituted benzene rings. This was done to ascertain the principles of the orientation of electrophilic substitution without the additional effect of a substituent already present in the molecule.

A peculiarity of the behavior of the indole molecule in electrophilic substitution reactions is that both the neutral and positively and negatively charged particles can undergo attack.



However, indole, being a weak acid (pK_a 21.3 [3]) and a weak base (pK_b −3.5 [4]), forms ions only in strongly basic or strongly acidic media. As a result of the nonuniform distribution of electron density in the neutral indole molecule (Table 1), the most nucleophilic site is position 3; to this virtually all electrophilic substitution reactions are directed. The formation of an anion increases the ability of the pyrrole ring to undergo electrophilic attack to an even greater extent. Substitution in the benzene ring should therefore be expected only if either a protonated particle or a neutral particle, but with an acceptor substituent in the pyrrole ring, is subjected to reaction. Because of the high multiplicity of the C_2—C_3 bond, addition of the reagent occurs in the case of 1,2,3-trialkylindoles, for which substitution might have taken place in the benzene ring.

It has been established by a study of the UV and NMR spectra [7-9], as well as kinetic studies [11-13], that the proton attacks primarily position 3; equilibrium between ions and ion pairs is observed in solutions of strong acids (sulfuric and perchloric acids). It has also been demonstrated [8] by a thorough study of solid salts of indoles and deuterium-exchange studies, that in a number of cases the proton also attacks other positions of the indole system.

*Deceased.

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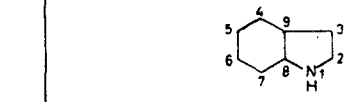
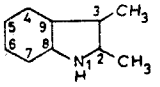
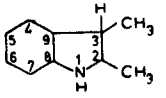
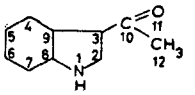
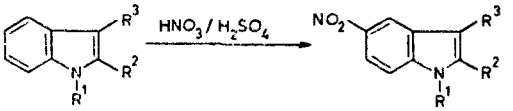
TABLE 1. Quantum-Mechanical Calculation of Indole Molecules [5, 6, 10]

Atom No.													
	Charge	Boundary orbital density	Cationic localization energy	Bond multiplicity	Charge	Boundary orbital density	Cationic localization energy	Charge	Boundary orbital density	Cationic localization energy	Charge	Boundary orbital density	Bond multiplicity
1	+0,234	0,108	—	$N_{(1)}$—$C_{(2)}$ 0,508	+0,231	—	—	+0.352		—	+0.269	0,080	$N_{(1)}$—$C_{(2)}$ 0,481
2	+0,024	0,425	—	$C_{(2)}$—$C_{(3)}$ 0,774	+0,025	—	—	+0,643	—	—	+0,186	0,338	$C_{(2)}$—$C_{(3)}$ 0,696
3	−0,122	0,506	—	$C_{(3)}$—$C_{(9)}$ 0,508	−0,124	—	—	—		—	−0,113	0,374	$C_{(3)}$—$C_{(9)}$ 0,420
4	−0,017	0,307	2,2740	$C_{(9)}$—$C_{(4)}$ 0,573	−0,019	0,297	2,2822	+0,002	0,104	3,1400	−0.016	0,306	$C_{(9)}$—$C_{(4)}$ 0.600
5	−0,028	0,002	2,4422	$C_{(4)}$—$C_{(5)}$ 0,708	−0,029	0,003	2,4398	−0,014	0,567	3,0018	−0,023	0,001	$C_{(4)}$—$C_{(5)}$ 0,692
6	−0,020	0,279	2,3804	$C_{(5)}$—$C_{(6)}$ 0,623	−0,022	0,266	2,3674	+0,002	0,104	3,1400	−0,016	0,289	$C_{(5)}$—$C_{(6)}$ 0,640
7	−0,031	0,125	2,3590	$C_{(6)}$—$C_{(7)}$ 0,702	−0,031	0,120	2,3584	−0,023	0,227	2,4056	−0,028	0,114	$C_{(6)}$—$C_{(7)}$ 0,658
8	−0,003	0,162	—	$C_{(7)}$—$C_{(8)}$ 0,595	−0,001	—	—	+0,046		—	+0,007	0,082	$C_{(7)}$—$C_{(8)}$ 0,624
9	−0,041	0,078	—	$C_{(8)}$—$C_{(9)}$ 0,545	−0,042	—	—	−0,023		—	−0,032	0,177	$C_{(8)}$—$C_{(9)}$ 0,648
10					+0,007	—	—				+0,330	0,028	$C_{(10)}$—$C_{(11)}$ 0,729
11					+0,006	—	—				−0,576	0,242	
12											+0,011	0,000	

Further electrophilic attack on the pyrrole ring is virtually excluded in the protonated indole molecule, and the orientation of the incorporation of a substituent consequently should depend on whether the protonated or neutral indole molecule is attacked. For this reason, in our subsequent description of the electrophilic reactions we will indicate the conditions, i.e., whether the neutral or positively charged particle is attacked.

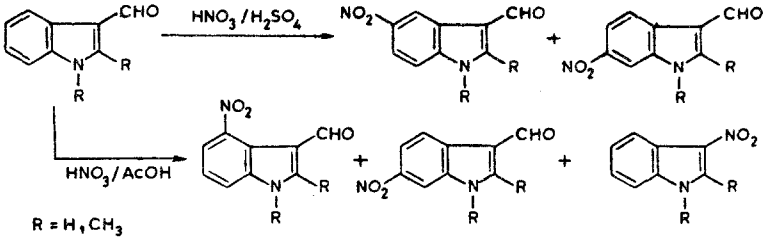
NITRATION

Nitration is the most extensively studied electrophilic substitution reaction in the indole series. Indole itself cannot be nitrated under ordinary conditions because of its extreme sensitivity to acidic agents (for example, see [14]). 3-Alkylindoles behave similarly. The presence of a 2-alkyl group stabilizes the cation formed upon protonation, and this makes it possible to nitrate such compounds successfully. In fact, 2-methyl- [15, 16], 2-ethyl- [17, 18], 1,2-dimethyl- [16], 2,3-dimethyl- [19-22], and 1,2,3-trimethylindoles [17, 18] form 5-nitro-substituted indoles smoothly under the influence of a nitrating mixture.



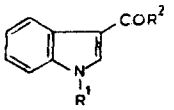
The proof of the structure is most often based on a study of the spectral characteristics or on alternative synthesis. In a study of the UV spectra of alkylindoles it was observed [23, 24] that the introduction of a nitro group in the 5 position gives rise to approximately identical bathochromic shifts of both indole bands, while a nitro group in the 4 and 6 positions shifts primarily the long-wave maximum. The 5-nitro isomer can be readily distinguished by this means.

Tetrahydrocarbazoles [22] behave similarly, i.e., they are nitrated in the 6 position (the 5 position of the indole system). If alkylindoles have a free 3 position and do not undergo prior protonation, substitution takes place in this free position. For example, 2-methyl- [25], 2-ethyl- [18], 2-phenyl- [18], and 1,2-dimethylindoles [18] readily form 3-nitroindoles under the influence of fuming nitric acid. The presence of a phenyl substituent in position 2 does not change the orientation [17]. In the case of 2,3-diphenylindole [18, 26, 27], one additionally observes side nitration in the 3-phenyl group. This is evidently associated with the fact that in the case of the addition of a proton the phenyl ring in the 3 position, in contrast to a 2-phenyl group, falls out of conjugation and is nitrated like the aromatic ring in alkylbenzenes. In fact, exclusively 6-nitro-2,3-diphenylindole is formed in acetic acid, in which protonation is absent. This dependence of the orientation on prior protonation is also observed in a number of other cases in which the structure of the indole makes it possible to carry out nitration both in a protonating (sulfuric acid) and a nonprotonating (acetic acid) medium. A photometric study of the reaction mixture after nitration of 3-formyl- [28] and 1- and 2-methyl-3-formylindoles [29] in sulfuric acid showed that an almost equimolar mixture of the 5- and 6-nitro isomers is formed. However, only 5-nitro-3-formylindole was isolated preparatively in the case of 3-formylindole [30]. A mixture of 4- and 6-nitro isomers is formed in the nitration of the same formylindoles in acetic acid [27, 28, 30, 31]; replacement of the formyl group by a nitro group (nitrodeacylation) also occurs in this case.



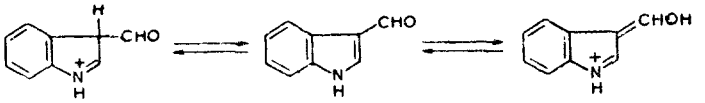
3-Acetyl- [10, 32], 1-methyl-3-acetyl- [10], and 2-methyl-3-acetylindoles [25] also form mixtures of 3-, 4-, and 6-nitro isomers under the influence of nitric acid in acetic acid. A thorough study [10] of the action of various nitrating agents on 3-acylindoles (Table 2) leads to the conclusion that nitration takes place in the positions 4 and 6 in all cases. Substitution of the 3-acyl group predominates in the case of acyl nitrates ob-

TABLE 2. Nitration of 3-Acylindoles with Fuming Nitric Acid (Method A), a Mixture of Fuming Nitric Acid with Acetic Acid (Method B), Nitrogen Pentoxide in Acetonitrile Containing Triethylamine (Method C), or Acetyl (Benzoyl) Nitrate in Acetonitrile (Method D) [10]



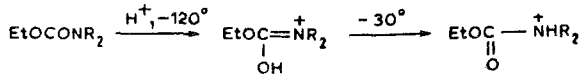
R¹	R²	Yield of nitration products, %											
		3-nitro isomer				4-nitro isomer				6-nitro isomer			
		A	B	C	D	A	B	C	D	A	B	C	D
H	H	0	18	22	—	0	0	0	—	32	29	8	—
CH_3	H	—	15	—	17	—	8	—	6	—	14	—	13
H	CH_3	0	24	16	0	0	Traces	0	—	30	18	17	—
CH_3	CH_3	3	32	35	30	10	5	13	Traces	28	17	14	9

tained from acyl halides and silver nitrate and in the case of mixtures of nitric acid with acetic acid. This process is suppressed to a considerable extent in nitric acid. In comparing these data with the results of nitration of 3-acylindoles in sulfuric acid one should acknowledge that even in fuming nitric acid, substitution of the hydrogen atoms in the benzene ring of 3-acylindoles occurs due to electrophilic attack on the unprotonated molecule. The problem of the site of addition of the proton arises in connection with the change in the orientation of nitration of 3-acylindoles on passing from acetic to sulfuric acid. It has been assumed [29] that the proton, as in the case of alkylindoles, attacks position 3 of the molecule. The possibility of acidic deacylation of 3-acylindoles [33] confirms this idea. However, in this case, nitration should proceed just as in the case of alkylindoles, i.e., only in the 5 position, since the change in the hybridization of C_3

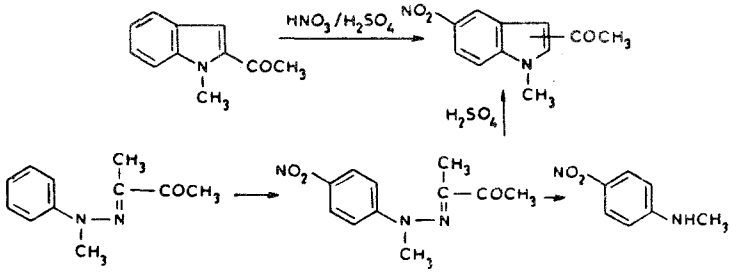


upon protonation draws the acyl substituent out of conjugation with the aromatic system.

In addition, it is known [34] that protonated 2-acylindoles undergo isomerization to the 3-acyl isomers, while the isomerization of protonated alkyl(aryl)indoles proceeds in the opposite direction [9]. A study of the PMR spectra of 3-acylindoles in fluorosulfonic acid at low temperatures showed [35] that a proton adds to the carbonyl oxygen atom, on which, according to quantum-mechanical calculations (Table 1), the highest electron density of the molecule is concentrated. However, on the other hand, the existence of deacylation reactions, viz., protodeacylation, nitrodeacylation, and halodeacylation (see below), compels us to assume electrophilic attack also directly (or in a rebound manner) on the C_3 atom. The situation here is evidently the same as in the case of carbamic acid esters, in which, as established in [36], a proton kinetically attacks the oxygen atom, while the N-protonated particle is thermodynamically more stable.

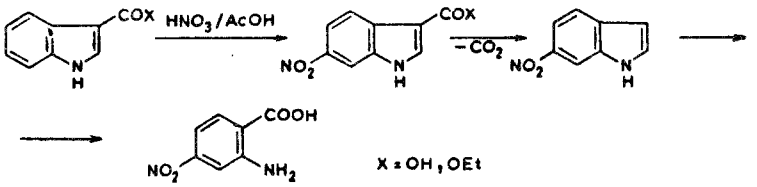


In one of the early studies [37] it was shown that 2-acylindoles are nitrated in position 5 in sulfuric acid. The proof was based on the alternative synthesis of the product from the corresponding p-nitrophenylhydrazone. In the light of what we stated above and taking into account the fact that in proving the structure the cyclization of the p-nitrophenylhydrazone was carried out under strongly acidic conditions (concentrated H_2SO_4), in which case the 3-acyl isomers are formed instead of the expected 2-acylindoles [38, 39], these data are doubtful and require verification.

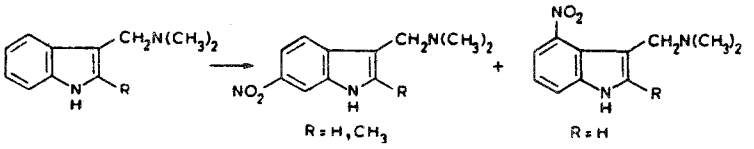


A change in the orientation when the medium was changed was demonstrated in the case of esters and amides of 3-indolylglyoxylic acid [40, 41]. Whereas a mixture of 4- and 6-nitro isomers (with predominance of the latter) is formed in acetic acid, positions 5 and 6 (primarily the position 5) are attacked in sulfuric acid.

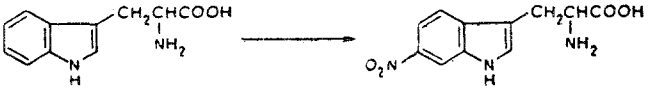
3-Indolylcarboxylic acid and its ethyl ester are readily nitrated in acetic acid [42-46] in position 6. The structure has been proved reliably.



If the carbethoxy group is located in position 2 rather than in position 3, nitration in acetic acid takes place in position 4 [47]. It is interesting that 2-indolylcarboxylic acid itself gives only the 3-nitro isomer in fuming nitric acid [18, 48, 49]. An unexpected effect of a methyl group in position 2 on the ratio of the 4- and 6-nitro isomers was observed in the nitration of 3-substituted indoles. Although the nitration of amides of 3-indolylglyoxylic acid (see above) and gramine [50, 51] leads to mixtures of 4- and 6-nitro isomers, the 6-nitro isomer is formed exclusively when a methyl group is introduced in position 2 of the same molecules; in this case there was some vagueness associated with the proof of the structure, in which the 5-nitro structure was initially [52] assigned to the nitrogramine, but the structures of the nitration products were subsequently [50, 53] established reliably.

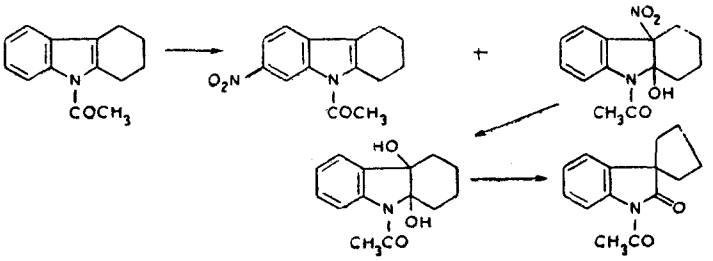


This effect of the methyl group is apparently explained by the steric effect of the substituent. The positively charged nitrogen atom in 2-methylgramine shields the 4 position from electrophilic attack to a greater degree than in the case of gramine itself. When there is a bulkier substituent in position 3, as, for example, in tryptophan, the 4-nitro isomer is not formed even in the absence of a 2-methyl group [54].

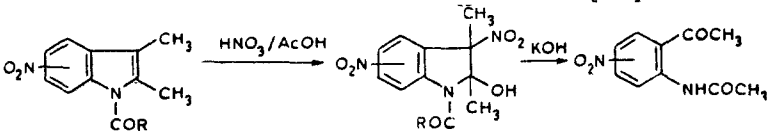


The nitration of N-acylindoles has been studied quite extensively. English chemists headed by Plant have devoted ∿30 publications to this problem. These studies are summarized briefly in a review [55]. It was shown that the competitive addition of nitric acid to the C_2—C_3 bond of indole takes place simultaneously with nitration in the benzene ring (in positions 6 and 4). The direction of the reaction (substitution or addition) depends not only on the structure of the indole but also on the experimental conditions. Thus, for example, the nitration of 1-acetyl-1,2,3,4-tetrahydrocarbazole in the case of pronounced dilution with acetic acid leads primarily to substitution in the benzene ring [56, 57]. A decrease in the amount of solvent leads to an increase in the yield of the product of addition to the multiple bond. The orientation of the addition of nitric acid was demonstrated in the case of 1-benzoyl-2,3-dimethylindole [58]. The addition products are unstable and

undergo hydrolysis to give glycols or products of pinacol rearrangement of the latter even during the isolation process.

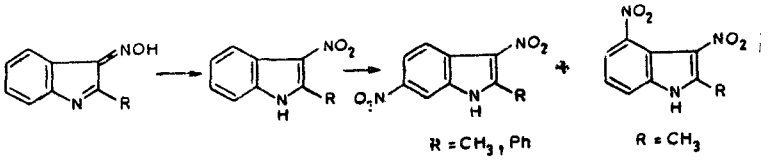


A method for decomposition of the pyrrole ring to establish the position of the substituent in the benzene part of the indole molecule was based on this property of the addition products. For example, primarily the 6-nitro isomer [20, 59-61] containing a small amount of the 4-nitro derivative [21] and a trans-glycol [20, 59, 60] are formed in the nitration of a 1-acyl-2,3-dimethylindole. The structures of the nitro isomers were established by successive treatment with nitric acid and alkali [59].



We have already mentioned above that the orientation of incorporation of the nitro group in the benzene ring is the same when the reaction is carried out in both acetic acid and fuming nitric acid. To this we should add that 3-cyanoindole gives a mixture of 4- and 6-nitro derivatives under the influence of fuming nitric acid [18].

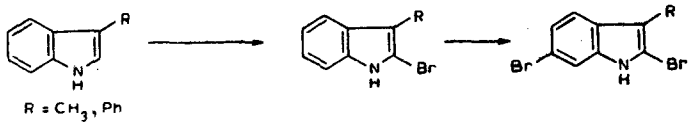
It is surprising that under the same conditions 3-nitroindole is nitrated in positions 6 and 5 [18]. This result compels us to assume an error (or simply a typographical error in the abstract) in the proof of the structure, since according to the data of the same authors [25], 3-hydroxyimino-2-methylindolenine (3-nitroso-2-methylindole) under the same conditions gives a mixture of 3,4- and 3,6-dinitroindoles. The nitration of 2-phenyl-3-hydroxyiminoindolenine leads to the corresponding 3,6-dinitroindole [62]. The hydroxyimino group apparently undergoes oxidation initially (the authors also assume this), and the resulting 3-nitroindole undergoes subsequent nitration.



Two dissertation works [18, 25] and a series of communications [16, 17, 26, 30, 53, 63] have been devoted to the behavior of indoles in fuming nitric acid.

HALOGENATION

As we have already noted, indoles are extremely acidophobic. In the case of the direct action of halogens on compounds with an unsubstituted pyrrole ring primarily halogenated polymers are therefore obtained. For example, indole reacts violently with bromine to give resinous products [64]. Skatole behaves similarly. However, 2,6-dibromoskatole is formed by the action of N-bromophthalimide [65, 66] and N-bromosuccinimide [67] on skatole. A small amount of the 2,5-dibromo isomer is also formed in the case of 3-phenylindole [68]. The presence of methyl and acetyl groups in the 1 position does not change the direction of

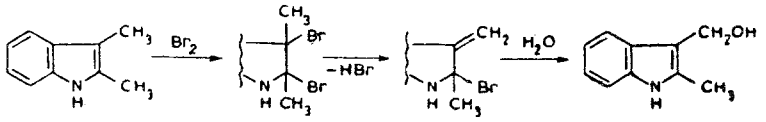


the process, although an acetyl group slows down the reaction somewhat. The presence of a bulky substituent in 3-tert-butylindole and particularly in 1,3-di-tert-butylindole hinders substitution in position 2, and the 6-bromo isomers are formed immediately [69]. Japanese researchers observed the curious isomerization of 2-bromoindoles: the corresponding

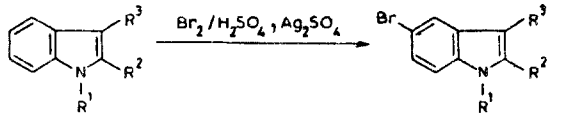
6-bromoindoles are formed in 20% yields when 2-bromo-3-phenylindole is refluxed in acetic acid [68] or when 2-bromo-3-tert-butylindole [69] is treated with HCl in alcohol.

R = Ph, $(CH_3)_3C$

2,3-Dialkylindoles add halogens to the C_2—C_3 multiple bond when they are halogenated in acetic acid. Thus 2,3-dibromo-2,3-dimethylindoline is formed initially in the bromination of 2,3-dimethylindole [20], after which hydrogen bromide is split out, and the second bromine atom undergoes hydrolysis accompanied by allyl rearrangement.



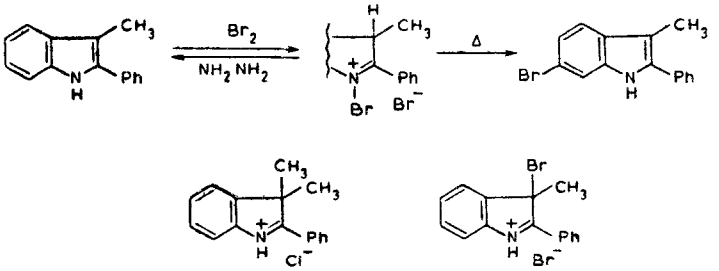
Halogens have a similar effect on derivatives of tetrahydrocarbazole and 2,3-trimethyleneindole [70]. However, as in the case of nitration, if the indole molecule is protonated beforehand, bromination is directed to position 5. Thus 5-bromo-2,3-dimethylindole is formed by the action of bromine in sulfuric acid on 2,3-dimethylindole in the presence of silver sulfate [71]. 2- Methyl- and 1,2,3-trimethylindoles and tetrahydrocarbazole also form the corresponding 5-bromo derivatives in 60-75% yields under these conditions [72].



$R^1=R^3=H$, $R^2=CH_3$; $R^1=R^2=R^3=CH_3$; $R^1=H$, $R^2=R^3=CH_3$; $R^1=H$, $R^2=R^3=-(CH_2)_4-$

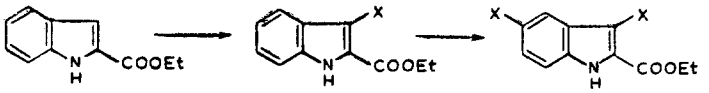
As in the case of nitration, competitive substitution and addition to the multiple bond are observed in the halogenation of N-acylindoles in acetic acid, although the tendency for addition is higher in the case of halogenation [20].

If there is at least one phenyl group in the pyrrole ring of the indole, bromination takes place only in position 6 of the benzene ring. 2-Phenyl-3-methyl- and 2,3-diphenylindoles and their 1-acyl derivatives react in this way [20, 66, 73]; in this case, in contrast to nitration, substitution in the phenyl group was not observed. In the case of 2-phenyl-3-methylindole researchers [20, 66] were able to isolate an intermediate with the composition $C_{15}H_{13}Br_2N$, which liberated iodine from potassium iodide, readily underwent an intramolecular rearrangement to 6-bromo-2-phenyl-3-methylindole, and was converted to the starting compound on reaction with hydrazine. A structure described as "the perbromide of the indolenine form of 2-phenylskatole" was proposed [66] for this intermediate on the basis of the similarity between its UV and IR spectra and the spectra of 3,3-dimethyl-2-phenylindolenine hydrochloride. However, since electrophilic attack is always directed to the β-carbon atom in the neutral indole molecule, the intermediate probably appears as a bromonium ion in the case of addition to the multiple bond. All of the properties of this compound presented above correspond satisfactorily to this structure.



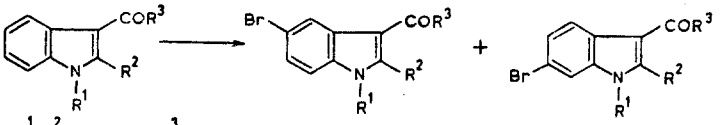
Thus, indoles with alkyl or phenyl substituents in the pyrrole ring (or without these substituents) and their 1-acyl derivatives are halogenated in the pyrrole ring or competitively add halogen to the C_2—C_3 bond. Bromination in position 6 is realized in some cases, and this also possibly proceeds through a step involving the intermediate addition of halogen to the C_2—C_3 bond.

Indoles with electron-acceptor substituents in position 2 or 3 are halogenated with an orientation that depends on the position of the substituent. Thus 2-carbethoxyindole is halogenated initially in position 3, after which a second halogen atom is incorporated in position 5 [74, 75].



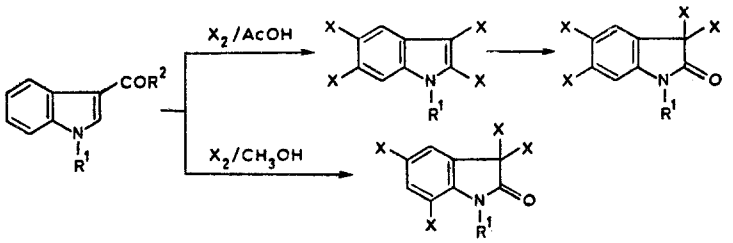
X = Cl, Br

However, if the carbethoxy group occupies position 3, bromination is immediately directed to the benzene ring [43], and a mixture of 5- and 6-bromo derivatives is formed [76]. 3-Formylindole and its methyl homologs, as well as ethyl 3-indolylglyoxylate, are halogenated in precisely the same way [77, 78]. It should be noted that the resulting mixture of 5- and 6-bromo-3-carbethoxyindoles, as well as the corresponding mixture of bromo-3-indolylglyoxylates, has a constant melting point that remains unchanged in the case of recrystallization. This mixture was initially assumed [43, 76] to be an individual substance, and it became possible to separate the 5- and 6-bromoindoles only after saponification and decarboxylation [78].



$R^1, R^2 = H, CH_3$; $R^3 = H, OEt, COOEt$

As in the case of nitration, the halogenation of 3-acylindoles is accompanied by displacement of the acyl group (halodeacylation). Thus, mainly 2,3,5,6-tetrabromo-1-methylindole is formed in the reaction of excess bromine in acetic acid with 1-methyl-3-formylindole [79]. If the 3-acylindoles are halogenated in methanol, the principal product is 3,3,5,7-tetrahalooxindole [80]. If, however, the halogenation of the 2,3-dihaloindoles is continued, the corresponding 3,3-dihalooxindoles are formed in good yields [79]. The difference in the orientation of the incorporation of halogen in the benzene ring in the case of halogenation in acetic acid and methanol is associated with the fact that 2,3-dibromoindole is formed in the first case, while an oxindole is formed in the second.



$R^1 = H, CH_3$; $R^2 = H, CH_3, CCl_3, C_3H_7$; X = Cl, Br

The proof of the structures of the products of halogenation of indoles gives rise to certain difficulties. It should be noted that, in addition to the formation of the mixtures with constant melting points mentioned above, the UV spectra of the isomeric haloindoles are virtually identical [81, 82], and the use of these spectra for the determination of the position of the halogen in the indole ring, which has been successful for the nitro derivatives, is difficult. The utilization of IR spectroscopy [71, 76] and the NMR spectra [72] seems more promising.

ACYLATION

2,3-Dialkylindoles give 1,6-diacyl derivatives under the conditions of the Friedel—Crafts reaction. It is possible that acylation takes place initially at the nitrogen atom and subsequently in the benzene ring, since 1-acylindoles undergo Friedel—Crafts acylation in position 6. Thus N-acetyl-2,3-dimethylindole [83, 84] and N-acyl-1,2,3,4-tetrahydrocarbazoles [85] form 1,6-diacyl compounds upon reaction with acyl halides in the presence of aluminum halides. It might have been assumed that a rearrangement of the Fries type

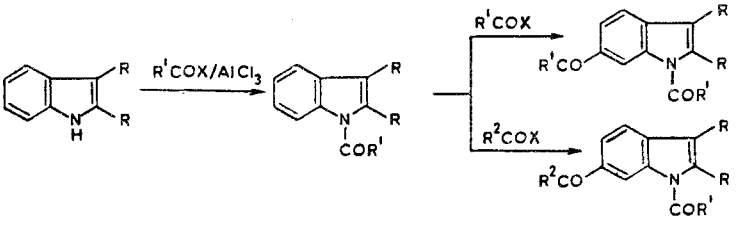
TABLE 3. Electrophilic Substitution in 5-Hydroxyindole Derivatives

X	R¹	R²	R³	R⁴	Yield, % 4-X	Yield, % 6-X	Literature
NO_2	H	H	COCOOEt	$PhCH_2$	28	3,5	98
NO_2	CH_3	CH_3	COOEt	CH_3	55	13	95
NO_2	CH_3	CH_3	COOEt	H	4,6-Dinitro	(72%)	95
NO_2	CH_3	CH_3	COOEt	CH_3CO	—	17	95
NO_2	CH_3	CH_3	COOEt	$PhCH_2$	47	—	95
NO_2	—(CH₂)₃—		CHO	$PhCH_2$	95	—	98
NO*	CH_3	CH_3	COOEt	CH_3	49	Traces	95
Br	CH_3	CH_3	COOEt	H	—	86	99
Br	CH_3	CH_3	COOEt	CH_3CO	—	85	99
Br	CH_3	CH_3	COOEt	CH_3	—	80	99
Br	CH_3	CH_3	COOEt	PhCO	—	78	99
Br	Ph	CH_3	COOEt	CH_3CO	—	73	99
Br	Ph	CH_3	COOEt	H	—	35	99
Br	Ph	CH_3	COOEt	CH_3	—	78	99
R_2NCH_2	H	H	H	H	81	—	96, 95
R_2NCH_2	H	CH_3	H	H	72 (50)†	—	96
R_2NCH_2	H	CH_3	COOEt	H	57 (70)	—	96
R_2NCH_2	H	—(CH₂)₄—		H	78 (60)	—	96
R_2NCH_2	CH_3	—(CH₂)₄—		H	84	—	96

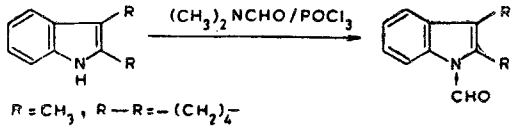
*The 4-nitroindole was obtained in the case of nitrosation.

†The yield in the Mannich reaction is indicated in parentheses, while the yield with piperidine is indicated in the absence of parentheses.

occurs, as observed for N-acylcarbazoles [83]. However, N-acylindoles remain unchanged under the reaction conditions [86].



Under the same conditions, 1,2,3-trimethylindole forms a monoacetyl derivative, to which the 5-acetyl-1,2,3-trimethylindole structure was initially assigned [84]. The research of N. N. Suvorov and co-workers [87-89] established that the acetyl group is located in position 6 rather than in position 5. Small amounts of the 4- and 5-isomers are formed as side products. Under the less severe conditions of the Vilsmeier–Haack reaction the formylation of 2,3-dialkylindoles stops at the step involving the formation of N-formylindoles. However, if the nitrogen atom is alkylated, formylation is directed to the 6 position [90].

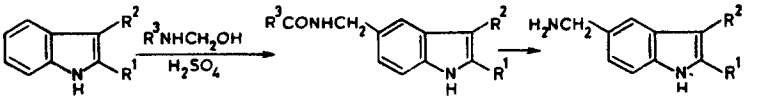


OTHER ELECTROPHILIC SUBSTITUTION REACTIONS

The sulfonation of 2-alkylindoles with concentrated (99%) sulfuric acid has been described in two papers [91, 92]. It was shown that a sulfo group is incorporated in the benzene ring, but the precise position was not established. In analogy with other electrophilic substitution reactions, 5-sulfoindoles are apparently formed. The compounds obtained were used as surfactants.

Mannich aminomethylation does not occur when there are no substituents in the benzene ring. However, the action of N-methylolphthalimide and methyloltrichloroacetamide in concentrated sulfuric acid leads to acylated 5-aminomethylindoles in good yields. The corre-

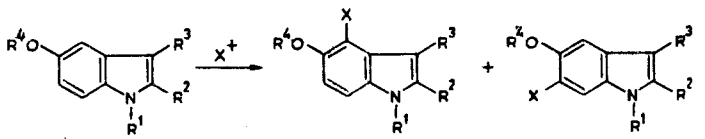
sponding 5-aminomethylindoles were obtained by hydrazinolysis of phthalimide derivatives. If the reaction is carried out in an alkaline medium rather than in an acidic medium, amidomethylation is directed to the pyrrole ring [93, 94].

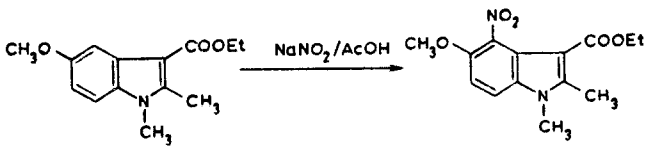


R^1=H, R^2=CH_3; R^1=R^2=CH_3; R^1—R^2=$-(CH_2)_4-$; R^3=CCl_3, phthalyl

Effect of Substituents in the Benzene Ring of Indole on the Orientation of Electrophilic Substitution

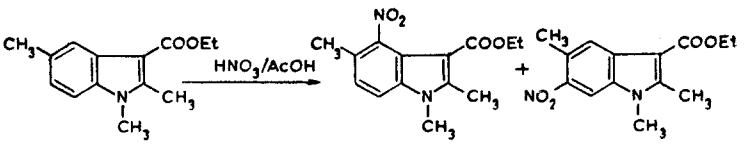
The result of the presence of strong donor substituents (hydroxy, methoxy, benzyloxy, and other groups) in the benzene ring is that it is precisely their presence that determines the site of attack of the electrophilic agent. Thus 5-hydroxyindoles with a carbethoxy group in position 3 are nitrated [95] and aminomethylated [96, 97] mainly in position 4. On the other hand, the bromination of the same compounds is directed almost exclusively to the 6 position (Table 3). However, if a carbethoxy group is absent, such compounds are nitrated in position 6, while the orientation of aminomethylation remains unchanged. It is interesting that the action of nitrous acid on 1,2-dimethyl-3-carbethoxy-5-methoxyindole does not lead to the nitroso compound but rather to the 4-nitroindole [95].



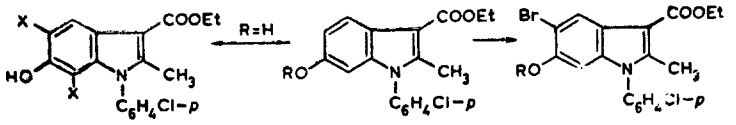


It is completely natural that if position 6 is occupied by, for example, a methyl group, substitution takes place entirely in position 4. However, the 4,6-dinitro derivative is formed in the nitration of 2-methyl-3-carbethoxy-5-hydroxy-6-bromindole in acetic anhydride, i.e., a bromine atom is replaced.

A methyl group in position 5 also orients nitration to positions 6 and 4 (with predominance of nitration in position 4) [100].

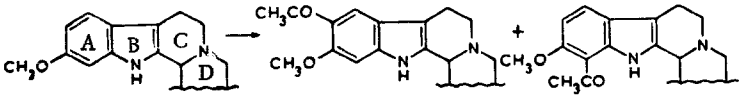


If there is a donor substituent in position 6, primarily the 5-isomers or (in the case of nitration) the 5,7-disubstituted products are formed [101].

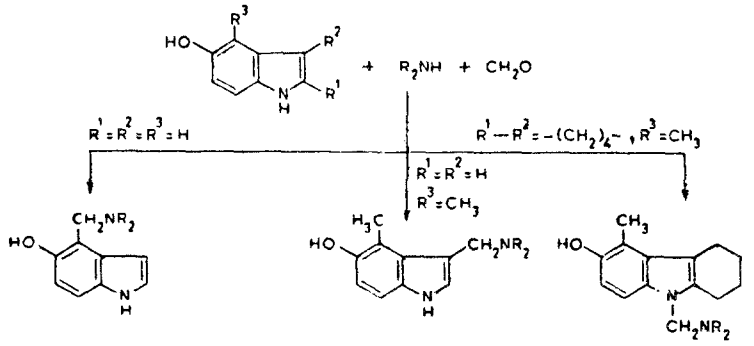


X = Br, NO_2; R = CH_3, CH_3CO

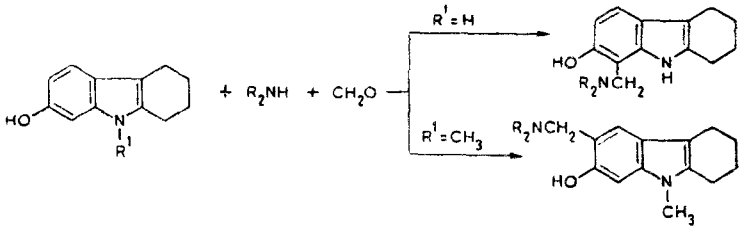
Under the influence of acetic anhydride and perchloric acid, reserpine [102] undergoes smooth acetylation in the benzene ring (the A ring), and a mixture of 5- and 6-acetyl derivatives is formed.



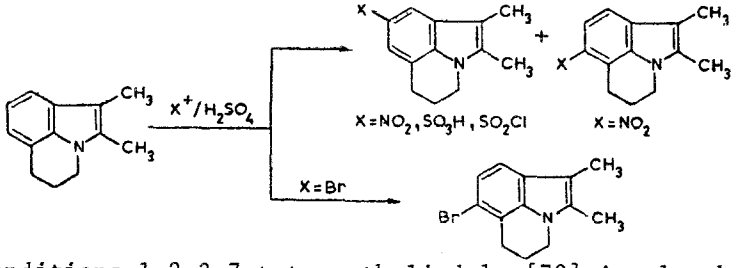
The effect of a hydroxy group on the orientation has been followed from the behavior of benzoyindoles in the Mannich reaction [96, 97]. It was found that even when position 3 was unsubstituted, aminomethylation was always directed to the benzene ring. Thus 4-hydroxyindole is aminomethylated in position 5, 5-hydroxyindole is aminomethylated in position 4, 6-hydroxyindole is aminomethylated in position 7, and 7-hydroxyindole is aminomethylated in position 6. Thus the reaction is always directed to the ortho position relative to the hydroxy group and moreover, in the ortho position with the higher bond multiplicity (Table 1). However, if this position is occupied by a methyl group, the reaction is directed to position 3 of the pyrrole ring, whereas if it is occupied, as, for example, in tetrahydrocarbazoles, substitution takes place at the nitrogen atom.



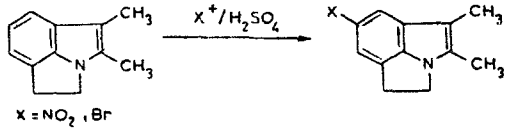
When excess aminomethylating agent is present, a second group is incorporated either in position 3 (if it is unoccupied) or at the nitrogen atom but never in the second ortho position. However, 7-hydroxy-9-methyl-1,2,3,4-tetrahydrocarbazole is aminomethylated in position 6 rather than in position 8, as is known for the N-unsubstituted compound [96].



Electrophilic substitution in the benzene ring of 2,3-dimethyl-1,7-trimethyleneindole has been studied in detail. It was shown that nitration [103, 104], sulfonation [105], and chlorosulfonation [106] are directed to position 5, i.e., the orientation corresponds to benzene ring-unsubstituted indole. However, the 6-isomer is formed as a side product in nitration, whereas bromination in sulfuric acid (in which case we are dealing with a protonated indole molecule) takes place entirely in position 6 [72].



Under the same conditions 1,2,3,7-tetramethylindole [72] is also brominated in position 6. At the same time, 2,3-dimethylindole is nitrated [19-22] and brominated [71] in position 5 in sulfuric acid. A decrease in the size of the saturated ring by one methylene group leads to a change in the orientation of bromination [71].



Thus in this case there are complex and as yet incomprehensible interrelationships between the attacking agent and the substrate.

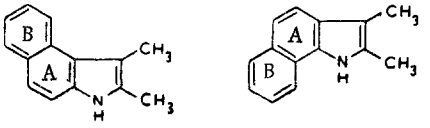
TABLE 4. Deuterium Exchange in 2,3-Dimethyl-1,7-trimethyleneindole [107]

Positions of the protons	Exchange in D_2SO_4,*		Exchange in CD_3COOD, %	
	after 24 h	after 24 h	after 92 h	after 92 h
4	0	0	34	74
5	0	10	59	72
6	20	50	59	87
Overall exchange	8	20	50	83

*The percent exchange was determined by integration of the corresponding signals in the PMR spectrum.

We observed [107] a similar process in a study of deuterium exchange in 2,3-dimethyl-1,7-trimethyleneindole in sulfuric and acetic acids. It should be noted that no exchange whatsoever was observed in pure deuteroacetic acid in the case of contact for a week. The results presented in Table 4 were obtained when catalytic amounts of sulfuric acid were added. Only the aromatic protons undergo exchange, and exchange takes place more rapidly in acetic acid than in sulfuric acid. This is in agreement with the fact that in the first case an unprotonated particle undergoes electrophilic attack, whereas in the case of sulfuric acid a cation or an ion pair undergoes attack [108]. Furthermore, as in the case of bromination, the proton in position 6 is exchanged in sulfuric acid, while all three aromatic protons undergo exchange with equal ease in acetic acid.

A study of substitution in benzindoles showed that bromination [109] and acetylation [86] are directed to the A ring, while nitration in sulfuric acid is directed to the B ring [110].

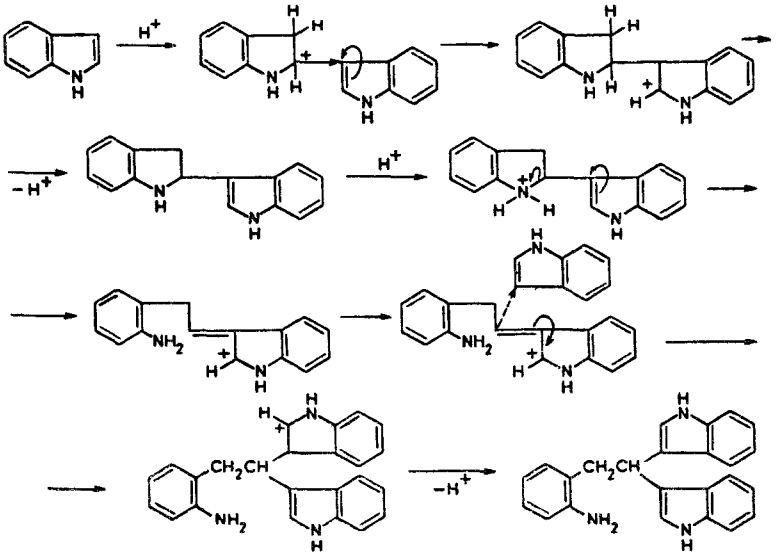


Orientation in the Case of Electrophilic Substitution of Indole

As a result of the nonuniform distribution of the electron density in the indole molecule, it behaves like an amphoteric compound, adding a proton in strong acids and forming an anion under strongly alkaline conditions. It is known that indoles form saltlike compounds with alkali and alkaline earth metals. The prior production of such salts is used in alkylation and acylation reactions. The resulting ambident anion (see the initial scheme presented in this review) can undergo attack by an electrophilic agent both in positions 1 and 3. The direction of substitution depends on the degree of ionic character of the nitrogen–metal bond (a proton is removed precisely from the nitrogen atom). In the case of alkali metal salts, in which case this bond is highly ionic [111, 112], substitution generally takes place at the nitrogen atom, whereas in the case of, for example, indolylmagnesium halides, in which the nitrogen–metal bond is covalent to a considerable extent, one observes substitution in position 3.

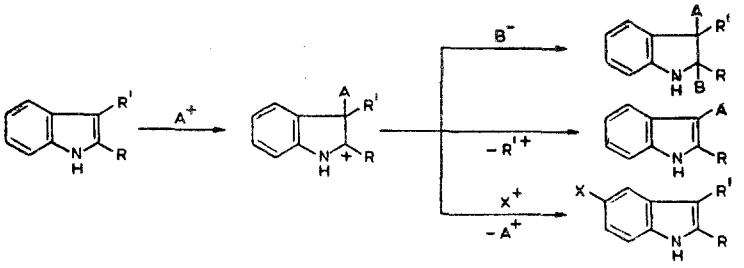
The neutral indole molecule is attacked primarily at the site of the highest electron density, viz., position 3. Thus the orientations of substitution in the neutral indole molecule and in the anion coincide, but, of course, the rate of the reaction is lower in the case of the neutral indole. This difference amounts to a factor of 10^8 in the case of diazo coupling [113].

The acidophobic character of indole consists in the fact that under the influence of an acid the molecule is protonated, and the resulting cation attacks the neutral indole molecule. The new cation is a substituted indole that is protonated in the β position, and this new species undergoes splitting out of a proton to give an indole dimer that has a basic nitrogen atom. When it is protonated, it undergoes ring opening to give a new cation, which upon reaction with another indole molecule gives a protonated indole trimer. The indole dimer and trimer have been isolated in the individual state [14].

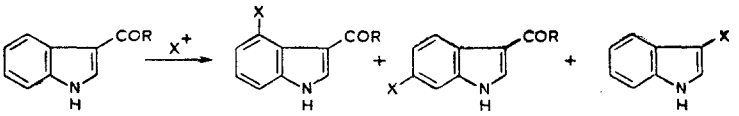


In contrast to 3-alkylindoles, 2-alkylindoles are resistant to the action of acids. This difference is due to the fact that in the case of protonation the alkyl substituent reduces the positive charge due to its inductive effect and sterically hinders nucleophilic attack in this position. Protonated 3-alkyl(aryl)indoles therefore often undergo rearrangement to 2-alkyl(aryl)indole cations [9].

In addition, 2-alkylindoles undergo electrophilic substitution in the benzene ring in solutions of strong acids (i.e., when the protonated particle is attacked). However, 3-substituted indoles are formed in neutral media. Protonation should therefore be regarded as primary electrophilic attack, while substitution itself is a subsequent process. This primary electrophilic attack is always directed to position 3 of alkylindoles. The subsequent fate of the resulting cation (or ion pair) is diversified in character. First, nucleophilic attack by the B^- anion in position 2 is possible. As a result, electrophilic addition of the reagent to the C_2—C_3 bond will occur. As shown above, halogens and nitric acid add to the C_2—C_3 bond in 2,3-dialkylindoles, when the reaction is carried out in acetic acid. Second, splitting out of R' in the form of a cation and electrophilic substitution in position 3 are possible. The ratio of these two reactions depends on the ease with which R' can form a sufficiently stable cation. According to the literature data, substitution in position 3 was observed when R^1 = H, HCO, RCO, COOH, and CN. Third, secondary electrophilic attack on the benzene ring of the molecule is possible. This possibility is realized when the positive charge introduced by the A^+ cation is localized mainly in the pyrrole ring, and the benzene ring remains slightly perturbed; substitution generally occurs in position 5 in this case. Electrophilic substitution of 2-alkyl- and 2,3-dialkylindoles in solutions of strong acids, i.e., when A^+ is a proton, proceeds via this pathway.

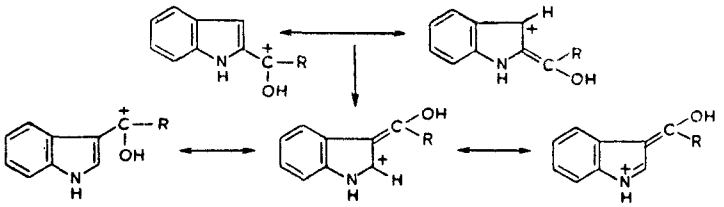


If the pyrrole ring contains an electron-acceptor substituent in the 3 position, substitution may take place in positions 3, 4, and 6.



This reaction pathway correlates satisfactorily with the electron density on the upper occupied orbital in each position [10].

The possibility of electrophilic attack (protonation, for example) at the oxygen atom exists for acylindoles; 2-acylindoles undergo isomerization to the 3-isomers in this case [34].



Protonation does not remove the substituent from conjugation with the rest of the molecule in this case, and the substituent should affect the orientation during subsequent substitution. It is known that 3-acylindoles undergo nitration in sulfuric acid to give a mixture of 5- and 6-nitro isomers.

If there is a substituent in the benzene ring of the indole, substitution occurs primarily in position 3 when the pyrrole ring is unsubstituted. However, strongly electron-donor substituents (OH, for example) may direct electrophilic attack to the benzene ring even in the case of an unsubstituted position 3.

However, if there is a donor substituent in the benzene ring, it is precisely this substituent that determines the direction of electrophilic attack to one of the adjacent positions; one of the possible isomers is generally formed in this case. For example, a hydroxy group in position 4 orients to position 5 (but not to position 7). The same OH group in the 5 position orients primarily to position 4. From position 6 the hydroxy group directs electrophilic reaction to position 7 and, to a lesser extent, to position 6, whereas 7-hydroxyindoles give almost exclusively the 6-isomers (but not the 4-isomers) in the case of substitution. The carbon atom that is bonded to the carbon atom that bears the orienting substituent and has a high multiplicity index is always primarily attacked. One should also bear in mind the steric shielding of positions 4 and 7 by the substituents from positions 3 and 1. In addition, position 7 is apparently markedly shielded by the positively charged nitrogen atom. In fact, despite the high electron density and the low value of the cationic localization energy in this position, electrophilic substitution in position 7 is virtually never observed when substituents are absent in the benzene ring.

The principles presented above by no means can be regarded as definitive, since they are based on rather limited data, mainly on nitration and halogenation reactions. In addition, indoles are rather strong π donors and can form charge-transfer complexes with the electrophile in an intermediate step. In this case the orientation correlates with the spin-density distribution [114].

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SYNTHESIS OF CONDENSED SYSTEMS ON THE BASIS OF THE REACTIONS OF HETEROCYCLIC COMPOUNDS CONTAINING AN AMIDINE FRAGMENT WITH BIFUNCTIONAL REAGENTS (REVIEW)

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The general principles of the creation of condensed heterocyclic systems with a bridged nitrogen atom on the basis of the reactions of α-amino nitrogen heterocycles with bifunctional compounds are examined. The mechanisms of the examined condensations, as well as the possibilities of the use of the examined reagents for the modification of the components of nucleic acids, are discussed.

The aim of the present review is to attempt to examine the general principles of the creation of condensed heterocyclic systems with a bridged nitrogen atom on the basis of the reactions of α-amino nitrogen heterocycles with bifunctional compounds for the search for new reagents that are potentially applicable for the modification of the heterocyclic bases of nucleic acids.

Despite the voluminous data on the synthesis of condensed systems, review works that examine the data from this point of view are not available. The data published up to 1959 is primarily summarized in the monograph by Mosby [1], which, however, classifies the literature with respect to the methods of synthesis of certain systems but not with respect to the reagents. This sort of attempt was made during an examination of the methods of synthesis of imidazopyrimidines [2]; however, the limited scope of the problem posed does not make it possible to formulate a general concept.

The overwhelming majority of reagents used for the solution of the formulated problem have been investigated in the case of the reaction with 2-aminopyridine. This makes it possible to restrict ourselves primarily to an examination of the reactions of 2-aminopyridine (I) with the aid of only individual examples to illustrate the generality of the method, possible complications in the process, and special details of the mechanism. Only α-amino nitrogen heterocycles constitute the subject of the examination, and in our subsequent use of the term heterocycle we will understand it to mean only such compounds.

For the creation of a new ring on the basis of an amidine fragment of a heteroring the reagent should have two electrophilic groupings, the distance between which determines the size of the resulting ring. Quite a few agents of this type can be conceived of in theory. In fact, however, the choice turns out to be considerably more limited, since not every pair of functional groups is compatible in the same molecule. Since very little is known regarding the mechanisms of cyclizations of the type under consideration, we were forced to construct our exposition of the material available on the character of the effect of agents with a clear understanding of the absolutely arbitrary character of the division introduced.

Dialkylating (Arylating) Reagents

2-Aminopyridine (I) reacts with alkyl halides primarily at the ring nitrogen atom [3] to give the N-alkyl derivative (II), which can either undergo intramolecular alkylation to give cyclization product III or react with a second molecule of the amine to give disub-

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