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SYNTHESIS AND AUTOOXIDATION OF 2-AMINO-1,3-DIALKYLINDOLES

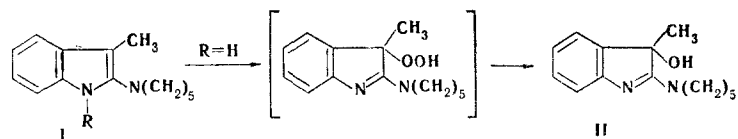
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Autooxidation occurs during the liberation of the bases from the salts of 1,3-dialkyl-2-aminoindoles, and stable 3-hydroperoxides are formed. The same compounds can also be obtained without prior isolation of the salts via heterocyclization of 1-acyl-2-arylhydrazines. If one of the nitrogen atoms is not alkylated, the corresponding 3-hydroxy compounds are obtained.

Indole compounds readily undergo autooxidation to give 3-hydroxy and 3-peroxyindolenines or products of their subsequent transformation, viz., substituted oxindoles, 2-acylindoles, dimeric structures, or compounds with an opened pyrrole ring (see the previous reviews [1, 2]). The electron-donor amino group of 2-aminoindoles facilitates autooxidation substantially [3], since only the corresponding 2-imino-3-hydroxy-3-alkyl(phenyl)-indolenines can often be obtained in the isolation of these amines from salts [4-6].

It has been established [4, 7] that imine I ($R = CH_3$) is resistant to air oxidation, while the nitrogen-unmethylated analog of I ($R = H$) cannot be isolated from its hydrobromide, since during the reaction it is converted to hydroxy compound II.



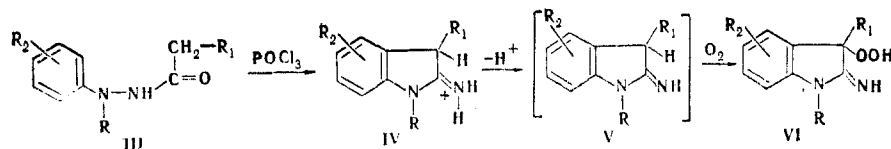
Nakagawa and co-workers [8] assume that the formation of hydroxy compound II proceeds through a step involving a hydroperoxide, since 3-hydroperoxides have been previously isolated in the autooxidation of 2,3-dialkylindoles [9]. The hydroperoxide itself was not isolated, but its intermediate formation is confirmed indirectly by the fact that in the presence of dihydrocollidinedicarboxylic acid ester (the Hantzsch ester), which is stable with respect to autooxidation under these conditions, it undergoes aromatization in almost quantitative yield.

We used our previously described method of heterocyclization of 1-acyl-2-arylhydrazines (III) [10] for the synthesis of the hydrochlorides of some 2-amino-1,3-dialkylindoles (IV) and unexpectedly observed [11] that the bases of these amines, which exist in the form of 2-iminoindolines (V), form stable 3-hydroperoxides (VI) upon brief standing in air and sometimes even during isolation from the salts; attempts to isolate 3-hydroperoxides VII from the

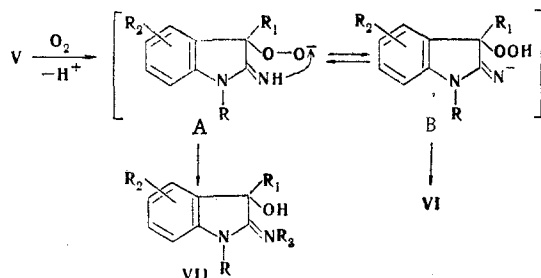
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products of oxidation of 2-aminoindoles were previously unsuccessful [5, 6], and these compounds are not converted spontaneously to the hydroxy compounds under ordinary conditions (a reducing agent must be introduced).



Thus when there is a hydrogen atom attached to one or the other nitrogen atom of the 2-aminoindole, autooxidation leads to 3-hydroxyindolenine II or VII, although peroxide compounds formed as side products were always detected in the reaction mixture by means of a test with potassium iodide [11]. However, if there is an alkyl group attached to the indole nitrogen but the amino group is completely unsubstituted, the reaction proceeds with the formation of hydroperoxides VI when alkyl (or benzyl) substituents are present in position 3 of indole. Oxidation evidently takes place primarily during migration of the C₂-C₃ double bond, and the hydrogen atom of the imino group promotes stabilization of anion B, i.e., the formation of a hydroperoxide. However, alkylation of the imino group increases the basicity of the amine and stabilizes anion A with subsequent decomposition of the latter and the formation of hydroxy compounds VII.



The structures of 3-peroxy-2-iminoindolines VI are proved by means of the mass spectra. Molecular ions can be obtained only at low ionization energies. By way of illustration, a molecular-ion peak ($[M]^+$) at 298* is present in the mass spectrum of 1-methyl-3-peroxy-3-(p-methoxybenzyl)-2-iminoindoline (VIb), along with ion peaks with mass 282 (ejection of an oxygen atom from the molecular ion) and mass 266 (splitting out of a molecule of oxygen). The appearance of an intense peak of an ion with mass 251 is probably associated with rearrangement processes, i.e., with detachment of a methoxy group and the formation of a tetrahydroindoloquinoline structure. The maximum peak is the peak of an ion with m/e 161, which is formed as a result of elimination of a p-methoxybenzyl grouping; this is also characteristic for the remaining structures of this series. A molecular-ion peak is observed at m/e 220 in the spectrum of 1,3-diethyl-3-peroxy-2-iminoindoline (VIh), which coincides with the calculated value, as well as intense $[M-33]^+$ (the maximum peak in the spectrum) and $[M-32]^+$ ion peaks, which correspond to the elimination of an OOH group and a molecule of oxygen by the molecular ion. The IR spectra of the resulting 3-peroxy-2-iminoindolines contain absorption bands at $1660-1665\text{ cm}^{-1}$ (C=N) and a broad band of an associated OH group at $3400-3550\text{ cm}^{-1}$. The PMR spectrum (in trifluoroacetic acid) of 1-methyl-3-benzyl-3-peroxy-2-iminoindoline (VIa) contains a singlet of a methyl group at 3.1 ppm (3H), a singlet of a methylene group at 3.4 ppm (2H), two one-proton signals at 8.4 and 8.1 ppm, which can be assigned to NH and OH groups, and a multiplet of aromatic protons centered at 7 ppm (9H). The PMR spectrum of VIh in the same solvent contains a triplet (3H, 0.63 ppm) and a quartet (2H, 2.07 ppm) of the C₂H₅ group in the 3 position, a triplet (3H, 1.38 ppm) and a quartet (2H, 4.01 ppm) of an N-C₂H₅ group, a multiplet of four aromatic protons at 7.0-7.6 ppm, and a broad signal at 8.25 ppm (NH and OH).

EXPERIMENTAL

The PMR spectra of the compounds in trifluoroacetic acid were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The IR spectra of mineral oil suspensions of the compounds were recorded with an IKS-22 spectrometer. The UV spectra of solutions of the compounds were recorded with a Specord spectrophotometer. The

*Here and subsequently, the m/e values are given.

TABLE 1. Hydrocinnamic Acid 1-Methyl-1-phenylhydrazides
III (R = CH₃)

Com- pound No.	R ₁	mp, °C	UV spec- trum, λ _{max} , nm (log ε)	IR spectrum ν, cm ⁻¹	PMR spec- trum, ppm	Found, %		Empirical formula	Calc., %		Yield, %
						C	H		C	H	
IIIa	CH ₂ C ₆ H ₅	100— 101 ^a	240 (4.1), 285 (3.3)	3200 (NH), 1670 (C=O)	2.8 (m, 4H), 3.2 (s, 3H), 6.9 (m, 5H), 7.2 (m, 5H)	75.7	7.0	C ₁₆ H ₁₈ N ₂ O	75.6	7.1	70
IIIb	CH ₂ C ₆ H ₄ — p-OCH ₃	109— 110 ^b	240 (4.0), 285 (3.4)	3220 (NH), 1660 (C=O)	2.8 (m, 4H), 3.4 (s, 3H), 3.7 (s, 3H), 6.7 (q, 4H), 7.2 (s, 5H)	71.5	7.1	C ₁₇ H ₂₀ N ₂ O ₂	71.8	7.1	47
IIIc	CH ₂ C ₆ H ₄ — o-OCH ₃	114— 115 ^c	240 (4.1), 280 (3.5)	3150 (NH), 1676 (C=O)	2.8 (m, 4H), 3.4 (s, 3H), 3.6 (s, 3H), 6.8—7.1 (m 9H)	71.9	7.3	C ₁₇ H ₂₀ N ₂ O ₂	71.8	7.1	68
IIId	CH ₂ C ₆ H ₄ — p-Br	163— 166 ^d	238 (4.0), 285 (3.3)	3200 (NH), 1660 (C=O)	2.7 (m, 4H), 3.3 (s, 3H), 6.5—7.0 (m 9H)	57.7	5.2	C ₁₆ H ₁₇ BrN ₂ O	57.6	5.1	53

^aFrom 50% ethanol. ^bFrom benzene. ^cFrom benzene-heptane (1:1). ^dFrom ethanol.

TABLE 2. 2-Aminoindole Hydrochlorides IV (R = CH₃)

Com- pound No.	R ₁	mp, °C	UV spec- trum, λ _{max} , nm (log ε)	IR spectrum ν, cm ⁻¹	PMR spec- trum, ppm	Found, %		Empirical formula	Calc., %		Yield, %
						C	H		C	H	
IVa	CH ₂ C ₆ H ₅	236— 239	210 (4.1), 260 (3.5)	3100— 2700, 1700 (C=N)	3.4 (d, 2H), 3.5 (s, 3H), 4.7 (t, 1H), 7.3 (m, 9H), 7.9 (2H)	70.0	6.4	C ₁₆ H ₁₇ ClN ₂	70.4	6.2	42
IVb	CH ₂ C ₆ H ₄ — p-OCH ₃	231— 234	215 (4.2), 260 (3.9)	3100— 2600, 1696 (C=N)	3.4 (d, 2H), 3.3 (s, 3H), 3.5 (s, 3H), 7.5—7.7 (m 8H)	66.9	6.0	C ₁₇ H ₁₉ ClN ₂ O	67.5	6.3	60
IVc	CH ₂ C ₆ H ₄ — o-OCH ₃	211— 213	215 (4.2), 250 (3.8)	3100— 2800, 1700 (C=N)	3.1 (d, 2H), 3.3 (s, 3H), 3.6 (s, 3H), 4.4 (t, 1H), 7.1 (m, 8H)	67.6	6.8	C ₁₇ H ₁₉ ClN ₂ O	67.5	6.3	42
Vd	CH ₂ C ₆ H ₄ — p-Br	221— 224	215 (4.2), 260 (3.9)	3100— 2800, 1700 (C=N)	3.4 (d, 2H), 3.48 (s, 3H), 7.1—7.5 (m, 8H)			—			57

mass spectra were obtained with a Varian Mat CH-8 spectrometer at an ionizing-electron energy of 15 eV with introduction of the substances into the ionization region at 150–200°C. The 1-alkyl-1-hydrazides of aliphatic acids and the corresponding hydrochlorides of 3-alkyl-2-aminoindoles, from which VIe–g were obtained, were previously described [6, 10], while hydroperoxides VIh, i were obtained without prior isolation of the salts of 2-aminoindoles.

Hydrocinnamic Acid 1-Methyl-1-phenylhydrazides. A mixture of 1.53 g (1.23 mmole) of 1-methyl-1-phenylhydrazine, 1.24 ml (1.23 mmole) of triethylamine, and 2.08 g (1.23 mmole) of hydrocinnamoyl chloride in 10 ml of absolute benzene was refluxed in a flask equipped with a reflux condenser fitted with a calcium chloride tube, after which the mixture was cooled and treated with 25 ml of water. The aqueous layer was extracted with benzene, and the combined extracts were evaporated to give 2.64 g (70%) of hydrazide IIIa, which was recrystallized from 50% ethanol. The other hydrazides (III) were similarly obtained (Table 1).

2-Aminoindole Hydrochlorides (IV). A mixture of 0.254 g (1 mmole) of hydrocinnamic phenylhydrazide (IIIa) and 0.27 ml (3 mmole) of freshly distilled phosphorus oxychloride in

TABLE 3. 3-Peroxy-2-iminoindolines (VI)

Compound	R	R ₁	R ₂	mp, °C	UV spectrum, λ_{max} , nm (log ϵ)	Found, %		Empirical formula	Calc., %		Yield, %
						C	H		C	H	
VIa	CH ₃	CH ₂ C ₆ H ₅	H	185—187	263 (4,0), 295 (3,3)	71,4	6,4	C ₁₆ H ₁₆ N ₂ O ₂	71,6	6,0	51
VIb	CH ₃	CH ₂ C ₆ H ₄ — <i>p</i> -OCH ₃	H	155—157	265 (4,0), 295 (3,3)	68,4	6,3	C ₁₇ H ₁₈ N ₂ O ₃	68,5	6,0	71
VIc	CH ₃	CH ₂ C ₆ H ₄ — <i>o</i> -OCH ₃	H	136—138	270 (4,0), 295 (3,4)	67,2	6,5	C ₁₇ H ₁₈ N ₂ O ₃	68,5	6,0	46
VI d	CH ₃	CH ₂ C ₆ H ₄ — <i>p</i> -Br	H	153—155	265 (4,1), 298 (3,3)	55,9	4,3	C ₁₆ H ₁₅ BrN ₂ O ₂	55,6	4,3	57
VIe	CH ₃	CH ₃	H	138—139	264 (4,1), 297 (3,4)	62,4	6,5	C ₁₀ H ₁₂ N ₂ O ₂	62,5	6,3	49
VI f	CH ₃	CH ₃	5-Br	140—141	262 (4,02), 297 (3,2)	44,1	4,0	C ₁₀ H ₁₁ BrN ₂ O ₂	44,3	4,1	45
VIg	CH ₂ C ₆ H ₅	CH ₃	H	139—140	264 (4,07), 298 (3,3)	71,6	6,0	C ₁₆ H ₁₆ N ₂ O ₂	71,6	6,0	53
VIh	C ₂ H ₅	C ₂ H ₅	H	135—137	265 (4,03), 297 (3,2)	65,7	7,3	C ₁₂ H ₁₆ N ₂ O ₂	65,4	7,3	43
VI i	CH ₃	<i>i</i> -C ₃ H ₇	H	119—121		65,5	7,3	C ₁₂ H ₁₆ N ₂ O ₂	65,4	7,3	41

5 ml of absolute dioxane was refluxed in a flask equipped with a reflux condenser protected from air moisture for 2 h, after which it was cooled, and the solvent and excess phosphorus oxychloride were removed by distillation in vacuo, and the precipitate was washed with dry ether and recrystallized from absolute propanol with dry ether (1:1). The yields and constants of IV are presented in Table 2.

1-Methyl-3-peroxy-2-iminoindolines (VI). A 0.28-g (1 mmole) sample of aminoindole hydrochloride IVa was mixed with 10 ml of 2 N sodium hydroxide solution, and the mixture was extracted with ether. The extract was allowed to stand with access to the air for 6 h, after which it was evaporated, and the precipitate was recrystallized from petroleum ether with the addition of *n*-propanol. Compounds VIb, c, e-g were similarly obtained (Table 3).

3-Peroxy-1,3-diethyl-2-iminoindoline (VIh). A mixture of 2.1 g (10 mmole) of 1-ethyl-1-phenyl-2-butylhydrazine and 4.6 ml (30 mmole) of phosphorus oxychloride was refluxed for 48 h in 50 ml of absolute ether, after which the solvent was removed by distillation, and the residue was treated with water, made alkaline to pH 9, and extracted with ether. The extract was allowed to stand in the air for 12 h, after which the ether was removed by distillation, and the residue was recrystallized from benzene-heptane (1:1).

3-Peroxy-1-methyl-3-isopropyl-2-iminoindoline (VIi). A mixture of 2.1 g (10 mmole) of 1-methyl-1-phenyl-2-isovalerylhydrazine and 4.6 g (30 mmole) of phosphorus oxychloride in 50 ml of absolute methylene chloride was refluxed for 60 h, after which the solvent was removed by vacuum distillation, and the residue was treated with water, neutralized with solid potassium carbonate (with cooling), and extracted with ether. The extract was allowed to stand with access to the air for 6 h, after which the solvent was removed by distillation, and the residue was recrystallized from benzene-petroleum ether.

3-Peroxy-1-methyl-3-(*p*-bromobenzyl)-2-iminoindoline (VI d). A mixture of 0.332 g (1 mmole) of *p*-bromohydrocinnamic acid 1-methyl-1-phenylhydrazide and 0.27 ml (3 mmole) of phosphorus oxychloride was refluxed in 5 ml of absolute dioxane for 3 h, after which the solvent was removed by distillation, and the residue was made alkaline with ammonium hydroxide and extracted with ether. After air drying for 6 h, the solution was evaporated, and the residue was recrystallized from carbon tetrachloride.

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DIRECT SYNTHESIS OF MOLECULAR SELF-COMPLEXES IN THE INDOLE SERIES

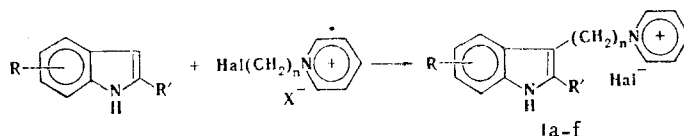
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A method for the alkylation of 3-unsubstituted indoles by means of 1-(ω -haloalkyl)-pyridinium salts via the Friedel-Crafts reaction with the aid of complex catalysts, viz., complexes of zinc, tin, and titanium chlorides with pyridine, was developed. On the basis of a study of the electronic spectra of the resulting 1-(3-indolyl-alkyl)pyridinium salts it was shown that they are molecular self-complexes. The stabilities of the molecular self-complexes were investigated as a function of the length of the alkyl chain and the character of the substituents in the indole ring.

An independent research area, viz., the study of intramolecular charge-transfer complexes (CTC) (molecular self-complexes), in which interaction of a donor and acceptor contained in a single molecule and separated by an alkyl chain that does not conduct conjugation, has recently evolved in studies of CTC (for example, see [1]).

For the synthesis of molecular self-complexes of the indole series we have developed a method for the direct alkylation of 3-unsubstituted indoles with alkyl halides that contain an acceptor pyridinium ring at the end of the chain.



One example of the preparation of 1-(3-indolylalkyl)pyridinium salts (I) via the Zincke reaction [2], which is based on the use of difficult-to-obtain tryptamines and requires that they be present in a twofold excess as compared with the Zincke salt, is known in the literature.

A complex catalyst for the alkylation of indoles via the Friedel-Crafts reaction, viz., dipyridinezinc chloride [3], which is a weak Lewis acid and does not resinify acidophobic indoles, was recently discovered. We used this catalyst for the alkylation of indoles with 1-(ω -haloalkyl)pyridinium salts and obtained salts I in 50-75% yields. The alkylation process proved to be the primary process, although one might have expected that the strongly nucleophilic indole and substituted indoles would undergo hetarylation by the pyridinium cations (for example, see [4, 5]).

In addition to dipyridinezinc chloride, we also used complexes to Ti(IV) and Sn(IV) chlorides as the alkylation catalysts. A previous attempt [6] to use these catalysts was unsuccessful. This is evidently due to the fact that the catalysts were prepared directly

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