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XXXIX.* ORIENTATION DURING THE NITRATION OF 5-HYDROXYINDOLE DERIVATIVES

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5-Methoxy-3-carbethoxyindoles are nitrated primarily in the 4 position. Replacement of the methoxy group by an acetoxy group leads to a change in orientation – only the 6 isomer is obtained. In the case of the similarly constructed 5-hydroxyindoles, monosubstitution cannot be accomplished under various conditions, and only the 4,6-dinitro derivative is formed. The synthesis of the corresponding amines by reduction of the nitro compounds is described.

The data on orientation in the nitration of 5-hydroxyindole and its O-substituted derivatives are somewhat contradictory [2, 3], and the structure of the substances either has not been proved in all cases or there is no indication of the formation or absence of isomeric compounds. For example, it has been reported that 5-alkoxyindoles form 4-nitro derivatives [3], but the formation of both the 4 isomer and the 6 isomer, with, however, predominance of the former, has been noted for some 5-benzyloxyindoles [2].

In this connection, we investigated the nitration of a number of 5-hydroxyindole derivatives. The experiments were set up in the case of 3-carbethoxy derivatives, which are more stable with respect to oxidation and prototropic polymerization as well as more accessible.

Two nitro groups enter the benzene ring at once in the reaction of 20-30% nitric acid with 1,2-dimethyl-3-carbethoxy-5-hydroxyindole (Ia), and 1,2-dimethyl-3-carbethoxy-4,6-dinitro-5-hydroxyindole (IIa) is formed in 10-15% yield. The yield of IIa can be raised to 72% by nitration with nitric acid in acetic anhydride at −15°C in a stream of argon. The latter apparently limits oxidative processes to a considerable extent, since the stream of gas carries off the resulting oxides of nitrogen, which accelerate oxidation to quinoid structures (see [4] for information regarding this sort of oxidation). At lower temperatures (−30°), practically no nitration occurs even when the mixture is allowed to stand for many hours. However, if the temperature is gradually raised to −20°, the formation of dinitro compound IIa commences immediately, although there is still much starting Ia in solution, judging from the thin-layer chromatogram. We were unable to obtain the mononitro compound under various other conditions.

The formation of only a dinitro compound in the nitration of 2-methyl-3-carbethoxy-5-hydroxyindole was reported in [5]. Such phenomena are known in the nitration of phenols, have been observed in halogenation reactions, and have even been dubbed the "suction catalysis effect" [6].

It is possible that the formation of this sort of dinitro compound is associated with reduction of the nitric acid to nitrous acid (due to oxidation of the hydroxyindole) with subsequent nitrosation and oxidation of the nitro group. This is confirmed indirectly by the fact that although we observed only profound resinification in the nitrosation of Ia, the 4-nitro compound (IVa) [containing a trace of the 6-nitro isomer (V)] rather than the nitroso compound was formed in the case of 5-methoxyindole (IIIa) by the action of nitrous

*See [1] for communication XXXVIII.

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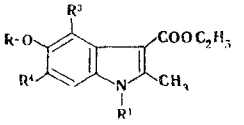
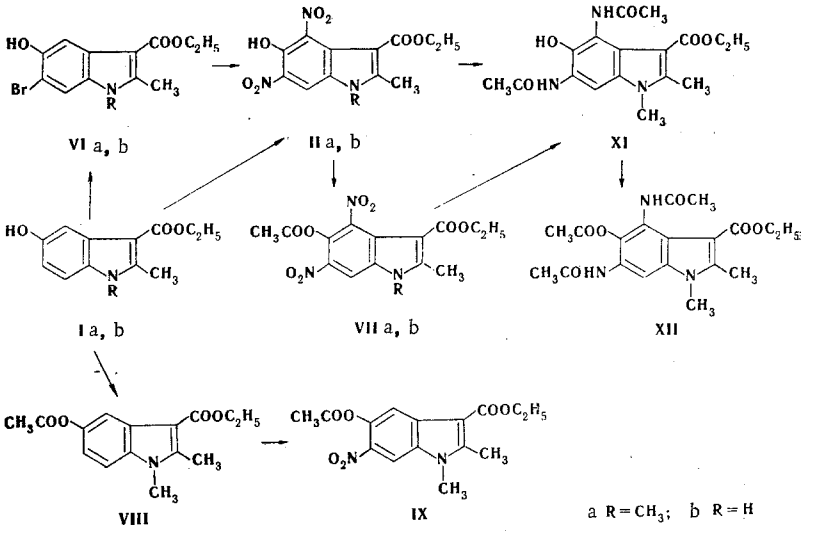
TABLE 1



Compound	R¹	R²	R³	R⁴	mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	UV spectrum λ_{max}, nm	UV spectrum lg ε	IR spectrum, cm⁻¹ ν_{CO}	IR spectrum, cm⁻¹ ν_{NO_2}	PMR spectrum, δ, ppm[a] 1-CH₃	2-CH₃	C₂H₅	4-H	OR²	6-H	7-H	Yield, %
IIa	CH_3	H	NO_2	NO_2	239—240[b]	$C_{13}H_{13}N_3O_7$	48,6	4,1	12,9	48,3	4,1	13,0	270 365	4,59 4,49	1710	1550, 1320								72
IIb	H	H	NO_2	NO_2	275—276[b]	$C_{12}H_{11}N_3O_7$	46,5	3,5	13,3	46,7	3,6	13,7	265 366	4,21 4,18	1680; 3230 (NH)	1540, 1340								50
VIIa	CH_3	CH_3CO	NO_2	NO_2	252—253	$C_{15}H_{15}N_3O_8$	49,7	4,3	11,1	49,4	4,1	11,5	267 324 345	4,28 3,96 3,95	1795, 1695	1555—1535, 1340—1310	2,67s	2,33s	4,20 q 1,23 t		3,76s		8,37s	92
VIIb	H	CH_3CO	NO_2	NO_2	262—263[b]	$C_{14}H_{13}N_3O_8$	47,9	3,8	11,6	47,9	3,7	11,9	263 340	4,10 3,81	1810, 1685; 3350 (NH)	1555—1540, 1340—1310		2,64s	4,27 q 1,23 t		2,34s		8,20s	80
IVa	CH_3	CH_3	NO_2	H	193—194	$C_{14}H_{16}N_2O_5$	57,1	5,5	9,4	57,5	5,5	9,6	217 242 287	4,67 4,40 3,50	1700	1530 1310	3,27s	2,23s	3,97 q 1,00 t		3,54s	6,55 d J_{67}=9 Hz	7,00 d	55
IVb	CH_3	$CH_2C_6H_5$	NO_2	H	180—181	$C_{20}H_{21}N_2O_5$	65,3	5,4	7,6	65,2	5,7	7,6	290	3,91	1695	1530, 1320					7,63 s[c]	7,93 d J_{67}=9 Hz	7,48 d	47
V	CH_3	CH_3	H	NO_2	145—146	$C_{14}H_{16}N_2O_5$	57,7	5,5	9,4	57,5	5,5	9,6	213 273 349	4,30 4,16 3,72	1695	1520, 1310	3,25s	2,30s	4,02 q 1,03 t	7,27s	3,55s		7.56s	13
IX	CH_3	CH_3CO	H	NO_2	173—174	$C_{15}H_{16}N_2O_6$	56,5	4,9	8,4	56,3	5,0	8,7	211 380	4,42 3,42	1770	1530, 1340	2,36s	2,10s	4,08 q 1,08 t	7,47s	3,37s		7,84s	17
Xa	CH_3	CH_3	NH_2	H	99—100	$C_{14}H_{18}N_2O_3$	64,2	6,8	10,9	64,2	6,8	10,7	224 251 313	4,51 4,24 3,99	1660	3450—3300 (NH)	3,83s[d]	2,91s	4,73 q 1,73 t	6,07 m (NH_2)	4,03s	6,77 d J_{67}=9 Hz	7,19 d	84
Xb	CH_3	CH_3	$NHCOCH_3$	H	119—120	$C_{16}H_{20}N_2O_4$	63,1	6,6		63,2	6,6		219 248 293	4,57 4,10 3,98	1720, 1780	3430—3350 (NH)								89
XI	CH_3	H	$NHCOCH_3$	$NHCOCH_3$	256—257	$C_{17}H_{21}N_3O_5$	59,4	6,2	12,0	59,0	6,1	12,1	266 318	4,48 4,18	1680 1635	3350 (NH)	3,66s	2,70s	4,45 q 1,47 t	2,53s 10,51 (NH)		2,47 s 9,14 (NH)	7,78s	50
XII	CH_3	CH_3CO	$NHCOCH_3$	$NHCOCH_3$	216—217	$C_{19}H_{23}N_3O_6$	58,9	5,8	10,5	58,8	5,9	10,8	223 250	4,57 4,04	1780, 1720, 1700	3350 (NH)								90

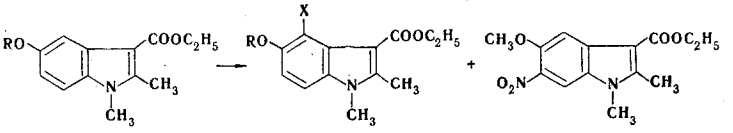
[a]The following abbreviations are used here and elsewhere: s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet.
[b]With decomposition.
[c]PMR spectrum in dimethyl sulfoxide.
[d]PMR spectrum in chloroform.

acid. Consequently, the nitroso compound thus formed was oxidized by excess nitrous acid, as was observed, for example, in the nitrosation of some benzophenones [7].



When a bromine atom is introduced into the 6 position (VIa, b), nitration proceeds with substitution of both the hydrogen atom in the 4 position and the bromine atom; this leads to the same substances (IIa, b). The 6-bromo-4-nitro derivative could not be detected. The aromatic portion of the PMR spectrum of the O-acetyl derivative (VIIa) of IIa has a 7-H singlet (8.37 ppm), which is shifted by 1.53 ppm as compared with the starting compound under the influence of the two nitro groups. The IR-spectral data (the absence of an OH band; see Table 1) indicate a strong intramolecular hydrogen bond in IIa, b. In analogy with dinitrophenols [8], it can be supposed that the 4-nitro group deviates from the plane, especially when it is adjacent to the carbethoxy group. On passing from II to acetyl derivative VII, the long-wave absorption maximum of the UV spectrum is shifted hypsochromically by 40 nm, and the overall absorption intensity decreases; this corresponds to disruption of the hydrogen bond and to a certain weakening of the electronic effect of the substituent.

A mixture of 4- and 6-nitro compounds (IVa and Va) is formed in the nitration of 5-methoxyindole (IIIa) under various conditions.



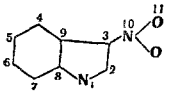
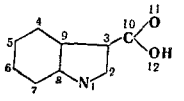
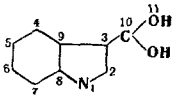
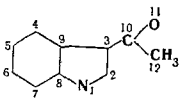
III, IV a $R=CH_3$, $X=NO_2$; b $R=CH_2C_6H_5$, $X=NO_2$; X a $R=CH_3$, $X=NH_2$; b $R=CH_3$, $X=NHCOCH_3$

Substances IVa and V are quite readily separated by chromatography and differ with respect to their UV spectra; this can be used to establish the position of the substituent. For definitive proof, we used the data from the PMR spectra (two doublets of an AB system at 7.00 and 6.55 ppm with J = 9 Hz for IVa, and two broad singlets at 7.26 and 7.59 ppm for V).

Replacement of the methoxy group by a benzyloxy group (IIIb) led to somewhat greater specificity of the process. 4-Isomer IVb (two doublets at 7.93 and 7.48 ppm with J = 9 Hz) was isolated in 47% yield, and an impurity – apparently the 6-nitro isomer – was detected in the reaction mass only by chromatography. Thus even replacement of the O-methyl group by an O-benzyl group was reflected in the orientation during nitration. The change in orientation proved to be even more substantial on passing to O-acetyl derivative VIII. Nitration of VIII led only to 6-nitro-substituted IX, and no contamination with the 4 isomer was detected chromatographically (broad singlets at 7.46 and 7.84 ppm in the PMR spectrum). No nitro compound at all could be obtained when the acetyl group was replaced with a benzoyl group.

The isolated nitro compounds were characterized by conversion to the corresponding amines and their acetyl derivatives by the action of hydrazine hydrate, during which the reduction of VIIa proceeds with simultaneous removal of the acyl group. We were unable to accomplish partial reduction of the dinitro compound.

TABLE 2. Charges and Electron Densities on the Boundary Orbitals of 3-Nitro-, 3-Carboxy-, and 3-Acylindoles

	Atom No.	Overall charge	Density on the boundary orbital
	1	+0,272	0,065
	2	+0,207	0,309
	3	−0,157	0,355
	4	−0,016	0,339
	5	−0,023	0,000
	6	−0,016	0,348
	7	−0,028	0,165
	8	+0,007	0,091
	9	−0,028	0,176
	10	+0,821	0,001
	11	−0,519	0,075
	1	+0,264	0,083
	2	+0,169	0,352
	3	−0,121	0,396
	4	−0,017	0,310
	5	−0,024	0,000
	6	−0,017	0,290
	7	−0,029	0,155
	8	+0,007	0,082
	9	−0,031	0,114
	10	+0,329	0,023
	11	−0,628	0,200
	12	+0,098	0,008
	1	+0,278	0,056
	2	+0,232	0,254
	3	−0,115	0,326
	4	−0,015	0,342
	5	−0,022	0,049
	6	−0,015	0,361
	7	−0,027	0,169
	8	+0,009	0,093
	9	−0,029	0,196
	10	+0,448	0,108
	11	+0,129	0,036
	1	+0,353	0,058
	2	+0,188	0,366
	3	−0,099	0,356
	4	−0,013	0,288
	5	−0,019	0,000
	6	−0,014	0,294
	7	−0,023	0,125
	8	+0,005	0,093
	9	−0,026	0,134
	10	+0,333	0,025
	11	−0,568	0,231
	12	+0,011	0,001

Thus the character of the replacement of the hydrogen atom of the 5-hydroxyl group is reflected substantially in the orientation during nitration of indole derivatives. It can be supposed that the presence of a 3-carbethoxy group plays a substantial role. Calculation of the electron density by the Pariser–Parr–Pople method, which was carried out for 5-hydroxyindole-3-carboxylic acid* (Fig. 1), did not make it possible to prefer nitration in the 4 or 6 position. Calculation of the model structures of the 3-acyl- or 3-carboxyindole type (Table 2) permits attack on C_5 for the neutral molecule and on C_4 for the protonated molecule during evaluation with respect to the density on the boundary orbitals (as usual for such structures, the overall charges correlate poorly with the experimental values). Data obtained by computation within the Hückel approximation [9] correspond somewhat better to the experimental values. Here, the densities on the boundary orbitals for 3-acylindoles have close values for the 3, 4, and 6 positions, without, however, making it possible to choose among them.

It follows from the calculation for indole-3-carboxylic acid that protonation at oxygen (or initial attack of the nitronium ion at oxygen) promotes preferred nitration in the 6 position. In fact, for 3-acetyl- and 3-carbethoxyindoles the introduction of a threefold amount of acetic acid, which weakens the degree of protonation, increases the relative percentage of the 4 isomer by 5-6%. As seen, this effect should not be so strong as to completely determine almost exclusive substitution in the 4 or 6 position, as described above.

*Data obtained by V. I. Minkin (Rostov State University).

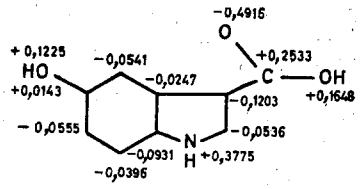


Fig. 1. Electron-density distribution in 3-carboxy-5-hydroxyindole (calculated by the Pariser–Parr–Pople method).

TABLE 3. Bond Multiplicities in the 3-Nitroindole Molecule

Atom No.	Bond multiplicity
$N—C_2$	0,489
$C_2—C_3$	0,694
$C_3—C_9$	0,420
$C_9—C_4$	0,600
$C_4—C_5$	0,692
$C_5—C_6$	0,640
$C_6—C_7$	0,682
$C_7—C_8$	0.624
$C_8—C_9$	0,641

On comparison of the data on nitration and bromination of compounds of the indole series it is seen that the direction of entry of bromine (into the 6 position) is extremely selective, i.e., it is independent of the character of the substituent in the 5 position and is determined, correspondingly, by the overall distribution of electron density in the indole molecule. The 4 position is not sterically hindered, since 5,6-disubstituted indoles are readily brominated in the 4 position. The presence of a 3-carbethoxy group does not disrupt the general principle during bromination [10]. The nitronium ion, being a considerably more reactive reagent, is, in conformity with the Bell–Evans–Polyani principle [11], less selective, i.e., it is capable of attacking both the 6 and 4 positions. However, the preference for one or another position in substitution is determined by other factors.

The predominant formation of the 4 isomer in 5-alkoxy-3-carbethoxyindoles can be explained by the fact that attack on the carbonyl oxygen atom is realized not by the proton but by the nitronium ion, which is subsequently transferred to C_4. This sort of transfer of a substituent to the ortho carbon atom has been observed repeatedly [12]. In the case of the 5-acetoxy derivatives, competition between the two nucleophilic oxygen atoms comes into play, transfer of the nitronium cation to C_4 is prohibited in view of the steric interaction of these ester groups, and only substitution at C_6 is realized. The proposed scheme does not claim to be conclusive, since we do not have the kinetic data at our disposal, and it is completely admissible that another reaction mechanism, for example, one based on addition-cleavage, is realized for any model. In fact, calculation of the 3-nitroindole model (Table 3) shows that the multiplicity of the C_2-C_3, C_4-C_5, and C_6-C_7 bonds is considerably higher than unity. The same results were also obtained for 3-acyl- and 3-carboxyindoles.

If the 3-carbethoxy group is removed, a nitro compound cannot be obtained from 5-hydroxyindoles under the usual conditions by the action of nitric acid. In sulfuric acid, in which the pyrrole ring is protonated, primarily 1,2-dimethyl-5-hydroxy-6-nitroindole [containing a slight amount of the 4-nitro isomer (9:1)] is formed from 1,2-dimethyl-5-hydroxyindole under very mild conditions. These results will be discussed in our next paper.

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with IKS-22 and UR-10 spectrometers. The UV spectra of methanol or chloroform (IIa, b, IVb, VIIa, b) solutions were recorded with a Cary-15 spectrophotometer. The PMR spectra of trifluoroacetic acid solutions were recorded with a Varian S-60T spectrometer with hexamethyldisiloxane (HMDS) as the external standard. The process was monitored by chromatography in a thin layer of aluminum oxide (activity III in the Brockmann classification) in benzene–ethyl acetate-heptane (4:1:3) for the mononitro- and monoaminoindoles and on Silufol in benzene–ethyl acetate (7:1, 5:1, or 3:1) for the dinitro- and diacetamidoindoles.

1,2-Dimethyl-3-carbethoxy-4,6-dinitro-5-hydroxyindole (IIa, Table 1). A 2.52-g (0.04 mole) sample of nitric acid (sp. gr. 1.5) and 50 ml of glacial acetic acid were added to a suspension of 4.7 g (0.02 mole) of 1,2-dimethyl-3-carbethoxy-5-hydroxyindole (Ia) and 50-70 mg of copper nitrate in 150 ml of acetic anhydride under argon while maintaining the temperature at −16°. The mixture was then stirred at this temperature for 1 h and poured into ice water. The precipitate was recrystallized from dioxane or glacial acetic acid to give 4.7 g of IIa with R_f 0.3. Compound IIa was also obtained in 30% yield by nitration of 1,2-dimethyl-3-carbethoxy-5-hydroxy-6-bromoindole (VIa) [10]. The IR spectra of the samples were identical.

2-Methyl-3-carbethoxy-4,6-dinitro-5-hydroxyindole (IIb, Table 1). The nitration of 2-methyl-3-carbethoxy-5-hydroxyindole (Ib) was carried out as in the nitration of Ia. The product was recrystallized from dioxane to give a substance with R_f 0.5. Compound IIb was also obtained in 14% yield by nitration of 2-methyl-3-carbethoxy-5-hydroxy-6-bromoindole (VIb) [13]. The IR spectra of the samples were identical.

1,2-Dimethyl-3-carbethoxy-5-acetoxy-6-nitroindole (IX, Table 1). A 0.126-g (0.002 mole) sample of nitric acid (sp. gr. 1.43) was added by drops at room temperature to a solution of 0.55 g (0.002 mole) of 1,2-dimethyl-3-carbethoxy-5-acetoxyindole (VIII) in 7 ml of glacial acetic acid. The solution was heated to 50° in the course of 10 min and held at this temperature for 1 h. It was then cooled and poured into water. After 2-3 h, a brownish resinous precipitate formed; it was washed on the filter with a small amount of methanol and recrystallized from methanol to give 110 mg of IX with R_f 0.6. Other methods of nitration also gave 6-nitro derivative IX but in lower yields.

1,2-Dimethyl-3-carbethoxy-4,6-dinitro-5-acetoxyindole (VIIa, Table 1). This compound was obtained by refluxing hydroxyindole IIa in acetic anhydride for 15-20 min. It was recrystallized from benzene to give a product with R_f 0.4.

2-Methyl-3-carbethoxy-4,6-dinitro-5-acetoxyindole (VIIb, Table 1). This compound was obtained by refluxing hydroxyindole IIb in acetic anhydride for 1 h. The precipitate was removed by filtration, dried, and dissolved in methanol. Aluminum oxide (10-15 g per gram of substance) was added to the solution, and the mixture was stirred at room temperature for 2 h. It was then passed through a column filled with Al_2O_3 (elution with methanol). The solvent was removed, and the residue was recrystallized from methanol to give VIIb.

1,2-Dimethyl-3-carbethoxy-4-nitro-5-methoxyindole (IVa) and 1,2-Dimethyl-3-carbethoxy-6-nitro-5-methoxyindole (V, Table 1). A 1-g (0.016 mole) sample of nitric acid (sp. gr. 1.43) was added at room temperature with stirring to a solution of 3.6 g (0.014 mole) of 1,2-dimethyl-3-carbethoxy-5-methoxyindole (IIIa) in 60 ml of glacial acetic acid. The temperature was raised to 30°, and a yellow precipitate formed after 3-5 min. The mixture was cooled and poured into cold water. The aqueous mixture was filtered, and the solid material was washed with water and dried on the filter. The resulting mixture of two isomers had mp 173-175°. Recrystallization from benzene gave 2.49 g of IVa with R_f 0.4. Evaporation of the benzene filtrate to half of its original volume and cooling precipitated V. It was recrystallized from benzene to give 0.6 g of a product with R_f 0.6. A column filled with Al_2O_3 and elution with benzene–heptane (1:1) were used for purer separation of the isomers.

Compound IVa was also obtained in 49% yield by the action (at 5° for 30 min) of sodium nitrite on IIIa in acetic acid–acetic anhydride. The samples were identical with respect to their UV and IR spectra.

1,2-Dimethyl-3-carbethoxy-5-benzyloxyindole (IIIb). A suspension of 6.99 g (0.03 mole) of indole Ia, 5.7 g (0.045 mole) of benzyl chloride, and 26 g of anhydrous potassium carbonate in 150 ml of dry acetone [13] was refluxed for 44 h. The solvent was removed in vacuo, and the residue was dissolved in a hot mixture of 200 ml of water and 200 ml of ethyl acetate. The aqueous phase was extracted with ethyl acetate, and the extract was washed with water, dried with magnesium sulfate, and concentrated. The concentrate was cooled to 0° to precipitate crystals of IIIa. The product was recrystallized from heptane to give 7.17 g (74%) of a material with mp 105-106° and R_f 0.74. Found: C 74.5; H 6.8; N 4.5%. $C_{20}H_{22}NO_3$. Calculated: C 74.1; H 6.8; N 4.3%. IR spectrum: 1695 cm^{-1} (CO). UV spectrum, λ_{max}, nm (log ε): 216, 244, 288 (4.78, 4.57, 4.10). PMR spectrum: δ 7.56 (6-H, d), 6.74-7.23 (multiplet of aromatic protons), 5.17 (5-CH_2, s), 4.37 (3-CH_2, q), 3.43; 2.56 (N-CH_3, 2-CH_3, s), 1.45 ppm (3-CH_3, t).

1,2-Dimethyl-3-carbethoxy-4-nitro-5-benzyloxyindole (IVb, Table 1). A 0.25-ml (0.006 mole) sample of nitric acid (sp. gr. 1.5) was added with stirring to a solution of 1.62 g (0.005 mole) of indole IIIb in 40 ml of glacial acetic acid, and the mixture was held at 30-40° for 5-10 min. It was then stirred at room temperature for 30 min and poured into water. The resulting precipitate was removed by filtration, washed with water, dried, washed with ether, and recrystallized from benzene to give 0.87 g of IVb with R_f 0.5.

1,2-Dimethyl-3-carbethoxy-4-amino-5-methoxyindole (Xa, Table 1). A small amount of Raney nickel and hydrazine hydrate (~8 ml) were added by drops to a suspension of 1.2 g (0.004 mole) of nitroindole IVa in 80 ml of ethanol until all of the nitro compound had dissolved and the yellow solution became colorless (~40 min). The mixture was then refluxed for 15 min, and the hot solution was filtered. The filtrate was evaporated, and the residue was recrystallized from heptane to give 0.75 g of Xa with R_f 0.7.

1,2-Dimethyl-3-carbethoxy-4-acetamido-5-methoxyindole (Xb, Table 1). A 1.3-g (0.005 mole) sample of indole Xa was refluxed with 10 ml of acetic anhydride for 5 min. The product was recrystallized from aqueous methanol to give 1.35 g of Xb with R_f 0.2.

1,2-Dimethyl-3-carbethoxy-4,6-diacetamido-5-hydroxyindole (XI, Table 1). Raney nickel and hydrazine hydrate (~10 ml) were added by drops to a suspension of 1.8 g (0.0055 mole) of dinitroindole IIa

in 75 ml of ethanol until the solution became colorless. After all of the hydrazine had reacted (as evidenced from the lack of gas evolution on addition of Raney nickel), 10 ml of acetic anhydride was added, and the mixture was refluxed for 20 min. The hot solution was filtered, and the solvent was evaporated to less than half its original volume. The brown oily liquid was poured into cold water, and the precipitate was removed by filtration, washed with water, and recrystallized from methanol to give 1 g of XI with R_f 0.4. Compound XI was similarly obtained in 46% yield by reduction of dinitroindole VIIa. The IR spectra and the melting points of the samples were identical.

1,2-Dimethyl-3-carbethoxy-4,6-diacetamido-5-acetoxyindole (XII, Table 1). A 0.35-g (0.001 mole) sample of hydroxyindole XI was refluxed with 10 ml of acetic anhydride for 2 h. The mixture was then cooled and poured into cold water. The resulting precipitate was removed by filtration, washed several times with water, dried, and recrystallized from methanol to give 0.34 g of XII with R_f 0.2.

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