The Mitomycin Antibiotics. Synthetic Studies. XVIII.[1] Preparation of 1-(β-Substituted ethyl)indoloquinone Analogs

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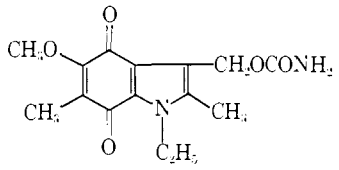
Reaction of 1-(β-hydroxyethyl)-5-methoxy-2,6-dimethyl-4-nitro-3-indolecarboxaldehyde methanesulfonate (XI) with KF and sodium acetate (followed by ester hydrolysis) gave the 1-β-fluoroethyl and 1-β-hydroxyethyl derivatives; similar treatment of 4-amino-1-(β-hydroxyethyl)-5-methoxy-2,6-dimethyl-3-indolecarboxaldehyde methanesulfonate (XII) with NaN_3, LiCl, and sodium methylmercaptide gave the 1-β-azidoethyl, 1-β-chloroethyl, and 1-β-methylmercaptoethyl derivatives, respectively. The various products were converted into 1-(β-substituted ethyl)-3-hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-dione methylcarbamates (XIV) using established procedures.

In a previous paper from this laboratory we described the preparation of the mitomycin-related indoloquinone I and noted the *in vitro* and *in vivo* antibacterial activity of this substance.[2] One aspect of our analog program was the synthesis and antibacterial evaluation of certain indoloquinones having substituents in the β position of the 1-ethyl group, which we now report.



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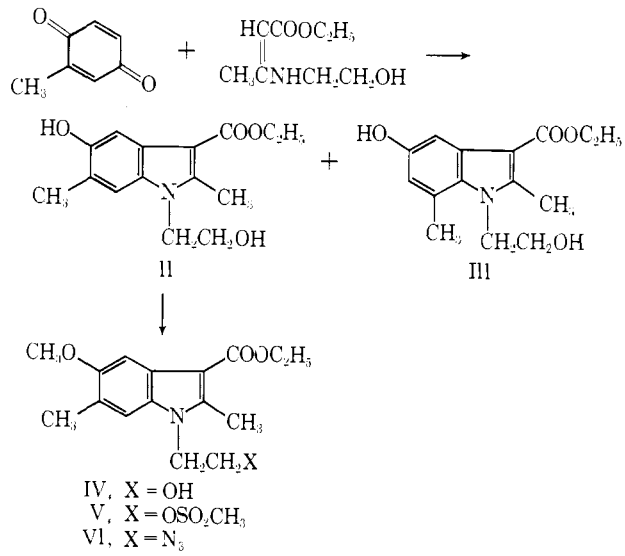
The convenient preparation of a significant number of analogs obviously required that we be able to effect nucleophilic substitution at the β-carbon atom of a 1-ethylindole possessing as many features of a methoxyindoloquinone carbamate (see I) as possible. However, we were cognizant of the fact that C-5 and the carbamoyloxy C-3 methyl group in a fully elaborated derivative represented potential competitive sites for such displacements. In view of the known susceptibility of Sn2 displacements to steric factors,[3] the feasibility of the desired nucleophilic substitution was first tested with an appropriate model system, the 1-β-mesyloxyethylindole V. This indole was prepared by a Nenitzescu[4] condensation of ethyl β-(2-hydroxyethylamino)crotonate (available from reaction of aminoethanol with ethyl acetoacetate) with toluquinone, methylation of the 5-hydroxyindole ester II, and finally mesylation of the resulting 1-β-hydroxyethyl-5-methoxy derivative IV (see Scheme I). We would note that in the condensation giving indole ester II, the isomeric 5-hydroxy-7-methylindole ester III can be isolated in minute quantity.[5] Although treatment of mesylate V with potassium thiocyanate in boiling acetone (2.5 hr) gave nearly quantitative recovery of V, sodium azide in dimethylformamide gave the 1-β-azidoethyl derivative VI in excellent yield, thus demonstrating at least limited applicability of the projected approach.

SCHEME I



Indole ester II was also used for the synthesis of the desired analogs. Thus, decarbethoxylation of II was effected by saponification followed by heating of the resulting crude indole acid in methanol. (Mineral acid from acidification of the hydrolysis solution was probably present at this stage.) The resulting 1-β-hydroxyethyl-5-hydroxyindole VII was converted *via* the 5-methoxy derivative VIII into the mesylate IX and then to the 3-carboxaldehyde derivative X[6] (see Scheme II). Nitration of this aldehyde with fuming nitric acid in glacial acetic acid then furnished the 4-nitro-3-indolecarboxaldehyde XI in 71% yield. It may be noted that in this preparation of XI no appreciable formation of the corresponding 3-nitro product was observed; in contrast, similar nitrations of other 1,2,6-trialkyl-5-methoxy-3-indolecarboxaldehydes have been found to give 3,4-dinitroindoles as well as 4-nitro-3-indolecarboxaldehydes.[7,8]

Initially, it was our intent to convert the nitroaldehyde XI to the fully elaborated 1-β-mesyloxyethyl-5-

(1) Paper XVII: G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Med. Chem.*, **10**, 14 (1967).

(2) (a) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 3877 (1964); (b) G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.*, **10**, 1 (1967).

(3) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp 154–160.

(4) C. D. Nenitzescu, *Bul. Soc. Chim. România*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 1108 (1930).

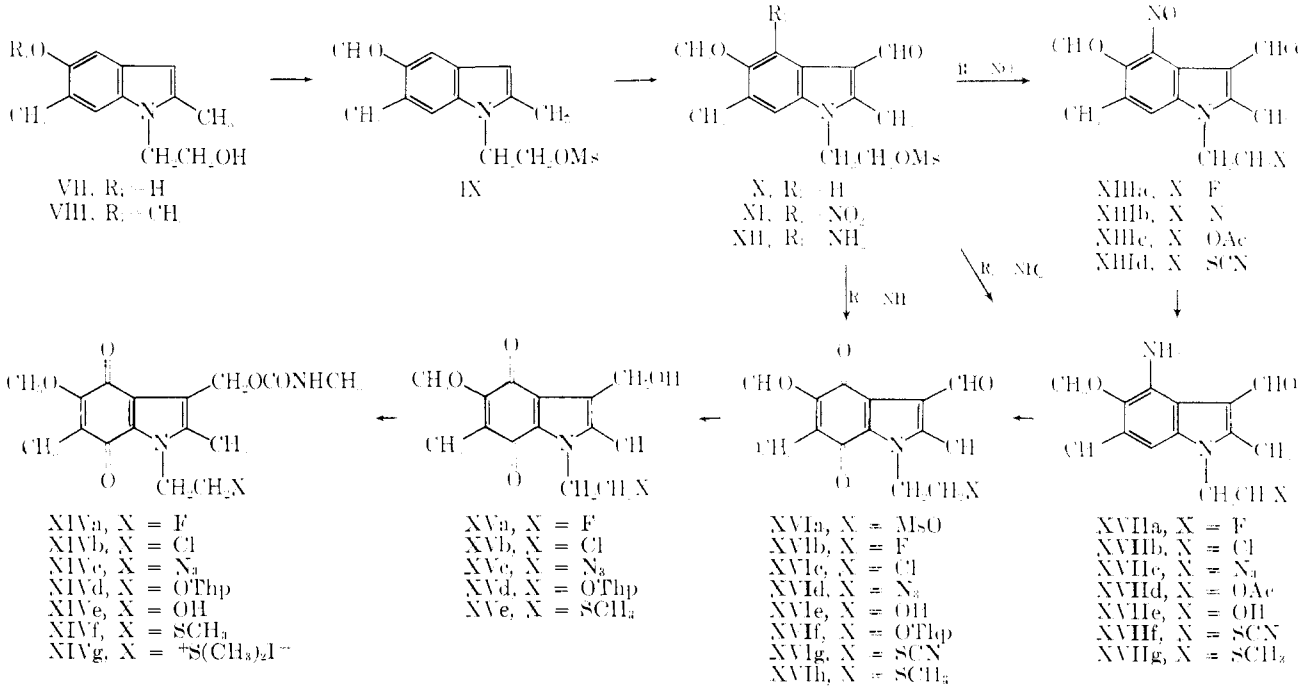
(5) G. R. Allen, Jr., C. Pidacks, and M. J. Weiss, *J. Am. Chem. Soc.*, **88**, 2536 (1966).

(6) A. Vilsmeier and A. Haack, *Ber.*, **60**, 119 (1927).

(7) G. R. Allen, Jr., L. J. Binovi, and M. J. Weiss, *J. Med. Chem.*, **10**, 7 (1967).

(8) A similar observation is recorded for the nitration of 1- (and/or 2-) alkyl-3-indolealdehydes: (a) G. Berti, A. Da Settimo, and O. Livi, *Tetrahedron*, **20**, 1397 (1964); (b) W. E. Noland, L. R. Smith, and K. R. Rush, *J. Org. Chem.*, **30**, 3457 (1965).

SCHEME II



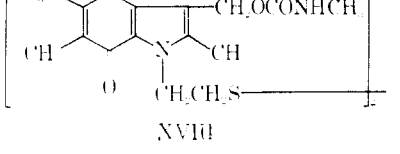
methoxyquinone carbamate (XIV, X = OMs), and then to effect the desired displacements on this latter substance. Thus, reduction of XI with iron in acetic acid gave the corresponding aminoaldehyde XII, which on oxidation with potassium nitrosodisulfonate[9] afforded the *p*-quinone-3-aldehyde XVIa. However, sodium borohydride reduction of this quinonealdehyde followed by regeneration of the quinone system with acidic ferric chloride failed to give the corresponding quinonecarbinol. Preliminary efforts to effect displacement of methanesulfonate in quinonealdehyde XVIa by acetate were unrewarding, no reaction occurring in boiling methanol (16 hr) and only the formation of an intractable oil being noted in dimethylformamide at steam-bath temperature. Thus, the nitroaldehyde XI and the aminoaldehyde XII represented the intermediates, nearest to the final analogs, with which we could effect the desired displacements.

Treatment of nitroaldehyde mesylate XI with potassium fluoride and sodium acetate gave the corresponding 1-(β-substituted ethyl)aldehydes XIIIa and XIIIc, respectively. Reduction of the nitro group in the 1-β-fluoroethyl XIIIa and 1-β-acetoxyethyl XIIIc derivatives was accomplished with iron in acetic acid to give the 4-amino derivatives XVIIa and XVIId, respectively. However, when this reduction procedure was applied to the 1-β-azidoethyl-4-nitroaldehyde XIIIb, obtained by reaction of sodium azide with XII, concomitant acetolysis of the azido group occurred, and the 1-β-acetoxyethyl-4-aminoaldehyde XVIId was obtained in 54% yield. Saponification of XVIId to the 1-β-hydroxyethylaldehyde XVIIe was accomplished with potassium carbonate in aqueous methanol. Other 1-(β-substituted ethyl)aminoaldehydes were obtained by displacements on the aminoaldehyde mesylate XII with appropriate reagents, thus, the preparation of the 1-β-chloroethyl, 1-β-azidoethyl, 1-β-thiocyanoethyl, and 1-β-methylthioethyl derivatives (XVIIb, c, f, and g).

(9) H. Teuber and M. Rasselbach, *Ber.*, **92**, 671 (1959).

The various 1-(β-substituted ethyl)-4-aminoaldehydes XVII were then converted into the corresponding 5-methoxy-4,7-indoloquinone-3-aldehydes by oxidation with Fremy's salt;[9] these products are listed in Table I. We would note the general excellence of these oxidations, which proceeded in yields superior to those observed in the parallel preparation of a series of 1,2,6-trialkyl-4,7-indoloquinone-3-aldehydes.[7]

Elaboration of the hydroxymethylcarbamate ester side chain from the quinonealdehydes was achieved by sodium borohydride reduction of the latter compounds and regeneration of the quinone system with acidic ferric chloride. For the preparation of the 1-β-hydroxyethyl member of this series, the precursor aldehyde XVIe was blocked as the tetrahydropyranyl ether XVIf prior to reduction. Most of the quinonecarbinols were obtained as oils which were used without purification. These materials were then converted into the desired N-methylcarbamate[10] analogs by treatment with methyl isocyanate (Table II). It should be noted that, in the reduction of the 1-β-thiocyanoethyl derivative XVIg, at least partial cleavage of the S-CN bond occurred,[11] and none of the desired thiocyano derivative was obtained. Inasmuch as this reduction product was treated with ferric chloride for the regeneration of the quinone system, the final product was the disulfide analog XVIII (poor yield). Acid



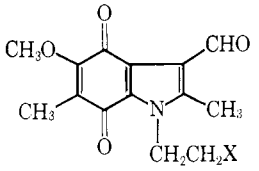
XVIII

(10) As a result of earlier work,[7] it was known that the methylcarbamates had an order of activity equivalent to the unsubstituted carbamate I.

(11) The hydrogenolysis of the S-CN bond with LiAlH4 is well known [N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p 883]; recently R. K. Olsen and H. R. Snyder [*J. Org. Chem.*, **30**, 184 (1965)] have also noted this transformation with NaBH4.

TABLE I

1-(β-SUBSTITUTED ETHYL)-5-METHOXY-2,6-DIMETHYL-4,7-DIOXO-3-INDOLECARBOXALDEHYDES

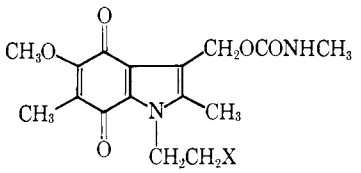


Compd	X	Yield,[a] %	Recrystn solvent	Mp, °C[b]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Solfor/Halogen, % Calcd	Solfor/Halogen, % Found
XVIa	SO_3CH_3	71	Me_2CO–petr ether	143–144	$C_{15}H_{17}NO_7S$	50.71	51.07	4.82	5.18	3.94	4.09	9.03	8.90
XVIb	F	49	Me_2CO–petr ether	114–117	$C_{14}H_{14}FNO_4$	60.21	60.04	5.06	5.37	5.02	5.43	6.81	6.96
XVIc	Cl	58	CH_2Cl_2–petr ether	113–114	$C_{14}H_{14}ClNO_4$	56.86	56.79	4.77	5.14	4.74	4.81	11.99	11.91
XVId	N_3	69	CH_2Cl_2–petr ether	78–79	$C_{14}H_{14}N_4O_4$	55.62	55.94	4.67	4.88	18.54	18.71		
XVIe	OH	76	CH_2Cl_2–petr ether	129–131	$C_{14}H_{15}NO_5$	60.64	60.39	5.45	5.31	5.05	5.46		
XVIg	SCN	30	CH_2Cl_2–petr ether	137–138	$C_{15}H_{14}N_2O_4S$	56.60	56.28	4.43	4.83	8.80	8.75	10.07	9.75
XVIh	SCH_3	58	CH_2Cl_2–petr ether	85–86	$C_{15}H_{17}NO_4S$	58.63	58.71	5.58	5.80	4.56	4.71	10.43	10.25

[a] Represents yield of material with sufficient purity for further transformations. [b] These products had λ_{max} 213–218, 240–248, 268–271, 280–282 (sh), 330–339, 430–435 mμ (ε 19,200–24,800, 11,800–13,100, 11,900–13,500, 11,100–12,100, 4280–5180, 890–1060); λ 3.51–3.52, 5.94–6.00, 6.02–6.04, 6.09–6.14, 6.18–6.25, 6.51–6.53, 6.60–6.64, 9.03–9.06 μ; pmr, 115.5–118 (3s, 6-CH_3), 156.5–160 (3s, 2-CH_3), 237–240 (3s, OCH_3), 615–631 cps (C*H*O), in addition to the expected NCH_2CH_2X resonances.

TABLE II

1-(β-SUBSTITUTED ETHYL)-3-HYDROXYMETHYL-5-METHOXY-2,6-DIMETHYLINDOLE-4,7-DIONE METHYLCARBAMATES



Compd	X	Yield,[a] %	Recrystn solvent	Mp, °C[b]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Solfor/Halogen, % Calcd	Solfor/Halogen, % Found
XIVa	F	62	CH_2Cl_2–petr ether	162–163	$C_{16}H_{19}FN_2O_5$	56.79	56.53	5.66	5.69	8.28	8.11	5.62	5.81
XIVb	Cl	49[c]	CH_2Cl_2–petr ether	157.5–159.5[d]	$C_{16}H_{19}ClN_2O_5$	54.16	54.25	5.39	5.92	7.89	7.29	10.00	10.64
XIVc	N_3	46[c]	CH_2Cl_2–petr ether	139–140	$C_{16}H_{19}N_5O_5$	53.18	53.30	5.30	5.45	19.38	19.28		
XIVd	OThp	27[e]	CH_2Cl_2–petr ether	133.5–135.0[f]	$C_{21}H_{28}N_2O_7$	59.99	60.14	6.71	6.78	6.66	6.40		
XIVe	OH	27	CH_2Cl_2–petr ether	153–154	$C_{16}H_{20}N_2O_6$	57.13	56.90	5.99	6.24	8.33	8.32		
XIVf	SCH_3	60	CH_2Cl_2–petr ether	151–152	$C_{17}H_{22}N_2O_5S$	55.73	55.58	6.05	6.10	7.65	7.47	8.72	8.76
XIVg	$^+S(CH_3)_2I^-$	71	Methanol-ether	128.0–129.5[g] dec	$C_{18}H_{25}IN_2O_5S$	42.52	42.63	4.96	5.58	5.51	5.29	6.31 24.97	7.07 24.00
XVIII	SS	5[h]	Me_2CO-hexane	112–115[i]	$C_{32}H_{38}N_4O_{10}S_2$[j]	54.69	54.64	5.45	5.77	7.97	7.60	9.12	8.87

[a] Represents yield of material with analytical melting point. [b] Compounds XIVa–f had λ_{max} 230–231, 284–286, 341–346, 450–455 mμ (ε 17,000–18,900, 14,200–15,100, 3300–3740, 1210–1240); λ 2.98–3.05, 5.90–5.95, 6.00–6.04, 6.08–6.12, 6.20–6.25, 6.48–6.51, 6.60–6.63, 7.90–8.02, 8.95–9.06 μ; pmr,[13] 111–116 (3s, 6-CH_3), 137–143 (3s, 2-CH_3), 154–166 (3d, J = 4.5 cps NHCH_3), 234–241 (3s, OCH_3), 305–315 (2s, CH_2O), 410–415 cps (1, broad, N*H*CH$_3$). [c] Yield based on the corresponding quinone-3-aldehyde XVI, the previous crystalline intermediate. [d] Purified by partition chromatography using a heptane–ethyl acetate–methanol–water (85:15:17:4) system; hold-back volume 4.1 (V_m/V_s = 3.0). [e] Yield based on XVIe, the last previous crystalline intermediate. [f] Purified by partition chromatography using a heptane–methanol solvent system; hold-back volume 2.7 (V_m/V_s = 2.82). [g] λ_{max} 222, 287, 340, 450 mμ (ε 34,600, 16,800, 3300, 1270). [h] Yield based on XVIg, the last crystalline intermediate. [i] Purified by partition chromatography using a heptane–ethyl acetate–methanol–water (70:30:17:4) system; hold-back volume 6.4 (V_m/V_s = 2.54); λ_{max} 232, 286, 345, 455 (ε 33,800, 28,200, 6820, 2390). [j] *Anal.* Calcd: mol wt, 703. Found: mol wt, 767.

hydrolysis of the tetrahydropyranyl ether carbamate XIVd afforded the 1-β-hydroxyethyl derivative XIVe, and reaction of the thioether carbamate XIVf with methyl iodide gave the sulfonium analog XIVg.

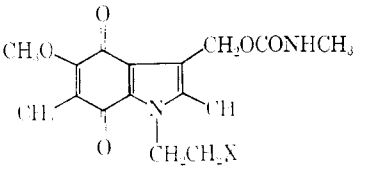
Biology.—The *in vitro* antibacterial activity of the various analogs XIVa–f is given in Table III. All compounds approach the lead indoloquinone I in effectiveness, but no distinct advantage is observed for any.

Experimental Section

Melting points were determined in open capillary tubes and are corrected. Ultraviolet spectra were determined in methanol solution using a Cary recording spectrophotometer, and the infrared spectra were determined in KBr disks with a Perkin-Elmer Model 21 spectrophotometer. The pmr spectra were measured with a Varian A-60 spectrometer using tetramethylsilane as an internal standard; in the description of these spectra, the signals are expressed as xs (singlet), xd (doublet), xt (triplet), xq (quartet), or xm (multiplet), where x is the number of protons indicated by integration. The petroleum ether used was that

TABLE III

In Vitro ANTIBACTERIAL ACTIVITY OF THE 1-(β-SUBSTITUTED ETHYL)-5-HYDROXYMETHYL-5-METHOXY-2,6-DIMETHYLINDOLE-4,7-DIONE METHYLCARBAMATES



Organism	I, X = H[b]	XIVa, X = F	XIVb, X = Cl	XIVc, X = N₃	XIVd, X = OThp	XIVe, X = OH	XIVf, X = SCH₃
	Minimum inhibitory conc (μg/ml)[a] for—						
Mycobacterium smegmatis, ATCC 607	6.25	6.25	6.25	6.25	6.25	25	3.12
Staphylococcus aureus, ATCC 6538P	1.56	3.12	6.25	12.5	12.5	3.12	6.25
Staphylococcus aureus, var. Rose	1.56	3.12	12.5	6.25	25	3.12	6.25
Sarcina lutea, ATCC 9341	6.25	6.25	12.5	12.5	25	6.25	6.25
Streptococcus faecalis, ATCC 8043	12.5	50				12.5	
Streptococcus pyogenes, C203	0.78	0.39	1.56	0.78	3.12	0.78	0.78
Streptococcus sp., β-hemolytic, 80	3.12	12.5	6.25	25	25	6.25	12.5
Streptococcus sp., nonhemolytic, 11	3.12	6.25	25	25	25	6.25	12.5
Bacillus subtilis, ATCC 6633	1.56	0.78	0.78	6.25	3.12	1.56	1.56
Corynebacterium xerose, NIRL B1397	6.25	12.5	25	25	25	6.25	12.5
Bacillus cereus, ATCC 10702	0.39	0.39	0.78	0.78	3.12	0.78	0.39
Pasteurella multocida ATCC 310	6.25	0.78	1.56	1.56	6.25	0.78	3.12

[a] Highest test level: 50 μg/ml. All data are from concurrent assays. [b] Data for unsubstituted carbamate ester.

fraction boiling at 30–60°. All evaporations were carried out at reduced pressure. Nitrogen analyses were determined by the Dumas technique using a combustion temperature of 950° for 10 min.

Ethyl 5-Hydroxy-1-hydroxyethyl-2,6-dimethyl-3-indolecarboxylate (II).—2-Aminoethanol (46.7 g, 0.75 mole) was added dropwise to 98.5 g (0.746 mole, 100 ml) of ethyl aceloacetate with stirring at such a rate that the reaction temperature remained at 40–45°; 90 min was required for the addition. The resulting solution was then stirred at 35–45° for 3 hr. Volatile material was removed by heating the reaction solution slightly at water-pump pressure; this gave 128.1 g (100%) of crude **ethyl β-(2-hydroxyethylamino)crotonate.** In an earlier experiment an attempted distillation of this material at water-pump pressure caused decomposition.

The crotonate was treated with a solution of 90.5 g (0.74 mole) of tolnquinone in 500 ml of acetone. An exothermic reaction which caused boiling for 30 min ensued. The resulting dark solution was heated on the steam bath for 90 min and then concentrated by distillation, 300 ml of distillate being collected. The concentrate was chilled in an ice bath and filtered to give 33.1 g (15%) of gray solid, mp 190–193°. This material was used for further transformations.

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.09; H, 7.04; N, 5.09.

A 1.000 g-aliquot of this material was purified by partition chromatography on Celite (diatomaceous silica) using a heptane–ethyl acetate–methanol–water (60:40:15:6) system.[12] The fraction with peak hold-back volume 2.4 (V_m/V_s = 3.0) was evaporated, and the residue was recrystallized from acetone–hexane to give 790 mg of pure ester as white crystals: mp 195–196°; λ_{max} 218, 244, 291–300 mμ (ε 34,900, 15,800, 13,300); λ 2.97, 3.08, 6.04, 6.13, 8.41, 8.69, 8.88 μ; pmr,[13] 83 (3t, J = 7 cps, CH_3CH_2), 139 (3s, 6-CH_3), 163 (3s, 2-CH_3), 224 (ill-defined m, CH_2OH), 249 (t, J = 5.5 cps, NCH_2), 259 (q, J = 7 cps, OCH_2CH_3), 296 (1t, J = 5 cps, CH_2OH), 431 (1s, 7-H), 452 (1s, 4-H), 535 cps (1s, aryl OH).

Anal. Found: C, 64.89; H, 6.79; N, 5.10.

The fraction with peak hold-back volume 3.4 was evaporated, and the residue was recrystallized from acetone–hexane to give 78 mg of **ethyl 5-hydroxy-1-hydroxyethyl-2,7-dimethyl-3-indolecarboxylate (III)** as white crystals: mp 155–157°; λ_{max} 220, 243, 291 mμ (ε 30,200, 16,200, 10,800); λ 3.00, 6.04, 6.21, 8.55, 8.86, 9.10 μ; pmr,[13] 81 (3t, J = 7 cps, CH_3CH_2), 154 (3s, 7-CH_3), 161 (3s, 2-CH_3), 220 (3t, J = 5.5 cps, CH_2OH), 255 (4m, CH_2CH_3, NCH_2), 297 (1t, J = 5.5 cps, CH_2OH), 385 (1d, J = 2.5 cps, 6-H), 439 (1d, J = 2.5 cps, 4-H), 522 cps (1s, aryl OH).

Anal. Found: C, 65.29; H, 7.18; N, 5.06.

Ethyl 1-Hydroxyethyl-5-methoxy-2,6-dimethyl-3-indolecarboxylate (IV).—To a stirred solution of 2.91 g (10.5 mmoles) of II in 20 ml of ethanol and 35 ml of 2 *N* NaOH solution was added dropwise at reflux temperature 6.0 g (48 mmoles, 4.45 ml) of of methyl sulfate. The solution was heated at reflux temperature for 90 min after completion of the addition. The cooled solution was distributed between CH_2Cl_2 and water; the organic phase was washed with saline, dried, and evaporated. The residue was recrystallized from CH_2Cl_2–petroleum ether and then from acetone–hexane to give 1.44 g (47%) of white needles, mp 120–122°. An additional recrystallization from the latter solvent pair gave white needles: mp 127–129°; λ_{max} 218, 243, 295 mμ (ε 36,700, 18,700, 12,800); λ 2.93, 5.95, 6.00, 8.30, 8.45, 8.88 μ; pmr,[13] 81.5 (3t, J = 7 cps, CH_3CH_2), 136 (3s, 6-CH_3), 161 (3s, 6-CH_3), 161 (3s, 2-CH_3), 224 (obscured, CH_2OH), 229 (3s, OCH_3), 249 (obscured, NCH_2), 256 (q, OCH_2CH_3), 295 (1t, J = 5 cps, CH_2OH), 434 (1s, 7-H), 449 cps (1s, 4-H).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.89; H, 7.13; N, 4.87.

Ethyl 1-Hydroxyethyl-5-methoxy-2,6-dimethyl-3-indolecarboxylate Methanesulfonate (V).—A solution of 434 mg (1.48 mmoles) of IV in 5 ml of pyridine was treated with 0.2 ml of methanesulfonyl chloride and allowed to stand at 5° for 21 hr. The solution was diluted with water to give 515 mg (94%) of white needles, mp 134–137°. One recrystallization from acetone–hexane gave white crystals: mp 143–144°; λ_{max} 218, 242, 288–293 mμ (ε 38,000, 19,200, 13,600); λ 5.95, 7.40, 7.48, 8.33, 8.50, 8.80, 9.12 μ.

Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.28; H, 6.28; N, 3.79; S, 8.68. Found: C, 55.65; H, 6.28; N, 3.92; S, 8.32.

Ethyl 1-Azidoethyl-5-methoxy-2,6-dimethyl-3-indolecarboxylate (VI).—A mixture of 312 mg (0.85 mmole) of V and 350 mg of NaN_3 in 25 ml of DMF was heated on the steam bath for 15 hr. Sufficient water to increase the volume to 100 ml was added and the solid was collected to give 247 mg (92%) of white needles, mp 122–124°. One recrystallization from acetone–hexane gave white needles: mp 121–122°; λ_{max} 216, 240, 288 mμ (ε 35,400, 18,350, 12,500); λ 4.70, 4.76, 4.86, 5.94, 8.89, 9.21 μ; pmr,[14] 85 (3t, J = 7.5 cps, CH_3CH_2), 140 (3s, 6-CH_3), 161 (3s, 2-CH_3), 214 (2t, J = 7 cps, CH_2N_3), 233 (3s, OCH_3), 244 (2t, J = 7 cps, NCH_2), 263.5 (2q, J = 7.5 cps, OCH_2CH_3), 418 (1s, 7-H), 456 cps (1s, 4-H).

Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.74; H, 6.37; N, 17.71. Found: C, 60.42; H, 6.41; N, 17.76.

[12] For a complete description of this technique as developed by C. Pidacks see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Cosria, *Tetrahedron*, **20**, 357 (1964).

[13] Determined in DMSO-d_6 solution.

[14] Determined in $CDCl_3$ solution.

5-Hydroxy-1-hydroxyethyl-2,6-dimethylindole (VII).—A solution of 183.1 g (0.66 mole) of II in 2000 ml of 2 *N* NaOH solution was heated at reflux temperature under nitrogen with stirring for 2 hr. The cooled solution was made acid to litmus with HCl. The moist precipitated solid, which had mp 155–159° (gas) and λ_{max} 3.00, 3.80, 4.20, 6.08 μ, was suspended in 1500 ml of methanol. This solution was warmed on the steam bath. Before the solution reached boiling, copious evolution of gas bubbles was noted. Once boiling temperature was attained all solid had dissolved; this solution was heated at its boiling point for 1 hr and then concentrated to 700 ml. Water (1300 ml) was added, and the solution was chilled overnight. Filtration gave 108.7 g (81%) of crystals, mp 118–120°. A sample was obtained from acetone–hexane as white needles: mp 121–123°; λ_{max} 208, 278, 294, 308 mμ (ϵ 26,300, 8840, 6980, 4930); λ 2.98 μ; pmr,[13] 135 (3s, 2-CH_3), 140 (3s, 6-CH_3), 220 (2m, CH_2OH), 241 (2t, J = 5 cps), 287 (1t, J = 5 cps, CH$_2$OH), 355 (1s, 3-H), 408 (1s, 4-H), 419 cps (1s, 7-H).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; Found: C, 70.57; H, 7.58; N, 6.83.

1-(β-Hydroxyethyl)-5-methoxy-2,6-dimethylindole (VIII).—Methyl sulfate (204 g, 1.63 moles, 155 ml) was added dropwise under nitrogen over 4.5 hr to a stirred, boiling solution of 100 g (0.49 mole) of VII in 1.25 l. of 2 *N* NaOH. Heating was continued for 0.5 hr after completion of the addition. The crude product was isolated with ethyl acetate and adsorbed from CH_2Cl_2 onto a Florisil (magnesia–silica gel) column. The column was washed with CH_2Cl_2; evaporation of the initial 1 l. of elute gave 98.5 g (92%) of a pale yellow oil that crystallized on standing. This material was of sufficient purity for further use. A sample was recrystallized from CH_2Cl_2–petroleum ether to give white crystals: mp 78–80°; λ_{max} 210, 278, 294, 308 mμ (ϵ 28,000, 9100, 7480, 4820); λ 3.05 μ; pmr,[14] 135 (3s), 138 (3s, 2-CH_3 and 6-CH_3), 214 (m, CH_2OH), 226 (3s, OCH_3), 230 (m, NCH_2), 359 (1s, 3-H), 408 (1s, 4-H), 413 cps (1s, 7-H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.87; H, 8.00; N, 6.33.

1-(β-Hydroxyethyl)-5-methoxy-2,6-dimethylindole Methanesulfonate (IX).—With ice cooling, 69.0 g (0.6 mole) of methanesulfonyl chloride was added dropwise over 1 hr to a stirred solution of 92.0 g (0.42 mole) of VIII in 400 ml of pyridine. A solid separated during the addition; this mixture was stored at 0–5° for 16 hr, whereafter it was poured with stirring onto cracked ice. The amorphous material was extracted into CH_2Cl_2, and this solution was washed with saline and evaporated. The residual solution, pyridine being present, was diluted with methanol to give 77.0 g of pale yellow crystals, mp 112–113° dec. The filtrate was evaporated, and the pyridine was azeotropically distilled with toluene. Chromatography on Florisil gave starting material which was recycled to give an additional 17.7 g (76% total) of crystals, mp 110–113° dec.

Material from a similar experiment was recrystallized from CH_2Cl_2–petroleum ether to give white crystals: mp 118–120° dec; λ_{max} 210, 276, 295, 306 mμ (ϵ 29,300, 9380, 6850, 4760); λ 7.45, 8.55 μ; pmr,[14] 140 (6s), 146 (3s, CH_3SO$_2$, 2-CH_3, and 6-CH_3), 228 (3s, OCH_3), 254, 256 (4t, $J \simeq 5$ cps, NCH_2CH_2OMs), 368 (1s, 3-H), 414.5 (1s, 4-H), 419 cps (1s, 7-H).

Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.56; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.66; H, 6.79; N, 5.06; S, 10.61.

1-(β-Hydroxyethyl)-5-methoxy-2,6-dimethyl-3-indolecarboxaldehyde Methanesulfonate (X).—With ice cooling, 21.8 g (0.143 mole, 13.0 ml) of $POCl_3$ was added dropwise with stirring to 75 ml of DMF at such a rate that the temperature remained at 0–5°. A solution of 42.2 g (0.142 mole) of IX in 225 ml of DMF was then added at 5° or less; this addition required approximately 3 hr. The resulting dark solution was then stirred at room temperature for 1 hr. With ice cooling, a solution of 50 g of Na_2CO_3 in 500 ml of water was added dropwise until approximately one-half of the solution was added, the remainder being added rapidly. Water (500 ml) was added, and the mixture was stirred at room temperature for 1 hr and filtered to give 38.9 g (84%) of solid, mp 185–187° dec, of sufficient purity for further transformations.

Material from a similar experiment was recrystallized from acetone and then from methanol to give white needles: mp 187.5–189° dec; λ_{max} 214, 254, 282, 305 mμ (ϵ 30,700, 19,200, 15,600, 13,800); λ 3.55, 3.67, 6.08, 7.40, 8.50 μ; pmr (80°),[13] 140 (3s, 6-CH_3), 164 (3s, 2-CH_3), 181 (3s CH_3SO$_2$), 232 (3s, OCH_3), 273 (4s, NCH_2CH_2OSO$_2$), 441 (1 s, 7-H), 459 (1s, 4-H), 504 cps (1s, CHO).

Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.38; H, 5.89; N, 4.15; S, 9.84. Found: C, 55.38; H, 5.93; N, 4.22; S, 9.85.

1-(β-Hydroxyethyl)-5-methoxy-2,6-dimethyl-4-nitro-3-indolecarboxaldehyde Methanesulfonate (XI).—Yellow fuming nitric acid (34 ml) was added dropwise to a stirred mixture of 34.1 g (0.105 mole) of X in 500 ml of glacial acetic acid; the reaction temperature was maintained at 16–20° by ice cooling as it was required. Stirring was continued for 30 min at room temperature after completion of the addition; the reaction was never free of undissolved solid. The mixture was filtered, and the solid was washed with water. The combined filtrate and washings were extracted with CH_2Cl_2, and the organic solution was evaporated. All material was combined and recrystallized from acetone–petroleum ether (bp 60–70°) to give 23.6 g of crystals, mp 181.5–183.0° dec. Concentration of the mother liquor gave an additional 4.00 g (71% total), mp 175–177°.

Material from a similar experiment was recrystallized from acetone–hexane to give crystals: mp 182.5–184.0° dec; λ_{max} 214, 243, 290 mμ (ϵ 32,900, 15,500, 12,300); λ 3.52, 6.04, 6.51, 7.42, 8.54 μ; pmr,[13] 147 (3s, 6-CH_3), 165 (3s, 2-CH_3), 190 (3s, CH_3SO$_3$), 230 (3s, OCH_3), 278 (4s, broad, NCH_2CH_2OSO$_2$), 465 (1s, 7-H), 515 cps (1s, CHO).

Anal. Calcd for $C_{15}H_{18}N_2S$: C, 48.65; H, 4.90; N, 7.57; S, 8.64. Found: C, 48.80; H, 4.85; N, 7.91; S, 8.61.

1-(β-Fluoroethyl)-5-methoxy-2,6-dimethyl-4-nitro-3-indolecarboxaldehyde (XIIIa).—A mixture of 5.00 g (13.5 mmoles) of XI and 5.00 g of KF·2H$_2$O in 160 ml of methanol was heated in a stainless steel bomb at 150° for 18 hr. The contents of the bomb were distributed between CH_2Cl_2 and water. The material in the organic phase was recrystallized from acetone–petroleum ether (bp 60–70°) to give 2.58 g (65%) of yellow crystals, mp 175–178°. Material from a similar experiment was obtained from acetone–hexane as yellow crystals: mp 183.0–184.5°; λ_{max} 214, 246, 290 mμ (ϵ 31,500, 14,500, 11,600); λ 3.67, 6.03, 6.51 μ; pmr,[13] 147 (3s, 6-CH_3), 165 (3s, 6-CH_3), 230 (3s, OCH_3), 265 (2s, low-order coupling with CH_2F), 302 (2, pair of triplets, J_{H-F} = 20 cps, J_{H-H} = 5 cps, CH_2F), 465 (1s, 7-H), 595 cps (1s, CHO).

Anal. Calcd for $C_{14}H_{15}FN_2O_4$: C, 57.14; H, 5.14; F, 6.45; N, 9.52. Found: C, 57.30; H, 5.21; F, 6.24; N, 9.79.

1-(β-Azidoethyl)-5-methoxy-2,6-dimethyl-4-nitro-3-indolecarboxaldehyde (XIIIb).—A mixture of 370 mg (1.0 mmole) of XI and 350 mg of NaN_3 in 25 ml of DMF was heated on the steam bath for 18 hr. The solution was diluted with water, cooled, and filtered to give 262 mg (83%) of crystals, mp 133–135°. Recrystallization from acetone–petroleum ether (bp 60–70°) gave crystals: mp 136–137°; λ_{max} 218, 246, 293 mμ (ϵ 30,800, 14,600, 11,700); λ 3.52, 4.68, 4.76, 6.04, 6.50 μ; pmr,[13] 146 (3s, 6-CH_3), 165 (3s, 2-CH_3), 229 (overlapping signals, OCH_3, CH_3, CH_2N$_3$), 266 (2t, J = 7.5 cps, NCH_2), 464 (1s, 7-H), 595 cps (1s, CHO).

Anal. Calcd for $C_{14}H_{15}N_5O_4$: C, 52.99; H, 4.77; N, 22.07. Found: C, 52.81; H, 4.92; N, 22.19.

1-(β-Hydroxyethyl)-5-methoxy-2,6-dimethyl-4-nitro-3-indolecarboxaldehyde Acetate (XIIIc).—A mixture of 5.00 g (13.5 mmoles) of XI and 10.0 g of sodium acetate in 150 ml of DMF was heated on the steam bath for 15.5 hr. The solution was diluted with water and filtered to give 4.03 g (89%) of crystals, mp 172–176°. Material from a similar experiment was recrystallized from acetone–petroleum ether (bp 60–70°) to give crystals: mp 179–180°; λ_{max} 217, 248, 295 mμ (ϵ 42,500, 19,100, 15,400); λ 3.54, 3.65, 5.78, 6.00, 6.51, 8.00 μ.

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.09; H, 5.52; N, 8.57.

5-Methoxy-2,6-dimethyl-4-nitro-1-(β-thiocyanoethyl)-3-indolecarboxaldehyde (XIIId).—A solution of 200 mg of 1-(β-hydroxyethyl)-5-methoxy-2,6-dimethyl-4-nitro-3-indolecarboxaldehyde methanesulfonate (XI) and 200 mg of potassium thiocyanate in 5 ml of DMF was heated on the steam bath for 20 hr. The product, obtained by precipitation with water, was recrystallized from acetone–petroleum ether (bp 60–70°) to give 114 mg (63%) of crystals: mp 185–187°; λ_{max} 218, 246, 292 mμ (ϵ 31,600, 15,500, 12,300); λ 3.52, 3.65, 4.65, 6.04, 6.51 μ.

Anal. Calcd for $C_{15}H_{15}N_3O_4S$: C, 54.05; H, 4.54; N, 12.61; S, 9.60. Found: C, 54.14; H, 4.86; N, 12.56; S, 9.38.

4-Amino-1-(β-hydroxyethyl)-5-methoxy-2,6-dimethyl-3-indolecarboxaldehyde Methanesulfonate (XII).—A stirred solution of 15.00 g (40.5 mmoles) XI in 450 ml of glacial acetic acid and 45 ml of water was heated to steam-bath temperature, and 20.0 g of iron filings were added in 13 approximately equal portions over

2 hr. An additional 45 ml of water was added after 45 min, and the reaction was heated 30 min after the last addition of iron filings. The mixture was diluted with water and extracted with CH_2Cl_2. The washed and dried organic solution was evaporated, and the residue was recrystallized from CH_2Cl_2–petroleum ether to give 9.55 g (69%) of tan crystals, mp 133–135°. Material from a similar experiment was obtained as tan crystals: mp 134.5–136.0°; λ_{max} 228, 250, 280, 345 mμ (ε 30,600, 15,700, 9200, 4760); λ 3.55, 6.14, 6.25, 7.45, 8.51 μ; pmr,[13] 136 (3s, 6-CH_3), 157 (3s, 2-CH_3), 183 (3s, CH_3SO_3), 218 (3s, OCH_3), 266 (4s, $NCH_2CH_2OSO_2$), 366 (2, broad, NH_2), 390 (1s, 7-H), 584 cps (1s, CHO).

Anal. Calcd for $C_{15}H_{20}N_2O_5S$: C, 52.93; H, 5.92; N, 8.23; S, 9.42. Found: C, 52.87; H, 5.84; N, 8.53; S, 9.13.

4-Amino-1-(β-fluoroethyl)-5-methoxy-2,6-dimethyl-3-indolecarboxaldehyde (XVIIa).—Compound XIIIa (2.065 g, 7.05 mmoles) was reduced with iron filings (2.67 g) in acetic acid as as described above. Recrystallization of the crude product from CH_2Cl_2–petroleum ether gave 1.716 g (92%) of crystals, mp 134–139°. An additional recrystallization gave crystals: mp 139–141°; λ_{max} 224, 251, 279, 345 mμ (ε 27,200, 15,100, 9250, 4480); λ 2.94, 3.05, 3.55, 6.13, 6.28 μ; pmr,[13] 138 (3s, 6-CH_3), 145 (3s, 2-CH_3), 222 (3s, OCH_3), 230–260 (3m), 298 (1, apparent triplet), 353 (2, broad, NH_2), 370 (1s, 7-H), 577 cps (1s, CHO).

Anal. Calcd for $C_{14}H_{17}FN_2O_2$: C, 63.62; H, 6.49; F, 7.16; N, 10.60. Found: C, 63.70; H, 6.65; F, 6.99; N, 10.40.

4-Amino-1-(β-hydroxyethyl)-5-methoxy-2,6-dimethyl-3-indolecarboxaldehyde Acetate (XVIId). A.—In the manner described above XIIIc (4.03 g, 12 mmoles) was reduced with iron filings (6.0 g) in acetic acid. Recrystallization of the crude product from CH_2Cl_2–petroleum ether gave 2.48 g (68%) of tan crystals, mp 172–176°. Two additional recrystallizations from the same solvents gave crystals: mp 178–180°; λ_{max} 228, 253, 280, 347 mμ (ε 27,900, 14,750, 8700, 4730); λ 2.90, 3.05, 3.55, 5.74, 6.12, 6.23 μ; pmr,[13] 116 (3s, CH_3COO), 136 (3s, 6-CH_3), 159 (3s, 2-CH_3), 218.5 (3s, OCH_3), 260 (4s, NCH_2CH_2OAc), 367 (2 broad, NH_2), 391 (1s, 7-H), 586 (1s, CHO).

Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 62.47; H, 6.32; N, 9.02.

B.—Reduction of XIIIb (500 mg, 1.58 mmoles) with 667 mg of iron filings in 50 ml of glacial acetic acid gave 260 mg (54%) of the acetate ester as tan crystals, mp 175–179°; the infrared spectrum of this material had a weak band at 4.75 μ indicating contamination by the corresponding 1-(β-azidoethyl) derivative.

4-Amino-1-(β-azidoethyl)-5-methoxy-2,6-dimethyl-3-indolecarboxaldehyde (XVIIc).—A solution of 1.522 g (4.48 mmoles) of XII and 1.50 g of NaN_3 in 45 ml of DMF was heated on the steam bath for 16 hr. The resulting solution was poured into 500 ml of water, and the resulting turbid solution was chilled for 4 hr to give 794 mg (62%) of crystals, mp 117–120°. Material from a similar experiment was recrystallized from CH_2Cl_2–petroleum ether to give tan crystals: mp 123–124°; λ_{max} 226, 252, 280, 348 mμ (ε 34,800, 18,100, 10,300, 5160); λ 2.92, 3.05, 3.55, 4.73, 6.12, 6.23 μ; pmr,[13] 137 (3s, 6-CH_3), 148 (3s, 2-CH_3), 219 (2, partially hidden, CH_2N_3), 222 (3s, OCH_3), 240 (2t, J = 5 cps, NCH_2), 352 (2, broad, NH_2), 372 (1s, 7-H), 581 cps (1s, CHO).

Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.33; H, 5.96; N, 24.33.

4-Amino-1-(β-hydroxyethyl)-5-methoxy-2,6-dimethyl-3-indolecarboxaldehyde (XVIIe).—A solution of 2.466 g (8.12 mmoles) of XVIId in 100 ml of methanol was treated with 6 ml of 10% K_2CO_3 and stirred at room temperature under nitrogen for 1 hr. Glacial acetic acid (0.45 ml) was added and approximately one-half the solvent was removed. Water (200 ml) was added, and after 16 hr filtration gave 1.668 g (79%) of tan needles, mp 157–159°. A sample was recrystallized twice from CH_2Cl_2 to give needles: mp 160–161°; λ_{max} 228, 254, 280, 348 mμ (ε 30,200, 16,200, 9600, 5390); λ 2.93, 3.04, 3.55, 6.28 μ; pmr,[13] 138 (3s, 6-CH_3), 159 (3s, 2-CH_3), 220 (3s, OCH_3), 226 (2m, CH_2OH), 246 (2t, J = 5 cps, NCH_2), 297 (1t, J = 5 cps, CH_2OH), 368 (broad NH_2), 389 (1s, 7-H), 584.5 cps (1s, CHO).

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.47; H, 7.13; N, 10.50.

4-Amino-5-methoxy-2,6-dimethyl-1-(β-thiocyanoethyl)-3-indolecarboxaldehyde (XVIIf). A solution of 500 mg (1.47 mmoles) of XII and 500 mg of potassium thiocyanate in 10 ml of DMF was heated on the steam bath for 15 hr. The resulting gel was poured into 50 ml of water to give 369 mg (78%) of crystals, mp 190–193°. Combustion analysis of this material indicated it to be impure, but it was used for further transformations.

Anal. Calcd for $C_{15}H_{17}N_3O_2S$: C, 59.34; H, 5.65; N, 13.86; S, 10.57. Found: C, 58.52; H, 5.63; N, 12.95; S, 10.16.

4-Amino-1-(β-chloroethyl)-5-methoxy-2,6-dimethyl-3-indolecarboxaldehyde (XVIIb).—A mixture of 2.000 g (5.90 mmoles) of XII and 1.224 g of LiCl in 40 ml of DMF was heated on the steam bath for 17 hr. Precipitation with water gave 1.186 g (71%) of tan solid, mp 120–122°. A sample was recrystallized from CH_2Cl_2–petroleum ether to give tan crystals: mp 125.0–126.5°; λ_{max} 228, 250, 280, 345 mμ (ε 28,800, 15,800, 9400, 5060); λ 2.91, 3.04, 3.55, 6.12, 6.23 μ; pmr,[13] 140 (3s, 6-CH_3), 153 (3s, 2-CH_3), 224 (overlapping signals, CH_2O, CH_2Cl), 255 (2t, J = 7 cps, NCH_2), 354 (2, broad, NH_2), 374 (1s, 7-H), 585 cps (1s, CHO).

Anal. Calcd for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; Cl, 12.63; N, 9.98. Found: C, 60.41; H, 6.35; Cl, 12.53; N, 10.50.

4-Amino-5-methoxy-2,6-dimethyl-1-(β-methylmercaptoethyl)-3-indolecarboxaldehyde (XVIIg).—A mixture of 1.000 g (2.94 mmoles) of XII and 700 mg of sodium methylmercaptide in 50 ml of acetone was stirred at room temperature for 15 hr. Water was added until the solid dissolved and the acetone was removed. The resulting solid was collected and recrystallized from CH_2Cl_2–petroleum ether to give 567 mg (66%) of yellow crystals, mp 126.5–128.5°. Two additional recrystallizations gave yellow crystals: mp 128.5–130.0°; λ_{max} 218, 245, 268, 350 mμ (ε 28,500, 15,600, 9350, 5120); λ 2.94, 3.05, 3.55, 6.12, 6.23 μ; pmr,[13] 124 (3s, CH_3S), 141 (3s, 6-CH_3), 154 (3s, 2-CH_3), 169 (2t, J = 7.5 cps, CH_2S), 225 (3s, OCH_3), 245 (2t, J = 7.5 cps, NCH_2), 355 (broad, NH_2), 376 (1s, 7-H), 584 cps (1s, CHO).

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.63; H, 6.90; N, 9.58; S, 10.99. Found: C, 61.27; H, 6.61; N, 9.56; S, 10.85.

1-(β-Substituted ethyl)-5-methoxy-2,6-dimethyl-4,7-dioxo-3-indolecarboxaldehydes. The following preparation of 1-(β-hydroxyethyl)-5-methoxy-2,6-dimethyl-4,7-dioxo-3-indolecarboxaldehyde methanesulfonate (XVIIe) is illustrative of the general procedure. To a stirred solution of 3.41 g (13 mmoles) of potassium nitrosodisulfonate in 60 ml of water and 30 ml of 0.167 *M* KH_2PO_4 was added a solution of 1.000 g (3.24 mmoles) of XVIIe in 90 ml of acetone. The resulting deep red solution was stirred at room temperature for 17 hr, whereafter it was diluted with water and extracted with CH_2Cl_2. The crude product was chromatographed on Florisil; the material eluted by 1250 ml of chloroform–acetone (9:1) was recrystallized from acetone–petroleum ether (bp 60–70°) to give 736 mg of red crystals, mp 141–144°. Further characterization of this substance is given in Table I.

5-Methoxy-2,6-dimethyl-4,7-dioxo-1-[β-(2-tetrahydropyranyloxy)ethyl]-3-indolecarboxaldehyde (XVIf).—To a stirred solution of 1.048 g (3.80 mmoles) of 1-(β-hydroxyethyl)-5-methoxy-2,6-dimethyl-4,7-dioxo-3-indolecarboxaldehyde (XVIe) and 16 mg of *p*-toluenesulfonic acid monohydrate in 25 ml of ethyl acetate was added 0.67 ml of dihydropyran at 50°. The resulting solution was stirred at room temperature for 30 min, whereafter it was washed successively with $NaHCO_3$ solution and saline, dried, and evaporated to give an oil which was utilized without purification.

1-(β-Substituted ethyl)-3-hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-diones.—The following preparation of XVa is illustrative of the general procedure. A stirred solution of 336 mg (1.2 mmoles) of 1-(β-fluoroethyl)-5-methoxy-2,6-dimethyl-4,7-dioxo-3-indolecarboxaldehyde (XVIb) in 100 ml of methanol was swept with nitrogen, heated to reflux temperature, and treated with 400 mg of $NaBH_4$. Heating was discontinued after approximately 2 min, and the resulting pale yellow solution was stirred under nitrogen at room temperature for 1 hr. Acetone (5 ml) was added, and after 5 min 3 ml of a solution of 1 *N* $FeCl_3$ in 0.1 *N* HCl was added. The resulting mixture was distributed between CH_2Cl_2 and water. The aqueous phase was extracted further with CH_2Cl_2, and the combined, dried organic extracts were evaporated. The residue was recrystallized from acetone–hexane to give 263 mg (78%) of **1-(β-fluoroethyl)-3-hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-dione (XVa)** as red crystals, mp 114–116°. Recrystallization from the same solvent pair gave red crystals: mp 116–118°; λ_{max} 230, 286, 345, 460 mμ (ε 18,300, 14,600, 3380, 1380); λ 2.92, 6.05, 6.14, 6.28, 6.62 μ; pmr,[13] 116 (3s, 2-CH_3), 136 (3s, 6-CH_3), 240 (3s, CH_3O), 260 (2, low-order coupling, NCH_2), 276 (2s, CH_2O), 296 cps (2, pair of triplets, J_{H-F} = 20 cps, J_{H-H} = 5 cps).

Anal. Calcd for $C_{13}H_{16}FNO_5$: C, 59.78; H, 5.73; F, 6.75; N, 4.98. Found: C, 59.93; H, 5.97; F, 6.58; N, 5.12.

3-Hydroxymethyl-5-methoxy-1-(β-methylmercaptoethyl)-2,6-dimethylindole-4,7-dione (XVe) was obtained from ether–petroleum ether as red crystals: mp 91–93°; λ_{max} 230, 286, 345, 460 mμ (ε 18,200, 14,500, 3160, 1300); λ 2.90, 6.03, 6.12, 6.21, 6.65 μ: pmr,[14] 116 (3s, 6-CH_3), 131 (3s, SCH_3), 137 (3s, 2-CH_3), 166 (2t, J = 7 cps, NCH_2CH_2S), 239 (3s, OCH_3), 265 (2t, J = 9 cps, NCH_2CH_2S), 270 cps (2s, CH_2O).

Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.24; H, 6.19; N, 4.53; S, 10.36. Found: C, 58.55; H, 6.89; N, 4.70; S, 10.11.

Reduction of 1-(β-azidoethyl)-5-methoxy-2,6-dimethyl-4,7-dioxo-3-indolecarboxaldehyde (XVId), 1-(β-chloroethyl)-5-methoxy-2,6-dimethyl-4,7-dioxo-3-indolecarboxaldehyde (XVIc), 5-methoxy-2,6-dimethyl-4,7-dioxo-1-[β-(2-tetrahydropyranyloxy)-ethyl]-3-indolecarboxaldehyde (XVIf), and 5-methoxy-2,6-dimethyl-4,7-dioxo-1-(β-thiocyanoethyl)-3-indolecarboxaldehyde (XVIg) gave oils which were converted into the carbamate esters without purification.

General Procedure for Conversion of the Indoloquinone Alcohols into the Carbamate Esters.—The following preparation illustrates this procedure. 1-(β-Fluoroethyl)-3-hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-dione (XVa) (387 mg, 1.38 mmoles) and 15 ml of methyl isocyanate were heated at gentle reflux for 20 hr. The excess isocyanate was removed and the residue was recrystallized from CH_2Cl_2–petroleum ether to give 290 mg (62%) of the methylcarbamate XIVa as orange needles, mp 162–163°. Complete characterization of this substance and the other compounds (XIVb–d and g) prepared analogously is given in Table II.

1-(β-Hydroxyethyl)-3-hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-dione 3-Methylcarbamate (XIVe).—A solution of 300 mg (0.72 mmole) of 3-hydroxymethyl-5-methoxy-2,6-dimethyl-1-[β-(2-tetrahydropyranyloxy)ethyl]indole-4,7-dione methylcarbamate (XIVd) in 60 ml of methanol and 15 ml of 0.1 N HCl was stirred at room temperature for 23 hr. Thin layer chromatography showed two spots, each being more polar than starting quinone. The crude material was isolated with CH_2Cl_2 and adsorbed from benzene onto a column prepared from silica gel and benzene. The column was washed with ether; upon eluting the first orange band, 125-ml fractions were collected. After collection of 12 fractions, the more polar band was eluted with acetone to furnish the product, the characterization of which is given in Table II.

3-Hydroxymethyl-5-methoxy-2,6-dimethyl-1-(β-dimethylsulfoniumethyl)indole-4,7-dione Methylcarbamate Iodide (XIVg).—A solution of 50 mg (0.14 mmole) of XIVf in 5 ml of CH_3I was allowed to stand at ambient temperature in the dark for 6 days, after which time the solvent was removed. Characterization of the product is given in Table II.

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Antimicrobial Properties of Pyrrole Derivatives[1]

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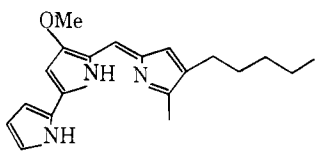
The activity of pyrroles, 2,2′-dipyrrylmethenes, 2,2′,2″-tripyrrylmethenes, 2,2′-bipyrrole, and congeners against representative bacteria, fungi, and yeast, and of prodigiosin against pathogenic fungi is described. The activities of the pyrroles and methenes vary with substitution. Reversal studies indicate that 2-pyrrol-2-yl-1-pyrroline interferes with glycine metabolism.

There have been a number of studies[2–10] devoted to an investigation of the bipyrrylpyrrylmethene prodigiosin (**1**), which occurs in the pigment produced by the bacterium *Serratia marcescens*. Notable among these is the claimed[5,6] activity of this compound against the pathogenic fungus *Coccidiodes immitis*, the causative agent for coccidioidomycosis (San Joaquin Valley fever). The potential application of the bacterial metabolite has been hampered apparently by its toxicity. In view of the activity that has been described for this compound and the generally important role of pyrrole derivatives in biological systems, it was of interest to investigate the antibiotic properties of simpler and more readily attainable pyrroles, dipyrrylmethenes, and certain congeners.



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Among a number of pyrroles investigated (alkyl derivatives, aldehydes, ketones, esters), 2,4-dimethyl-3-ethylpyrrole was found to be qualitatively active (agar diffusion–filter paper disk method) against *Bacillus subtilis, Staphylococcus aureus, Mycobacterium smegmatis, Candida albicans, Trichophyton mentagrophytes, Penicillium* sp., *Aspergillus niger*, and *Saccharomyces cerevisiae*. An isomeric mixture of 2- and 3-heptylpyrrole (5.4:1) showed activity against *B. subtilis, S. aureus, Pseudomonas aeruginosa, C. albicans, A. niger*, and *S. cerevisiae*. In contrast 2-methylpyrrole, 2,4-dimethylpyrrole, and an isomeric mixture of 2- and 3-ethylpyrrole (2- chiefly) were shown to be inactive against the same microorganisms. However, all of the alkyl-

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