The Mitomycin Antibiotics. Synthetic Studies. XVII.[1] Indoloquinone Analogs with Variants at the 2 Position

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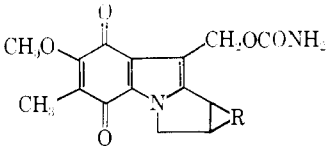
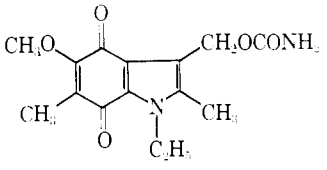
1-Ethyl-2,3-bis(hydroxymethyl)-5-methoxy-6-methylindole-4,7-dione 3-methylcarbamate (**30**) was prepared by an eleven-step sequence from methyl 5-methoxy-6-methyl-2-indolecarboxylate (**12**). Thionyl chloride treatment of **30** gave the 2-chloromethyl analog **25**, also of use as an intermediate for the preparation of other analogs *via* appropriate displacements, thus, the synthesis of the 2-acetylthiomethyl (**26**), 2-methoxymethyl (**27**), 2-fluoromethyl (**28**), and 2-aminomethyl (**29**) analogs. Manganese dioxide oxidation of **30** gave the 2-formyl analog **33**, which afforded the corresponding semicarbazone **34**, oxime **35**, and methoxime **36**. Preferential reaction of the 2-formyl group was achieved despite the presence of the quinone system. Additionally, the preparation of analogs containing the cyano (**37**), carboxamido (**49**), and carbomethoxy (**50**) groups at the 2 position is reported. The *in vitro* antibacterial spectrum of 13 derivatives has been measured.

The mitomycin antibiotics,[2] in particular mitomycin C, have received considerable attention as antitumor agents.[3] Moreover, in experimental animals these compounds show a high degree of oral effectiveness as broad-spectrum antibacterial agents.[4] It has already been shown that the closely related aziridinopyrroloindoloquinone **1** has a similar order of activity,[5] and we have found that the deaziridinopyrroloindoloquinone **2**,[6] as well as indoloquinones such as **3**,[7] retain a significant degree of antibacterial activity. We now report the synthesis and *in vitro* activity of a series of C-2 variants based on **3**.



1, R = NCH_3
2, R = H



3

We have previously recorded the preparation of the 2-demethyl and 2-ethyl analogs[1] and have found that these changes result in decreased antibacterial effectiveness. Our efforts in this area were then directed to the preparation of certain 2-substituted methyl derivatives, as well as analogs derived by transformation of 2-carboxy and 2-formyl functions. Although all analogs were of interest on an empirical basis, the substituted methyl compounds were of special interest since their benzylic character conceivably provides an additional site for biological alkylation. Furthermore, this site corresponds to that in the parent antibiotics which is most prone to solvolytic ring opening of the fused aziridine function.[2] This possibility affords a rational basis for the preparation of these compounds, since biochemical evidence indicates that biological alkylation may play an important role in the mechanism by which the mitomycins exert their effect.[8]

In principle, a convenient approach to the synthesis of various 2-substituted methyl analogs involved the preparation of a fully elaborated indoloquinone carbamate having at the 2 position a CH_2X group which could then be subjected to appropriate displacements. Since the development of the requisite CH_2X group was envisioned as proceeding *via* the reduction of a 2-carbalkoxy group, the previously described[6] methyl 5-methoxy-6-methyl-2-indolecarboxylate (**12**) appeared to be a most suitable starting material. This compound is available in good yield from 2,5-xylenol *via* the Reissert indole synthesis, and its eleven-step conversion into the 2-hydroxymethylquinone carbamate **30** proceeded as follows.

Alkylation of indole ester **12** with ethyl sulfate and sodium hydride gave the N-ethyl ester **13**, which on reduction with lithium aluminum hydride afforded the 2-indolylmethanol **14** (see Scheme I). Conversion of this last compound, *via* the acetate **15**, into the 3-carboxaldehyde **16** was effected by the Vilsmeier–Haack technique.[9]

For the elaboration of the quinone system, aldehyde **16** was converted into its 4-nitro derivative **23** by fuming nitric acid in glacial acetic acid.[10] Reduction of the latter compound with ferrous ammonium sulfate gave the 2-acetoxymethyl aminoaldehyde **21** in a mixture with the 2-hydroxymethylaminoaldehyde **22**. Extension of the reaction time from 15 min to 1 hr led to the

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

(2) For the structure elucidation of these antibiotics, see (a) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, **84**, 3185, 3187 (1962); (b) A. Tulinsky, *ibid.*, **84**, 3188 (1962).

(3) R. Jones, Jr., U. Jonsson, J. Colsky, H. E. Lessner, and A. Franzino, "Fourth National Cancer Conference Proceedings, 1960," J. B. Lippincott, Philadelphia, Pa., 1961, p 175.

(4) (a) T. Hata, Y. Sano, R. Sugawara, A. Matsumae, K. Kanamori, T. Shima, and T. Hoshi, *J. Antibiotics* (Tokyo), **A9**, 141 (1956); (b) C. L. Stevens, K. G. Taylor, M. E. Munk, W. S. Marshall, K. Noll, G. D. Shah, L. G. Shah, and K. Uzu, *J. Med. Chem.*, **8**, 1 (1965); (c) A. C. Dornbush and G. S. Redin, private communication.

(5) J. B. Patrick, R. P. Williams, W. E. Meyer, W. Fulmor, D. B. Cosulich, R. W. Broschard, and J. S. Webb, *J. Am. Chem. Soc.*, **86**, 1889 (1964).

(6) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *ibid.*, **86**, 3877 (1964); *J. Org. Chem.*, **30**, 2897 (1965).

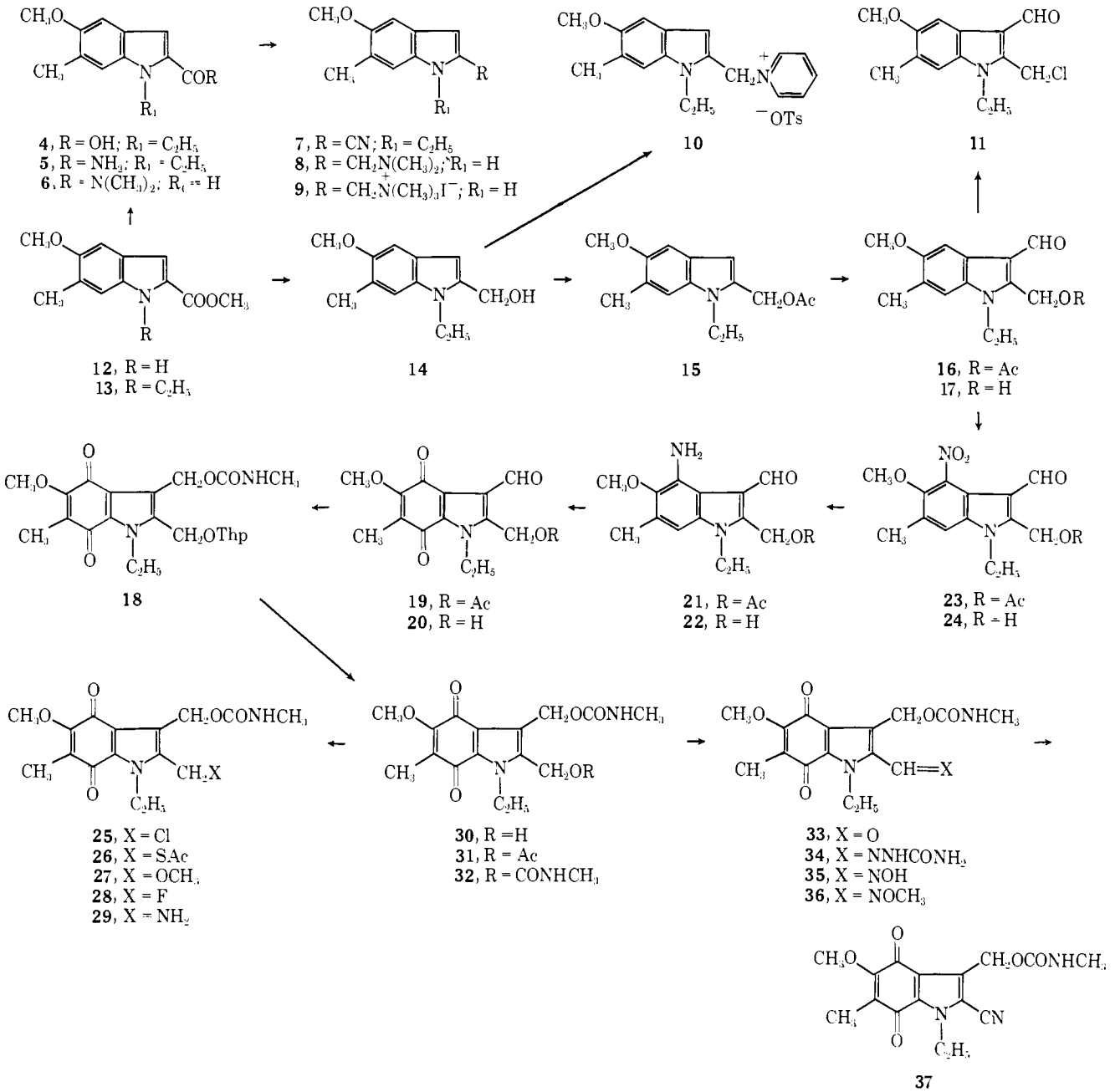
(7) (a) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 3878 (1964); (b) G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.*, **10**, 1 (1967).

(8) (a) V. N. Iyer and W. Szybalski, *Science*, **145**, 55 (1964); (b) A. Weissbach and A. Lisio, *Biochemistry*, **4**, 196 (1965).

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

(10) For prior elaborations of the 4,7-indoloquinone system *via* a 4-nitroindole see ref 1 and 7a.

SCHEME I



exclusive formation of **22**. However, best yields of **22** were obtained by reduction of the 2-acetoxymethyl-4-nitro derivative **23** with iron in acetic acid followed by deacylation. Potassium nitrosodisulfonate (Fremy's salt) oxidation[11] of **22** then gave the 4,7-indoloquinone **20**. A preliminary attempt to prepare **20** by deacetylation (methanolic triethylamine or sodium methoxide) of the 2-acetoxymethyl-5-methoxy-4,7-quinone **19**, obtained by a parallel oxidation of **21**, failed, presumably as a result of involvement with the methoxyquinone system.

Prior to elaboration of the requisite side chain at C-3 it was necessary to block the alcohol function in 2-hydroxymethylquinone-3-aldehyde **20**, which objective was accomplished with the corresponding tetrahydropyranyl ether.[12] Reduction of this derivative with sodium borohydride and regeneration of the quinone system with acidic ferric chloride gave the noncrystalline 2-tetrahydropyranyloxymethyl-3-carbinol, which was transformed into the carbamate ester **18** by methyl isocyanate.[7a] In the first preparation of **18** by this sequence, it was accompanied by 2,3-biscarbamate **32**. The formation of **32** was presumably the result of incomplete etherification of 2-hydroxymethyl-3-aldehyde **20**, since subsequent preparations of **18**, in which ether formation was monitored by thin layer chromatography, were not contaminated with biscarbamate **32**. The blocking group was readily hy-

(11) H. J. Teuber and M. Hassellbach, *Ber.*, **92**, 674 (1959).

(12) The suitability of the tetrahydropyranyl ether for this purpose was initially demonstrated with model system **17**. This aldehyde could be converted into a noncrystalline ether from which **17** was regenerated on mineral acid treatment (see Experimental Section).

drolyzed by dilute mineral acid[12] to give the desired 2-hydroxymethyl-5-methoxyquinone 3-carbamate **30**, which afforded acetate **31** on treatment with acetyl chloride in pyridine.

This synthesis of **30**, no step of which proceeded in less than 60% yield, made feasible its accumulation in quantities sufficient for transformation to other analogs. However, in order to achieve these transformations it was necessary to develop an appropriate procedure for the conversion of the 2-hydroxymethyl group into a CH_2X function, wherein X is a readily displaceable group. We undertook this study with model systems available from the above synthetic sequence. Treatment of carbinol **14** with tosyl chloride in pyridine at 0° gave the pyridinium tosylate **10**, but at −18° only carbinol **14** was isolated.[13] With neither *sym*-collidine nor sodium hydride in benzene could any identifiable material be obtained. Moreover, a preliminary attempt to to prepare the mesylate of **14** was similarly unsuccessful. The behavior of 2-hydroxymethyl-3-indolecarboxaldehyde **17** toward tosyl chloride contrasts sharply with that of carbinol **14**, the former substance being recovered unchanged after treatment with tosyl chloride in pyridine (ambient temperature). This result is analogous to that observed with a 1-hydroxypyrrolo[1,2-*a*]indole-9-carboxaldehyde, which was recovered from an even more vigorous treatment (steam bath, 30 hr).[14]

Since displacements of the desired type have been effected with (2-indolylmethyl)trimethylammonium methosulfate,[15] we attempted to use such a quaternary derivative. For this purpose indole ester **12** was converted *via* dimethylamide **6** into tertiary amine **8** and then to the methiodide **9**. Inasmuch as we were interested in a group that would undergo displacement with a wide spectrum of nucleophiles, we studied the reaction of **9** with fluoride ion, a nucleophile of reputed low activity.[16] Since treatment of **9** with either silver fluoride or potassium fluoride under a variety of conditions failed to give the 2-fluoromethyl derivative, the approach based on a quaternary ammonium compound was abandoned.

Success was finally achieved with the 2-chloromethyl group. Thus, it was found that treatment of 2-acetoxymethyl-3-aldehyde **16** with hydrogen chloride in acetic anhydride permitted the preparation of the 2-chloromethyl-3-aldehyde **11**, albeit in low yield. Although this procedure failed (recovered starting material) with the 4-nitroaldehyde **23** and the quinonealdehyde **19**, presumably as a result of the further deactivating effect of the nitro group or quinone system, its success in the preparation of **11** indicated that a chlorination of hydroxymethylquinone **30**, in which only one deactivating system is present, might be effected. Indeed, this proved true, for treatment of this quinone with thionyl chloride in the presence of dimethylaniline gave 2-chloromethyl-5-methoxyquinone 3-carbamate **25** in good yield.

This quinone fulfilled the requirements of our original concept, inasmuch as it was fully elaborated, and displacements could be effected with the 2-CH_2Cl group. Thus, treatment of **25** with potassium thioacetate or 5% methanolic potassium hydroxide smoothly furnished the acetylthiomethyl- (**26**) and methoxymethylquinones (**27**), respectively. Moreover, reaction of **25** with silver fluoride in acetonitrile gave the 2-fluoromethylquinone **28** in moderate yield.[17] Additionally, on exposure to ammonia in tetrahydrofuran, **25** furnished the 2-aminomethylquinone **29** in poor yield. When this last displacement was attempted in methanol the 2-methoxymethylquinone **27** resulted.

The 2-hydroxymethylquinone **30** also proved useful for the preparation of other analogs. Thus, oxidation of **30** with manganese dioxide gave the 2-aldehyde **33** in 52% yield. Interestingly, on reaction with excess semicarbazide, hydroxylamine, and methoxyamine, quinone-2-aldehyde **33** yielded only the aldehyde derivatives **34**, **35**, and **36**, respectively. Moreover, aldehyde **33** was converted into the 2-carbonitrile **37** by *O*,*N*-bis(trifluoroacetyl)hydroxylamine.[18] Alternatively, **37** was prepared from oxime **35** by dehydration with thionyl chloride in dimethylaniline. An initial attempt to prepare the 2-cyano analog **37** was made with 1-ethyl-5-methoxy-6-methyl-2-indolecarbonitrile (**7**), available from **12** *via* the acid **4** and amide **5**. This approach failed since **7** proved to be unreactive in the Vilsmeier–Haack aldehyde synthesis.

In addition to the analogs described above, we have also prepared the 2-carboxamido- and 2-carbomethoxyquinones **49** and **50**, respectively. The synthesis of these compounds was achieved in the following manner (see also Scheme II). Indole ester **13** was converted into its 3-formyl derivative **38** and, then, into the 4-nitro-3-carboxaldehyde **39**. In the preparation of this last compound, two experiments gave the 4-nitro derivative as the sole product (62–65%). However, at a later date (3 months), repetition (twice) with the same bottle of nitric acid gave *o*-quinone **41** (18 and 22%) in addition to the expected **39** (65 and 75%). The structure of **41** was demonstrated by the following series of transformations. Thiele acetoxylation[19] transformed the red quinone **41** into a colorless substance, which, without purification, was hydrolyzed by 5% sodium hydroxide. Aeration of the alkaline solution, followed by acidification, gave the hydroxy-*p*-quinone acid **45**. Methylation of this substance with methyl sulfate and potassium carbonate afforded the corresponding methoxyquinone ester, which on sodium borohydride reduction and regeneration of the quinone system with acidic ferric chloride furnished the quinonecarbinol **44**. This material was identical with that

(13) R. S. Tipson in "Advances in Carbohydrate Chemistry," Vol. 8, Academic Press Inc., New York, N. Y., 1953, pp 117–127.

(14) W. A. Remers, R. D. Roth, and M. J. Weiss, *J. Org. Chem.*, **30**, 2910 (1965).

(15) E. C. Kornfeld, *ibid.*, **16**, 806 (1951).

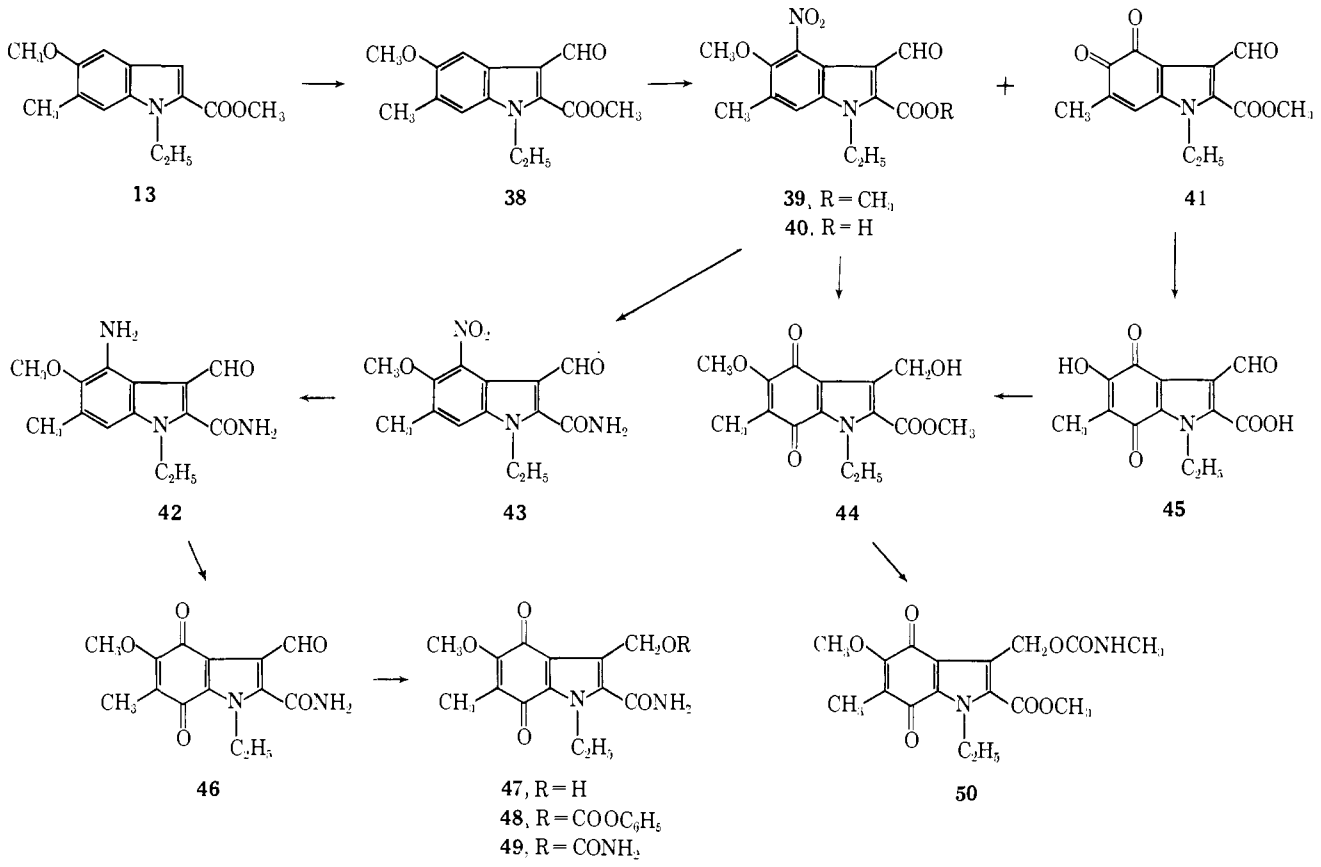
(16) (a) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p 140. (b) However, recent work [S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Letters*, **No. 9**, 24 (1960)] with the dissociated tetrabutylammonium halides demonstrated that the true order of nucleophilic activity is $I^- < Br^- < Cl^-$, thus suggesting that F^- is a good nucleophile. H. B. Henbest and W. R. Jackson [*J. Chem. Soc.*, 954 (1962)] utilized this concept in the preparation of certain fluoro steroids from tetrabutylammonium fluoride and tosylate esters. Moreover, F^- has been shown to be a powerful nucleophile in aprotic dipolar solvents [J. Miller and A. J. Parker, *J. Am. Chem. Soc.*, **83**, 117 (1961)].

(17) With respect to the preparation of the 2-fluoromethylquinone **28**, we note that reaction of 2-hydroxymethylquinone **30** or 2-hydroxymethylindole **14** with *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine [D. E. Ayer, *Tetrahedron Letters*, **No. 23**, 1065 (1962); L. H. Knox, E. Verlarde, S. Berger, D. Candriello, and A. D. Cross, *ibid.*, **No. 26**, 1249 (1962)] gave complex mixtures, whereas 2-hydroxymethyl-3-indolecarboxaldehyde **17** was recovered unchanged after treatment with this reagent.

(18) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, **81**, 6340 (1959).

(19) J. Thiele, *Ber.*, **31**, 1248 (1958).

SCHEME II



prepared by catalytic reduction of nitroaldehyde **39**, and oxidation of the presumed 4-amino-3-indolecarbinol with Fremy's salt.[20] Alcohol **44** was then converted into the desired analog **50** on treatment with methyl isocyanate.

For the preparation of the 2-carboxamido analog **49** the 3-formyl-4-nitro ester **39** was converted into the corresponding acid **40**. The mixed carbonic anhydride[21] prepared from this acid and ethyl chloroformate reacted with ammonia to give amide **43**.[22,23] Reduction of this last substance with ferrous ammonium sulfate furnished the amino amide **42**, which was converted by Fremy's salt into the *p*-quinone **46**. The elaboration of the side chain was then accomplished in the usual manner. Reduction of the quinonealdehyde **46** with sodium borohydride and subsequent regeneration of the quinone system with acidic ferric chloride solution gave carbinol **47**. Although the transformation of **47** into a carbamate could not be achieved by the isocyanate procedure, this material was converted into unsubstituted carbamate **49** *via* phenylcarbonate **48**.

Biology.—The *in vitro* antibacterial activity of the indoloquinones having variants at the 2 position is given in Table I. In general, such analogs show no enhancement of activity when compared to the 2-alkyl-indoloquinone **3**. Of some interest is that conversion of the 2-aldehydo analog **33**, which has only marginal activity, into its semicarbazone **34** and oxime **35** derivatives gives compounds having an effectiveness similar to **3**.

(20) For a complete discussion of this procedure for the simultaneous elaboration of the quinone system and the 3-carbinol side chain, especially with respect to its serious limitations, see ref 1.

(21) (a) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951); (b) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).

(22) The utility of this procedure for the preparation of 2-indolecarboxamide was indicated by an earlier transformation of 2-indolecarboxylic ester **38** *via* the mixed anhydride of the corresponding acid into a carboxamide (see Experimental Section).

(23) It may be noted that an early attempt to proceed to this compound from amide **5** *via* Vilsmeier–Haack formylation gave the 2-carbonitrile **7**.

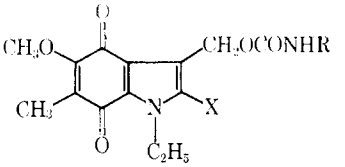
Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are corrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer, and infrared spectra were measured in pressed KBr disks with a Perkin-Elmer Model 21 spectrophotometer. Pmr spectra were determined on a Varian A-60 spectrometer using $CDCl_3$ (unless noted otherwise) as solvent with tetramethylsilane as an internal standard; in the description of these spectra, the signals are expressed as *x*s (singlet), *x*d (doublet), *x*t (triplet), or *x*q (quartet) where *x* indicates the number of protons indicated by integration. The petroleum ether used was that fraction boiling at 30–60°, unless stated otherwise. All evaporations were carried out at reduced pressure. Analyses for nitrogen were performed by the Dumas technique using a combustion temperature of 950° for 10 min.

Methyl 1-Ethyl-5-methoxy-6-methyl-2-indolecarboxylate (13).—A solution of 21.9 g (0.10 mole) of methyl 5-methoxy-6-methyl-2-indolecarboxylate in 900 ml of benzene was distilled azeotropically, about 250 ml of benzene being collected. The cooled solution was treated with stirring with 8.90 g (0.20 mole) of a 54.7% dispersion of 98.5% NaH in mineral oil; a gray solid separated almost immediately. The mixture was stirred at ambient temperature for 15 min and then heated to reflux temperature. Ethyl sulfate (60 ml) was added dropwise, and heating was continued for 2 hr. The cooled mixture was washed with water, and the dried organic phase was evaporated. The residue was recrystallized from ether–petroleum ether to give, in three crops, 18.9 g (77%) of material with suitable purity for further work. Material from a similar experiment was recrystallized from acetone–hexane and then methanol to give white needles: mp 101–102°; λ_{max} 212, 303 mμ (ε 26,700, 22,000);

TABLE I

In Vitro ANTIBACTERIAL ACTIVITY OF THE 1-ETHYL-3-HYDROXYMETHYL-5-METHOXY-6-METHYL-2-SUBSTITUTED 4,7-INDOLOQUINONE CARBAMATES



			Minimum inhib conen (μg/ml)[a] against—										
Compd	R	X	*Myco.* 607	*Staph.* 6538P	*Staph.* Rose	*S. lutea*	*Strep. faec.*	*Strep.* C203	*Strep.* β 80	*Strep.* γ 11	*B. subt.*	*C. xerose*	*B. cereus*	*Past.* 310
3	H	CH_3	6.25	1.56	1.56	6.25	12.5	0.78	3.12	3.12	1.56	6.25	0.39	6.25
18	CH_3	CH_2OThp	6.25	...	...	...	...	6.25	...	...	6.25	...	6.25	12.5
25	CH_3	CH_2Cl	12.5	3.12	3.12	12.5	50	1.56	25	25	1.56	25	0.39	1.56
27	CH_3	CH_2OCH_3	12.5	...	...	...	...	50	...	...	12.5	...	6.25	3.12
28	CH_3	CH_2F	12.5	3.12	3.12	12.5	50	1.56	25	25	1.56	25	0.78	1.56
29	CH_3	CH_2NH_2	12.5	3.12	3.12	12.5	50	0.39	12.5	12.5	1.56	12.5	0.39	1.56
30	CH_3	CH_2OH	12.5	3.12	3.12	12.5	50	1.56	25	25	1.56	25	0.39	0.78
31	CH_3	CH_2OAc	12.5	6.25	12.5	...	...	1.56	50	50	3.12	25	1.56	3.12
32	CH_3	$CH_2OCONHCH_3$	25	1.56	3.12	25	...	0.39	25	25	0.39	6.25	0.39	0.78
33	CH_3	CHO	50	...	...	...	...	...	...	...	50	...	50	50
34	CH_3	$CH{=}NNHCONH_2$	12.5	3.12	3.12	3.12	6.25	≤0.2	12.5	12.5	1.56	1.56	0.78	1.56
35	CH_3	$CH{=}NOH$	6.25	3.12	1.56	12.5	50	0.39	12.5	12.5	0.78	6.25	0.39	0.78
49	H	$CONH_2$	25	3.12	3.12	12.5	25	≤0.2	25	12.5	0.78	50	0.78	0.78

[a] Highest test level: 50 μg/ml. All data are from concurrent assays. Abbreviations for microorganisms: *Myco.* 607 = *Mycobacterium smegmatis*, ATCC 607; *Staph.* 6538P = *Staphylococcus aureus*, ATCC 6538P; *Staph.* Rose = *Staphylococcus aureus* var. Rose; *S. lutea* = *Sarcina lutea*, ATCC 9341; *Strep faec.* = *Streptococcus faecalis*, ATCC 8043; *Strep.* C203 = *Streptococcus pyogenes*, C203; *Strep.* β 80 = *Streptococcus* sp., β-hemolytic, 80; *Strep.* γ 11 = *Streptococcus* sp., nonhemolytic, 11; *B. subt.* = *Bacillus subtilis*, ATCC 6633; *C. xerose* = *Corynebacterium xerose*, NRRL B1397; *B. cereus* = *Bacillus cereus*, ATCC 10702; *Past.* 310 = *Pasteurella multocida*, ATCC 310.

λ 5.85, 8.30 μ; pmr, 80 (3t, J = 7 cps, NCH_2CH_3), 140 (3s, 6-CH_3), 225, 229 (3s each, OCH_3), 269 (2q, J = 7 cps, NCH_2CH_3), 414 (1s, 3-H), 424 (1s, low-order coupling, 7-H), 426 cps (1s, 4-H).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.44; H, 6.93; N, 5.62. Found: C, 67.84; H, 6.98; N, 5.57.

1-Ethyl-2-hydroxymethyl-5-methoxy-6-methylindole (14).—A mixture of 7.00 g (28.4 mmoles) of **13** and 2.17 g of $LiAlH_4$ in 470 ml of ether was stirred at reflux temperature for 2.5 hr and then at room temperature for 16.5 hr. The excess hydride was destroyed by addition of ethyl acetate and then water. The organic layer was decanted from the aqueous phase which was extracted with ethyl acetate. The residue remaining after removal of the solvent from the combined organic solutions was recrystallized from ether–petroleum ether to give 5.494 g (87%) of white needles, mp 103–106°. Material from a similar experiment was obtained as white needles: mp 112.0–113.5°; λ_{max} 213, 278, 300, 310 mμ (ε 32,000, 10,700, 6570, 4600); λ 3.02, 3.09 μ; pmr, 79 (3t, J = 7.5 cps, NCH_2CH_3), 115 (1s, OH, erased on exchange with deuterium oxide), 141 (3s, 6-CH_3), 229.5 (3s, OCH_3), 248 (2q, J = 7.5 cps), 279 (2s, CH_2OH), 377 (1s, 3-H), 418 (1s, 4-H), 424 (1s, low-order coupling, 7-H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.95; H, 7.97; N, 6.45.

On acylation with acetic anhydride and pyridine this material gave acetate **15** as white needles, mp 97–98°, after recrystallization from CH_2Cl_2–petroleum ether; λ_{max} 213, 278, 300, 312 mμ (ε 39,200, 11,400, 6000, 4570); λ 5.75, 8.04, 8.31 μ; pmr, 80 (3t, J = 7.5 cps, CH_3CH_2N), 122 (3s, CH_3CO), 142 (3s, 6-CH_3), 228 (3s, OCH_3), 245 (2q, J = 7.5 cps, NCH_2CH_3), 312 (2s, CH_2OH), 386 (1s, 3-H), 418 (1s, 4-H), 424 cps (1s, 7-H).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.15; H, 7.30; N, 5.65.

1-Ethyl-2-hydroxymethyl-5-methoxy-6-methyl-3-indolecarboxaldehyde Acetate (16).—With ice cooling, 3.67 g (24.0 mmoles, 2.2 ml) of $POCl_3$ was added dropwise to 15 ml of dimethylformamide (DMF) at such a rate that the temperature did not exceed 10°. A solution of 6.15 g (23.6 mmoles) of 1-ethyl-2-hydroxymethyl-5-methoxy-6-methylindole acetate (**15**) in 30 ml of DMF was added dropwise at such a rate that the temperature remained below 10°. After completion of the addition, the solution was stirred at 30–35° for 1 hr. Cracked ice was added followed by 100 ml of 1 N NaOH solution. The resulting mixture was stirred for 1 hr and filtered. The solid was dissolved in CH_2Cl_2, and this solution was washed with a $KHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was chromatographed on Florisil (magnesia–silica gel). The material eluted by CH_2Cl_2 was recrystallized from CH_2Cl_2–petroleum ether to give 4.12 g (58%) of white needles: mp 124–125°; λ_{max} 218, 256, 280, 311 mμ (ε 28,800, 19,400, 9700, 13,000); λ 3.55, 3.66, 5.75, 6.05, 6.52, 8.25 μ; pmr, 85 (3t, J = 7.5 cps, CH_3CH_2N), 125 (3s, CH_3CO), 141 (3s, 6-CH_3), 234 (3s, OCH_3), 250 (2q, J = 7.5 cps, NCH_2CH_3), 327 (2s, CH_2O), 427 (1s, 7-H), 465 (1s, 4-H), 612 cps (1s, CHO).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.51; H, 6.97; N, 5.04.

1-Ethyl-2-hydroxymethyl-5-methoxy-6-methyl-3-indolecarboxaldehyde (17).—A solution of 1.50 g of the above acetate **16** in 150 ml of 5% methanolic NaOH was heated at reflux temperature for 15 min. The product was isolated with CH_2Cl_2 and recrystallized from CH_2Cl_2–ether to give 838 mg of crystals: mp 172–174°; λ_{max} 218, 258, 282, 302 mμ (ε 29,400, 20,500, 12,250, 13,800); λ 3.06, 6.14 μ.

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.03; H, 7.10; N, 5.75.

1-Ethyl-5-methoxy-6-methyl-2-(2-tetrahydropyranyloxy)-methyl-3-indolecarboxaldehyde.—A solution of 186 mg (0.75 mmole) of **17**, 92 mg of dihydropyran, and 10 mg of *p*-toluenesulfonic acid hydrate in 20 ml of benzene was stirred at room temperature for 4 hr. The solution was washed with water, dried, and evaporated to give the tetrahydropyranyl ether as an oil having no OH absorption in the infrared. This material was stirred with 0.1 N HCl for 1.5 hr, after which CH_2Cl_2 was added; stirring was continued for 0.5 hr. The material isolated from the organic solution was identical with **17**.

1-Ethyl-2-hydroxymethyl-5-methoxy-6-methyl-4-nitro-3-indolecarboxaldehyde Acetate (23).—Fuming yellow nitric acid (3.65 ml) was added dropwise to a stirred solution of 3.65 g (12.6 mmoles) of 1-ethyl-2-hydroxymethyl-5-methoxy-6-methyl-3-indolecarboxaldehyde acetate (**16**) in 65 ml of glacial acetic acid at such a rate that the temperature remained below 20°. The mixture was stirred at room temperature for 30 min, diluted with water, and filtered to give 3.74 g (89%) of crystals, mp 195–197°. A sample was recrystallized from acetone–hexane to give crystals: mp 198–200°; λ_{max} 217, 249, 304 mμ (ε 33,300, 17,000, 12,200); λ 3.52, 3.65, 5.72, 6.00, 6.50, 8.25 μ.

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.33; H, 5.41; N, 8.47.

1-Ethyl-2-hydroxymethyl-5-methoxy-6-methyl-4-nitro-3-indolecarboxaldehyde (24).—To a stirred suspension of 200 mg (0.60 mmole) of **23** in 8 ml of methanol, under nitrogen, was added 0.42 ml of 10% K_2CO_3. The reaction mixture was stirred at room temperature for 1 hr during which time solution occurred. The reaction was terminated by the addition of 0.03 ml of glacial

acetic acid, and on addition of water and cooling 137 mg (81%) of a tan solid was obtained, mp 155–160°. Recrystallization of the solid from acetone–petroleum ether (60–70°) gave 97 mg of a solid, mp 145° (resolidifies and melts at 160–162°); λ_{max} 215, 248, 298 mμ (ε 40,500, 17,520, 12,550); λ 2.94, 3.41, 6.09, 6.5 μ.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.08; H, 5.46; N, 9.75.

4-Amino-1-ethyl-2-hydroxymethyl-5-methoxy-6-methyl-3-indolecarboxaldehyde (22). A.—To a boiling, stirred solution of 4.24 (12.7 mmoles) of **23** in 350 ml of ethanol was added a solution of 35.2 g (0.127 mole) of $FeSO_4 \cdot 7H_2O$ in 350 ml of water. The resulting turbid solution was treated at 1–2-min intervals with 5-ml portions of concentrated NH_4OH (45 ml total); the dark mixture was stirred at steam-bath temperature for 1 hr after the last addition. The mixture was filtered, and the residue was washed well with CH_2Cl_2. The combined filtrate and washings were diluted with water. The organic phase was separated, and the aqueous phase was extracted further with CH_2Cl_2. The combined organic solutions were washed with water and then extracted well with dilute HCl (8:2). The combined acid extracts were neutralized with Na_2CO_3, and the resulting mixture was extracted with CH_2Cl_2. The dried extracts were evaporated, and the residue was recrystallized from CH_2Cl_2 to give 1.370 g (41%) of cream-colored crystals: mp 182.0–183.5°; λ_{max} 228, 256, 276 (sh), 350 mμ (ε 28,900, 15,500, 9850, 4720); λ 3.04, 3.16, 3.54, 3.75, 6.10, 6.25 μ; pmr, 79 (3s, J = 7.5 cps, NCH_2CH_3), 139 (3s, 6-CH_3), 220 (3s, OCH_3), 250 (2q, J = 7.5 cps, NCH_2CH_3), 292 (2d, J = 7 cps, CH_2OH), 333 (1t, J = 7 cps, CH_2OH), 372 (2 broad, NH_2), 390 (1s, 7-H), 593 cps (1s, CHO).

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.57; H, 7.06; N, 10.37.

In a preliminary experiment utilizing 3.523 g of **23** the reaction mixture was heated for 15 min after the last addition of NH_4OH. The crude product was recrystallized from CH_2Cl_2–petroleum ether to give 419 mg (15%) of **22**. Concentration of the mother liquor gave 1.435 g (45%) of the acetate ester **21** as tan crystals, mp 132–134°. An additional recrystallization gave material with mp 136–138°; λ_{max} 229, 255, 275 (sh), 355 mμ (ε 33,500, 17,200, 12,000, 4860); λ 2.90, 3.03, 3.52, 5.71, 6.09, 6.23, 8.23, μ; pmr, 82.5 (3t, J = 7.5 cps, NCH_2CH_3), 124 (3s, CH_3CO), 142 (3s, 6-CH_3), 224 (3s, OCH_3), 247 (2q, J = 7.5 cps, NCH_2CH_3), 323 (2s, CH_2O), 349 (2 broad, NH_2), 383 (1s, 7-H), 593 cps (1s, CHO).

Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 62.82; H, 6.91; N, 9.53.

B.—4-Amino-1-ethyl-2-hydroxymethyl-5-methoxy-6-methyl-3-indolecarboxaldehyde acetate (**21**) (6.10 g, 23.3 mmoles) was hydrolyzed as described in the preparation of **24** with 13 ml of 10% K_2CO_3 in 120 ml of methanol to give 4.347 g (83%) of solid, mp 182–185°.

C.—Reduction of **24** (6.62 g, 22.7 mmoles) by the procedure of method A gave 3.20 g (54%) of tan crystals, mp 185–187°.

4-Amino-1-ethyl-2-hydroxymethyl-5-methoxy-6-methyl-3-indolecarboxaldehyde Acetate (21).—A stirred solution of 9.00 g (27 mmoles) of **23** in 850 ml of glacial acetic acid and 86 ml of water was heated to steam-bath temperature and 17.4 g of iron filings were added in portions over 1.5 hr. Additional water (86 ml) was added after 45 min. The cooled mixture was diluted with water and extracted with CH_2Cl_2. The extracts were washed successively with water, Na_2CO_3 solution, and water, dried, and concentrated to give 6.106 g (74%) of solid, mp 133–140°, which was used without further purification.

1-Ethyl-2-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxo-3-indolecarboxaldehyde (20).—A solution of 1.472 g (5.62 mmoles) of **22** in 240 ml of acetone was added to a stirred solution of 3.09 g (11.5 mmoles) of Fremy's salt in 160 ml of water and 80 ml of 0.167 M KH_2PO_4; the resulting solution was stirred at room temperature for 16 hr. Water was added, and the product was isolated with CH_2Cl_2. The material was chromatographed on Florisil. The material that was eluted by $CHCl_3$ was recrystallized from acetone–hexane to give 1.008 g (65%) of yellow needles, mp 128–129°. An additional recrystallization from the same solvents gave yellow needles: mp 128.5–130.0°; λ_{max} 215, 248, 270, 281 (sh), 328, 415 mμ (ε 20,200, 13,600, 14,100, 13,000, 4720, 832); λ 2.85, 3.51, 5.98, 6.05, 6.20, 6.53, 6.62, 9.06 μ; pmr, 84 (3t, J = 7 cps, NCH_2CH_3), 119 (3s, 6-CH_3), 242 (3s, OCH_3), 271 (2q, J = 7 cps, NCH_2CH_3), 287 (2s, CH_2OH), 626 cps (1s, CHO).

Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.38; H, 5.62; N, 5.03.

1-Ethyl-2-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxo-3-indolecarboxaldehyde Acetate (19).—Compound **21** (1.235 g, 3.74 mmoles) was oxidized with 3.08 g (11.5 mmoles) of Fremy's salt as described in the preparation of **20**. The product was recrystallized from CH_2Cl_2–petroleum ether to give 837 mg (70%) of light orange crystals, mp 137–140°. The analytical specimen had mp 142–144°; λ_{max} 214, 245, 272, 325, 400 (ε 19,100, 13,700, 15,200, 4450, 796); λ 3.50, 5.70, 5.95, 6.03, 6.06, 6.21, 6.50, 6.60, 8.10, 9.05 μ; pmr, 85 (3t, J = 7.5 cps, CH_3CH_2N), 119 (3s, 6-CH_3), 126.5 (3s, CH_3CO), 243.5 (3s, OCH_3), 267 (2q, J = 7.5 cps, CH_3CH_2N), 330 (2s, CH_2O), 630 cps (1s, CHO).

Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 59.65; H, 5.35; N, 4.59.

1-Ethyl-3-hydroxymethyl-5-methoxy-6-methyl-2-(2-tetrahydropyranyloxy)methylindole-4,7-dione Methylcarbamate (18).—A solution of 922 mg (3.33 mmoles) of **20**, 368 mg (4.4 mmoles) of dihydropyran, and 40 mg of *p*-toluenesulfonic acid monohydrate in 120 ml of benzene was stirred at room temperature for 17 hr. The solution was washed successively with $NaHCO_3$ solution and water, dried, and evaporated to give the tetrahydropyranyl ether as a yellow oil. This material was dissolved in 100 ml of methanol, and this solution was swept with nitrogen, heated to reflux with stirring, and treated with 1.000 g of $NaBH_4$. The resulting colorless solution was heated for 2–3 min and then stirred at room temperature for 1 hr. Acetone (10 ml) was added, and stirring was continued for 10 min, whereafter 10 ml of a 1 N $FeCl_3$ in 0.1 N HCl solution was added. The resulting mixture was diluted with water, and the crude product was isolated with methylene chloride.

The resulting 3-hydroxymethyl derivative was treated with 10 ml of methyl isocyanate at reflux temperature for 25 hr. The excess isocyanate was removed, and the residue was recrystallized from CH_2Cl_2–petroleum ether to give 232 mg (17%) of **1-ethyl-2,3-bis(hydroxymethyl)-5-methoxy-6-methylindole-4,7-dione bismethylcarbamate (32)** as yellow crystals, mp 191.0–191.5° (softening from 185°). Recrystallization of this material from the same solvents furnished 189 mg of yellow crystals: mp 193.5–194.0° (softening from 185°); λ_{max} 233, 285, 337, 415 mμ (ε 24,000, 15,700, 3730, 1180); λ 3.02, 5.86, 6.01, 6.07, 6.19, 6.45, 6.63, 7.85, 9.06 μ; pmr,[24] 79 (3t, J = 7.5 cps, NCH_2CH_3), 113 (3s, 6-CH_3), 156 (3d, J = 5 cps, $NHCH_3$), 236 (3s, OCH_3), 263 (2q, J = 7.5 cps, NCH_2CH_3), 313 (4s, CH_2O), 415 cps (2 broad, $NHCH_3$).

Anal. Calcd for $C_{18}H_{23}N_3O_7$: C, 54.95; H, 5.89; N, 10.68. Found: C, 55.13; H, 6.04; N, 10.63.

Concentration of the mother liquor gave 966 mg of yellow crystals, mp 103–110°. A 250-mg sample of this material was recrystallized from CH_2Cl_2–petroleum ether to give 166 mg (49%) of **18** as yellow needles: mp 119–121°; λ_{max} 231, 284, 340, 420 mμ (ε 21,800, 14,300, 3620, 1140); λ 3.01, 5.87, 6.02, 6.08, 6.23, 6.48, 6.64, 7.91, 8.75, 9.06 μ: pmr, 84 (3t, J = 7.5 cps, CH_3CH_2N), 98 (m, alkyl ring H's), 117 (3s, 6-CH_3), 166 (3d, J = 5 cps, $NHCH_3$), 225 (2m, CH_2O in alkyl ring), 241 (3s, OCH_3), 267 (2q, J = 7.5 cps, NCH_2CH_3), 285 (3m, 2-CH_2O, OCHO), 303 (broad, $NHCH_3$), 319 cps (2s, 3-CH_2O).

Anal. Calcd for $C_{21}H_{28}N_2O_7$: C, 59.99; H, 6.71; N, 6.66. Found: C, 59.48; H, 6.76; N, 7.03.

1-Ethyl-2,3-bis(hydroxymethyl)-5-methoxy-6-methylindole-4,7-dione 3-Methylcarbamate (30).—A solution of 716 mg (1.7 mmoles) of **18** (remaining crude from previous experiment) in 120 ml of methanol and 30 ml of 0.1 N HCl was allowed to stand at room temperature for 18 hr. The product was isolated with CH_2Cl_2 and recrystallized twice from CH_2Cl_2–petroleum ether to give 246 mg of yellow crystals, mp 164–166°. The material in the mother liquors was again treated as above to give an additional 92 mg (59%) of yellow needles: mp 160–162°; λ_{max} 233, 286, 340, 425 mμ (ε 20,500, 14,500, 3420, 1040); λ 2.95, 5.87, 6.01, 6.07, 6.19, 6.51, 6.63, 7.94, 8.90, 9.12 μ: pmr, 82 (3t, J = 7.5 cps, NCH_2CH_3), 115 (3s, 6-CH_3), 160 (3d, J = 5 cps, $NHCH_3$), 233 (3s, OCH_3), 268 (2q, J = 7.5 cps, NCH_2CH_3), 280 (m, 2-CH_2O, after exchange with methanol-d_4 this resonance coalesced into sharp singlet), 314 (2s, 3-CH_2O), 388 cps (broad, NH).

Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.13; H, 5.99; N, 8.33. Found: C, 57.56; H, 6.31; N, 8.51.

With pyridine–acetic anhydride this alcohol gave a monoacetate (**31**) which was obtained as yellow needles, mp 143–145°, from ether–petroleum ether; λ_{max} 234, 284, 338, 415 mμ (ε

(24) Determined in dimethyl sulfoxide-d_6.

22,700, 14,700, 3550, 1100); λ 2.98, 5.76, 5.86, 6.00, 6.08, 6.21, 6.48, 6.64, 7.87, 8.84, 9.06 μ; pmr, 83 (3t, J = 7.5 cps, NCH_2CH_3), 118 (3s, 6-CH_3), 125 (3s, CH_3CO), 167 (3d, J = 5 cps, $NHCH_3$), 242 (3s, OCH_3), 265 (2q, J = 7.5 cps, NCH_2CH_3), 290 (broad, $NHCH_3$), 318 and 321 cps (two singlets, 2- and 3-CH_3O).

Anal. Calcd for $C_{18}H_{22}N_2O_7$: C, 57.13; H, 5.86; N, 7.40. Found: C, 57.02; H, 6.14; N, 7.67.

(1-Ethyl-5-methoxy-6-methyl-2-indolyl)methylpyridinium Tosylate (10).—To an ice-chilled solution of 1.000 g (4.56 mmoles) of **14** in 14 ml of dry pyridine was added 1.907 g (10 mmoles) of *p*-toluenesulfonyl chloride, and the resulting solution was stored in the refrigerator overnight. The reaction mixture was diluted with water and filtered. The filtrate was extracted with CH_2Cl_2 to give a residue that was crystallized from acetone to give 714 mg (34%) of crystals: mp 129–130°; λ_{max} 8.35, 14.80 μ; pmr, 52 (3t, J = 7 cps, NCH_2CH_3), 137.5, 139.5 (6, 6-CH_3 and CH_3 of tosylate), 229.5 (3s, OCH_3), 243 (2q, J = 7 cps, NCH_2CH_3), 375 (2s, CH_2O), series of multiplets at 403–455 cps (aryl protons).

Anal. Calcd for $C_{25}H_{28}N_2O_4S$: C, 66.50; H, 6.25; N, 6.22; S, 7.08. Found: C, 66.87; H, 6.50; N, 6.15; S, 7.14.

(5-Methoxy-6-methyl-2-indolylmethyl)trimethylammonium Iodide (9).—A mixture of 10.0 g of 5-methoxy-6-methyl-2-indolecarboxylic acid[9] and 12.0 g of PCl_5 in 150 ml of acetyl chloride was stirred at room temperature for 2 hr. The volatile material was removed, the residue was dissolved in benzene, and the solvent was removed. The benzene addition and removal was repeated several times. The crude acid chloride was converted into the dimethylamide **6** by treatment with dimethylamine as described in the preparation **5**; yield 4.0 g (35%); mp 225–230°; λ_{max} 3.02, 6.30, 6.65 μ.

The carboxamide **6** was reduced with 1.97 g of $LiAlH_4$ in 250 ml of THF as described in the preparation of **14** to give **8** as a viscous oil: no carbonyl in the infrared region.

A solution of 2.67 g of the crude dimethylaminomethyl derivative **8** in 80 ml of methanol was treated with 80 ml of methyl iodide. Crystallization began almost immediately; after 30 min at room temperature the mixture was filtered to give 3.66 g of white crystals. A sample was recrystallized three times from methanol to give yellow crystals, which slowly decomposed above 190°: λ_{max} 212, 271, 302, 312 mμ (ε 45,800, 11,200, 6300, 5400); no CO absorption in the infrared.

Anal. Calcd for $C_{14}H_{21}IN_2O$: C, 46.68; H, 5.88; I, 35.24; N, 7.78. Found: C, 46.39; H, 6.24; I, 33.46; N, 8.06.

2-Chloromethyl-1-ethyl-5-methoxy-6-methyl-3-indolecarboxaldehyde (11).—A solution of 200 mg of **16** in 15 ml of acetic anhydride chilled to 0° was saturated with HCl. The solution was allowed to stand at room temperature for 2 hr after which it was cautiously poured into an aqueous $NaHCO_3$ slurry and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated. The residue was recrystallized from ether–petroleum ether to give 46 mg of a yellow solid, mp 132–135°. A color change from yellow to red occurred in the methanolic solution on standing preparatory to running the ultraviolet spectrum; hence the recorded spectrum is probably not that of **11**, but that of a transformation product: λ_{max} 215, 255, 280, 395, 500 mμ (ε 28,000, 12,750, 10,000, 10,900, 5030); λ 3.66, 6.09 μ.

Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.24; H, 6.06; Cl, 13.34; N, 5.27. Found: C, 63.00; H, 6.15; Cl, 13.70; N, 5.36.

2-Chloromethyl-1-ethyl-3-hydroxymethyl-5-methoxy-6-methylindole-4,7-dione Methylcarbamate (25).—A stirred solution of 720 mg (2.14 mmoles) of **30**, 0.152 ml (2.14 mmoles) of $SOCl_2$, and 0.27 ml of dimethylaniline in 80 ml of benzene was intermittently warmed on a water bath. After 20 min several more drops of $SOCl_2$ were added and warming was continued. The reaction mixture was cooled and partitioned between benzene and water. The organic solution was washed with saline, dried, and evaporated. The residue was chromatographed on silica gel; the material eluted by ether was recrystallized from ether–petroleum ether to give 530 mg (70%) of yellow crystals: mp 143–144°; λ_{max} 238, 285, 342, 437 mμ (ε 17,400, 13,300, 3190, 1062); λ 3.02, 5.89, 6.01, 6.09 μ.

Anal. Calcd for $C_{16}H_{19}ClN_2O_5$: C, 54.16; H, 5.40; Cl, 10.00; N, 7.90. Found: C, 54.55; H, 5.46; Cl, 10.18; N, 7.89.

1-Ethyl-3-hydroxymethyl-5-methoxy-6-methyl-2-mercaptomethylindole-4,7-dione 3-Methylcarbamate 2-Acetate (26).—To a stirred solution of 50 mg (0.14 mmole) of **25** in 10 ml of acetone was added 16.1 mg (0.14 mmole) of potassium thiolacetate. The reaction mixture was stirred at room temperature for 40 min, diluted with water, and extracted with methylene chloride. The organic solution was washed with water, dried, and evaporated. The residue was recrystallized from CH_2Cl_2–petroleum ether to give 41 mg (74%) of orange solid: mp 143–144°; λ_{max} 242, 285, 342 mμ (ε 24,800, 14,600, 3944); λ 2.94, 3.02, 5.77, 5.9, 6.0, 6.1 μ.

Anal. Calcd for $C_{18}H_{22}N_2O_6S$: C, 54.82; H, 5.62; N, 7.10; S, 8.13. Found: C, 55.05; H, 5.80; N, 6.79; S, 7.67.

1-Ethyl-3-hydroxymethyl-5-methoxy-2-methoxymethyl-6-methylindole-4,7-dione Methylcarbamate (27).—A solution of 100 mg of **25** in 30 ml of 5% methanolic KOH was stirred at room temperature for 10 min. The product was isolated with CH_2Cl_2 and recrystallized from CH_2Cl_2–ether–petroleum ether to give 44 mg (33%) of yellow solid: mp 165–166°; λ_{max} 233, 285, 345, 425 mμ (ε 21,000, 14,700, 3500, 1070); λ 3.02, 5.91, 6.01, 6.1, 9.06, 9.18 μ.

Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.27; H, 6.33; N, 8.00. Found: C, 58.29; H, 6.56; N, 7.55.

1-Ethyl-2-fluoromethyl-3-hydroxymethyl-5-methoxy-6-methylindole-4,7-dione Methylcarbamate (28).—A Soxhlet extractor was charged with 1.3 g of AgF and 100 ml of acetonitrile. The AgF was extracted for 1 hr after which time 245 mg (0.69 mmole) of **25** was added to the reaction flask. The reaction was maintained at reflux for 2 hr, then filtered, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2, washed successively with water and saline, and evaporated. The residue was chromatographed on silica gel, the product being eluted with ether. The first ether fraction (50 ml) was evaporated, and recrystallization of the residue from ether–petroleum ether gave 70 mg (30%) of yellow crystals: mp 137–138°; λ_{max} 234, 285, 339, 412 mμ (ε 19,600, 14,200, 3180, 946); λ_{max} 3.03, 5.9, 6.01, 6.12 μ.

Anal. Calcd for $C_{16}H_{19}FN_2O_5$: C, 56.79; H, 5.66; F, 5.61; N, 8.25. Found: C, 57.19; H, 5.90; F, 5.44; N, 8.05.

2-Aminomethyl-1-ethyl-3-hydroxymethyl-5-methoxy-6-methylindole-4,7-dione 3-Methylcarbamate (29).—A solution of 500 mg (1.42 mmoles) of **25** in 200 ml of THF saturated with NH_3 was allowed to stand for 5 days in a stoppered bottle. The residue obtained after evaporation of the solvent was chromatographed on Celite (diatomaceous silica) using a heptane–ethyl acetate–DMF–water (100:100:40:5) system.[25a] The material eluted at peak hold-back volume 1.7 (V_m/V_s = 2.3) was recrystallized from CH_2Cl_2–petroleum ether to give 72 mg (15%) of orange crystals: mp 129–130°; λ_{max} 235, 285, 340, 440 mμ (ε 19,400, 13,700, 3350, 1110); λ 2.99, 5.88, 6.04, 6.10, 6.21, 6.63, 7.90, 8.88 μ. Acceptable carbon, hydrogen, and nitrogen analyses could not be obtained for this substance.

Anal. Calcd for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53. Found: C, 56.24; H, 6.07; N, 12.02.

Thin layer chromatography showed this material to be contaminated with a small amount of another substance. Compound **29** was insoluble in water, but freely soluble in dilute HCl.

1-Ethyl-3-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxo-2-indolecarboxaldehyde Methylcarbamate (33).—A mixture of 50 mg (0.67 mmole) of **30** and 300 mg of activated MnO_2[26] in 125 ml of ether was stirred at room temperature for 24 hr. The mixture was filtered, and the residue was washed well with ether. After removal of the solvent from the combined filtrate and washings, the residue was recrystallized from ether–petroleum ether to give 26 mg (52%) of yellow needles: mp 147.0–148.5°; λ_{max} 282, 335, 390 mμ (ε 32,800, 2100, 1070); λ 3.00, 5.90, 5.96, 6.03, 6.07, 6.30, 6.45, 6.65, 7.87, 8.80, 9.10 μ; pmr, 82 (3t, J = 7.5 cps, NCH_2CH_3), 119 (3s, 6-CH_3), 167 (3d, J = 5 cps, $NHCH_3$), 244.5 (3s, OCH_3), 290 (2q, J = 7.5 cps, NCH_2CH_3), 332 (2s, CH_2O), 607 cps (1s, CHO).

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.25; H, 5.60; N, 8.33.

This material gave the following aldehyde derivatives on treatment with the appropriate reagents.

Semicarbazone (34): red crystals, mp 212–214°, from CH_2Cl_2–petroleum ether; λ_{max} 305, 475 mμ (ε 35,600, 1995); λ 2.95, 3.05, 5.93, 6.00, 6.09 μ. *Anal.* Calcd for $C_{17}H_{21}N_5O_6$: C, 52.17; H, 5.41; N, 17.90. Found: C, 52.14; H, 5.65; N, 17.50.

Oxime (35): red crystals, mp 190.0–190.5°, from CH_2Cl_2–petroleum ether; λ_{max} 282, 345, 462 mμ (ε 30,500, 2950, 1390); λ

(25a) For a complete description of this technique as developed by C. Pidacks of this laboratory, see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

(26) A product of Beacon Chemical Industries, Inc., Cambridge, Mass.

2.89, 3.00, 5.90, 6.08 μ. *Anal.* Calcd for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found: C, 55.08; H, 5.59; N, 11.98.

Methoxime (36). orange crystals, mp 165–167°, from CH_2Cl_2–petroleum ether; λ_{max} 286, 345, 455 mμ (ε 33,800, 2900, 1420); λ 3.02, 5.90, 6.00, 6.10 μ. *Anal.* Calcd for $C_{17}H_{21}N_3O_6$: N, 11.57. Found: N, 11.24.

1-Ethyl-3-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxoindole-2-carbonitrile Methylcarbamate (37). A.—A solution of 100 mg (0.3 mmole) **33**, 67.5 mg (0.3 mmole) of O,N-bis(trifluoroacetyl)hydroxylamine, and 0.09 ml of pyridine in 10 ml of benzene was stirred at room temperature for 1 hr. Thin layer chromatography showed one spot, that of starting material. The reaction mixture was heated to reflux and excess O,N-bis(trifluoroacetyl)hydroxylamine was added in portions until the disappearance of starting material was noted by tlc. The reaction mixture was cooled and partitioned between benzene and water. The organic phase was washed with saline, dried, and evaporated. The residue was recrystallized from ether–petroleum ether to give 62 mg (62%) of yellow solid: mp 148–149°; λ_{max} 243, 278, 328, 410 mμ (ε 28,100, 14,100, 2480, 992); λ 3.0, 4.47, 5.84, 6.0, 6.07 μ.

Anal. Calcd for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 58.01; H, 5.20; N, 12.53.

B.—A stirred solution of 50 mg (0.14 mmole) of 1-ethyl-3-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxoindole-2-carboxaldehyde oxime (**35**), 0.010 ml (0.141 mmole) of $SOCl_2$, and 0.018 ml of dimethylaniline in 5 ml of benzene was intermittently warmed on the steam bath. After 0.5 hr several drops of $SOCl_2$ were added, and heating was continued several more minutes. The reaction mixture was cooled and diluted with benzene. The organic solution was washed with saline, dried, and evaporated. The residue was chromatographed on silica gel; the material eluted by ether was recrystallized from ether–petroleum ether to give 16 mg (34%) of yellow crystals, mp 146–148°. The identity of this material with that of method A was shown by the usual criteria.

1-Ethyl-5-methoxy-6-methyl-2-indolecarboxylic Acid (4).—A mixture of 1.628 g (6.9 mmoles) of methyl 1-ethyl-5-methoxy-6-methyl-2-indolecarboxylate (**12**) and 50 ml of 5% NaOH solution was heated at reflux temperature for 105 min. The resulting solution was cooled, whereupon the sodium salt of the crude acid separated. The mixture was acidified with HCl, and the solid was recrystallized from aqueous acetone to give 1.254 g (78%) of white crystals: mp 208–209° (gas, prior sintering); λ_{max} 217, 300 mμ (ε 33,100, 20,700); λ 3.40, 3.86, 5.99, 8.20 μ.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.22; H, 6.67; N, 5.78.

1-Ethyl-5-methoxy-6-methyl-2-indolecarboxamide (5).—1-Ethyl-5-methoxy-6-methyl-2-indolecarboxylic acid (**4**) (14.6 g, 62.6 mmoles) was converted into the acyl halide by stirring with 150 ml of acetyl chloride and 15 g of PCl_5 for 3.5 hr at room temperature. After removal of the excess solvents, the residue was dissolved in 150 ml of benzene. Ammonia was introduced for 1 hr, and the crude product was recrystallized from acetone–hexane to give 8.34 g (57%) of white crystals: mp 220.0-221.5°; λ_{max} 215, 300 mμ (ε 37,300, 17,100); λ 2.95, 3.05, 6.10, 6.25, 6.65 μ.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.26; H, 7.15; N, 12.29.

1-Ethyl-5-methoxy-6-methyl-2-indolecarbonitrile (7).—A mixture of 7.00 g (30.1 mmoles) of **5** and 70 ml of $POCl_3$ was heated at reflux temperature for 5 min. The brown solution was cooled and poured with stirring onto a mixture of cracked ice and 140 ml of NH_4OH. The mixture was maintained at an alkaline pH by the periodic addition of NH_4OH. After the excess $POCl_3$ had hydrolyzed, the solid was recrystallized from dilute methanol to give 5.91 g (92%) of needles, mp 94–96°. A second recrystallization sharpened the melting point to 93.5–95.0°; λ_{max} 218, 285, 293, 323, 333 mμ (ε 33,000, 18,000, 20,100, 6850, 6000); λ 4.54. 6.14, 6.41 μ; pmr, 81 (3t, J = 7.5 cps, CH_3CH_2N), 141 (3s, 6-CH_3), 227 (3s, OCH_3), 250 (2q, J = 7.5 cps, CH_3CH_2N) 413, 415 (1s each, 3-H, 4-H), 423 cps (1s, 7-H).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.96; H, 6.58; N, 12.98.

Methyl 1-ethyl-3-formyl-5-methoxy-6-methyl-2-indolecarboxylate (38) was obtained in 82% yield by formylation of **13** as described in the preparation of **16**. On recrystallization from acetone–hexane it was obtained as yellow needles: mp 178.5–180.0°; λ_{max} 219, 252, 335 mμ (ε 22,000, 19,800, 14,300); λ 5.85, 6.06, 8.25, 9.58 μ.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.32; H, 6.46; N, 5.40.

Methyl 1-Ethyl-3-formyl-5-methoxy-6-methyl-4-nitro-2-indolecarboxylate (39).—A stirred suspension of 10.6 g (38.5 mmoles) of **38** in 300 ml of acetic acid was nitrated with 10.6 ml of yellow fuming nitric acid as described in the preparation of **23**. The solution was diluted with water, cooled, and filtered to give 8.00 g (65%) of orange solid, mp 170–175°. In a preliminary experiment this material was obtained in 62% yield as light orange crystals: mp 179–182°, after recrystallization from acetone–hexane: λ_{max} 222, 250, 320 mμ (ε 29,600, 19,900, 15,000); λ 5.80, 6.00, 6.47, 8.11, 8.62, 9.60, 9.95 μ.

Anal. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.23; H, 5.06; N, 8.66.

The filtrate was extracted with CH_2Cl_2, and the extracts were washed with saline, dried, and evaporated. The residue was recrystallized from acetone to give 1.98 g (18%) of *o*-quinone **41** as red crystals: mp 209–211°; λ_{max} 278, 345, 480 mμ (ε 28,300, 2200, 1100); λ 5.82, 5.95, 6.0 μ.

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.30; H, 4.94; N, 5.16.

1-Ethyl-3-formyl-5-hydroxy-6-methyl-4,7-dioxo-2-indolecarboxylic Acid (45).—To a stirred mixture of 2.000 g (7.3 mmoles) of methyl 1-ethyl-3-formyl-6-methyl-4,5-dioxo-2-indolecarboxylate (**41**) in 40 ml of acetic anhydride was added 1 ml of boron trifluoride etherate. All solid dissolved, and the solution was stirred at room temperature for 20 min. This solution was poured onto cracked ice and stirred until the excess anhydride hydrolyzed. The solid was collected by filtration to give 3.025 g; λ_{max} 5.70, 5.75, 8.30-8.50, 9.28 μ. It was treated with 160 ml of 5% NaOH solution at reflux temperature under nitrogen for 30 min. The deep brown solution was filtered, and the filtrate was aerated for 30 min. The resulting purple solution was acidified with HCl to give an orange solid. This material was recrystallized from acetone–hexane to give 1.118 g (55%) of orange crystals, mp 137–138°. A 100-mg sample of this material was recrystallized from the same solvents to give 77 mg of orange crystals: mp 161–163°; λ_{max} 235 (sh), 269, 280, 291, 332, 430 mμ (ε 7330, 18,700, 17,800, 18,200, 3330, 570); λ 3.00, 4.00, 5.75, 6.08, 6.21, 6.58, 6.65, 9.24 μ; pmr, 80 (3t, J = 7.5 cps, CH_3CH_2N), 109 (3s, 6-CH_3), 272 (2q, J = 7.5 cps, NCH_2CH_3), 613 (1s, C*H*O), 642 cps (2 broad, O*H*, COO*H*).

Anal. Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.18; H, 4.17; N, 5.23.

Methyl 1-Ethyl-3-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxo-2-indolecarboxylate (44). A.—A mixture of 463 mg (1.45 mmoles) of **39**, 100 mg of 10% Pd–C, and 100 ml of ethanol was shaken under hydrogen. After 65 min a pressure drop corresponding to 3 equiv of hydrogen was noted; no further pressure drop was observed in the ensuing 25 min. The mixture was filtered, and the solvent was removed. Trituration with ether caused partial crystallization.

A solution of this material in 60 ml of acetone was added with magnetic stirring to a solution of 804 mg (3.0 mmoles) of Fremy's salt in 40 ml of water and 20 ml of 0.167 *M* KH_2PO_4 solution. The blue solution became deep red in color and stirring was continued for 3 hr. The resulting mixture was distributed between CH_2Cl_2 and water. The dried organic solution was evaporated, and the residue was chromatographed on Florisil. The yellow material eluted by chloroform was recrystallized from ether–petroleum ether to give 112 mg (25%) of yellow crystals, mp 80–82°. An additional recrystallization gave yellow crystals: mp 83–84°; λ_{max} 267, 340, 390 (sh) mμ (ε 29,200, 2610, 1120); λ 2.94, 5.75, 6.04, 6.20, 6.56, 6.67, 7.60, 7.73, 8.74 μ; pmr, 83 (3t, J = 7.5 cps, CH_3CH_2N), 120 (3s, 6-CH_3), 236 (3s, $COOCH_3$), 243 (3s, OCH_3), 260 (ill-defined, CH_2OH), 288 (2q, J = 7.5 cps, NCH_2CH_3), 298 cps (m, sharpened after exchange with methanol-d_4 into a singlet, CH_2OH).

Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.48; H, 5.63; N, 4.64.

B.—A stirred mixture of 277 mg (1.0 mmole) of **45** and 2.0 g of K_2CO_3 in 50 ml of acetone was treated with 2 ml of methyl sulfate at reflux temperature. After 35 min the orange mixture became purple; within the ensuing 5 min, the solution again became orange. Stirring was continued at room temperature for 15 hr. The mixture was filtered and the residue was washed well with acetone. The combined filtrate and washings were evaporated, the excess methyl sulfate being removed at oil-pump pressure.

The residual oil (251 mg) was treated with 250 mg of $NaBH_4$ as described in the preparation of **18**. The crude product was chromatographed on Florisil. The solid eluted by chloroform was recrystallized from ether–petroleum ether to give 105 mg (34%) of yellow needles, mp 82–84°. This material was identical by the usual criteria with that obtained above.

Methyl 1-Ethyl-3-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxo-2-indolecarboxylate Methylcarbamate (50).—Compound **44** (100 mg, 0.33 mmole) was treated with 10 ml of methyl isocyanate as described in the preparation of **18**. The crude product was purified by partition chromatography[25] on Celite using a heptane–methanol system. The fraction with peak hold-back volume 3.8 (V_m/V_s) was evaporated, and the residue was recrystallized from CH_2Cl_2–petroleum ether to give 38 mg of yellow crystals: mp 175–176°; λ_{max} 268, 340, 400 mμ (ε 27,400, 2910, 455); λ 2.96, 3.04, 5.83, 5.90, 6.00, 6.07, 6.23, 6.54, 6.65, 7.75, 8.70, 10.60 μ.

Anal. Calcd for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53. Found: C, 56.41; H, 5.72.

1-Ethyl-3-formyl-5-methoxy-6-methyl-4-nitro-2-indolecarboxylic Acid (40).—Compound **39** (8.00 g, 25 mmoles) was hydrolyzed with 250 ml of 5% NaOH. The solution was cooled and acidified with HCl to give 6.50 g (85%) of yellow solid, mp 208–210°. A sample was recrystallized from acetone to give crystals: mp 216–217° dec; λ_{max} 222, 298 mμ (ε 38,640, 7470); λ 5.8, 6.18, 6.46 μ.

Anal. Calcd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.95; H, 4.80; N, 9.16.

1-Ethyl-3-formyl-5-methoxy-6-methyl-2-indolecarboxamide.—Compound **38** (400 mg) was hydrolyzed with 10 ml of 5% NaOH at reflux temperature for 2 hr. Acidification gave 357 mg of solid: mp 232–235° dec; λ_{max} 2.90, 3.95, 5.90, 6.30 μ.

To an ice-chilled, magnetically stirred solution of 150 mg (0.574 mmole) of this acid and 58 mg (0.57 mmole) of triethylamine in 6 ml of DMF was added 62 mg (0.574 mmole) of ethyl chlorocarbonate. A solid separated; NH_3 was then introduced for 10 min, after which time water was added and solution occurred. The white crystals that formed on cooling were filtered, washed with water, and dried. Recrystallization from methanol–water gave 84 mg (56%) of white crystals: mp 201–203°; λ_{max} 214, 256, 315 mμ (ε 24,700, 19,550, 12,780); λ 2.99, 3.55, 6.08, 6.18 μ.

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.27; H, 6.20; N, 10.69.

1-Ethyl-3-formyl-5-methoxy-6-methyl-4-nitro-2-indolecarboxamide (43).—In the manner described in the previous experiment 2.154 g (7.0 mmoles) of **40** was converted into the mixed carbonic anhydride with 1.14 ml of triethylamine and 0.79 ml of ethyl chlorocarbonate. Reaction of this intermediate with NH_3 gave 1.677 g (78%) of solid, mp 241–247°. A sample was recrystallized from acetone to give crystals: mp 252–254°; λ_{max} 217, 250, 305 mμ (ε 30,800, 19,500, 13,100); λ 2.96, 3.65, 5.95, 6.02 μ.

Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.77. Found: C, 55.08; H, 5.11; N, 13.22.

4-Amino-1-ethyl-3-formyl-5-methoxy-6-methyl-2-indolecarboxamide (42).—Compound **43** (3.236 g, 10.6 mmoles) was reduced with 28.8 g of $FeSO_4 \cdot 7H_2O$ as described in the preparation of **22**. After filtration of the hot mixture, the cooled filtrate was extracted with CH_2Cl_2. The organic solution was extracted with dilute HCl (4:1), and the combined acid extracts were neutralized by pouring onto a Na_2CO_3 slurry. The mixture was extracted with CH_2Cl_2, and the dried extracts were evaporated to give a solid residue, which was recrystallized from CH_2Cl_2–petroleum ether to give 496 mg (17%) of yellow crystals: mp 202–203°; λ_{max} 228, 253, 282, 355 mμ (ε 26,700, 14,600, 11,550, 4120); λ 3.04, 3.43, 6.00, 6.25 μ.

Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.17; H, 6.44; N, 14.90.

The methylene chloride solution, after extraction with HCl, was washed with water, dried, and concentrated to small volume to give 1.72 g (53%) of starting material.

1-Ethyl-3-formyl-5-methoxy-6-methyl-4,7-dioxo-2-indolecarboxamide (46).—A solution of 872 mg (3.17 mmoles) of **42** in 300 ml of acetone was oxidized with a solution of 2.9 g (12.68 mmoles) of potassium nitrosodisulfonate in 100 ml of 0.167 *M* KH_2PO_4 and 200 ml of water as described in the preparation of **20**. The product was isolated with CH_2Cl_2, and this solution was concentrated until solid crystallized. Filtration gave 264 mg of yellow solid, mp 195–197°. The filtrate was taken to dryness, dissolved in benzene and chromatographed on Florisil. The material eluted by acetone was recrystallized from acetone–petroleum ether (60–70°) to give 186 mg (49%) of yellow crystals: mp 197–199°; λ_{max} 211, 260, 277 (s), 325 mμ (ε 15,250, 15,700, 15,100, 4060); λ 2.93, 3.15, 5.9, 6.00, 6.06, 6.20 μ.

Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 58.28; H, 4.91; N, 9.66.

1-Ethyl-3-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxo-2-indolecarboxamide (47).—A stirred solution of 314 mg (1.08 mmoles) of **46** in 60 ml of methanol was reduced with 314 mg of $NaBH_4$ as described for **18**. The product was recrystallized from acetone–hexane to give 232 mg (73%) of yellow crystals: mp 200–202°; λ_{max} 262, 286 (s), 342, 412 mμ (ε 21,780, 13,600, 2630, 1023); λ 2.94, 3.02, 3.42, 5.90, 6.0, 6.1, 6.21 μ.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.27; H, 5.24; N, 9.19.

1-Ethyl-3-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxo-2-indolecarboxamide Phenylcarbonate (48).—To a well-stirred, ice-cooled solution of 50 mg (0.17 mmole) of **47** in 5 ml of dry pyridine was added 0.022 ml (0.17 mmole) of phenyl chloroformate. The reaction mixture was stirred at room temperature for several hours during which time the orange gum which had formed dissolved. Water was then added to the reaction mixture, and the precipitate was filtered to give 65 mg (91%) of orange solid, mp 158–164°. An analytical sample was prepared by recrystallization from CH_2Cl_2–petroleum ether; mp 174–176°; λ_{max} 252, 282, 332 mμ (ε 16,500, 14,400, 3290); λ 2.91, 5.65, 5.95, 6.03, 6.1, 8.0, 8.2 μ.

Anal. Calcd for $C_{21}H_{20}N_2O_7$: C, 61.16; H, 4.89; N, 6.79. Found: C, 60.59; H, 5.02; N, 6.30.

1-Ethyl-3-hydroxymethyl-5-methoxy-6-methyl-4,7-dioxo-2-indolecarboxamide Carbamate (49).—Ammonia was introduced into a solution of 215 mg (0.52 mmole) of **48** in 20 ml of CH_2Cl_2 chilled in a Dry Ice–acetone bath. The reaction mixture was stirred at room temperature for several hours. The excess NH_3 and solvent were evaporated, and the residue was recrystallized from acetone to give 140 mg (80%) of yellow crystals: mp 247–248°; λ_{max} 255, 285, 335 mμ (ε 18,900, 15,400, 3353); λ 2.90, 3.05, 5.85, 6.0, 6.06, 6.25 μ.

Anal. Calcd for $C_{15}H_{15}N_3O_6$: C, 53.73; H, 5.11; N, 12.53. Found: C, 53.90; H, 5.02; N, 12.27.

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