The Mitomycin Antibiotics. Synthetic Studies. XVI.[1] The Utilization of 5-Methoxy-4-nitro-3-indolecarboxaldehydes for the Synthesis of Related 4,7-Indoloquinones[2]

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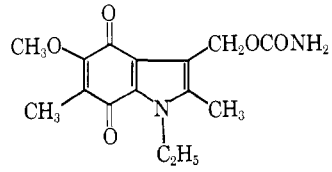
A series of 4,7-indoloquinone mitomycin analogs having alkyl variants at N-1, C-2, and C-6 were prepared. These compounds are related to the previously described I, an antibacterial agent of some interest. For the elaboration of the quinone chromophore, the appropriate indolealdehyde IX was nitrated at C-4. Displacement of the aldehyde group by nitro to give 3,4-dinitroindoles X was observed to be a side reaction in this process. Reduction of the 4-nitroindolealdehydes XI gave the corresponding amino compounds XII, which furnished the *p*-quinones XIII on oxidation with potassium nitrosodisulfonate. This three-step sequence for the quinone elaboration is shorter than that based on Thiele acetoxylation of an *o*-quinone, but does not proceed in as satisfactory over-all yield.

The demonstration[1] that a significant portion of the antibacterial properties[3] of the mitomycin antibiotics[4] is retained by the related 1,2-dialkylindoloquinone I prompted the initiation of a comprehensive program for the preparation of analogs of I. One aspect of this effort was the synthesis of indoloquinones having variants at N-1, C-2, and C-6,[5] which we now report. Since the preparation of a considerable number of such analogs was contemplated, an integral part of this investigation focused on an attempt to devise a more convenient, or at least shorter, procedure than that originally reported[1] (five steps) for the transformation of a 5-methoxy-6-alkylindole into the corresponding 5-methoxy-6-alkylindoloquinone.

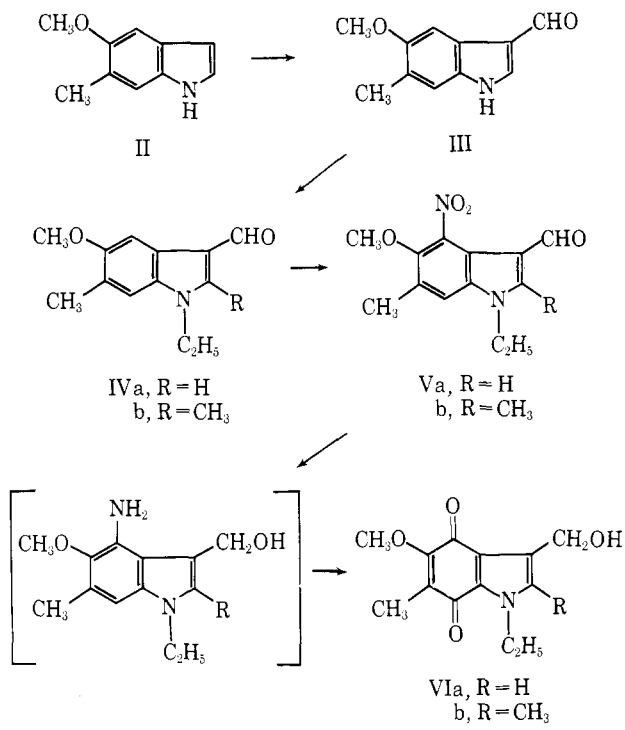


I

Initially, the preparation of the 2-demethyl analog of I was undertaken. For this purpose the previously described[6] 5-methoxy-6-methylindole (II) was converted into the corresponding 3-carboxaldehyde III by the Vilsmeier–Haack technique,[7] and then by N-alkylation to the 1-ethyl derivative IVa (Scheme I).

Previous methods for the elaboration of the indoloquinone system characteristic of I had proceeded from an aldehyde such as IVa *via* the corresponding 4,5-quinone.[1,6,8] A direct approach to the *p*-quinone system predicated on the introduction of an amino group at either C-4 or C-7 of a substance such as IVa also appeared feasible. Thus, nitration of IVa with an equivalent of sodium nitrate in sulfuric acid[9] afforded the nitroaldehyde Va in 52% yield. A similar nitration of the previously described 2-methylaldehyde IVb[1] gave only 8% of Vb; however, fuming nitric acid in acetic acid furnished 69% of this latter substance. (In view of this experience with IVb, subsequent nitrations in this series were conducted with the latter reagent.) The position of the nitro group in aldehydes Va and Vb was indicated by a comparison of the pmr spectra of these compounds with those of their precursors. Specifically, the spectrum of the 2-methylaldehyde IVb had single proton

SCHEME I



(1) For paper XV see G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.*, **10**, 1 (1967).

(2) A portion of this work was described in a preliminary communication: G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 3878 (1964).

(3) (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.

(4) These antibiotics, particularly mitomycin C, are also of interest as antitumor agents: 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.

(5) Other indoloquinones having variants at C-6 are described in a separate paper: W. A. Remers and M. J. Weiss, *J. Am. Chem. Soc.*, **88**, 804 (1966).

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

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

(8) (a) W. A. Remers, P. N. James, and M. J. Weiss, *J. Org. Chem.*, **28**, 1169 (1963); (b) H. Teuber and G. Thaler, *Ber.*, **91**, 2253 (1958).

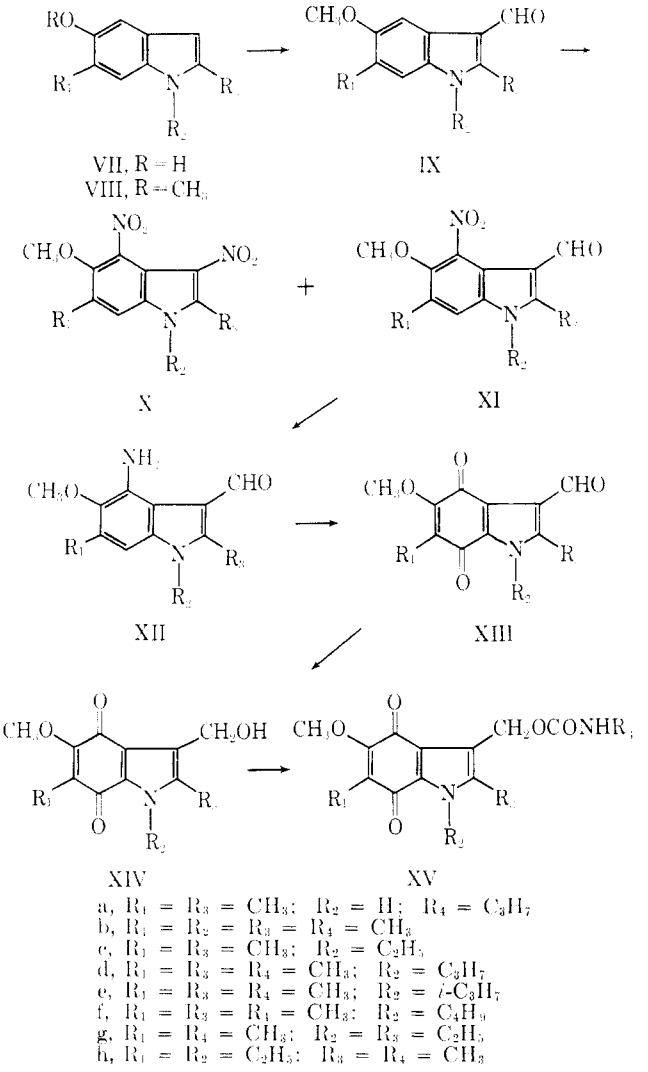
(9) (a) G. Berti and A. Da Settimo, *Gazz. Chim. Ital.*, **91**, 728 (1961); (b) W. E. Noland and R. D. Rieke, *J. Org. Chem.*, **27**, 2250 (1962).

resonances at 427 and 470 cps, the first being assigned to the C-7 proton in view of the low-order secondary coupling manifest in this resonance.[10] Since a similar resonance was evident in the spectrum of the nitro derivative Vb (439 cps), the position of the nitro substituent is restricted to C-4. An analysis of the spectra in the 2-demethyl series did not permit an unequivocal assignment, but did exclude C-7 from consideration. Thus, the spectrum of aldehyde IVa had single proton resonances at 441, 468, and 479 cps, low-order coupling being evident only in the first. For the nitro derivative Va a resonance with similar coupling was observed at 440 cps in addition to a 468-cps signal. The chemical shift of the latter resonance did not vary with concentration, a phenomenon reported for the 2-proton resonance of indole.[11] Nevertheless, the transformations described below demonstrate that the 468-cps resonance is due to the 2-proton and that the nitration product is indeed Va.

For conversion of the nitro group into the required amino function, nitroaldehydes Va and Vb were subjected to catalytic hydrogenation. Somewhat unexpectedly, an uptake of 4 molar equiv of hydrogen was observed, indicating concomitant aldehyde reduction.[12] In view of the known instability of 3-indolylmethanols,[13] the reduction products, without isolation, were treated immediately with potassium nitrosodisulfonate (Fremy's salt) to give the desired quinone alcohols VIa and VIb in 29 and 14% yield, respectively.[14] Although the over-all yield of the 4,7-indoloquinone-3-carbinols, *e.g.*, VI, is lower when prepared by this sequence than when the quinone is elaborated *via* Thiele acetoxylation,[1] the nitration procedure shortens the preparation of these alcohols by four steps. In view of this advantage, the nitration method, in modified form, was applied to the preparation of other analogs, namely, those with hydrogen, methyl, propyl, isopropyl, or butyl at N-1, as well as those with ethyl at C-2 or C-6 (Scheme II).

For the preparation of these analogs the required 5-hydroxyindoles VII were obtained by Nenitzescu condensation[15] of the appropriate benzoquinone and ethyl β-aminocrotonate followed by decarbethoxylation of the resulting 5-hydroxy-3-indolecarboxylates; these preparations have been described in detail elsewhere.[16,17] Transformation of the resulting 5-hydroxyindoles VII into the intermediate nitroaldehydes XI was achieved

SCHEME II



by O-methylation, Vilsmeier–Haack formylation, and nitration (Scheme II). Combustion analysis of several of the nitroaldehydes XI gave high nitrogen values. Moreover, the ultraviolet spectra of these preparations did not exhibit the well-defined minimum (280 mμ) interposed between the maxima (247–248, 295 mμ) present in the spectra of pure Va and Vb. The nature of the impurity was established for the 1-propyl-2,6-dimethyl series (d in Scheme II) from the pmr spectrum. In addition to the resonances anticipated for the desired 4-nitro-3-indolecarboxaldehyde XId, there were present weaker signals at 168, 251, and 447 cps. Of particular significance was the greater chemical shift observed for the 2-methyl resonance (168 *vs.* 159 cps) in the impurity, implying the presence of a group at C-3 having a greater deshielding effect than that of the aldehydo grouping. A nitro substituent at this position might fulfill this requirement. A separation of the two major components was achieved with hydroxylamine in ethanol. The material that crystallized had a pmr spectrum identical with the impurity portion of the above-discussed spectrum and gave combustion analyses consistent with the 3,4-dinitro structure Xd. Subsequent to these observations, other investigators[18] reported that

(10) For other examples of secondary coupling between aryl methyl protons and adjacent ring protons see (a) H. Rottendorf and S. Sternhell, *Tetrahedron Letters*, **No. 20**, 1289 (1963); (b) P. M. Nair and G. Gopakumar, *ibid.*, **No. 13**, 709 (1964), and references cited therein.

(11) M. G. Reinecke, H. W. Johnson, Jr., and J. F. Sebastian, *Chem. Ind.* (London), 151 (1964).

(12) Although the catalytic reduction of 3-indolecarboxaldehyde to give 3-indolylmethanol has been reported [J. Madinaveitia, *J. Chem. Soc.*, 1927 (1937)], Leete[13] was unable to duplicate this transformation.

(13) E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959).

(14) H. Teuber and M. Hasselbach [*Ber.*, **92**, 674 (1959)] have described the conversion of certain di- and trisubstituted anilines into the corresponding *p*-benzoquinones by Fremy's salt.

(15) C. D. Nenitzescu, *Bul. Soc. Chim. România*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930).

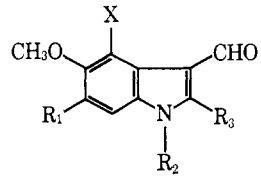
(16) G. R. Allen, Jr., C. Pidacks, and M. J. Weiss, *J. Am. Chem. Soc.*, **88**, 2536 (1966).

(17) In principle the present effort would have been simplified had it proved possible to N-alkylate an appropriate later-stage intermediate in the 1-hydrogen (a) series (see Scheme II). However, our inability to find a convenient procedure for the purification of ethyl 5-hydroxy-2,6-dimethyl-3-indolecarboxylate [R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951)] until this investigation was nearly completed precluded such an approach.

(18) (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).

TABLE I

5-METHOXY-1,2,6-TRISUBSTITUTED 3-INDOLECARBOXALDEHYDES AND THEIR 4-NITRO AND 4-AMINO DERIVATIVES



Compd	X	R_1	R_2	R_3	Yield, %[a]	Mp, °C[b]	Recrystn solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
IXa[c]	H	CH_3	H	CH_3	86	227.0–228.5	Me_2CO–hexane	$C_{12}H_{13}NO_2$	70.91	70.59	6.42	6.52	6.89	6.94
IXb[c]	H	CH_3	CH_3	CH_3	96	187–188	Me_2CO–hexane	$C_{13}H_{15}NO_2$	71.86	71.64	6.96	6.94	6.45	6.62
IXd[c]	H	CH_3	C_3H_7	CH_3	84	117.5–119.5	Me_2CO–hexane	$C_{15}H_{19}NO_2$	73.44	72.94	7.81	7.86	5.71	5.65
IXe[c]	H	CH_3	i-C_3H_7	CH_3	93	172–174	Me_2CO–hexane	$C_{15}H_{19}NO_2$	73.44	72.96	7.81	7.89	5.71	5.87
IXf[c]	H	CH_3	C_4H_9	CH_3	85	96–97	Me_2CO–hexane	$C_{16}H_{21}NO_2$	74.10	74.32	8.16	8.01	5.40	5.36
IXg[c]	H	CH_3	C_2H_5	C_2H_5	73	95.5–97.0	Dil methanol	$C_{15}H_{19}NO_2$	73.44	73.14	7.81	7.83	5.71	5.66
IXh[c]	H	C_2H_5	C_2H_5	CH_3	68	109–110	Me_2CO–hexane	$C_{15}H_{19}NO_2$	73.44	73.19	7.81	7.99	5.71	5.80
XIa[d]	NO_2	CH_3	H	CH_3	78	>280	Me_2CO	$C_{12}H_{12}N_2O_4$						
XIb[d]	NO_2	CH_3	CH_3	CH_3	55	192–193	Me_2CO–hexane	$C_{13}H_{14}N_2O_4$						
XId[d]	NO_2	CH_3	C_3H_7	CH_3	68	136–138	Me_2CO–hexane	$C_{15}H_{18}N_2O_4$						
XIf[d]	NO_2	CH_3	C_4H_9	CH_3	57	127–128	Me_2CO–hexane	$C_{16}H_{20}N_2O_4$						
XIg[d]	NO_2	CH_3	C_2H_5	C_2H_5	66	165–169	Me_2CO–hexane	$C_{15}H_{18}N_2O_4$						
XIh[d]	NO_2	C_2H_5	C_2H_5	CH_3	92	181.0–182.5	Me_2CO–hexane	$C_{15}H_{18}N_2O_4$						
XIIb[e]	NH_2	CH_3	CH_3	CH_3	54	157–158	CH_2Cl_2–petr ether	$C_{13}H_{16}N_2O_2$	67.22	67.02	6.94	7.02	12.06	12.42
XIIc[e]	NH_2	CH_3	C_2H_5	CH_3	40	117.5–118.5	CH_2Cl_2–petr ether	$C_{14}H_{18}N_2O_2$	68.27	68.02	7.37	7.25	11.37	11.36
XIId[e]	NH_2	CH_3	C_3H_7	CH_3	67	128–129	CH_2Cl_2–petr ether	$C_{15}H_{20}N_2O_2$	69.20	68.87	7.74	7.94	10.76	11.04
XIIf[e]	NH_2	CH_3	C_4H_9	CH_3	45	129.5–131.0	CH_2Cl_2–petr ether	$C_{16}H_{22}N_2O_2$	70.04	70.19	8.08	7.52	10.21	10.23
XIIh[e]	NH_2	C_2H_5	C_2H_5	CH_3	74	110.5–112.5	CH_2Cl_2–petr ether	$C_{15}H_{20}N_2O_2$	69.20	69.14	7.74	7.68	10.76	11.09

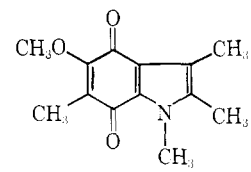
[a] Represents a yield of material with sufficient purity for further transformations. [b] Melting point of analytical sample. [c] Aldehyde IXa had λ_{max} 212 mμ (ε 28,200), 252 (15,950), 282 (16,350), 305 (11,400), whereas IXb–h had λ_{max} 216–218 mμ (ε 28,000–30,200), 257–258 (18,250–20,100), 282–284 (14,250–16,700), 308–310 (13,500–14,600). The infrared spectra of these aldehydes had λ_{max} 3.53–3.56, 3.65–3.70, 6.08–6.11 μ. In addition to the expected alkyl proton resonances, the pmr spectra of aldehydes IX had single proton resonances at 458.3–465.0 (4-H), 419–424 (7-H), and 601–605 cps (*CHO*); however, the 7-proton resonance for IXa (433 cps) and IXe (437 cps) was significantly downfield from the above range. [d] Satisfactory analyses could not be obtained for compounds XIa–h; they are presumed to be contaminated with the corresponding 3,4-dinitro derivative X (see discussion). Aldehyde XIa had λ_{max} 212 mμ (ε 48,000), 242 (19,400), 270 (17,100), whereas XIb–h had λ_{max} 215–218 mμ (ε 30,200–43,000), 248–249 (13,600–18,900), 290–294 (10,900–14,000). The infrared spectra of these nitro aldehydes had λ_{max} 6.00–6.03, 6.50 μ. [e] Aldehydes XIIb–h had λ_{max} 226–229 mμ (ε 28,500–35,000), 252–255 (15,300–18,500), 278–280 (9000–10,900), 348 (5100–6750); λ 2.95, 3.05, 3.55, 6.10–6.14, 6.21–6.30 μ; pmr, 223–225 (3s, OCH_3), 346–353 (2 protons, broad, erased by methanol-d_4, NH_2), 371–380 (1s, 7-*H*), and 574–581.5 cps (1s, *CHO*) in addition to the expected alkyl proton resonances.

displacement of the carboxaldehyde grouping usually occurs during the nitration of 1- (and/or 2-) alkyl-3-indolealdehydes. In general, no effort was made to purify the crude nitration products of Table I, which proved to be of sufficient purity for further transformations (see below).

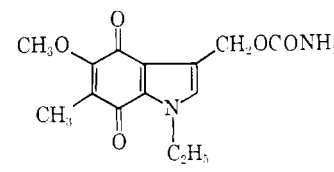
Although catalytic hydrogenation of nitroaldehydes Va and Vb provided a convenient synthesis of the corresponding carbinols VIa and VIb, this reaction did not prove to be generally useful. Thus, hydrogenation of the 1,2-dimethyl-4-nitroaldehyde XIb proceeded slowly and short of theoretical uptake. Fremy's salt oxidation of the reduction filtrate gave a mixture from which only the 3-methylquinone XVI could be isolated. The structure of this product was indicated by the presence of five discrete methyl proton resonances in its pmr spectrum, the absence of hydroxyl absorption in its infrared spectrum, and its recovery on treatment with phenyl chloroformate. Hydrogenation of 1-propyl-4-nitroaldehyde XId, followed by Fremy's salt treatment, gave a complex mixture from which no recognizable product was isolated.

It was apparent that these difficulties could be circumvented by a preferential reduction of the nitro group in nitroaldehydes XI, since the resulting amino group would permit the preparation of the corresponding quinone-3-aldehydes XIII, a method for the satisfactory transformation of which into the 3-carbinols had already been demonstrated.[1,6] This reduction was effected with ferrous ammonium sulfate in dilute alcohol or iron in acetic acid. The latter reagent appeared to be superior, probably as a result of the greater solubility of the starting material in the reduction medium. The intermediate aminoaldehydes XII are listed in Table I. Fremy's salt oxidation of these compounds gave the requisite quinone-3-aldehydes XIII (Table II). Sodium borohydride reduction of XIII followed by regeneration of the quinone system with acidic ferric chloride furnished the corresponding indoloquinone-3-carbinols XIV.

The various carbinols were then converted into the carbamate analogs by ammonolysis of the intermediate phenylcarbonate ester (XVII only) or reaction with the appropriate alkyl isocyanates. Inasmuch as the N-



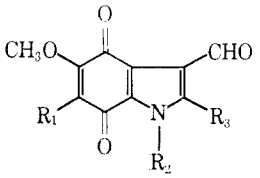
XVI



XVII

TABLE II

5-METHOXY-1,2,6-TRISUBSTITUTED 4,7-DIOXO-3-INDOLECARBOXALDEHYDES

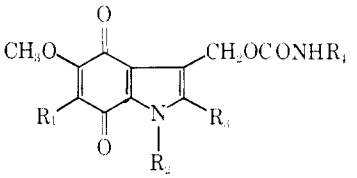


Compd	R_1	R_2	R_3	Yield, %[a]	Mp, °C[b]	Recrystn solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
XIIIa	CH_3	H	CH_3	4[c]	236–240	Me_2CO–hexane	$C_{12}H_{11}NO_4$	61.80	61.96	4.75	5.08	6.01	5.94
XIIIb	CH_3	CH_3	CH_3	45	146–148	CH_2Cl_2–petr ether	$C_{13}H_{13}NO_4$	63.15	62.80	5.30	5.37	5.67	5.71
XIIIc	CH_3	C_2H_5	CH_3	18	125–129[d]	CH_2Cl_2–petr ether							
XIIId	CH_3	C_3H_7	CH_3	32	134–135	CH_2Cl_2–petr ether	$C_{14}H_{15}NO_4$	65.44	65.25	6.22	6.35	5.09	5.26
XIIIe	CH_3	i-C_3H_7	CH_3	21[c]	97–99	CH_2Cl_2–petr ether[e]	$C_{14}H_{15}NO_4$	65.44	65.34	6.22	6.49	5.09	5.11
XIIIf	CH_3	C_4H_9	CH_3	16	82.5–83.0	Petr ether[f]	$C_{15}H_{19}NO_4$	66.42	66.05	6.62	6.65	4.84	4.77
XIIIg	CH_3	C_2H_5	C_2H_5	10[c]	76.0–77.5	CH_2Cl_2–petr ether[g]	$C_{15}H_{17}NO_4$	65.44	65.26	6.22	6.48	5.09	5.26
XIIIh	C_2H_5	C_2H_5	CH_3	22	83.0–83.5	Petr ether[h]	$C_{15}H_{17}NO_4$	65.44	65.07	6.22	6.49	5.09	5.02

[a] Material of analytical purity. [b] These indoloquinone-3-aldehydes had λ_{max} 217–218 mμ (ε 21,300–25,200), 238–246 (11,300–13,600), 268–270 (11,800–14,600), 280–283 (sh) (11,000–13,200), 330–344 (4680–5800), 430–435 (775–1000); λ 3.48–3.53, 5.95–5.96, 6.03–6.10, 6.10–6.15, 6.18–6.25, 6.53–6.55, 6.60–6.65 μ; pmr, 240–243 (3s, OCH_3) and 625–631 cps (CHO) in addition to the expected alkyl proton resonances. [c] Based on the corresponding nitroaldehyde XI, the last solid intermediate. [d] Identical according to the usual criteria with material prepared in another manner.[1] [e] Purified by partition chromatography using a heptane–methanol system; the product was eluted at peak hold-back volume 1.3 (V_m/V_s = 2.46). [f] Purified by partition chromatography using a heptane–methanol system; the product was eluted at peak hold-back volume 1.3 (V_m/V_s = 2.07). [g] Purified by partition chromatography using a heptane–ethyl acetate–2-methoxyethanol–water (95:5:17:3) system; the product was eluted at peak hold-back volume 1.0 (V_m/V_s = 2.64). [h] Purified by partition chromatography using a heptane–methanol system; the product was eluted at peak hold-back volume 1.1 (V_m/V_s = 2.02).

TABLE III

3-HYDROXYMETHYL-5-METHOXY-1,2,6-TRISUBSTITUTED 4,7-INDOLOQUINONE CARBAMATES



Compd	R_1	R_2	R_3	R_4	Yield, %[a]	Mp, °C[b,c]	Recrystn solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
XVII	CH_3	C_2H_5	H	H	60	165–166[d]	Ethyl acetate–hexane	$C_{14}H_{16}N_2O_5$	57.53	57.71	5.52	5.62	9.59	9.57
XVa	CH_3	H	CH_3	C_3H_7	43	>270	Me_2CO–hexane	$C_{16}H_{20}N_2O_5$	59.99	59.86	6.29	6.57	8.75	8.94
XVb	CH_3	CH_3	CH_3	CH_3	71	209–210	CH_2Cl_2–petr ether	$C_{15}H_{18}N_2O_5$	58.81	58.86	5.92	5.88	9.15	9.00
XVd	CH_3	C_3H_7	CH_3	CH_3	39	170–172	CH_2Cl_2–petr ether	$C_{17}H_{22}N_2O_5$	61.06	60.75	6.63	6.67	8.38	8.02
XVe	CH_3	i-C_3H_7	CH_3	CH_3	49	172.0–173.5	CH_2Cl_2–petr ether	$C_{17}H_{22}N_2O_5$	61.06	61.14	6.63	6.68	8.38	8.32
XVf	CH_3	C_4H_9	CH_3	CH_3	77	127–129	CH_2Cl_2–petr ether	$C_{18}H_{24}N_2O_5$	62.05	62.23	6.94	6.90	8.04	7.52
XVg	CH_3	C_2H_5	C_2H_5	CH_3	69	157–159	Ether–petr ether	$C_{17}H_{22}N_2O_5$	61.06	61.11	6.63	6.77	8.38	8.02
XVh	C_2H_5	C_2H_5	CH_3	CH_3	83	142–145	CH_2Cl_2–petr ether	$C_{17}H_{22}N_2O_5$	61.06	61.30	6.63	6.81	8.38	8.21

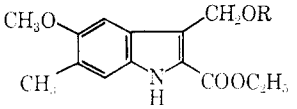
[a] Material of analytical purity. [b] These products except XVa had λ_{max} 230–232 mμ (ε 17,700–19,600), 285–287 (14,000–15,700), 344–346 (3340–3670), 450–455 (1170–1340); for XVa, λ_{max} 230 mμ (ε 18,200), 282 (13,900), 339 (3680), 460 (1250); infrared maxima, 3.00 3.05, 5.90–5.93, 6.00–6.03, 6.10–6.13, 6.20–6.26, 6.47–6.50, 6.60–6.65, 7.85–7.90, 8.99–9.05 μ. [c] Pmr (XVb–f, h), 155–157 (3d, J = 5 cps, $NHCH_3$), 234–236 (3s, OCH_3), 3.08–308.5 (2s, CH_2O), 400–414 (1m, erased by methanol-d_4, $NHCH_3$). [d] Pmr, 245 (3s, OCH_3) 298 (2 protons, broad, erased by methanol-d_4, NH_2), 322 (2s, CH_2O), 424 cps (1s, 2-H) in addition to expected alkyl proton resonances

methyl and N-propyl derivatives of I[19] were found to have the same order of antibacterial activity as I, the more convenient isocyanate procedure was routinely applied.[20] These analogs are given in Table III.

Finally, with regard to the pure 4-amino-3-aldehydes XII, we would note that the position (6.23 μ)[22] of the carbonyl band in the infrared represents a considerable bathochromic shift (Δ 0.13 μ) from that of the parent 4-unsubstituted compounds, presumably as a result of hydrogen bonding. With the 4-nitro-3-aldehydes XI a small (Δ 0.07 μ) hypsochromic shift is observed. This shift is probably the result of dipole–dipole interaction[23] or the electronic interaction of the nitro group with the hetero atom.[24]

(19) See ref 2 for the preparation of these compounds.

(20) As a model system for the preparation of the 1-hydrogen carbamate ester XVa, the 3-indolylmethanol i[21] was treated with butyl isocyanate. Only the O-acylated product ii was formed (see Experimental Section).



i, R = H
ii, R = $CONHC_4H_9$

(21) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 4612 (1964).

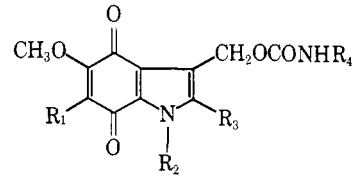
(22) Without exception the CO band of these compounds appeared as doublets (6.10, 6.23 μ) whether the spectra were measured in CH_3CN solutions or KBr disks. The shorter wavelength peak was of moderate intensity, whereas the second peak was of the intensity usually associated with this function.

(23) (a) E. J. Corey, *J. Am. Chem. Soc.*, **76**, 175 (1954); (b) R. E. Schaub, W. Fulmor, and M. J. Weiss, *Tetrahedron*, **20**, 373 (1964).

(24) Other examples of a *peri* effect in 3,4-disubstituted indoles have been noted.[5]

TABLE IV

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



					Minimum inhib conen (μg/ml)[a] against									
Compd	R_1	R_2	R_3	R_4	*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
I	CH_3	C_2H_5	CH_3	H	6.25	1.56	1.56	6.25	12.5	0.78	3.12	3.12	1.56	6.25	0.39	6.25
XVII	CH_3	C_2H_5	H	H	6.25	1.56	1.56	12.5	50	1.56	12.5	6.25	0.78	25	0.39	6.25
XVa	CH_3	H	CH_3	C_3H_7	50	...	50	...	...	50	...	...	50	...	25	6.25
XVb	CH_3	CH_3	CH_3	CH_3	6.25	3.12	3.12	6.25	50	0.39	3.12	3.12	0.39	6.25	≤0.2	0.78
XVd	CH_3	C_3H_7	CH_3	CH_3	6.25	6.25	6.25	25	...	1.56	25	25	1.56	50	0.39	12.5
XVe	CH_3	*i*-C_3H_7	CH_3	CH_3	25	12.5	12.5	50	...	3.12	50	50	6.25	...	1.56	6.25
XVf	CH_3	C_4H_9	CH_3	CH_3	3.12	6.25	6.25	6.25	...	0.39	6.25	6.25	0.78	12.5	0.39	12.5
XVg	CH_3	C_2H_5	C_2H_5	CH_3	6.25	6.25	6.25	25	...	1.56	12.5	12.5	3.12	50	0.39	6.25
XVh	C_2H_5	C_2H_5	CH_3	CH_3	12.5	6.25	6.25	25	...	3.12	6.25	6.25	3.12	50	0.78	6.25

[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*, NIRL B1397; *B. cereus* = *Bacillus cereus*, ATCC 10702; *Past.* 310 = *Pasteurella multocida*, ATCC 310.

Biology.—Most of the indoloquinone carbamates (XVa–h and XVII) showed an order of activity similar to that of the lead compound I when tested *in vitro* against a spectrum of gram-positive organisms (Table IV). The notable exception is the 1-hydrogen analog XVa, which has only marginal activity. Included in the spectrum of microorganisms are a tetracycline-resistant species (*Staphylococcus aureus* var. Rose) and tetracycline- as well as penicillin-resistant species (*Streptococcus* sp., β-hemolytic, 80, and *Streptococcus* sp., nonhemolytic, 11). However, with the exception of *Pasteurella multocida*, ATCC 310, only marginal activity against gram-negative species was noted for these compounds.

Experimental Section

Melting points were determined in open capillary tubes and are corrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer. Infrared spectra were determined in KBr disks, unless noted otherwise, with a Perkin-Elmer Model 21 spectrophotometer. Pmr spectra were determined in $CDCl_3$, unless noted otherwise, with a Varian A-60 spectrometer using 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), *x*q (quartet), or *x*m (multiplet), where *x* refers to the number of protons indicated by integration. The petroleum ether used was that fraction boiling at 30–60°. All nitrogen analyses were obtained by the Dumas technique using a combustion temperature of 950° for 10 min; the usual conditions (850° for 5 min) used in this laboratory often gave results that were 20–30% low.

5-Methoxy-6-methyl-3-indolecarboxaldehyde (III).—To 3.5 ml of dimethylformamide (DMF) was added with stirring and ice cooling 1.69 g (11 mmoles, 1 ml) of $POCl_3$. To this solution was then added dropwise a solution of 1.61 g (10 mmoles) of 5-methoxy-6-methylindole (II)[6] in 8 ml of DMF. The temperature of the reaction was kept below 10° during the addition which required 20 min. A solid separated 15 min after the start of the addition. Upon completion of the addition, the ice bath was removed and replaced by a warm-water bath. The paste was kept at 30–35° with stirring for 45 min. Crushed ice was added to the mixture which was then treated with a solution of 4.5 g of NaOH in 20 ml of water. The mixture was brought to boiling and then chilled in an ice bath to give 1.60 g (85%) of tan solid, mp 198–201°. A 200-mg sample was recrystallized from acetone–hexane to give 173 mg of crystals: mp 200–201°; λ_{max} 211, 251, 275, 299 mμ (ε 28,200, 16,800, 15,100, 10,800); λ 2.90, 3.12, 3.55, 6.10, 8.28, 9.35 μ; pmr (DMSO-d_6), 139 (3s, 6-CH_3), 235 (3s, OCH_3), 445, 463, 494 (each 1s, aryl H), 604 cps (1s, C*H*O).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.47; H, 6.03; N, 7.43.

The 5-methoxy-1,2,6-trisubstituted 3-indolecarboxaldehydes (IX) of Table I were prepared in a similar manner from the corresponding 5-methoxy-1,2,6-trisubstituted indoles (VIII) (see below).

1-Ethyl-5-methoxy-6-methyl-3-indolecarboxaldehyde (IVa).—A mixture of 10.60 g (55 mmoles) of III and 180 ml of 40% KOH solution was heated with stirring on the steam bath. When the mixture became hot, all solid dissolved and 60.0 g (0.39 mole, 51 ml) of ethyl sulfate was added dropwise over 75 min. The solution was allowed to cool, whereupon crystals separated from the aqueous solution. The mixture was extracted with ethyl acetate, and the extract was washed with saline, dried ($MgSO_4$), and evaporated. The residue crystallized from ether–petroleum ether to give 10.06 g (89%) of crystals, mp 97–98°. A sample was recrystallized twice from dilute alcohol to give cream-colored crystals: mp 96–98°; λ_{max} 215, 256, 276, 306 mμ (ε 41,200, 21,500, 15,800, 14,200); λ 3.59, 3.63, 3.69, 6.02–6.08 μ; pmr, 90 (3t, *J* = 7 cps, CH_3CH$_2$), 144 (3s, 6-CH_3), 239 (3s, CH_3O), 251 (2q, partially hidden, *J* = 7 cps, CH$_3$CH_2), 441 (1s, broad base, 7-H), 468, 479 (1s each, 2- and 4-H), 605 cps (C*H*O).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.95; H, 6.71; N, 6.28.

1-Ethyl-5-methoxy-6-methyl-4-nitro-3-indolecarboxaldehyde (Va).—To an ice-chilled, stirred solution of 1.085 g (5.0 mmoles) of IVa in 12 ml of concentrated H_2SO_4 was added dropwise over 30 min a solution of 0.425 g (5.0 mmoles) of $NaNO_3$ in 7 ml of concentrated H_2SO_4. The resulting solution was stirred for an additional 45 min and then poured onto a cracked ice–water mixture. The solid was extracted into CH_2Cl_2, and the extract was washed to neutrality with saline, dried ($MgSO_4$), and evaporated. The residue was crystallized from acetone–hexane to give 525 mg of light yellow solid, mp 150–152°. Material from a similar experiment was obtained as yellow crystals: mp 150–152°; λ_{max} 215, 248, 295 mμ (ε 29,100, 15,100, 10,750); λ 3.55, 6.00, 6.11, 6.50 μ; pmr, 93 (3t, *J* = 7 cps, CH_3CH$_2$), 148 (3s, 6-CH_3), 235 (3s, CH_3O), 257 (2q, *J* = 7 cps, CH$_3$CH_2), 427 (1s, broad base, 7-H), 470 (1s, 4-H), 591 cps (1s, C*H*O).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.83; H, 5.28; N, 10.53.

1-Ethyl-5-methoxy-2,6-dimethyl-4-nitro-3-indolecarboxaldehyde (Vb). A.—In the manner described above 462 mg (2.00 mmoles) of 1-ethyl-5-methoxy-2,6-dimethyl-3-indolecarboxaldehyde (IVb)[1] was nitrated with 170 mg (2.00 mmoles) of $NaNO_3$ in H_2SO_4. The crude product was subjected to par-

tition chromatography[25] on Celite (diatomaceous silica) using a cyclohexane–dioxane–water (75:25:8) system, and the fraction with peak hold-back volume at 2.0 (V_m/V_t = 2.8) was evaporated; the residue was recrystallized from acetone–hexane to give 42 mg (8%) of orange crystals: mp 155–157°; λ_{max} 218, 247, 295 mμ (ε 39,900, 16,000, 12,100); λ 3.50, 6.03, 6.13, 6.50, 10.00 μ.

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.75; H, 5.41; N, 9.98.

B.—To a solution of 5.44 g (23.5 mmoles) of IVb in 150 ml of glacial acetic acid was added dropwise with stirring 5.4 ml of yellow fuming nitric acid; the reaction temperature was kept below 20° during the addition. The resulting solution was stirred at room temperature for 1 hr, whereafter it was poured onto cracked ice and water. The mixture was filtered to give 5.04 g of orange solid, mp 128–135°. This material was recrystallized from acetone–hexane to give 3.95 g of crystals, mp 149–152°. The mother liquor was evaporated, and the residue was dissolved in CH_2Cl_2 and passed through a Florisil (magnesia–silica gel) column, methylene chloride being used as the wash liquid. The solvent was removed from the eluates, and the residue was recrystallized from acetone–hexane to give 522 mg (69% total) of yellow crystals: mp 149–152°; pmr, 32 (3t, J = 7 cps, CH_3CH_2), 146 (3s, 6-CH_3), 160 (3s, 2-CH_3), 232 (3s, CH_3O), 251 (2q, J = 7 cps, CH_2CH_3), 439 (1s, 7-H), 594 cps (1s, CHO).

The crude 5-methoxy-4-nitro-1,2,6-trisubstituted 3-indolecarboxaldehydes (XI) of Table I were prepared in a similar manner from the corresponding 5-methoxy-1,2,6-trisubstituted 3-indolecarboxaldehydes (IX) (Table I).

1-Ethyl-3-hydroxymethyl-5-methoxy-6-methylindole-4,7-dione (VIa).—A mixture of 532 mg (2.06 mmoles) of Va and 105 mg of a 10% Pd–C catalyst in 100 ml of ethanol containing 1 ml of water was shaken under hydrogen for 105 min. A pressure drop corresponding to 4 molar equiv of hydrogen was observed. The mixture was filtered, and the filtrate was added with stirring to a solution of 5.60 g of potassium nitrosodisulfonate in 40 ml of water and 120 ml of 0.167 M KH_2PO_4 solution. The blue color was immediately discharged and within 10 min an orange color developed. Stirring was continued for 80 min, and the solution was diluted with water and extracted three times with CH_2Cl_2. The organic solution was dried ($MgSO_4$) and evaporated. The residue crystallized from ether–petroleum ether to give 149 mg (29%) of orange needles, mp 78–81°. Material from a similar experiment was obtained as orange needles, mp 74–75°, having qualitative ultraviolet and infrared spectra in accord with the desired structure.

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 63.05; H, 6.32; N, 5.91.

1-Ethyl-3-hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-dione (VIb).—In the manner described above, 830 mg (3.0 mmoles) of Vb, 85 mg of 10% Pd–C catalyst, 100 ml of ethanol, and 1 ml of water was shaken under hydrogen in the Parr apparatus. Hydrogen consumption was slow and two batches (200 and 330 mg) of fresh catalyst were added 75 min and 4 hr after the start of the reduction. Hydrogen uptake was complete (4 molar equiv) after 4.25 hr. The mixture was filtered, and the filtrate was added to a stirred solution of 3.22 g (12 mmoles) of potassium nitrosodisulfonate in 120 ml of 0.167 M KH_2PO_4 and 240 ml of water. After 1 hr the crude product was isolated with CH_2Cl_2 and chromatographed on Florisil. The material eluted by benzene and methylene chloride was recrystallized from petroleum ether to give 112 mg (14%) of orange crystals, mp 75–79°. This material was identical with that prepared previously.[1]

5-Methoxy-1,2,3,6-tetramethylindole-4,7-dione (XVI).—5-Methoxy-1,2,6-trimethyl-4-nitro-3-indolecarboxaldehyde (XIb) (6.50 g, 23 mmoles) was hydrogenated as described above. After 30 hr, 88% of 4 equiv of hydrogen was absorbed; the reduction solution was oxidized with Fremy's salt, and the crude product was isolated with CH_2Cl_2. Chromatography of this material on Florisil gave in the methylene chloride eluate 1.00 g (18%) of orange needles, mp 121–124°. A sample was recrystallized from methylene chloride–petroleum ether to give needles; mp 123–125°; λ_{max} 231, 285, 365, 470 mμ (ε 17,300, 15,300, 3500, 1830); λ 6.05, 6.12, 6.20, 8.14, 8.88 μ; pmr, 115 (3s, 6-CH_3), 128.5 (3s, 3-CH_3), 133.5 (3s, 2-CH_3), 230 (3s, 1-CH_3), and 238.5 cps (3s, OCH_3).

(25) 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. Coscia, *Tetrahedron*, **20**, 357 (1964).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.88; H, 6.72; N, 6.34.

Isolation of Ethyl 5-Hydroxy-2,6-dimethyl-3-indolecarboxylate.—The condensation of 400 g of ethyl β-aminocrotonate with 392 g of toluquinone was carried out as described previously. The crude product (417.1 g, mp 182–205°) was divided into three parts and each was stirred with the lower phase (20 ml/g) of a heptane–ethyl acetate–methanol–water (70:30:15:6) system for 45 min to 2 hr. The undissolved solids (31.2 g) were then combined and treated similarly for 1 hr with 310 ml of the lower phase of the above system to give 28.6 g of solid, mp 218–225°. Thin layer chromatography of this material showed it to contain a small portion of the 5,7 isomer, but it was used without further purification.

It should be noted that attempts to purify the original crude material by recrystallization from ethanol (*cf.* the reference cited in footnote 14) did not improve the melting range.

5-Methoxy-1,2,6-trisubstituted Indoles (VIII).—The following experiment illustrates the general procedure. To a stirred solution of 13.5 g (0.084 mole) of 5-hydroxy-2,6-dimethylindole (VIIa) in 150 ml of ethanol and 300 ml of 2 N NaOH solution was added dropwise at reflux temperature and under nitrogen 50.0 g (0.40 mole, 37 ml) of methyl sulfate. This addition was performed over 90 min, and after its completion, heating was continued for 30 min. The cooled mixture was diluted with water and extracted with ethyl acetate. The material contained in these extracts was adsorbed from benzene onto a Florisil column. The first 1 l. of benzene eluate from this column contained 13.70 g (93%) of crystals of suitable purity for subsequent work. A sample was recrystallized from acetone–hexane to give 5-methoxy-2,6-dimethylindole (VIIIa) as white crystals: mp 94–96°; λ_{max} 211, 273, 294, 298, 304 mμ (ε 25,600, 7260, 6750, 6120, 5250); λ 2.95, 6.29 μ; pmr, 130 (3s, 2-CH_3), 137.5 (3s, 6-CH_3), 225.5 (3s, OCH_3), 363 (1m, 3-H), 400 (1s, low-order secondary coupling, 7-H), 414 (1s, 4-H), and 427 cps (broad resonance erased on exchange with methanol-d_4, NH).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.99; H, 7.29; N, 7.71.

5-Methoxy-1,2,6-trimethylindole (VIIIb) was obtained (97%) as white plates, mp 101–103°, after recrystallization from methylene chloride–petroleum ether: λ_{max} 219, 280, 297, 308 mμ (ε 27,400, 8610, 7380, 4730); no OH absorption in the infrared; pmr, 138, 141 (6, two s, 2-CH_3 and 6-CH_3), 208 (3s, NCH_3), 229 (3s, OCH_3), 366 (1s, 3-H), 416, 417 cps (2, overlapping s, 4-H and 7-H).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.95; H, 8.12; N, 7.32.

The remainder of the 5-methoxy-1,2,6-trialkylindoles were obtained as colorless or pale amber oils which were utilized without characterization for the preparation of the corresponding 3-carboxaldehydes.

Isolation of 5-Methoxy-2,6-dimethyl-3,4-dinitro-1-propylindole (Xd).—The crude nitration product (Table I, IXd) (316 mg, 1.09 mmoles) was treated with 76 mg (1.10 mmoles) of hydroxylamine hydrochloride and 57 mg (0.55 mmole) of Na_2CO_3 in 10 ml of boiling ethanol for 45 min. The cool solution deposited 68 mg of long yellow needles, mp 160–163°, on standing at room temperature for 24 hr. This material was recrystallized from ethanol to give 51 mg of needles, mp 169–172°, the melting range of which was raised to 171–173° by an additional recrystallization: λ_{max} 216, 262, 281, 345 mμ (ε 39,400, 8600, 7990, 8920); λ 6.50, 7.43 μ; pmr, 61 (t, J = 6 cps, $CH_2CH_2CH_3$), 110 (m, CH_2CH_2-CH_3), 148 (3s, 6-CH_3), 168 (3s, 2-CH_3), 231 (3s, OCH_3), 251 (2t, J = 7.5 cps, $CH_2CH_2CH_3$), 447 cps (1s, 7-H).

Anal. Calcd for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.68. Found: C, 54.57; H, 5.78; N, 14.01.

4-Amino-1,2,6-trisubstituted 3-Indolecarboxaldehydes (XII). A. Ferrous Ammonium Sulfate Procedure.—The following experiment illustrates this procedure. To a stirred mixture of 2.63 g (10 mmoles) of 5-methoxy-1,2,6-trimethyl-4-nitro-3-indolecarboxaldehyde (XIb) in 250 ml of 50% ethyl alcohol was added a solution of 26.8 g (0.10 mole) of $FeSO_4 \cdot 7H_2O$ in 250 ml of water. The resulting mixture was heated to steam-bath temperature, and at 5-min intervals, 5-ml portions of 17% NH_4OH (30 ml total) were added. The resulting dark mixture was heated for an additional 10 min and then filtered while hot. The filter cake was washed thoroughly with acetone, and the combined filtrate and washings were extracted with CH_2Cl_2. The combined extracts were washed with dilute HCl (4:1); the washes were neutralized with Na_2CO_3 and extracted with CH_2Cl_2.

Removal of the solvent gave the product, the characterization of which is included in Table I.

B. Iron and Acetic Acid Procedure.—A stirred solution of 4.29 g (14.8 mmoles) of 1,6-diethyl-5-methoxy-2-methyl-4-nitro-3-indolecarboxaldehyde (XIh) in 300 ml of glacial acetic acid and 30 ml of water was heated to steam-bath temperature and treated with ten approximately equal portions of iron filings (6.67 g total) over 90 min. Additional water (30 ml) was added after 45 min. The hot solution was decanted from the excess iron filings into a large volume of water. This solution was extracted several times with CH_2Cl_2, and the combined extracts were washed successively with water, Na_2CO_3 solution, and again with water. Evaporation of the dried organic solution gave 2.83 g (74%) of solid of suitable purity for the subsequent oxidation. The characterization of this substance is given in Table I.

5-Methoxy-1,2,6-trisubstituted 4,7-Dioxo-3-indolecarboxaldehydes (XIII).—The following experiment illustrates the general procedure. A solution of 5.38 g (23.2 mmoles) of 4-amino-5-methoxy-1,2,6-trimethyl-3-indolecarboxaldehyde (XIIb) in 1 l. of acetone was added to a stirred solution of 25.0 g (93.4 mmoles) of potassium nitrosodisulfonate in 800 ml of water and 400 ml of 0.167 *M* KH_2PO_4 solution. The resulting brown solution was stirred for 2 hr and then allowed to stand for 15 hr. The crude product was isolated with CH_2Cl_2 and chromatographed on Florisil. The material in the first 4.5 l. of CH_2Cl_2 eluate was recrystallized from methylene chloride–petroleum ether to give, in three crops, 2.664 g (45%) of orange needles. Further characterization of this substance is given in Table II.

Several of these substances required a subsequent partition chromatography on Celite for purification. The details of this chromatography are given in Table II.

3-Hydroxymethyl-5-methoxy-1,2,6-trisubstituted Indole-4,7-diones (XIV).—The following preparation illustrates the general procedure. A stirred solution of 831 mg (3.36 mmoles) of 5-methoxy-1,2,6-trimethyl-4,7-dioxo-3-indolecarboxaldehyde (XIIIb) in 100 ml of methanol was degassed with a stream of nitrogen, heated to reflux temperature, and treated with 565 mg of $NaBH_4$. Within 30 sec the red-orange solution became pale yellow and heating was discontinued after 2 min. The solution was stirred at room temperature for 1 hr, whereafter 10 ml of acetone was added; 5 min later 6 ml of a 1 *N* $FeCl_3$ in 0.1 *N* HCl solution 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 extracts were washed successively with water and saline, dried ($MgSO_4$), and evaporated. The residue was recrystallized from methylene chloride–petroleum ether to give 636 mg (76%) of **3-hydroxymethyl-5-methoxy-1,2,6-trimethylindole-4,7-dione (XIVb)** as red crystals which slowly decomposed at 123–>145°; a sample inserted at 145° melted rapidly and cleanly, however; λ_{max} 230, 285, 350, 465 mμ (ε 18,200, 14,200, 3340, 1290); λ 2.95, 6.04 (sh), 6.11, 6.21, 8.88, 9.11, 10.10 μ; pmr, 115.5 (3s, 6-CH_3), 133.5 (3s, 2-CH_3), 231 (3s, NCH_3), 240 (3s, OCH_3), 275 cps (2s, CH_2O).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: 62.46; H, 6.22; N, 5.62.

3-Hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-dione (XIVa) was obtained in 55% yield and recrystallized from acetone–hexane to give red crystals: mp 233–235° dec; λ_{max} 230, 282, 342, 470 mμ (ε 17,700, 13,200, 3060, 1250); λ 2.95 (sh), 3.09, 6.00, 6.10, 6.22, 9.06, 10.01 μ.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.46; H, 5.57; N, 6.19.

3-Hydroxymethyl-1-isopropyl-5-methoxy-2,6-dimethylindole-4,7-dione (XIVe) was purified by partition chromatography on Celite using a heptane–methanol system. The product was isolated from that fraction having peak hold-back volume 2.4 (V_m/V_s = 2.50) and, after crystallization from methylene chloride–petroleum ether, was obtained as red needles: mp 87.5–88.0°; λ_{max} 231, 286, 349, 460 mμ (ε 17,900, 14,700, 3330, 1360); λ 2.90, 6.14, 6.27, 9.08, 10.03 μ; pmr, 92 (6d, *J* = 8 cps, CH(CH_3)$_2$), 117 (3s, 6-CH_3), 140 (3s, 2-CH_3), 237 (3s, OCH_3), 250 (d, *J* = 6.5 cps, O*H*, erased with methanol-d_4), 278 (2d, *J* = 6 cps, CH_2O, coalesced by methanol-d_4 into singlet at 278 cps), 315 cps [broad resonance, C*H*(CH_3)$_2$].

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.95; H, 7.18; N, 4.79.

1-Butyl-3-hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-dione (XIVf) was obtained in 86% yield from ether–petroleum ether as red-orange needles: mp 68–70°; λ_{max} 232, 287, 350, 460 mμ (ε 17,800, 14,500, 3200, 1310); λ 3.10, 6.01, 6.12, 6.21, 9.07, 10.00 μ; pmr, 59 (t, *J* = 6 cps, $C_3H_6CH_3$), 93 (m, CH_2-$CH_2CH_2CH_3$), 117 (3s, 6-CH_3), 135 (3s, 2-CH_3), 239 (3s, OCH_3), 252 (apparent partially hidden quartet, *J* = 7.5 cps, NCH_2 and O*H*), 276 cps (2s, CH_2O).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.69; H, 7.40; N, 5.08.

1,6-Diethyl-3-hydroxymethyl-5-methoxy-2-methylindole-4,7-dione (XIVh) was obtained in 66% yield from methylene chloride–petroleum ether as red needles: mp 128–129°; λ_{max} 231, 288, 350, 460 mμ (ε 19,100, 14,700, 3410, 1250); λ 3.00, 6.00, 6.12, 6.24, 8.80, 8.99, 10.16 μ; pmr, 64 (3t, *J* = 7.5 cps, 6-CH_2CH_3), 79 (3t, *J* = 7 cps, NCH_2CH_3), 135 (3s, 2-CH_3), 149 (2q, *J* = 7.5 cps, 6-CH_2CH_3), 239 (3s, OCH_3), 261 (2q, *J* = 7 cps, NCH_2CH_3), 275 cps (2m, CH_2O, coalesced by methanol-d_4 into sharp singlet).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.61; H, 6.84; N, 5.31.

The remaining members (XIVd and XIVg) of this series were obtained as oils which were used without purification for the preparation of the carbamates.

1-Ethyl-3-hydroxymethyl-5-methoxy-6-methylindole-4,7-dione Carbamate (XVIII).—To a stirred, ice-chilled solution of 149 mg (0.6 mmole) of VIa in 5 ml of pyridine was added 0.5 ml of phenyl chloroformate. The resulting mixture was stirred at room temperature for 90 min, after which water was added and the oily mixture was extracted with CH_2Cl_2. The extract was washed with saline, dried ($MgSO_4$), and evaporated. The residue was dissolved in toluene, and the solvent was evaporated to remove traces of pyridine. The residue was dissolved in 15 ml of CH_2Cl_2 and cooled in an acetone–Dry Ice bath with stirring; ammonia was introduced until the volume of the solution was approximately 30 ml. This solution was stirred at room temperature for 90 min, after which a warm-water bath was placed under the reaction vessel to remove the excess NH_3. The concentrate was washed successively with saline, Na_2CO_3 solution, and finally with saline, dried ($MgSO_4$), and evaporated. The residue was recrystallized from methylene chloride–petroleum ether to give 106 mg (60%) of orange needles, mp 165–168°. Further characterization of this substance is given in Table III.

3-Hydroxymethyl-5-methoxy-1,2,6-trisubstituted Indole-4,7-dione Alkylcarbamates.—The following experiment illustrates the general procedure. A solution of 400 mg (1.6 mmoles) of XIVb in 15 ml of methyl isocyanate was heated at reflux temperature for 18 hr. The excess isocyanate was removed under reduced pressure; the residue was recrystallized from methylene chloride–petroleum ether to give 349 mg of 3-hydroxymethyl-5-methoxy-1,2,6-trimethylindole-4,7-dione methylcarbamate (XVb) as orange needles, mp 209–210°. Further characterization of this substance is given in Table III.

Ethyl 3-Hydroxylmethyl-5-methoxy-6-methyl-2-indolecarboxylate Butylcarbamate (ii).—A mixture of 500 mg of ethyl 3-hydroxymethyl-5-methoxy-6-methyl-2-indolecarboxylate (i)[21] and 8 ml of butyl isocyanate was heated on the steam bath for 3 hr. The cooled solution was diluted with petroleum ether to give 243 mg of white solid, mp 151–154° (gas). This material separated as a gel from methylene chloride–petroleum ether; on drying it had mp 156–157° (gas); λ_{max} 210, 302 mμ (ε 31,900, 19,900); λ 3.02, 5.90, 5.94, 6.51, 8.00, 8.75, 9.84 μ; pmr (DMSO-d_6), 52 (ill-defined t, *J* = 6 cps, $C_3H_6CH_3$), 82 (t, *J* = 7.5 cps, OCH_2CH_3 superimposed on $CH_2CH_2CH_2CH_3$), 137 (3s, 6-CH_3), 182 (m, $CH_2C_3H_7$), 230 (3s, OCH_3), 261 (2q, *J* = 7.5 cps, OCH_2-CH_3), 335 (2s, CH_2O), 424 (broad resonance, N*H*CO) 432, 436 (1s each, 4-H and 7-H), 695 cps (1s, N_1H).

Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.96; H, 7.23; N, 7.73. Found: C, 62.94; H, 7.10; N, 7.61.

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