described above) was dried over magnesium sulfate for 16 hr. at room temperature, the solution turned black. It was filtered and concentrated under reduced pressure and the dark residue was purified by chromatography on Florisil[17] with benzene as eluent. Concentration of the golden eluate afforded 236 mg. of golden yellow plates. Recrystallization from methanol gave 195 mg. (5%) of methyl 7-benzyloxy-1-chloropyrrolo[1,2-*a*]indole-3-methylenecarboxylate (III) as golden needles, m.p. 146°; $\lambda_{max}$ 5.9, 6.2 $\mu$; 261 ($\epsilon$ 12,000), 280 ($\epsilon$ 11,000), 407 ($\epsilon$ 23,000) m$\mu$; n.m.r.: 6.23 (three protons, methyl ester), 4.93 (two protons, benzylic), 4.12 (proton on exocyclic double bond), 3.65 (C-9 proton), 2.63 (C-2 proton), 3.05 (doubled doublet, $J_{5,6}$ = 9 c.p.s., $J_{6,8}$ = 2 c.p.s., C-6 proton), 2.88 (doublet, $J_{6,8}$ = 2 c.p.s., C-8 proton), 2.75 (doublet, $J_{5,6}$ = 9 c.p.s., C-5 proton), 2.60 (five protons, phenyl) $\tau$.

*Anal.* Calcd. for $C_{21}H_{16}ClNO_3$ (365.80): C, 68.93; H, 4.41; Cl, 9.69; N, 3.83. Found: C, 69.15; H, 4.68; Cl, 10.17; N, 3.38.

**Methyl 7-Benzyloxy-9H-pyrrolo[1,2-*a*]indole-3-oxalate (VIII).**—An ice-cooled solution of 520 mg. (2 mmoles) of 7-benzyloxy-9H-pyrrolo[1,2-*a*]indole (VI)[5] in 10 ml. of methylene chloride was treated with 254 mg. (2 mmoles) of oxalyl chloride. After 2 hr. the mixture was concentrated under reduced pressure and the residue was treated with methanol and solid sodium bicarbonate. This mixture was boiled and filtered, then cooled. Tan prisms, m.p. 83–85°, crystallized from the filtrate. Recrystallization from methanol afforded 283 mg. (41%) of methyl 7-benzyloxy-9H-pyrrolo[1,2-*a*]indole-3-oxalate (VIII) as yellow needles, m.p. 83–85°; $\lambda_{max}$ 5.75 (ester carbonyl), 6.05 (oxalyl keto group); ultraviolet spectrum in Fig. 1; n.m.r.: 6.18 (two protons, C-9 methylene), 6.03 (three protons, methoxyl), 4.95 (two protons, benzylic methylene), 3.78 (doublet, $J_{1,2}$ = 4 c.p.s., C-1 proton), 3.08 (doubled doublet, $J_{5,6}$ = 9 c.p.s., $J_{6,8}$ = 2 c.p.s., C-6 proton), 3.03 (doublet, $J_{6,8}$ = 2 c.p.s., C-8 proton), 2.60 (five protons, phenyl), 2.53 (doublet, $J$ = 4 c.p.s., C-2 proton), 1.40 (doublet, $J$ = 9 c.p.s., C-5 proton) $\tau$.

*Anal.* Calcd. for $C_{21}H_{15}NO_4$ (347.35): C, 72.61; H, 4.93; N, 4.03. Found: C, 72.56; H, 5.04; N, 3.72.

**1-Chloro-3-chlorooxalyl-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole (IX).**—To an ice-cooled solution of 1.08 g. (5 mmoles) of 2,3-dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo[1,2-*a*]indole (VII)[10] in 75 ml. of methylene chloride was added a solution of 1.27 g. (10 mmoles) of oxalyl chloride in 10 ml. of methylene chloride. After 20 min. the orange needles that separated were collected, washed with cold methylene chloride, and dried. This procedure gave 0.45 g. of 1-chloro-3-chlorooxalyl-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole (IX), m.p. 154–160°. Work-up of the mother liquor and wash gave 0.58 g. of orange needles, m.p. 142–145°. After two recrystallizations from methylene chloride, orange needles, m.p. 164–167°, were obtained; $\lambda_{max}$ 5.65 (acid chloride carbonyl), 6.03 (oxalyl keto group) $\mu$, no 1-keto group; $\lambda_{max}^{CHCl_3}$ 247 ($\epsilon$ 13,000), 305 ($\epsilon$ 10,000), 330 ($\epsilon$ 10,000) m$\mu$; positive test with alcoholic silver nitrate; n.m.r.: 7.72 (three protons, 6-methyl), 6.36 (two protons, C-9 methylene), 6.15 (three protons, O-methyl), 3.07 (C-8 proton), 2.70 (C-2 proton), 1.60 (C-5 proton) $\tau$.

*Anal.* Calcd. for $C_{15}H_{11}Cl_2NO_5$ (324.15): C, 55.58; H, 3.42; Cl, 21.88; N, 4.32. Found: C, 55.85; H, 3.57; Cl, 22.01; N, 4.48.

When a mixture of 86 mg. (0.4 mmole) of 2,3-dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo[1,2-*a*]indole (VII) and 51 mg. (0.4 mmole) of oxalyl chloride in 5 ml. of ether was kept at 25° for 20 hr., then concentrated under reduced pressure, the tan solid residue (80 mg.) had an infrared absorption spectrum identical with that of starting material.

**Methyl 1-Chloro-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole-3-oxalate (X).**—A sample of 1-chloro-3-chlorooxalyl-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole (IX) was dissolved in warm methanol. The yellow solid that crystallized from the solution was methyl 1-chloro-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole-3-oxalate (X), m.p. 148°; $\lambda_{max}$ 5.77 (ester carbonyl), 6.05 (oxalyl keto group) $\mu$; 247 ($\epsilon$ 13,000), 305 ($\epsilon$ 10,000), 330 ($\epsilon$ 10,000,) m$\mu$; n.m.r.: 7.77 (three protons, 6-methyl), 6.24 (two protons, C-9 methylene), 6.18 (three protons, C-7 methoxyl), 6.04 (three protons, methyl ester), 3.13 (C-8 proton), 2.68 (C-2 proton), 1.57 (C-5 proton) $\tau$.

*Anal.* Calcd. for $C_{16}H_{14}ClNO_4$: C, 60.09; H, 4.41; Cl, 11.09; N, 4.38; mol. wt., 319.74. Found: C, 60.18; H, 4.61; Cl, 11.07; N, 4.88; mol. wt., 329.

**Acknowledgment.**—The author is indebted to Mr. G. Morton and Mr. W. Fulmor for spectral data and assistance in interpretation; to Mr. L. Brancone and staff for microanalyses; to Dr. G. R. Allen, Jr., for a generous supply of certain compounds; to Dr. A. S. Kende for molecular orbital calculations; and to Dr. M. J. Weiss and Dr. J. S. Webb for helpful discussions and encouragement.

(17) Florisil is the trademark of the Floridin Co. for a magnesia–silica gel adsorbent.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO., PEARL RIVER, NEW YORK]

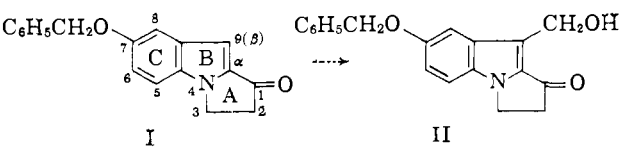
# The Mitomycin Antibiotics. Synthetic Studies. IV.[1] Introduction of the 9-Hydroxymethyl Group into the 1-Ketopyrrolo[1,2-*a*]indole System

BY WILLIAM A. REMERS, RETA H. ROTH, AND MARTIN J. WEISS

RECEIVED JULY 1, 1964

The development of a method for preparing 9-hydroxymethylpyrrolo[1,2-*a*]indoles (*e.g.*, II) bearing a group such as a carbonyl in ring A was important to the synthesis of mitomycin analogs. It was not possible to prepare such compounds by Dieckmann cyclizations with 1-cyanoethyl-2-carbethoxyindoles having potential hydroxymethyl groups at the 3-position. However, by formylation at C-9 (directly in poor yield or in higher yield *via* ketone reduction, acetylation, 9-formylation, deacetylation, and oxidation) of a precyclized 1-ketopyrrolo[1,2-*a*]indole (I), followed by preferential reduction of the 9-formyl group with diborane, a useful method for preparing compounds such as II was obtained. The 1-keto group of II effectively stabilized the potentially labile 9-hydroxymethyl group.

As part of a comprehensive program for the synthesis of analogs of the mitomycin antibiotics[2] it was necessary to develop a useful method for the introduction of the 9-hydroxymethyl substituent into a pyrrolo[1,2-*a*]indole having at the 1-position a functional group (*e.g.*, carbonyl) suitable for subsequent elaborations in ring A of the aziridine and other groups.[3]

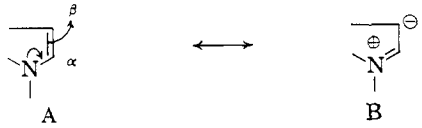



I II

(1) Preceding papers in this series: G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, (a) **86**, 3877 (1964); (b) **86**, 3878 (1964).

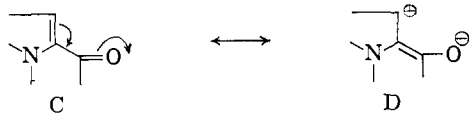
(2) (a) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *ibid.*, **84**, 3185, 3187 (1962); (b) A. Tulinsky, *ibid.*, **84**, 3188 (1962).

Two factors were considered pertinent to the problem of effecting substitution at the 9-position of a 1-ketopyrrolo[1,2-*a*]indole (*e.g.*, I). (1) In general, substitution reactions at the β-position of indoles are electrophilic in character and are dependent upon the delocalization of electrons from the heterocyclic nitrogen toward this position (A ↔ B).[4]



A B

(2) However, this delocalization will be opposed by the electron-withdrawing effect of a carbonyl group at the indole α-position (C ↔ D).[5]

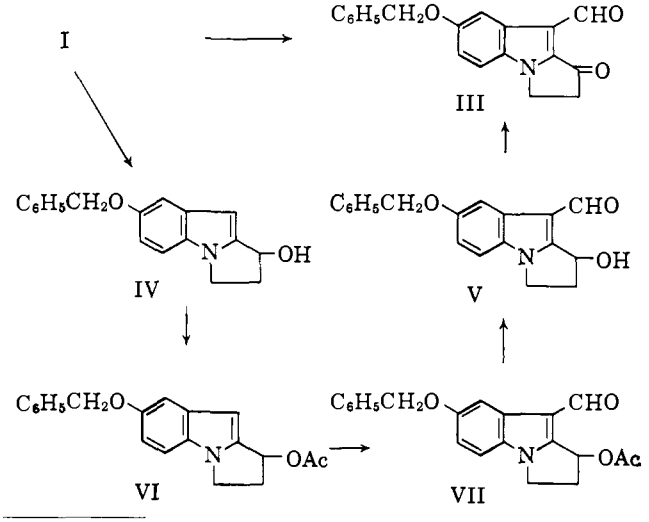


C D

In addition, a factor of critical importance to this problem is the need to stabilize the generally unstable β-hydroxymethyl group.[6] It was anticipated that such stabilization would be afforded by groups, such as the 1-carbonyl, able to conjugate with the α,β-double bond.[7a] Thus, a successful balance of all factors not only demanded that the carbonyl group in I no more than partially deactivate the molecule to electrophilic substitution at C-9, but also required that it afford sufficient stabilization of the intermediate hydroxymethyl derivatives.

In line with this reasoning we first attempted the most direct method for the introduction of the hydroxymethyl group, namely, treatment of I[8] (chosen for this study because of its relative availability) with formaldehyde in the presence of acid—despite the reported[6] observation that this reaction with nonstabilized indoles affords diindolylmethane derivatives. However, the ketone I was unreactive to these conditions and only starting material was obtained when the treatment was carried out in either methanol or benzene. The possibility of nucleophilic substitution[9] at C-9 (note resonance form D) was briefly investigated and found unpromising. For example, starting material was recovered from the treatment of I with nitromethane and trimethylamine. Proceeding further, compound I was treated with a variety of electrophiles of higher oxidation state than formaldehyde, although the 1-keto-9-aldehyde or 9-carboxylic acid derivatives thus prepared would require a preferential reduction of the group introduced in order to obtain the desired II. The deactivating effect of the 1-keto group was important here also, and no useful reaction was obtained by treatment of I with zinc cyanide and hydrochloric acid, with phosgene, or with ethyl chloroformate and silver perchlorate. Treatment of I with oxalyl chloride gave the product of an interesting rearrangement, which is the subject of an accompanying paper. After many attempts, a successful reaction was finally obtained with I and the dimethylformamide–phosphorus oxychloride complex (Vilsmeier–Haack conditions).[10] Although this reaction is reported to be facile with indoles,[11] including even indole-2-carboxylic acid esters,[12] considerable difficulty was encountered with I. At temperatures below 50° compound I was recovered unchanged[13]; at higher temperatures extensive decomposition occurred. The highest yield of the 9-formyl derivative III afforded by this procedure was only 7%.[14]

Thus, the carbonyl group in I, contrary to our expectations, is too strongly deactivating to allow effective electrophilic substitution of the desired type at C-9. Therefore, it was necessary to convert this group to a less deactivating function, from which the carbonyl group could be regenerated later. Since Vilsmeier–Haack formylation of the semicarbazone of I was unsuccessful, and many attempts to form a ketal from I failed, the most likely remaining course for an improved preparation of III appeared to be reduction of the carbonyl to the corresponding 1-ol, followed by acetylation, formylation, deacetylation, and then reoxidation to III. The reduction of I to the 1-ol IV with sodium borohydride in ethanol had already been accomplished,[8] and was



I III IV V VI VII

(3) Studies carried out in this laboratory on the elaboration of ring A will be published at a later date.

(4) (a) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953); (b) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).

(5) That the 1-ketone readily conjugates with the indole π-electron system is indicated by the bathochromic shift in its ultraviolet absorption maximum relative to the corresponding 1-hydroxy compound, and the shift to 5.85 μ of the carbonyl group in the infrared absorption spectrum. See J. M. Patterson, J. Brasch, and P. Drenchko, *J. Org. Chem.*, **26**, 4712 (1961), and references contained therein for a discussion of this effect in the corresponding pyrrole system.

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

(7) (a) Enhanced stability for 3-hydroxymethylindoles substituted with a 2-phenyl[6] or a 2-carboxyl[7b] group has been reported. Note also the relative stability of certain of the 9-hydroxymethyl- and 9-carbamyloxymethylquinone degradation products obtained from the mitomycins.[2a] (b) R. H. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 221 (1939).

(8) G. R. Allen, Jr., and M. J. Weiss, publication forthcoming.

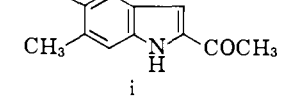
(9) Addition of a Grignard reagent to the 2-position of a 3-arylindole has been reported [J. Szmuszkovicz, *J. Org. Chem.*, **27**, 511 (1962)].

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

(11) (a) P. N. James and H. R. Snyder, *Org. Syn.*, **39**, 30 (1959); (b) R. C. Blume and H. G. Lindwall, *J. Org. Chem.*, **10**, 255 (1945).

(12) A. C. Shabica, E. E. Howe, J. B. Ziegler, and M. Tishler, *J. Am. Chem. Soc.*, **68**, 1156 (1946).

(13) A parallel observation was made in the case of 2-acetyl-5-methoxy-6-methylindole (i), prepared by Fischer synthesis from the appropriate hydrazone. These compounds are described in the experimental section.

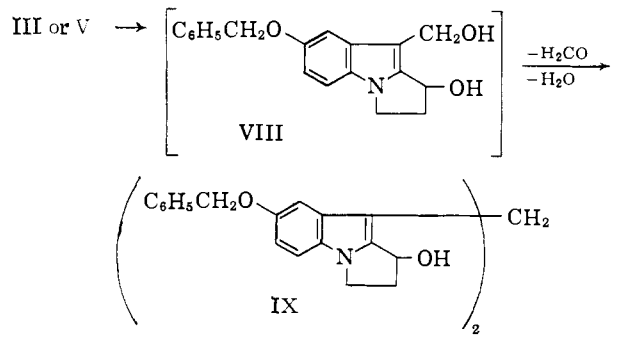


i

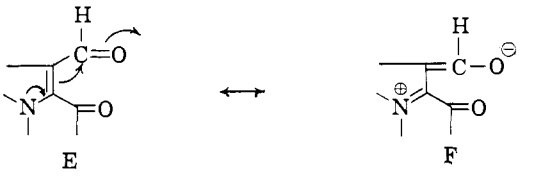
(14) An additional difficulty encountered in the preparation of III was its sensitivity to alkali, which ruled out alkaline hydrolysis of the intermediate obtained in the formylation reaction.

repeated in 84% yield. Acetylation to VI proceeded smoothly and the desired formylation was then effected in yields up to 85%. This formylation occurred at ice-bath temperature indicating that VI, as anticipated, is much more reactive than I (unreactive at 50°). Saponification of the 9-formyl-1-acetate VII afforded the corresponding 9-formyl-1-ol V in 62% yield. Oxidation of V with chromium trioxide–pyridine gave 9-formyl-1-one III in 69% yield. The over-all yield obtained by this route was 25%, which compares favorably with the 7% obtained by the direct formylation of I.

To conclude the preparation of 9-hydroxymethyl-1-one II it was necessary to effect a preferential reduction of the 9-formyl group in the dicarbonyl derivative III.[15] Procedures involving reduction of both carbonyl functions, followed by selective reoxidation, appeared unpromising in view of the recognized instability of alkyl-substituted β-hydroxymethylindoles.[6] However, as discussed above, it was a reasonable expectation that II would be stabilized by the presence of the keto function. Treatment of 9-formyl-1-one III with sodium borohydride in ethanol in an attempt to effect preferential 9-formyl reduction afforded only the diindolylmethane IX, apparently derived from the intermediate 9-hydroxymethyl-1-ol VIII. In fact, it appears that with this reagent the reduction of the 1-keto group is faster than that of the 9-formyl group—the exact opposite of the desired selectivity. Thus when the reaction mixture was examined after 10 min. in an ultraviolet spectrophotometer the absorption curve had the shape associated with a 9-formyl-1-ol such as V. After 30 min., this shape had radically changed to that expected for a 9-hydroxymethyl-1-ol such as VIII or a diindolylmethane such as IX (see Experimental). Several attempts to isolate V after a short reaction period were unsuccessful. Inseparable gummy mixtures were obtained. That the 9-formyl-1-ol V could be an intermediate in the conversion of 9-formyl-1-one III to the diindolylmethane IX was indicated when V was treated directly with sodium borohydride to give IX.




The apparent favored reduction of the 1-keto group in III is presumably a manifestation of preferential electron release from the indole nitrogen to the 9-formyl group (E ↔ F) causing this group to become less susceptible to nucleophilic attack by the borohydride ion than is the 1-carbonyl group.[16]




On this basis (note structure F), it was a reasonable expectation that the 9-formyl group would be more reactive than the 1-keto group to an electrophilic reagent such as diborane.[17] This expectation was borne out when treatment of III with diborane gave the desired preferential reduction of the 9-formyl group and afforded 9-hydroxymethyl-1-one II in good yield. That II was stable, as anticipated, and had not decomposed to a diindolylmethane was demonstrated by combustion analysis, molecular weight determination, and other evidence.

A parallel study on the synthesis of 9-hydroxymethyl-1-ketopyrrolo[1,2-*a*]indoles (*e.g.*, II) was based on an adaptation of the method previously developed in this laboratory for the preparation of 9-unsubstituted 1-ketopyrrolo[1,2-*a*]indoles.[1a] This method involved Dieckmann (Thorpe) ring closure of the adducts obtained on condensation of an indole-2-carboxylate with acrylic esters or nitriles,[18] followed by hydrolysis and decarboxylation. The application of this method to the purposes[19] of this investigation required the introduction of the hydroxymethyl group, or a suitable progenitor thereof, into the indole β-position prior to the cyclization step.

The starting indole for this study, methyl 5-methoxy-6-methyl-2-indolecarboxylate (X),[1a,19] was readily formylated under Vilsmeier–Haack conditions[10] but the 3-formyl compound XII thus obtained surprisingly failed to condense with methyl acrylate.[20] However, formylation of the 1-cyanoethyl derivative XI,[8] obtained by condensation of X with acrylonitrile, afforded a compound (XIII)[21] of the desired type. Reduction of XIII with sodium borohydride in ethanol gave *ethyl* 1-[β-cyanoethyl]-3-hydroxymethyl-2-indolecarboxylate (XV). The presence of the ethyl ester in XV, apparently the result of ester interchange during

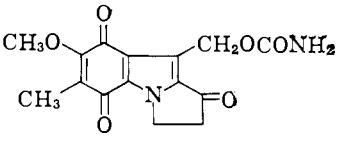
(15) An attempt to block preferentially the 1-carbonyl group of III prior to borohydride or other reduction by formation of a 1-oxime was not successful. When III was treated with 1 equiv. of hydroxylamine hydrochloride in pyridine a single product was isolated; however, its infrared absorption spectrum showed retention of carbonyl absorption at 5.85 μ (1-ketone) and a loss of carbonyl absorption at 6.10 μ (9-aldehyde), indicating preferential oximation of the 9-aldehyde of III. Two moles of hydroxylamine hydrochloride converted III to a dioxime (no carbonyl absorption in the infrared).

(16) A number of examples of the diminished susceptibility of indole-3-aldehydes to nucleophilic reagents are cited by W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954, p. 42.

(17) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957); *J. Am. Chem. Soc.*, **82**, 681 (1960).

(18) Previous examples of the cyanoethylation of indoles have been reported by Blume and Lindwall (ref. 11b) and by Almond and Mann [*J. Chem. Soc.*, 1870 (1952)].

(19) The 5-methoxy-6-methyl derivative, although not readily available, was utilized in this study since one of our goals was the synthesis of ii, the simplest quinone degradation product obtained from the mitomycin antibiotics by Webb and collaborators.[2a] However, the rapid confirmation of the mitomycin structures by X-ray analysis[2b] made such an undertaking unnecessary.

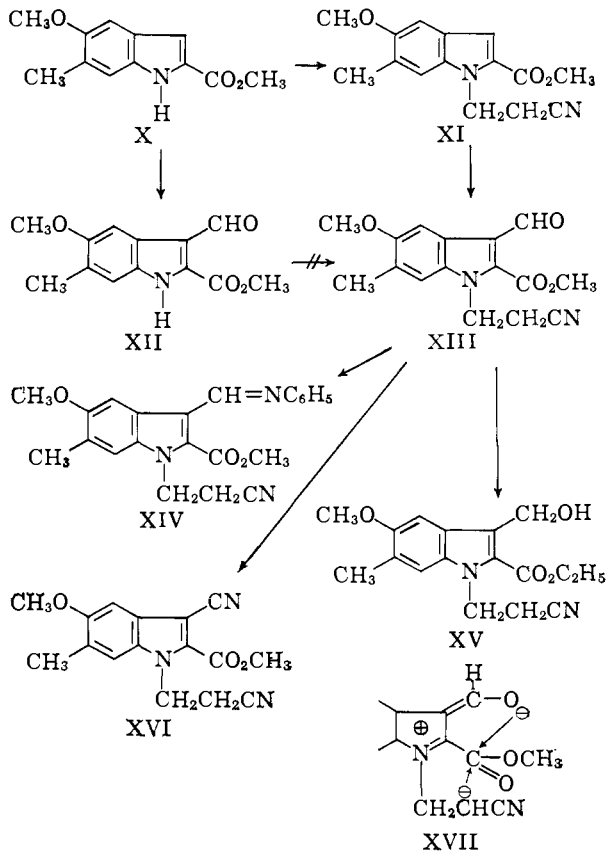



ii

(20) Blume and Lindwall (ref. 11b) have reported the condensation of 3-formyl-2-phenylindole with acrylonitrile.

(21) These experiments were performed by Mr. J. F. Poletto of these laboratories.

the borohydride reduction, was established unequivocally by its n.m.r. spectrum. The 3-hydroxymethyl derivative XV is stabilized by the 2-carbethoxy group and no decomposition to a diindolylmethane was observed under neutral or alkaline conditions.[7]




When the 3-hydroxymethyl derivative XV or the 3-formyl derivative XIII was submitted to the conditions (potassium *t*-butoxide in refluxing benzene) of the Dieckmann reaction, no cyclization was observed and starting material was recovered, in the latter instance in 74% yield. In contrast, the corresponding 3-unsubstituted indole had afforded the pyrroloindole β-keto nitrile in 67% yield under these very conditions.[1a] Variations of solvent and base, including potassium *t*-butoxide in xylene, potassium amide in benzene, and potassium triphenylmethide in tetrahydrofuran, were utilized in additional attempts to effect ring closure with XIII; however, these efforts were all unsuccessful.[21]

Two possible causes for the failure of XIII and XV to undergo Dieckmann cyclization were considered: (1) partial neutralization of the electrophilic character of the ester carbonyl by proximity to the negatively polarized oxygen in the aldehydo group (XVII arrows)[22] or to the anion derived from the 3-hydroxyl group in XV; (2) steric hindrance by the aldehydo or hydroxymethyl group to the attainment of the transition state wherein the ester carbonyl carbon goes from the trigonal to the tetrahedral form.

In order to minimize electronic deactivation of the ester carbonyl, the aldehyde XIII was converted to the anil XIV, a compound in which the partial negative charge on the anil nitrogen corresponding to the aldehydo oxygen in XIII is delocalized into the benzene ring. Despite this modification, attempts to effect the cyclization of XIV with potassium *t*-butoxide in refluxing benzene or xylene failed, and starting material was recovered.

Although the ester interchange that occurred in the reduction of aldehyde XIII to alcohol XV is evidence against the possible importance of steric hindrance by a 3-substituent to the expansion to tetrahedral geometry by the ester carbonyl carbon, we nevertheless investigated the effect of reducing the size of the group at C-3 on the facility of Dieckmann cyclization. Therefore, the aldehyde XIII was converted to the corresponding 3-nitrile XVI by treatment with O,N-bistrifluoroacetylhydroxylamine.[23] Although the product so prepared was contaminated with some XIII, it was of sufficient purity for cyclization studies. When this substance was heated with potassium *t*-butoxide or sodium hydride in xylene no cyclization was observed and starting material was recovered in high yield. We are unable at the present time to offer an explanation for the failure of the 3-substituted indoles described above to undergo the Dieckmann cyclization. Studies in this area were terminated when the 9-formylation of precyclized pyrrolo[1,2-*a*]indoles, such as VI, became feasible.

## Experimental

**General.**—**Melting points** are corrected. **Ultraviolet spectra** were determined in methanol using a Cary recording spectrophotometer. **Infrared spectra** were determined in potassium bromide disks on a Perkin–Elmer spectrophotometer (Model 21). **Nuclear magnetic resonance spectra** were determined in deuteriochloroform on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. Solutions were dried over magnesium sulfate.

**1-Acetoxy-7-benzyloxy-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole (VI).**—A solution of 1.97 g. (7.1 mmoles) of 7-benzyloxy-2,3-dihydro-1-hydroxy-1H-pyrrolo[1,2-*a*]indole (IV)[8] in 25 ml. of acetic anhydride was treated with 1.15 g. (14 mmoles) of sodium acetate and the resulting mixture was heated on a steam bath for 1.5 hr. After this mixture was cooled and poured onto ice, it was stirred until all of the acetic anhydride hydrolyzed and the crystalline acetate VI was present. This acetate was collected and washed well with water, dissolved in methylene chloride, washed two times with potassium bicarbonate solution, dried, and concentrated as petroleum ether (60–70°) was added. Cooling afforded 1.84 g. (81%) of 1-acetoxy-7-benzyloxy-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole (VI), white plates, m.p. 104–106°; $\lambda_{max}$ 5.75, 8.0 μ; 20 (ε 43,500), 278 (ε 9300), 302 (ε 4300), 315 (ε 2900) mμ. An analytical sample, recrystallized from acetone–petroleum ether (60–70°), had m.p. 109°.

*Anal.* Calcd. for $C_{20}H_{19}NO_3$ (321.36): C, 74.74; H, 5.96; N, 4.36. Found: C, 74.90; H, 6.03; N, 4.66.

**1-Acetoxy-7-benzyloxy-9-formyl-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole (VII).**—To 1.0 ml. of ice-cooled dimethylformamide was added 306 mg. (2 mmoles, 0.2 ml.) of freshly distilled phosphorus oxychloride. The mixture was stirred and cooled for 15 min., then treated with a solution of 642 mg. (2 mmoles) of 1-acetoxy-7-benzyloxy-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole (VI) in 5 ml. of dimethylformamide, added dropwise. After the resulting yellow solution was stirred at ice-bath temperature for 2 hr. it was poured onto a mixture of ice and 8 ml. of 1 *N* sodium hydroxide solution. The precipitate that formed was collected, washed with 1% sodium hydroxide solution, dissolved in methylene chloride solution, washed with potassium bicarbonate solution, dried, and concentrated. Crystallization of the residue from methanol afforded 602 mg. (85%) of 1-acetoxy-7-benzyloxy-9-formyl-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole (VII), white plates, m.p. 163–164°; $\lambda_{max}$ 3.5 (w), 3.6 (w), 5.70, 6.10, 8.25 μ; 257 (ε 21,000),

(22) Attack by the formyl oxygen on the ester carbonyl carbon in XVII would give a structure having some analogy to the postulated intermediate in the hydrolysis of methyl o-formylbenzoate [M. L. Bender and M. S. Silver, *J. Am. Chem. Soc.*, **84**, 4589 (1962)]; however, we found no evidence of this structure.

(23) J. H. Pomeroy and C. A. Craig, *ibid.*, **81**, 6340 (1959).

276 (ε 9800), 308 (ε 11,000) mμ. An analytical sample, recrystallized from methanol, had m.p. 164°.

*Anal.* Calcd. for $C_{21}H_{19}NO_4$ (349.37): C, 72.19; H, 5.48; N, 4.01. Found: C, 72.77, 72.51; H, 6.07, 5.66; N, 4.17.

**7-Benzyloxy-9-formyl-2,3-dihydro-1-hydroxy-1H-pyrrolo[1,2-*a*]indole (V).**—To a solution of 7.5 g. of sodium hydroxide in 10 ml. of water and 140 ml. of methanol was added 1.31 g. (3.75 mmoles) of 1-acetoxy-7-benzyloxy-9-formyl-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole (VI). The resulting mixture was heated on a steam bath for 20 min., cooled, and concentrated to 20 ml. The concentrate was treated with ether–methylene chloride (1:1) and water. The organic layer was washed with potassium bicarbonate solution, dried, and concentrated. Crystallization of the residue from methanol, with charcoal decolorization, afforded 719 mg. (26%) of 7-benzyloxy-9-formyl-2,3-dihydro-1-hydroxy-1H-pyrrolo[1,2-*a*]indole (V), m.p. 126–130°; $\lambda_{max}$ 2.9, 3.6 (w), 3.7 (w), 6.15 μ; 257 (ε 27,000), 275 (ε 14,000), 308 (ε 13,000) mμ. An analytical sample, recrystallized from methanol, had m.p. 127–130°.

*Anal.* Calcd. for $C_{19}H_{17}NO_3$ (307.33): C, 74.25; H, 5.58; N, 4.56. Found: C, 75.06; H, 5.79; N, 3.61.

**7-Benzyloxy-9-formyl-2,3-dihydro-1-oxo-1H-pyrrolo[1,2-*a*]indole (III).** (a) **From Oxidation of V.**—An ice-cooled solution of 102 mg. (0.33 mmole) of 7-benzyloxy-9-formyl-2,3-dihydro-1-hydroxy-1H-pyrrolo[1,2-*a*]indole (V) in 1 ml. of pyridine was treated with a slurry of 100 mg. (1.0 mmole) of chromium trioxide in 5 ml. of pyridine. The mixture was stirred at 5° for 54 hr., then treated with water and methylene chloride. The methylene chloride layer was filtered, washed with potassium bicarbonate solution, dried, and concentrated. Crystallization of the residue from ethanol, with charcoal decolorization, afforded 48 mg. (47%) of 7-benzyloxy-9-formyl-2,3-dihydro-1-oxo-1H-pyrrolo[1,2-*a*]-indole (III), m.p. 194–197°; $\lambda_{max}$ 3.6 (w), 3.7 (w), 5.85 (1-keto group), 6.10 (9-formyl) μ; 245 (ε 20,000), 253 (ε 21,000), 262 (ε 15,000), 280 (ε 7300), 343 (ε 16,000) mμ. When carried out on a 600-mg. scale this reaction afforded a 69% yield of III.

*Anal.* Calcd. for $C_{19}H_{15}NO_3$ (305.32): C, 74.74; H, 4.95; N, 4.59. Found: C, 75.09; H, 5.31; N, 4.70.

(b) **From Direct Formylation of I.**—To an ice-cooled mixture of 767 mg. (5 mmoles) of phosphorus oxychloride and 3 ml. of dimethylformamide was added a slurry of 552 mg. (2 mmoles) of 7-benzyloxy-2,3-dihydro-1-oxo-1H-pyrrolo[1,2-*a*]indole (I)[8] in 8 ml. of dimethylformamide. The mixture was warmed on a steam bath for 1 hr., cooled, and poured onto a mixture of ice and 5% sodium bicarbonate solution.[14] The precipitate that formed was extracted into methylene chloride and this extract was washed with sodium bicarbonate solution, dried, and concentrated on a steam bath as ethanol was added. Cooling this solution afforded dark crystals, m.p. 130–170°. This material was dissolved in benzene and purified by chromatography on a small Florisil column. The yellow band that was the first to be eluted afforded yellow solid, m.p. 194–196°, m.p. undepressed on admixture with 7-benzyloxy-9-formyl-2,3-dihydro-1-oxo-1H-pyrrolo[1,2-*a*]indole prepared from V; yield 43 mg. (7%).

**Bis[9-(7-benzyloxy-2,3-dihydro-1-hydroxy-1H-pyrrolo[1,2-*a*]-indolyl)]methane (IX).** (a) **From V.**—A solution of 614 mg. (2 mmoles) of 7-benzyloxy-9-formyl-2,3-dihydro-1-hydroxy-1H-pyrrolo[1,2-*a*]indole (V) in 40 ml. of warm ethanol was treated with 152 mg. (4 mmoles) of sodium borohydride. After 16 hr. this mixture was concentrated under reduced pressure and the residue was treated with water and 100 ml. of 1:1 ether–methylene chloride. The organic layer was washed with sodium bicarbonate solution, dried, and concentrated as petroleum ether (60–70°) was added. White solid, m.p. 205–208°, was obtained. Recrystallization of this solid from the same solvents afforded 318 mg. (56%) of bis[9-(7-benzyloxy-2,3-dihydro-1-hydroxy-1H-pyrrolo-[1,2-*a*]indolyl)]methane (IX), m.p. 206–209°; $\lambda_{max}$ 2.85 μ, no carbonyl absorption; 283 (ε 18,000), 300 (ε 11,000) sh, 315 (ε 7700) sh mμ.

*Anal.* Calcd. for $C_{37}H_{34}N_2O_4$ (570.66): C, 77.87; H, 6.01; N, 4.91. Found: C, 77.61; H, 5.99; N, 4.69.

(b) **From III.**—A solution of 145 mg. (0.5 mmole) of 7-benzyloxy-9-formyl-2,3-dihydro-1-oxo-1H-pyrrolo[1,2-*a*]indole (III) in 10 ml. of ethanol was treated with 380 mg. (10 mmoles) of sodium borohydride. After 10 min., an aliquot was withdrawn, diluted 1000-fold with ethanol, and examined in an ultraviolet spectrophotometer. It had $\lambda_{max}$ 257 (ε 28,000), 275 (ε 14,000), 308 (ε 13,000) mμ. After 30 min. the solution had $\lambda_{max}$ 283 (ε 18,000), 300 (ε 11,000) sh, 315 (ε 7700) sh mμ. It was concentrated under reduced pressure and the residue was treated with water and 25 ml. of 1:1 ether–methylene chloride. The organic layer was washed with sodium bicarbonate solution, dried, and concentrated as petroleum ether was added. White needles, m.p. 198–204°, were obtained. Recrystallization from the same solvents gave needles, m.p. 205–209°, undepressed on admixture with bis[9-(7-benzyloxy-2,3-dihydro-1-hydroxy-1H-pyrrolo[1,2-*a*]indolyl)]methane (IX) prepared from B. The two samples had an identical infrared spectrum (KBr disks); yield 64 mg. (45%).

In a similar experiment the solution was treated with a few drops of acetic acid after 10 min. and worked up as above. A gummy white residue that could not be crystallized by the usual techniques was obtained.

**7-Benzyloxy-2,3-dihydro-9-hydroxymethyl-1-oxo-1H-pyrrolo-[1,2-*a*]indole (II).**—Diborane, generated by dropwise addition of 38 mg. (1 mmole) of sodium borohydride in 5 ml. of diglyme to 213 mg. (1.5 mmoles) of boron trifluoride etherate in 5 ml. of diglyme,[17] was swept by nitrogen into a solution of 153 mg. (0.5 mmole) of 7-benzyloxy-2,3-dihydro-9-formyl-1-oxo-1H-pyrrolo-[1,2-*a*]indole (III) in 10 ml. of tetrahydrofuran. After the diborane addition was complete this solution was left for 16 hr., then treated with methanol to destroy any excess diborane. It was evaporated in a stream of nitrogen and the semisolid residue was treated with methanol and ether. The pale yellow crystals obtained by this treatment were recrystallized from methanol to afford 102 mg. (67%) of 7-benzyloxy-2,3-dihydro-9-hydroxymethyl-1-oxo-1H-pyrrolo[1,2-*a*] indole (II) as pale yellow needles, m.p. 165–173°; $\lambda_{max}$ 2.9, 5.85 μ; 322 (ε 22,000) mμ.

*Anal.* Calcd. for $C_{19}H_{17}NO_3$ (307.33): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.19; H, 5.98; N, 4.08; mol. wt., 316.

**Diacetyl 4-Methoxy-3-methylphenylhydrazone.**—A solution of 4-methoxy-3-methylphenylhydrazine (prepared from 0.10 mole of 4-methoxy-3-methylaniline)[24] in 250 ml. of 50% aqueous acetic acid was treated with a solution of 8.6 g. (0.10 mole) of diacetyl in 50 ml. of 50% aqueous acetic acid. After a few minutes yellow solid was formed. It was collected, washed with 50% aqueous acetic acid, dried, dissolved in 300 ml. of boiling methanol, treated with charcoal, filtered, and cooled. Yellow crystals of diacetyl 4-methoxy-3-methylphenylhydrazone, m.p. 180°, were formed; yield 4.65 g. (21%).

*Anal.* Calcd. for $C_{12}H_{16}N_2O_2$ (220.26): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.11; H, 7.22; N, 12.65.

**2-Acetyl-5-methoxy-6-methylindole (i).**—A suspension of 4.52 g. (21 mmoles) of diacetyl 4-methoxy-3-methylphenylhydrazone in 180 ml. of methanol and 90 ml. of concentrated hydrochloric acid was heated at reflux temperature in a nitrogen atmosphere for 2.5 hr. It was then poured onto ice and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and concentrated. The brown solid residue was digested with boiling petroleum ether (60–70°) and filtered. The filtrate, on cooling, gave a yellow solid. This yellow solid (1.0 g.) was dissolved in 25 ml. of the upper and 25 ml. of the lower phase of the system *n*-heptane–methanol and mixed thoroughly with 50 g. of Celite[25] diatomaceous earth. This mixture was packed on a column that had been prepared from 750 g. of Celite diatomaceous earth and 375 ml. of the lower phase of the heptane–methanol solvent system. The column (6.5 × 85 cm.) was eluted with the upper phase of the solvent system and the effluent was passed through a recording spectrophotometer that had been set at 315 mμ. The 2-acetyl-5-methoxy-6-methylindole (i) was contained in hold-back volumes 1.5–2.5 (1400 ml. per h.b.v.). Concentration of the effluent afforded 0.626 g. (15%) of this product as pale yellow needles, m.p. 152°; $\lambda_{max}$ 2.9, 6.10 μ; 315 (ε 31,000) mμ.

*Anal.* Calcd. for $C_{12}H_{13}NO_2$ (203.26): C, 70.91; H, 6.45. Found: C, 70.94; H, 6.70.

**Methyl 3-Formyl-5-methoxy-6-methyl-2-indolecarboxylate (XII).**—Freshly distilled phosphorus oxychloride (3.36 g., 0.022 mole) was added at −7° to 7 ml. of dimethylformamide. A solution of methyl 5-methoxy-6-methyl-2-indolecarboxylate[18a] (X, 4.4 g., 0.02 mole) in 7.5 ml. of dimethylformamide was added to this mixture during 1.5 hr. while the bath temperature was maintained at 0°. After the reaction mixture was stirred at 35° for 1 hr., crushed ice (10 g.) was carefully added and the solid that formed was collected, washed well with water, and dried. This solid was recrystallized two times from ethanol to give 2.58 g. (52%) of methyl 3-formyl-5-methoxy-6-methyl-2-indolecarboxyl-

(24) J. A. Cummins, B. F. Kaye, and M. L. Tomlinson, *J. Chem. Soc.*, 1414 (1954).

(25) Celite is the trademark of Johns-Manville Corp. for diatomaceous earth products.

ate (XII), m.p. 248°; $\lambda_{max}$ 5.81, 6.07 $\mu$; 218 ($\epsilon$ 24,100), 251 ($\epsilon$ 17,100), 335 ($\epsilon$ 12,200) m$\mu$. When this preparation was carried out with 0.035 mole of indole ester X, a 60% yield of XII was obtained.

*Anal.* Calcd. for $C_{13}H_{13}NO_4$ (247.2): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.07; H, 5.36; N, 5.91.

**Methyl 1-(β-Cyanoethyl)-3-formyl-5-methoxy-6-methyl-2-indolecarboxylate (XIII).**[21]—A solution of 4.56 g. (0.0338 mole) of N-methylformanilide and 5.15 g. (0.033 mole) of freshly distilled phosphorus oxychloride was stirred at room temperature for 15 min. To this solution was added 25 ml. of ethylene dichloride and the mixture was cooled in an ice bath. To this mixture was added 4.0 g. (0.0147 mole) of methyl 1-(β-cyanoethyl)-5-methoxy-6-methyl-2-indolecarboxylate (XI).[14a] The ice bath was removed and the reaction mixture was heated at reflux for 30 min. It was cooled and poured into 25 ml. of water containing 25 g. of sodium acetate. The solvent was removed by steam distillation and solid was collected. Recrystallization of this solid from methylene chloride gave 4.03 g. (90%) of methyl 1-(β-cyanoethyl)-3-formyl-5-methoxy-6-methyl-2-indolecarboxylate (XIII), yellow crystals, m.p. 227–228°; $\lambda_{max}$ 4.45, 5.85, 6.08 $\mu$; 251 ($\epsilon$ 19,450), 352 ($\epsilon$ 13,200) m$\mu$; n.m.r.: −0.63 (-CHO), 5.14 (triplet, $-N-CH_2-$), 5.95 (ester-$OCH_3$), 7.06 (triplet, $-CH_2-CN$) $\tau$.

*Anal.* Calcd. for $C_{16}H_{16}N_2O_4$ (300.3): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.73; H, 5.51; N, 9.45.

**Ethyl 1-(β-Cyanoethyl)-3-hydroxymethyl-5-methoxy-6-methyl-2-indolecarboxylate (XV).**[21]—Sodium borohydride (231 mg., 6.6 mmoles) was added to a boiling suspension of 1.0 g. (3.3 mmoles) of methyl 1-(β-cyanoethyl)-3-formyl-5-methoxy-6-methyl-2-indolecarboxylate (XIII) in 35 ml. of ethanol. The resulting mixture was heated at reflux temperature for 2 min. and allowed to stand at room temperature for 45 min., then concentrated to dryness. The residue was suspended in 25 ml. of 1% sodium hydroxide solution and extracted with methylene chloride. After drying this extract over sodium sulfate, the solvent was concentrated with concomitant addition of petroleum ether (30–60°) to the point of crystallization. This procedure gave 676 mg. (64%) of ethyl 1-(β-cyanoethyl)-3-hydroxymethyl-5-methoxy-6-methyl-2-indolecarboxylate (XV), white crystals, m.p. 151–152°; $\lambda_{max}$ 3.02, 4.45, 5.9, 6.53, 8.1 $\mu$; 213 ($\epsilon$ 30,200), 305 ($\epsilon$ 20,210) m$\mu$; n.m.r.: 4.95 ($-CH_2-O-$), 5.23 (triplet, $N-CH_2-$), 5.49 (quartet, $-O-CH_2-CH_3$), 6.07 ($-OCH_3$), 7.14 (triplet, 3 protons, $-CH_2-CN$, OH), 8.53 (triplet, $-O-CH_2-CH_3$) $\tau$.

*Anal.* Calcd. for $C_{17}H_{20}N_2O_4$ (316.35): C, 64.54; H, 6.37; N, 8.86. Found: C, 64.01; H, 6.58; N, 9.03.

**Methyl 3-Cyano-1-(β-cyanoethyl)-5-methoxy-6-methyl-2-indolecarboxylate (XVI).**—A mixture of 1.50 g. (5 mmoles) of methyl (β-cyanoethyl)-3-formyl-6-methoxy-5-methyl-2-indolecarboxylate (XIII), 1.5 ml. of pyridine, and 2.25 g. (10 mmoles) of O,N-bistrifluoroacetylhydroxylamine[24] in 250 ml. of dry xylene was refluxed for 18 hr. The yellow solution turned dark brown. This solution was filtered while hot and the cooled filtrate was extracted with water four times, dried, and concentrated. The dark brown solid residue was dissolved in a boiling mixture of 350 ml. of petroleum ether and 400 ml. of acetone, decolorized with charcoal, and then the solution was concentrated to 250 ml. On cooling, an amber solid (1.00 g.), m.p. 230–233°, was obtained. The infrared spectrum showed strong peaks (4.43, 5.82 $\mu$) in both the nitrile and aldehyde regions. A 350-mg. portion of this material was recrystallized from acetone–hexane, affording 260 mg. of amber solid, m.p. 236–239°; $\lambda_{max}$ 4.44, 5.83, 6.08 $\mu$; 316 m$\mu$. Analysis and infrared spectrum indicated contamination with unchanged 3-formyl derivative XII.

*Anal.* Calcd. for $C_{16}H_{15}N_3O_3$ (297.3): C, 64.63; H, 5.09; N, 14.14. Found: C, 63.36; H, 5.30; N, 13.76. Calcd. for $C_{16}H_{16}N_2O_4$ (310.3), starting material XIII: C, 63.99; H, 5.37; N, 9.33.

All the remaining material from the above reaction was treated again under the same conditions with 1.0 ml. of pyridine and O,N-bistrifluoroacetylhydroxylamine (1.5 g.) in 150 ml. of dry xylene. After 18 hr. of refluxing, the reaction mixture was worked up as described above and amber solid was obtained. The infrared spectrum still showed large amounts of carbonyl. The material could not be separated by partition chromatography because a suitable solvent system could not be found.

**Methyl 1-(β-Cyanoethyl)-5-methoxy-6-methyl-3-(N-phenylformimidoyl)-2-indolecarboxylate (XIV).**—A mixture of 1.5 g. (0.05 mole) of methyl 1-(β-cyanoethyl)-3-formyl-5-methoxy-6-methyl-2-indolecarboxylate (XIII), 1.0 g. (1.1 moles) of freshly distilled aniline, and 50 ml. of toluene was heated at reflux temperature for 16 hr. in an apparatus fitted with a Dean–Stark receiver filled with anhydrous magnesium sulfate. The resulting solution was filtered while hot and the filtrate was concentrated under reduced pressure. Crystallization of the residue from 300 ml. of methanol (charcoal) afforded 1.65 g. (88%) of methyl 1-(β-cyanoethyl)-5-methoxy-6-methyl-3-(N-phenylformimidoyl)-2-indolecarboxylate (XIV) as yellow needles, m.p. 181–183° (after being dried at 80° under reduced pressure); $\lambda_{max}$ 4.4, 5.89, 6.20, 6.30 $\mu$; 260, 337 m$\mu$.

*Anal.* Calcd. for $C_{22}H_{21}N_3O_3$ (375.41): C, 70.38; H, 5.64; N, 11.19. Found: C, 69.92; H, 5.94; N, 10.91.

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