The Mitomycin Antibiotics. Synthetic Studies. V.[1] Preparation of 7-Methoxymitosene

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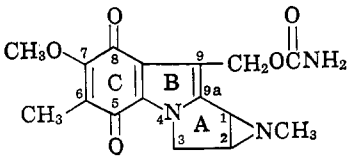
A facile procedure for the preparation of the 2,3-dihydro-1H-pyrrolo[1,2-*a*]indole system is described; condensation of an indole-2-carboxylic ester with an acrylate ester furnishes a β-keto ester having this fundamental ring system. Certain aspects of the chemistry of 3-indolylmethanols are discussed, including a method for the preparation of the carbamic acid ester of such compounds. The compatibility of these procedures with a method for the elaboration of the indoloquinone chromophore present in 7-methoxy-1,2-(N-methylaziridino)mitosene (I) is demonstrated by the synthesis of 7-methoxymitosene, a compound having biological interest.

During their investigation of the structures of the mitomycin antibiotics, Patrick, Webb, and co-workers prepared an aziridinopyrrolo[1,2-*a*]indoloquinone which was shown to have structure I.[2] This compound was found to possess potent antibacterial properties, being equivalent in activity to mitomycin B against *Streptococcus pyogenes* C-203 infections in mice (subcutaneous). Moreover, in this assay compound I was several times more potent than tetracycline, and of further significance was its oral activity. As the mitomycins and the related I are representatives of a new class of broad-spectrum antibacterial agents,[3] we were interested in the synthesis of appropriate analogs. Initially, we chose as our goal the preparation of analogs of I, inasmuch as this structure is uncomplicated by the 9a substituent and the asymmetry at C-9 present in the parent antibiotics.

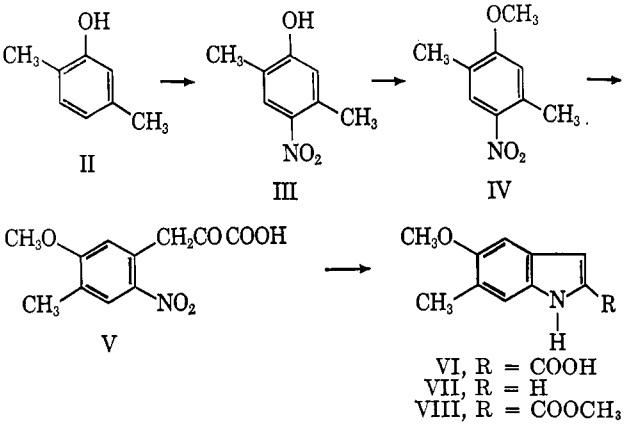


I

Before any rational synthesis of such analogs could be initiated, we required methods for the fabrication of three key structural features—namely, the fundamental ring system, the aziridine moiety fused to ring A, and the carbamoyloxymethyl group at C-9. A method based on the work of Teuber and Thaler[4] had already been devised in this laboratory for the elaboration of the fourth feature—the indoloquinone chromophore.[5]

For the preparation of the pyrrolo[1,2-*a*]indole system a feasible approach appeared to be the use of an appropriately substituted indole, which would ultimately serve as the B/C rings, and subsequent attachment to this molecule of the three-carbon fragment required for ring A. This approach required a 5-(alkyloxy-or aralkyloxy-) 6-methylindole, the 5-oxy function being necessary for the subsequent development of the pyrrolo[1,2-*a*]indoloquinone system by the procedure noted above.[5] After study of several of the classical procedures,[6] the requisite indole was readily prepared by the Reissert method.[7]

4-Nitro-2,5-xylenol (III),[8] the required starting material for this method, was best prepared by sulfonation of 2,5-xylenol (II), treatment of the sulfonic acid with nitrous acid, and oxidation of the crude nitroso derivative with nitric acid; this procedure parallels that reported for the preparation of 2-methyl-4-nitrophenol.[9] O-Methylation of III then was accomplished readily with methyl sulfate. For preparative purposes, the above operations could be performed without purification of intermediates giving IV in 55% over-all yield. Condensation of IV with ethyl oxalate followed by ester hydrolysis gave the phenylpyruvic acid V. Use of potassium ethoxide as the base and boiling ether as the reaction medium furnished V in 49% yield, whereas the more basic potassium *t*-butoxide in boiling benzene afforded an 80% yield. Reductive cyclization of V with ferrous ammonium sulfate furnished 56% of 5-methoxy-6-methyl-2-indolecarboxylic acid (VI) which could be decarboxylated thermally to give 5-methoxy-6-methylindole (VII). Either VI, VII, or the methyl ester VIII was potentially useful for the preparation of the pyrrolo[1,2-*a*]indole ring system.



II III IV

V

VI, R = COOH
VII, R = H
VIII, R = $COOCH_3$

(1) (a) Paper IV: W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 4612 (1964). (b) A portion of this work was the subject of a preliminary communication [*ibid.*, **86**, 3877 (1964)].

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

(3) The mitomycins, in particular mitomycin C, have received considerable attention as antitumor agents: R. Jones, Jr., U. Jonsson, J. Colsky, H. E. Lessner, and A. Franzino, 4th National Cancer Conference, 1960; Proceedings, J. B. Lippincott, Philadelphia, Pa., 1961, p. 175.

(4) H. Teuber and G. Thaler, *Ber.*, **91**, 2253 (1958).

(5) W. A. Remers, P. N. James, and M. J. Weiss, *J. Org. Chem.*, **28**, 1169 (1963).

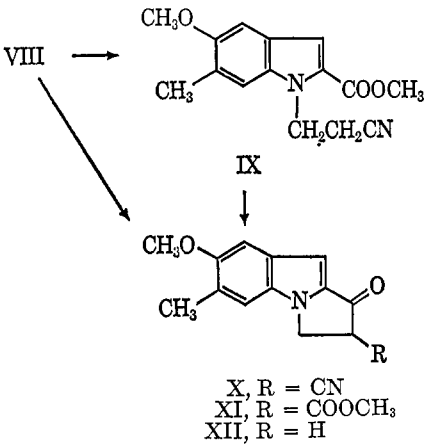
(6) Among these were the Fischer, Japp–Klingemann, Bischler, and Madelung procedures (see ref. 7 for a discussion of these methods), of which only the Madelung method showed some promise. However, its development was not pursued in view of the successful application of the Reissert synthesis.

(7) P. L. Julian, E. W. Meyer, and H. C. Printy in "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 18.

(8) K. Auwers and F. Michaelis, *Ber.*, **47**, 1289 (1914).

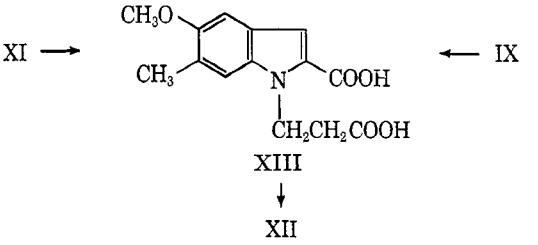
(9) C. F. Koelsch, *J. Am. Chem. Soc.*, **66**, 2019 (1944).

Thus, for the elaboration of ring A the methyl ester VIII was subjected to a process involving base-catalyzed 1,4 addition to an acrylic derivative followed by Dieckmann ring closure.[10] Reaction of methyl ester VIII with acrylonitrile (aqueous benzyltrimethylammonium hydroxide catalyst) gave the 1-β-cyanoethyl derivative IX which on treatment with potassium *t*-butoxide in boiling benzene furnished the desired β-ketonitrile X. Having demonstrated the feasibility of the Dieckmann condensation for the development of the pyrrolo[1,2-*a*]indole ring system, it appeared reasonable that these two reactions could be combined, for the anion generated in the course of the Michael addition is that required for the Dieckmann cyclization. This indeed proved true, and condensation of the indole ester VIII with acrylonitrile using an equivalent of *t*-butoxide furnished the β-ketonitrile X directly. This procedure was extended to include methyl acrylate which reacted with indole ester VIII to give the β-keto ester XI in 82% yield.

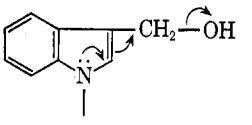


X, R = CN
XI, R = $COOCH_3$
XII, R = H

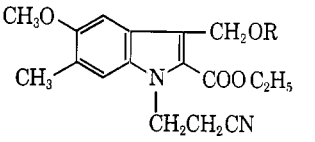
Many of the approaches to the fused aziridine moiety present in I were envisioned as best proceeding from the 1-ketone XII, and for this reason the decarbomethoxylation of XI was investigated. Although this transformation could be achieved by hydrochloric acid in boiling methanol, the yield was disappointing. After considerable study it was found that decarbomethoxylation could be effected in 86% yield by treating the β-keto ester XI with boiling 95% acetic acid. During this phase of the investigation an attempt was made to convert the β-keto ester XI to the corresponding β-keto acid, since decarboxylation of the latter was expected to be more facile. However, saponification of XI resulted in cleavage of ring A affording the diacid XIII, which was also obtained by alkaline hydrolysis of the 1-β-cyanoethylindole IX.[14] The attempted utilization of these pyrrolo[1,2-*a*]indoles and related compounds for the elaboration of the fused aziridino moiety is described in accompanying papers.[15]



The present investigation also included a study of methods for the preparation of the third key feature in I, namely the β-indolic carbamoyloxymethyl group. Considerable information concerning the preparation and properties of β-indolylmethanols had already been described in the literature.[16] It was apparent that this function was readily available from a 3-indolecarboxaldehyde or -carboxylic ester by metal hydride reduction.[17] However, the reported instability of β-indolylmethanols caused concern.[18] Nevertheless, it appeared that stability could be conferred to this moiety by the presence of electronegative substituents. Thus, at least a modicum of stability has been reported for a 2-phenyl-[16] and a 2-carboxy-3-indolylmethanol.[19] Furthermore, the stability observed for certain 9-hydroxymethylpyrroloindoloquinones was encouraging.[20] This enhanced stability could be readily understood as resulting from the mitigation of the usual electronic effects present in the 3-indolylmethanol system (XIV, arrows) by appropriately placed electronegative substituents. For this reason, we chose the 2-carbethoxy-3-indolylmethanol XV[1a] for model studies.



XIV



XV, R = H
XVI, R = $COOC_6H_5$
XVII, R = $CONH_2$

Following unsuccessful attempts to proceed from XV to its carbamate ester XVII *via* reaction with phosgene and ammonolysis of the presumed chloroformate, it was found that this transformation could be achieved by ammonolysis of the phenylcarbonate XVI,[21] which was readily prepared from XV by acylation with phenyl chloroformate in pyridine.

(10) Numerous attempts to prepare 2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-1-one by the cyclization of indole-1-propionic acid[11] and indole-1-propionitrile[11] failed. The failure of this approach is not apparent, for the indole 2 position is known to be receptive to electrophilic substitution, *e.g.*, the many recorded preparations of harmaline-type alkaloids from various tryptamine derivatives[12] and the reported reaction of skatole with cyclohexanone,[13a] cyclopentanone,[13a] and benzaldehyde.[13b]

(11) A. P. Terent'ev, A. N. Kost, and V. A. Smit, *Zh. Obshch. Khim.*, **25**, 1959 (1955); *Chem. Abstr.*, **50**, 4910*f* (1956).

(12) W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954, p. 208 ff.

(13) (a) A. Treibs and E. Herrmann, *Ann.*, **589**, 207 (1954); (b) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

(14) The diacid XIII could be cyclized to the 1-keto derivative XII by treatment with potassium cyanide in boiling acetic anhydride [*cf.* F. Uhle, *J. Am. Chem. Soc.*, **71**, 761 (1949)], a route which was inferior to the β-keto ester approach.

(15) (a) G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **30**, 2904 (1965); (b) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, **30**, 2910 (1965).

(16) See particularly E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959).

(17) The introduction of the 9-formyl group into the pyrrolo[1,2-*a*]indole system was the subject of a separate investigation (ref. 1a).

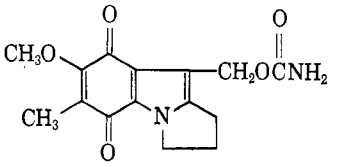
(18) We have assumed an order of stability for the 3-indolylmethanol carbamates approximating that of the parent alcohols.

(19) R. H. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 221 (1939).

(20) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, **84**, 3185 (1962).

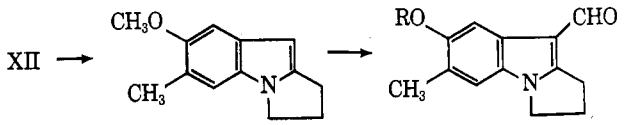
(21) W. M. McLamore, S. Y. P'An, and A. Bavley, *J. Org. Chem.*, **20**, 1379 (1955).

Having now available techniques for (1) the preparation of the pyrrolo[1,2-*a*]indole ring system, (2) the introduction of the 9-carbamoyloxymethyl substituent, and (3) the elaboration of the indoloquinone chromophore present in I, it was desirable to test the compatibility of these procedures, the successful combination of which would culminate in the preparation of 7-methoxymitosene (XVIII),[22] the desaziridino analog of the biologically important I.



XVIII

For this work pyrrolo[1,2-*a*]indol-1-one XII was converted into its 1-deoxy derivative XIX by Wolff–Kishner reduction as modified by Huang-Minlon. Vilsmeier–Haack formylation of the latter compound afforded the 9-carboxaldehyde XX, which on treatment with aluminum chloride in boiling xylene suffered de-O-methylation, giving XXI in excellent yield.[23] This aldehyde represented a key intermediate in the proposed sequence, since the 7-hydroxy group was a suitable entry for the elaboration of the indoloquinone system[5] and the 9-aldehyde function could serve for the development of the 9-carbamoyloxymethyl moiety.



XIX

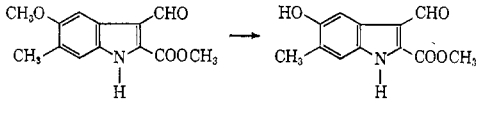
XX, R = CH_3
XXI, R = H

In light of the above comments concerning the stability of the β-indolylmethanol system, the elaboration of the quinone chromophore was initially investigated since this moiety would then serve as an appropriate electronegative stabilizing function.[24] Therefore, aldehyde XXI was treated with potassium nitrosodisulfonate to give *o*-quinone XXII. Treatment of this quinone with 0.1 *N* hydrochloric acid in aqueous methanol as described previously[5] gave the desired hydroxy-*p*-quinone XXIII in 18% yield. However, this low yield and the cumbersomeness of this procedure prompted the study of alternate methods. Thiele acetoxylation[25] of *o*-quinone XXII gave the hydroxyhydroquinone triacetate XXIV which, on treatment with base followed by aeration, furnished hydroxy-*p*-quinone XXIII; the over-all yield for these two steps was 67%. Reaction of XXIII with diazomethane readily gave the corresponding methoxy-*p*-quinone XXV. A direct preparation of XXV from *o*-quinone XXII, based on the method of Horner and Göwecke[26] for the conversion of *o*-benzoquinones into methoxy-*p*-benzoquinones, was also attempted. However, when XXII was treated with boron trifluoride etherate in methanol, only the hydroxy-*p*-quinone XXIII could be isolated (18%).[27]

The elaboration of the 9-hydroxymethyl grouping from quinonealdehydes XXIII and XXV was now studied. In an early experiment, it was noted that aeration of the colorless reaction solution obtained by sodium borohydride reduction of the 9-formylhydroxyquinone XXIII resulted in the development of a purple color, which on acidification changed to orange.[28] These observations indicated that air oxidation could be used for the regeneration of the quinone system following the borohydride treatment. However, many attempts to prepare the 9-hydroxymethyl derivatives corresponding to hydroxyquinone XXIII and methoxyquinone XXV failed. Consideration of these efforts indicated that the difficulty resided in the oxidation step. Had reduction of the aldehyde function in the hydroxyquinone XXIII not been achieved, oxidation of the reaction solution should have regenerated XXIII for its stability to air in alkaline solution was demonstrated by its preparation (XXIV → XXIII).[29] Therefore, the use of chemical oxidants for the regeneration of the quinone system was attempted and, indeed, permitted the successful preparation of the desired carbinol. Thus, reduction of the methoxyquinone aldehyde XXV with sodium borohydride and subsequent treatment *in situ* of the resulting hydroquinone with acidic ferric chloride solution gave in good yield the quinonecarbinol XXVI.[30] This product had an ultraviolet spectrum characteristic of the designated structure (XXVI)[20] and readily formed a

(22) For the suggested nomenclature in this series, see ref. 20.

(23) The stability of the 9-formyl group to these cleavage conditions had already been demonstrated by Dr. W. A. Remers (i → ii). We are grateful to him for this information.



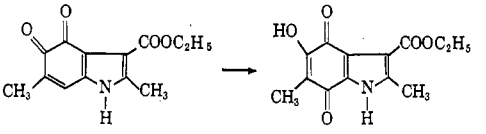
i ii

(24) Reduction of 9-aldehyde XX furnished the corresponding 9-carbinol. As expected, this product gave largely a diindolylmethane on attempted conversion to the carbamate ester.

(25) J. Thiele, *Ber.*, **31**, 1248 (1898).

(26) L. Horner and S. Göwecke, *ibid.*, **94**, 1291 (1961).

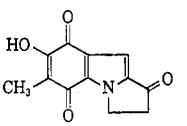
(27) Independent of our effort Dr. J. B. Patrick and Mr. R. P. Williams of these laboratories found that similar treatment of ethyl 2,6-dimethyl-4,5-dioxo-3-indole-carboxylate (iii) furnished the hydroxy-*p*-quinone iv.



iii iv

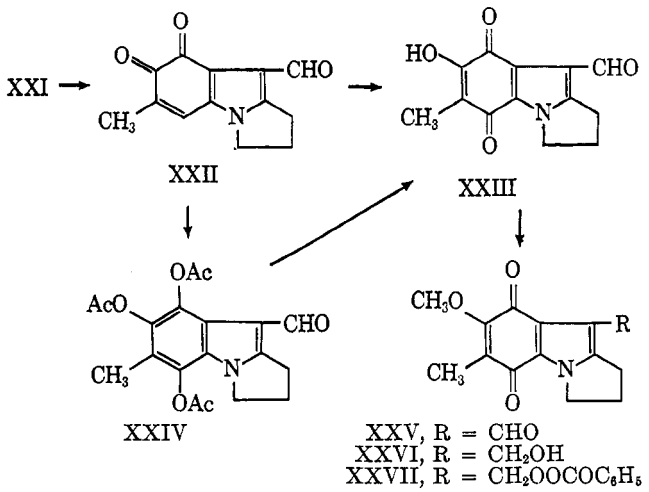
(28) These color changes in response to pH are characteristic of the hydroxyindoloquinones; see ref. 20.

(29) We interpret this difference in behavior between the 9-hydroxymethyl series and the 9-aldehyde series toward oxygen to be the result of the reduced nucleophilicity of C-9 in the 9-aldehyde series. [The facile reaction of 3-alkylindoles with oxygen is well known: B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2196 (1951), and previous papers.] From one such borohydride reduction of XXIII and air oxidation of the intermediate hydroquinone there was isolated in low yield a substance, the qualitative ultraviolet spectrum of which exhibited a single maximum at 295 mμ. This spectrum is reminiscent of that reported for the 1-ketopyrrolo[1,2-*a*]indoloquinone v (λ_{max} 289 mμ).[5] The formation of a compound with this chromophore can be envisioned as proceeding *via* electrophilic attack of oxygen at C-9 of the 9-hydroxymethylhydroquinone and subsequent rearrangement of the 9-hydroperoxide.



v

(30) The broad applicability of this procedure will be illustrated in succeeding papers.



monoacetate on treatment with acetyl chloride in pyridine. However, it should be noted that this carbinol gave polymeric products on extended exposure to acid, even though it does have greater stability than the 1,2-dialkyl-3-indolylmethanols described by Leete.[16]

Finally, the conversion of carbinol XXVI into 7-methoxymitosene (XVIII) was achieved by ammonolysis of the derived phenylcarbonate ester XXVII.

Biological Results.—7-Methoxymitosene (XVIII) has important antibacterial activity *in vitro* and in mice. *In vitro* this compound is markedly active against a variety of gram-positive organisms, including representative tetracycline- and penicillin-resistant species.[1b] However, it has only marginal activity against gram-negative organisms.

When administered orally to mice infected with *Staphylococcus aureus* var. Smith, 7-methoxymitosene is about one-third as active as tetracycline hydrochloride. However, despite its marked *in vitro* activity against a tetracycline-resistant *Staphylococcus* species and *Streptococcus pyogenes* C-203, 7-methoxymitosene is not effective *in vivo* against these organisms. This behavior against the last organism is in direct contrast to that exhibited by 7-methoxy-1,2-(N-methylaziridino)mitosene (I).[2]

Based on limited data, 7-methoxymitosene shows no acute toxicity when administered orally at 128 mg./kg. in mice.

When assayed against mammary adenocarcinoma 72J in C_3H mice 7-methoxymitosene showed activity at a dose of 13 mg./kg. administered once daily for 6 days by the interperitoneal route, causing a regression in tumor weight to about one-half that of controls. On limited preliminary assays against Sarcoma 180 and lymphosarcoma 6C3HED similar activities were noted. However, none of these antitumor activities was of sufficient interest to warrant further study.

Experimental

General.—Melting points were determined in an open capillary tube on a Mel-Temp apparatus and are corrected. The petroleum ether used was that fraction boiling at 30–60°, except where specified differently. Except where noted otherwise, the ultraviolet spectra were determined in methanol solution using a Cary recording spectrophotometer; for the acid and base spectra, the final dilution was made with 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide, respectively. The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer spectrophotometer, Model 21. All evaporations were carried out at reduced pressure. P.m.r. spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard; deuteriochloroform was used for solvent except with the carbamate XVIII where hexadeuteriodimethyl sulfoxide was used.

4-Nitro-2,5-xylenol (III). A.—Nitration of 2,5-xylenol according to the procedure of Albert and Sears[31] gave 4% of yellow needles, m.p. 122–124° (lit.[8] m.p. 121–123°).

B.—Following the procedure of Datta and Varma[32] a solution of 10 g. (82.6 mmoles) of 2,5-xylenol in 20 ml. of 96% sulfuric acid was warmed on the steam bath for 1 hr. The cooled solution was diluted with 75 ml. of water and treated with a stream of nitrogen oxides generated by the addition of acetic acid to an aqueous solution of sodium nitrite. After 3 hr. the initially green solution became yellow and a heavy precipitate had separated. This solid was recrystallized from benzene to give 3.94 g. of crystals, m.p. 120–122°. From the mother liquor an additional 5.29 g. of crystals, m.p. 116–117°, was obtained.

When this procedure was applied to 50.0 g. of 2,5-xylenol the yield of material of acceptable quality dropped from the above 67% to 18%.

C.—A mechanically stirred solution of 61.0 g. (0.5 mole) of 2,5-xylenol in 150 ml. of acetic acid and 20 ml. of sulfuric acid was treated with a solution of 35 g. of sodium nitrite in 100 ml. of water at such a rate that the temperature remained at 8–10°; the addition required about 100 min. The resulting mixture was stirred for an additional 10 min., poured into ice–water, and filtered to give crude 4-nitroso-2,5-xylenol, m.p. 166–167° dec. The partially dried material was added in portions to a mechanically stirred solution of 50 ml. of 70% nitric acid in 150 ml. of water at 40–50°. Stirring was continued until nitrogen oxides were no longer evolved; the mixture was poured into water and filtered to give 78.0 g. of solid, m.p. 100–113°. Recrystallization from benzene gave 64.4 g. (78%) of crystals, m.p. 116–119°.

2,5-Dimethyl-4-nitroanisole (IV).—A mechanically stirred suspension of 16.7 g. (0.1 mole) of 4-nitro-2,5-xylenol (III) in 50 ml. of water was treated at 40–45° alternately and in portions with a solution of 7.0 g. (0.175 mole) of sodium hydroxide in 18 ml. of water and 16.2 g. (0.128 mole, 12 ml.) of methyl sulfate. After 2 hr. the previously chilled reaction mixture was filtered, and the solid was recrystallized from dilute methanol to give 14.5 g. (80%) of needles, m.p. 90–92°.

Material from a similar experiment was obtained as long white needles: m.p. 91–92°; λ_{max} 312 mμ (ε 7600); λ_{max}^{NaOH} 331 mμ (ε 7200); λ_{max}^{HCl} 331 mμ (ε 7200); λ 6.14, 6.32, 6.55, 6.64, 7.45–7.53, and 9.37 μ.

Anal. Calcd. for $C_9H_{11}NO_3$ (181.19): C, 59.66; H, 6.12; N, 7.73. Found: C, 60.05; H, 5.86; N, 7.56.

For the preparation of large quantities of this material it proved expedient not to isolate and purify the intermediate 4-nitro-2,5-xylenol. Thus 1 mole of 2,5-xylenol was nitrated according to method C; without purification, the nitroxylenol was methylated to give 100 g. (55%) of material suitable for the next preparation.

5-Methoxy-4-methyl-2-nitrophenylpyruvic Acid (V). A.—To a mechanically stirred slurry of 2.15 g. (0.055 g.-atom) of potassium in benzene was cautiously added 6.25 ml. of ethanol. After all the potassium had dissolved, the solvents were removed by distillation. Additional benzene was added and removed in the same manner. The cooled residue was slurried with 100 ml. of ether and treated with 7.3 g. (0.05 mole, 6.75 ml.) of diethyl oxalate; all solid dissolved. A solution of 9.05 g. (0.05 mole) of 2,5-dimethyl-4-nitroanisole (IV) in 150 ml. of ether was added and a red solid separated almost immediately. This mixture was stirred at room temperature for 18 hr. and then at reflux temperature for 4 hr. The solid was then collected by filtration, washed well with ether, and dissolved in water. The red solution was heated on the steam bath for 30 min. during which time it became yellow. The cooled solution was extracted with ether and this extract was combined with the reaction filtrate and washings. The aqueous solution was acidified with hydrochloric acid solution, and the oil which separated rapidly crystallized. Filtration gave 6.12 g. (49%) of cream-colored material, m.p. 167–170°. Three recrystallizations from dilute methanol gave needles: m.p. 168–170°; λ_{max} 285 and 308 mμ

(31) H. E. Albert and W. C. Sears, *J. Am. Chem. Soc.*, **76**, 4979 (1954).
(32) R. L. Datta and P. S. Varma, *ibid.*, **41**, 2042 (1919).

(ϵ 7400 and 7280); λ_{max}^{NaOH} 318 mμ (ϵ 12,650); λ_{max}^{HCl} 331 mμ (ϵ 6900); λ 3.2–3.4 (broad), 5.72, 5.83, 6.15, 6.32, 6.57–6.64, 7.55, 7.90, and 9.34 μ.

Anal. Calcd. for $C_{11}H_{11}NO_6$ (253.21): C, 52.17; H, 4.38; N, 5.53. Found: C, 52.45; H, 4.59; N, 5.30.

The combined ether solutions were dried over magnesium sulfate and taken to dryness. The residue was recrystallized from dilute methanol to give 3.11 g. (34% recovery) of **2,5-dimethyl-4-nitroanisole (IV)** as needles, m.p. 88–90°.

B.—Potassium *t*-butoxide was prepared by allowing 15.8 g. (0.40 g.-atom) of potassium to react with 320 ml. of *t*-butyl alcohol. The excess alcohol was removed by distillation; 200 ml. of benzene was added and removed in the same manner. The benzene addition and removal was repeated, and the residue was suspended in 320 ml. of benzene. The mechanically stirred mixture was treated with 69.0 g. (0.47 mole, 65.3 ml.) of ethyl oxalate; an orange solution resulted. This solution was treated with a solution of 72.8 g. (0.40 mole) of 2,5-dimethyl-4-nitroanisole (IV) in 900 ml. of benzene (previously distilled until b.p. 80° was reached); a deep red solid precipitated within a few minutes. The mixture was stirred at reflux temperature for 24 hr. and then at room temperature for 24 hr. The solid was collected by filtration, washed well with ether, air dried, and then heated on the steam bath for 30 min. with 1.5 l. of water containing 50 g. of sodium bicarbonate. The cooled solution was extracted several times with ether and then acidified with hydrochloric acid to give 82.0 g. (80% yield) of light brown solid, m.p. 95–110°. This material was of suitable purity for the next step.

Material from a similar experiment was recrystallized three times from dilute methanol to give tan crystals, m.p. 108–112°. This low-melting material was that which was usually isolated; analysis indicated it to be solvated.

Anal. Calcd. for $C_{11}H_{11}NO_6 \cdot 1.33H_2O$ (277.23): C, 47.65; H, 4.97; N, 5.06; H_2O, 5.14. Found: C, 47.32; H, 4.82; N, 5.03; H_2O (Karl Fischer), 4.73.

5-Methoxy-6-methyl-2-indolecarboxylic Acid (VI).—A solution of 42.0 g. (0.166 mole) of 5-methoxy-4-methyl-2-nitrophenylpyruvic acid (V) in 230 ml. of 17% ammonium hydroxide and 115 ml. of water was treated with mechanical stirring with a hot solution of 300 g. of ferrous sulfate heptahydrate in 340 ml. of water. The mixture was heated on the steam bath with stirring for 1 hr., cooled, and filtered. The residue was washed with dilute ammonium hydroxide solution until a test portion of the filtrate became only milky on acidification. The combined filtrate and washings were acidified with hydrochloric acid, and the precipitated solid was collected by filtration. The moist solid was recrystallized from dilute acetic acid to give, in two crops, 19.0 g. (56%) of gray solid, m.p. 240–242° (gas) after prior darkening. Material from a similar experiment had m.p. 240–241° (gas); λ_{max} 294 mμ (ϵ 18,400); λ_{max}^{NaOH} 291 mμ (ϵ 17,500); λ_{max}^{HCl} 298 mμ (ϵ 19,500); λ 2.90, 3.35 (broad), 5.90–5.95, 6.32, 6.50, and 7.98–8.25 μ.

Anal. Calcd. for $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.15; H, 5.41; N, 6.89.

Methyl 5-Methoxy-6-methyl-2-indolecarboxylate (VIII).—A mixture of 38.7 g. (0.188 mole) of 5-methoxy-6-methyl-2-indolecarboxylic acid (VI) and 1 l. of methanolic hydrogen chloride was heated at reflux temperature for 3 hr. The solvent was removed from the resulting solution, and the residue was dissolved in about 1 l. of ether. This solution was treated with activated charcoal, filtered, and taken to dryness. Recrystallization of the residue from dilute methanol gave 35.4 g. of white needles, m.p. 149–150°. From the mother liquor there was obtained an additional 3.20 g. of needles, m.p. 145–147° (94% total).

Material from a similar experiment was obtained as white needles: m.p. 149–150°; λ_{max} 298 mμ (ϵ 19,900); λ 2.96, 5.88, 6.54, 8.00, and 8.20 μ.

Anal. Calcd. for $C_{12}H_{13}NO_3$ (219.23): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.70; H, 6.17; N, 6.46.

5-Methoxy-6-methylindole (VII).—5-Methoxy-6-methyl-2-indolecarboxylic acid (VI, 500 mg., 2.42 mmoles) was heated at 250–260° until the melt was quiescent; the melt was then heated to and held briefly at 300°. The cooled material was dissolved in ether, washed with a sodium carbonate solution, dried, treated with activated charcoal, and taken to dryness. Recrystallization of the residue from ether–petroleum ether (b.p. 60–70°) gave 276 mg. (71%) of white crystals, m.p. 118–120°. This material was recrystallized four times from the same solvent pair to give white crystals: m.p. 119–120°; λ_{max} 217, 271, 293, and 305 mμ (ϵ 24,200, 6940, 5480, and 4440); λ 2.96, 6.10, and 6.32 μ.

Anal. Calcd. for $C_{10}H_{11}NO$ (161.20): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.21; H, 6.51; N, 8.39.

Methyl 1-(β-Cyanoethyl)-5-methoxy-6-methyl-2-indolecarboxylate (IX).—A solution of 0.860 g. (3.92 mmoles) of methyl 5-methoxy-6-methyl-2-indolecarboxylate (VIII) and 0.212 g. (4.0 mmoles) of acrylonitrile in 15 ml. of dioxane containing 0.5 ml. of 35% aqueous benzyltrimethylammonium hydroxide was heated at 50° with magnetic stirring for 30 min. The solution was then allowed to stand at room temperature for 16 hr., diluted with water containing acetic acid, and extracted with chloroform. The extract was dried over magnesium sulfate and taken to dryness. Crystallization of the residual gum from methanol gave 0.500 g. (48%) of white crystals, m.p. 99–101°. Two recrystallizations from dilute methanol furnished white rods: m.p. 119–121°; λ_{max} 210 and 301 mμ (ϵ 27,400 and 22,100); λ 4.45, 5.86, 6.57, 7.95, 8.20, and 8.30 μ.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$ (272.29): C, 66.16; H, 5.92; N, 10.29. Found: C, 65.76; H, 6.00; N, 10.30.

Subsequent experiments gave the cyanoethyl derivative in 60–70% yield.

2,3-Dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo[1,2-*a*]indole-2-carbonitrile (X). A.—Potassium *t*-butoxide was prepared in the usual manner from 0.223 g. (5.7 mg.-atoms) of potassium and 25 ml. of *t*-butyl alcohol. A mechanically stirred suspension of the base in 25 ml. of benzene was treated with a solution of 1.550 g. (5.7 mmoles) of methyl 1-(β-cyanoethyl)-5-methoxy-6-methyl-2-indolecarboxylate (IX) in 50 ml. of benzene. The resulting mixture was stirred at reflux temperature for 24 hr. and then at room temperature for 16 hr. The mixture was treated with cracked ice and acidified with dilute hydrochloric acid solution. After distribution of the reaction mixture between methylene chloride and additional water, the organic layer was dried over magnesium sulfate and taken to dryness. The residue was recrystallized from methanol to give 0.917 g. (67%) of crystals, m.p. 215–219°. Several recrystallizations from methanol gave needles: m.p. 219–221°; λ_{max} 218 and 336 mμ (ϵ 32,800, and 21,800); λ_{max}^{NaOH} 221 and 345 mμ (ϵ 37,300 and 20,500); λ_{max}^{HCl} 215 and 343 mμ (ϵ 17,400 and 21,800); λ 4.44, 5.75, 6.50, and 8.26 μ.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$ (240.25): C, 69.99; H, 5.03; N, 11.66. Found: C, 69.79; H, 5.30; N, 11.44.

B.—To a suspension of potassium *t*-butoxide, prepared from 0.880 g. (22.5 mg.-atoms) of potassium and 50 ml. of *t*-butyl alcohol, in 50 ml. of benzene was added with mechanical stirring a solution of 4.923 g. (22.5 mmoles) of methyl 5-methoxy-6-methyl-2-indolecarboxylate (VIII) in 150 ml. of benzene and then 1.190 g. (22.5 mmoles, 1.47 ml.) of acrylonitrile. The resulting mixture was heated at reflux temperature for 6 hr., acidified with 5% hydrochloric acid solution, and extracted with methylene chloride. The combined organic extracts were dried over magnesium sulfate and taken to dryness. The residue was recrystallized twice from methanol to give 1.35 g. (25% yield) of crystals, m.p. 215–218°. The identity of this material with that prepared in method A was shown by mixture melting point and spectral comparisons.

Methyl 2,3-Dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo-[1,2-*a*]indole-2-carboxylate (XI).—A mechanically stirred suspension of potassium *t*-butoxide (prepared from 0.391 g., 10 mg.-atoms, of potassium and 25 ml. of *t*-butyl alcohol) in 25 ml. of benzene was treated with a solution of 2.190 g. (10 mmoles) of methyl 5-methoxy-6-methyl-2-indolecarboxylate (VIII) in 50 ml. of benzene followed by 0.860 g. (10 mmoles, 0.89 ml.) of methyl acrylate. The mixture was heated at reflux temperature for 2 hr. and then stirred at room temperature for 63 hr. The reaction was diluted with water, acidified with hydrochloric acid solution, and extracted with methylene chloride. The organic solution was dried over magnesium sulfate and taken to dryness. The residue was triturated with methanol and filtered to give 1.725 g. (63% yield) of near-white crystals, m.p. 175–179°. Two recrystallizations from acetone–petroleum ether (b.p. 60–70°) gave needles: m.p. 180–182°; λ_{max} 216 and 336 mμ (ϵ 30,200 and 21,800); λ 5.78, 6.52, 8.04, 8.25, and 8.56 μ.

Anal. Calcd. for $C_{15}H_{15}NO_4$ (273.28): C, 65.92; H, 5.53; N, 5.13. Found: C, 65.60; H, 5.59; N, 5.30.

A subsequent experiment utilizing 30.0 g. of indole ester gave the product in 82% yield.

2,3-Dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indol-1-one (XII). A.—A mixture of 3.00 g. (11 mmoles) of methyl 2,3-dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo[1,2-*a*]in-

dole-2-carboxylate (XI), 120 ml. of methanol, and 30 ml. of 37% hydrochloric acid solution was heated at reflux temperature for 1 hr. The solid dissolved during this period, and the green solution was poured into much water and extracted with methylene chloride. The extracts were washed with sodium bicarbonate solution, dried over magnesium sulfate, and taken to dryness. The residue was slurried with 50 ml. of ether and filtered to give 1.462 g. of tan solid, m.p. 204–208°. This material was recrystallized from acetone–petroleum ether (b.p. 60–70°) to give 1.000 g. (42%) of yellow crystals, m.p. 211–213°. Two additional recrystallizations from acetone gave yellow crystals: m.p. 213–215°; λ_{max} 218 and 331 mμ (ε 29,100 and 21,200); λ 5.82, 6.49, 8.21, and 8.40 μ; p.m.r. τ 2.90 (5H), 3.04 (8H), 3.17 (9H), 5.72 (triplet, >N–CH_2–), 6.17 (O–Me), 6.90 (triplet, O=C–CH_2–), and 7.68 (>C–Me).[33]

Anal. Calcd. for $C_{13}H_{13}NO_2$ (215.24): C, 72.54; H, 6.09; N, 6.51. Found: C, 71.78; H, 5.98; N, 6.58.

B.—A solution of 37.7 g. (0.138 mole) of methyl 2,3-dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo[1,2-*a*]indole-2-carboxylate (XI) in 800 ml. of 95% acetic acid was heated at reflux temperature for about 18 hr. The solution was cooled and filtered to give 23.2 g. of crystals, m.p. 216–218°. The filtrate was diluted with much water, and the precipitated solid was recrystallized from methylene chloride–petroleum ether to give 2.4 g. (86% total) of crystals, m.p. 210–215°.

C.—A solution of 900 mg. (3.14 mmoles) of 2-carboxy-5-methoxy-6-methyl-1-indolepropionic acid (XIII) and 60 mg. of potassium cyanide in 35 ml. of acetic anhydride was maintained at reflux temperature for 20 hr. The solvents were removed, and the residue was dissolved in a mixture of 25 ml. of 10% potassium hydroxide and 25 ml. of ethanol. The reaction mixture was refluxed for 1 hr. and treated with charcoal and the alcohol was evaporated. The aqueous phase was extracted with methylene chloride, and the extract was dried over magnesium sulfate and taken to dryness. Recrystallization from methylene chloride–petroleum ether furnished yellow crystals, m.p. 210–215°, infrared spectrum same as that obtained for products prepared by methods A and B.

2-Carboxy-5-methoxy-6-methyl-1-indolepropionic Acid (XIII). A.—A mixture of 500 mg. (1.83 mmoles) of methyl 2,3-dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo[1,2-*a*]indole-2-carboxylate (XI) and 10 ml. of 10% sodium hydroxide solution was heated at reflux temperature for 3 hr., 15 ml. of ethanol being added to effect solution. Acidification of the reaction solution gave 356 mg. (75% yield) of needles, m.p. 232–233° (gas).

Anal. Calcd. for $C_{14}H_{15}NO_5$ (277.27): C, 60.64; H, 5.45; N, 5.05. Found: C, 60.65; H, 5.75; N, 5.56.

B.—Methyl 1-(β-cyanoethyl)-5-methoxy-6-methyl-2-indolecarboxylate (IX, 4.80 g., 17.7 mmoles) was treated with 10% potassium hydroxide solution as described above. Acidification gave 4.70 g. (96%) of needles, m.p. 230–231° (gas). Recrystallization from acetone failed to alter the melting range; a sample mixed with that from method A melted at 230–232° (gas). This material had λ_{max} 218 and 298 mμ (ε 27,400 and 20,400); λ 3.20–3.40, 5.90, 6.57, and 8.24 μ.

Anal. Found: C, 60.66; H, 5.50; N, 5.27.

Ethyl 1-(β-Cyanoethyl)-3-phenoxycarbonyloxymethyl-5-methoxy-6-methyl-2-indolecarboxylate (XVI).—To a well-stirred, ice-cold solution of 2.98 g. (9.8 mmoles) of ethyl-1-(β-cyanoethyl)-3-hydroxymethyl-5-methoxy-6-methyl-2-indolecarboxylate (XV)[1a] in 26 ml. of dry pyridine was added 1.55 g. (9.8 mmoles) of phenyl chloroformate. The reaction mixture was stirred at room temperature for 2 hr. during which time the orange gum which had formed dissolved. Water was then added to the reaction mixture and the precipitate was collected to give 2.78 g. (69%) of white solid, m.p. 135–136°. An analytical sample was prepared by recrystallization from acetone–petroleum ether (b.p. 60–70°): m.p. 147–147.5°; λ_{max} 212 and 305 mμ (ε 35,800 and 20,100); λ 3.37, 4.44, 5.68, 5.90, and 7.85–8.3 μ.

Anal. Calcd. for $C_{24}H_{24}N_2O_6$ (436.45): C, 66.04; H, 5.54; N, 6.42. Found: C, 66.58; H, 5.67; N, 6.14.

Ethyl 3-Carbamoyloxymethyl-1-(β-cyanoethyl)-5-methoxy-6-methyl-2-indolecarboxylate (XVII).—To a solution of 2.78 g. (6.6 mmoles) of ethyl 1-(β-cyanoethyl)-3-phenoxycarbonyloxymethyl-5-methoxy-6-methyl-2-indolecarboxylate (XVI) in 100 ml. of methylene chloride, chilled in a Dry Ice bath, was added 100 ml. of liquid ammonia. The Dry Ice bath was removed and the reaction mixture was magnetically stirred under a Dry Ice condenser for 6 hr. The Dry Ice condenser was removed and the excess ammonia was allowed to evaporate. The reaction mixture was partitioned between water and methylene chloride. The organic phase was separated and washed with 100 ml. of 4% sodium hydroxide solution, 100 ml. of saturated sodium chloride solution, and finally with water and then dried over sodium sulfate. The solvent was evaporated with concomitant addition of petroleum ether to effect crystallization. The mixture was cooled and filtered to give 1.77 g. (79%) of white crystals: m.p. 194–195°; λ_{max} 211 and 303 mμ (ε 29,400 and 19,750); λ 2.85, 2.94, 4.42, and 5.86 μ.

Anal. Calcd. for $C_{18}H_{21}N_3O_5$ (359.37); C, 60.16; H, 5.89; N, 11.69. Found: C, 59.67; H, 6.13; N, 11.24.

2,3-Dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indole (XIX).—A mixture of 8.3 g. (38.6 mmoles) of 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indol-1-one (XII), 3.98 ml. of hydrazine hydrate, 5.6 g. of powdered 85% potassium hydroxide pellets, and 180 ml. of diethylene glycol was heated at reflux temperature for 6 hr. The cooled mixture was extracted several times with benzene, and the combined extracts were passed through a column prepared from 300 g. of Florisil.[34] The eluate was taken to dryness to give 4.40 g. (56%) of solid, m.p. 115–118°. A sample from a similar experiment was recrystallized from methanol to give crystals: m.p. 116–118°; λ_{max} 220, 279, 295, and 308 mμ (ε 31,300, 7930, 6930, and 4530); no carbonyl absorption in the infrared.

Anal. Calcd. for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.34; H, 7.77; N, 6.84.

2,3-Dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XX).—A mixture of 1.54 g. (11.4 mmoles) of N-methylformanilide and 1.76 g. (11.4 mmoles) of freshly distilled phosphorus oxychloride was stirred at room temperature for 15 min. Ethylene dichloride (10 ml.) was added and the reaction mixture was cooled to 0°. To this mixture was added 1.00 g. (4.96 mmoles) of 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo-[1,2-*a*]indole (XIX), and it was heated at reflux temperature for 20 min. The solution was cooled and poured, with vigorous stirring, into 50 ml. of cold water containing 6 g. of sodium acetate. The ethylene dichloride was removed by steam distillation and, after chilling the residue, filtration gave 985 mg. of solid, m.p. 190–192°.

The filtrate was extracted with methylene chloride and the dried extract was taken to dryness. Crystallization of the residue from methylene chloride–petroleum ether gave 70 mg. of pink crystals, m.p. 194–195°, total 1.055 g. (92%). Recrystallization from methylene chloride–petroleum ether furnished white crystals: m.p. 187–189°; λ_{max} 213, 256, 282, and 309 mμ (ε 43,000, 18,200, 16,800, and 13,500); λ 3.56, 3.66, 6.06, 6.5, and 7.95 μ.

Anal. Calcd. for $C_{14}H_{15}NO_2$ (229.27): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.06; H, 6.74; N, 6.98.

2,3-Dihydro-7-hydroxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XXI).—A mixture of 3.00 g. (13.1 mmoles) of 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XX) and 3.4 g. (25.6 mmoles) of aluminum chloride in 140 ml. of xylene was heated at reflux temperature with vigorous stirring for 5 hr. After cooling, the reaction mixture was poured onto ice and digested. The resulting red solid was filtered to give 2.36 g. (84%) of solid, m.p.. >300°. Recrystallization from a large volume of acetone furnished white crystals: m.p. >300°; λ_{max} 215, 256, 283, and 311 mμ (ε 29,800, 15,910, 14,910, and 13,000); λ 3.08, 3.35, 3.53, 6.1, 6.5, and 8.05 μ.

Anal. Calcd. for $C_{13}H_{13}NO_2$ (215.24): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.25; H, 6.06; N, 6.57.

2,3-Dihydro-6-methyl-7,8-dioxo-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XXII).—A solution of 215 mg. (1.0 mmole) of 2,3-dihydro-7-hydroxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XXI) in 250 ml. of boiling acetone was added, with stirring, to a solution of 402 mg. (1.5 mmoles) of potassium nitrosodisulfonate in 30 ml. of 1/6 *M* potassium dihydrogen phosphate and 60 ml. of water. The light blue solution turned to a dark purple color and 60 ml. of water was added. The solution was extracted with methylene chloride, and the extract was washed with saline solution, dried over sodium sulfate, and taken to dryness. The residue was triturated with ether and filtered to

(33) See N. S. Bhacca, L. F. Johnson, and J. N. Schoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 299.

(34) Florisil is the trade-mark of the Floridin Co. for a magnesia–silica gel adsorbent.

give 92 mg. (40%) of black solid, m.p. 230–240° dec. One recrystallization from methylene chloride–petroleum ether gave shiny black needles: m.p. 240–248° dec.; λ_{max} 225, 280, 345, and 520 mμ (ε 21,800, 5500, 2980, and 1600)[35]; λ 3.5, 6.0, 6.10, and 6.44 μ.

Anal. Calcd. for $C_{13}H_{11}NO_3$ (229.23): C, 68.11; H, 4.84; N, 6.11. Found: C, 68.46; H, 5.04; N, 6.31.

2,3-Dihydro-5,7,8-trihydroxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde Triacetate (XXIV).—A mixture of 400 mg. (1.75 mmoles) of 2,3-dihydro-6-methyl-7,8-dioxo-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XXII), 6 ml. of acetic anhydride, and 0.125 ml. of boron fluoride ethyl ether was warmed on the steam bath and then allowed to stand at room temperature for several hours. The reaction mixture was then poured into water and extracted with methylene chloride. The extracts were washed with water, and the dried combined organic layers were concentrated on the steam bath with concomitant addition of ether to effect crystallization. The mixture was cooled and filtered to give 500 mg. (77%) of gray solid, m.p. 260–265°. An additional recrystallization from methylene chloride–ether gave a solid: m.p. 264–265°; λ_{max} 218, 248, and 305 mμ (ε 28,000, 18,300, and 11,200); λ 5.65, 5.98, and 8.20–8.50 μ.

Anal. Calcd. for $C_{19}H_{19}NO_7$ (373.35): C, 61.12; H, 5.13. N, 3.75. Found: C, 61.11; H, 5.31; N, 3.67.

2,3-Dihydro-7-hydroxy-6-methyl-5,8-dioxo-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XXIII). A.—A suspension of 300 mg. (0.80 mmole) of 2,3-dihydro-5,7,8-trihydroxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde triacetate (XXIV) in 20 ml. of water, under nitrogen, was treated with 2.4 ml. of 25% aqueous sodium hydroxide. The reaction mixture was heated on the steam bath, with magnetic stirring, for 0.5 hr. or until solution was essentially complete. The undissolved starting material (45 mg.) was removed, and on exposure to air the filtrate turned a dark blue. After 0.5 hr. the dark blue solution was acidified with 2.4 ml. of concentrated hydrochloric acid, whereupon an orange solution resulted. The solution was extracted with methylene chloride and the extracts were washed with saline solution, water, and dried over anhydrous sodium sulfate. The solvent was evaporated with concomitant addition of petroleum ether to effect crystallization. The mixture was cooled and filtered to give 146 mg. (87%) of orange crystals: m.p. 219–221°; λ_{max} 219, 299, and 330 mμ (ε 21,300, 14,450, and 8100); λ 2.96, 5.95, 6.0, 6.07, and 9.12 μ.

Anal. Calcd. for $C_{13}H_{11}NO_4$ (245.32): C, 63.67; H, 4.52. Found: C, 63.45; H, 4.64.

B.—A solution of 2,3-dihydro-6-methyl-7,8-dioxo-1H-pyrrolo-[1,2-*a*]indole-9-carboxaldehyde (XXII, 200 mg., 0.87 mmole) in 2 l. of methanol was added to 18 l. of 0.1 *N* hydrochloric acid solution and the solution was kept at room temperature for 7 days. The product was isolated with methylene chloride and chromatographed on Celite[36] using a heptane–ethyl acetate–methanol–water (80:20:17:4) system.[37] The material eluted at peak holdback volume 3.7 (V_m/V_s 3.0) was recrystallized from ethyl acetate–petroleum ether (b.p. 60–70°) to give 39 mg. (18% yield) of orange needles, m.p. 220–222°. The identity of this material with that of method A was shown by the usual criteria.

C.—To a solution of 200 mg. (0.87 mmole) of 2,3-dihydro-6-methyl-7,8-dioxo-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XXII) in 5 ml. of methanol was added 2–3 drops of boron trifluoride etherate, and the solution was heated on the steam bath for about 3 min. and then kept at room temperature for 2 hr. Solvent was then removed, and the residue was subjected to partition chromatography on Celite as described in method B. The solid eluted at peak holdback volume 3.7 (V_m/V_s 3.0) was recrystallized from methylene chloride–petroleum ether to give 40 mg. (18% yield) of orange needles, m.p. 220–221°. The identity of this material with that prepared by the previous methods was shown by the usual criteria.

2,3-Dihydro-7-methoxy-6-methyl-5,8-dioxo-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XXV).—A mixture of 10 ml. of ether and 0.16 ml. of 45% aqueous potassium hydroxide, chilled in an ice bath and magnetically stirred, was treated with 86 mg. (0.58 mmole) of N-nitro-N¹-nitroso-N¹-methylguanidine portionwise. The reaction mixture was stirred for 0.5 hr. in the cold and then the organic phase was decanted onto potassium hydroxide pellets.

The dried ethereal diazomethane solution was added to a solution of 100 mg. (0.408 mmoles) of 2,3-dihydro-7-hydroxy-6-methyl-5,8-dioxo-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XXIII) in 20 ml. of methylene chloride and stirred at room temperature for 2 hr. The excess diazomethane and solvents were removed by introduction of a stream of dry nitrogen. The residue was recrystallized from methylene chloride–petroleum ether to give 85 mg. (93%) of red crystals, m.p. 210–215°. The analytical sample had m.p. 224–227°; λ_{max} 216, 243, 272, 289, and 332 mμ (ε 25,200, 14,900, 14,250, 13,870 and 7120); λ 5.92, 5.98, 6.07, 9.06, and 9.78 μ; p.m.r. τ −0.5 (—HC=O), 5.66 (>N–CH_2–, triplet, J = 7 c.p.s.), 5.88 (O–Me), 8.01 (>C–Me).

Anal. Calcd. for $C_{14}H_{13}NO_4$ (259.24): C, 64.86; H, 5.05; N, 5.40. Found: C, 64.53; H, 5.22; N, 5.17.

2,3-Dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo-[1,2-*a*]indole-5,8-dione (XXVI).—A magnetically stirred suspension of 250 mg. (0.96 mmole) of 2,3-dihydro-7-methoxy-6-methyl-5,8-dioxo-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (XXV) in 250 ml. of methanol was thoroughly swept with nitrogen and then treated with 250 mg. of sodium borohydride. The orange solid partially dissolved and a colorless solid separated; the mixture was heated at reflux temperature for about 3 min. causing complete solution. Stirring at room temperature was continued for an additional 45 min. under nitrogen. Acetone (10 ml.) was added followed by 5 ml. of a 1 *N* ferric chloride in 0.1 *N* hydrochloric acid solution; the solution immediately became orange. It was diluted with water and rapidly extracted with methylene chloride. The combined extracts were washed with saline solution, dried over magnesium sulfate, and taken to dryness. The residue was recrystallized from methylene chloride–petroleum ether to give in two crops, 201 mg. (80%), of red rosettes: m.p. 170–173°; λ_{max} 230, 287, 350, and 460 mμ (ε 17,800, 13,700, 3300, and 1310); λ 2.81, 6.01, 6.05, 6.21, 9.10, 9.50, and 9.82 μ. In a preliminary experiment this material was obtained as red needles: m.p. 180–182°; λ_{max} 230, 287, 350, and 460 mμ (ε 17,700, 13,600, 3340, and 1990); λ 2.89, 5.94, 6.06, 6.23, 9.05, and 9.78 μ.

Anal. Calcd. for $C_{14}H_{15}NO_4$ (261.27); C, 64.36; H, 5.79; N, 5.36. Found: C, 64.08; H, 5.72; N, 5.31.

On admixture the two crystalline forms melted at 170–173° and their infrared spectra in chloroform solution were identical with the solid-state spectrum of the needle modification, m.p. 180–182°.

2,3-Dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo-[1,2-*a*]indole-5,8-dione Acetate.—To an ice-chilled solution of 100 mg. (0.43 mmole) of 2,3-dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-5,8-dione (XXVI) in 10 ml. of pyridine was added 1 ml. of acetyl chloride; a gum separated immediately. The mixture was magnetically stirred for 2 hr., diluted with water, and extracted with methylene chloride. The organic solution was washed successively with 1 *N* hydrochloric acid solution and water, dried over magnesium sulfate, and taken to dryness. Toluene was added to the residue and removed under reduced pressure to remove traces of pyridine in the residue, which was then chromatographed on silica gel. Washing of the column with methylene chloride eluted a small amount of solid, which was discarded. A red band was then eluted by chloroform; removal of the solvent and recrystallization of the residue from methylene chloride–petroleum ether gave 84 mg. (64%) of orange needles: m.p. 149–151°; λ_{max} 230, 286, 346, and 450 mμ (ε 18,800, 14,300, 3800, and 1210); λ 5.77, 6.05 (sh), 6.09, 6.22, 8.05, 9.11, 9.78, 10.30, 10.41, and 13.45 μ; p.m.r. τ 4.68 (>C–CH_2O), 5.71 (>N–CH_2–, triplet, J = 7 c.p.s.), 5.90 (OCH_3), 7.87 ($COCH_3$), and 8.02 (>C–CH_3).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.40; H, 5.87; N, 4.59.[38]

2,3-Dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo-[1,2-*a*]indole-5,8-dione Phenylcarbonate (XXVII).—To a well-stirred, ice-cold solution of 250 mg. (0.60 mmole) of 2,3-dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-

(35) These values for the molar extinction coefficients supersede those given in our preliminary report (ref. 1b) which have subsequently been found to be erroneous.

(36) Celite is a Johns-Manville Co. trade-mark for diatomaceous silica products.

(37) For a complete description of this technique as developed by Mr. C. Pidacks of these laboratories, 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).

(38) Nitrogen determinations by the Dumas technique as usually run in these laboratories (combustion at 850° for 5 min.) consistently gave nitrogen values which were approximately 33% low. The reported value was obtained with a combustion temperature of 950° for 10 min.

5,8-dione (XXVI) in 10 ml. of dry pyridine was added 150 mg. (0.96 mmole) of phenyl chloroformate. The reaction mixture was stirred at room temperature for 2 hr. during which time the orange gum which had formed dissolved. Water was then added to the reaction mixture and the precipitate was filtered to give 366 mg. (100%) of light orange solid. An analytical sample was prepared by recrystallization from methylene chloride–petroleum ether: m.p. 137.5–138°; λ_{max} 230, 285, 345, and 450 mμ (ε 19,050, 13,900, 3800, and 950); λ 5.69, 6.03, 6.1, 6.22, and 7.85–8.1 μ.

Anal. Calcd. for $C_{21}H_{19}NO_6$ (381.37): C, 66.13; H, 5.02; N, 3.67. Found: C, 65.73; H, 5.23; N, 3.60.[38]

2,3-Dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-5,8-dione Carbamate (XVIII).—Ammonia gas was passed into a solution of 256 mg. (0.67 mmole) of 2,3-dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-5,8-dione phenylcarbonate (XXVII) in 15 ml. of methylene chloride, chilled in an acetone–Dry Ice bath, for 0.5 hr. The acetone–Dry Ice bath was removed, and the reaction mixture was magnetically stirred at room temperature for several hours. The excess ammonia was removed by warming on a water bath. Additional methylene chloride was added to cause solution, and the solution was washed with water. The dried solution was evaporated and the residue was recrystallized from methylene chloride–petroleum ether to give 151 mg. (74% yield) of orange needles, m.p. 206–207°. Recrystallization from ethyl acetate gave orange needles: m.p. 206–207°; λ_{max} 230, 287, 345, and 460 mμ (ε 19,200, 14,600, 3870, and 1390); λ 2.9, 2.99, 5.86, 5.96, 6.05, 6.18, 9.04, 9.5, and 9.65 μ; p.m.r. τ 3.40 ($CONH_2$), 4.90 (≥C–CH_2–O), 5.82 (>N–CH_2–, triplet, J = 7 c.p.s.), 6.03 (OCH_3), and 8.15 (CH_3–C≤).

Anal. Calcd. for $C_{15}H_{16}N_2O_5$ (304.29): C, 59.20; H, 5.30; N, 9.21. Found: C, 59.50; H, 5.57; N, 8.97.[38]

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The Mitomycin Antibiotics. Synthetic Studies. VI.[1] Transformations in the 2,3-Dihydro-1H-pyrrolo[1,2-*a*]indole System

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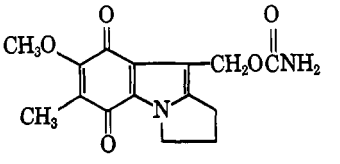
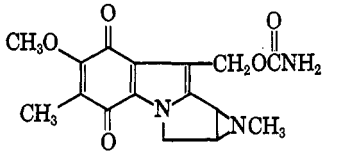
Certain transformations in the relatively rare 2,3-dihydro-1H-pyrrolo[1,2-*a*]indole system are described. Monobromination of the 2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-1-ones Va and Vb results in attack at the β-indolic carbon to give the 9-bromo derivatives VIa and VIb, respectively. Treatment of ketone Va with 2 equiv. of bromine furnishes the 2,9-dibromide XIII. The order of preference observed in the reaction of this system with bromine may be reversed *via* the intermediacy of an enamine derivative. Hence, bromination of enamine XV gives the 2-bromide XVII. Various approaches to the unknown 3H-pyrrolo[1,2-*a*]indole structure, *e.g.*, XXIII, are discussed. Catalytic reduction of enamine XV affords tertiary amine XIX, the methiodide of which, on treatment with potassium *t*-butoxide, furnishes the 9H-pyrrolo[1,2-*a*]indole XXV.

As the basis for a synthetic program related to the mitomycin antibiotics, we have developed methods for the preparation of the 2,3-dihydro-1H-pyrrolo[1,2-*a*]-indole system,[1] the introduction of a 9-aldehyde function into such a structure,[2] the elaboration of the hydroxymethyl carbamate from the resulting aldehyde,[1] and the preparation of the indoloquinone chromophore.[1,3] Subsequently, the compatibility of these procedures was demonstrated in the synthesis of 7-methoxymitosene (I),[1] an antibacterial agent. A major structural feature of the mitomycins and the biologically important 7-methoxy-1,2-(N-methylaziridino)mitosene (II)[4] for which we lacked appropriate synthetic procedures is the fused aziridine moiety. We describe here certain transformations in the pyrrolo[1,2-*a*]indole system which were designed to set the stage for the introduction of this moiety.

Our procedure[1] for the preparation of the pyrrolo[1,2-*a*]indole system afforded a 1-keto derivative,



I



II

e.g., V, which seemed particularly useful for the present purpose. As a model for this study we chose the benzyloxy derivative Vb, since it was readily accessible from the commercially available ethyl 5-benzyloxyindole-2-carboxylate (III). Thus, condensation of III with methyl acrylate afforded a mixture of the methyl (IVa) and ethyl (IVb) β-keto esters, which could be separated, but was more conveniently decarboxylated to give the benzyloxy ketone Vb. A preliminary attempt to avoid this mixture by the use of ethyl acrylate in the condensation with indole

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