Comparable treatment of **4b** with 2 *M* methanolic potassium hydroxide at −5° for 40 min gave mainly aldol cyclization. Resorcylic ester **6b** was isolated in 49% yield by crystallization from chloroform. The nmr spectrum of the supernatant solution indicated that it contained principally resorcylic ester **6b** and unaltered triketo ester **4b** in approximately equal quantities.

General Methods of Synthesis of Indole Alkaloids. VI. Syntheses of *dl*-Corynantheidine and a Camptothecin Model[1,2]

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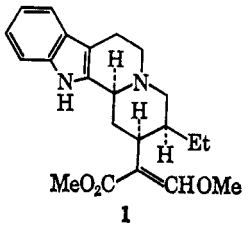
Abstract: The alkaloid corynantheidine has been synthesized by a reaction scheme involving most importantly hydrogenation of an N-alkylnicotinic ester salt and acid-induced, hydrolytic, and decarboxylative cyclization of the resultant tetrahydropyridine derivative. An early synthetic intermediate, 4-methyl-5-ethylnicotinonitrile, has been employed in a four-step conversion into a heteropentacyclic compound structurally closely related to the alkaloid camptothecin. A possible biosynthetic relationship of the latter with indole alkaloids is portrayed.

The recent synthesis of eburnamonine[3] introduced a new procedure for the construction of the indoloquinolizidine skeleton common to a large group of indole alkaloids. It is based on the palladium-catalyzed, partial hydrogenation of 1-[β-(3-indolyl)ethyl]-3-acylpyridinium salts and the acid-induced cyclization of the resultant 2-piperideines. Since the first utilization of this reaction scheme it has been shown to be most successful in cases of employment of N-alkylnicotinic ester salts.[2] Furthermore its first step, the unusual hydrogenation, has been shown to be a general process.[4] Thus the time appeared ripe for the application of the two-step reaction scheme to the synthesis of further indole alkaloids. The present communication describes the synthesis of *dl*-corynantheidine (**1**)[5] and the utilization of an early intermediate in the synthesis of a heteropentacyclic substance structurally closely related to camptothecin (**2**).[6]



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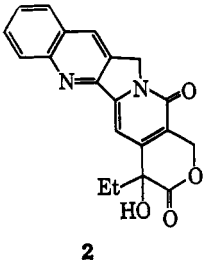
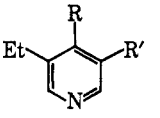
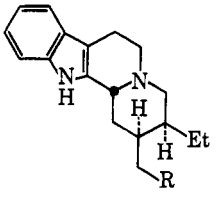


2

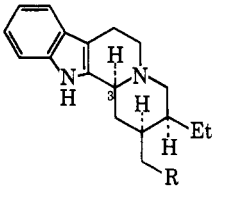
Corynantheidine (1). Methyl 4-carbomethoxymethyl-5-ethylnicotinate (**3a**), a vital intermediate in the syntheses of 3-isocorynantheidol (**4a**) and corynantheidol (**5a**),[2] served as starting material for the synthesis of the indole alkaloid. Alkylation of **3a** with tryptophyl bromide yielded a salt which was characterized as the perchlorate **6**. Palladium-induced hydrogenation of the latter produced the tetrahydropyridine **7**.



3a, R = CH_2CO_2Me; R′ = CO_2Me
b, R = Me; R′ = CN

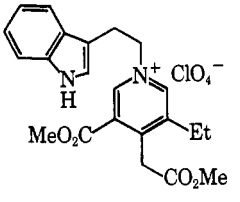


4

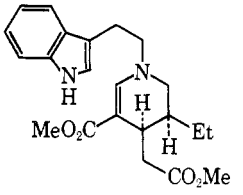


5

a, R = CH_2OH
b, R = CO_2Me



6

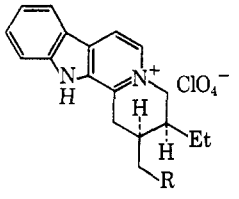


7

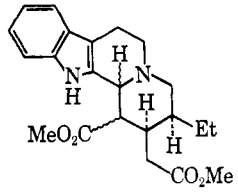
Two methods for the cyclization and decarboalkoxylation of tetrahydronicotinates of structure type **7** had been developed[2] and both were applied in the present investigation. Alkaline hydrolysis of the vinylogous urethan **7** followed by reesterification with methanolic acid led to the tetracyclic ester **4b**, isolated as its hydrochloride. Dehydrogenation of the product with palladium black in aqueous maleic acid solution yielded a tetradehydro substance which could be characterized as the perchlorate **8b**. Reduction of the latter with sodium borohydride afforded the ester **5b**, isolated as its hydrochloride. The ester conversion, **4b** into **5b**,

(1) This work was supported by the U.S. Department of Health, Education and Welfare (Grant GM-11571).
(2) Part V: E. Wenkert, K. G. Dave, and F. Haglid, *J. Am. Chem. Soc.*, **87**, 5461 (1965).
(3) E. Wenkert and B. Wickberg, *ibid.*, **87**, 1580 (1965).
(4) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, in press.
(5) (a) M.-M. Janot, R. Goutarel, and J. Chabasse-Massoneau, *Bull. Soc. Chim. France*, 1033 (1953); (b) M.-M. Janot, R. Goutarel, A. LeHir, G. Tsatsas, and V. Prelog, *Helv. Chim. Acta*, **38**, 1073 (1955); (c) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).
(6) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *ibid.*, **88**, 3888 (1966).

followed the outline of the C-3 isomerization of the corynantheidol isomers (**4a** → **5a**).[2,7] While this analogy of chemical operations permitted assignment of stereochemistry of the esters as depicted in **4b** and **5b**, conversion of these compounds into the alcohols **4a** and **5a**, respectively, by reduction with lithium aluminum hydride corroborated this structure assignment.



8a, R = CH_2OH
b, R = CO_2Me



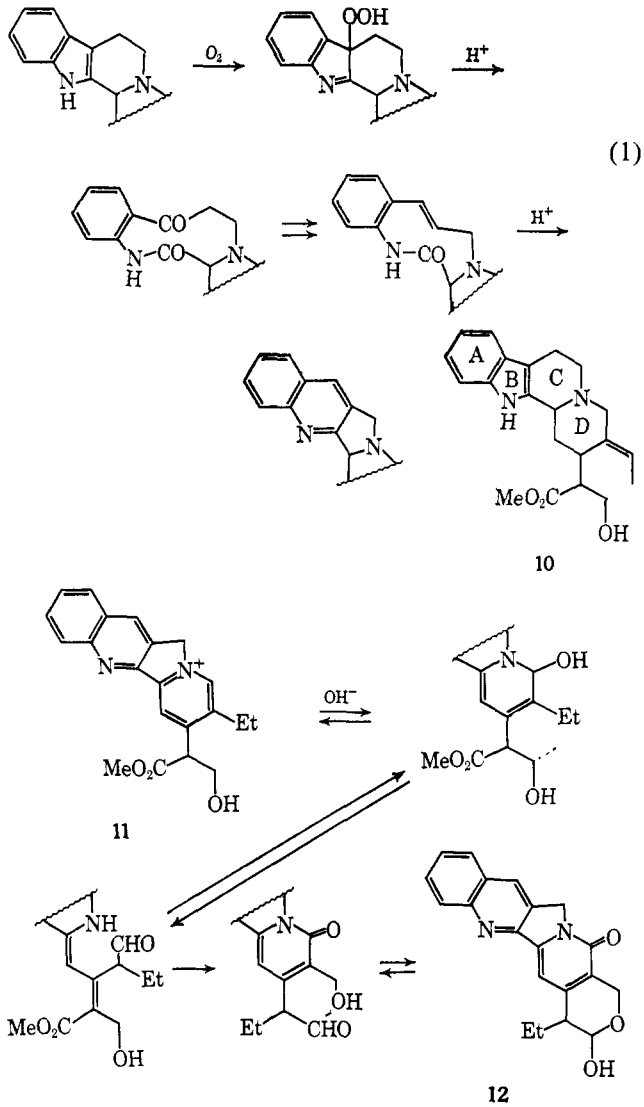
9

The alternate route to the desired ester **5b** involved methanolic acid treatment of **7**, acid hydrolysis of the resultant tetracyclic diester **9**, dehydrogenation with palladium black and maleic acid and reesterification. This reaction sequence led to the salt **8b** whose reduction (*vide supra*) readily produced **5b**. Thus a five-step, stereospecific synthesis of the tetracyclic ester **5b** was on hand and only two, mundane reactions, formylation and O-methylation, were left to be executed for completion of a total synthesis of *dl*-corynantheidine (**1**). However, these reactions were reported toward the end of this work as part of an independent synthesis of the alkaloid.[8] Direct comparison of **5b** hydrochloride with a sample of this substance from the other synthesis[8,9] proved their identity.

Camptothecin Model. The recent report on the isolation and structure elucidation of the quinoline alkaloid camptothecin (**2**)[6] drew our attention, mainly because an interpretation of its possible route of biosynthesis suggested it to be a masked indole alkaloid of the corynantheidine type and because its pentacyclic nucleus appeared to be capable of being synthesized easily by the utilization of intermediates of the above corynantheidine synthesis.

Modification of the customary tetrahydrocarboline unit of the indole alkaloids can be envisaged to take place in the plant by the precedented changes[5b,10] or slight variants thereof shown in eq 1.

The origin of the nontryptophan portion of the camptothecin structure can be discerned readily if it is assumed that a pyrroloquinoline, ring D dehydro modification (**11**) of isositsirikine (**10**) or related alkaloids[11] undergoes ring D unravelling and reclosing reminiscent of the suggested biosynthetic relationship of vallesiachotamine to geissoschizine[12] and that the product (**12**) undergoes further oxidation.



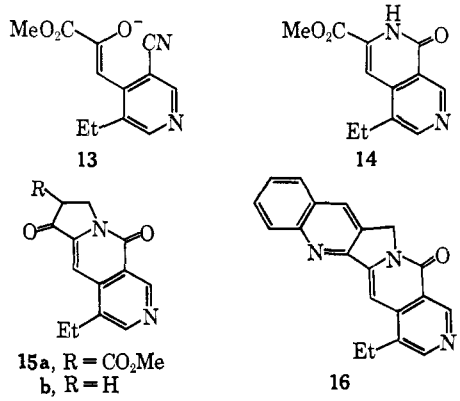
(1)

10

11

12

Our goal of synthesis was the heteropentacycle **16** on the assumption of its being a potential precursor of camptothecin (**2**) or of the synthesis acting as a model route for the later construction of the alkaloid. The starting compound, 4-methyl-5-ethylnicotinonitrile (**3b**), had served already as progenitor of the pyridine derivative in the above corynantheidine synthesis.[2] Potassium *t*-butoxide induced condensation of **3b** with dimethyl oxalate followed by exposure of the enolate salt (**13**) to aqueous solution at pH 6.5 yielded the azaisocarbostyril **14**. Condensation thereof with methyl acrylate and sodium carbonate in dimethylformamide solution produced the ester **15a**-enol, whose acid hydrolysis



13

14

15a, R = CO_2Me
b, R = H

16

(7) This two-step transformation also had proceeded *via* a tetradehydro intermediate, which however had not been isolated.[2] The present Experimental Section includes the isolation of this intermediate and its characterization as perchlorate **8a**.

(8) J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim, and B. C. Douglas, *Tetrahedron Letters*, 3457 (1965).

(9) The authors are indebted to Dr. Weisbach for the comparison data.

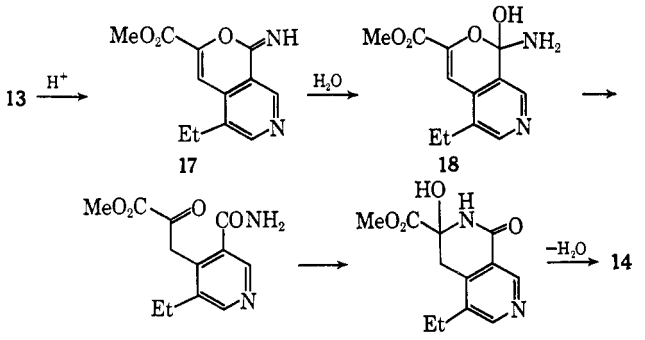
(10) *Cf.* B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, 73, 2196 (1951), and references therein; B. Witkop and S. Goodwin, *ibid.*, 75, 3371 (1953).

(11) Th. H. van der Meulen and G. J. M. van der Kerk, *Rec. Trav. Chim.*, 83, 148, 154 (1964); J. P. Kutney and R. T. Brown, *Tetrahedron*, 22, 321 (1966).

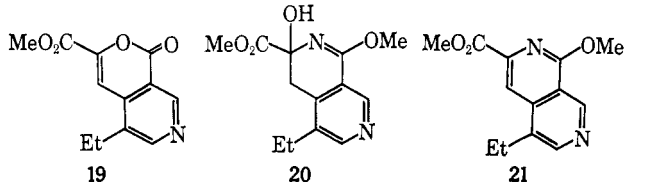
(12) C. Djerassi, H. J. Monteiro, A. Walser, and L. J. Durham, *J. Am. Chem. Soc.*, 88, 1792 (1966).

afforded the tricyclic ketone **15b**. Interaction of the latter with anthranilaldehyde and sodium hydroxide in a Friedländer synthesis[13] led to the desired pentacyclic substance **16**.

While the facile preparation of **14** was based on a recent isocarbostyril synthesis,[14] the intricate details of the unusual structural changes in the conversion of **13** into **14** were unknown. As a consequence the following possible rationale was submitted to test.



A solution of the salt **13** in water at pH 7.5 for a short while yielded the imino ether **17**. Exposure of **13** to 50% sulfuric acid solution produced the lactone **19**[2] instantaneously. Since the latter represents a predictable product of acid-induced deamination of **18**, the first two intermediates in the above-formulated reaction scheme were confirmed. While no further intermediates could be isolated, a parallel set of experiments validated the remaining members of the above scheme. Short refluxing of a methanolic solution of **17** yielded an alternate imino ether (**20**), whose treatment with 10% acetic acid led to the fully aromatic heterocycle **21**. Tie-up of the latter with the azaisocarbostyril (**14**) was achieved by pyrolysis of **21** hydrochloride and esterification of the product with methanol.



Experimental Section[15]

Melting points were determined on a Reichert micro hot stage and are uncorrected. Neutral alumina of activity IV was used for chromatography. Proton magnetic resonance spectra of deuteriochloroform solutions with tetramethylsilane acting as internal standard were recorded on a Varian A-60 spectrometer.

1-[β-(3-Indolyl)ethyl]-3-carbomethoxy-4-carbomethoxymethyl-5-ethylpyridinium Perchlorate (6). A solution of 500 mg of methyl 4-carbomethoxymethyl-5-ethylnicotinate (**3a**) and 690 mg of tryptophyl bromide in 40 ml of ether was left standing at room temperature for 17 hr. The solvent was removed and the residual gum heated for 15 min on a steambath under nitrogen and then extracted with hot water. The cooled extract was saturated with sodium perchlorate. Crystallization of the precipitate, 982 mg, from methanol yielded the salt **6**, mp 162.5–165°; infrared spectrum (Nujol): NH 2.90(m), C=O 5.78(s), and C=C 6.14(m) μ.

Anal. Calcd for $C_{22}H_{25}O_8N_2Cl$: C, 54.68; H, 5.20; N, 5.82. Found: C, 54.87; H, 5.19; N, 5.85.

Esters 4b and 9. A mixture of 0.50 g of palladium–charcoal and 0.6 ml of triethylamine in 50 ml of absolute methanol was saturated with hydrogen. A solution of 2.40 g of the salt **6** in 200 ml of methanol was added and the mixture hydrogenated at atmospheric pressure until hydrogen uptake ceased. The catalyst was filtered, the filtrate evaporated, and the residue taken up in benzene. The precipitated triethylammonium perchlorate was filtered, the filtrate evaporated, and the residue extracted with methylene chloride. The extract was washed with water, ice-cold, dilute hydrochloric acid, and saturated sodium bicarbonate solution and dried over anhydrous potassium carbonate. Solvent removal led to a viscous oil which could not be induced to crystallize. Its benzene solution was passed through a short alumina column and solvent removal yielded 1.85 g of colorless, oily ester **7**; spectra: [infrared (CCl_4)] NH 2.88(w), 3.02(w), C=O and C=C 5.78(s), 5.98(s), and 6.18(s) μ; [ultraviolet (95% ethanol)] λ_{max} 222 mμ (log ε 4.3) and 2.92 mμ (log ε 4.2); (pmr) three-proton multiplet *ca.* 0.9 (C-Me), six-proton singlet 3.63 (O-Me), one-proton doublet 6.90 (J = 2.0 cps) (indolyl α-H), one-proton singlet 7.21 ppm (olefinic H). In view of its instability in air (*e.g.*, it rapidly discolors) the product was used in the follow-up experiments without further analysis.

A mixture of 400 mg of the ester **7** and 2.0 g of potassium hydroxide in 5 ml of methanol and 5 ml of water was refluxed with stirring under nitrogen for 36 hr. The solvents were removed under vacuum and the residue dried in a dessicator for 18 hr. It then was dissolved in absolute methanol which was saturated for 2 hr with hydrogen chloride gas. After standing for 48 hr the mixture was poured slowly onto a suspension of excess of sodium bicarbonate in 200 ml of methylene chloride. The mixture was filtered and the filtrate evaporated to dryness. The residue was extracted with cyclohexane and the extract chromatographed on alumina. Elution with 20:1 cyclohexane–ether gave the ester **4b** whose instability in air (it turns brown rapidly) necessitated its conversion into a derivative. Its ether solution was saturated with hydrogen chloride gas. Crystallization of the resultant precipitate from methanol–acetone yielded 267 mg of **4b** hydrochloride, mp 261–262°; infrared spectrum (Nujol) NH 3.17(m), NH^+ 3.74, 3.84, 3.92(m), C=O 5.79(s) μ.

Anal. Calcd for $C_{20}H_{27}O_2N_2Cl$: C, 66.12; H, 7.43; N, 7.71. Found: C, 66.30; H, 7.23; N, 7.63.

A solution of 500 mg of ester **7** in 50 ml of anhydrous methanol was saturated for 2 hr with hydrogen chloride gas and then left standing at room temperature while the progress of the reaction was followed by ultraviolet spectroscopy. The two-maxima, equal-intensity pattern changed to absorption characteristic of an indole chromophore. After standing for 12 hr the solution was poured slowly onto a suspension of excess of sodium bicarbonate in 200 ml of methylene chloride. The mixture was filtered, the filtrate evaporated, and the residue extracted with cyclohexane. Alumina chromatography and elution with 20:1 cyclohexane–ether gave a solid whose crystallization from hexane yielded 415 mg of diester **9**, mp 118–120°; spectra: [infrared (Nujol)] NH 2.98(m), C=O 5.76(s), 5.86(s) μ; pmr three-proton multiplet *ca.* 0.9 (C-Me), three-proton singlets 3.67, 3.80 (O-Me).

Anal. Calcd. for $C_{22}H_{28}O_4N_2$: C, 68.72; H, 7.34; N, 7.28. Found: C, 68.97; H, 7.54; N, 7.46.

The product could be converted into **9** hydrochloride, mp 176–178° (from methanol–acetone), infrared spectrum (Nujol) NH 3.18(m), C=O 5.77(s) μ.

***dl*-3-Isocorynantheidol (4a).** A suspension of 200 mg of **4b** hydrochloride and 200 mg of lithium aluminum hydride in 30 ml of tetrahydrofuran was refluxed for 2 hr. A moist sodium sulfate slurry was added to the cooled suspension and the mixture shaken and filtered. Evaporation of the filtrate and crystallization of the residue from benzene–ethyl acetate yielded 120 mg of colorless **4a**, mp and mmp 191–192° (lit.[2] mp 191–192°); infrared spectrum identical with that of an authentic sample.

Salts 8a and 8b. A mixture of 100 mg of 3-isocorynantheidol (**4a**), 45 mg of maleic acid, and 50 mg of palladium black in 10 ml of water was refluxed under nitrogen for 18 hr. (The course of the reaction was followed by ultraviolet spectroscopy and optimal absorption at 367 mμ accepted as indication of the end of the reaction.) The catalyst was filtered and the filtrate evaporated to dryness under vacuum. The residue was dissolved in a saturated solution of sodium perchlorate. The resultant precipitate was filtered and crystallized from methanol yielding 60 mg of pale yellow crystals of **8a**, mp 158–160°; infrared spectrum (KBr) OH, NH 3.03(m), 3.26(m), C=C 6.13(s), 6.35(m), 6.59(m), and 6.70(m) μ.

Anal. Calcd for $C_{19}H_{23}O_5N_2Cl$: C, 57.79; H, 5.87. Found: C, 57.82; H, 5.77.

A mixture of 180 mg of **4b** hydrochloride, 130 mg of maleic acid, and 200 mg of palladium black in 20 ml of water was treated in the

(13) *Cf.* G. Kempter and S. Hirschberg, *Chem. Ber.*, **98**, 419 (1965).
(14) E. Wenkert, D. B. R. Johnston, and K. G. Dave, *J. Org. Chem.*, **29**, 2534 (1964).
(15) The authors acknowledge the technical assistance of Mr. J. Goldberger.

above manner. Crystallization of the tetradehydro product several times from methanol yielded 127 mg of yellow crystals of **8b**, mp 201–203°; spectra: [infrared (Nujol)] NH 3.04(w), C=O 5.76(s), C=C 6.10(s), 6.32(m), 6.54(m), and 6.65(m) μ; [ultraviolet (95% ethanol)] λ_{max} 253, 307, and 367 mμ (log ϵ 4.32, 4.15, 3.59); λ_{min} 227, 278, and 326 mμ (log ϵ 4.02, 3.62, and 3.29).

Anal. Calcd for $C_{20}H_{23}O_6N_2Cl$: C, 56.76; H, 5.43. Found: C, 56.74; H, 5.30.

A solution of 400 mg of diester **9** in 20 ml of 10% hydrochloric acid was refluxed for 2 hr and then evaporated under vacuum to dryness. A mixture of the residue, 130 mg of maleic acid, and 300 mg of palladium black in 20 ml of water was treated in the above manner. (The reaction time was 48 hr.) Crystallization of the tetradehydro product several times from methanol, during which esterification appeared to have taken place, yielded 172 mg of yellow, crystalline **8b**, mp and mmp 201–202°; infrared and ultraviolet spectra identical with those of the sample above.

Reductions of Salts 8a and 8b. A solution of 55 mg of **8a** and 100 mg of sodium borohydride in 10 ml of methanol was stirred at room temperature for 2 hr. Upon the usual work-up the product was crystallized from benzene–hexane yielding 32 mg of *dl*-corynantheidol (**5a**), mp and mmp 158–160° (lit.[2] mp 158–160°); infrared spectrum identical with that of an authentic specimen;[2] **5a** hydrochloride, mp 235–237° (from methanol–acetone).

A solution of 100 mg of **8b** and 200 mg of sodium borohydride in 20 ml of methanol was stirred at room temperature for 2 hr. The solvent was removed under vacuum and the residue dried in a desiccator. A solution of the residue in 50 ml of absolute methanol was saturated with hydrogen chloride gas for 2 hr and then left at room temperature for 36 hr. Upon the usual work-up the product (in cyclohexane solution) was chromatographed on alumina and eluted with 20:1 cyclohexane–ether. In view of its instability in air it was converted to a hydrochloride. Crystallization from methanol–acetone yielded **5b** hydrochloride, mp 256–258° dec (lit.[8] mp 257–258° dec); infrared spectrum (Nujol) NH 3.12(m), NH^+ 3.74, 3.84, 3.92(m), and C=O 5.79(s) μ (lit.[8] C=O 5.79 μ); the infrared spectrum and the thin layer chromatographic behavior identical with those of the Weisbach sample.[8,9]

Anal. Calcd for $C_{20}H_{27}O_2N_2Cl$: C, 66.12; H, 7.43; N, 7.71. Found: C, 66.07; H, 7.66; N, 7.91.

***dl*-Corynantheidol (5a).** A suspension of 100 mg of **5b** hydrochloride and 100 mg of lithium aluminum hydride in 30 ml of tetrahydrofuran was refluxed for 2 hr. A moist sodium sulfate slurry was added to the cooled suspension and the mixture shaken and filtered. Evaporation of the filtrate and crystallization of the residue from benzene–hexane yielded 67 mg of colorless, crystalline **5a**, mp 158–160°; infrared spectrum identical with that of the above sample.

3-Carbomethoxy-5-ethyl-7-azaisocarbostyril (14). A mixture of 365 mg of 4-methyl-5-ethylnicotinonitrile (**3b**), 443 mg of dimethyl oxalate, and powdered potassium *t*-butoxide (from 127 mg of potassium) in 6 ml of anhydrous benzene was stirred for 6 hr under nitrogen at room temperature. The yellow precipitate was filtered, washed with anhydrous ether and dried. Its solution in 110 ml of water buffered (phosphate) at pH 6.0 was left standing for 18 hr and then extracted with methylene chloride. The extract was dried over sodium sulfate and evaporated. A methylene chloride solution of the residue was passed through a short silicic acid column and evaporated yielding 178 mg of solid product. Crystallization from methanol and sublimation of the solid afforded colorless crystals of **14**, mp 200–201°; spectra: [infrared (Nujol)] C=O 5.75(s), 5.94(s), C=C 6.14(m), and 6.24(m) μ; [ultraviolet (methanol)] λ_{max} 206, 229, 262, and 327 mμ (log ϵ 4.33, 4.09, 4.00, and 4.14); $\lambda_{shoulder}$ 268, 318, and 337 mμ (log ϵ 3.97, 4.07, and 4.07); [pmr (deuteriodimethyl sulfoxide)] three-proton triplet 1.24 (J = 7.0 cps) (C–Me), two-proton quartet 2.93 (J = 7.0 cps) (methylene), three-proton singlet 3.92 (OMe), and one-proton singlets 7.35, 8.74, and 9.31 ppm (pyridone, α to ethyl pyridyl, α to acyl pyridyl hydrogens, respectively).

Anal. Calcd for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.75; H, 5.28; N, 12.11.

Azaisocarbostyril Derivative 15a-Enol. A mixture of 3.89 g of **14**, 7.3 ml of methyl acrylate and 1.94 g of anhydrous sodium carbonate in 50 ml of dimethylformamide was stirred at 100° under nitrogen for 6 hr. After then standing at room temperature for 18 hr the mixture was filtered and the newly formed precipitate washed with methanol. Acidification of a solution of the solid in 100 ml of water to pH 3.5 yielded a precipitate. Crystallization thereof from ethanol gave 3.58 g of orange yellow crystals of **15a-enol**, mp 215° dec; spectra: [infrared (Nujol)] C=O 5.90(s), 5.97(s), C=C 6.13(m), 6.18(s), 6.27(m) μ; [ultraviolet (methanol)] λ_{max} 209, 257, and 365 mμ (log ϵ 4.49, 4.08, and 4.36); $\lambda_{shoulder}$ 223 and 358 mμ (log ϵ 4.20 and 4.34).

Anal. Calcd for $C_{15}H_{14}O_4N_2$: C, 62.93; H, 4.93; N, 9.78. Found: C, 62.96; H, 4.84; N, 9.83.

Azaisocarbostyril Derivative 15b. A solution of 50 mg of **15a-enol** in 7 ml of concentrated hydrochloric acid was refluxed under nitrogen for 1 hr and then evaporated to dryness. A suspension of the residue and sodium bicarbonate in methylene chloride was shaken thoroughly and filtered and the residue washed with methylene chloride. The combined extracts were passed through a short alumina column and evaporated. Crystallization of the residue from benzene yielded 30 mg of colorless, crystalline ketone **15b**, mp 165° dec; spectra: [infrared (Nujol)] C=O 5.74(s), 6.05(s), C=C 6.13(w), and 6.26(m) μ; [ultraviolet (methanol)] λ_{max} 212, 268, and 364 mμ (log ϵ 4.38, 3.70, and 3.98); $\lambda_{shoulder}$ 236, 250, 277, 337, and 356 mμ (log ϵ 3.96, 3.70, 3.65, 3.92, and 3.96); (pmr) three-proton triplet 1.33 (J = 7.0 cps) (Me), four-proton quartet 2.95 (J = 7.0 cps) (ethyl and α-keto methylenes), two-proton triplet 4.41 (J = 7.0 cps) (α-amidomethylene), and one-proton singlets 7.22, 8.61, and 9.46 ppm (pyridone, α to ethyl pyridyl, α to acyl pyridyl hydrogens, respectively).

Anal. Calcd for $C_{13}H_{12}O_2N_2$: C, 68.42; H, 5.26; N, 12.27. Found: C, 68.57; H, 5.42; N, 12.07.

Quinoline Derivative 16. A solution of 1.4 g of ketone **15b**, 605 mg of freshly prepared anthranilaldehyde,[16] and 200 mg of sodium hydroxide dissolved in 1 ml of water and 15 ml of ethanol was kept at room temperature for 24 hr. The crystalline precipitate was filtered and washed with methanol. Its (1.05 g) crystallization from ethanol yielded 903 mg of colorless crystals of **16**, mp 303–305°; spectra: [infrared (Nujol)] C=O 6.02(s), C=C 6.12(s), and 6.31 (m) μ; [ultraviolet (methanol)] λ_{max} 217, 252, 367, and 383 mμ (log ϵ 4.59, 4.72, 4.41 and 4.39); $\lambda_{shoulder}$ 280, 300, and 305 mμ (log ϵ 4.14, 3.97, and 4.20); (pmr) three-proton triplet 1.39 (J = 7.5 cps) (Me), two-proton quartet 3.00 (J = 7.5 cps) (ethyl's methylene), two-proton broad singlet 5.29 (amidomethylene), six-proton multiplet 7.52–8.35 (pyridone and quinoline hydrogens), and one-proton singlets 8.63 and 9.58 ppm (α to ethyl and α to acyl pyridine hydrogens, respectively).

Anal. Calcd for $C_{20}H_{15}ON_3$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.49; H, 5.14; N, 13.11.

Pyridine Derivatives 17, 19, and 20. A solution of 500 mg of **13** in 284 ml of water buffered (phosphate) at pH 7 was stirred for 15 min and then extracted with three 50-ml portions of methylene chloride. The combined extracts were dried over sodium sulfate and evaporated. Crystallization of the residue (499 mg, *ca.* 70% **17** and 30% the *t*-butyl ester equivalent of **17** according to pmr analysis) from ether yielded 281 mg of colorless imino ether **17**, mp 94–95°; spectra: [infrared (Nujol)] NH 3.18(m), C=O 5.78(s), C=N 5.96(s), and C=C 6.28(m) μ; [ultraviolet (methylene chloride)] λ_{max} 258, 267, and 313 mμ (log ϵ 4.26, 4.20, and 3.85); $\lambda_{shoulder}$ 242, 250, and 322 mμ (log ϵ 3.97, 4.12, and 3.81); (pmr) three-proton triplet 1.28 (J = 7.5 cps) (C–Me), two-proton quartet 2.81 (J = 7.5 cps) (methylene), three-proton singlet 3.96 (OMe), and one-proton singlets 7.20, 8.56, and 9.28 ppm (iminopyrone, α to ethylpyridyl, α to iminopyridyl hydrogens, respectively).

Anal. Calcd for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.23; H, 5.46; N, 12.17.

The salt **13**, 523 mg, was added slowly to a rapidly stirring, ice-cold solution of 50% sulfuric acid. After 5 min the colorless solution was brought to pH 3.5 by the addition of 15% sodium hydroxide solution at first and dilute ammonium hydroxide thereafter. The resultant precipitate was filtered and washed with cold water. Sublimation of the solid, 290 mg, produced lactone **19**, mp and mmp 124–125°; spectra identical with those of an authentic sample.[2]

A solution of 131 mg of imino ether **17** in 5 ml of methanol was evaporated by heating on a steam bath. A solution of the residual oil in 2 ml of benzene was left standing at 0° for 24 hr. This led to 117 mg of **20**, mp 117–118°; spectra: [infrared (Nujol)] OH 3.00 (m), C=O 5.73(s), C=N 6.04(s), C=C 6.29(m) μ; [ultraviolet (methanol)] λ_{max} 209, 241, 262, and 280 mμ (log ϵ 4.19, 3.69, 3.50, and 3.43); (pmr) three-proton triplet 1.20 (J = 7.5 cps) (C–Me), two-proton quartet 2.68 (J = 7.5 cps) (ethyl's methylene), AB pair of doublets, two-proton four-line signal 2.85, 3.12, 3.28, and 3.55 (ring methylene), three-proton singlets 3.71 and 3.92 (methoxyls), and one-proton broad singlets 8.45 and 8.74 ppm (pyridine hydrogens).

(16) L. L. Smith and J. Opie, *Org. Syn.*, **28**, 11 (1948).

Methyl 1-Methoxy-5-ethyl-7-azaisoquinoline-3-carboxylate (21). A solution of 117 mg of **20** in 16 ml of 6% acetic acid was left standing at room temperature for 18 hr. The resultant precipitate was filtered, the filtrate neutralized with sodium bicarbonate, and a second precipitate also filtered. Sublimation of the combined solids, 72 mg, yielded colorless crystals of **21**, mp 130–132°; spectra: [infrared (Nujol)] C=O 5.80(s), C=C 6.16(w), 6.26(w), and 6.41(m) μ; [ultraviolet (methanol)] λ_{max} 211, 221, 250, 321, and 334 mμ (log ϵ 4.41, 4.38, 3.94, 3.90, and 3.90); $\lambda_{shoulder}$ 287 mμ (log ϵ 3.74); (pmr) three-proton triplet 1.38 (J = 7.5 cps) (C–Me), two-proton quartet 3.02 (J = 7.5 cps) (methylene), three-proton singlets 4.02 and 4.23 (methoxyls), and one-proton singlets 8.12, 8.56, and 9.40 ppm (aromatic hydrogens).

Anal. Calcd for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.39; H, 5.82; N, 11.35.

After treatment of a solution of 70 mg of **21** in 2 ml of methanol with excess of dry hydrogen chloride the solvent was removed and the residue heated at 160° for 30 min. The infrared spectrum of the product contained absorption bands characteristic of the isocarbostyril nucleus. A solution of the solid in 5 ml of methanol saturated with hydrogen chloride was kept at room temperature for 2 days. The solvent was removed, the residue dissolved in 2 ml of water, and the solution neutralized. Filtration of the resultant precipitate yielded 27 mg of the isocarbostyril **14**, mp 200–202°; the infrared spectrum was identical with that of the above sample.

The Total Synthesis of Racemic Aflatoxin B_1[1]

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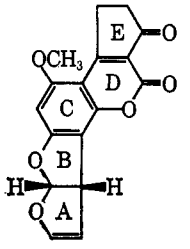
Abstract: Aflatoxin B_1 has been prepared in the form of its racemate from phloroglucinol by a 12-step sequence.

Aflatoxin B_1 (**1**) belongs to a group of acutely toxic and highly carcinogenic mold metabolites produced by *Aspergillus flavus*.[4] After having completed structural studies on these toxins,[5] we turned to contemplation of their synthesis.



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Taking notice of the lability which the vinyl ether grouping imparts to the molecule, it was decided to introduce this functionality at the very end of the synthesis. As a precursor for such a group we chose a lactone function. The Pechmann reaction seemed admirably suited for the construction of the coumarin ring and we[5] as well as others[6,7] have demonstrated with a model compound that the cyclopentenone ring could be closed by dehydration of the corresponding carboxylic acid. For the elaboration of the phenol **19** containing rings A, B, and C, we chose a 4-methylcoumarin already having the required number of carbon atoms. This plan for the construction of the tricyclic intermediate incidentally is the result of some speculative thinking on the biogenesis of the aflatoxins. The initial phase of the synthesis was thus concerned with the preparation of 5-benzyloxy-7-methoxy-4-methylcoumarin (**7**).

Acetylation of phloroacetophenone (**2**) with 2 equiv of hot acetic anhydride produced comparable amounts of 2,4-diacetoxy-6-hydroxyacetophenone (**3**) and 2,6-diacetoxy-4-hydroxyacetophenone (**4**). Crystallization from chloroform gave the phenol **4** and the chelate **3** could be isolated from the mother liquor. The nuclear magnetic resonance spectrum of **4** revealed a symmetrical arrangement of substituents while the spectrum of the unsymmetrical isomer **3** exhibited three distinct methyl signals and an AB quartet for the nonequivalent aromatic protons. Methylation of the phenol **4** with diazomethane followed by acid hydrolysis afforded phloroacetophenone 4-methyl ether (**5**) identical with a sample prepared in poor yield by direct methylation of **2**.[8] Alkylation with 1 equiv of benzyl bromide led to the ether **6** which was transformed to the coumarin **7** with the aid of a Wittig reaction. This synthetic sequence (Chart I) leads to a coumarin of defined structure but the over-all yield is low and we subsequently developed two more satisfactory procedures.

Addition of 1 equiv of benzyl bromide to a suspension of potassium carbonate in acetone–tetrahydrofuran containing the readily accessible 5,7-dihydroxy-4-methylcoumarin (**8**) afforded the 5,7-dibenzyloxy ether **9** and what turned out to be the desired 5-benzyloxy-7-hydroxy-4-methylcoumarin (**10**). The latter was isolated in 20% yield from the insoluble part of the reaction mixture. Methylation gave the coumarin **7** identical with that prepared by the structurally unambiguous

(1) Announced previously in a communication to the editor by G. Büchi, D. M. Foulkes, M. Kurono, and G. F. Mitchell, *J. Am. Chem. Soc.*, **88**, 4534 (1966).

(2) National Science Foundation Graduate Fellow, 1964–1966.

(3) National Institutes of Health Postdoctoral Fellow, 1966–1967.

(4) For a summary, *cf.* G. N. Wogan, *Bacteriol. Rev.*, **30**, 460 (1966).

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