The Mitomycin Antibiotics. Synthetic Studies. XXIII. (1) An Attempted Synthesis of a 3*H*-Pyrrolo[1,2-*a*]indole-9-carboxaldehyde.

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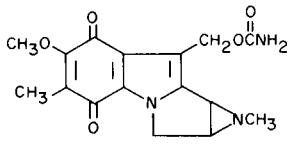
In previous papers of this series we have described our efforts to effect a total synthesis of the biologically important aziridinomitosene **1** which Patrick, Webb and coworkers (2) had prepared in the course of their elucidation (3) of the structures of the mitomycin antibiotics. This work afforded procedures for the preparation of the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole system (4), introduction of a 9-carboxaldehyde function into such a structure (5), the elaboration of the hydroxymethyl carbamate from the resulting aldehyde (4), and the preparation of the indoloquinone system (4,6). The compatibility of these procedures permitted a synthesis of 7-methoxymitosene (**2**) (4), a compound lacking only the fused aziridine moiety of **1**.



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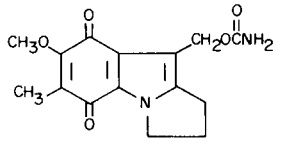

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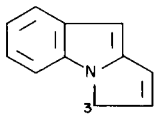
Our earlier efforts to effect annelation of the aziridine function onto the pyrrolo[1,2-*a*]indole system were abortive (7). An attractive approach to this problem was *via* a 3*H*-pyrrolo[1,2-*a*]indole (**3**), but this was thwarted by the propensity of such systems (9-unsubstituted) to undergo prototropic rearrangement to the isomeric 9*H*-system **4** (7a,8). However, molecular orbital calculations suggested a small difference in delocalization energy for these systems (5). Therefore, we anticipated that a conjugative substituent at the 9-position would stabilize a 3*H*-structure and permit an investigation of the aziridine annelation *via* the C_1–C_2 double bond. Experimental basis for this suggestion was provided quite recently by Franck and Bernady (9), who reported a synthesis of an alkyl 3*H*-pyrrolo-[1,2-*a*]indole-9-carboxylate. In the present report we describe an effort to secure a 3*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde.



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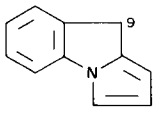

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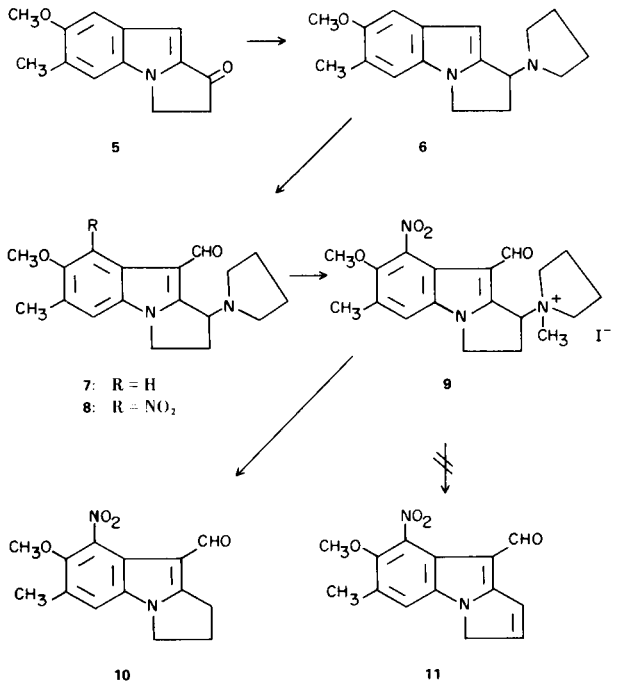
Our approach to the preparation of the required aldehyde, considering available intermediates, was based on a Hoffmann elimination of a 1-quaternary amine function from an appropriate 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde. In the absence of the 9-carboxaldehyde, such eliminations proceed with rearrangement to furnish the 9*H*-pyrrolo[1,2-*a*]indole system (7a).

For the present purpose the 1-keto-1*H*-pyrrolo[1,2-*a*]-indole **5** (4) was converted into the 1-pyrrolidinyl-9-formyl derivative **7** by enamine formation with pyrrolidine, reduction of the enamine double bond, and Vilsmeier-Haack

SCHEME I



5 6

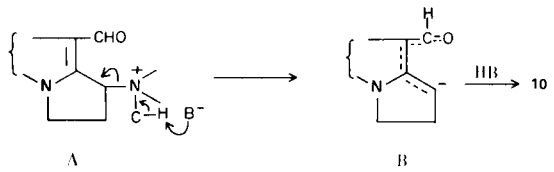
7: R = H
8: R = NO_2

9

10 11

formylation of the resulting **6** (See Scheme I). In view of our ultimate goal, pyrrolidinylaldehyde **7** was converted into the 8-nitro derivative **8**, from which the indoloquinone system could be elaborated (10).

Unexpectedly, treatment of the derived methiodide **9** with potassium *t*-butoxide in dimethylformamide gave 40% of the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **10**, rather than the desired 3*H*-pyrrolo[1,2-*a*]indole **11**. The limited quantities of **9** precluded study of the details of this reaction. However, abstraction of an α-proton by base (see A) to give the stabilized carbanion B, protonation of which affords **10**, is a reasonable explanation for this result (11).



A B

Finally, we note that the recently reported (14) annelation of the aziridine moiety onto an 8-nitro-3*H*-pyrrolo-[1,2-*a*]indole-9-carboxylate presages a synthesis of the aziridinomitosene **1**. Accordingly, our efforts toward this objective have been terminated.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer. Infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. All evaporations were conducted under reduced pressure.

7-Methoxy-6-methyl-1-(*N*-pyrrolidinyl)-3*H*-pyrrolo[1,2-*a*]indole.

A solution of 5.115 g. (23.8 mmoles) of 2,3-dihydro-7-methoxy-6-methyl-1-oxo-1*H*-pyrrolo[1,2-*a*]indole (**5**), 4.55 g. (64.0 mmoles, 5.0 ml.) of pyrrolidine, and 200 mg. of *p*-toluenesulfonic acid monohydrate in 150 ml. of benzene was heated at reflux temperature for 3 hours. The solution was evaporated under reduced pressure, and the crystalline residue was triturated with ether and filtered to give 5.30 g. of solid, m.p. 128-132°. Evaporation of the ether filtrate gave 0.65 g. (95% total), m.p. 125-130°. A sample was recrystallized from ether to give bright yellow crystals, m.p. 132-134° dec., after darkening from 110°; uv max 215, 250, 363 mμ (ε, 30,800; 11,800; 29,500); ir 6.26 μ.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.01; H, 7.79; N, 10.26.

2,3-Dihydro-7-methoxy-6-methyl-1-(*N*-pyrrolidinyl)-1*H*-pyrrolo-[1,2*a*]indole (**6**).

A mixture of 5.52 g. (20.6 mmoles) of 7-methoxy-6-methyl-1-(*N*-pyrrolidinyl)-3*H*-pyrrolo[1,2-*a*]indole and 200 mg. of platinum oxide in 150 ml. of ethyl acetate was shaken under hydrogen in a Parr apparatus; a theoretical uptake was observed within 30 minutes. The residue obtained upon filtration and solvent removal was recrystallized from ether-hexane to furnish 4.59 g. (83%) of crystals, m.p. 103-105°. A sample recrystallized from acetone-hexane had m.p. 107-109°; uv max 218, 278, 298, 308 mμ (ε, 38,600; 9730; 7300; 5130).

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.51; H, 8.60; N, 10.41.

2,3-Dihydro-7-methoxy-6-methyl-1-(*N*-pyrrolidinyl)-1*H*-pyrrolo-[1,2-*a*]indole-9-carboxaldehyde (**7**).

With salt-ice cooling and magnetic stirring 4.95 g. (32.4 mmoles, 2.96 ml.) of phosphorus oxychloride was added dropwise to 25 ml. of dimethylformamide. A solution of 4.37 g. (16.2 mmoles) of 2,3-dihydro-7-methoxy-6-methyl-1-(*N*-pyrrolidinyl)-1*H*-pyrrolo-[1,2-*a*]indole (**6**) in 60 ml. of dimethylformamide was added dropwise at such a rate that the temperature did not exceed 5°; the resulting solution was stirred at room temperature for 1 hour. Cracked ice was added, and 100 ml. of 1*N* sodium hydroxide solution was added dropwise. An oil separated near the end of this addition and the mixture was heated to 90° and then allowed to cool to room temperature. The mixture was extracted with methylene chloride and the extracts were dried and evaporated to furnish an oil. This material was chromatographed on diatomaceous silica using a heptane-methanol (1:1 system); the fraction with peak-hold-back volume 2.2 (V_m/V_s=2.4) was evaporated (12). The residue was recrystallized from acetone-hexane to give 1.976 g. (41%) of white needles, m.p. 117-118°; uv max 215, 257, 280, 311 mμ (ε, 33,700; 20,000; 13,700; 14,000); ir 3.58, 6.08 μ.

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.30; H, 7.87; N, 9.48.

2,3-Dihydro-7-methoxy-6-methyl-8-nitro-1-(*N*-pyrrolidinyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (**8**).

To a stirred solution of 298 mg. (1.0 mmole) of 2,3-dihydro-7-methoxy-6-methyl-1-(*N*-pyrrolidinyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (**7**) in 5 ml. of glacial acetic acid was added 0.4 ml. of 90% nitric acid (sp. gr. 1.50). Stirring was continued at ambient temperature for 1 hour, whereafter the solution was poured onto cracked ice-water. The solution was added with stirring to a sodium carbonate slurry, and the resulting mixture was extracted with methylene chloride. The dried extract was evaporated to give a residue that was recrystallized from acetone-hexane to furnish 282 mg. (82%) of crystals, m.p. 190-191°; uv max 215, 250, 298 mμ (ε, 31,600; 16,100; 10,500); ir 3.58, 6.02, 6.50 μ; nmr (DMSO-d_6) δ 9.90 (1, s, C*H*O), 9.10 (1, s, 5-*H*), 4.96 (1, t, J=5.0 Hz, 1-*H*), 4.23 (2, t, J=6.0 Hz, 3-CH_2), 3.78 (3, s, OCH_3), 2.42 (s, 6-CH_3), 1.67 (4, *m*, β-CH_2 of pyrrolidine).

Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.73; H, 6.27; N, 12.07.

1-(2,3-Dihydro-9-formyl-7-methoxy-6-methyl-8-nitro-1*H*-pyrrolo-[1,2-*a*]indol-1-yl)-1-methylpyrrolidinium Iodide (**9**).

A solution of 171 mg. (0.5 mmole) of 2,3-dihydro-7-methoxy-6-methyl-8-nitro-1-(*N*-pyrrolidinyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (**8**) and 2 ml. of methyl iodide in 10 ml. of methylene chloride was allowed to stand protected from light at ambient temperature for 16 hours. The mixture was filtered to give 251 mg. of white needles. On attempted recrystallization from acetone the solid changed crystalline form to micro crystals that were largely insoluble in the medium; filtration gave 171 mg. (70%) of solid, m.p. 218-220° dec., uv max 216, 240, 309 mμ (ε, 27,200; 8970; 6300); ir 6.00, 6.53 μ.

Anal. Calcd. for $C_{19}H_{24}IN_3O_4$: C, 47.02; H, 4.99; I, 26.15;

N, 8.66. Found: C, 46.89; H, 4.95; I, 25.83; N, 8.67.

2,3-Dihydro-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (**10**).

A solution of 171 mg. (0.35 mmole) of 1-(2,3-dihydro-9-formyl-7-methoxy-6-methyl-8-nitro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)-1-methylpyrrolidinium iodide (**9**), and 40 mg. (0.35 mmole) of potassium *t*-butoxide in 40 ml. of dimethylformamide was heated under argon on the steam bath for 3 hours. The cooled, dark solution was poured into water, and this solution was extracted with methylene chloride. The combined extracts were washed with saline, dried and decolorized by passage through activated carbon supported on diatomaceous silica and using acetone as the wash solvent. Evaporation of the combined organic solutions gave 32.4 mg. (40%) of yellow crystals, m.p. 195-198° after recrystallization from methanol. A further recrystallization from acetone-hexane gave pale yellow needles, m.p. 204°; uv max 216, 248, 292 mμ (ε, 33,200; 16,200; 10,300); ir 3.58, 6.02, 6.50 μ; nmr (DMSO-d_6); δ 9.73 (1, s, C*H*O), 7.59 (1, s, 5-*H*), 4.20 (2, t, J=7.0 Hz 3-CH_2), 3.80 (3, s, OCH_3), 3.33 (multiplet, obscrued by H_2O, 1-CH_2), 2.75 (2, m. 2-CH_2), 2.42 (s, obscured by DMSO, 6-CH_3).

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.61; H, 5.24; N, 10.18.

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