Approaches to the Mitomycins. A Meta Photo-Fries Reaction

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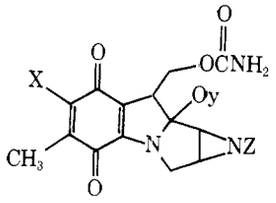
The synthesis of pyrrolo[1,2-*a*]indole **25** is accomplished using a unique meta photo-Fries reaction. The novelty of the rearrangement required a structure proof of the product by x-ray crystallography.

The tricyclic pyrrolo[1,2-*a*]indole framework of the mitomycin antibiotics **1** has been the target compound in several synthesis programs. In our laboratory and one other[1] the aromatic heterocycle **2**, incompletely substituted, has been the starting material for studies of the introduction of C_{10} and the aziridine. We felt it necessary to develop a scheme for the synthesis of 5,6,7,8-substituted heterocycle as a possible starting material so that our model studies could be extended to a system that would be in the natural series.



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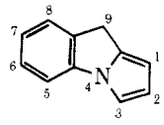

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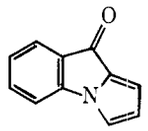

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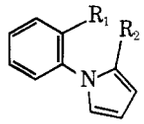
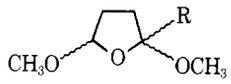


4, R_1 = H; R_2 = CO_2H
5, R_1 = CO_2H; R_2 = H

An attractive route to this hetero analogue of fluorene involves reduction of the ketone **3** which in turn has been prepared by Friedel–Crafts cyclizations of two different acids **4** and **5**.[2] Pyrroles of type **4** are readily prepared from anilines and the tetrahydrofuran **6a** while type **5** pyrroles arise from anthranilic acids and tetrahydrofuran **6b**.[1] Since convenient

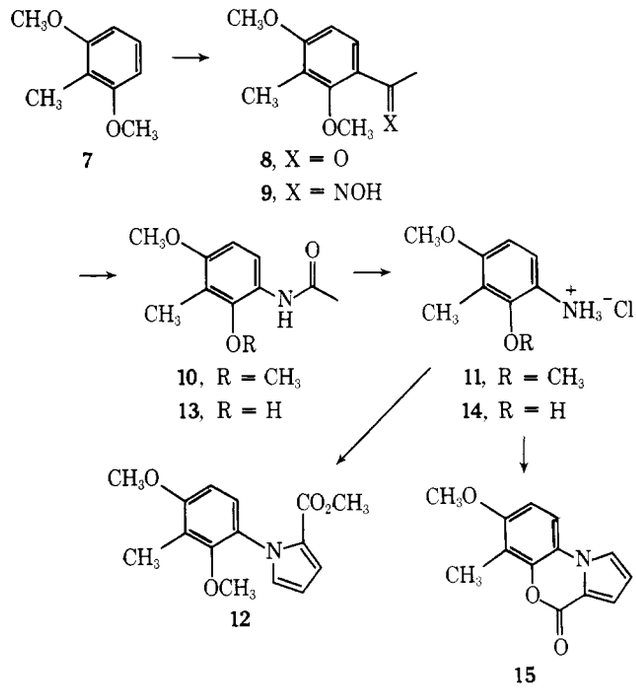


6a, R = CO_2H
b, R = H

syntheses and inexpensive commercial starting materials for the alkoxy toluic acid precursors to the anthranilic acids required for the type **5** approach were not available, we focused on producing a type **4** compound. The preparation of starting materials is outlined in Scheme I.

Our manipulation of aromatic functionality began with dimethoxytoluene **7**. Nitrogen was introduced indirectly via acylation followed by Beckmann rearrangement of the oxime of acetophenone **8**. Acetanilide **10** could be converted to pyrrole **12** first by generation of the free aniline **11** followed by heterocyclization using tetrahydrofuran **6a**. Interestingly, the deactivated pyrrole of **12** was competitive in reactivity toward electrophiles with the carbocyclic ring. Thus attempts to introduce the final substituent in **12** failed; and the intramolecular Friedel–Crafts reaction of the pyrrole carboxyl to the meta position which would have formed a nearly complete tricyclic also failed. Acetanilide **10** could be cleanly demethylated using $AlCl_3/CH_2Cl_2$ to afford the free phenol **13**. Hydrolysis of **13** afforded the air-sensitive amine hydrochloride

Scheme I



7

8, X = O
9, X = NOH

10, R = CH_3
13, R = H

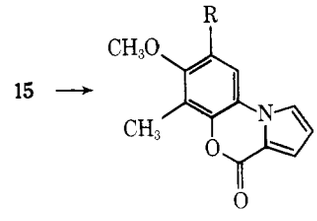
11, R = CH_3
14, R = H

12

15

14 which was condensed with tetrahydrofuran **6a** in an atmosphere of oxygen-free nitrogen to yield the highly crystalline lactone **15**.

In contrast to pyrrole ester **12**, the lactone **15** was remarkably stable to electrophilic attack. For example, nitration with nitric acid–sulfuric acid, conditions which usually result in oxidative degradation as well as nitration, in this case gave a

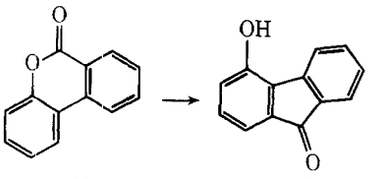


16, R = NO_2
17, R = NH_2
18, R = NHAc

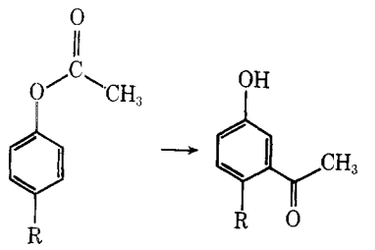
clean mononitro derivative **16**. The nitro compound could be reduced cleanly to the amine **17** provided that the Pd catalyst was prereduced and that a nonprotic solvent such as ether was used. The acetanilide **18** was prepared as well.

With these compounds, every atom required for the target heterocycle **2** is present and an intramolecular acylation of the free aromatic position is all that is required to complete the scheme. When **18** was subjected to the acid-catalyzed Fries-rearrangement conditions (polyphosphoric acid, 90 °C, $TiCl_4$, $PhNO_2$, 60 °C) no reaction was observed. Thus we undertook a photo-Fries reaction. Although the ortho–para photo-Fries

is well known,[3] only three examples of meta orientation have been detected. The single example of product isolation is the work of Finnegan,[4] where a very low yield of fluorenone **20** was obtained upon photolysis of lactone **19**. In the case of simple

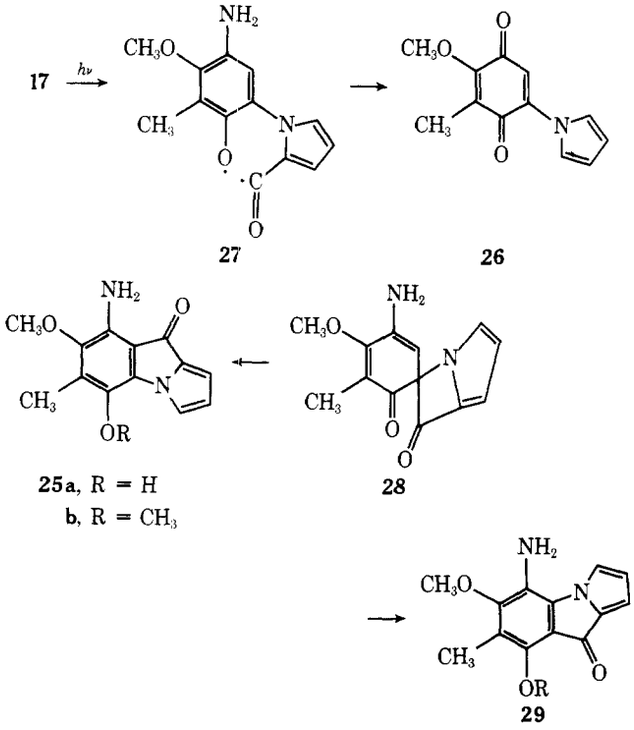


19 **20**



21, R = H **22**, R = H
23, R = CH_3 **24**, R = CH_3

esters, Andersen and Reese[5] using GLC detected 0.3% of meta product **22** upon photolysis of **21**, while Adam detected a CIDNP signal for **24** while irradiating **23**.[6] Furthermore, Adam has used CIDNP evidence and sensitization and quenching experiments to demonstrate that the photo-Fries reaction proceeds via a singlet excited state and forms free radicals that then are partitioned through several product-forming pathways.[7] In the event of irradiation of **17** with a sun lamp through a plate-glass filter (wavelengths greater than 310 nm transmitted) in THF solvent with a purge of oxygen-free nitrogen, a clean and essentially quantitative conversion to an isomer **25** occurred. These conditions were developed when,



25a, R = H
b, R = CH_3

in photolyses without rigorous oxygen exclusion or with less effective hydrogen-donating solvents, there was isolated a compound presumed to be quinone **26**. This air sensitivity was taken as evidence that an intermediate diradical such as **27** was present and that oxidation could consume it in competition with a cyclization pathway. Although the proposed structure **25** is consistent with this mechanistic speculation, there exists an alternate structural assignment.[8] Diradical **27** could form the spiro intermediate **28** which could rearrange to either **25** or **29**. This spiro intermediate has been invoked by Gutsche to explain the alcoholysis of dihydrocoumarins upon photolysis.[9] No evidence for Fries products was detected in his experiments. Shift reagent studies on methyl ether **25b**, readily prepared from **25a** using methyl sulfate, gave gradients as follows: NH_2, 9.82; pyrrole C_1 H, 4.18; C_2 H, 1.52; C_3 H, 2.51; OCH_3, 1.87, 1.67; CCH_3, 1.97. The crucial assignment of the pyrrole proton resonances is based on the coupling constants of 2.6 and 0.8 Hz for the signal at 7.06 (C_3 H), 3.8 and 0.8 Hz at 6.53 (C_1 H), and 3.8 and 2.6 Hz at 6.11 (C_2 H). These values are consistent with those obtained in our earlier work.[10] Thus, by locating the europium at a position where chelation can occur,[11] we can rationalize the observation that C_1 H in **25** could have the largest shift gradient. For C_1 H to have the greatest gradient in **29b**, one would have to assume a chelation of the Eu between the carbonyl and methoxy groups (and a concomitant methoxy gradient) rather than complexation at the free NH_2. If the latter, expected locus of Eu were to obtain, then C_3 H should have had a higher gradient. For a reaction of this uniqueness, it was decided to reinforce our structure proof with an x-ray crystallographic study.

Table I

	hkl		*E*	Phase angle	
2	19	0	3.91	0	
0	10	5	2.91	0	Origin
3	0	9	2.66	$3\pi/2$	
4	9	9	3.09	$\pi/2$	Enantiomorph
6	8	0	2.65	0	
8	14	0	2.37	0	From Σ_1
8	0	2	2.06	π	
0	0	6	1.83	π	
2	7	3	3.03	$\pi/4$, $3\pi/4$, $5\pi/4$, $7\pi/4$	

The crystals of the molecule believed to be **25b** were studied. The system was orthorhombic with the unit cell parameters a = 8.955 (2), b = 16.250 (3), c = 8.794 (2) Å. The space group was determined by systematic absences to be $P2_12_12_1$. Three-dimensional x-ray diffraction data were collected using an Enraf-Nonius CAD-4 diffractometer with Cu Kα radiation. The intensities of 1448 reflections were measured significantly above background. The structure was solved by direct methods with a program[12] based on the tangent formula. The set of starting phases used is given in Table I. The phases of the 281 strongest normalized structure factors were calculated. When the phase of the general reflection was set at $5\pi/4$, the resulting phase set led to an R_K value of 0.157. The E map from this set revealed the 19 nonhydrogen atoms corresponding to the expected isomer. Using a block-diagonal least-squares program,[12] an R value of 0.061 was obtained after anisotropic refinement. The hydrogen atoms were then found from a difference-electron density map. Refining on these isotropically and the nonhydrogen atoms anisotropically resulted in a final R value of 0.034. The bond distances and angles are given in Figure 1. Not shown are the estimated standard deviations of the bond angles, all 0.2°.[13]

In a brief study carried out to test the generality of the reaction, lactones **15**, **16**, and **18** were also photolyzed. While **15** was photostable, both **16** and **18** were consumed upon irradiation using conditions similar to those that were successful for the cyclization of **17**. Nitro derivative **16** yielded an extremely complex mixture of products and we were not successful in characterizing satisfactorily any cyclized product.

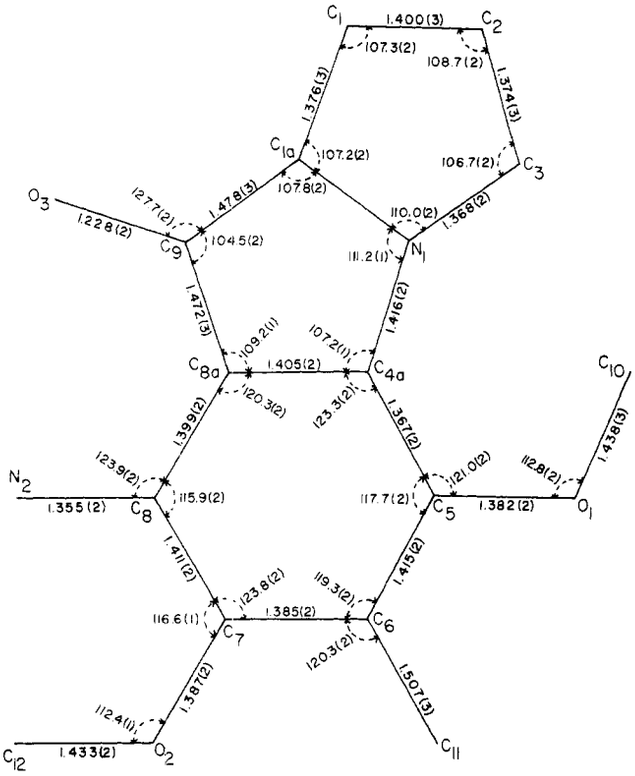
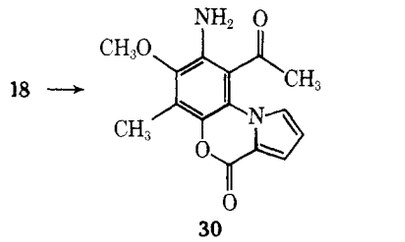


Figure 1. Bond lengths and bond angles for **25b.**

Acetanilide **18** appeared to undergo cleavage of the amide function (disappearance of the ir peak at 1690 cm^{-1}). An ortho Fries product **30** could then undergo a photoreduction to a product simply characterized by its intact lactone carbonyl. We also studied a simple dihydrocoumarin **31** with a strongly activating group[14] which should be a better substrate for cyclization than any studied by Gutsche. We independently synthesized[15] the desired indanone cyclization product **32.** Photolysis of **31** led to its disappearance and the formation of many new compounds. However, no trace of **32** could be detected. Presumably, the carbonyl radical in this example does not have the lifetime required for cyclization.[16]



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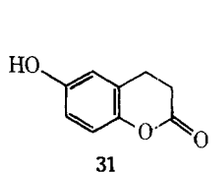
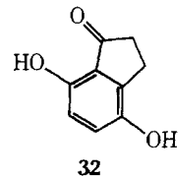


31



32

Experimental Section

^1H NMR spectra were recorded on Varian Models A-60, A-60A, and XL-100 instruments. Infrared spectra were recorded on a Perkin-Elmer Model 137. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

2,4-Dimethoxy-3-methylacetophenone (8). In a three-neck flask fitted with a reflux condenser, mechanical stirrer, and addition funnel was placed a solution of 50 g (0.262 mol) of titanium tetrachloride and 20.4 g (0.262 mol) of acetyl chloride. After being cooled to 0 °C, a solution of 20 g (0.131 mol) of 2,6-dimethoxytoluene (Aldrich, 99%) in 60 ml of dry benzene was added dropwise under an atmosphere of argon. The mixture was stirred for an additional 20 min at 0 °C and then quenched by the cautious addition of 5% HCl.

The organic layer was separated and the aqueous layer was extracted with 60 ml of ether. The combined organic portions were then washed successively with 5% HCl, saturated sodium bicarbonate, and finally with water. After drying with sodium sulfate the solvent was removed and the remaining dark oily residue was then distilled in vacuo with product distilling over at 107 °C (1.5 mm). The product crystallized upon standing and was recrystallized from hexane: mp 31–32 °C; yield 25.1 g (99%); NMR ($CDCl_3$, Me_4Si) δ 1.76 (s, 3 H), 2.18 (s, 3 H, $PhCH_3$), 3.34 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3); ir ($CHCl_3$) 1670 (s, ArC=O), 2850 cm^{-1} (m, OCH_3).

2,4-Dimethoxy-3-methylacetophenone Oxime (9). In a 250-ml round-bottom flask fitted with a reflux condenser, drying tube, and magnetic stirrer were placed 19.13 g (0.099 mol) of the previously prepared 2,4-dimethoxy-3-methylacetophenone (8), 20.3 g (0.292 mol) of hydroxylamine hydrochloride, 30 ml of reagent grade pyridine, and 30 ml of absolute ethanol. After heating under reflux for 3 h, the ethanol and pyridine were removed on a rotary evaporator. Distilled water was then added to the residue and the milky mixture was extracted with chloroform. After drying the organic layer over anhydrous sodium sulfate and removing the solvent, there was left a solid residue, which was recrystallized from hexane: mp 86–88 °C; yield 19.3 g (72%); NMR ($CDCl_3$, Me_4Si) δ 2.18 (s, 3 H, $ArCH_3$), 2.27 (s, 3 H, $N=CCH_3$), 3.70 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3); ir ($CHCl_3$) 3400 (-OH), 1570 (s, N=O), 945 (m, N-O), 2850 cm^{-1} (s, OCH_3).

Anal. Calcd for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.07; H, 7.21; N, 6.68.

2,4-Dimethoxy-3-methylacetanilide (10). In a 250-ml round-bottom flask filled with a reflux condenser and cooled to 0 °C in an ice bath were placed 14.0 g (0.0699 mol) of the previously prepared oxime and 15 ml of trifluoroacetic acid. After allowing the mixture to come to room temperature with stirring, it was gently refluxed for 20 min. Excess TFA was then destroyed by the addition of saturated sodium bicarbonate solution. The anilide was extracted out of solution with chloroform and this chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue recrystallized several times from distilled water: mp 119–120 °C; yield 13.76 g (98%); NMR ($CDCl_3$, Me_4Si) δ 2.21 (s, 6 H, $O=CCH_3$ and $ArCH_3$), 3.72 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3); ir ($CHCl_3$) 1760 (s, C=O), 3650 cm^{-1} (m, NH).

Anal. Calcd for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.09; H, 7.28; N, 6.73.

2-Hydroxy-4-methoxy-3-methylacetanilide (13). In a dry 250-ml three-neck flask fitted with an addition funnel, reflux condenser, and magnetic stirrer was placed 13.2 g (0.1 mol) of anhydrous aluminum chloride. To this was added, under an atmosphere of N_2, 9.0 g (0.043 mol) of the previously prepared 2,4-dimethoxy-3-methylacetanilide (10) in 110 ml of dry methylene chloride. The mixture was stirred at room temperature overnight under an atmosphere of N_2. The mixture was then cooled to 0 °C in an ice bath and any excess aluminum chloride destroyed by the cautious addition of 5% hydrochloric acid. The organic layer was separated and the aqueous layer was extracted three times with methylene chloride. The combined organic portions were dried over anhydrous sodium sulfate. The solvent was removed and the resulting residue recrystallized from carbon tetrachloride: mp 117–119 °C; yield 6.24 g (74%); NMR ($CDCl_3$, Me_4Si) δ 2.21 (s, 6 H, $O=CCH_3$ and $PhCH_3$), 3.81 (s, 3 H, OCH_3), 8.0–10.4 (m 2 H, PhH), 7.63–7.85 (m 1 H, NH); ir ($CHCl_3$) 1639 (s, C=O), 2941 cm^{-1} (m, NH).

2-Hydroxy-4-methoxy-3-methylaniline Hydrochloride (14). In a 500-ml three-neck round-bottom flask was placed 8.44 g of the phenol 13 dissolved in 154 ml of absolute ethanol. After thoroughly degassing the system, 79 ml of a solution of 50% HCl in water was added dropwise. This mixture was refluxed for 24 h under nitrogen which was passed through Fieser's solution.[17]

After refluxing the solvent was removed leaving a brown residue which was diluted with water and extracted with chloroform. The remaining aqueous layer was reduced to dryness in vacuo. The resulting residue can be partially purified by boiling in chloroform, yield 6.12 g (75%).

6-Methyl-7-methoxy-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (15). In a 100-ml round-bottom flask were placed 3.0 g (0.0158 mol) of the anilinium salt **14,** 3.04 g (0.0158 mol) of tetrahydrofuran **6a,** 1.3 g of sodium acetate, and 37 ml of glacial acetic acid.[18] The mixture was refluxed for 24 h under nitrogen passed through Fieser's solution. After refluxing the mixture was diluted with water and extracted five times with chloroform. The combined chloroform layers

were dried over anhydrous sodium sulfate and the solvent removed. The dark residue which resulted was then heated in methanol and the brown crystals of lactone **16** were collected by suction and dried: mp >300 °C; yield 1.96 g (54%); NMR (TFA) δ 2.24 (s, 3 H, $PhCH_3$), 3.93 (s, 3 H, OCH_3), 6.62–6.92 (m, 2 H, vinylic), 7.35–7.72 (m, 2 H, ArH).

6-Methyl-7-methoxy-8-nitro-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]-benzoxazine (16). A solution of 2.6 g of concentrated nitric acid and 3.3 g of concentrated sulfuric acid was stirred for 5 min and then 100 ml of glacial acetic acid was added. A 2-g (8.8 mmol) portion of 6-methyl-7-methoxy-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (**15**) was then slowly added with stirring and within 2–3 min after addition a solid crystallized from the reaction mixture. Stirring was continued for an additional 30 min. The reaction mixture was poured onto ice and the crude solid was filtered with suction and washed several times with water yielding 2.5 g (99%) of nitrolactone **16**, mp 237–238 °C. The crude product was dissolved in chloroform and passed through a sintered glass funnel filled with dry column silica gel. A yellow band which moved rapidly through the silica gel was collected. Evaporation of the solvent yielded 2.8 g (91%) of **16** as a pale yellow solid. An analytical sample was prepared by two recrystallizations from acetone yielding the desired nitrolactone **16** as white needles: mp 251–252 °C; ir (chloroform) 2994, 1749, 1605, 1522, 1410, 1372, 1349, 1294, 1154, 1104, 1063, 1043, 996, 924 cm^{-1}; uv (ethanol) 205 nm (ϵ 24 400), 227 sh (13 800), 268 (14 000); NMR (chloroform-d_1–dimethyl sulfoxide-d_6) δ 2.38 (s, 3, CH_3), 3.89 (s, 3, OCH_3), 6.76 (dd, 1, J_{12} = 2.8, J_{23} = 3.8 Hz, C-2), 7.33 (dd, 1, J_{23} = 3.8, J_{13} = 1.3 Hz, C-3), 8.37 (dd, 1, J_{12} = 2.8, J_{13} = 1.3 Hz, C-1), 8.66 ppm (s, 1, C-9).

Anal. Calcd for $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.22. Found: C, 56.85; H, 3.81; N, 10.20.

6-Methyl-7-methoxy-8-amino-4-oxo-4*H*-pyrrolo[2,1-*c*]-[1,4]benzoxazine (17). A solution of 286 mg (1.1 mmol) of 6-methyl-7-methoxy-8-nitro-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (**16**), 60 mg of 10% Pd/C, and 125 ml of ethyl acetate was hydrogenated at atmospheric pressure for 1.5 h. The catalyst was removed by filtration with suction through Celite 545. Evaporation of the solvent yielded 269 mg (100%) of a crude brown solid. Thin layer chromatography on silica gel eluting with chloroform indicated three major components with R_f values of 0.55, 0.17, and 0.08 corresponding to nitrolactone **16**, product amine **17**, and a by-product of the reaction, respectively. All attempts at purification of the crude material were unsuccessful. Elution chromatography on a silica gel column 0.13 cm in diameter and eluting with chloroform yielded 36 mg of recovered nitrolactone **16** as a light yellow solid. Successive elution with increasing percentages of ethyl acetate in chloroform and finally pure ethyl acetate failed to isolate the desired product. Chromatography on a silica gel preparative thin layer plate eluting with chloroform was also unsuccessful. For this reason the amine was always used as a crude material.

Ir (chloroform) 3461, 3372, 2939, 1728, 1628, 1505, 1467, 1417, 1367, 1305, 1169, 1071, 995 cm^{-1}; uv (ethanol) 237 nm (ϵ 11 200), 267 (5500), 332 (5100); NMR (chloroform-d_1) δ 2.38 (s, 3, CH_3), 3.82 (s, 3, OCH_3), 6.64 (dd, 1, J_{12} = 2.9, J_{23} = 3.9 Hz, C-2), 6.81 (s, 1, C-9), 7.34 (dd, 1, J_{23} = 3.9, J_{13} = 1.5 Hz, C-3), 7.48 ppm (dd, 1, J_{12} = 2.9, J_{13} = 1.5 Hz, C-1).

Irradiation of 6-Methyl-7-methoxy-8-amino-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (17) in Anhydrous Tetrahydrofuran. A solution of 200 mg of crude 6-methyl-7-methoxy-8-amino-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (**17**) and 200 ml of anhydrous tetrahydrofuran, freshly distilled from lithium aluminum hydride, was placed in a photochemical reaction vessel equipped with a water-cooled immersion well. Nitrogen gas, passing through Fieser's solution to remove traces of oxygen in the tank of nitrogen, was continually bubbled through the solution. The solution was irradiated with a Sears-Roebuck sun lamp no. 7081 mounted 2.5 cm from the reaction vessel. Two thicknesses of plate glass served as a filter. The progress of the reaction was followed by thin layer chromatography on silica gel eluting with chloroform and following the disappearance of the starting aminolactone **17** with an R_f of 0.18. After 22 h the solution had turned from a pale yellow to a deep orange, and no more **17** could be detected. Thin layer chromatography indicated the presence of an orange component with an R_f of 0.13. Evaporation of the solvent yielded a crude red oil which was chromatographed on a silica gel dry column 40 cm long and 2.5 cm in diameter eluting with chloroform. A light yellow band moved with the solvent front and after elution from the column yielded 42 mg (21%) of recovered nitrolactone **17**. An orange band, approximately 10 cm from the origin, was removed and the material eluted from the silica gel with tetrahydrofuran. Evaporation of the solvent yielded 67 mg (34% yield, 48% conversion) of crude product. An analytical sample was prepared by preparative thin layer chromatography on silica gel eluting with chloroform. A bright orange band, 2.5 cm from the origin, was removed and the material was eluted from the silica gel with tetrahydrofuran. Evaporation of the solvent yielded 27 mg (14% yield, 19% conversion) of a red solid. Two recrystallizations from ethyl acetate afforded bright red crystals, mp 222–232 °C dec, of **25a:** ir (chloroform) 2924, 2899, 1724, 1667, 1613, 1456, 1357, 1290, 1093, 1031 cm^{-1}; uv (ethanol) 208 nm (ϵ 23 900), 222 (25 300), 244 (16 400), 298 (7400), 310 sh (5800), 419 (6700); NMR (dimethyl sulfoxide-d_6) δ 5.83 (bs, exchangeable protons, NH_2, OH), 6.25 (m, 1, C-2), 6.62 (m, 1, C-1), 7.35 (m, 1, C-3); *m/e* 244.0848 (calcd for $C_{13}H_{12}N_2O_3$, 244.0846).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.65; H, 4.69; N, 11.05.

8-Amino-5-hydroxy-7-methoxy-6-methyl-9-keto-9*H*-pyrrolo-[1,2-*a*]indole (25a). A hydrogenation catalyst was prepared by reducing a mixture of 120 mg of 10% Pd/C and 250 ml of K_2CO_3 stirred with 250 ml of EtOAc under an atmosphere of H_2. To this was added 600 mg of powdered nitrolactone **16** through a side arm connection of Gooch tubing. When hydrogen uptake was complete, detected both by volume measurements and the complete disappearance of the suspension of the highly insoluble nitro compound, the catalyst was removed and the solvent was evaporated yielding **17.** The resultant aminolactone **17** was then photolyzed as described above in 500 ml of THF for 11.5 h. Upon solvent removal, there was obtained 534 mg (99%) of crystalline **25a,** comparable in purity to that of the analytical sample.

8-Amino-5,7-dimethoxy-6-methyl-9-keto-9*H*-pyrrolo[1,2-*a*]indole (25b). A mixture of 20 mg (0.082 mmol) of aminophenol **25a,** 7.6 μl (0.082 mmol) of $(CH_3)_2SO_4$, 2 ml of acetone, and anhydrous K_2CO_3 was stirred at 25 °C for 4 h. The mixture was diluted with water and extracted with $CHCl_3$. The organic extract yielded material which was purified by preparative TLC on silica gel by threefold elution with chloroform. The desired methyl ether **25b** was obtained as 20 mg of an orange solid (95% yield) which could be recrystallized from $CHCl_3$–hexane to afford crystals, mp 135–137 °C, which were submitted for x-ray analysis: NMR ($CDCl_3$) δ 2.12 (3 H, s, CCH_3), 3.60, 3.66 (each 3 H, s, $ArOCH_3$), 5.23 (2 H, bs, NH_2), 6.09 (1 H, dd, H_2), 6.51 (1 H, dd, H_1), 7.04 (1 H, dd, H_3).

Registry No.—**6a,** 60512-79-0; **8,** 60512-80-3; **9,** 60512-81-4; **10,** 60512-82-5; **13,** 60512-83-6; **14,** 60512-84-7; **15,** 55609-73-9; **16,** 55609-74-0; **17,** 55609-75-1; **25a,** 55609-76-2; **25b,** 55609-77-3; acetyl chloride, 75-36-5; 2,6-dimethoxytoluene, 5673-07-4.

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