Synthesis of Ring-Fused Pyrroles. II. 1,3-Dipolar Cycloaddition Reactions of Munchnone Derivatives Obtained from Tetrahydroisoquinoline-1-carboxylic Acids

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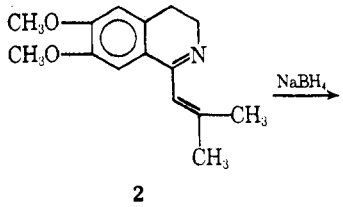
The reactions of mesoionic oxazolium 5-oxides (munchnones) derived from 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**1a**, **1b**, and **5**) are reported and involve the 1,3-dipolar cycloaddition to the acetylenic dipolarophiles, dimethyl acetylenedicarboxylate and phenylacetylene. In the latter case, the reaction was found to be regiospecific, yielding **7a** and **7b**, respectively, as the only products. An isomeric pyrrolo[2,1-*a*]isoquinoline (**8**) was prepared by an unambiguous route and a comparison of the PMR spectra of **7a** and **8** is presented. Furthermore, irradiation of a methanolic solution of **7a** in the presence of trace amounts of iodine resulted in a photocylization yielding the indolizinophenanthrene (**9a**). Unsuccessful attempts at the preparation of the analog, **9b**, *via* photocyclization or Pschorr cyclization reactions are also discussed.

The conversion of secondary amino acids into pyrroles via intermediate mesoionic oxazolium 5-oxides (munchnones)[1] has been utilized in converting the "cyclic" amino acids, tetrahydro-β-carboline-1- and -3-carboxylic acids, into novel indolizinoindoles.[2] This paper will report on the above reaction with another type of cyclic amino acid ring system, namely, the 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids, and the subsequent synthetic use of a pyrrolo[2,1-*a*]isoquinoline in a photocyclization reaction will be discussed.

For the purposes of this study, 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, **1a**, was prepared by the catalytic hydrogenation of isoquinoline-1-carboxylic acid,[3] which in turn was synthesized from isoquinoline via a Reissert reaction[4] and subsequent acid hydrolysis of the Reissert salt.[5] The preparation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1b**), however, was not as straightforward. Reaction of homoveratrylamine with glyoxylic acid furnished **1b** in low and variable yields (0–20%).[6] An alternate, though circuitous, synthesis was used here and involved the sodium borohydride reduction of **2**[7]



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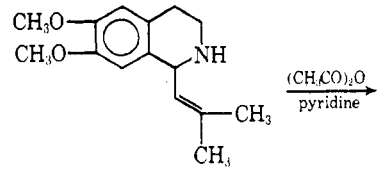

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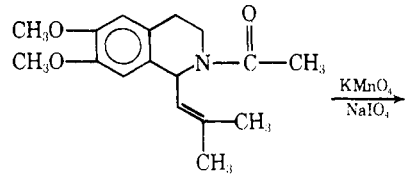

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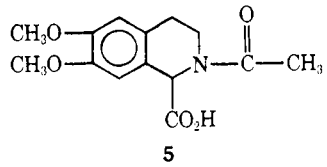

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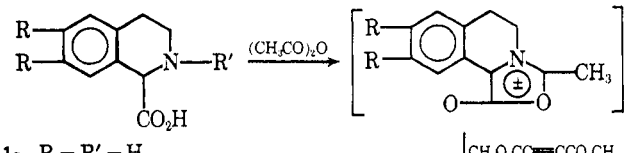
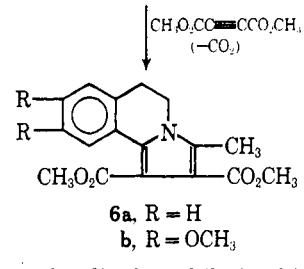
and subsequent acetylation of the tetrahydroisoquinoline **3** with acetic anhydride–pyridine to furnish the amide **4**. Oxidative cleavage of the olefinic substituent of **4** using either ozone, followed by a hydrogen peroxide work-up, or reaction with ruthenium tetroxide failed to give the desired *N*-acetyl tetrahydroisoquinoline-1-carboxylic acid, **5**. This oxidative cleavage reaction was successfully carried out, however, when potassium permanganate–sodium metaperiodate was used.[8]

Since the first step in the formation of the oxazolium 5-oxide involves N-acetylation of the amino acid, compound **5** would represent a suitable reactant for this reaction, since it would be formed in situ from **1b** and acetic anhydride. In fact, when either **1b** or **5** was treated with dimethyl acetylenedicarboxylate and acetic anhydride, the corresponding pyrrolo[2,1-*a*]isoquinoline, **6b**, was isolated in 65–80% yields. In a similar manner, the tetrahydroisoquinoline **1a** provided **6a** in 62% yield.



1a, R = R′ = H
1b, R = OCH_3; R′ = H
5, R = OCH_3; R′ = $COCH_3$

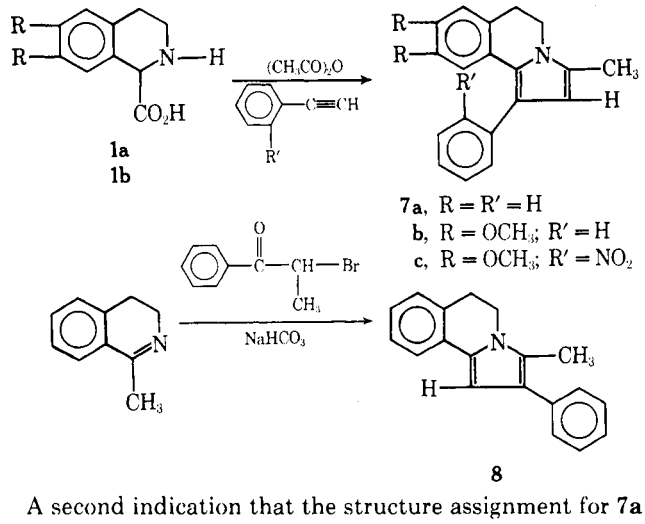


6a, R = H
b, R = OCH_3

The use of phenylacetylene as the dipolarophile in this particular 1,3-dipolar cycloaddition reaction has been reported previously and has been observed to be regiospecific in its reaction with the munchnone dipoles used thus far.[1,2] When phenylacetylene was allowed to react with either **1a** or **1b** in acetic anhydride, once again a single product, **7a** and **7b**, respectively, was isolated in good yield. The structure assignments for these products were made in the following manner: 2-phenyl-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (**8**) was prepared by treating 1-methyl-3,4-dihydroisoquinoline with α-bromopropiophenone under mild alkaline conditions using the procedure of Casagrande.[9] A comparison of the two isomeric pyrrolo[2,1-*a*]-isoquinolines, **7a** and **8**, was made by ^1H NMR spectroscopy and the expected differences in the chemical shifts and coupling constants for the pyrrole ring protons for each compound were noted.

While the pyrrole ring proton (H-2) for compound **7a** appeared at δ 6.00 as a quartet with long-range coupling to the adjacent methyl group (J_{H,CH_3} = 1.0 Hz),[1] the pyrrole ring proton of 8 (H-1) was observed at δ 6.68 as a sharp singlet. The deshielding of H-1 in 8 vs. H-2 in **7a** is undoubtedly due to the anisotropic effect of the aromatic carbocyclic portion of the tetrahydroisoquinoline ring. Furthermore, using the pulsed Fourier transform technique,[10] a nuclear Overhauser effect (NOE) was observed with **7a** but not with 8. Irradiation of the 3-methyl substituent of **7a** resulted in a 19% enhancement in the integral of the signal for the adjacent ring proton, H-2, while irradiation of the methyl group in 8 increased the integral of H-1 by only 2%.

By establishing the structure of **7a** unequivocally, the structure assignment for **7b** was then made by a comparison of its ^{1}H NMR spectrum, and particularly the ^{1}H NMR parameters of the pyrrole ring proton, with that of compound **7a.**



1a
1b

7a, R = R′ = H
b, R = OCH$_3$; R′ = H
c, R = OCH$_3$; R′ = NO$_2$

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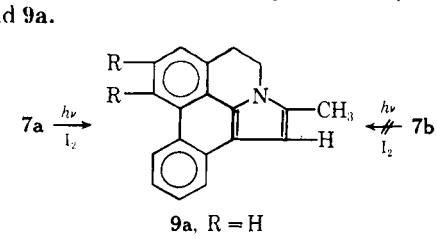
A second indication that the structure assignment for **7a** was correct was obtained when irradiation of a degassed, methanolic solution of **7a,** in the presence of a trace of iodine, resulted in a photocyclization reaction yielding compound **9a** in 8% isolated yield. The structural assignment for **9a** was based on the expected changes in both the uv and NMR spectra for this product as compared to those of the starting material, **7a** (see Experimental Section).

Surprisingly, **7b** failed to undergo photocyclization to **9b** under analogous reaction conditions. An alternate attempt to prepare **9b** was also unsuccessful. This involved the treatment of **1b** with acetic anhydride and *o*-nitrophenylacetylene to furnish the 1-(*o*-nitrophenyl)pyrrolo[2,1-*a*]isoquinoline (**7c**). Subsequent catalytic hydrogenation of the nitro group provided the amine **7d.** Several attempts were then made to convert **7d** into **9b** via a Pschorr cyclization reaction, but all efforts were unsuccessful. Examination of the reaction mixture after diazotization and treatment with copper powder failed to show the characteristic ultraviolet and ^{1}H NMR spectra exhibited by the analogous, cyclized compound **9a.**



9a, R = H
b, R = OCH$_3$

Experimental Section

Melting points were taken on a Thomas-Hoover Uni-Melt capillary apparatus which was calibrated against known standards. Ultraviolet spectra were recorded in CH_3OH solutions on a Beckman DK-2A spectrometer; infrared spectra were determined in $CHCl_3$ solutions or KBr disks on a Beckman IR-12 spectrometer; ^{1}H NMR spectra were obtained on a Varian Associates A-60, T-60, or HA-100 spectrometer from $CDCl_3$ or $(CD_3)_2SO$ solutions using tetramethylsilane as an internal standard; mass spectra were run on an A.E.I. MS-30. Microanalyses were performed by the Searle Laboratories Microanalytical Department.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (1b). A solution consisting of β-(3,4-dimethoxyphenyl)ethylamine (36.25 g, 0.20 mol), glyoxylic acid hydrate (29.6 g), concentrated hydrochloric acid (50 ml), and water (500 ml) was stirred and warmed to 75° for 3 hr and then allowed to stand at 25° for 18 hr. The resultant yellow solution was neutralized with 5 *N* sodium hydroxide solution until pH 5.0 was reached (163.8 ml required, pH meter used). The mixture was then cooled in an ice–water bath and filtered, and the solid that had been collected was washed with a small amount of cold water. A colorless solid (9.60 g, 20%) was obtained: mp 252–257°; ir (KBr) ν_{NH_2} 2250–2700 cm^{-1}, ν_{CO_2} 1610 cm^{-1}; ^{1}H NMR (C_5D_5N–D_2O mixture) δ 3.10 (t, CH_2, J = 6 Hz), 3.71 (t, CH_2, J = 6 Hz), 3.91 and 4.03 (s, OCH_3), 6.67 and 7.53 (s, aromatic protons).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.59; H, 6.35; N, 5.83.

The above experiment was repeated several times after this initial reaction had been carried out, and the yield of the product, **1b,** obtained ranged from 0 to 20%.

1-(2′-Methyl-1′-propenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3). The dihydroisoquinoline salt **2** (135.2 g, ca. 0.4 mol), obtained by the Bischler–Napieralski reaction of *N*-1β-(3,4-dimethoxyphenyl)ethyl]-3-methyl-2-butenamide with phosphorous oxychloride in benzene,[7] was dissolved in methanol (1300 ml) and cooled to 5°. A 20% sodium hydroxide in methanol solution was added until the pH of the resultant mixture was >10 (ca. 400 ml was required). Sodium borohydride (50.4 g) was then added to the alkaline mixture in small portions, and the temperature was kept at 5° throughout this addition. The reaction mixture was stirred overnight at room temperature, and then evaporated to dryness in vacuo. Water (1 l.) was added to the residue and the resultant alkaline mixture was extracted with methylene chloride (4 × 400 ml). The combined CH_2Cl_2 extract was washed with brine (2 × 400 ml), dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo. The yellow oil that remained was taken up in dry ether (1500 ml) and treated with a solution of HCl in isopropyl alcohol to form a cream-colored, crystalline hydrochloride salt (87.6 g, 77%), mp 223–229°. Recrystallization from acetonitrile furnished a colorless, crystalline solid: mp 230–231°; ir ($CHCl_3$) ν_{NH} 2400–2810 cm^{-1}, $\nu_{C=C}$ 1620 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] δ 1.90 and 2.00 (s, CH_3), 3.00–3.80 (m, 2 CH_2), 3.81 and 3.86 (s, OCH_3), 4.95–5.65 (m, 2 CH), 6.50 and 6.61 (s, aromatic protons).

Anal. Calcd for $C_{15}H_{21}NO_2$·HCl: C, 63.48; H, 7.81; N, 4.94; Cl, 12.49. Found: C, 63.22; H, 7.95; N, 5.11; Cl, 12.64.

1-(2′-Methyl-1′-propenyl)-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4). A mixture of **3** (14.2 g, 0.05 mol), pyridine (100 ml), and methylene chloride (100 ml) was stirred, cooled to 10°, and treated with acetic anhydride (25 ml). The temperature of the reaction mixture was allowed to return to 25°, and kept at that temperature overnight (16 hr). The reaction mixture was poured into a slurry of concentrated hydrochloric acid (50 ml) and ice (300 ml). After the resultant two-phase mixture was separated, the aqueous acidic layer was extracted further with methylene chloride (2 × 100 ml). The combined CH_2Cl_2 extract was washed cautiously with a 5% $NaHCO_3$ solution (foaming) and then dried (Na_2SO_4). Removal of the solvent in vacuo and trituration of the residue with hexane afforded a colorless solid (12.0 g, 83%): mp 104–106.5°; ir ($CHCl_3$) $\nu_{C=O}$ 1670 cm^{-1}, $\nu_{C=C}$ 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 and 2.05 (s, CH_3), 2.13 (s, CH_3), 5.00–5.50 (m, 2 CH).

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.26; H, 7.96; N, 4.46.

2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (5). A solution consisting of **4** (14.45 g, 0.05 mol), potassium carbonate (27.65 g, 0.20 mol), *tert*-butyl alcohol (400 ml), and water (400 ml) was vigorously stirred in a creased three-necked flask using a mechanical stirrer. To this stirred mixture, two solutions, one consisting of potassium permanganate (0.8 g, 0.005 mol) in water (50 ml) and the other comprised of sodium metaperiodate (42.8 g, 0.20 mol) in water (300 ml), were added at room temperature simultaneously over a 1-hr period. The reaction mixture was then stirred for an additional 8 hr and then allowed to

stand at room temperature overnight. Isopropyl alcohol (75 ml) was added, and the reaction mixture was stirred at 25° for 1 hr and then diluted further with water (600 ml). Acetic acid (100 ml) was added in small portions (caution—foaming) and the resultant acidic mixture was extracted with chloroform (2 × 500 ml). The organic extract was washed with a 5% sodium thiosulfate solution (500 ml) and then with brine (500 ml) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was triturated with ether and yielded a yellow solid. Recrystallization of this solid from ethyl acetate furnished a light-tan powder (8.0 g, 57%): mp 207.5–210°; ir ($CHCl_3$) ν_{OH} 3300–3000 cm^{-1}, $\nu_{C=O}$ 1760, 1725, 1650 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 2.10 (s, CH_3), 2.83 (t, CH_2, J = 6 Hz), 3.73 (t, CH_2, J = 6 Hz), 3.75 (s, OCH_3), 5.60 (s, CH), 6.83 and 7.08 (s, aromatic protons).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.00; H, 6.23; N, 5.01.

Dimethyl 3-Methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (6a). A mixture consisting of **1a** (5.3 g, 0.03 mol), dimethyl acetylenedicarboxylate (5.70 g, 0.04 mol), and acetic anhydride (150 ml) was stirred and heated to 90°. Within 15 min, an orange solution had developed and carbon dioxide evolution had ceased. This solution was cooled and evaporated to dryness in vacuo. The residue was recrystallized from methanol, yielding a cream-colored, crystalline solid (5.55 g, 62%): mp 118–119°; ir ($CHCl_3$) $\nu_{C=O}$ 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (s, CH_3), 2.98 (t, CH_2, J = 6 Hz), 3.76 (t, CH_2, J = 6 Hz), 3.80 and 3.90 (s, OCH_3), 7.00–7.60 (m, aromatic protons).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.22; H, 5.81; N, 4.65.

Dimethyl 3-Methyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (6b). The procedure just described for compound **6a** was repeated using **1b** (3.55 g, 0.015 mol), dimethyl acetylenedicarboxylate (3.10 g, 0.022 mol), and acetic anhydride (75 ml). A colorless, crystalline solid was obtained on recrystallization of the crude product from methanol (4.20 g, 78%): mp 173–174°; ir ($CHCl_3$) $\nu_{C=O}$ 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (s, CH_3), 2.95 (t, CH_2, J = 6 Hz), 3.81 and 3.90 (s, OCH_3, 12 protons), 3.91 (t, CH_2 J = 6 Hz), 6.71 and 7.46 (s, aromatic protons).

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.37; H, 5.86; N, 3.81.

Repeating this experiment, but replacing **1b** with **5** (4.15 g, 0.015 mol), resulted in the isolation of product **6b** in 65% yield.

1-Phenyl-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (7a). A mixture composed of **1a** (3.55 g, 0.02 mol), phenylacetylene (4.10 g, 0.04 mol), and acetic anhydride (100 ml) was stirred and heated to 80° for 30 min. The resultant solution was cooled and evaporated to dryness in vacuo. Recrystallization of the residue from methanol provided light-tan needles (3.50 g, 69%): mp 120–122°; λ_{max} (CH_3OH) 319 nm (ϵ = 14,000), 259 (13,500); ^1H NMR ($CDCl_3$) δ 2.28 (s, CH_3), 3.03 (t, CH_2, J = 6 Hz), 3.91 (t, CH_2, J = 6 Hz), 6.00 (q, pyrrole H, J_{H,CH_3} = 1.0 Hz), 6.83–7.60 (m, aromatic protons); mass spectrum m/e 259 (M^+).

Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 87.61; H, 6.56; N, 5.25.

1-Phenyl-3-methyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (7b). The procedure just described for compound **7a** was repeated using either compound **1b** (3.55 g, 0.015 mol) or compound **5** (5.6 g, 0.02 mol), phenylacetylene (3.05 g, 0.03 mol), and acetic anhydride (100 ml). Recrystallization of the crude product from ethanol furnished an ivory-colored solid (3.30 g, 69% from **1b** and 4.60 g, 72% from **5**): mp 174–176°; ^1H NMR ($CDCl_3$), δ 2.28 (s, CH_3), 3.03 (t, CH_2, J = 6 Hz), 3.90 (t, CH_2, J = 6 Hz), 3.43 and 3.86 (s, OCH_3), 6.00 (q, pyrrole H, J_{H,CH_3} = 1.1 Hz), 6.70 and 6.88 (s, aromatic protons), 7.16–7.66 (m, aromatic protons).

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.73; H, 6.62; N, 4.34.

2-Phenyl-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (8). α-Bromopropiophenone (10.65 g, 0.05 mol) was added in dropwise portions over a 15-min period at room temperature to a stirred mixture of 1-methyl-3,4-dihydroisoquinoline[11] (7.25 g, 0.05 mol) and sodium bicarbonate (12.6 g) in ethanol (130 ml). The reaction mixture was heated to reflux for 3 hr, then cooled to 5° and filtered. The solid collected was washed with ethanol (100 ml) and water (200 ml) and then recrystallized from 1-butanol to yield a light-yellow, crystalline solid (2.3 g, 18%): mp 171–173°; λ_{max} (CH_3OH) 314 nm (ϵ 15,500), 240 (16,300); ^1H NMR ($CDCl_3$) δ 2.36 (s, CH_3), 3.03 (t, CH_2, J = 6 Hz), 3.96 (t, CH_2, J = 6 Hz), 6.68 (s, pyrrole proton), 7.00–7.70 (m, aromatic protons).

Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 88.13; H, 6.81; N, 5.51.

6-Methyl-4,5-dihydroindolizino[1,7,8,8a-*a,b,c*]phenanthrene (9a). A solution of **7a** (1.000 g, 3.8 mmol) in methanol (300 ml) containing iodine crystals (0.1 g) was degassed and irradiated, under a nitrogen atmosphere with constant stirring, by using a medium-pressure, 450-W Hanovia lamp. A Vycor filter was used in this photochemical experiment; no reaction was observed to occur when a Pyrex filter was used. After 20 hr, additional iodine (0.1 g) was added, and the reaction mixture was irradiated for another 20 hr. Throughout this experiment, the reaction mixture was monitored by TLC (15% ethyl acetate–85% cyclohexane/phosphomolybdic acid spray). After 40 hr, only a trace of **7a** remained (R_f 0.39) along with the product (R_f 0.31). The methanolic solution was filtered and evaporated to dryness in vacuo, and the residue was redissolved in benzene (200 ml). The brown benzene solution was washed with a 5% sodium sulfite solution (3 × 100 ml) and water (100 ml) and then dried ($MgSO_4$). Removal of the solvent in vacuo left a brown semisolid residue which crystallized on standing overnight at room temperature. Recrystallization from ethanol afforded an off-white powder (0.077 g, 8%): mp 151–155°; λ_{max} (MeOH) 293 nm (ϵ 16,000), 262 (65,000), 254 (44,000); ^1H NMR ($CDCl_3$, 100 MHz) δ 2.48 (s, CH_3), 3.44 (t, CH_2, J = 6 Hz), 4.20 (t, CH_2, J = 6 Hz), 6.69 (broad s, pyrrole H), 7.20–8.66 (m, aromatic protons); mass spectrum m/e 257 (M^+).

Anal. Calcd for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.28; H, 6.12; N, 5.28.

Examination of the ethanolic mother liquor of **9a** indicated the presence of additional product contaminated with unreacted starting material, **7a.** Several attempts were made to obtain additional pure product by subjecting the mother liquor to preparative thin layer or dry column chromatography. Complete separations, however, could not be achieved.

The analogous experiment was conducted using **7b** in an attempt to prepare **1,2-dimethoxy-4,5-dihydro-6-methylindolizino[1,7,8,8a-*a,b,c*]phenanthrene (9b).** After 40 hr of irradiation, examination of the reaction mixture by TLC showed only the presence of unreacted **7b.** Evaporation of this photolysate to dryness and examination of the residue by uv and ^1H NMR spectroscopy confirmed the presence of only unreacted **7b.**

1-(*o*-Nitrophenyl)-3-methyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (7c). Using the reaction conditions described for the preparation of **7a,** a mixture of **1b** (4.75 g, 0.020 mol), *o*-nitrophenylacetylene[12] (3.25 g, 0.022 mol), and acetic anhydride (100 ml) was stirred and heated to 90° for 1 hr. The residue obtained, by using the previously described work-up procedure, was recrystallized from 1-butanol and a red-colored powder, compound **7c,** was isolated (6.0 g, 82%): mp 190–191°; ^1H NMR ($CDCl_3$) δ 2.25 (s, CH_3), 2.96 (t, CH_2, J = 6 Hz), 3.36 and 3.80 (s, OCH_3), 3.90 (t, CH_2, J = 6 Hz), 5.90 (q, pyrrole H, J_{H,CH_3} = 1.0 Hz), 6.45 and 6.68 (s, aromatic protons), 7.10–7.90 (m, aromatic protons).

Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.21; H, 5.72; N, 7.79.

1-(*o*-Aminophenyl)-3-methyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (7d). A solution of **7c** (3.64 g, 0.01 mol) in 1,2-dimethoxyethane (50 ml) was treated with platinum oxide catalyst (364 mg) and the mixture was hydrogenated at room temperature and atmospheric pressure on a Parr shaker apparatus for 24 hr. The reaction mixture was then filtered and evaporated to dryness in vacuo, and the solid residue was recrystallized from ethanol, yielding a light-orange solid (2.0 g, 60%): mp 177–179°; ir ($CHCl_3$) μ_{NH_2} 3480, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) similar spectrum as described for **7c,** except for the presence of a broad exchangeable signal centered at δ 3.52 and integrating for two protons.

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 74.95; H, 6.67; N, 8.21.

Attempts to cyclize **7d** into **9b** using a Pschorr cyclization reaction were unsuccessful. These efforts involved diazotization of a solution of **7d** (668 mg, 2 mmol) in concentrated sulfuric acid (20 ml)–water (50 ml) with sodium nitrite (152 mg, 2.2 mmol) in water (10 ml), followed by heating the reaction mixture with copper powder. Work-up of this reaction furnished tarry residues which did not exhibit the characteristic uv absorptions in the 250–260-mμ region (see uv data on **9a**).

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Registry No.—**1a**, 41034-52-0; **1b**, 41143-95-7; **2**, 53957-21-4; **3**, 53927-32-5; **4**, 53927-33-6; **5**, 13326-60-8; **6a**, 53927-34-7; **6b**, 53927-35-8; **7a**, 53927-36-9; **7b**, 53927-37-0; **7c**, 53927-38-1; **7d**, 53927-39-2; **8**, 53957-18-9; **9a**, 53927-40-5; β-(3,4-dimethoxyphenyl)ethylamine, 120-20-7; glyoxylic acid, 298-12-4; dimethyl acetylenedicarboxylate, 762-42-5; phenylacetylene, 536-74-3; α-bromopropiophenone, 2114-00-3; 1-methyl-3,4-dihydroisoquinoline, 2412-58-0; o-nitrophenylacetylene, 16433-96-8.

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Synthesis of Substituted 2*H*-1,3-Oxazine-2,6-diones by Reaction of Trimethylsilyl Azide with Maleic Anhydrides[1]

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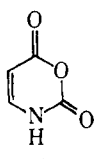
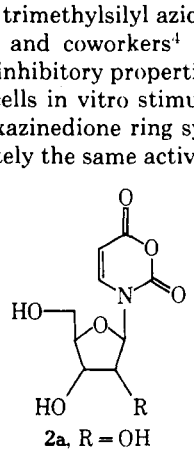
The synthesis of 4-bromo-, 4-chloro-, 4,5-dichloro-, 4-fluoro-, and 4-methyl-2*H*-1,3(3*H*)-oxazine-2,6-dione, as well as an improved synthesis of 2*H*-1,3(3*H*)-oxazine-2,6-dione, by reaction of trimethylsilyl azide with the corresponding maleic anhydride is described. This route is superior to other methods for preparation of 4-substituted oxaziniones. N-Methylation of the oxazinedione ring may be readily accomplished with dimethyl sulfate buffered by sodium bicarbonate.

The heterocycle derived from uracil by isosteric replacement of the imidic nitrogen, 2*H*-1,3(3*H*)-oxazine-2,6-dione or oxauracil (**1a**), was first prepared by Rinkes[2] in 1927 by sodium hypochlorite oxidation of maleimide. In 1972 this laboratory reported an alternate preparation of **1a** by reaction of maleic anhydride with trimethylsilyl azide.[3] Shortly thereafter, reports by Škoda and coworkers[4] and Bobek and coworkers[5] of the growth inhibitory properties of **1a** vs. *E. coli* and L1210 leukemia cells in vitro stimulated a renaissance of interest in the oxazinedione ring system. The *N*-riboside **2a** had approximately the same activity as **1a** in



1a

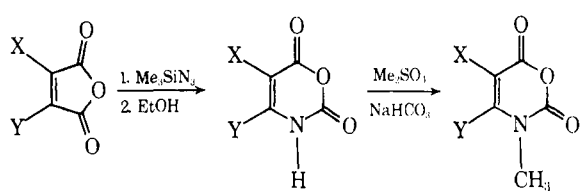


2a, R = OH
3a, R = H

inhibiting growth of L5178Y cells in culture,[6] while oxathymine **1i** was less inhibitory in microbial and tumor cell systems, and the deoxyriboside **3a** was about 1000 times more potent than **1a** in inhibiting *S. faecium* growth.[5] 5-Fluorooxauracil (**1h**) is active vs. the L1210 cell line, but toxic.[5b] The Škoda group has recently reported on the mechanism of inhibition of *E. coli* growth by **1a**, and detailed conditions of the hydrolytic fission of the oxazinedione ring.[7]

Our interest in the regioselective synthesis of alkyl- and halooxaziniones as agents against neoplastic and protozoan disease, particularly malaria, leads us to detail improved synthetic pathways to these heterocycles.

Synthesis. Oxauracil (**1a**) was first prepared by Rinkes by oxidation of maleimide[2] with basic aqueous sodium hypochlorite. Similar oxidation of citraconimide to 5-methyl-2*H*-1,3(3*H*)-oxazine-2,6-dione (oxathymine) has been reported.[5] Other syntheses of the ring system in **1** involve cyclization of the appropriate β-(ethoxycarbonylamino)-acrylic acid to the oxazinedione[5] or lead tetraacetate oxidation of maleic acid monoamide.[7] In a preliminary report[3] we synthesized **1a** by reaction of trimethylsilyl azide with maleic anhydride in benzene solvent.



1 **4**

The original trimethylsilyl azide–maleic anhydride reaction has been exteded to methyl- and halooxaziniones and appears to be the method of choice. Since the oxazinedione ring undergoes facile thermal decarboxylative polymerization to yield polyamides[8] and suffers hydrolytic ring fission at 25° in either acidic or basic media yielding formylacetic acid,[7] any synthetic procedure must be carried out at moderate temperature under essentially neutral conditions. In our hands, the Rinkes hypochlorite oxidation of either maleimide[2] or citrazonimide[5a] did not yield the corresponding oxazinedione even after several attempts in which the pH was carefully controlled.