K_2CO_3 or *n*-BuLi) did not result in production of **5a**.[19]

The mild conditions of the CH_3SiI reaction in conjunction with the potential ability to directly isolate an enol silyl ether cyclization product incapable of retro-Michael processes under the reaction conditions make this reaction of considerable possible utility.

The second CH_3SiI reaction serves as an adjunct to our palladium-based methodology[20] in promoting an S_N2' reaction of aminoallylic alcohols. The precursor for this reaction (**6**) was prepared by DiBAL-H reduction ($PhCH_3$, -5 °C, 75%) on the enone amine **4** (Scheme II). Treatment of **6** with 1.5 equiv of CH_3SiI (1 equiv of NEt_3, CH_3CN, -20 °C) effected cyclization of **7** in 40% isolated yield. Comparable yields were obtained with the primary amine **14** (R = H) and the allyl amine **15** (R = allyl) (Scheme II).

Conversion of the spirocyclic olefin (**7**) to desamyl-PHTx (**8**)[12] was accomplished by hydroboration-oxidation (BH_3-Me_2S, 1.1 equiv, THF, room temperature, 19 h, excess H_2O_2, NaOH, diglyme, 80 °C, 10 h,[21] which provided a 2:1 mixture of the isomeric alcohols (**16**/**17**) in 40% yield. Debenzylation of **16** (60 psi, H_2, EtOH, 48 h) yielded **8** in 85% yield. Alternatively the crude oxidation mixture could be converted to a 2:1 mixture of **5a**/**5b** in 33% yield by Swern oxidation.[22] Epimerization and Li/NH_3 reduction again provided **8**.

We have found this reaction to be a useful complement to the palladium methodology in allowing cyclization of, for example, **15**, which could not be effected by Pd(0).[23]

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Supplementary Material Available: Full experimental data are included (7 pages). Ordering information is given on any current masthead page.

(19) The trimethylsilyl amine derivative of **4** was prepared and found *not* to cyclize on treatment with CH_3SiI, NEt_3 in CH_3CN at -20 °C for 12 h.

(20) 1-Azaspirocycles, Godleski, S. A.; Meinhart, J. D.; Miller, D. J.; Van Wallendael, S. *Tetrahedron Lett.* **1981**, 2247.

(21) These conditions for oxidation were provided to us by Professor A. J. Pearson.

(22) The direct oxidation of the hydroboration product to the ketones using dichromate was not successful. The Swern oxidation on the alcohol was run as described in Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *42*, 2480. Omura, K.; Swern, D. *Tetrahedron* **1978**, 1651.

(23) The palladium reaction fails in the case of the *N*-allyl derivative because the catalyst is effectively sequestered by the allylamine and rendered inert.

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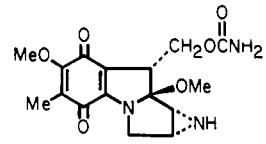
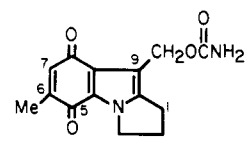
Expeditious Synthesis of 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indoles, Pyrroloindole Quinones, and Related Heterocycles via Nenitzescu-Type Condensation of Quinone Monoketals with Exocyclic Enamino Esters

Summary: Condensation of exocyclic enamino esters with 3-methoxyquinone 4-monoketals gives rise to bicyclic Michael adducts (see Table I) which undergo acid-catalyzed aromatization to 5-methoxypyrroloindole-9-carboxylates suitable for elaboration to mitosenes.

Sir: The antitumor activity of the mitomycin antibiotics (e.g., mitomycin A, **1**)[1] has stimulated a considerable effort



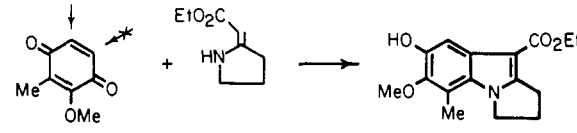
1



2

aimed at the synthesis of the natural products, as well as various analogues based on the parent 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole nucleus[1-3] (e.g., mitosene, **2**). Although only one approach has as yet culminated in a total synthesis of the natural mitomycins,[4] the antitumor activity of the simpler mitosenes[1a,5] and the antibacterial properties of related indoloquinones[6] provide incentive for the development of new synthetic routes to these heterocyclic compounds. We have discovered a novel variation of the Nenitzescu indole synthesis[7] which affords directly 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates with a substitution pattern suitable for ready elaboration of the pyrroloindole quinone characteristic of the mitomycins.

Indoles bearing carboxyl and hydroxyl groups at C-3 and C-5 (C-9 and C-7 on mitosene), respectively, are readily prepared by the Nenitzescu reaction of enamino esters and quinones.[7,8] Unfortunately the attractively convergent annelation of toluquinone with ethyl (pyrrolidin-2-ylidene)acetate (**4**) and the corresponding nitrile gives rise to



3 4 5

mixtures in which the required 7-hydroxy-6-methyl pyrroloindole isomers are minor components.[9] Similarly, and not unexpectedly,[8] we have found that the initial Michael addition step of the Nenitzescu reaction between 2-methoxy-3-methylquinone (**3**)[10] and **4**[11] occurs exclusively "para" to the methoxy group and that the usual equilibrating conditions (1:1 CH_3OH-AcOH, reflux) give the

(1) (a) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley: New York, 1979; Vol. 1, pp 221-276. (b) Franck, R. W. *Prog. Chem. Org. Nat. Prod.* **1979**, *38*, 1-45.

(2) For reviews see: (a) Takahashi, K.; Kametani, T. *Heterocycles* **1979**, *13*, 411-467. (b) Kametani, T.; Takahashi, K. *Ibid.* **1978**, *9*, 293-351.

(3) For recent syntheses of pyrroloindoles and references to others see: (a) Hutchins, C. H.; Coates, R. M. *J. Org. Chem.* **1979**, *44*, 4742-4744. (b) Rebek, J., Jr.; Shaber, S. H. *Heterocycles* **1981**, *16*, 1173-1177.

(4) (a) Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 4835-4836. (b) Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *Ibid.* **1977**, *99*, 8115-8116. (c) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295-4298. (d) Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549-568.

(5) Hodges, J. C.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1981**, *24*, 1184-1191.

(6) Allen, G. R., Jr.; Weiss, M. J. *J. Med. Chem.* **1967**, *10*, 1-6 and following papers. For a summary of the biological activity data see ref 1a.

(7) Allen, G. R. *Org. React.* **1973**, *20*, 337-454.

(8) (a) Allen, G. R., Jr.; Pidacks, C.; Weiss, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 2536-2544. (b) Allen, G. R., Jr.; Weiss, M. J. *J. Org. Chem.* **1968**, *33*, 198-200. (c) Littell, R.; Allen, G. R., Jr. *Ibid.* **1968**, *33*, 2064-2069.

(9) (a) Yamada, Y.; Matsui, M. *Agric. Biol. Chem.* **1970**, *34*, 724-728. (b) Yamada, Y.; Matsui, M. *Ibid.* **1971**, *35*, 282-284.

(10) Mandell, L.; Roberts, E. C. *J. Heterocycl. Chem.* **1965**, *2*, 479-480.

(11) Yamazaki, T.; Matoba, K.; Yajima, M.; Nagata, M.; Castle, R. N. *J. Heterocycl. Chem.* **1975**, *12*, 973-979.

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Scheme I

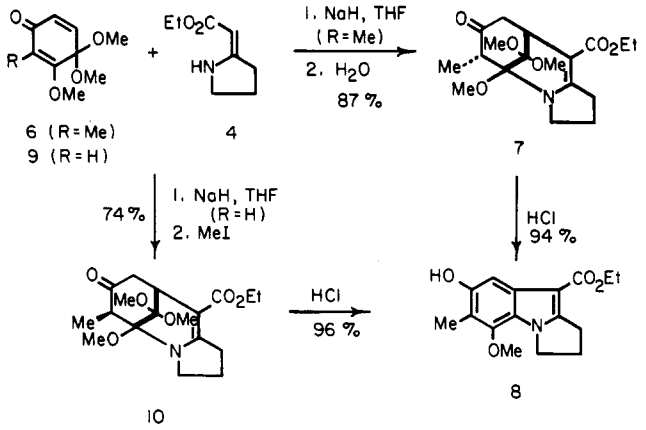
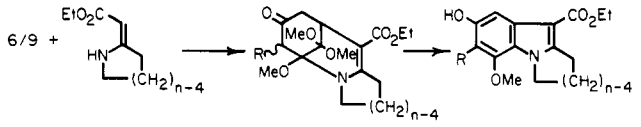


Table I. [1,2-a]-Annelated Indole-9-carboxylates from 3-Methoxyquinone 4-Monoketals and Various Exocyclic Enamines



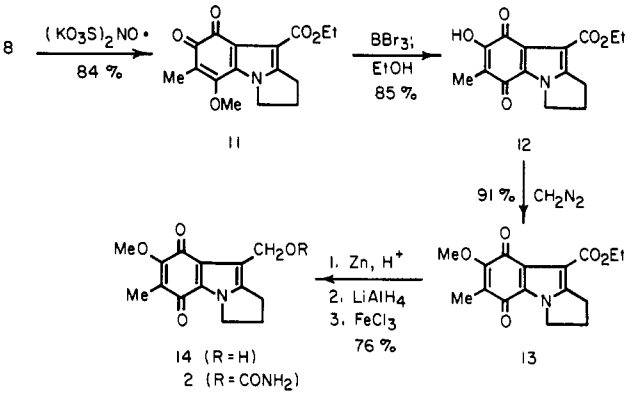
quinone monoketal R	enamine (ring size) n	% yield: bicyclic adduct	% yield: annelated indole
H	5	87	89
H	5	74 (R = Me)[a]	96 (R = Me)
Me	5	87	94
H	6[b]	85	99
Me	6[b]	c	59[d]
H	7[b]	75	89
Me	7[b]	c	64[d]

[a] The methyl group was incorporated by adding 10 equiv equiv of methyl iodide after the initial bicyclization (see text). [b] KH (1.25 equiv) was used instead of 1.1 equiv of NaH. [c] An ~2:1 mixture of epimeric adducts was formed which was not purified. [d] Overall yield.

undesired 6-methoxy-5-methylpyrroloindole **5** (56%, mp 248–250 °C).[12,13]

It occurred to us that control over the regioselectivity of the Nenitzescu reaction might be effected by using quinone monoketals[14–16] instead of quinones. The sodium salt of enamino ester **4** formed from 1.1 equiv of sodium hydride at 0 °C reacted smoothly with quinone monoketal **6** (1.0 equiv)[17] in tetrahydrofuran (−15 to +25 °C) to give, after addition of water, the bridged bicyclic adduct **7** (Scheme I): mp 94–96 °C; yield 81–87%.[18,19] Exposure of **7** to a catalytic amount of concentrated hydrochloric acid (acetone, 25 °C) promoted immediate rearrangement to the desired 7-hydroxy-5-methoxy-6-methylpyrroloindole **8**: mp 272–273 °C; yield 86–94%.[20] Alternatively condensation of the sodium salt of **4** with the more readily available quinone monoketal **9**[14b,17] followed by in situ methylation (10 equiv of CH_3I, THF, 25 °C, 20 h) gave predominantly the epimeric adduct **10**: mp 104–106 °C; yield 74%. The structure of **10** was confirmed by equilibration to **7** (NaOEt, EtOH–Et_2O) and rearrangement to **8** (HCl, acetone, 25 °C; 96%). Evidently the bicyclization reaction of **4** and **9** gives rise to the enolate anion which undergoes regio- and stereoselective alkylation with methyl iodide.

Scheme II



The scope of this heteroannelation reaction was investigated with five-, six-, and seven-membered endocyclic enamine esters[21] (Table I). The overall yields of methoxy-substituted [1,2-a]-annelated indole-3-carboxylate esters ranged from 59% to 84%. Although analogous bridged adducts were also obtained from the 3-methylquinone 4-monoketal, these compounds which lack the bridgehead methoxyl group have so far resisted attempts to effect acid-catalyzed aromatization to indoles.

The methoxyl group at C-5 was instrumental in the development of an efficient, six-step process (Scheme II)[22] for converting pyrroloindole **8** into decarbamoyl-7-methoxymitosene **14** (49% overall yield). Oxidation of **8** with 3 equiv of Fremy's salt (1:1 DMF/0.17 M aqueous KH_2PO_4, 25 °C, 1 day) afforded orthoquinone **11** as purple needles: mp 231–233 °C, yield 84%. Cleavage of the methyl ether was accomplished by exposure of **11** to boron tribromide (6 equiv, CH_2Cl_2, −78 °C, overnight) followed by addition of excess ethanol to reesterify the carboxyl group (−78 to +25 °C, 1.5 h). The resulting 7-hydroxypyrroloindoloquinone **12** (red platelets, mp 213–215 °C)

(12) All new compounds reported in this paper gave IR and NMR spectra consistent with the structures shown and combustion analyses for C, H, and N within ±0.35 of the calculated values.

(13) (a) The orientation of the methoxy and methyl groups in **5** was established by catalytic reduction (10% Pd/C, AcOH, 1500 psi, 25 °C, 20 h) of the *N*-phenyltetrazolyl ether[13b] to the deoxygenated pyrroloindole (**5**, H in place of OH). The latter (mp 141–142 °C) was distinctly different from its 5-methoxy-6-methyl isomer (mp 123–124 °C) prepared previously by reductive annelation[3a] of *N*-(2-methoxy-3-methylphenyl)-hydroxylamine in this laboratory by C. H. Hutchins. (b) Musliner, W. J.; Gates, J. W. *Org. Synth.* **1971** *51*, 82–85.

(14) Methods of preparation: (a) McKillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Mihaly, N.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282–287. (b) Büchi, G.; Chu, P. S.; Hoppmann, A.; Mak, C. P.; Pearce, A. *Ibid.* **1978**, *43*, 3983–3985. (c) Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. *Ibid.* **1980**, *45*, 3422–3433.

(15) Reviews: (a) Koelsch, P. M.; Tanis, S. P. *Kodak Lab. Chem. Bull.* **1980**, *52*, 1–7. (b) Fujita, S. *J. Synth. Org. Chem. Jpn.* **1982**, *40*, 307–320.

(16) Recent applications in natural product synthesis: (a) Büchi, G.; Chu, P.-S. *Tetrahedron* **1981**, *37*, 4509–4513. (b) Evans, D. A.; Tanis, S. P.; Hart, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 5813–5821. (c) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *Ibid.* **1981**, *103*, 5263–5264. (d) See also ref 14c.

(17) Parker, K. A.; Kang, S. *J. Org. Chem.* **1980**, *45*, 1218–1224.

(18) IR ($CHCl_3$) ν_{max} 1700 (C=O), 1645 (C=O) cm^{-1}; 220-MHz ^1H NMR ($CDCl_3$) δ 1.09 (d, J = 7 Hz, 3 H), 1.24 (t, J = 7 Hz, 3 H), 1.84 (quintet, J = 7.5 Hz, 2 H), 2.45 (dd, J = 2, 14 Hz, 1 H), 2.80 dd, J = 4, 15 Hz, 1 H), 3.03 (unsymmetrical q, J = 7.5 Hz, 2 H), 3.32 (m, 4 H), 3.40 (s, 3 H), 3.54 (s, 3 H), 3.60 (s, 3 H) 4.08 (q, J = 7 Hz, 2 H).

(19) Similar bridged Michael adducts from condensation of β-keto esters with quinone monoketals have recently been reported by Parker and Kang.[17]

(20) IR (KBr) ν_{max} 3350 (OH), 1655 (C=O) cm^{-1}. ^1H NMR (Me_2SO-d_6) δ 1.33 (t, J = 7.5 Hz, 3 H), 2.14 (s, 3 H), 2.55 (quintet, J = 7.5 Hz, 2 H), 3.10 (t, J = 7.5 Hz, 2 H), 3.78 (s, 3 H), 4.20 and 4.23 (superimposed q and t, J = 7 Hz, 4 H), 7.19 (s, 1 H), 8.97 (s, 1 H, D_2O exchangeable).

(21) Célérier, J. P.; Deloisy, E.; Lhommet, G.; Maitte, P. *J. Org. Chem.* **1979**, *44*, 3089.

(22) The latter steps of this reaction sequence had been carried out previously by C. H. Hutchins. We are grateful to him for this assistance.

was converted to the methyl ether **13** (yellow needles, mp 165–166 °C)[23] by treatment with 3 equiv of diazomethane (ether, 25 °C, 1 h). Reduction of the hydroquinone of **13** (Zn, 3:1 THF –0.1 M HCl, 25 °C) with lithium aluminum hydride (10 equiv, THF, 0 °C, 2 h; $HOCH_2CH_2OH$ quench) and immediate reoxidation with ferric chloride (0.1 M HCl, 25 °C, 3 min) provided **14**: mp 176–177.5 °C (lit.[24] mp 180–182 °C); 76% yield. Attachment of the carbamate according to published procedures (PhOCOCl, C_5H_5N; NH_3, CH_2Cl_2)[24] afforded 7-methoxymitosene **2** [mp 205–206 °C (lit.[24] mp 206–207 °C)] the IR and NMR spectral data for which are in accord with those reported.[24]

(23) IR ($CHCl_3$) ν_{max} 1720, 1670, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, J = 7 Hz, 3 H), 1.94 (s, 3 H), 2.57 (quintet, J = 7 Hz, 2 H), 3.10 (t, J = 7 Hz, 2 H), 4.05 (s, 3 H), 4.28 (t, J = 7 Hz, 2 H), 4.32 (q, 2 H, J = 7 Hz).

(24) Allen, G. R., Jr.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* **1965**, *30*, 2897–2904.

The quinone monoketal variation of the Nenitzescu reaction offers a direct and efficient synthesis of 7-methoxymitosene and opens the way to various [1,2-*a*]-annelated indoloquinones. It should be possible to prepare analogues and derivatives of these compounds by altering the C-6 substituent and/or by using suitably substituted endocyclic enamino esters.

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