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SYNTHETIC APPROACH TOWARD MITOMYCINS. EFFICIENT SYNTHESIS OF MITOSANE PRECURSORS FROM (2,4-PENTADIENYL)-p-QUINONES[1)]

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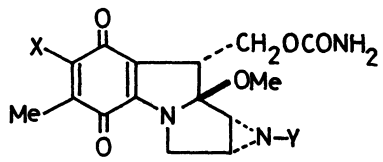
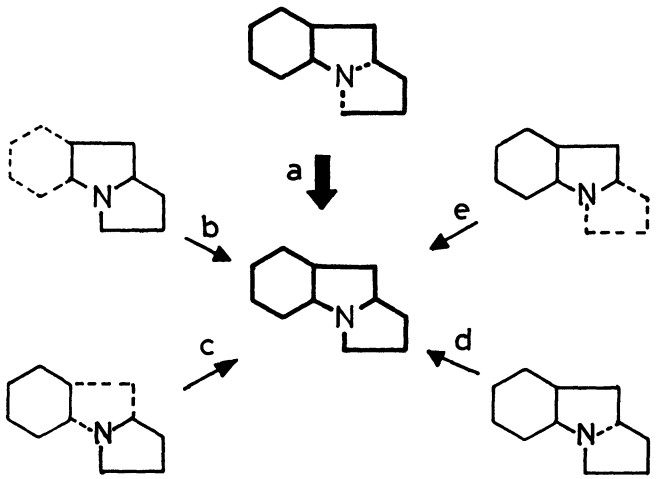
Introduction of 2,4-pentadienyl side chain to halogenated p-quinones is performed with (2,4-pentadienyl)trimethylstannane to afford 2-halo-3-(2,4-pentadienyl)-1,4-quinones. Pyrolytic decomposition of the corresponding azidoquinones derived from the obtained haloquinones affords 3*H*-pyrrolo[1,2-*a*]indol-5,8-dione derivatives in good yields.

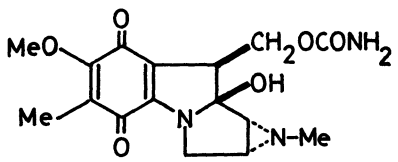
Since the first success on the isolation of mitomycin A (1),[2)] B (2),[2)] C (3),[3)] and porfiromycin (4)[4)] at the late 1950's, these unique quinones with complex functionality have attracted much attention of chemists.[5)] Especially mitomycin C was shown to have the strongest and broadest activity against tumors and has been used in practice in cancer chemotherapy.[6)] Total synthesis of mitomycins was achived by Kishi and co-workers.[7)] Development of a rapid entry to the general ring system is still urgent subject allowing for structural modification for the mitomycin skelton.[8)] Reported strategies toward synthesis of pyrrolo[1,2-*a*]-indole are devided into four patterns (Scheme 1, paths **b-e**), each of which involves the stepwise construction of the required ring system. We recently developed a new and efficient route (path **a**), which contains simultaneous double ring cyclization and leads to a shortening of reaction processes.



1: mitomycin A
X=OMe, Y=H
3: mitomycin C
X=NH_2, Y=H
4: porfiromycin
X=NH_2, Y=Me

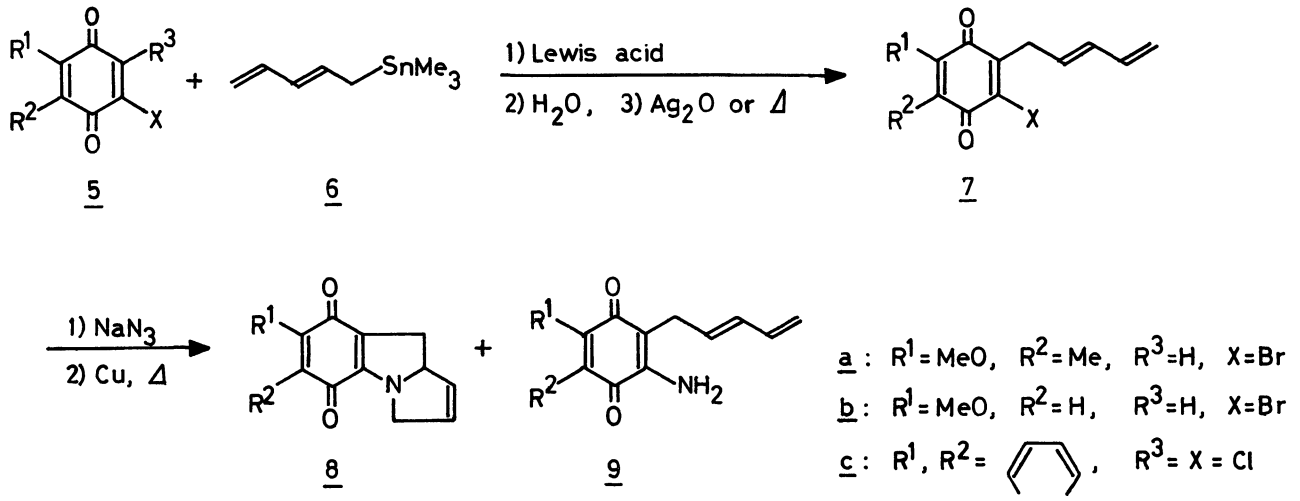
Scheme 1[5c)]





2: mitomycin B

Scheme 2



We described herein our successful results in pyrrolo[1,2-*a*]indol-5,8-dione synthesis.

Our synthetic scheme is based on 2-halo-3-(2,4-pentadienyl)-1,4-quinones (7), which were easily obtained by Lewis acid mediated 2,4-pentadienylation of p-quinones with (2,4-pentadienyl)trimethylstannane (6) and followed by mild oxidation.[9] Synthesis of 7a was shown as a typical example. To a CH_2Cl_2 solution (10 ml) of a quinone 5a[10, 11] (1.0 mmol) 2M $AlCl_3$ (3.0 mmol, as etherate) was added at -78°C under N_2 atmosphere followed by the dropwise addition of the stannyl reagent 6 (1.2 mmol). After 0.5 h the reaction mixture was quenched with water, aqueous layer was extracted several times with CH_2Cl_2. Organic extracts were dried over $MgSO_4$ and then concentrated *in vacuo*. After the residue was treated with Ag_2O in ether, chromatographic separation afforded the quinone 7a[10] in 63% yield.

Similar procedure was applied to a quinone 5b to afford 7b[10] in 58% yield. Synthesis of 7c was performed by modified method. After reaction of 5c with 6,[12] the crude product obtained was refluxed in chlorobenzene for 1 h to give 7c[10] in 40% overall yield.

The 2-halo-3-(2,4-pentadienyl)quinones (7) were easily converted to the corresponding azides[10] in almost quantitative yields by treatment with sodium azide.[13] Pyrolytic decomposition of the azidoquinone was performed under reflux of a benzene solution for 4 h in the presence of copper powder[14] to afford two products after chromatographic separation. Surprisingly, the main fraction was 7-methoxy-6-methyl-3*H*-pyrrolo[1,2-*a*]indol-5,8-dione (8a)[15] (53%), dark purple crystals, mp 119-121°C. The detailed structure was confirmed by 270 MHz ^{1}H-NMR (Fig. 1 and Table 1) and other spectroscopic methods. The minor product was assigned to be the corresponding aminoquinone 9a[10] (35%). The other azidoquinones afforded the corresponding indolquinones 8b[15] (45%) and 8c[15] (43%), respectively. Photochemical (λ>360 nm) and pyrolytic decomposition with metal salts ($AgBF_4$, $RhCl_3$, $Rh(OAc)_3$ etc.) were not effective to the formation of 8. Although the present reaction has not been mechanistically clarified, it could presumably proceed *via* trapping an intermediary nitrene by a diene.[16]

This route including new cyclization reaction is clearly one of the most promising route to mitosane. The total synthesis of mitomycins is now under way.

Fig. 1. 270 MHz ^{1}H-NMR Spectrum of 8a (in $CDCl_3$)

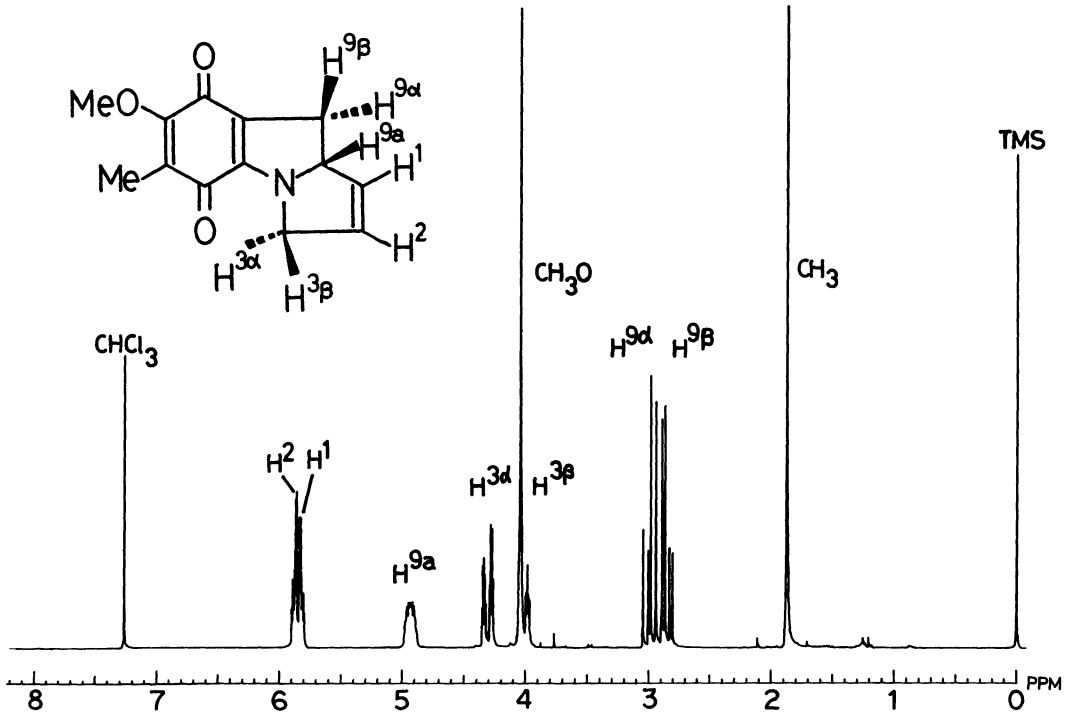


Table 1. Chemical Shifts and Coupling Constants of 8a (in $CDCl_3$)

Proton	Chemical shift (δ, ppm)	Coupling constant (Hz)
CH_3	1.87 (s)	
CH_3O	4.04 (s)	
H^1	5.82 (m)	$J_{1,2}$=6.2, $J_{1,3\alpha}$=1.9, $J_{1,3\beta}$=2.6
H^2	5.87 (m)	$J_{2,3\alpha}$=1.6, $J_{2,3\beta}$=1.3
$H^{3\alpha}$	4.30 (dq)	$J_{3\alpha,3\beta}$=16.1, $J_{3\alpha,9a}$=3.6
$H^{3\beta}$	4.01 (dq)	$J_{3\beta,9a}$=4.2
$H^{9\alpha}$	2.85 (dd)	$J_{9\alpha,9\beta}$=16.8, $J_{9\alpha,9a}$=6.9
$H^{9\beta}$	2.99 (dd)	$J_{9a,9\beta}$=11.5
H^{9a}	4.93 (m)	

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10) This substance gave satisfactory elemental analysis and/or ms spectra and IR and ^{1}H-NMR spectra consisted with the assigned structure.
11) We have recently developed a synthetic method of 5a from 2,6-dimethoxytoluene by the following sequence of reactions, i.e., (1) $Cl_2CHOCH_3/TiCl_4/CH_2Cl_2/0°C$, (2) Br_2/dioxane/r.t., (3) $H_2O_2/0°C$, (4) $NaOCH_3$/MeOH.
12) In this stage, 1,2 addition product to quinone carbonyl group was obtained. Subsequent allylic rearrangement was inhibited. Mechanistic studies concerning this field, see: Y.Naruta, J. Am. Chem. Soc., 102, 3774 (1980).
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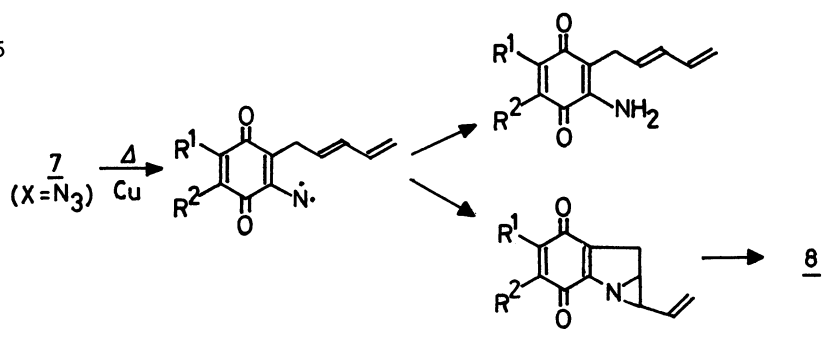
14) Cu powder was heated at ∿200°C under H_2 stream prior to use.
15) Physical and spectroscopic data of typical compounds are shown below; 8a: ^{13}C-NMR ($CDCl_3$) δ 8.28(s), 30.88(t), 56.65(t), 61.23(q), 71.22(d), 119.22(s), 124.63(s), 128.35(d), 130.88(d), 154.09(s), 157.60(s), 179.78(s), 183.32(s); IR (KBr) 1650(s), 1630(s), 1580(s), 1400cm^{-1}(s); UV λ_{max}(log ε) 220(4.10), 324(3.80), 536nm(3.11); MS(20eV) m/e 231(M^+). 8b: purple crystals, mp 112°C, decomp.; 100 MHz ^{1}H-NMR ($CDCl_3$) δ 2.85(dd,1H,J=11.5,17Hz), 3.09(dd,1H,J=10.5,17Hz), 3.80(s,3H), 4.10(dd,1H,J=3.5, 16Hz), 4.37(dd,1H,J=4.5,16Hz), 4.97(m,1H,J=3.5,4.5,7.5,10.5Hz), 5.85(br,2H), 5.60 (s,1H),; IR(KBr) 1655(vs), 1630cm^{-1}(vs); MS(70eV) m/e 217(M^+). 8c: red purple crystals, mp 135-136°C; 100 MHz ^{1}H-NMR($CDCl_3$) δ 2.96(dd,1H,J=8,18Hz), 3.18(dd,1H,J=11, 18Hz), 4.06(dd,1H,J=3.5,16Hz), 4.42(dd,1H,J=4.5,16Hz), 4.92(m,1H,J=3.5,4.5,8,11Hz), 5.85(br,2H), 7.58(m,2H), 7.95 (m,2H); IR(KBr) 1665(vs), 1625 cm^{-1}(vs); MS(20eV) m/e 237 (M^+).
16) Formation of aminoquinone 9 as by-product is suggestive of nitrene mechanism. Intermediary vinylaziridine would rearrange to 8.



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