SYNTHESIS OF NOVEL QUINOLINE QUINOLS AND ISOQUINOLINE QUINOLS FROM QUINONES

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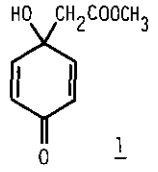
Abstract- Quinoline quinols and Isoquinoline quinols were synthesized from the corresponding quinoline quinones and isoquinoline quinones, respectively, by the series of reactions, protection of one carbonyl with trimethylsilyl cyanide, reaction with methyl lithium or the enolate of methyl acetate, and hydrolytic deprotection with aqueous silver fluoride.

There has been a particular interest in the chemistry and biological activity of quinols. Up to the present, the antitumor active benzoquinol, jacaranone (1) was isolated from Jacaranda caucana[1], and a p-quinol antibiotic metabolite, 2,6-dibromo-4-carbamoylmethyl-4-hydroxy-2,5-cyclohexadien-1-one (2) was obtained from the sponge Verongia cauliformis.[2] Because of the relatively high biological activity of these simple benzoquinols, many synthetic methods of quinols have been developed. In principle there are two potentially attractive routes to the synthesis of p-quinols, one being the oxidation of the appropriately substituted phenol and the other being the regioselective nucleophilic addition of a carbon nucleophile to the quinone. The use of phenol oxidation methods as an effective means of producing p-quinols has been disappointing.[3] On the other hand, Evans et al. have developed the capability of regioselectively monoprotecting substituted p-quinones, and have demonstrated that such substrates are excellent general precursors to p-quinols.[4] This methodology has been applied to the synthesis of benzoquinols including 1 and 2, and naphthoquinols.[5-7] We wish to report here on the application of such methodology to the regioselective synthesis of quinoline and isoquinoline quinols unknown in the literatures. Thus,



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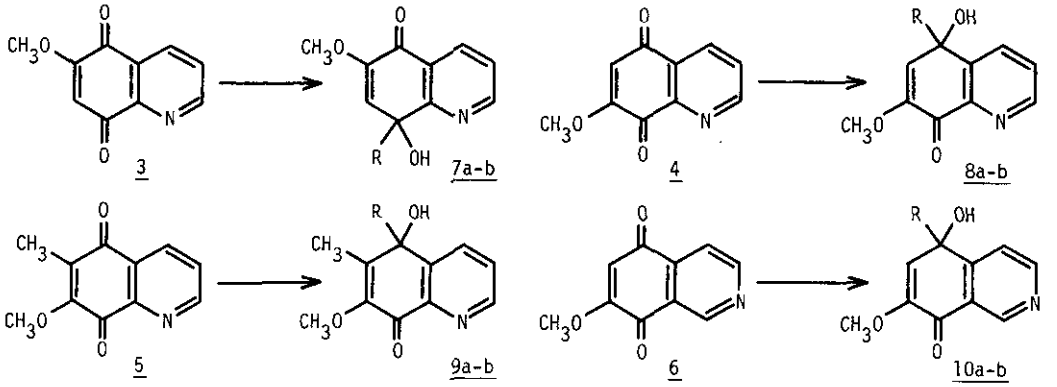


3 → 7a-b; 4 → 8a-b; 5 → 9a-b; 6 → 10a-b

a, R = CH_3, b, R = CH_2COOCH_3

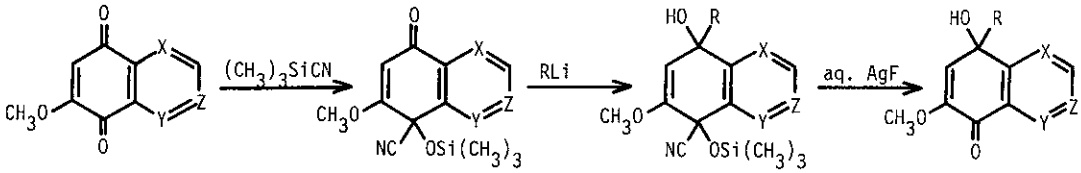
Table 1. Quinoline and Isoquinoline Quinols

	R	Yield [%]	mp [°C]	UV(EtOH)[a] λ_{max}[nm]	IR(KBr)[b] [cm^{-1}]	^{1}H-NMR($CDCl_3$)[c] [δ]
7a	CH_3	36.6	196-197	242(3.72) 276(3.53)	1675 3200	1.74(3H,s), 3.5-4.2(1H)*, 3.79(3H,s), 6.13(1H,s), 7.44(1H,dd,8,5), 8.43(1H,dd,8,2), 8.80(1H,dd,5,2)
7b	CH_2COOCH_3	55.1	151-152	240(3.75) 275(3.55)	1675 1735 3200	3.03(1H,d,14), 3.14(1H,d,14), 3.60(3H,s), 3.79(3H,s), 4.44(1H,s)*, 6.16(1H,s), 7.40(1H, dd,8,4), 8.35(1H,dd,8,2), 8.71(1H,dd,4,2)
8a	CH_3	30.0	192-193	239(3.77) 273(3.74) 305(3.43)	1680 3330	1.72(3H,s), 2.66(1H,s)*, 3.75(3H,s),5.99(1H,s), 7.53(1H,dd,8,4), 8.18(1H,dd,8,2), 8.75(1H,dd, 4,2)
8b	CH_2COOCH_3	25.9	188-189	240(3.73) 274(3.68) 305(3.36)	1690 1728 3160	3.06(2H,s), 3.43(3H,s), 3.73(3H,s), 6.18(1H,s), 7.66(1H,dd,8,5), 8.26(1H,dd,8,2), 8.66(1H,dd, 5,2)
9a	CH_3	37.0	144-146	236(3.86) 270(3.81) 295(3.71)	1662 3380	1.57(3H,s), 2.11(3H,s), 3.3-3.9(1H)*, 3.72(3H,s), 7.42(1H,dd,8,4), 8.17(1H,dd,8,2), 8.49(1H,dd,4,2)
9b	CH_2COOCH_3	48.7	158-159	238(3.91) 270(3.81) 297(3.67)	1670 1730 3320	2.12(3H,s), 3.01(2H,s), 3.39(3H,s), 3.72(3H,s), 4.5-5.0(1H)*, 7.45(1H,dd,8,5), 8.15(1H,dd,8,2), 8.50(1H,dd,5,2)
10a	CH_3	26.3	183-184	244(3.91) 282(3.60)	1675 3160	1.66(3H,s), 3.72(3H,s), 3.7-4.2(1H)*, 5.96 (1H,s), 7.61(1H,d,5), 8.62(1H,d,5), 9.01(1H,s)
10b	CH_2COOCH_3	41.4	185-186	244(3.93) 283(3.61)	1678 1718 3090	2.75(1H,d,16), 3.03(1H,d,16), 3.71(3H,s), 3.75(3H,s), 4.39(1H,s)*, 6.12(1H,s), 7.65(1H, d,5), 8.79(1H,d,5), 9.28(1H,s)

a) Log ε in parentheses. *b)* Only $\nu_{C=O}$ and ν_{O-H} are indicated.

c) No. of protons, multiplicities, and coupling constants(Hz) in parentheses. Asterisked protons are exchangeable with D_2O. The spectrum of 8b was measured in CD_3OD.

quinoline or isoquinoline quinone would have one of the carbonyl groups protected with trimethylsilyl cyanide, methyl lithium or the enolate of methyl acetate would be added to the other carbonyl, and hydrolytic deprotection with aqueous silver fluoride would generate the quinol.



(One of X, Y, and Z is N, others are C-H)

This approach was successful with quinoline quinones (3-5) and an isoquinoline quinone (6). When methyl lithium was used, only one isomer 7a-10a was obtained from the corresponding quinone 3-6, respectively, due to the strong directive effect of the methoxyl group during the protection with trimethylsilyl cyanide.[4] When the enolate of methyl acetate was used, the quinols 7b-10b were obtained in 26-55% yield. The structures of the quinols were completely consistent with their UV, IR, ^{1}H-NMR and MS spectra, as well as analytical data. These results are summarized in Table 1. The structure of the quinol 7a was further confirmed by an X-ray crystallographic analysis as shown in Fig. 1.

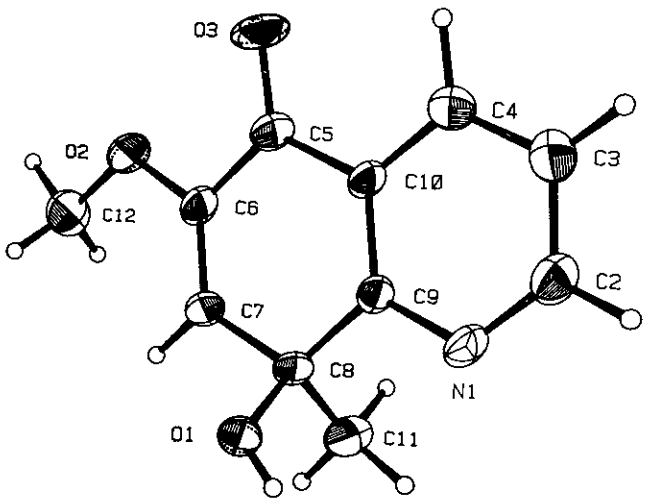


Fig. 1. Molecular Structure of the Quinoline Quinol (7a)

In summary, the present method should be generally applicable for the regioselective synthesis of heterocyclic quinols from the corresponding quinones possessing an electron directing group on the quinone ring.

We are currently investigating the synthesis of other heterocyclic quinols and biological activities of them.

EXPERIMENTAL

General Procedure for the Synthesis of Quinols 7-10. To a solution of 1 mmol of the quinone 3-6 in 5 ml of $CHCl_3$ was added 0.16 ml (1.2 mmol) of distilled trimethylsilyl cyanide and 8 mg of triphenylphosphine. The mixture was stirred for 4 hr. The solution was evaporated to dryness, dissolved in 5 ml of tetrahydrofuran(THF), cooled to -78°C, and then 1 mmol of methyl lithium was added at once. The solution was warmed to 0°C for 1 hr, and 53 mg (1 mmol) of NH_4Cl dissolved in the minimum amount of water was added. A portion of Na_2SO_4 was added, and the solution was filtered and evaporated. The residue was dissolved in 5 ml of THF, and a solution of 127 mg (1 mmol) of AgF in 0.5 ml of water was added. The mixture was stirred for 2 hr and a small amount of brine was added. After filtering and washing the residue with CH_2Cl_2, the solution was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated. The residue was chromatographed on a silica gel column. The obtained crude quinol 7a-10a was recrystallized from CH_2Cl_2-ether or ethyl acetate. The quinols 7b-10b were synthesized by using the same procedure for the synthesis of 7a-10a except that a solution of the enolate of methyl acetate prepared by means of the following method was used instead of methyl lithium. A solution of lithium diisopropylamide was prepared from 0.14 ml (1 mmol) of diisopropylamine and 1 mmol of n-butyllithium in 4 ml of dry THF. This solution was cooled to -78°C, and 0.08 ml (1 mmol) of methyl acetate was added and maintained at -78°C for 2 hr.

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