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THE REACTIONS OF N-HALOSUCCINIMIDES WITH 2-HYDROXY-3-(β-ALKYLVINYL)-1,4-NAPHTHOQUINONES[1]

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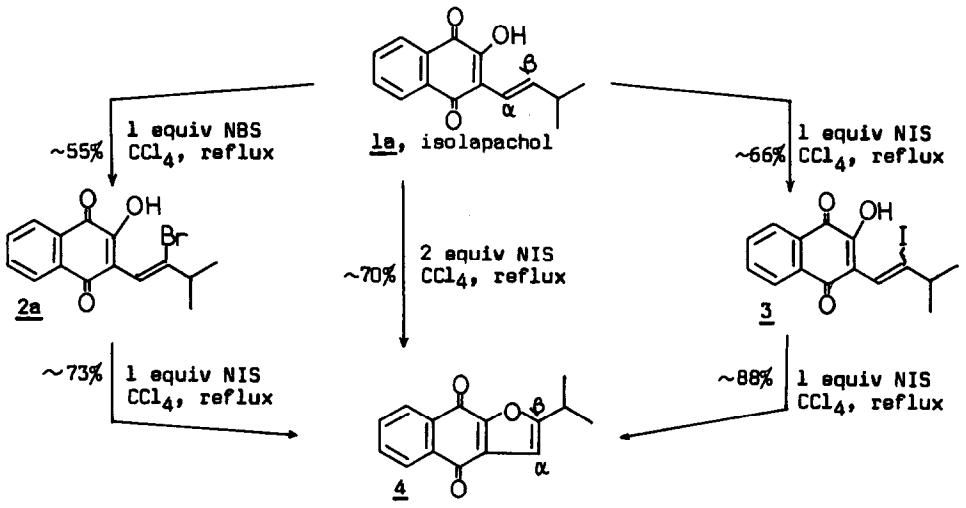
Our interest in modifying analogs of known antimalarial drugs[3] led us to investigate the reaction of various N-halosuccinimides with 2-hydroxy-3-(trans-β-alkylvinyl)-1,4-naphthoquinones. As seen in Scheme I, the reactions of equimolar quantities of either N-bromosuccinimide (NBS) or N-iodosuccinimide (NIS) with isolapachol (1a) in refluxing carbon tetrachloride yielded 2-hydroxy-3-(β-halo-β-isopropylvinyl)-1,4-naphthoquinones (e.g., 2a and mixture 3, respectively); the reaction of N-chlorosuccinimide (NCS) and 1a under similar conditions failed to give any product. Such examples of vinyl-hydrogen substitution by halogen are, to our knowledge, unprecedented in the chemistry of these oxidizing and halogenating agents.[4,5]

Scheme I



Inasmuch as the conversion of 1a→2a was carried out under conditions which customarily afford an allylic brominated product,[4] it was of interest[6] to examine also the NBS brominations of 2-hydroxy-3-(trans-β-alkylvinyl)-1,4-naphthoquinones having primary

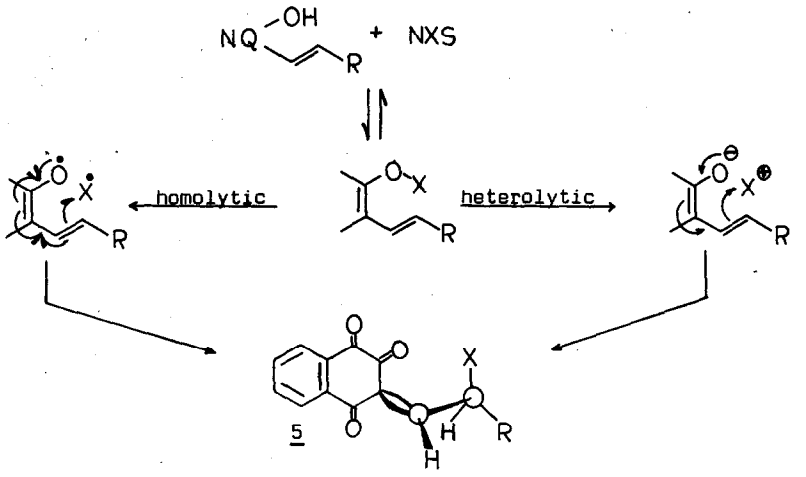
and secondary hydrogen in the allylic positions (note Table I). Substrates 1b and 1c [side chains: $-CH=CHCH_2CH_3$ and $-CH=CHCH_3$, respectively] provided analogous bromination products (e.g., 2b and 2c), each of which was characterized by the appearance of a singlet (or doublet, J = ~1 cps) for H_α in the vinyl region of its nmr spectrum. If, in any event, the halogen atom had been incorporated at the α-carbon of the side chain, one would expect the β-vinyl hydrogen to have appeared as a doublet with a coupling constant ≃6cps.[7]

The nmr spectra of 2a and 2b, which contain the more bulky $-CH(CH_3)_2$ and $-CH_2CH_3$ groups, were consistent with the formulation of each as a pure β-substituted geometrical isomer, while the spectrum of 2c ($-CH_3$ group) indicated that the sample was comprised of both β-bromo isomers. The physical data for the components of mixture 2c, which was separated by fractional crystallization, are recorded in Table I; the pertinent nmr signals (α-vinyl hydrogen and β-vinyl methyl hydrogens) of each of the isomers exhibited allylic coupling constants in the order of 1.0 cps. In the case of the inseparable iodination product 3, m.p. 95-111°, the nmr trace is the leading evidence for its characterization as a mixture of β-iodo isomers. The spectrum contained two sharp singlets for the α-hydrogen at 6.84 and 6.69 ppm (0.57 and 0.43 proton, respectively), two sets of doublets for the methyl resonances [$-CH(\underline{CH_3})_2$, J = 7 cps], and two sets of multiplets for the tertiary hydrogen [$-C\underline{H}(CH_3)_2$].

Although it is not clear whether an ionic or radical mechanism is operative for the initial insertion of halogen at the β-vinyl position (e.g., Chart I),** the observed stereoselectivity is plausibly explained by an intermediate such as 5. In the cases where the bulk of the alkyl group is much greater than that of halogen, the preferred conformation of 5 for the prototropic exchange step would lead to a cis relationship of halogen to hydroxynaphthoquinone. We emphasize, however, that the stereochemistry of the geometrically pure products (e.g., 2a and 2b) has not been rigorously ascertained, and that the contention for cis assignments is based merely on (1) a presumed mechanism which offers a basis for stereochemical integrity, and (2) the close similarity of the chemical shift parameters of side chain protons to those values observed for the corresponding protons in the starting materials.[8]

**The requisite formation of hypohalite as indicated in Chart I was substantiated by the fact that O-acetylisolapachol failed to undergo bromination (even in the presence of azoisobutyronitrile (AIBN)) under the normal conditions of the reaction.

Chart I



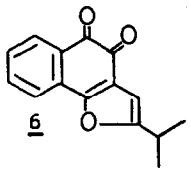
Exposure of isolapachol (1a) to two equivalents of NIS, and its β-halo derivatives (e.g., 2a and 3) to one equivalent of NIS, provokes a cyclization reaction leading predominantly to β-isopropylfurano-1,4-naphthoquinone (4).[9] Visual inspection of the reaction solutions containing either 1a or 3 indicated that the principal secondary products are succinimide and iodine. β-Iodoisolapachol (3), which is undoubtedly an intermediate in the conversion of 1a→4, required a full equivalent of NIS for ring closure and failed to give appreciable amounts of 4 when the cyclization was attempted using a catalytic quantity of NIS. In the absence of NIS, the cyclization of 3→4 could not be effected by either a catalytic quantity or a full equivalent of iodine.

In reviewing to date the cyclization reactions of 2-hydroxy-1,4-naphthoquinone derivatives, Ettlinger[10] and Thomson[11] note that concentrated, strong acid-induced cyclizations lead to a preponderance of ortho naphthoquinone derivative, unless the conditions** are such that the kinetic product, the ortho derivative, suffers rearrangement to its para naphthoquinone counterpart. In marked contrast to these examples, where cyclization to a para naphthoquinone apparently involves the intermediacy of

**Ettlinger[10] has shown in the case of the β-methyldihydropyranonaphthoquinones that the ortho derivative (pK_a -3.45), which is 800 times as basic as its para counterpart, affords the more stable of the two quinone cations. On the other hand, the para quinone is the more stable of the free quinones, and when less than 75% sulfuric acid is employed for cyclization or equilibration an appreciable quantity of the free para quinone is produced.

ortho derivative, the base-induced cyclization of chlorohydrolapachol [side chain: $-CH_2CH_2\underset{Cl}{C}(CH_3)_2$] gives directly the para naphthoquinone, α-lapachone, albeit in mixture with β-lapachone.[11,12] The non-specificity of this latter cyclization is not surprising if one recalls related examples of alkylation of anionic hydroxynaphthoquinones.[13]

The NIS-induced cyclization is of special interest in view of its nature to provide a high yield of linear furanonaphthoquinone 4. Closer examination of the reaction revealed that the corresponding ortho furanonaphthoquinone 6 was produced to the extent of 8-10% (crude yield after chromatographic separation), but we have been unable to establish the intermediacy of 6 in the production of 4. Thus, when the reaction of 1.0 equivalent of 1a and 2.0 equivalents of NIS, which normally gave ~0.7 equivalent of 4 and ~0.1 equivalent of 6, was conducted in the presence of 0.5 equivalent of 6, we isolated by chromatographic separation ~0.7 equivalent of 4 and ~0.6 equivalent of 6.



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As may be seen in Chart II, a potential mechanistic pathway, which closely follows principles proposed by Heusler et al,[14] utilizes hydroxynaphthoquinone radicals in important roles, and we suggest that the preponderance of 4 may reflect that a para hydroxynaphthoquinone radical (e.g., Ψ_{ABC}) is qualitatively the more stable of the two radicals (e.g., Ψ_{ABC} vs. Ψ_{DEF}).

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Chart II

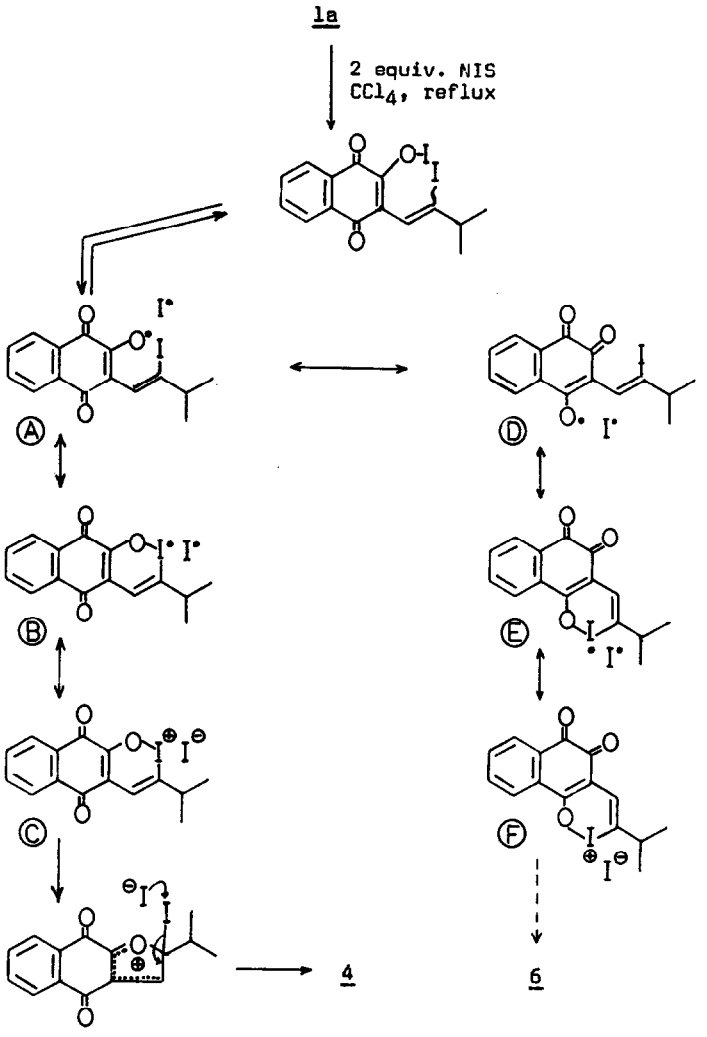
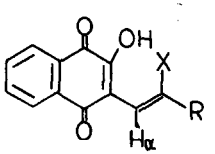


Table I

Substrate side chain[a]	Product side chain[b]	M.p.[c]	Nmr Data ($CDCl_3$, δ ppm)[d]
1a, $-CH=CHCH(CH_3)_2$			H_α,6.59; H_β,7.13; $\underline{CH}(CH_3)_2$,2.50; $CH(\underline{CH_3})_2$,1.13
	2a, $-CH=C(Br)CH(CH_3)_2$	132.5-136	6.57 ---- 2.50 1.10
1b, $-CH=CHCH_2CH_3$			H_α,6.54; H_β,7.10; $\underline{CH_2}CH_3$,2.32; $CH_2\underline{CH_3}$,1.12
	2b, $-CH=C(Br)CH_2CH_3$	152.5-155.5	6.55; ---- 2.35 1.14
1c, $-CH=CHCH_3$			H_α,6.60; H_β,7.13; CH_3,1.97
	2c, $-CH=C(\sim Br)CH_3$	115-119.5 185-187.5	cis 6.52 ---- 2.54 trans 6.66 ---- 2.26
	3, $-CH=C(\sim I)CH(CH_3)_2$	95-111	cis H_α,6.70(0.43p); trans H_α,6.86(0.57p); $CH(CH_3)_2$, 0.98(2.5p), 1.18(3.5p)

(a) S. C. Hooker, J. Am. Chem. Soc., 58, 1163 (1936); J. Chem. Soc., 69, 1356 (1896). The nmr spectra of these derivatives showed $J_{H_\alpha H_\beta}$ = 16-18 cps. (b) Satisfactory analyses have been obtained for these derivatives. (c) Melting points were determined on a Kofler microscope hot stage and are corrected. (d) Nmr spectra were measured on Varian HA-100 and Perkin-Elmer R-20 instruments.

Nomenclature: X = halogen
R = alkyl



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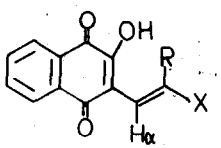

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(8) E. L. Eliel, "Stereochemistry of Carbon Compounds", pp. 335-336, McGraw-Hill Book Co., Inc., New York (1962).

(9) Contrasting to this NIS-induced cyclization, the mercuric acetate oxidation of isolapachol provided a high yield of β-isopropylfurano-1,2-naphthoquinone. K. H. Dudley and H. W. Miller, J. Org. Chem., 32, 2341 (1967).

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