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SYNTHESES OF α- AND β-LAPACHONES AND THEIR HOMOLOGUES BY WAY OF PHOTOCHEMICAL SIDE CHAIN INTRODUCTION TO QUINONE [1)]

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1,4-Naphthoquinone photochemically reacted with 3-methyl-2-butenal to give 2-(3-methyl-2-butenoyl)-1,4-naphthalenediol 3b, regiospecifically. The product 3b was successively treated with acid, with dichloroaluminum hydride, and finally with iron(III) chloride to derive in turn to cromanon 4b, dihydropyran 5b, and β-lapachone 6b. β-Lapachone was easily transformed to α-lapachone 7b by treating with acid. Likewise, from other α,β-unsaturated aliphatic aldehydes and 1,4-naphthoquinone α- and β-lapachone analogues were prepared.

Little was known about the photochemical behavior of 1,4-naphthoquinone in the presence of aldehydes.[2)] Investigating on the photochemical reaction of p-quinone, we found α,β-unsaturated aliphatic aldehydes reacted regio- and/or stereospecifically with photo-excited 1,4-naphthoquinone to give 2-(2-alkenoyl)-1,4-naphthalendiol, in contrast to 1,2-naphthoquinone.[3)]

Of naturally occurring quinones, α- and β-lapachones have long been known as their antimicrobial[4a)] and antitumor activity.[4b,c)]

In this paper we shall report on the new effective synthetic route of α- and β-lapachones and their homologues *via* the photochemical introduction of 2-alkenoyl group to quinone nucleus.

Photochemical reaction was undertaken in the following manner: 1,4-naphthoquinone 1 (14 mM) and α,β-unsaturated aliphatic aldehyde 2a - 2c (28 mM) dissolved in dry benzene were irradiated under an atmosphere of nitrogen through a Pyrex immersion cell and 1 cm layer of 0.2% 2,7-dimethyl-3,6-diazacyclohepta-1,6-dieneperchlorate solution by the light from a 300W high-pressure Hg arc lamp.

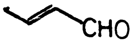
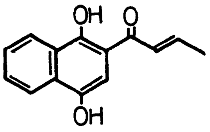
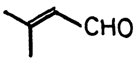
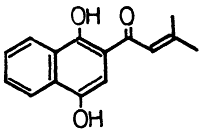
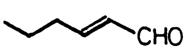
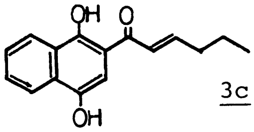
After irradiation for 20 - 25 h and the usual work-up, we obtained 2-(2-alkenoyl)-1,4-naphthalenediol in a fairly good yield as the sole product. As for the reactions of three alkene carbaldehydes 2a - 2c, the isolated yields of hydroquinones are summarized in Table 1. In each case no quinol monoesters 8 were detected. This reaction has been interpreted in term of the initial abstraction of formyl proton by photo-excited naphthoquinone followed by the in-cage coupling of the resulting acyl and semiquinone radicals.6)

It is outstanding difference that in a similer reaction (e.g. with crotonaldehyde) p-benzoquinone gives, in general, both alkenoylquinol and quinol monoester.7)

The compounds 3a and 3c were acetylated in Ac_2O-Py at room temperature to afford 9a and 9b, respectively. The α-protons of the alkenoyl group on 9a and 9b showed each ^{1}H-NMR coupling constant: $J_{H_\alpha-H_\beta}$ = 16 Hz, and IR absorptions at 975 and 955 cm^{-1}, respectively. So stereochemistry of the double bond in the side chain was assigned to *trans* indicating the photochemical reaction proceeded with retention of configuration.

After 3b was refluxed for 1.5 h with concentrated hydrochloric acid and tin(II) chloride in dioxan, 3-hydro-2,2-dimethyl-4-oxy-2H-naphtho[1.2-b]pyran-6-ol 4b was quantitatively yielded, yellow prisms, mp 185-186°C; IR (KBr) 3270, 1663, 1625, 1418 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ 1.55(s, 6H, $2CH_3$), 2.82(s, 2H, CH_2), 6.73(bs, 1H, OH), 7.41(s, 1H, aromatic-H), 7.4-8.3(m, 4H, aromatic-H). With three to four equivalents of dichloroaluminum hydride,8) 4b was quantitatively reduced to 3,4-dihydro-2,2-dimethyl-2H-

Table 1. The yields of 2-(2-alkenoyl)-1,4-naphthalendiols5)

Aldehyde	Photoadduct	mp , °C	Isolated * yield, %
 2a	 3a	167.0-7.5	53
 2b	 3b	151-2	43
 2c	 3c	167-8	48

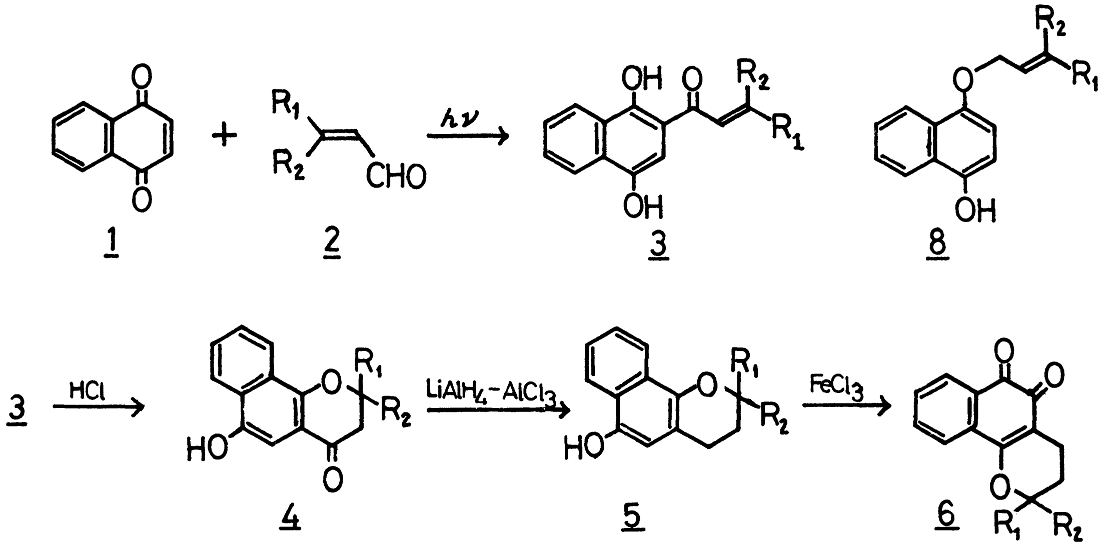
* Calculated on the basis of the consumed 1,4-naphthoquinone

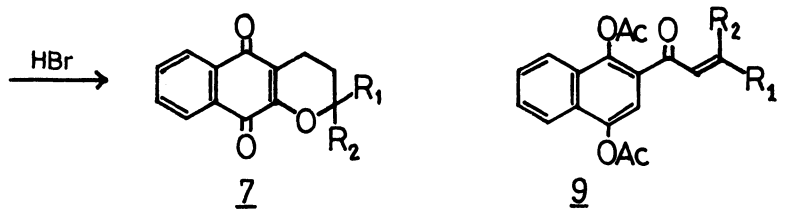
2,2-dimethyl-2H-naphtho[1,2-b]pyran-6-ol 5b, colorless needles, mp 86-87°C (lit. 74-75°C).[9] In methanol solution 5b was refluxed for 2h with an excess of iron(III) chloride to yield 3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]pyran-5,6-dion (β-lapachone) 6b, orange red needles, mp 155-156 °C (lit, 155-156 °C)[10]; IR(KBr) 1695, 1637, 1597 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 1.47(s, 6H, $2CH_3$), 1.86(t, 2H, CH_2), 2.48 (t, 2H, CH_2), 7.8(m, 3H, aromatic-H), 8.04(m, 1H, aromatic-H).

Thus, iron(III) chloride oxydation occurred exclusively at the position-5 of the compound 5b to give 1,2-quinone derivative 6b. A similar example was known about γ-tochopherol.[13]

Utilizing the method of Hooker,[11] we treated β-lapachone with 48% hydrobromic acid at 70°C to obtain 3,4-dihydro-2,2-dimethyl-2H-naphtho[2,3-b]pyran-5,10-dion (α-lapachone) 7b, yellow needles, mp 112-115°C(lit. 119°C)[10]; IR(KBr) 1675, 1638, 1610, 1572 cm^{-1}; ^1H-NMR($CDCl_3$):δ 1.44(s,6H,$2CH_3$), 1.80(t,2H,CH_2), 2.59(t,2H,CH_2), 7.64(m, 2H,aromatic-H), 8.02(m,2H,aromatic-H).

Starting from 3a and 3c, we obtained quantitatively β-lapachone analogues, 6a and 6c, respectively, by the similar reactions; 6a, mp 167-168°C(lit.164°C)[12]; IR(KBr)1695, 1645, 1570 cm^{-1}; ^1H-NMR($CDCl_3$): δ 1.56(d,3H,CH_3), 1.80(m,2H,CH_2), 2.60(m, 2H,CH_2), 4.40(m,1H,CH), 7.4-7.9(m,3H,aromatic-H), 8.05(m,1H,aromatic-H).





a, $R_1=CH_3$,$R_2=H$
b, $R_1=R_2=CH_3$
c, $R_1=CH_3CH_2CH_2$
$R_2=H$

6c, mp 117.5-118.5°C; IR (KBr) 1692, 1643, 1600cm^{-1}; ^{1}H-NMR ($CDCl_3$):δ 1.04(t, 3H, CH_3), 1.6-2.0(m, 6H, $3CH_2$), 2.60(m, 2H, CH_2), 4.20(m, 1H, CH), 7.60(m, 3H, aromatic-H), 7.98(m, 1H, aromatic-H).

On treating with acid 6a and 6c were effectively converted to α-lapachone analogues, 7a, mp 126.5-127.0°C; IR (KBr) 1668, 1645, 1614cm^{-1}; ^{1}H-NMR ($CDCl_3$):δ 1.50 (d, 3H, CH_3), 1.6-2.3(m, 2H, CH_2), 2.6(m, 2H, CH_2), 4.3(m, 1H, CH), 7.66(m, 2H, aromatic-H), 8.03(m, 2H, aromatic-H). 7c, mp 88-90°C; IR (KBr) 1665, 1640, 1595cm^{-1}; ^{1}H-NMR ($CDCl_3$):δ 1.00(t, 3H, CH_3), 1.4-2.2(m, 6H, $3CH_2$), 2.67(m, 2H, CH_2), 4.16(m, 1H, CH), 7.68(m, 2H, aromatic-H), 8.08(m, 2H, aromatic-H).

Through this route, starting from α,β-unsaturated aliphatic aldehydes with arbitrary chain length and 1,4-naphthoquinone, one can conveniently obtain cromanone, dihydropyran, α- and β-lapachone analogues.

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