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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.

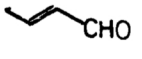
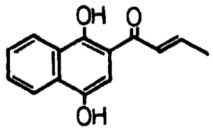
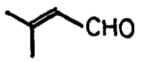
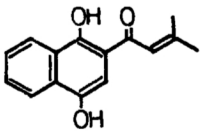
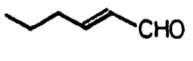
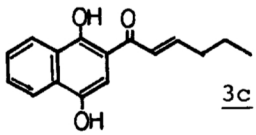
After irradiation for 20 - 25 h and the usual work-up, we obtained 2-(2-alkenoyl)-1,4-naphthalenediol in a fairly good yield as the sole product. As for the reactions of three alkene carbaldehydes 2a - 2c, the isolated yields of hydroquinones are summarized in Table 1. In each case no quinol monoesters 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, 1418cm^{-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-naphthalendiols[5)]

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

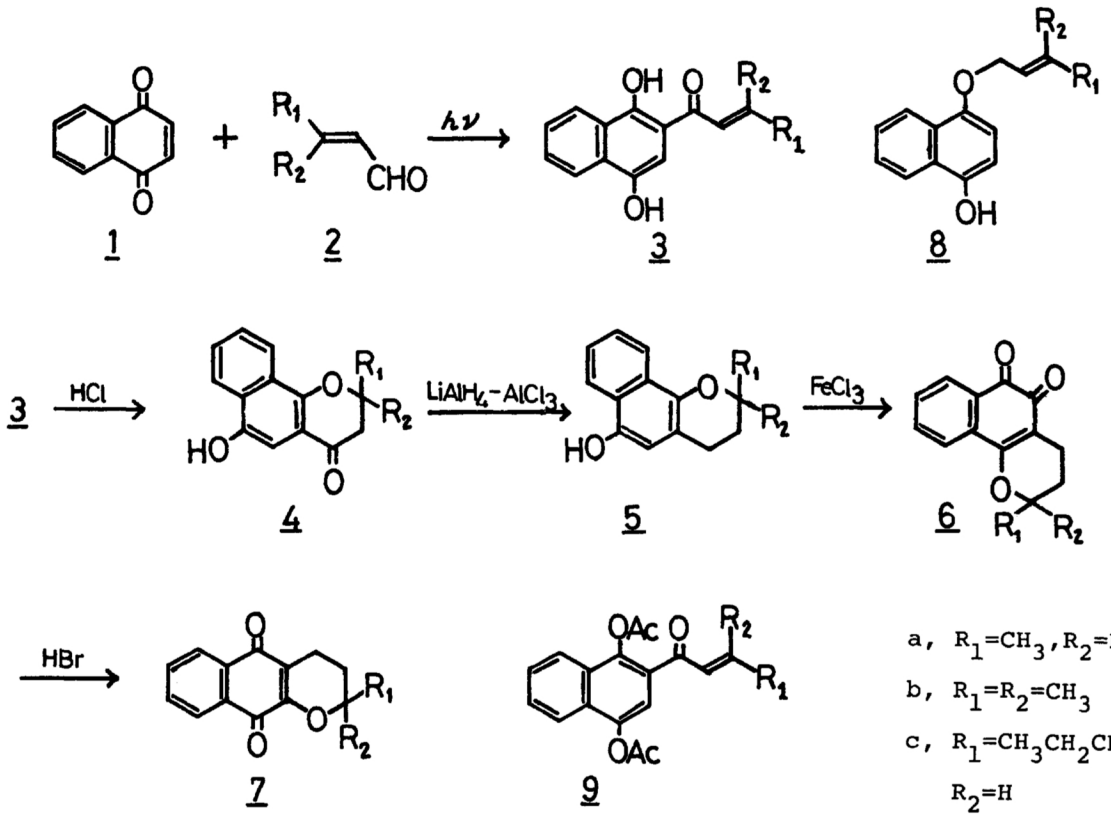
* Calculated on the basis of the consumed 1,4-naphthoquinone

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}; ^{1}H-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}; ^{1}H-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}; ^{1}H-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).



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.

References

1) Synthesis of naturally occurring quinones. Part 1.
2) L.M.Bruce, Quart. Rev., 21, 405 (1967); G.O.Schenck and G.Koltzenburg, Naturwiss. 41, 452 (1954).
3) A.Takuwa, Bull. Chem. Soc. Jpn., 49, 2790 (1976).
4) (a) O.Goncalves de Lima, I.Lencio d'Albaquerque, Clausius Goncalves de Lima and M.H.Dalia Maria, Rev. Inst. Antibiot. Univ. Recife, 4, 3 (1962) (b) I.Leoncio d'Albuquerque, ibid., 8, 73 (1968); (c) O.Goncalves de Lima, I.Lencio d'Albuquerque, A.Lacerda and D.G.Martins, ibid., 8, 89 (1968).
5) Satisfactory (a) spectroscopic, (b) mass spectroscopic, and/or (c) analytical data were obtained for all products.
6) K.Maruyama and Y.Miyagi, Bull. Chem. Soc. Jpn., 47, 1303 (1974).
7) J.M.Bruce and E.Cutts, J. Chem. Soc., C, 1966, 449.
8) R.F.Nystrom and C.R.A.Berger, J. Am. Chem. Soc., 80, 2896 (1958).
9) H.Inouye, T.Hayashi and T.Shingu, Chem. Pharm. Bull., 23, 392 (1975).
10) R.H.Thomson, "Naturally Occurring Quinones", 2nd Ed. Academic Press, New York(1971).
11) S.C.Hooker, J. Am. Chem. Soc., 58, 1168 (1936).
12) L.F.Fieser, lbid., 49, 857 (1929).
13) P.W.R.Eggitt and F.W.Norris, J. Sci. Food Agr., 7, 493 (1956).

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