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REGIOSELECTIVE SYNTHESIS OF D-RING SUBSTITUTED BENZ[a]ANTHRACENES BY ONE-POT PHOTOCHEMICAL REACTION

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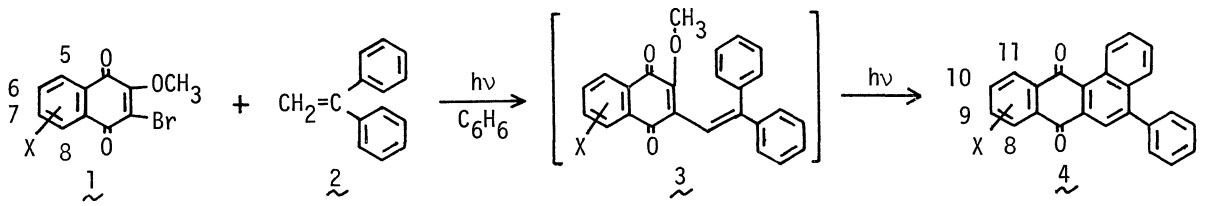
Benz[a]anthracene-7,12-diones containing methoxy group on the 8-, 9-, 10-, and/or 11-positions(D-ring) were synthesized regioselectively by one-pot photochemical reaction of 2-bromo-3-methoxy-1,4-naphthoquinone derivatives with 1,1-diphenylethylene.

To test the carcinogenic activity of benz[a]anthracenes, many efforts have been directed toward the synthesis of their possible metabolic products.[1] Among the available synthetic routes one-pot synthesis is much attractive for its simplicity and a relative high yield of the aimed product, compared with the multi-step one.[2] The one so far reported involves the thermal Diels-Alder reaction of substituted 1,4-naphthoquinones with styrenes.[3] However, the regioselectivity of the condensation products was quite discouraging.

Here, one-pot regioselective synthesis of the 8-, 9-, 10-, and/or 11-methoxybenz[a]anthracene-7,12-diones is described by applying our photochemical reaction of substituted 2-halogeno-1,4-naphthoquinones.[4] As a typical example, a benzene solution (25 ml) of 2-bromo-3,5-dimethoxy-1,4-naphthoquinone 1a[5] (0.5 mmol) and 1,1-diphenylethylene 2 (1.0 mmol) was irradiated with a high-pressure Hg lamp (300 W) in the presence of pyridine (0.5 mmol) at room temperature without any effort to exclude oxygen. Within about 10 h, the starting quinone was consumed completely. Purification of the reaction mixture by column chromatography on silica gel gave orange needles, 11-methoxy-5-phenylbenz[a]anthracene-7,12-dione 4a, exclusively (yield, 36%).[6] Similarly, other 2-bromo-3,x-polymethoxy-1,4-naphthoquinones 1b-e gave successfully the corresponding methoxybenz[a]anthracene-7,12-diones 4b-e in a regioselective manner in the photochemical reaction with

1,1-diphenylethylene 2 (Scheme I). Physical properties of the products obtained are shown in Table 1. They are all compatible with the corresponding structures. The position of the methoxy group, e.g., for 4a, was confirmed by



a:X=5-CH_3O
b:X=6-CH_3O
c:X=7-CH_3O
d:X=8-CH_3O
e:X=6,8-CH_3O

a:X=11-CH_3O
b:X=10-CH_3O
c:X= 9-CH_3O
d:X= 8-CH_3O
e:X=8,10-CH_3O

Scheme I

Table 1. The Physical Properties of Methoxybenz[a]anthracene-7,12-diones.

Benz[a]anthracene-7,12-dione	11-Methoxy-(4a)	10-Methoxy-(4b)	9-Methoxy-(4c)	8-Methoxy-(4d)	8,10-Dimethoxy-(4e)
Starting 2-Bromo-1,4-naphthoquinone	3,5-Dimethoxy-(1a)	3,6-Dimethoxy-(1b)	3,7-Dimethoxy-(1c)	3,8-Dimethoxy-(1d)	3,6,8-Trimethoxy-(1e)
Yield(%)	36	51	46	37	45
mp(°C)	147-148	204-205	201-202	213-215	245-247
NMR,δ ($CDCl_3$)	4.03(3H,s) 7.0-8.0(11H,m) 8.16(1H,s) 9.37(1H,dd, J=2,7 Hz)	3.92(3H,s) 7.1-8.2(11H,m) 8.25(1H,s) 9.70(1H,d, J=9 Hz)	3.90(3H,s) 7.1-8.1(11H,m) 8.2(1H,s) 9.75(1H,d, J=8 Hz)	3.97(3H,s) 6.8-8.0(11H,m) 8.23(1H,s) 9.60(1H,d, J=8 Hz)	3.93(3H,s) 3.95(3H,s) 7.1-8.0(10H,m) 8.25(1H,s) 9.59(1H,d, J=9 Hz)
IR,cm^{-1}(KBr)	1650(C=O)	1655(C=O)	1665(C=O)	1655(C=O)	1650(C=O)
UV max,nm(log ε) ($CHCl_3$)	403(3.23) 362(3.16) 338(2.99) 292(4.01)	425(sh)(3.44) 380(3.87) 344(3.90) 292(4.67)	440(sh)(3.63) 425(3.66) 383(3.56) 346(3.93) 299(4.33)	392(3.99) 298(4.50) 289(4.56)	446(sh)(3.38) 392(4.06) 318(sh)(4.06) 293(4.69)
Anal. Found	C,82.33 H,4.29	C,82.77 H,4.47	C,82.35 H,4.42	C,82.31 H,4.48	C,79.12 H,4.32
Calcd.	C,82.40 H,4.43 ($C_{25}H_{16}O_3$)	C,82.40 H,4.43 ($C_{25}H_{16}O_3$)	C,82.40 H,4.43 ($C_{25}H_{16}O_3$)	C,82.40 H,4.43 ($C_{25}H_{16}O_3$)	C,79.18 H,4.60 ($C_{26}H_{18}O_4$)
MS,m/e	364(M^+)	364(M^+)	364(M^+)	364(M^+)	394(M^+)

analyzing the ^{1}H-NMR chemical shifts of the ring protons induced by addition of shift reagent as Eu(fod)$_3$. Although the intermediate 3 has not been isolated in this work,[7] the regioselective condensation to benz[a]anthracene-7,12-diones may be understood in terms of the two-step condensation mechanism as depicted in Scheme I.

Methoxybenz[a]anthracene-7,12-diones thus obtained were hydrolyzed to the corresponding hydroxybenz[a]anthracene-7,12-diones. The hydrolysis of 4a (0.1 mmol), for example, was performed by refluxing it in an acetic acid solution (10 ml) in the presence of hydrobromic acid (47%, 1 ml) for 1 h, giving 11-hydroxy-5-phenylbenz[a]anthracene-7,12-dione 5a as orange needles (yield, 80%).[8]

Thus, the present photochemical reaction provides us a facile regioselective synthetic route to D-ring substituted benz[a]anthracene-7,12-diones, which, in turn, can readily be reduced to benz[a]anthracenes or transformed to 7,12-dimethylbenz[a]anthracenes.[3a]

References and Notes.

1) The carcinogenicity of 7,12-dimethylbenz[a]anthracenes was suggested to originate from their oxidative metabolites on the 8-, 9-, 10-, and/or 11-positions (D-ring). cf., P.Sims, Biochem.Pharmacol., 19, 795 (1970).

2) a) C.E.Moreal and V.Alks, J.Chem.Eng.Data, 22, 118 (1977).
b) J.Pataki and P.Ballick, ibid., 22, 114 (1977).
c) M.S.Newman and S.Kumar, J.Org.Chem., 43, 370 (1978).
d) M.S.Newman , J.M.Khana, K.Kanakarijan, and S.Kumar, ibid., 43, 2553 (1978).

3) a) W.B.Manning, G.M.Muschik, and J.E.Tomaszewski, ibid., 44, 699 (1979).
b) W.B.Manning, Tetrahedron Lett., (1979) 1661.

4) The previous reports on this photochemical reaction:
a) K.Maruyama and T.Otsuki, Chem.Lett., (1975) 87.
b) K.Maruyama, T.Otsuki, and K.Mitsui, Bull.Chem.Soc.Jpn., 42, 2361 (1976).
c) K.Maruyama, T.Otsuki, and K.Mitsui, J.Org.Chem., 45, 1424 (1980).

5) 2-Bromo-3,x-polymethoxy-1,4-naphthoquinones were synthesized by bromination of the appropriate polymethoxy-1,4-naphthoquinones with molecular bromine in acetic acid/sodium acetate: 2-Bromo-3,5-dimethoxy-1,4-naphthoquinone (1a):mp 138-139°C. 2-Bromo-3,6-dimethoxy-1,4-naphthoquinone (1b): mp 138-139°C. 2-Bromo-3,7-di-

methoxy-1,4-naphthoquinone (1c): mp 165-166°C. 2-Bromo-3,8-dimethoxy-1,4-naphthoquinone (1d): mp 191-192°C. 2-Bromo-3,6,8-trimethoxy-1,4-naphthoquinone (1e): mp 183-185°C. The spectroscopic properties of these 2-bromo-3,x-polymethoxy-1,4-naphthoquinones are satisfactory. Syntheses of these polymethoxy-1,4-naphthoquinones subjected to the bromination were described in the literatures: J.M.Lyons and R.H.Thomson, J.Chem.Soc., (1953) 2910, B.W. Bycraft and J.C.Roberts, ibid., (1962) 2063, R.H.Thomson, J.Org.Chem., 13, 870 (1948).

6) Resinous matters produced in this photochemical reaction can be removed by this operation.

7) Formation of the intermediate 3, though not isolated in this work, was detected at the earlier stage of the reaction by TLC analysis of the reacting mixture. Isolation of the intermediate 3 was described elsewhere (see ref. 4c). The intermediate 3 was found to cyclize quantitatively to the corresponding benz[a]-anthracene-7,12-dione derivative upon irradiation.

8) The physical properties of 5a: mp 214-216°C. NMR($CDCl_3$):δ;7.25-8.00ppm(11H,m), 8.27(1H,s), 9.83(1H,d,J=8 Hz), 12.85(1H,s). IR(KBr): 1665 cm^{-1}. UV max($CHCl_3$): 460nm(logε:3.77), 441(3.78), 379(3.49), 298(4.41). MS:m/e; 350(M^+). Anal. Found:C,82.34;H,4.12. Calcd. for $C_{24}H_{14}O_3$:C,82.27;H,4.03.

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