SUBSTITUTED 6-ETHYNYL-1,4-NAPHTHOQUINONES

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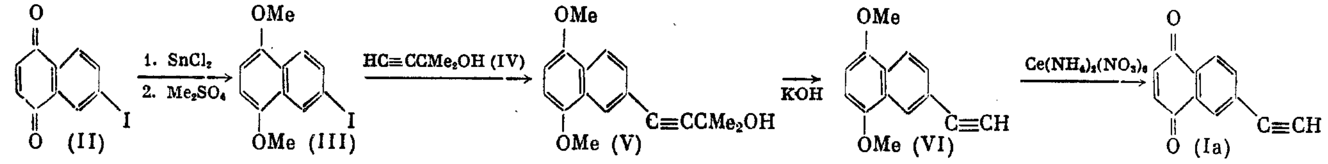
UDC 542.91:547.655.6

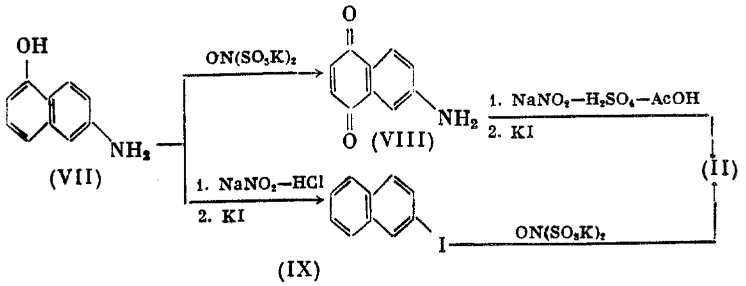
Ethynylquinones are promising intermediates in the synthesis of quinoid compounds. In previous work [1, 2], we described the preparation of 5-ethynyl-1,4-naphthoquinone and its derivatives and, in the present work, we synthesized 6-ethynyl-1,4-naphthoquinones (I).

Ethynylnaphthoquinone (Ia) was obtained from 6-iodo-1,4-naphthoquinone (II) similarly to the 5-ethynyl isomer [1]:



Iodide (II) was reduced by $SnCl_2$ in dilute methanolic HCl and the dihydroxy compound formed was methylated with Me_2SO_4 in aqueous methanolic NaOH to give dimethoxynaphthalene (III) in 55.5% overall yield, which was condensed with 2-methyl-3-butyn-2-ol (IV) using the $Pd(PPh_3)_2\cdot Cl_2-CuI-Et_3N$ catalytic system (Table 1). Acetylenic alcohol (V) was cleaved by the action of KOH powder in toluene at 100°C to give ethynylnaphthalene (VI) and Me_2CO. Oxidation of (VI) by $Ce(NH_4)_2(NO_3)_6$ in acetonitrile at 20°C to give ethynylquinone (Ia).

Starting iodide (II) was synthesized from 6-amino-1-naphthol (VII), which was oxidized by Fremy's salt to give 6-amino-1,4-naphthoquinone (VIII) in 69% yield and then the amino group was replaced by iodine to give (II) in 76% yield or (VIII) was initially converted to 6-iodo-1-naphthol (IX) in 44% yield and then (IX) was oxidized to give (II) in 71.5% yield.



Fremy's salt is a specific oxidizing agent to convert 1-naphthols and 1-naphthylamines to quinones [3]. Thus, we expected the selective oxidation of acetylenic 1-naphthol derivatives by this reagent with retention of the triple bond, which permits a significant shortening of the pathway for the synthesis of 6-ethynyl-substituted 1,4-naphthoquinones (I). Indeed, substituted ethynylquinones (Ib) and (Ic) (Table 1) are easily obtained by the condensation of (IX) with (IV) and phenylacetylene (X) and subsequent oxidation of (XIb) and (XIc). Product (XIb) was cleaved similarly to (V) and ethynylnaphthol (XIa) was oxidized to give quinone (Ia) (see scheme on following page).

EXPERIMENTAL

The PMR spectra were taken on a Varian XL-200 spectrometer in $CDCl_3$. The IR spectra were taken on an IK-20 spectrometer in $CHCl_3$.

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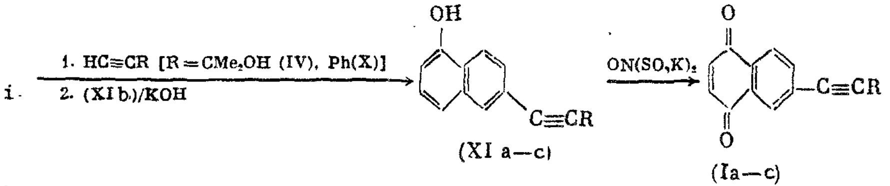
0568-5230/88/3702-0404$12.50

TABLE 1. Product Indices

Compound	Yield, %	Mp, °C	Chemical formula	Found/Calculated, % C	Found/Calculated, % H	PMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}
(V)	97,7	67–68 (subl.)	$C_{17}H_{18}O_3$	75,56 75,53	6,72 6,71	1,65 (CH_3-C), 2,42 br (OH), 3,91, (OCH_3), 6,65 ($H^{2,3}$) 7,48 d (H^7), 8,12 d (H^8), 8,31 (H^5)	2220 ($C=C$), 3600 and 3430 br (OH)
(VI)	87,8	83,5–85 (hexane)	$C_{14}H_{12}O_2$	79,27 79,22	5,61 5,70	3,13 ($HC\equiv C$), 3,93 (OCH_3), 6,69 ($H^{2,3}$) 7,54 d.d (H^7), 8,14 d (H^8), 8,40 d (H^5)	2115 and 3315 ($H-C\equiv C$)
(XIa)	53,3	114–115 (hexane)	$C_{12}H_8O$	85,44 85,69	4,92 4,79	3,15 ($HC=C$), 4,60 br (OH), 6.83 d (H^2), 7,30–7,45 m (H^3, $H^{4(7)}$), 7,99 (H^5), 8,14 d (H^8)	2115 and 3300 ($H-C\equiv C$) 3595 and 3300 br (OH)
(XIb)	70,7	116–117 (benzene–hexane)	$C_{15}H_{14}O_2$	79,35 79,62	6,43 6,24	1,66 (CH_3), 2,18 br, 5,72 br (OH), 6,85 d (H^2) 7,30–7,40 m (H^3, $H^{4(7)}$), 7,45 d ($H^{7(4)}$), 7,89 (H^5), 8,12 d (H^8)	3600 and 3300 br (OH)
(XIc)	79,5	151–152 (benzene-hexane)	$C_{18}H_{12}O$	88.00 88,50	5.02 4.95	5,15 br (OH), 6,82 d (H^2), 7,30–7,45 m ($H^{3,4,7}$, $2H_{cyl}$) 7,55–7,6 m ($3H_{cycl}$), 8,01 (H^5), 8.15 d (H^8)	2210 ($C\equiv C$), 3590 and 3300 br (OH)
(Ia)	97,2 [from (VI)] 41,7 [from (IX)]	122–123 (benzene)	$C_{12}H_6O_2$	79.19 79,11	3.29 3,32	3,34 ($HC\equiv C$), 6,99 ($H^{2,3}$), 7,82 d.d (H^7) 8,04 d (H^8), 8,16 d (H^5)	2120 and 3315 ($H-C\equiv C$), 1680 ($C=O$)
(Ib)	50,0	99–100.5 (hexane)	$C_{15}H_{12}O_3$	75,02 74,99	5.27 5,03	1,62 (CH_3), 2,10 br (OH), 6,97 ($H^{2,3}$) 7.73 d.d (H^7), 8,01 d (H^8), 8,08 d (H^5)	2225 ($C\equiv C$), 3595 (OH), 1670 ($C=O$)
(Ic)	75.5	110–112 (benzene–hexane)	$C_{18}H_{10}O_2$	83.36 83,71	4.13 3.90	6,99 ($H^{2,3}$), 7.35–7,40 m and 7,50–7,60 m (Ph), 7,85 d.d (H^7), 8,06 d (H^8), 8,20 d (H^5)	2205 sh, 2230 ($C\equiv C$), 1670 ($C=O$)



R = H (a), CMe_2OH (b), Ph (c).

6-Iodo-1-1,4-naphthoquinone (II). A sample of 1.7 g $NaNO_2$ in 4 ml water was added to 2 g (VIII) in 70 ml acetic acid, 40 ml concentrated H_2SO_4, and 40 ml water at 10°C, stirred for 1 h, and carefully poured to a rapidly stirred mixture of 7 g KI in 200 ml water and 200 ml toluene heated to 60°C. Upon cooling, the organic layer was separated, washed with aqueous $NaHCO_3$, and dried over Na_2SO_4. Chromatography on silica gel in toluene gave 2.5 g (76.2%) (II), mp. 123-124°C (from benzene–hexane). Found, %: C 42.17; H 1.80; I 44.50. $C_{10}H_5IO_2$. Calculated, %: C 42.28; H 1.77; I 44.68. PMR spectrum (δ, ppm): 6.94 ($H^{2,3}$), 7.72 d (H^8), 8.08 d. d (H^7), 8.36 d (H^5).

6-Iodo-1-naphthol (IX). A sample of 3.2 g (VII) in a solution of 100 ml concentrated hydrochloric acid and 100 ml water was diazotized with 1.5 g $NaNO_2$ in 15 ml water over 1 h at 5°C. Then, 200 ml ether and 6.6 g KI in 50 ml water was added and the mixture was stirred for 1.5 h. Chromatography on silica gel with 1:1 chloroform–benzene as the eluent gave 2.5 g (44%) (IX), mp. 158-159°C (from benzene). Found, %: C 44.62; H 2.79; I 46.71. $C_{10}H_7IO$. Calculated, %: C 44.47; H 2.61; I 46.99.

6-Iodo-1,4-dimethoxynaphthalene (III). A sample of 1.5 g $SnCl_2$ in a solution of 10 ml concentrated hydrochloric acid and 50 ml water was added to 1 g (II) in 80 ml methanol with stirring, heated at reflux for 4 h, and methanol was distilled off in vacuum. The residue was cooled to 0°C. The precipitate was filtered off, dried in vacuum over KOH, and dissolved under argon in 50 ml methanol containing 50 mg $Na_2S_2O_4$. A sample of 1 ml Me_2SO_4 was added to the solution. Then, 0.3 g NaOH in 4 ml water was added gradually and the mixture was stirred for 30 min. An additional 0.5 ml Me_2SO_4 and 0.3 g NaOH in 4 ml water were introduced. The mixture was warmed to 30°C and stirred for 10 min. The mixture was poured into 50 ml toluene. Methanol was distilled off in vacuum. The residue was diluted with 50 ml toluene and 200 ml ether, washed with water, and dried over Na_2SO_4. Chromatography on alumina in toluene gave 0.6 g (55.5%) (III), mp 93-94°C (from hexane). Found, %: C 46.08; H 3.63; I 40.22. $C_{12}H_{11}IO_2$. Calculated, %: C 45.88; H 3.53; I 40.40. PMR spectrum (δ, ppm): 3.92 (OCH_3), 6.68 ($H^{2,3}$), 7.74 d.d (H^7), 7.92 d (H^8), 8.58 d (H^5).

6-(3'-Methyl-3'-hydroxybutyn-1'-yl)-1-naphthol (XIb). A sample of 1.4 g (IX), 0.7 g (IV), 53 mg $Pd(PPh_3)_2Cl_2$, and 26 mg CuI in 65 ml Et_3N in an argon atmosphere was stirred for 20 min at 55°C. The reaction was monitored by thin-layer chromatography on Silufol plates with $CHCl_3$–ether as the eluent. The mixture was diluted with 300 ml ether and filtered. The solvent was distilled off in vacuum. The residue was subjected to chromatography on silica gel with 1:1 chloroform–ether as the eluent to give 0.8 g (XIb). An analogous procedure gave (XIc) and (V) (Table 1).

1,4-Dimethoxy-6-ethynylnaphthalene (VI). A sample of 0.53 g (V) and 0.20 g powdered KOH in 65 ml abs. toluene was heated for 12 min at 100°C. The reaction was monitored by thin-layer chromatography on Silufol plates with chloroform elution. Upon cooling, the reaction mixture was filtered through silica gel to give 0.36 g (VI). Product (XIa) was obtained by analogy (Table 1).

6-Ethynyl-1,4-naphthoquinone (I). a) A sample of 3.60 g $Ce(NH_4)_2(NO_3)_6$ in 8 ml water was added over 20 min to 0.42 g (VI) in 28 ml acetonitrile, stirred for 30 min, diluted with 200 ml ether, washed with water, and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silica gel in benzene to give 0.35 g (Ia) (Table 1).

b) A sample of 400 mg Fremy's salt [3] in 6.5 ml 0.166 M KH_2PO_4 and 23 mg water was added with stirring to 110 mg (XIa) in 6.5 mg methanol. Product (Ia) was extracted with benzene and subjected to chromatography on silica gel in the same solvent to give 50 mg product. Products (Ib) and (Ic) were obtained analogously (Table 1). Product (II) was obtained in 71.4% yield and (VIII) was obtained in 69% yield, dec. >190°C (from ethanol), mp ~230°C (dec.) upon heating at ~3°C/sec. Found, %: C 69.13; H 4.26; N 8.22. $C_{10}N_2NO_2$. Calculated, %: C 69.36; H 4.07; N 8.09. PMR spectrum in DMSO-d_6 (δ, ppm): 6.59 (NH_2), 6.82 d.d (H^7), 6.85 ($H^{2,3}$), 7.04 d (H^5), 7.66 d (H^8). IR spectrum (ν, cm^{-1}): 3430, 3530 (NH_2), 1670, 1630 (O=C–C=C–C=O).

CONCLUSIONS

Syntheses are reported for substituted 6-ethynyl-1,4-naphthoquinone by the condensation of 6-iodo-1,4-dimethoxynaphthalene or 6-iodo-1-naphthol with terminal acetylenes and subsequent oxidation using $Ce(NH_4)_2(NO_3)_6$ and $ON(SO_3K)_2$.

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