HETEROCYCLES, Vol. 53, No. 5, 2000, pp. 1029 - 1040, Received, 20th December, 1999

POLYCYCLIC HYDROXYQUINONES. PART 31.[1] REGIOSELECTIVE REACTIONS OF 6-ETHYLSULFONYL-3-PHENYLFURO[3,4-*d*]ISOXAZOL-4(6*H*)-ONE ANION WITH QUINONE MONOKETALS. APPLICATION TO THE PREPARATION OF HETEROANTHRACYCLINONE ANALOGUES

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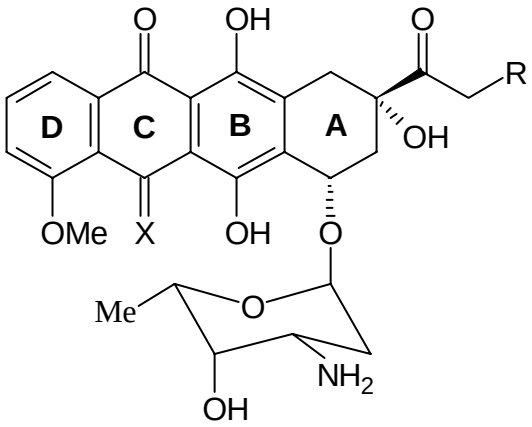
Abstract-The development of a general strategy for the construction of heteroanthracyclinones based on an annelation reactions of the anion generated from 6-ethylsulfonyl-3-phenylfuro[3,4-*d*]isoxazol-4(6*H*)-one (**3**) with quinone monoketals is described.

INTRODUCTION

The anthracycline antibiotics daunomycin (**1a**) and adriamycin (**1b**) are powerful antitumor agents in the treatment of a variety of human cancer cells.[2] However, these compounds display various side effects, the most serious being a cumulative dose-dependent cardiotoxicity.[3] In the last decade considerable efforts have been devoted to develop new structurally modified anthracyclines with an improved antineoplastic activity and a low cardiotoxicity.



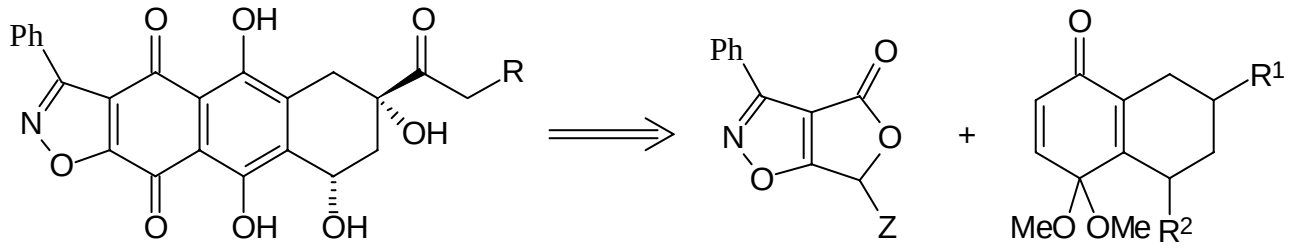
1a : X=O; R= H
1b : X=O; R= OH
1c : X=NH; R= H

5-Iminodaunomycin (**1c**),[4] a quinone-modified analog developed by Acton *et al*., shows significantly less cardiotoxicity than daunomycin while retaining the antitumor efficacy. The lower cardiotoxicity has been credited to its poor redox capability for catalytic production of reactive oxygen species.[5] It is also well known that the synthetic 4-demethoxy-[6] and 11-deoxyanthracyclines[7] are less toxic than the parent compounds while retaining the antitumor efficacy. It would be of interest to synthesize heterocyclic anthracycline analogues, since the heteroaromatic ring provides a useful bioisosteric replacement of the

benzene ring D, that would change the redox potential. It is also known that synthetic heterocyclic anthracycline, for example, the D-ring thiophene[8] and indole[9] analogues of daunomycin (**1a**), shows inhibitory activity against L1210 cell growth (*in vitro*) comparable to that of **1a**. The same observations were reported for D-ring pyridine and pyrazine analogues of 11-deoxydaunomycin.[10]

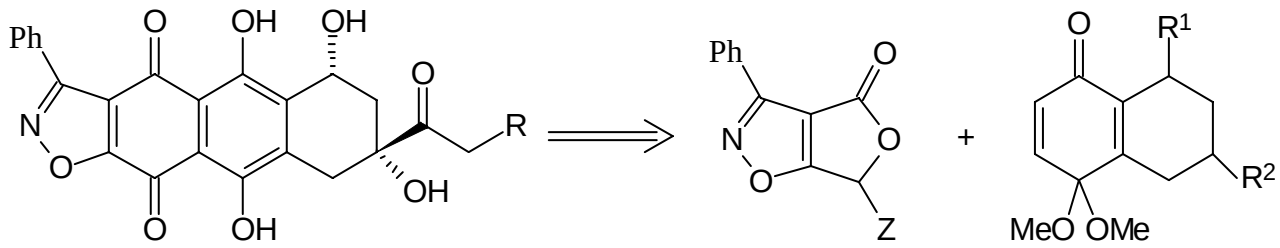
Some years ago,[11] as part of our studies on the synthesis of anthracyclinones, we have reported the utility of the Diels-Alder reaction with BCD synthons in the synthesis of the tetracyclic systems. Recently,[12] we have developed a new route to differently substituted 1,4-anthraquinones, by annelation reactions of the anion generated from 4-halo-5-thiosubstituted-furan-2(5*H*)-ones with dimethylnaphthoquinone mono-ketals. The presence of a sulfur bearing group at the 2-position of the anthraquinone plays a significant role in controlling the regiochemical course of the cycloaddition with an appropriate 1,3-disubstituted buta-1,3-diene.

On the other hand, we have also reported[13] the synthesis of 6-ethylsulfonyl-3-phenylfuro[3,4-*d*]isoxazol-4(6*H*)-one (**3**). In principle, these fused heterocyclic ring systems could be appropriate CD synthons for a DC+BA strategy, to prepare heterocyclic anthracyclinones.



2a

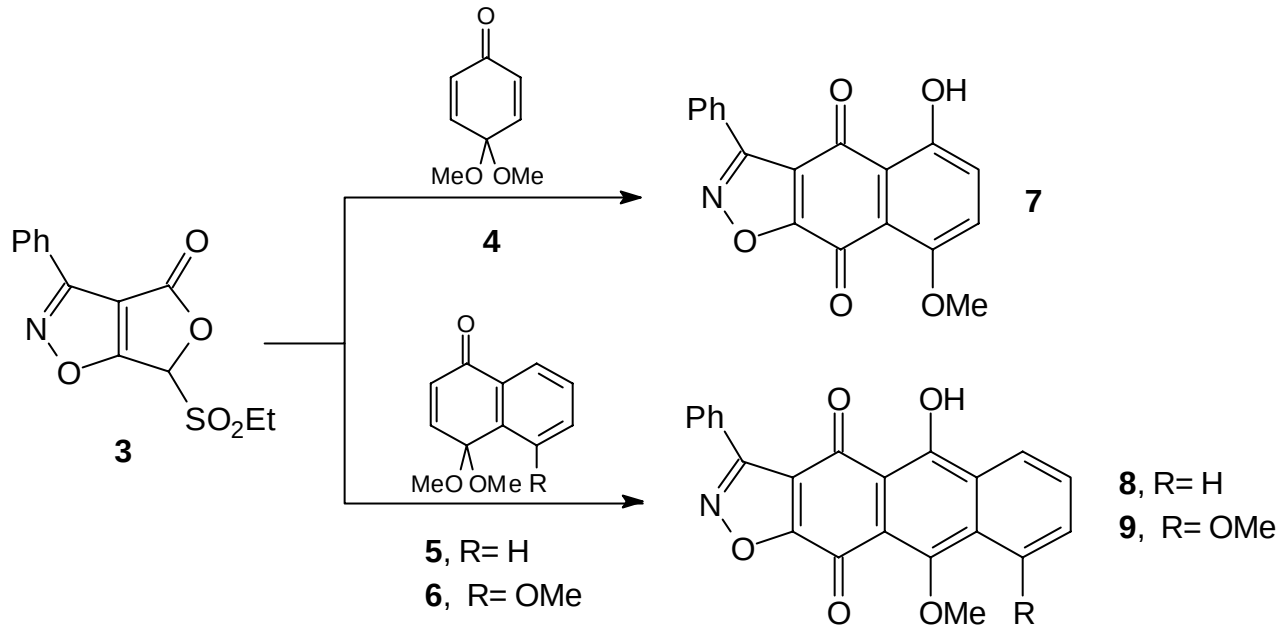
In the present paper, we report the behavior of the anion generated from 6-ethylsulfonyl-3-phenylfuro-[3,4-*d*]isaxazol-4(6*H*)-one (**3**), toward several quinone monoketals. The results obtained would provide information on the reactivity and regioselectivity of the Michael addition and offer a possible quick entry into the construction of heterocyclic quinones. We also have developed a route to tetracyclic systems related to those present in heterocyclic analogues of type (**2a**) and (**2b**) based on a DC+ BA strategy. [14] We now report our finding in detail.



2b

RESULTS AND DISCUSSION

We initially explored the reactions between the anion generated from 6-ethylsulfonyl-3-phenylfuro-[3,4-*d*]isoxazol-4(6*H*)-one (**3**)[13] with dimethylquinone monoketals[15] of type (**4**-**6**) (Scheme 1).



Scheme 1

The anion was generated by the treatment with lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LHMDS) at -78°C in tetrahydrofuran and the reactions were carried out under conditions indicated in Table 1.

Table 1. Reactions of the anion generated from isoxazole (3) with monoketals (4-6, 13-14 and 21)

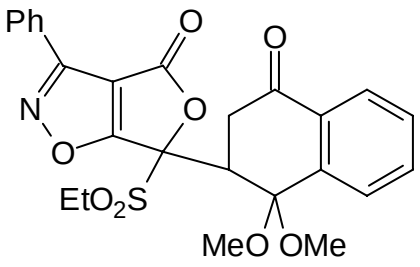
Monoketal	Base	Temp(°C)	Time [a]	Anthraquinone	Yield (%)
4	LDA	-2	5 hours	**7**	50
4	$(TMS)_2NLi$	-15	15 days	**7**	40[b]
5	LDA	-2	5 days	**8**	50
5	$(TMS)_2NLi$	-2	5 days	**8**	42
6	LDA	-2	5 days	**9**	40
13	LDA	-2	5 days	**15**	40
13	$(TMS)_2NLi$	-2	5 days	**15**	40
14	LDA	-2	5 days	**16**	40
14	$(TMS)_2NLi$	-2	5 days	**16**	40
21	LDA	-2	5 days	**22**	56

[a] The reaction of annelation was kept previously for 90 min at -78°C. [b] Adduct (**11**) was also obtained in 17%.

The reaction occurs regiospecifically at the 6 position of the furoisoxazole (**3**), in accordance with our previous results with 5-thio-furan-2(5*H*)-ones and naphthoquinone monoketals[12] and other types of Michael acceptors.[16]

The anion generated by deprotonation of isoxazole (**3**) with LDA reacts with *p*-benzoquinone monoketal (**4**) at –2ºC for five hours, to afford exclusively the naphthoisoxazole (**7**)[17] in moderate yield. It is noteworthy that the reaction proceeds with subsequent ring closure to the quinone.

Under similar conditions, the anion of furoisoxazole (**3**) reacted with naphthoquinone monoketals (**5**) and (**6**), to afford after 5 days, the corresponding anthraisoxazolequinones (**8**) and (**9**) in 50% and 40% yields, respectively. When the reaction with monoketal (**5**) was quenched after 90 min at –78ºC, the crude residue afforded a mixture of unreacted isoxazole (**3**) and monoketal (**5**), tetracycle (**8**) (3%) and the Michael adduct (**10**) (14%).



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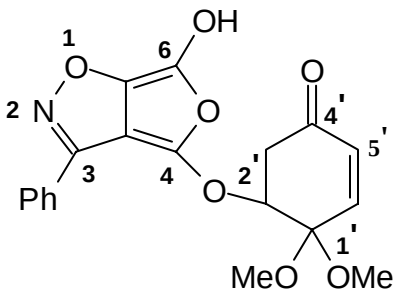

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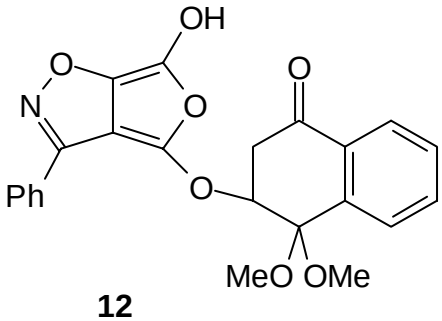

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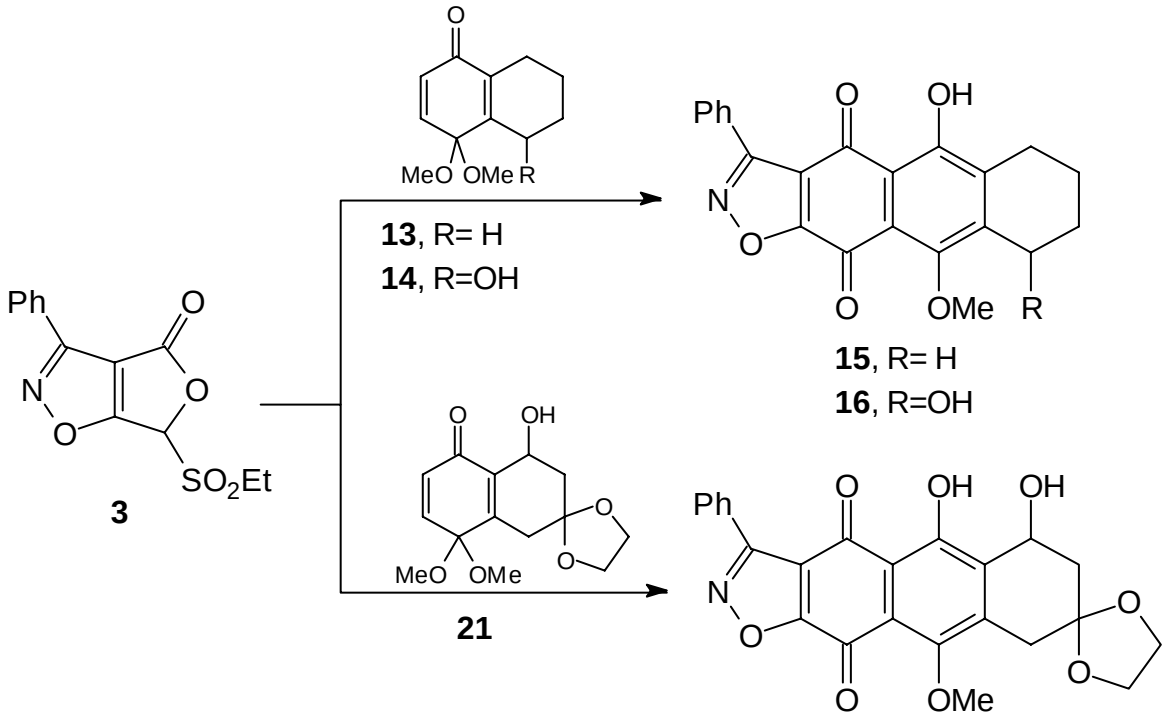
The formation of the anthraisoxazolequinones (**8**) and (**9**) and the structure of Michael adduct (**10**) were evidenced by their elemental analyses and spectral data.

The annelation reaction between the anion of isoxazole (**3**) generated with LHMDS and monoketal (**4**), afforded after 15 days at –15ºC a mixture of naphthoisoxazole (**7**) (40%) and compound (**11**) (17%). However, the annelation reaction with monoketal (**5**) after 5 days at –2ºC led exclusively to the anthraisoxazole (**8**) (42%). When the reaction mixture was quenched after 90 min at –78ºC, the crude residue afforded a mixture of unreacted isoxazole (**3**) and monoketal (**5**), tetracycle (**8**) (3%), the Michael adduct (**10**) (14%) and compound (**12**) (14 %). These results suggest that under these conditions used, the resonance-stabilized anion[18] also react through the oxygen at the 4 position and derivatives (**11**) and (**12**) arise from subsequent hydrolysis. Their structures were confirmed by elemental analyses and spectral data.

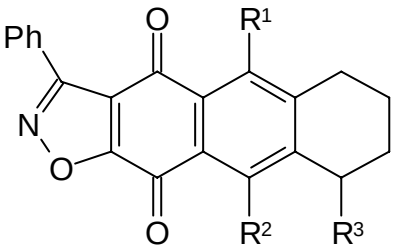
We then investigated the annelation reaction with monoketals (**13**) and (**14**) (Scheme 2), which are adequately functionalized to be precursors for ring-A. The anion generated from furoisoxazole (**3**) with LDA or LHMDS (Table 1), reacted with the monoketals (**13**) and (**14**) at –2ºC for 5 days to afford exclusively the tetracyclic systems (**15**) and (**16**) respectively, in 40% yield.



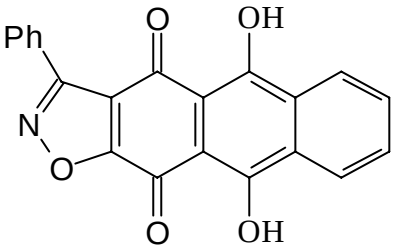
Scheme 2

The structures of anthraquinones (**15**) and (**16**) were confirmed by their elemental analyses and spectral data.

After achieving an effective preparation of analogues of type (**2a**), the experimental conditions to remove the methoxy group had to be carefully chosen because of the easy aromatization of the A-ring in the tetra-



17, R^1= OH; R^2= OH; R^3= H
19, R^1= OH; R^2= OH; R^3= OH



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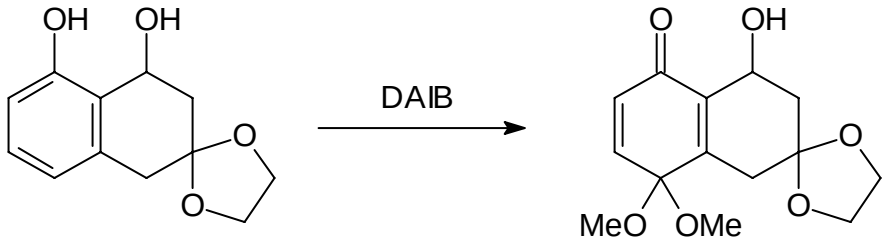
cyclic structures. The demethylation reaction of quinone (**15**) with 1.2 equiv of boron tribromide at –78ºC for 2 h and at room temperature for 2 h gave **17** in 80 % yield. In contrast, treatment of quinone (**16**) under the above conditions, afforded the fully aromatized compound (**18**). Numerous reagents and

conditions have been tried to remove the methyl group and the best proved to be 20 equiv of boron trichloride at –78ºC for 45 min which gave 50% yield of the desired compound (**19**).

In order to prepare daunomycinone analogues of type (**2b**), we studied further the annelation reaction of furoisoxazole (**3)** with 6,6-ethylenedioxy-8-hydroxy-4,4-dimethoxy-5,6,7,8-tetrahydronaphthalen-1-one (**21**), which was prepared by the method previously reported by us,[15] oxidation of hydroxytetra-hydronaphthalene (**20**) with (diacetoxyiodo)benzene (DAIB) (2 equiv, rt, 10 min) in methanol.[19]



20 **21**

The anion generated from furoisoxazole (**3**) with LDA (Scheme 2) reacted with monoketal (**21**) at –2°C for 5 days to afford the tetracyclic system (**22**) in a 56% yield and again structure was confirmed by their elemental analyses and spectral data.

Since the complete functionalization of the position 9 in the anthracyclinones has previously been accomplished by us[11b] and other workers,[2a,20] and suitable methods exist for the cleavage of ethers in this type of compounds, the route we have described might be considered as a regiospecific approach to heteroanthracyclinones of type (**2b**).

In summary, the foregoing results confirm the utility of the furoisoxazole (**3**) as a useful DC synthon in the synthesis of heterocyclic quinones. Furthermore, the synthetic methodology described herein may be applicable to the preparation of new heteroanthracyclinone analogues with modified pharmacological properties.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed with a Heraeus analyser model CHN-O-rapid. IR spectra were recorded on a Perkin-Elmer model 681 grating spectrophotometer as nujol mulls, unless otherwise stated, ν values in cm^{-1}. ^{1}H-NMR spectra were recorded on either a Varian Gemini 200, a Bruker AM-200 or a Varian XL-300 spectrometer, in $CDCl_3$ solution, unless otherwise stated. ^{13}C-NMR were recorded on either a Varian XL-300, a Bruker AM-200 or a Varian Unity-500, in $CDCl_3$ solution, unless otherwise stated. Chemical shifts were reported in ppm (δ) downfield from Me_4Si. MS spectra were recorded on a VG-12-250

spectrometer. Silica gel Merk 60 (70-230 mesh) and DL-alufolien 60F_{254} were used for flash column chromatography and analytical tlc, respectively.

The furoisoxazole (**3**)[13] and the monoketals[15] (**4**, **5**, **6**, **13**, **14**) were prepared according to the methods previously reported by us.

Generation of furoisoxazole anion and reaction with quinone monoketals. General procedures.

Method A. Lithium diisopropylamide was prepared by the addition at -78°C, under argon, of a 1.5 M (0.11 mL, 0.17 mmol) solution of *n*-butyllithium in hexane to a solution of diisopropylamine (0.024 mL, 0.17 mmol) in dry tetrahydrofuran (1 mL). Furoisoxazole (**3**) (40 mg, 0.14 mmol) in dry tetrahydrofuran (2 mL) was added and the mixture stirred for 15 min at -78°C, after which the quinone monoketal (0.14 mmol) in tetrahydrofuran (2 mL) was added, and the reaction mixture stirred for 90 min at -78ºC and then kept under the conditions indicated in each case (Table 1). The solution was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel.

Method B. To a solution of the furoisoxazole (**3**) (40 mg, 0.14 mmol) and the quinone monoketal (0.14 mmol) in dry tetrahydrofuran (5 mL) was added at -78ºC, under argon, a 1 M solution of lithium bis(trimethyilsilyl)amide in tetrahydrofurane (0.17 mL, 0.17 mmol). The reaction mixture was stirred for 90 min at -78ºC and then kept under the conditions indicated in each case (Table 1). The solution was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel.

Reaction of furoisoxazole (3) with monoketal(4)

Following method A, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (*n*-hexane-ethyl acetate,3:1) to afford **5-hydroxy-8-methoxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione**(**7**), (22 mg, 50%), mp 202ºC (from carbon tetrachloride/ petroleum ether). Anal. Calcd for $C_{18}H_{11}NO_5$: C, 67.29; H, 3.45; N, 4.36. Found: C, 67.18; H, 3.20; N, 4.59. IR: 1665, 1645, 1580. ^{1}H-NMR: 12.77 (s, 1H, OH); 8.11-8.07 (m, 2H, arom.); 7.59-7.48 (m, 3H, arom.); 7.40, 7.38 (AB syst., 2H, H-7, H-6, J=9.3 Hz); 4.04 (s, 3H, OMe). ^{13}C-NMR: 184.7, 171.3, 166.9, 160.7, 158.1, 156.2, 131.2, 129.6, 129.5, 128.7, 127.6, 126.2, 123.5, 117.5, 115.6, 57.0. MS (*m/z*): 321 (M^+, 26), 77 (100).

Following method B, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (*n*-hexane-ethyl acetate, 3:1) to afford of **5-hydroxy-8-methoxy-3-phenylnaphth[2,3-*d*]isoxazole-4,9-dione** (**7**) (16 mg, 40%) and **6-hydroxy-4-[1',1'-dimethoxy-4'-oxocyclohex-5'-en-2-yloxy]-3-phenylfuro[3,4-*d*]isoxazole** (**11**) (9 mg, 17%), mp 225ºC (from ethyl acetate). Anal. Calcd for $C_{19}H_{17}NO_7$: C, 61.45; H, 4.61; N, 3.77. Found: C, 61.23; H, 4.80; N, 3.50. IR:

3390, 1700, 1670, 1620. ^{1}H-NMR: 7.87-7.83 (m, 2H, arom.); 7.57-7.50 (m, 3H, arom.); 6.87 (d, 1H, H-6', J=10.5 Hz); 6.11 (dd, 1H, H-6', J=10.5 Hz, J=1.0 Hz); 4.77-4.74 (m, 1H, H-2'); 3.50 (s, 3H, OMe); 3.29 (s, 3H, OMe); 2.85 (s, 1H, OH); 2.73 (dd, 1H, H-3', J=17.1 Hz, J=4.9 Hz); 2.62 (ddd, 1H, H-3', J=17.1 Hz, J=2.7 Hz, J=1.0 Hz). MS (*m/z*): 371 (M^+, 0.1), 151 (100).

Reaction of furoisoxazole (3) with monoketal (5)

Following method A, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (toluene) to afford **5-hydroxy-10-methoxy-3-phenylanthra-[2,3-*d*]isoxazole-4,11-dione** (**8**) (26 mg, 50%), mp 232-235ºC (from toluene/*n*-hexane). Anal. Calcd for $C_{22}H_{13}NO_5$: C, 71.16; H, 3.53; N, 3.77. Found: C, 70.89; H, 3.65; N, 3.85. IR: 1670, 1640, 1610, 1575. ^{1}H-NMR: 14.88 (s, 1H, OH); 8.56-8.54 (m, 1H, H-6); 8.39-8.37 (m, 1H, H-9); 8.15-8.12 (m, 2H, arom.); 7.83-7.78 (m, 2H, H-7, H-8); 7.58-7.54 (m, 3H, arom.); 4.10 (s, 3H, OMe). ^{13}C-NMR: 183.8, 171.1, 167.4, 162.1, 160.9, 156.2, 133.2, 132.0, 131.2, 130.9, 130.2, 129.6, 128.6, 126.5, 125.5, 125.4, 119.1, 117.7, 109.1, 62.8. MS (*m/z*): 371 (M^+, 100).

Following method A, the reaction mixture was quenched after 90 min at –78ºC and the crude reaction mixture was chromatographed (petroleum ether-ethyl acetate, 5:1) to afford unreacted isoxazole and monoketal, quinone (**8**) (2 mg, 3%) and **6-ethylsulfonyl-6-[1',1'-dimethoxy-4'-oxo-1',2',3',4'-tetrahydro-naphthalen-2'-yl]-3-phenylfuro[3,4-*d*]isoxazol-4(6*H*)one** (**10**) (10 mg, 14%), mp 142-145ºC (from *n*-hexane). Anal. Calcd for $C_{25}H_{23}NO_8S$: C, 60.35; H, 4.66; N, 2.82; S, 6.44. Found: C, 60.08; H, 4.84; N, 2.85; S, 6.64. IR: 1810, 1695, 1610, 1600, 1580, 1330, 1135. ^{1}H-NMR: 8.03-7.99 (m, 1H, H-5'); 7.84-7.80 (m, 2H, arom.); 7.55-7.37 (m, 4H, H-8', arom.); 7.32-7.25 (m, 2H, H-6', H-7'); 4.18 (dd, 1H, H-2', J=4.6 Hz, J=3.3 Hz); 3.56 (s, 3H, OMe); 3.42-3.39 (m, 2H, H-3'); 3.03-2.84 (m, 1H, S-CH_2); 2.81 (s, 3H, OMe); 2.68-2.50 (m, 1H, S-CH_2); 1.32 (t, 3H, CH_3, J=7.4 Hz). ^{13}C-NMR: 194.6, 186.7, 157.0, 155.5, 136.7, 132.9, 132.2, 132.1, 130.0, 129.3, 128.0, 127.5 126.0, 125.1, 114.9, 97.4, 94.4, 49.2, 48.7, 42.7, 40.2, 37.6, 5.3. MS (*m/z*)*:* 404 (M^+-SO_2Et, 53), 202 (100).

Following method B, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (toluene) to afford quinone (**8**) (15 mg, 42%).

Following method B, the reaction mixture was quenched after 90 min at –78ºC and the crude reaction mixture was chromatographed (petroleum ether-ethyl acetate, 5:1) to afford unreacted isoxazole and monoketal, quinone (**8**) (2 mg, 3%), Michael adduct (**10**) (10 mg ,14%) and **6-hydroxy-4-[1',1'-dimethoxy-4'-oxo-1'-2',3'-4'tetrahydronaphthalen-2'-yloxy]-3-phenylfuro[3,4-*d*]isoxazole** (**12**) (8 mg, 14%), mp100-102ºC (from toluene/*n*-hexane). Anal. Calcd for $C_{23}H_{19}NO_7$: C, 65.56; H, 4.54; N, 3.32. Found: C, 65.22; H, 4.75; N, 3.20. IR: 3320, 1680, 1600. ^{1}H-NMR: 8.07-8.04 (m, 1H, H-5'); 7.68-7.65 (m, 1H, H-8'); 7.60-7.40 (m, 7H, arom., H-6', H-7'); 4.78 (dd, 1H, H-2', J=5.6 Hz, J=2.0 Hz); 3.50 (s, 3H, OMe); 3.22 (dd, 1H, H-3', J=18.2 Hz, J=5.6 Hz); 2.94 (s, 3H, OMe); 2.89 (dd, 1H, H-3', J=18.2 Hz, J=2.0 Hz). MS (*m/z*): 421 (M^+, 6), 388 (100).

Reaction of furoisoxazole (3) with monoketal (6)

Following method A, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (toluene- ethyl acetate, 3:1) to afford **9,10-dimethoxy-5-hydroxy-3-phenylanthra[2,3-*d*]isoxazole-4,11-dione** (**9**), (22 mg, 40%), mp 250ºC (from toluene). Anal. Calcd for $C_{23}H_{15}NO_6$: C, 68.83; H, 3.77; N, 3.49. Found: C, 69.33; H, 4.09; N, 3.48. IR: 1665, 1630, 1600, 1570. ^{1}H-NMR: 14.85 (s, 1H, OH); 8.18 (dd, 1H, H-6, J=1.0 Hz, J=8.1 Hz); 8.15-8.11 (m, 2H, arom.); 7.69 (t, 1H, H-7, J=8.1 Hz); 7.56-7.54 (m, 3H, arom.); 7.20 (dd, 1H, H-8, J=1.0 Hz, J=8.1 Hz); 4.04 (s, 3H, OMe); 3.99 (s, 3H, OMe). ^{13}C-NMR: 183.6, 170.9, 162.5, 160.8, 161.4, 159.5, 157.8, 132.6, 131.7, 131.2, 129.8, 128.6, 126.6, 123.8, 118.4, 117.8, 113.3, 113.1, 109.4, 62.3, 56.8. MS (*m/z*): 401 (M^+, 3), 77 (100).

Reaction of furoisoxazole (3) with monoketal (13)

Following method A, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (toluene- ethyl acetate, 20:1) to afford **5-hydroxy-10-methoxy-3-phenyl-6,7,8,9-tetrahydroanthra[2,3-*d*]isoxazole-4,11-dione** (**15**) (21 mg, 40%), mp 208-210ºC (from ethanol). Anal. Calcd for $C_{22}H_{17}NO_5$: C, 70.39; H, 4.56; N, 3.73. Found: C, 70,16; H, 4,28; N, 3,86. IR: 1680, 1640, 1590, 1570. ^{1}H-NMR: 13.33 (s, 1H, OH); 8.10-8.07 (m, 2H, arom.); 7.55-7.52 (m, 3H, arom.); 3.86 (s, 3H, OMe); 2.79-2.75 (m, 4H, H-6, H-9); 1.81-1.77 (m, 4H, H-7, H-8). ^{13}C-NMR: 184.5, 171.6, 166.8, 160.7, 159.3, 155.0, 144.4, 139.7, 131.2, 129.5, 128.6, 126.3, 119.5, 118.1, 112.1, 61.0, 24.1, 23.7, 21.5, 21.2. MS (*m/z*): 375 (M^+, 1), 77 (100).

Following method B, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (toluene- ethyl acetate, 20:1) to afford quinone (**15**) (21 mg, 40%).

Reaction of furoisoxazole (3) with monoketal (14)

Following method A, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (toluene- ethyl acetate, 9:2) to afford **5,9-dihydroxy-10-methoxy-3-phenyl-6,7,8,9-tetrahydroanthra[2,3-*d*]isoxazole-4,11-dione** (**16**) (22 mg, 40%), mp 160-162ºC (from chloroform/*n*-hexane). Anal. Calcd for $C_{22}H_{17}NO_6$: C, 67.52; H, 4.38; N, 3.58. Found: C, 67.36; H, 4.60; N, 3.28. IR: 3480, 1675, 1640, 1590, 1580. ^{1}H- NMR: 13.30 (s, 1H, OH); 8.08-8.05 (m, 2H, arom.); 7.56-7.49 (m, 3H, arom.); 5.06-5.04 (m, 1H, H-9); 3.99 (s, 3H, OMe), 2.98-2.90 (m, 1H, H-6); 2.60-2.53 (m, 2H, OH, H-6); 2.09-2.04 (m, 1H, H-8); 1.90-1.80 (m, 3H, H-7, H-8). ^{13}C-NMR: 184.6, 171.2, 166.7, 160.7, 159.3, 155.4, 143.6, 140.8, 131.3, 129.5, 128.6, 126.1, 119.9, 118.1, 113.3, 62.6, 62.3, 29.7, 24.0, 16.4. MS (*m/z*): 391(M^+, 37), 77 (100).

Following method B, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (toluene- ethyl acetate, 9:2) to afford quinone (**16**) (22 mg, 40%).

5,10-Dihydroxy-3-phenyl-6,7,8,9-tetrahydroanthra[2,3-*d*]isoxazole-4,11-dione (**17**)

A solution of 5-hydroxy-10-methoxy-3-phenyl-6,7,8,9-tetrahydroanthra[2,3-*d*]isoxazole-4,11-dione (**15**) (94 mg, 0.25 mmol) in dry dichloromethane (5 mL) was added dropwise to a stirred solution of boron

tribromide (0.3 mL, 0.3 mmol) in dry dichlorometane (0.5 mL) cooled to –78ºC under argon. The reaction mixture was stirred at -78ºC for 2 h and then kept 2 h at rt. Then water (0.5 mL) and 10% Na_2CO_3 solution (0.5 mL) were added and the organic layer was successively washed with saturated $Na_2S_2O_3$ solution, water, and dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography (petroleum ether-ethyl acetate, 4:1), to afford 72 mg (80%) of the quinone (**17**), mp 234-235ºC (from carbon tetrachloride/*n*-hexane). Anal. Calcd for: $C_{21}H_{15}NO_5$: C, 69.80; H, 4.18; N, 3.88. Found: C, 69.16; H, 4.44; N, 3.51. IR: 1620, 1560. ^{1}H-NMR: 13.57 (s, 1H, OH); 13.11 (s, 1H, OH); 8.12-8.09 (m, 2H, arom.); 7.56-7.51 (m, 3H, arom.); 2.76-2.74 (m, 4H, H-6, H-9); 1.82-1.79 (m, 4H, H-7, H-8). ^{13}C-NMR: 180.6, 173.0, 166.2, 161.8, 161.0, 160.8, 143.1, 140.2, 131.3, 129.6, 128.7,126.4, 119.7, 109.9, 109.2, 23.8, 23.3, 21.2, 21.1. MS (*m/z*): 361 (M^+, 10), 41 (100).

5,10-Dihydroxy-3-phenylanthra[2,3-*d*]isoxazole-4,11-dione (**18**)

A solution of 5,9-dihydroxy-10-methoxy-3-phenyl-6,7,8,9-tetrahydroanthra[2,3-*d*]isoxazole-4,11-dione (**16**) (98 mg, 0.25 mmol) in dry dichloromethane (5 mL) was added dropwise to a stirred solution of boron tribromide (0.3 mL, 0.3 mmol) in dry dichlorometane (0.5 mL) cooled to –78ºC under argon. The reaction mixture was stirred at -78ºC for 2 h and then kept for 1 h at rt. Then water (0.5 mL) and 10% Na_2CO_3 solution (0.5 mL) were added and the organic layer was successively washed with saturated $Na_2S_2O_3$ solution, water, and dried (Na_2SO_4). The solvent was removed and the residue was purified by crystallization from toluene/*n*-hexane to give 85 mg (95%) of quinone (**18**), mp 187-185ºC (from toluene). Anal. Calcd for $C_{21}H_{11}NO_5$: C, 70.59; H, 3.10; N.3.92. Found C, 70.26; H, 3.26; N, 3.74. IR: 1630, 1590. ^{1}H-NMR: 14.90 (s, 1H, OH); 13.59 (s, 1H, OH); 8.41-8.37 (m, 2H, H-6, H-9); 8.13-8.06 (m, 2H, arom.); 7.85-7.82 (m, 2H, H-7, H-8); 7.58-7.52 (m, 3H, arom.). ^{13}C-NMR: 186.5, 184.9, 160.8, 159.9, 158.5, 157.6, 134.9, 134.4, 133.7, 133.2, 130.8, 129.8, 128.5, 127.2, 127.1, 126.5, 119.5, 117.2, 108.4. MS (*m/z*): 357 (M^+, 100) .

5,9,10-Trihydroxy-3-phenyl-6,7,8,9-tetrahydroanthra[2,3-*d*]isoxazole-4,11-dione (**19**)

To a solution of 5,9-dihydroxy-10-methoxy-3-phenyl-6,7,8,9-tetrahydroanthra[2,3-*d*]isoxazole-4,11-dione (**16**) (98 mg, 0.25 mmol) in dry dichloromethane (5 mL) at -78ºC, under argon, was added dropwise a 1M boron trichloride solution (5 mL, 5 mmol) in dry dichlorometane (0.5 mL). The reaction mixture was stirred at -78ºC for 45 min and then saturated $NaHS_2O_3$ solution (1 mL) was added, and then extracted with dichlorometane. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was subjected to thin layer chromatography (toluene-ethyl acetate, 6:1) and afforded 47 mg (50%) of **19,** mp 193-194ºC (from toluene/*n*-hexane). Anal. Calcd for $C_{21}H_{15}NO_6$: C, 66.84; H, 4.00; N, 3.71. Found: C, 66.42; H, 3.66; N, 3.51. IR: 3420, 1620, 1560. ^{1}H-NMR: 13.39 (s, 1H, OH); 13.20 (s, 1H, OH); 8.13-8.08 (m, 2H, arom.); 7.58-7.48 (m, 3H, arom.); 5.13-5.09 (m, 1H, H-9); 3.11-2.89 (m, 3H, OH; H-8); 2.64-2.54 (m, 2H, H-6 or H-7); 2.11-2.05 (m, 2H, H-7 or H-6). MS (*m/z*): 377 (M^+, 2), 77 (100).

6,6-Ethylenedioxy-8-hydroxy-4,4-dimethoxy-5,6,7,8-tetrahydronaphthalen-1-one (**21**)

To a solution of 6,6-ethylenedioxy-1,8-hydroxy-5,6,7,8-tetrahydronaphthalene (**20**) (444 mg, 2 mmol) in dry methanol (30 mL), were added anhydrous potassium carbonate (552 mg, 4 mmol) and (diacetoxyiodo)benzene (DAIB) (1.28 g, 4 mmol). The reaction mixture was stirred for 10 min at rt. Then saturated solution of $NaHCO_3$ was added and the mixture was extracted with ether. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether, ethyl ether, triethylamine, 3:7:0.2) to afford 290 mg (55%) of monoketal (**21**). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.60; H, 6.43. Found: C, 59.71; H, 6.60. IR (film): 3520, 1675, 1630, 1620. ^{1}H-NMR: 6.76, 6.43 (AB systm., 2H, H-3 H-2, J=10,3 Hz); 4.94-4.88 (m, 1H, H-8); 4.05-3.96 (m, 4H, O-$(CH_2)_2$-O); 3.75 (d, 1H, OH, J=5.8 Hz); 3.22 (s, 3H, OMe); 3.19 (m, 3H, OMe); 2.58, 2.49 (AB systm., 2H, H-5, J=19.1 Hz); 2.18-1.98 (m, 2H, H-7). ^{13}C-NMR: 184.8, 150.3, 143.7, 136.4, 132.3, 107.3, 94.5, 64.6, 64.5, 64.4, 50.9, 50.8, 38.1, 33.7. MS (*m/z*): 264 (M^+-18, 0,1), 86 (100).

Reaction of furoisoxazole (3) with monoketal (21)

Following method A, the reaction mixture was kept under the conditions indicated in Table 1. The crude reaction mixture was chromatographed (petroleum ether-ethyl acetate, 2:1) to afford 5,6-dihydroxy-8,8-ethylenedioxy-10-methoxy-3-phenyl-6,7,8,9-tetrahydroanthra[2,3-*d*]isoxazole-4,11-dione (**22**) (35 mg, 56%), mp 205ºC. (from toluene/petroleum ether). Anal. Calcd for $C_{24}H_{19}NO_8$: C, 64.14; H, 4.26; N, 3.11. Found: C, 64.30; H, 4.65; N, 3.16. IR*:* 3460, 1675, 1640, 1590, 1575. ^{1}H-NMR: 13.58 (s, 1H, OH); 8.08-8.05 (m, 2H, arom.); 7.56-7.49 (m, 3H, arom.); 5.32-5.28 (m, 1H, H-6,); 4.12-4.01 (m, 4H, O-$(CH_2)_2$-O); 3.94 (d, 1H, OH, J=7.3 Hz); 3.87 (s, 3H, OMe); 3.16, 2.92 (AB systm., 2H, H-9, J=18.2 Hz); 2.24-2.23 (m, 2H, H-7). ^{13}C-NMR: 184.5, 171.2, 166.5, 160.6, 159.3, 154.3, 141.5, 137.6, 131.2, 129.4, 128.6, 126.0, 121.4, 118.1, 113.5, 107.3, 64.9, 64.7, 64.3, 61.2, 37.6, 34.5. MS (*m/z*): 449 (M^+, 3), 87 (100).

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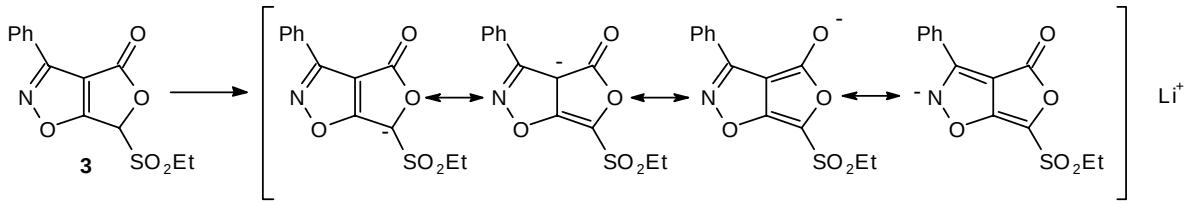
17. This compound also has been prepared by us, see: F. Fariña, M.V. Martín, M. Muñoz, M.C. Paredes, and R. Rodriguez, *Heterocycles*, 1995, **40**, 413.
18 . Anion in which the negative change is resonance stabilized, as shown in the figure:



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