Studies on Quinones. XIII. Synthesis and Reactivity in Acid Medium of Cyclic *O,N*-Ketals Derived from Acylbenzoquinones and Enamines [1]

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A series of cyclic *O,N*-ketals **14-20** derived from benzo[*b*]furan has been synthesized by reaction of acylbenzoquinones and enamines. Compounds **14-20**, in warm aqueous sulfuric acid, react to give elimination or rearrangement products depending on the structure of the substrate. The behavior of heterocycles **14-20** in acid conditions is interpreted on the basis of the arrangement of the carbon substituents on the furan ring.

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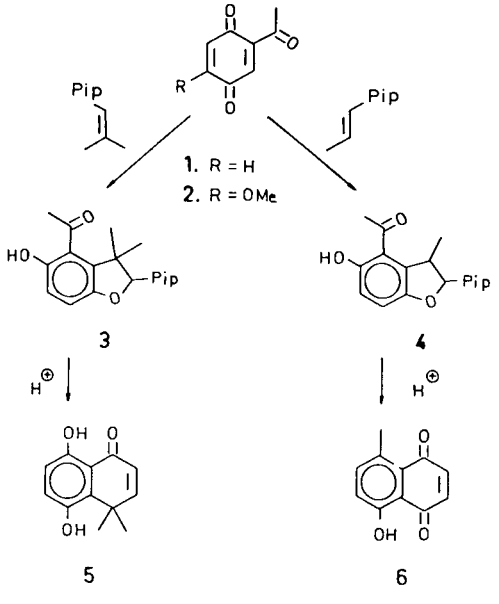
Introduction.

Previous results [2,3] from our laboratory have indicated the viability of the acid-catalyzed rearrangement of some 4-acetyl-2,3-dihydro-5-benzo[*b*]furanols, containing a cyclic *O,N*-acetal group, in generating a 1(4*H*)-naphthalenone or a 1,4-naphthoquinone system (*e.g.* **5** and **6**) depending on the degree of substitution of the substrate **3,4** at the C-3 position. As presented in Scheme 1, acid treatment of heterocyclic substrates **3** and **4**, obtained from 2-acetyl-1,4-benzoquinones **1, 2** and enamines, affords compounds **5** and **6**.

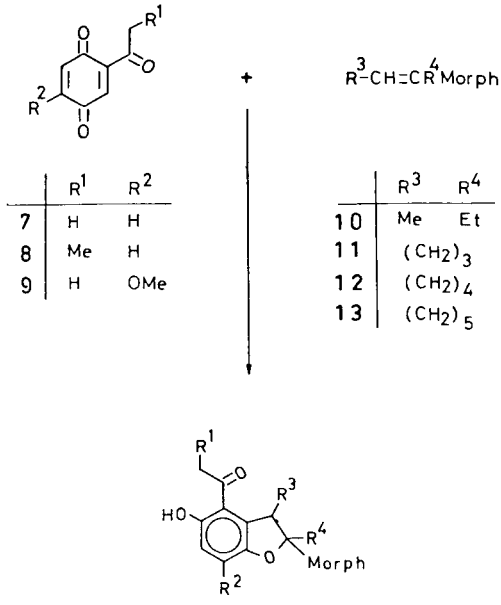


Scheme 1

In connection with our studies in the field of quinones [4] we decided to investigate the behavior of cyclic *O,N*-ketals of 4-acyl-2,3-dihydro-5-benzo[*b*]furanols in acidic medium in order to extend the rearrangement of these substrates to the preparation of angular tricyclic quinones.

Results and Discussion.

The cyclic *O,N*-ketals **14-20** selected for our purpose were obtained by reaction of 2-acyl-1,4-benzoquinones **7-9** with the enamines **10-13** as shown in Scheme 2.



	R^1	R^2
7	H	H
8	Me	H
9	H	OMe

	R^3	R^4
10	Me	Et
11	$(CH_2)_3$	
12	$(CH_2)_4$	
13	$(CH_2)_5$	

14 – 20

Scheme 2

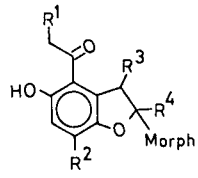
Since *O,N*-ketals **14-20** possess two chiral centers, the occurrence of diastereoisomers was anticipated. However under the reaction conditions only one product was isolated in each case and no isomers were detected by ^{1}H-nmr and tlc. The yields, physical constants and spectroscopic data of these compounds are described in Tables 1 and 2.

After an inspection of Drieding models and on analysis of the proton nmr spectra of compounds **15** and **16** it seemed reasonable to assign a *cis*-ring junction to these products. The signal of the methine proton of these compounds in ^{1}H-nmr appears as a doublet at δ 3.95 and 3.94 ppm respectively with coupling constants of 10 Hz. This fact indicates that one of the dihedral angles involved with the methine group is close to 90° which agrees with the conformation assignment and with the stereochemistry of related systems [5,6].

The ^{1}H-nmr spectra of adducts **14, 17-20** reveals that the methine proton signal, which is partially overlapped by the signals of the system -CH_2-O-CH_2-, appears approxi-

Table 1

Physical and Analytical Data of Cyclic *O,N*-Ketals **14-20**



Compound	R¹	R²	R³	R⁴	Mp (°C) (solvent)	Yield (%)	Formula	Analysis %, Calcd./Found C	H	N
14	H	H	Me	Et	155-157 benzene	96	$C_{17}H_{23}O_4N$	66.86 66.56	7.59 7.77	4.59 4.77
15	H	H	$(CH_2)_3$		170-171 benzene-cyclohexane	99	$C_{17}H_{21}O_4N$	67.31 67.12	6.98 7.15	4.62 4.62
16	Me	H	$(CH_2)_3$		155-156 cyclohexane	66	$C_{18}H_{23}O_4N$	68.12 67.81	7.30 7.13	4.41 4.39
17	H	H	$(CH_2)_4$		137-139 cyclohexane	59	$C_{18}H_{23}O_4N$	68.12 67.92	7.31 7.10	4.41 4.53
18	H	OMe	$(CH_2)_4$		177-178 cyclohexane	72	$C_{19}H_{25}O_5N$	65.69 65.38	7.25 7.13	4.03 4.21
19	Me	H	$(CH_2)_4$		108-109 cyclohexane	61	$C_{19}H_{25}O_4N$	68.86 68.81	7.60 7.41	4.23 4.12
20	H	H	$(CH_2)_5$		162-164 cyclohexane-acetone	96	$C_{19}H_{25}O_4N$	68.86 68.96	7.60 7.82	4.23 4.43

Table 2

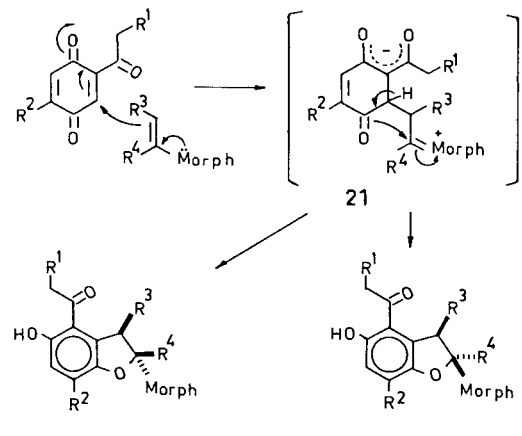
Spectral Data of Cyclic *O,N*-Ketals **14-20**

Compound	IR (cm^{-1}) ν C=O	^{1}H-NMR δ (ppm)
14	1630	11.79 (s, 1H), 6.89 (d, 1H, J ~ 7 Hz), 6.76 (d, 1H, J ~ 7 Hz), 3.8-3.4 (m, 5H), 2.72 (s, 3H), 2.8-2.5 (m, 4H), 2.04 (m, 2H), 1.26 (d, 3H, J ~ 7 Hz), 1.01 (t, 3H, J ~ 8 Hz)
15	1640	13.16 (s, 1H), 6.91 (d, 1H, J ~ 8 Hz), 6.77 (d, 1H, J ~ 8 Hz), 3.93 (d, 1H, J ~ 10 Hz), 3.69 (t, 4H, J ~ 5 Hz), 2.74 (t, 4H, J ~ 5 Hz), 2.65 (s, 3H), 2.5-1.4 (m, 6H)
16	1630	12.17 (br, 1H), 6.88 (d, 1H, J ~ 9 Hz), 6.78 (d, 1H, J ~ 9 Hz), 3.94 (d, 1H, J ~ 10 Hz), 3.69 (t, 4H, J ~ 5 Hz), 2.96 (q, 2H, J ~ 7 Hz), 2.73 (t, 4H, J ~ 5 Hz), 2.5-1.6 (m, 6H), 1.23 (t, 3H, J ~ 7 Hz)
17	1625	11.72 (s, 1H), 6.92 (d, 1H, J ~ 9 Hz), 6.77 (d, 1H, J ~ 9 Hz), 3.8-3.5 (m, 5H), 2.66 (s, 3H), 2.9-2.6 (m, 4H), 2.4-1.2 (m, 8H)
18	1610	12.88 (s, 1H), 6.35 (s, 1H), 3.92 (s, 3H), 3.8-3.4 (m, 5H), 2.8-2.6 (m, 4H), 2.62 (s, 3H), 2.5-1.2 (m, 8H)
19	1625	11.60 (br, 1H), 6.91 (d, 1H, J ~ 8 Hz), 6.77 (d, 1H, J ~ 8 Hz), 3.8-3.4 (m, 5H), 2.96 (q, 2H, J ~ 7 Hz), 2.8-2.4 (m, 4H), 2.4-1.0 (m, 8H), 1.23 (t, 3H, J ~ 7 Hz)
20	1630	11.44 (s, 1H), 6.84 (d, 1H, J ~ 9 Hz), 6.75 (d, 1H, J ~ 9 Hz), 3.8-3.5 (m, 5H), 2.8-2.6 (m, 4H), 2.63 (s, 3H), 2.2-1.2 (m, 10H)

mately at δ 3.6 ppm. The upperfield occurrence of the methinic proton in these adducts probably is due to a *trans* arrangement of the carbon substituents on the furan ring.

It is interesting to note that the regioselectivity involved in the formation of the cyclic *O,N*-ketals **14-20** has been previously observed in related compounds generated by reaction of enamines with acetylbenzoquinones [2] and with *o*-phenolic Mannich bases [7].

On the basis of these results, the exclusive formation of one product in the reaction of acylquinones **7-9** and enamines **10-13** can be rationalized by considering the participation of the zwitterion **21** which may undergo cyclization to give the *cis* or *trans* isomer depending on the stability of the product (Scheme 3).

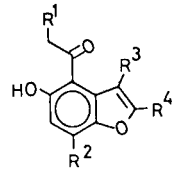


Scheme 3

We first examined the reactivity of the obtained cyclic *O,N*-ketals in acid media with compound **14**. When this adduct was warmed in 10% aqueous sulfuric acid followed

Table 3

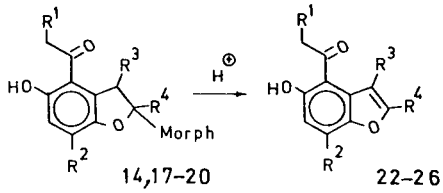
Physical and Analytical Data of Elimination Products **22-26**



Compound	R^1	R^2	R^3	R^4	Mp (°C) (solvent)	Yield [a] (%)	Formula	Analysis %, Calcd./Found C	H
22	H	H	Me	Et	134-134.5 cyclohexane	90	$C_{13}H_{14}O_3$	71.54 71.86	6.47 6.42
23	H	H	$(CH_2)_4$		61-62 petroleum ether (40-70°)	52	$C_{14}H_{14}O_3$	73.02 72.86	6.13 6.18
24	H	OMe	$(CH_2)_4$		153-154 cyclohexane	72	$C_{15}H_{16}O_4$	69.21 68.96	6.20 6.39
25	Me	H	$(CH_2)_4$		100-101 petroleum ether (40-70°)	40	$C_{15}H_{16}O_3$	73.75 73.60	6.60 6.57
26	H	H	$(CH_2)_5$		97.5-98 petroleum ether (40-70°)	78	$C_{15}H_{16}O_3$	73.75 73.51	6.60 6.45

[a] Yields are based on pure products. No attempts were made to improve yields.

by addition of water, 4-acetyl-2-ethyl-3-methyl-5-benzo[*b*]-furanol (**22**) was isolated in 90% yield. Compounds **17-20** under the same conditions produced the corresponding elimination products **23-26** (Scheme 4).



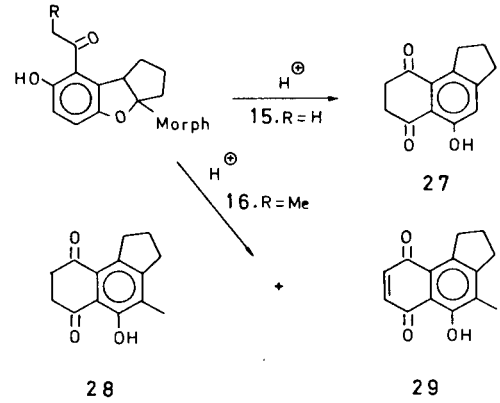
	R^1	R^2	R^3	R^4
14,22	H	H	Me	Et
17,23	H	H	$(CH_2)_4$	
18,24	H	OMe	$(CH_2)_4$	
19,25	Me	H	$(CH_2)_4$	
20,26	H	H	$(CH_2)_5$	

Scheme 4

The structures of these heterocyclic compounds **22-26** were determined by spectral data and elemental analyses (Tables 3 and 4).

In contrast to these results, acid treatment of the *cis*-fused adducts **15** and **16** gave the rearranged products **27**, **28** and **29**, as outlined in Scheme 5, and no elimination products were detected.

These results clearly show a dependence between the structure of adducts **14-20** and its reactivity in acid medium, which probably is related with the proposed configurations of these compounds. In fact adduct **14** and *trans*-fused compounds **17-20** undergo 1,2-elimination re-



Scheme 5

Table 4

Spectral Data of Products **22-26**

Compound	IR (cm^{-1}) ν C=O	^{1}H-NMR δ (ppm)
22	3360 w (O-H) 1660 (C=O)	11.85 (s, 1H), 7.41 (d, 1H, J ~ 9 Hz), 6.77 (d, 1H, J ~ 9 Hz), 2.87 (q, 2H, J ~ 8 Hz), 2.63 (s, 3H), 2.22 (s, 3H), 1.31 (t, 3H, J ~ 8 Hz)
23	3640 w (O-H) 1620 (C=O)	11.70 (s, 1H), 7.55 (d, 1H, J ~ 8 Hz), 6.90 (d, 1H, J ~ 8.5 Hz), 3.0-2.5 (m, 4H), 2.68 (s, 3H), 2.5-1.5 (m, 4H)
24	3450 w (O-H) 1615 (C=O)	13.15 (s, 1H), 6.42 (s, 1H), 4.06 (s, 3H), 3.0-2.5 (m, 4H), 2.65 (s, 3H), 2.5-1.6 (m, 4H)
25	3330 w (O-H) 1675 (C=O)	10.49 (s, 1H), 7.40 (d, 1H, J ~ 9 Hz), 6.76 (d, 1H, J ~ 9 Hz), 2.98 (q, 2H, J ~ 7 Hz), 2.8-2.6 (m, 4H), 2.1-1.6 (m, 4H), 1.23 (t, 3H, J ~ 7 Hz)
26	3240 s (O-H) 1680, 1650 (C=O)	10.64 (s, 1H), 7.44 (d, 1H, J ~ 9 Hz), 6.80 (d, 1H, J ~ 9 Hz), 3.1-2.8 (m, 2H), 2.8-2.4 (m, 2H), 2.57 (s, 3H), 2.0-1.5 (m, 6H)

actions due to the anti-orientation of the leaving groups (morpholino and the methine proton). By contrast, in adducts **15** and **16** the elimination reaction is not favored, because the potential leaving groups have a *cis*-orientation and an acid-catalyzed rearrangement is produced.

Further investigation on the chemistry of cyclic *O,N*-ketals **16** and **17**, directed towards the preparation of 1,4-phenanthraquinone precursors, is currently under study.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope and are uncorrected. The ir spectra were recorded in potassium bromide on a Perkin-Elmer 567 spectrometer. The ^{1}H-nmr spectra were measured in deuteriochloroform solution with a Varian XL-100 spectrometer using TMS as internal standard. Elemental analysis were performed by Instituto de Química Orgánica General, Madrid.

Acylbenzoquinones **7-9** were synthesized according to previously described procedures [8,9,10]. The enamines **10-13** were obtained by condensation of morpholine with the appropriate ketone according to Stork's procedure [11].

Preparation of Adducts **14-20**. Typical Procedure.

Twenty g (12.9 mmoles) of the enamine **10** in 20 ml of benzene were added dropwise to a stirred solution of 1.75 g (11.67 mmoles) of quinone **7** in 50 ml of benzene, and the reaction mixture was allowed to stand overnight at room temperature. The solvent was removed under vacuum and the residue was washed with cyclohexane. Recrystallization of the product from benzene gave 3.4 g (11.20 mmoles, 95%) of pure **14** as yellow needles.

Analytical data of compounds **14-20**, including yields, recrystallization solvents, melting points and combustion analysis are given in Table 1. The ir and nmr spectral characteristics are summarized in Table 2.

Elimination Reactions of Adducts **14, 17-20** in Acid Medium.

A solution of compound **14** (250 mg, 0.82 mmole) in 10% aqueous sulfuric acid (20 ml) was heated at 80° until tlc showed that all substrate **14** has reacted (about 30 minutes). The reaction mixture was diluted with water and the solid was collected by filtration and washed several times with water. Recrystallization from cyclohexane afforded 160 mg (0.74 mmole, 90%) of pure 4-acetyl-2-ethyl-3-methyl-5-benzo[*b*]furanol (**22**) as white needles.

Under similar conditions compounds **17-20**, reacted in aqueous sulfuric acid. The corresponding deamination products **23-26** were isolated from the reaction mixture as above and chromatographed on a silica gel column which was eluted with benzene. The properties of compounds **22-26** are summarized in Tables 3 and 4.

Rearrangement Reactions of Adducts **15** and **16**.

A solution of 500 mg (1.65 mmoles) of **15** in 10% aqueous sulfuric acid (50 ml) was heated at 80° for 10 hours. The resulting orange solution was diluted with water and extracted with chloroform. The organic phase was washed with saturated sodium bicarbonate solution, water and dried over magnesium sulfate. Evaporation left an orange solid which was chromatographed on silica gel using chloroform as the eluent. Concentration of the eluate gave 310 mg (1.43 mmoles, 87%) of 5-hydroxy-2,3,7,8-tetrahydro-1*H*-benz[*e*]inden-6,8-dione (**27**) as orange needles, mp 129-130°; ir: 1680 and 1640 (C=O); ^{1}H-nmr: δ 13.50 (s, 1H), 7.20 (s, 1H), 3.23 (t, 2H, J ~ 7 Hz), 3.1-2.8 (m, 6H), 2.09 (quint, 2H, J ~ 7 Hz) ppm.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.20; H, 5.59. Found: C, 72.09; H, 5.80.

A solution of 500 mg (1.58 mmoles) of **16** in 10% sulfuric acid (50 ml) was heated at 80° for 4 hours. After the usual work-up as described above, the crude residue was separated by preparative tlc on silica gel using benzene as the eluent. From the upper band 125 mg (0.54 mmole, 35%) of pure 2,3-dihydro-5-hydroxy-4-methyl-1*H*-benz[*e*]indene-6,9-dione (**29**) were isolated, as a red solid, mp 159-160° (from cyclohexane); ir: 1645 and 1618 (C=O); ^{1}H-nmr: δ 12.88 (s, 1H), 6.84 (d, 1H, J ~ 11 Hz), 6.78 (d, 1H, J ~ 11 Hz), 3.26 (t, 2H, J ~ 7 Hz), 2.86 (t, 2H, J ~ 7 Hz), 2.25 (s, 3H), 2.10 (m, 2H) ppm.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.33; H, 5.34.

From the lower band 84 mg (0.37 mmole, 23%) of pure dione **28** were isolated as orange crystals, mp 104-105° (from cyclohexane); ir: 1675 and 1626 (C=O); ^{1}H-nmr: δ 12.84 (s, 1H), 3.25 (t, 2H, J ~ 8 Hz), 3.08 (m, 6H), 2.26 (s, 3H), 2.06 (quint, 2H, J ~ 8 Hz) ppm.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found; C, 73.19; H, 6.13.

Acknowledgement.

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