Synthesis and Stereochemistry of Bis-(3,4-disubstituted 5-oxo-2,5-dihydrofuran-2-yl) Ethers

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Dehydration of 3,4-disubstituted 5-hydroxyfuran-2(5*H*)-ones by sulphuric acid or thionyl chloride gave the racemic and *meso* isomers of the corresponding ethers, bis-(3,4-disubstituted 5-oxo-2,5-dihydrofuran-2-yl) ethers. The stereochemistry of the diastereoisomers has been studied by i.r., u.v., and n.m.r. spectroscopy.

SOME bis-(3,4-dihalogeno-5-oxo-2,5-dihydrofuran-2-yl) ethers exhibit fungitoxic activity.[1] Ethers of this type are available from the dehydration of the appropriate 3,4-disubstituted 5-hydroxyfuran-2(5*H*)-ones.[2-4]. In this way Mowry [3] obtained two stereoisomeric forms of the tetrachloro-ether (IV) from mucochloric acid (I). On repeating the synthesis we found that the properties of the α-isomer differed from those given by Mowry. We now report the preparation of a series of ethers (IV)—(VI) and the characterisation of their pure stereoisomeric forms. The products show low fungitoxic activity. The compounds were prepared by a modified procedure [2]

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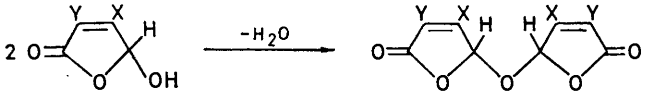
[1] U.S.P., 2,861,919/1958.

[2] D. T. Mowry, *J. Amer. Chem. Soc.*, 1950, **72**, 2535.

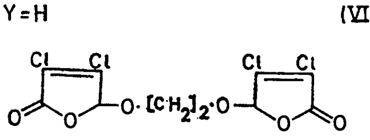
[3] U.S.P., 2,951,083/1960.

[4] U.S.P., 2,957,026/1960.

from the appropriate 3,4-disubstituted 5-hydroxyfuran-2(5*H*)-ones.



(I) X = Y = Cl (IVa,b)
(II) X = Y = Br (Va,b)
(III) X = Cl, Y = H (VIa,b)

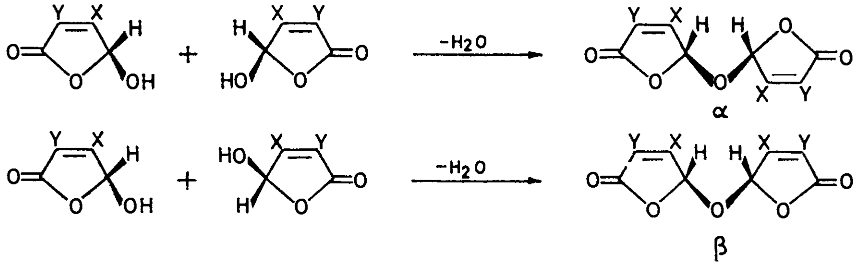


(VII)

Mowry reported that the action of thionyl chloride on the alcohol (I) gave only the α-form (IVa) of the corresponding ether. In our hands similar reactions using sulphuric acid, oleum, or thionyl chloride gave a mixture of ethers. Attempts to prepare the ethers by the condensation of 3,4,5-trichlorofuran-2(5*H*)-one with the alcohol (I) were not successful even when prolonged periods of heating with zinc chloride were employed.

EXPERIMENTAL

Measurements.—I.r. spectra were recorded with a Unicam SP 100 double-beam instrument. N.m.r. spectra were measured with a Tesla BS 487 spectrometer (80 MHz) for $CDCl_3$ solutions using hexamethyldisiloxane as internal standard. U.v. spectra were recorded with a Perkin-Elmer 450 instrument in 1·0 mm cells with concentrations of 1 mM in methanol. G.l.c. analyses were performed with a Fractovap C chromatograph (C. Erba) using a column of NPGZ and 1% Chromosorb W.



SCHEME

Materials.—CCl_4 and CH_3OH (spectroscopic grade) were used without further purification. AnalaR $CHCl_3$ was dried several times by passing it through a column of silica gel before using directly.

Bis-(3,4-*dichloro-*5-*oxo-*2,5-*dihydrofuran-*2-*yl*) *Ethers* (IVa, b).—A mixture of the ethers (IVa, b) was prepared by dehydration of mucochloric acid (I) (10 g, 0·06 mol) with 100% sulphuric acid (26 g). After 24 h at room temperature the solution was poured into water. The precipitated solid (82·3%) was washed with aqueous $NaHCO_3$ and then crystallised from benzene. Fractional crystallisation from dioxan gave the β-*isomer* (IVb), m.p. 180—180·5° (Found: C, 30·3; H, 0·8; Cl, 44·4. $C_8H_2Cl_4O_5$ requires C, 30·1; H, 0·6; Cl, 44·3%); evaporation of the mother liquor gave the α-*isomer* (IVa), m.p. 165—166° (from benzene–dioxan) (Found: C, 30·1; H, 0·7; Cl, 44·5%).

The action of thionyl chloride with zinc chloride [3] gave a similar mixture of ethers (18·6%), b.p. 175—185° at 1 mmHg, m.p. 144—156°, together with 3,4,5-trichlorofuran-2(5*H*)-one (70·5%), b.p. 132° at 52 mmHg. Similarly the action of toluene-*p*-sulphonic acid in dioxan [3] gave the ethers (IVa and b) and 1,2-*bis-*(3,4-*dichloro-*5-*oxo-*2,5-*dihydrofuran-*2-*yloxy*)*ethane* (VII), m.p. 139—140° (from chloroform) (Found: C, 33·2; H, 1·8; Cl, 39·1. $C_{10}H_6Cl_4O_6$ requires C, 33·0; H, 1·7; Cl, 39·0%).

Bis-(3,4-*dibromo-*5-*oxo-*2,5-*dihydrofuran-*2-*yl*) *Ethers* (Va, b).—A mixture of the ethers (45%) was prepared by dehydration of the corresponding alcohol (II) (10·5 g, 0·04 mol) with 98% sulphuric acid (25 g) (Found: C, 19·6; H, 0·6; Br, 63·9. Calc. for $C_8H_2Br_4O_5$: C, 19·5; H, 0·4; Br, 64·2%). Chromatography on silica gel with hexane–dioxan (10 : 1) as eluant gave the α-*isomer*, m.p. 175—176° (from benzene) and the β-*isomer*, m.p. 207—208° (from dioxan).

Ethers (VIa, b).—Similar treatment of the alcohol (III) [5] (6·7 g, 0·05 mol) and sulphuric acid (26 g) gave a mixture of bis-(3-chloro-5-oxo-2,5-dihydrofuran-2-yl) ethers (VI) (5·2 g, 82·8%) (Found: C, 38·5; H, 1·7; Cl, 28·4. Calc. for $C_8H_4Cl_2O_3$: C, 38·3; H, 1·6; Cl, 28·2%). Chromatography on silica gel with hexane–dioxan (1 : 1) as eluant gave the α-*isomer*, m.p. 139° (from dioxan) and the β-*isomer*, m.p. 156° (from benzene).

1,2-*Bis-*(3,4-*dichloro-*5-*oxo-*2,5-*dihydrofuran-*2-*yloxy*)-*ethane*. (VII)—Treatment [3] of mucochloric acid (36 g, 0·21 mol) with ethylene glycol (6·3 g, 0·1 mol) in the presence of toluene-*p*-sulphonic acid (0·3 g) gave the bisether (VII) (5·2 g, 14%), identical in all respects with the compound obtained from the action of toluene-*p*-sulphonic acid on mucochloric acid in dioxan.

RESULTS AND DISCUSSION

The formation of two stereoisomers by dehydration of 3,4-disubstituted 5-hydroxyfuran-2(5*H*)-ones is explained

TABLE 1

I.r. data for bis-(3,4-disubstituted 5-oxo-2,5-dihydrofuran-2-yl) ethers in CCl_4 (saturated solution)

Compound	ν(C=O)/cm^{-1}		ν(C–H)/cm^{-1}	
(IVa)	1810	1815	2940	
(IVb)	1805		2948	2981
(Va)	1802	1815	2938	
(Vb)	1814		2913	2957
(VIa)	1805	1812	2937	
(VIb)	1808		2950	2961

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[5] S. Kovac, E. Solcaniova, E. Beska, and P. Rapos, preceding paper.

in the Scheme. The i.r. spectra of the two diastereoisomers differ markedly in the 1320—1340 [ν(C–O)] and 2800—3000 cm^{-1} regions [ν(C–H)] (Table 1). Two bands in the C–H region in the spectra (in CCl_4) of the β-isomers [compounds (IVb—VIb)] can be assigned to the stretching absorptions of two different C–H bonds. The bands at lower wavenumbers can be assigned to the stretching mode of the C–H group participating in hydrogen bonding with the oxygen of a lactone ring. This assumption is reasonable because the hydrogen attached to a carbon atom of the lactone ring is acidified by the electron-withdrawing power of the oxygen and halogen atoms. The two bands observed in the region 1320—1340 cm^{-1} in the spectra of the β-isomers support this assignment (Table 2). The larger number of the bands in the spectra (Nujol) of the β-isomers in the finger-print region as compared with those of α-isomers suggest that the β-isomers are the *meso*-forms.

TABLE 2

I.r. data for bis-(3,4-disubstituted 5-oxo-2,5-dihydrofuran-2-yl) ethers in $CHCl_3$

	C–O		C=C			C=O					
Compound	ν	ε	ν	$\Delta\nu_{\frac{1}{2}}$	ε	ν	$\Delta\nu_{\frac{1}{2}}$	ε	ν	$\Delta\nu_{\frac{1}{2}}$	ε
(IVa)	1320	sh	1637	11	250				1812	20	850
(Ib)	1320	85	1637	16	205	1813	17	(725)	1830		(170)
(Va)	1315		1616	13	195	1799	17	860	1807		(315)
(Vb)	1315	95	1617	15	175	1799	(32)	555	1809		(550)
(VIa)	1323	sh	1627	7	365	1788		165	1812	16	(995)
(VIb)	1323	110	1622	13	280	1788		155	1813	23	800

ν and $\Delta\nu_{\frac{1}{2}}$ are in cm^{-1}; ε in l mol^{-1} cm^{-1}, calculated for one group; sh = shoulder; values in parentheses are approximate.

TABLE 3

U.v. and n.m.r. data for bis-(3,4-disubstituted 5-oxo-2,5-dihydrofuran-2-yl) ethers

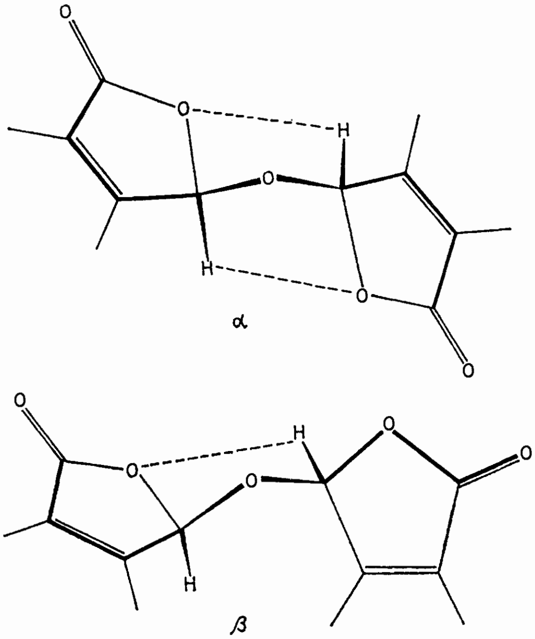
Compound	$\lambda_{max.}$(MeOH)/nm	log ε	τ(C–H) ($CHCl_3$)
(IVa)	231·5	4·33	3·90
(IVb)	230·5	4·28	3·98
(Va)	245·0	4·33	3·88
(Vb)	244·0	4·29	3·98
(VIa) [a]	213	4·40	3·93
(VIb) [a]	212·5	4·44	4·05
(VII) [b]			4·28

[a] τ(=C–H) at 3·72 and 3·75 respectively. [b] τ(CH_2) at 6·08.

The presence of only one band in the 2800—3000 [ν(C–H)] and also in the 1320—1340 cm^{-1} region [ν(C–O)] in the spectra (in CCl_4) of the α-isomers (racemic forms) (Table 1) suggests that the two hydrogen atoms can be similarly hydrogen-bonded intramolecularly to the oxygen atoms of lactone ring.

Examination of Dreiding molecular model (Figure) of the racemic form of the compounds suggests that two nearly planar, five-membered rings with hydrogen bonds are possible, in which the O · · · C distance is *ca.* 3 Å.

We have attempted, with only limited success, to find further evidence bearing on the conformation adopted by the ethers by use of n.m.r. and u.v. spectroscopy. All compounds studied exhibit high-intensity bands in the region of 212—244 nm, characteristic of lactones. The n.m.r. spectra of all compounds, except (VII), contain a singlet due to the proton on the furanone ring (Table 3). We expected two singlets belonging to the two variously shielded protons of the β-isomers which would be in accordance with the i.r. data.



Planar projection of the Dreiding molecular models of the α- and β-isomers

[1/683 *Received, 4th May,* 1971]