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Synthesis of Dihydro-2*H*-thiopyran-3-ones

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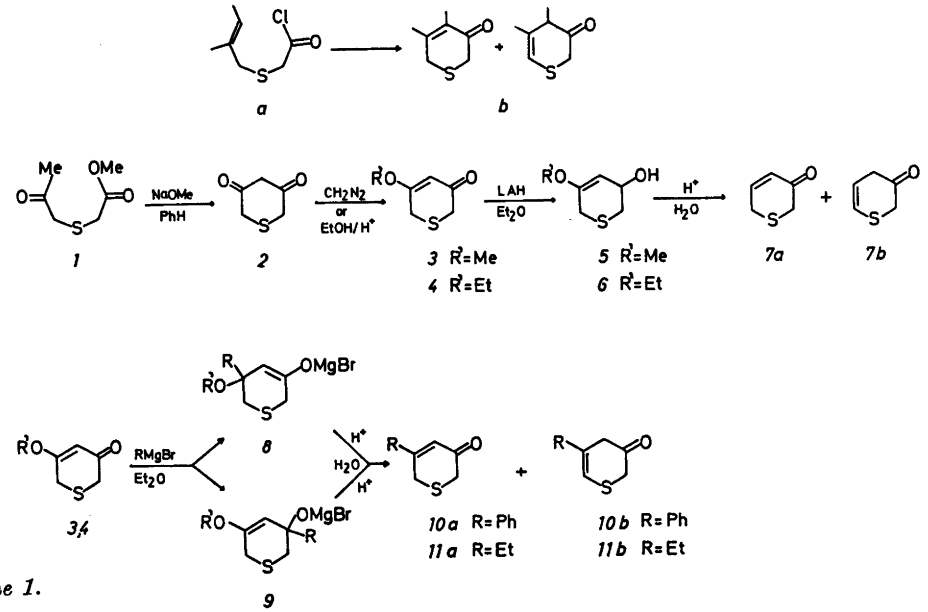
Dihydro-2*H*-thiopyran-3-ones have been synthesised from tetrahydrothiopyran-3,5-dione *via* the monoenol ether. Reduction of the latter with lithium aluminium hydride gave 96 % isomer pure 3,6-dihydro-2*H*-thiopyran; Grignard reactions gave 5-substituted 3,4-dihydro- and 3,6-dihydro-2*H* isomers.

The dihydro-2*H*-thiopyran-3-one system *b* (Scheme 1) can be synthesised from allylthioacetic acid derivatives *a* by Friedel-Crafts cyclisations; the yields are highly variable.[1] By this method dihydro-2*H*-thiopyran-3-one was obtained as an almost equimolar mixture of the 3,6-dihydro *7a* and the 3,4-dihydro *7b* isomers which has been separated by GLC.[1] For other work we required ready access to the 3,6-dihydro isomer *7a*. By analogy to 2-hydroxythiophene which exists almost exclusively as the α,β-unsaturated thiolactone 3-thiolen-2-one,[2] tautomeric equilibria in a mixture of *7a* and *7b* would be expected to be strongly in favour of *7a*. But attempts to obtain *7a*, which has the carbon–carbon double bond in conjugation with the carbonyl group, by acid or base catalysed tautomerisation of *7b* in the isomer mixture, resulted in extensive decomposition. An alternative synthesis to this class of compounds was therefore worked out.

The starting material methyl acetonylthioacetate *1* was cyclised by means of sodium methoxide to tetrahydrothiopyran-3,5-dione *2*, and the latter converted into the methyl enol ether *3* by means of diazomethane.[3] For large-scale work, however, it was more convenient to



Scheme 1.

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prepare the ethyl homologue *4*, which was available from *2* and ethanol by acid catalysis and azeotropic removal of the water formed. An ethereal solution of the enol ether *3* or *4* was readily reduced with lithium aluminium hydride (LAH). GLC showed that the product *7* was composed of 96 % of the 3,6-dihydro isomer *7a* and 4 % of the 3,4-dihydro isomer *7b* after acid catalysed alcohol elimination from the reduction product *5* or *6*. Prolonged treatment with acid under the condition used in the elimination reactions had no apparent effect on the isomer ratio. Using water alone for the hydrolysis of the reduction complex in the case of *3* led to isolation of the intermediate allylic alcohol *5*. Hence it is the carbonyl group and not the carbon – carbon double bond which is preferentially reduced. Preferential reaction of the carbonyl group has also been observed in the analogous reduction of 5-ethoxy-2-cyclohexenone;[4] the reduction product of the latter on acid catalysed elimination of ethanol, gave the 2-cyclohexenone and 3-cyclohexenone isomers in the ratio 97:3.[5]

Grignard reagents add 1,2 or 1,4 to α,β-unsaturated ketones.[6] 1,4-Addition is favoured for β-aryloxy and β-alkoxy unsaturated ketones, and is also enhanced in cycloaliphatic α,β-unsaturated ketones.[6] In Grignard reactions of the enol ethers *4* and *5*, which are without a 2- or 6-substituent, either reaction path will yield the same 5-substituted dihydro-2*H*-thiopyran-3-ones after hydrolysis and eliminations from the Grignard adducts *8* or *9*. The reactions of *4* and *5* with phenyl and ethyl magnesium bromide were slow, and the yields of *10* and *11* were of the order 30 – 40 %. Substantial amounts of tetrahydropyran-3,5-dione were formed. Presumably the basic properties of the Grignard reagents lead to extensive enolate formation in the carbonyl reactant, which may in part be ascribed to activation of the hydrogens on C-2 and C-6 by the adjacent sulfur atom. In the phenylated product *10* the ratios between the 3,6-dihydro *10a* and the 3,4-dihydro *10b* isomers in the crude product varied between 6:1 and 4:1; the ratio was affected by the time of acid treatment in the elimination step. After distillation variable isomer ratios 4:1 to 2:1 for *10a*:*10b* were obtained. In the ethylated product the isomer mixtures contained 5 – 12 % of the 3,4-dihydro isomer *11b*, which is more like the isomer distribution in the parent compound *7*. The higher tendency for formation of the 3,4-dihydro isomer for the phenyl derivative than for the ethyl derivative may be rationalised by the importance of conjugation between the sulfur chromophore and the phenyl ring.

The isomers were separated by chromatography on silica gel. The NMR and MS spectra are consistent with the assigned structures. In IR the carbonyl bands for the 3,6-dihydro isomers *10a* and *11a* are at 1660 and 1670 cm^{-1}, respectively, and in the 3,4-dihydro isomers *10b* and *11b* at 1710 and 1720 cm^{-1}, respectively.

EXPERIMENTAL

*5-Methoxy-3,6-dihydro-2*H*-thiopyran-3-one* 3 was prepared from tetrahydrothiopyran-3,5-dione.[3]

*5-Ethoxy-3,6-dihydro-2*H*-thiopyran-3-one* 4. A solution of tetrahydrothiopyran-3,5-dione [3] (13.0 g, 0.1 mol), *p*-toluenesulfonic acid (0.3 g) and ethanol (30 ml) in benzene (180 ml) was heated under reflux using a Dean and Stark separator to remove the water generated by azeotropic distillation with benzene. The reaction had gone to completion after *ca.* 2 h. The cold solution was decolourised with active charcoal, washed with sat. $NaHCO_3$ solution and water, dried ($MgSO_4$), the solvent distilled off and the residue recrystallised from light petroleum (b.p. 60 – 80 °C); yield 9.5 g (60 %), m.p. 62 – 63 °C. Anal. $C_7H_{10}O_2S$: C, H. ^1H NMR ($CDCl_3$): δ 1.37 and 3.93 (OEt), 3.23 (2H-2, s), 3.33 (2H-6, br. s), 5.35 (H-4, br. s). ^{13}C NMR ($CDCl_3$): δ 14.1 and 64.8 (OEt), 28.0 (C6, t, $^1J_{CH}$ 139 Hz), 34.1 (C2, t, 140), 102.3 (C4, d, 160), 174.3 (C5, s), 193.4 (C3, s). IR (KBr): 1660 cm^{-1} (α,β-unsat. CO). MS [IP 70, ev; *m/e* (% rel.int.)]: 158 (90, M), 112(74), 109(14), 97(15), 95(20), 85(11), 84(*100*), 69(53) 68(81).

*3-Hydroxy-5-methoxy-3,6-dihydro-2*H*-thiopyran* 5. A solution of LAH (1.35 g, 0.036 mol) in ether (40 ml) was added dropwise over 90 min with stirring to a solution of 5-methoxy-3,6-dihydro-2*H*-thiopyran-3-one (10.1 g, 0.07 mol) in ether (175 ml) at room temperature. The mixture was heated under reflux for 30 min after the addition was completed. The mixture was then allowed to reach room temperature and water (100 ml) added. The two phases were separated, the aqueous phase extracted with ether, the combined ether solutions washed with water and dried ($MgSO_4$), and the solvent distilled off. The title compound thus obtained was practically pure. It could be stored at 5 °C for several weeks and with acid catalysis was converted into 3,6-dihydro-2*H*-thiopyran as described below. ^1H NMR (CCl_4): δ 2.7 – 3.1

(2H-2, 2H-6, m), 3.55 (OMe), 4.4 (H-3, m), 4.90 (H-4, d, *J* 5 Hz). IR (film): 3290 (br. OH), 1660 cm^{-1} (C=C). MS [70 eV; *m/e* (% rel. int.)]: 146 (79, M), 100 (*100*).

*3,6-Dihydro-2*H*-thiopyran-3-one* 7a. The reduction with LAH (0.036 mol) of 5-methoxy-3,6-dihydro-2*H*-thiopyran-3-one (0.07 mol) or 5-ethoxy-3,6-dihydro-2*H*-thiopyran-3-one (11.1 g, 0.07 mol) was carried out as described for *5* above. After the reduction was completed, water (5 ml) was added dropwise to the reaction mixture and the resultant mixture poured into ice-cold 10 % sulfuric acid (150 ml). The mixture was stirred for 30 min, the phases separated, the aqueous phase extracted twice with ether, the combined ether solutions washed with sat. $NaHCO_3$ and water and dried ($MgSO_4$), the ether evaporated and the residue distilled; yield 6.0 g (75 %), b.p. 68–69 °C/2.5 Torr (lit.[1] b.p. 70–72 °C/4 Torr). GLC showed the product to contain 4 % of the 3,4-dihydro-2*H*-thiopyran-3-one isomer.[1] The GLC was run on 20 % SE30 (column 240 cm, 3 mm) at 120 °C; retention time for *7a* 9 min, for *7b* 6 min. ^{13}C NMR ($CDCl_3$): δ 25.5 (C6, t, $^1J_{CH}$ 140 Hz), 34.3 (C2, t, 140), 129.2 (C4, d, 165), 145.6 (C5, d, 161), 191.3 (C3, s).

*5-Phenyl-3,6-dihydro-2*H*-thiopyran-3-one* 10a *and 5-phenyl-3,4-dihydro-2*H*-thiopyran-3-one* 10b. Phenyl magnesium bromide was prepared from bromobenzene (9.9 g, 0.063 mol) and magnesium powder (1.53 g) in ether (30 ml). A solution of 5-methoxy-3,6-dihydro-2*H*-thiopyran-3-one (7.2 g, 0.05 mol) or 5-ethoxy-3,6-dihydro-2*H*-thiopyran-3-one (7.9 g, 0.05 mol) in ether (135 ml) was added dropwise with stirring over 90 min to the Grignard solution kept at room temperature. The mixture was heated under reflux for 4 h after the addition was completed. Crushed ice (*ca.* 5 g) was added to the cold mixture followed by 6 M HCl (35 ml), and the resultant mixture stirred for 30 min. The two layers were separated, the aqueous layer extracted twice with ether, the combined ether solutions washed with sat. $NaHSO_3$, with sat. $NaHCO_3$ and with water, dried ($MgSO_4$), the ether evaporated from the solution and the residue distilled; yield 3.3 g (35 %), b.p. 119–122 °C/10.05 Torr. The isomer ratios for *10a:10b* varied from 4:1 to 2:1. The isomer ratios were determined by GLC on 20 % SE 30. The chromatograph was programmed for 10 °C/min from 135 to 250 °C; retention time for *10a* 13 min, for *10b* 12 min. The isomers were separated on a silica gel column using hexane–ethyl acetate (6:1); the 3,4-dihydro isomer is first eluted. The isomers were also separated using thick-layer chromatography on silica gel 60 PF_{254} Merck. The plates were developed four times with hexane–ethyl acetate (4:1). The 3,4-dihydro isomer has the higher R_F value.

3,6-Dihydro isomer 10a. M.p. 56–58 °C (light petroleum b.p. 40–60 °C). Anal. $C_{11}H_{10}OS$: C, H. ^1H NMR ($CDCl_3$): δ 3.33 (2H-2, s), 3.69 (2H-6, br.s), 6.36 (H-4, t, *J* 1.5 Hz), 7.40 (Ph, s). ^{13}C NMR ($CDCl_3$): δ 27.9 (C6, t, $^1J_{CH}$ 139 Hz), 34.0 (C2, t, 141), 125.3 (d, 165) and 130.7 (d, 158) (C4 and C*p*), 126.0 (d, 165) and 128.9 (d, 159) (C*o*, C*m*), 138.2 (s) and 156.6 (s) (C*x* and C5), 191.9 (C3, s). IR (film): 1660 cm^{-1} α,β-unsat. CO). MS [70 eV; *m/e* (% rel. int.)]: 190 (45, M), 147(8), 145(11), 144(*100*), 116(29), 114(49).

3,4-Dihydro isomer 10b. M.p. 65–67 °C (light petroleum b.p. 40–60 °C). Anal. $C_{11}H_{10}OS$: C, H. ^1H NMR ($CDCl_3$): δ 3.35 (2H-2, s), 3.42 (2H-4, br. s), 6.65 (H-6, br. s), 7.28 (Ph, s). ^{13}C NMR ($CDCl_3$): δ 36.5 (C2, t, $^1J_{CH}$ 143 Hz), 43.2 (C4, t, 129), 118,0 (d, 170) and 127.7 (d, 160) (C6 and C*p*), 124.9 (d, 158) and 128.6 (d, 160) (C*o*, C*m*), 134.1 (s) and 139.2 (s) (C5 and C*p*), 202.0 (C3, s). IR (film): 1710^{-1} (CO), MS [70 eV; *m/e* (% rel. int.)]: 190(*100*), 160(10), 148(22), 146(99), 144(20), 130(14), 129(9), 115(31).

*5-Ethyl-3,6-dihydro-2*H*-thiopyran-3-one* 11a *and 5-ethyl-3,4-dihydro-2*H*-thiopyran-3-one* 11b, were prepared as *10* above from ethyl magnesium bromide, and the reaction mixture was worked up in the same way; yield 35 %, b.p. 114–116 °C/0.15 Torr. The product was a yellowish oil. GLC analysis on 20 % SE 30 showed slight variations in the isomer ratios in various runs; 5–12 % of the product consisted of the 3,4-dihydro isomer *11b*. The chromatograph was programmed for 8 °C/min from 150 to 200 °C; retention time for *11a* 4 min, for *11b* 3 min.

The isomers were separated on a silica gel column using hexane–ethyl acetate (6:1); the 3,4-dihydro isomer was first eluted.

3,6-Dihydro isomer 11a. M.p. < 20 °C. Anal. $C_7H_{10}OS$: C, H. ^1H NMR ($CDCl_3$: δ 1.16 and 2.32 (Et), 3.25 (2H-2, 2H-6), 5.90 (H-4, t, J 1.5 Hz). IR (film): 1670 cm^{-1} (α,β-unsat. CO). MS [70 eV; *m/e* (% rel. int.)]: 142(65, M), 97(10), 96(*100*), 81(30), 68(18), 67(30)).

3,4-Dihydro isomer 11b. M.p. < 20 °C. ^1H NMR ($CDCl_3$): δ 1.05 and 2.13 (Et), 3.00 (2H-4, s), 3.25 (2H-2, s), 6.00 (H-6, s). IR (film): 1720 cm^{-1} (CO). MS [70 eV; *m/e* (% rel. int)]: 142(*100*, M), 100(17), 99(86), 96(19), 85(80), 67(24).

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