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SYNTHESIS AND EQUILIBRIUM STUDIES OF NEW DIHYDROTHIOPHENE SULFOXIDES

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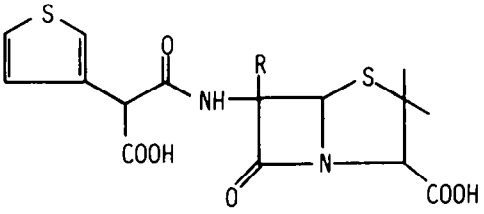
Abstract — Oxidation of the Knoevenagel condensation products 2 of 3-oxotetrahydrothiophene (1) and active methylene compounds of the type Z-CH_2-COOH with an H_2O_2/V_2O_5/t-BuOH reagent furnishes the corresponding sulfoxides 3 in excellent yields. The isomer distributions of the sulfides 2 and the sulfoxides 3 reflect peculiarities of hydrothiophenes as compared to similar open-chain systems and establish that the stabilizing effect of the sulfoxide group on β,γ-double bonds is greater than the corresponding effect of so strongly stabilizing groups as CN and COOR.

3-Substituted thiophenes play a role as intermediates in the synthesis of drugs[1] such as ticarcillin[2a] and temocillin[2b] as well as of potential "organic metals".[3]



ticarcillin (R = H)
temocillin (R = OCH_3)

However, the known methods for the synthesis of 3-substituted thiophenes[4,5] suffer from a number of drawbacks which would make a simple and efficient access route from the commercially available 3-oxotetrahydrothiophene 1[6] highly desirable.

In this context we considered it worthwhile to prepare and characterize the sulfides 2 (Z = CN or COOR) and the corresponding sulfoxides 3, interesting *per se* and as potential intermediates en route to 3-substituted thiophenes.

Our first efforts were directed towards the oxidation of 1 to 4 which in turn ought to form 3 in appropriate Knoevenagel condensations. The selective oxidation of sulfides to sulfoxides is well documented.[7,8] Among the recommended reagents we tried H_2O_2,[9] Bu_4NIO_4,[10] H_2O_2/SeO_2,[11] SeO_2,[12] Br_2,[13] and H_2O_2/V_2O_5/t-BuOH[14], but in all cases intractable tars resulted without any IR absorption attributable to a sulfoxide group. The spiro compound 5 (which we prepared by ketalation of 1 with

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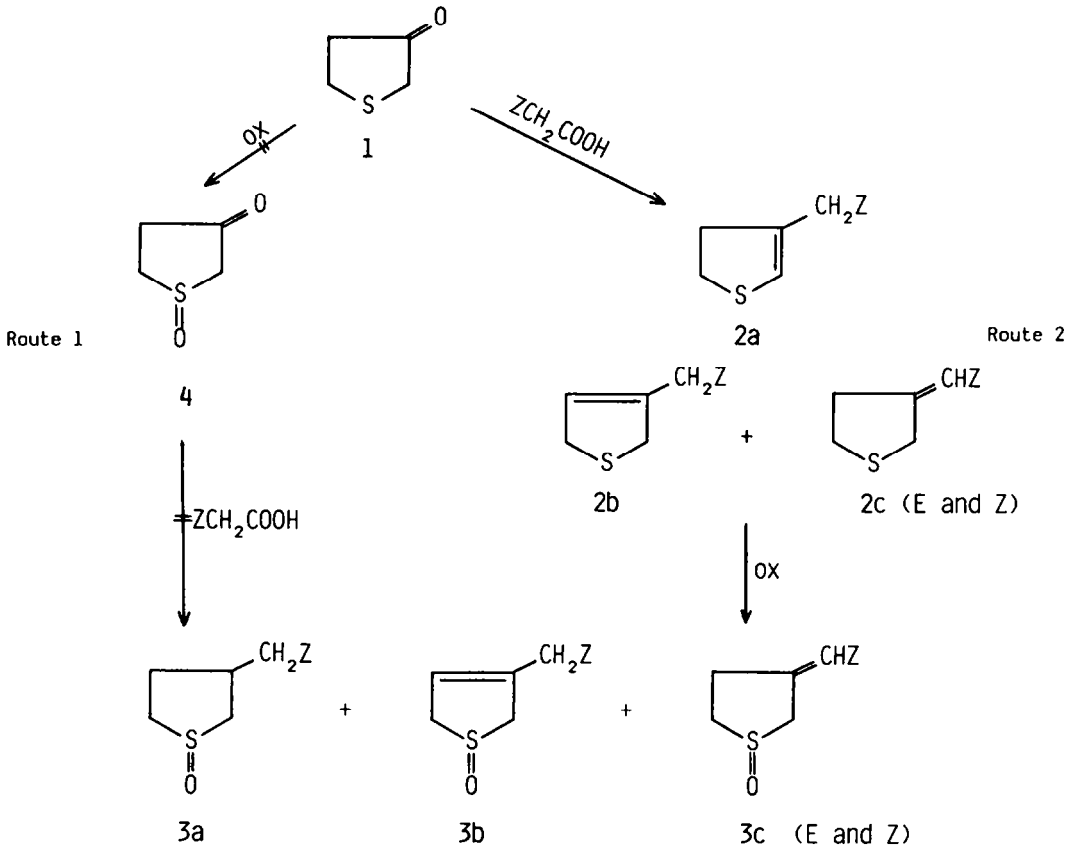
Scheme 1

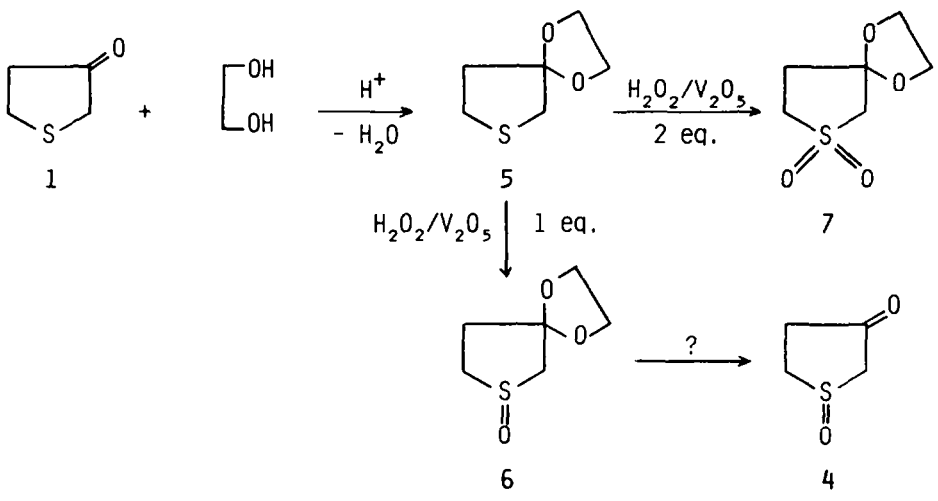


1,2-ethanediol) could be cleanly oxidized to the corresponding sulfoxide 6 (for reference purposes we also prepared the sulfone 7), but we were unable to convert 6 to 4 by direct hydrolysis or by transketalation with acetone. Compound 5 was dissolved in *t*-BuOH and oxidized with an H_2O_2/V_2O_5/*t*-BuOH reagent as described by Hardy, Speakman, and Robson.[14] With its characteristic color change from pale yellow to orange at the end point the reaction can be carried out as a titration. With one equivalent of oxidation reagent and at temperatures below 20 °C the sulfoxide 6 is obtained while the sulfone 7 is formed with two equivalents of oxidant at a reaction temperature of approximately 40 °C. Our failure to isolate the β-keto sulfoxide 4 and hence 3 via route 1 must be due to the inherent instability of 4: Since 1 is consumed by oxidation and 6 slowly yields 1,2-ethanediol by hydrolysis and 2,2-dimethyl-1,3-dioxolane by transketalation with acetone, respectively, 4 must be formed as an intermediate which then polymerizes to the observed tars. For these reasons we had to abandon route 1 and turn to route 2.

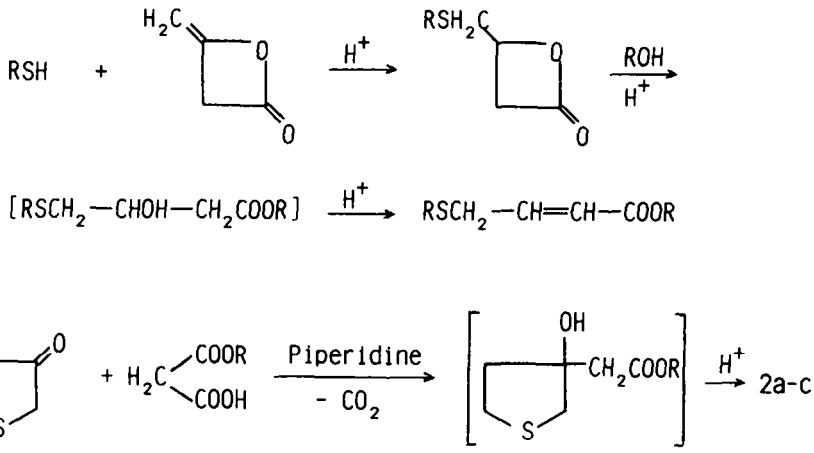
The Knoevenagel condensation of 1 with cyanoacetic acid being known[15] we were able to prepare the compounds 2 (Z = COOMe, COOEt) from the corresponding malonic acid hemiesters. The appropriate condensations are most conveniently performed in the classical manner with piperidine/acetic acid as catalyst and azeotropic removal of the water formed.[16] Since the conventional removal of the catalyst by washing with water[16] reduced the isolated yields by as much as 40 % compared to the glc yields we distilled the untreated crude product mixtures and obtained distilled yields close to the glc yields.

The compounds 2 form mixtures of three tautomers as shown in Scheme 1. A theoretically possible fourth tautomer, the 2,3-dihydro isomer (characterized by two nonequivalent coupling olefinic

Scheme 2



Scheme 3



protons in the NMR spectrum), was not observed. Since the isomer distribution in 2 remains unaffected by prolonged heating with piperidine in benzene or by treatment with potassium ethoxide in ethanol we regard the isomer distribution in 2 to represent the thermodynamic equilibrium.

Oxidation of 2 with the above-mentioned H_2O_2/V_2O_5/t-BuOH reagent yields 3. This demonstrates the selectivity of this procedure towards unsaturated sulfides as opposed to the C-hydroxylation encountered with H_2O_2/OsO_4/t-BuOH.[17] The S-oxidation with V_2O_5 is a mild and rapid reaction without concomitant formation of the corresponding sulfones.

Since the thermodynamic equilibrium ratios 2a:2b:2c and 3a:3b:3c are different the initially formed mixture of 3 tautomers is not in thermodynamic equilibrium, but this is rapidly attained by addition of a trace of piperidine to a chloroform solution of 3.

Tables 1 and 2 show the composition of the equilibrium mixtures. The relative amounts of the isomers were determined by integration of the olefinic proton signals in the ^{1}H NMR spectra. The assignments were made by comparison with calculated values obtained from semiempirical formulas.[18] The spectra of the compounds 2 (Z = COOR) contain only two olefinic proton signals. Since the semiempirical calculations predict identical olefinic proton shifts for the **b** and **c** isomers one might suspect the corresponding signals to coincide. This is, however, ruled out by the symmetry of the peak and the exact 1:4 integral ratio of the olefinic signal and the methylene signal at 3.7 ppm due to four α protons corresponding to a 2,5-dihydro isomer of type b, but not to a type c isomer. The characteristic olefinic coupling pattern of **2c** (Z = CN) is absent in the spectra of the esters. In view of the complexity of the ^{1}H NMR spectra (due to the tautomer equilibria and the additional endo-exo isomerism of the sulfoxides) we have evaluated the integral peak areas without attempting to make a full assignment of all spectral lines. Separation of the 3 isomers by column chromatography is possible, but was deemed unnecessary in the present context. A sample of pure crystalline **3b** (Z = CN) was, however, isolated. Its ^{1}H NMR spectrum contained, as expected, one olefinic and two methylene signals in the integral ratio 1:4:2. Upon equilibration in the presence of piperidine **3b** (Z = CN) reverted to the original tautomer mixture.

Table 1. Relative composition of the sulfides **2**

Z	Y	% a	% b	% c
CN	H	44	27	29
COOMe	H	61	39	0
COOEt	H	62	38	0

Table 2. Relative composition of the sulfoxides **3**

Z	Y	% a	% b	% c
CN	H	6	24	70
COOMe	H	22	35	43
COOEt	H	23	35	42

It is interesting to note that the sulfides **2** exhibit an equilibrium isomer distribution (see Table 1) which differs substantially from what one would expect for open-chain analogs. The acid catalyzed addition of thiols to diketene, followed by acidic alcoholysis,[19] proceeds via an intermediate which is analogous to the Knoevenagel intermediate in the present reaction (see Scheme 3). In the open-chain case the C=C double bond is exclusively located α,β to the ester group while the corresponding **2c** are absent for Z = COOR and only constitute 29 % of the equilibrium mixture for Z = CN. While the open-chain cases illustrate the general phenomenon that CN and COOR groups stabilize C=C double bonds much better than SR groups[20] the cyclic cases are remarkable for the unexpectedly high preponderance of **2a** and **2b**, *i.e.* isomers where the C=C double bond has moved away from its conjugation with the Z group.

While a rule applicable to six-membered rings predicts endocyclic double bonds to be favored over exocyclic double bonds in tautomeric equilibria[21] this effect appears to be relatively weak since the equilibrium between 1-cyclohexenecarbonitrile and cyanomethylenecyclohexane is essentially 100 % in favor of the exocyclic tautomer.[22] Thus, in our thiophene derivatives **2** and **3** the inherent preference for endocyclic C=C double bonds is much more pronounced than it is in the general case, *i.e.* the sulfur atom in **2** and **3** cannot be regarded as a mere spacer roughly equivalent to a CH_2CH_2 group. Birch reduction of thiophene and 3-methylthiophene leads to mixtures of the corresponding 2,5- and 4,5-dihydro compounds, the former predominating.[23] Our results show the same preference for 2,5- over 4,5-dihydro tautomers, even to the extent that the general trend towards C=C-Z conjugation is overruled, but a unified theoretical interpretation of these effects remains to be elaborated.

According to a general rule proposed by Ingold[24] one should expect that the increased electronegativity of the sulfur center and the increased acidity of the α-methylene protons in **3** as compared to **2** would make **3a** more important than **2a** in the respective equilibria. The opposite is the case in our experiments: upon oxidation the content of **a** isomer decreases relative to the sum of **b** and **c** isomer. Similar observations have been made by other investigators,[20,25] but our case is the first example of an allylic system with terminal Z and S(=O)R groups, *i.e.* with opposing effects of these groups on the position of the C=C double bond. The peculiar behavior of allylic sul-

foxides has been interpreted as a consequence of the -I effect of a sulfoxide group upon an adjacent C=C double bond being more pronounced that its corresponding -M effect.[20] While -M groups stabilize double bonds -I groups destabilize them (and +I groups are hence stabilizing).

EXPERIMENTAL

Sulfides 2, general procedure

A 100 ml two-necked flask equipped with a Dean-Stark water separator is charged with 10.2 g (0.1 mole) tetrahydrothiophene-3-one (1), 0.1 mole of the appropriate active methylene compound (ZCH_2COOH), 50 ml benzene, 4 ml acetic acid, and 2 ml piperidine. The mixture is refluxed until water separation ceases. The benzene is evaporated on a flash evaporator and the remaining oil distilled at moderate vacuum. To prevent crystallisation of piperidinium acetate the condenser is kept warm during the distillation of the foreruns.

By this procedure the following compounds have been prepared (unpublished data for 2 with Z = CN included).

3-Dihydrothiopheneacetonitrile mixture 2a-c (Z = CN)

Yield: 83%, b.p. 142-144 °C/20 mm Hg. ^{1}H NMR (δ, $CDCl_3$): 6.1 m (0.44 H), 5.9 m (0.27 H), 5.4-5.3 m (0.29 H), 3.8-2.5 m (6 H); IR (cm^{-1}, film): 2875 m, 2750 m, 2260 m, 2210 s, 1630 m, 1440 m, 1410 s, 800 s; MS (*m/z*, 70 eV): 125 (M), 98 (M-HCN), 85 (M-CH_2CN).

Ethyl 3-dihydrothiopheneacetate mixture 2a-c (Z = COOEt)

Yield: 44%, b.p. 138-145 °C/20 mm Hg. ^{1}H NMR (δ, $CDCl_3$): 5.86 m (0.62 H), 5.58 m (0.38 H), 4.1 q (2 H), 3.9-2.5 m (6 H), 1.3 t (3 H); IR (cm^{-1}, film): 1725 s, 1360 m, 1250 m, 1160 m, 1030 m; MS (*m/z*, 70 eV): 172 (M), 99 (M-COOEt). (Found: C, 55.70; H, 7.10; S, 18.37. Calc. for $C_8H_{12}O_2S$ (172.24): C, 55.79; H, 7.02; S, 18.61).

By using an additional 0.05 mole monoethyl malonate and by adding 1 ml piperidine after 12 hours a 59% yield, based on 1, is obtained after 24 h.

Methyl 3-dihydrothiopheneacetate mixture 2a-c (Z = COOMe)

Yield: 30%, b.p. 113 °C/10 mm Hg. ^{1}H NMR (δ, $CDCl_3$): 5.85 m (0.61 H), 5.65 m (0.39 H), 3.7-2.5 m (6 H), 3.6 bs (3 H); IR (cm^{-1}, film): 1750 s, 1450 s, 1280 m, 1250 m, 1180 m; MS (*m/z*, 70 eV): 158 (M), 99 (M-COOMe). (Found: C, 53.07; H, 6.50; S, 18.90. Calc. for $C_7H_{10}O_2S$ (158.22): C, 53.14; H, 6.37; S, 20.26).

1,4-Dioxa-6-thiaspiro[4.4]nonane 5

20.4 g (0.2 mole) 1, 13.65 g (0.22 mole) ethylene glycol, and 0.5 g *p*-toluenesulfonic acid are refluxed in 100 ml benzene in a 250 ml flask equipped with a Dean-Stark water separator until water formation ceases (3.5 ml). The cooled reaction mixture is washed with 50 ml 2 N sodium hydroxide and 50 ml water and dried over potassium carbonate. The benzene is evaporated and the crude product distilled under vacuum. Distilled yield: 22.2 g (74%) of colorless liquid, b.p. 92-96 °C/15 mm Hg, n_D^{20} 1.5152. ^{1}H NMR (δ, $CDCl_3$): 3.9 s (4 H), 2.7 t (2 H), 2.7 s (2 H), 2.0 t (2 H); ^{13}C NMR (δ, $CDCl_3$): 117.25, 69.22, 36.81, 26.23; IR (cm^{-1}, film): 1320 m, 1225 m, 1100 s, 1010 s; MS (*m/z*, 70 eV): 146 (M), 118 (M-C_2H_4), 100 (M-CH_2S), 99 (M-CH_3S). (Found: C, 47.98; H, 6.70; S 22.09. Calc. for $C_6H_{10}O_2S$ (146.20): C, 49.29; H, 6.89; S, 21.93).

Reagent for oxidation of 2 to 3

100 ml 35% hydrogen peroxide and 400 ml *t*-butanol are shaken with a small amount of sodium sulphate until water separates from the organic phase. The water is discarded and the organic phase dried repeatedly over sodium sulphate and finally over potassium sulphate. This procedure yields a 6% hydrogen peroxide solution in *t*-butanol.

For the oxidation of 10 mmole of sulfide 6 g of this solution (a small excess) is diluted with 15 ml *t*-butanol and 15 mg vanadium pentoxide are added. After standing for 1 h the orange reagent is ready for use.

Sulfoxides 3 and 6, general procedure

10 mmole of the dihydrothiophene is dissolved in 20 ml *t*-butanol in a three-necked flask equipped with a magnetic stirrer, thermometer and dropping funnel. The solution is cooled to 15-18 °C on a water bath. To prevent partial freezing of the reaction mixture up to 10 per cent water may be added without affecting the results. With intensive stirring the oxidation reagent is added dropwise at a rate slow enough to maintain a colorless solution at a temperature below 20 °C. The end point of this titration is reached when a permanent orange color remains after addition of a drop of the oxidation reagent. The *t*-butanol is evaporated and the product taken up in chloroform or a *t*-butanol/ether mixture to precipitate the inorganic material which is filtered off. Analytical samples can be obtained by passing the product through a short silica gel plug or by preparative TLC. By this procedure the following compounds were obtained:

3-Dihydrothiopheneacetonitrile S-oxide 3 (Z = CN)

Quantitative yield, pale yellow oil. ^{1}H NMR (δ, $CDCl_3$): 6.7 m (0.06 H), 6.0 m (0.24 H), 5.6-5.4 m (0.70 H), 4.0-2.5 m (6 H); IR (cm^{-1}, film): 2210 s, 1635 m, 1410 m, 1115 m, 1035 s; MS (*m/z*, 70 eV): 141 (M), 93 (M-SO), 66 (93-HCN). Exact mass found: 141.0248, calc. for C_6H_7NOS: 141.0248.

From a silica gel column (eluent: ether/ethanol) the 2,5-dihydro isomer can be isolated as a solid, m.p. 106-109 °C. ^{1}H NMR (δ, $CDCl_3$): 6.0 m (1 H), 4.1-3.1 m (6 H). Other data identical.

Methyl 3-dihydrothiopheneacetate 3-oxide mixture 3 (Z = COOMe)

Quantitative yield, colorless oil. ^{1}H NMR (δ, $CDCl_3$): 6.5 m (0.22 H), 6.0 m (0.35 H), 5.7 m (0.43 H), 3.6 s (1 H), 4.3-2.2 m (6 H); IR (cm^{-1}, film): 1735 s, 1720 s, 1440 m, 1360 m, 1280 m, 1230 s, 1170 m, 1040 s; MS (*m/z*, 70 eV): 174 (M), 143/142 (M-MeO(H)), 115 (M-COOMe).

Ethyl 3-dihydrothiopheneacetate S-oxide mixture 3 (Z = COOEt)

Quantitative yield, colorless oil. ^{1}H NMR (δ, $CDCl_3$): 6.5 m (0.23 H), 6.0 m (0.35 H), 5.8 m (0.42 H), 4.2 g (2 H), 3.9-2.5 m (6 H), 1.3 t (3 H); IR (cm^{-1}, film): 1730 s, 1720 s, 1370 m, 1260 s, 1230 s, 1180 m, 1040 s; MS (*m/z*, 70 eV): 188 (M), 143/142 (M-EtO(H)), 115 (M-COOEt). Exact mass found: 188.0507, calc. for $C_8H_{12}O_3S$: 188.0507.

1,4-Dioxa-6-thiaspiro[4.4]nonane S-oxide 6

Crude yield 88.7%. Distilled yield 71%, b.p. 103-106 °C/0.18 mm Hg, n_D^{21} 1.5203. ^{1}H NMR (δ, $CDCl_3$): 3.93 s (4 H), 2.4-2.0 m (6 H); IR (cm^{-1}, film): 1310 m, 1090 m, 1025 s; MS (*m/z*, 70 eV); 162 (M), 134 (M-C_2H_4), 100 (M-CH_2OS), 99 (M-CH_3OS). (Found: C, 44.48; H, 6.20; S, 19.07. Calc. for $C_6H_{10}O_3S$: C, 44.43; H, 6.21; S, 19.77).

1,4-Dioxa-6-thiaspiro[4.4]nonane S,S-dioxide 7

Procedure as above, but 2 eq. oxidation reagent used and reaction mixture kept at 30 °C. Yield 81%, colorless needles, m.p. 56-57 °C (chloroform/petroleum ether); ^{1}H NMR (δ, $CDCl_3$): 4.05 s (4 H), 3.30 t (2 H), 3.25 s (2 H), 2.44 t (2 H); ^{13}C NMR (δ, $CDCl_3$): 109.85, 64.74, 58.70, 52.17, 33.79; IR (cm^{-1}, KBr): 1415 s, 1375 s, 1200 m, 1090 s, 1020 m; MS (*m/z*, 70 eV): 178 (M), 162 (M-O), 134 (M-C_2H_4O), 100 (M-CH_2O_2S), 99 (M-CH_3O_2S) (Found: C, 40.44; H, 5.66; S, 17.70. Calc. for $C_6H_{10}O_4S$: C, 40.44; H, 5.66; S, 17.99).

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