Tetrahedron Vol 33, pp 2151 to 2156 Pergamon Press 1977 Printed in Great Britain

SYNTHETIC STUDIES RELATED TO 1,4-DITHIOCIN

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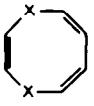
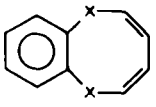
(*Received in UK 21 March 1977; Accepted for publication 29 March 1977*)

Abstract—Several approaches towards the synthesis of 1,4-dithiocin **1c**, a potential 10π-electron aromatic system, have been investigated. Starting from *trans* - 6,7 - dihydroxy - 5,6,7,8 - tetrahydro - 1,4 - dithiocin - 6,7 - bismethanesulfonate **13** or the corresponding bis-*p*-toluenesulfonate **14**, base catalyzed elimination reactions yielded, depending on the conditions, 6 - hydroxy - 5,6 - dihydro - 1,4 - dithiocin **18** and/or ring contraction products with 7 - membered (e.g. **23**) or 6-membered rings (e.g. **19**); **1c** was not obtained. **18** seemed to be an attractive precursor, but again all attempts to obtain **1c** by various methods led to decomposition or, in some cases, benzene, which is presumably formed thermally from **1c**.

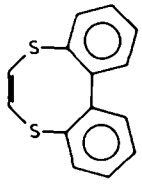
Recently much effort has been devoted to the synthesis of the diheterocins **1a–c**, which are isoelectronic with the aromatic dianion of cyclooctatetraene[1] and therefore, according to the Hückel 4n + 2 rule, potentially aromatic compounds. The benzoderivatives (**2a**,[4] **2b**,[5] **2c**[6] and **3**[7]) do not show aromatic character; in these cases one can argue that the stability of the benzene ring(s) prevents the delocalization of π electrons in the hetero ring system. Riley and Park synthesized the derivative (**4**) to which they assigned aromatic character on account of its ^{19}F NMR spectrum.[8] The first synthesis of a parent diheterocin was accomplished by Vogel *et al.*,[9] who obtained 1,4-dioxicin (**1a**) by isomerization of its valence isomer (**5a**). The physical and chemical properties of **1a**, however, show it to be clearly olefinic and not aromatic. Recently, Prinzbach *et al.*[10] succeeded in the synthesis of the N,N - dimethyl - 1,4 - diazocin (**6**), the properties of which are indicative of aromatic character. As the sulfur atom can replace a C=C double bond more effectively than other hetero atoms,[11] it was to be expected that of the diheterocins (**1a–c**), 1,4-dithiocin (**1c**) is the most likely to have aromatic character.



1a X=O
1b X=NH
1c X=S
6 X=NCH$_3$



2a X=O
2b X=NCH$_3$
2c X=S



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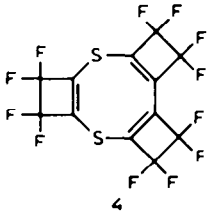

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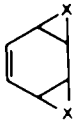
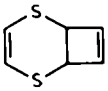


5a X=O
5b X=NCH$_3$
5c X=S



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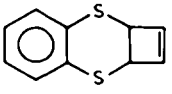


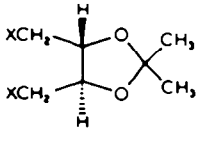
8

The synthesis of the parent compound (**1c**) has been attempted in several ways. Schroth *et al.* found that bis-addition of mercaptans to diacetylenes specifically led to *cis,cis* - 1,4 - disubstituted 1,3 - butadienes. However, addition of *cis* - 1,2 - bismercaptoethene to diacetylene did not give **1c**, but a dithiinderivative.[7] Coffen *et al.* tried the thermal and photochemical isomerization of the valence isomer (**7**[6]), but contrary to the reaction of the benzoderivative (**8**), 1,4-dithiocin was not obtained; instead fragmentation to benzene was the main reaction, presumably via **5c**.[12] A similar result was obtained by Vogel *et al.*,[12] who attempted the thermal isomerization of **5c**, in analogy with their synthesis of 1,4-dioxocin (**1a**). The difference in behaviour of **5a** and **5c** can be explained by the weakness of the C–S bond (65 kcal/mol) compared to the C–O bond (85.5 kcal/mol). Formation of benzene from **5c** through loss of sulfur will therefore probably be much easier and energetically more favourable than ring opening to **1c**.

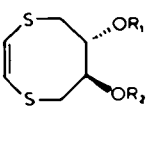
In this paper we wish to report our attempts to synthesize **1c**. Contrary to the above mentioned valence isomerizations we tried the synthesis of **1c** by elimination reactions from suitable di- and tetrahydro precursors.

TETRAHYDRO-1,4-DITHIOCINS AS PRECURSORS

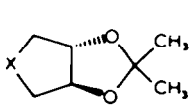
Our synthesis started with the dithioacetate **10**, which is readily available from **9**.[13] Saponification with KOH in EtOH followed by ring closure with *cis* 1,2-dichloroethene, according to the procedure of Schroth *et al.*,[14] afforded the pure ketal (**11**) in 40% yield. The actual yield was higher, but the purification of **11** from the byproducts (**15** and **16**) led to considerable loss of material. Hydrolysis of **11** with 80% acetic acid gave dihydroxy compound (**12**), which was transformed to the *trans*-dimesylate (**13**) or the *trans*-ditosylate (**14**) in the usual way.



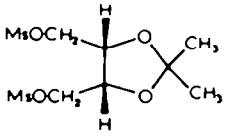
9 X=OMs, OTs
10 X=SAc



11 R$_1$,R$_2$ = >C(CH$_3$)$_2$
12 R$_1$=R$_2$=H
13 R$_1$=R$_2$=Ms
14 R$_1$=R$_2$=Ts
29 R$_1$=Ms, R$_2$=H
30 R$_1$=Ms, R$_2$=Ms



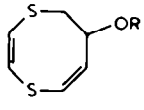
15 X=S-S
16 X=S



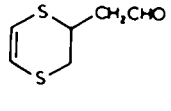
17

The same synthetic scheme could not be applied to the synthesis of the corresponding *cis*-compounds, because the reaction of the meso-dimesylate (17[15]) with sodium thioacetate yielded only low amounts of impure product,[16] which decomposed on distillation. Ring closure and the subsequent reactions with impure intermediate products did not lead to conclusive results.

The elimination reactions of **13** and **14** were carried out with a number of bases in several solvents. In none of these reactions could **1c** be detected as a product. Treatment of **13** and **14** with KO-t-Bu in DMSO or THF at −20° to +20° gave total destruction of the ring system, whereas almost no reaction occurred with 1,5 - diazabicyclo - [5.4.0]undec - 5 - ene (DBU) or 1,8 - bis-dimethylaminonaphthalene ("proton sponge"). Reaction of **13** with KO-t-Bu in t-BuOH or dimethoxyethane (DME) and with KOH in DMF-MeOH or DMF-H_2O at 0–20° afforded, besides tar, alcohol **18** as the main monomeric product, but in low yields. The structure of **18** follows from its spectra and was confirmed by an X-ray analysis of its acetate **32**.[17] The yield of **18** varied strongly and always decreased on scaling up the reaction from 1 to 5 or 10 mmoles.



18 R=H
22 R=Me
32 R=Ac
33 R=COCH$_3$
34 R=CSCH$_3$



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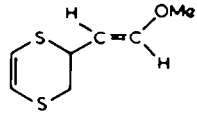

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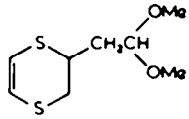

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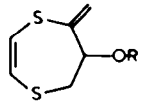


23 R=H
35 R=Ac
36 R=COCH$_3$

Depending on the solvent, several byproducts could be isolated. In some cases, an aldehyde was obtained in low yield to which the 6-membered structure **19** was assigned, based on the triplet at $\delta = 9.81$ ppm of the CHO proton in the NMR spectrum. When MeOH was used as (co)solvent also a mixture of isomeric methyl ethers was isolated of which **20** could be obtained in pure form. The structural assignment of **20** is based on its spectra and on its conversion with acidic MeOH to the acetal **21**, which was also obtained from **19** with 2,2-dimethoxypropane under acid catalysis. The remaining mixture of methyl ethers could not be separated. It contained *ca.* 60% of the methylether (**22**), as determined by comparison of the NMR spectrum of the mixture with that of pure **22**, prepared from **18** by methylation with MeI/NaH. The remaining ethers were not identified. The results of the elimination reactions are summarized in Table 1.

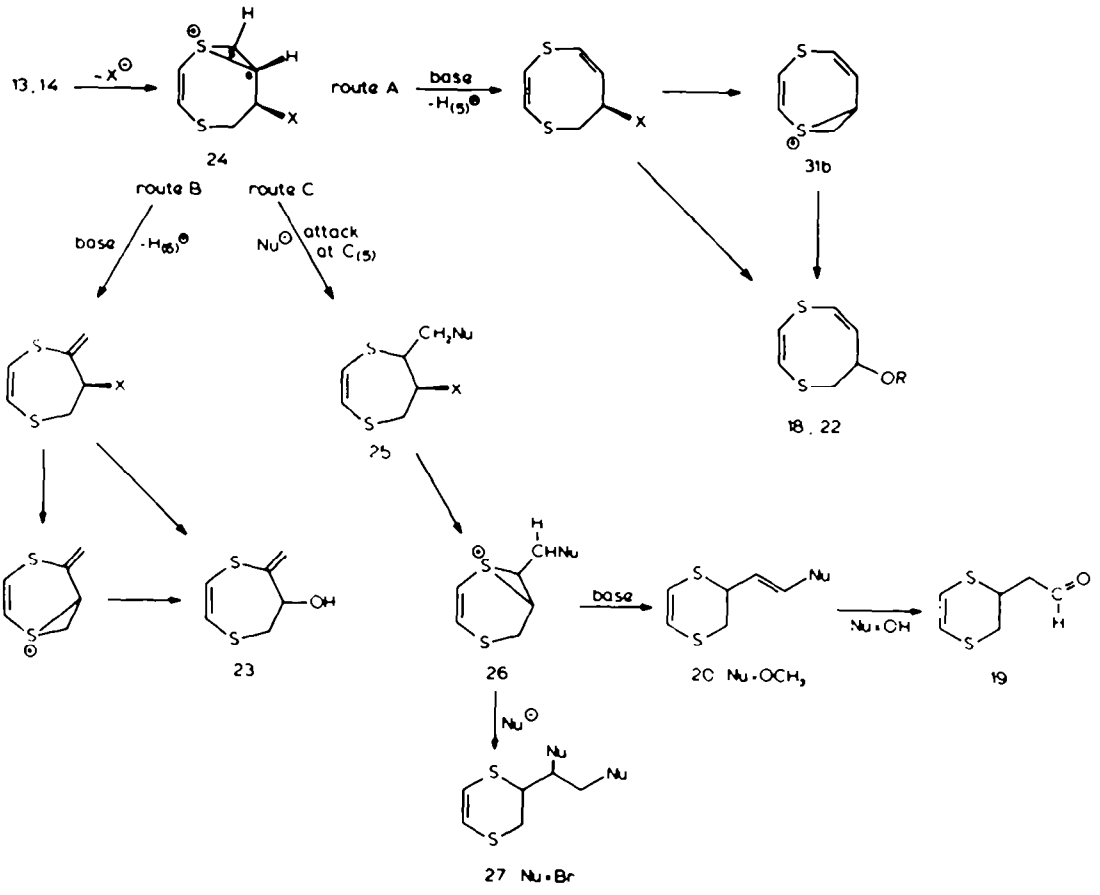
Table 1. Yields of products obtained from the base catalyzed elimination of **13** and **14**

Only with KO-t-Bu in t-BuOH, did the ditosylate (**14**) give the same result as the dimesylate (**13**). However, with KO-t-Bu in DME, or with KOH in DMF-MeOH or in DMF-H_2O, a new alcohol was formed which was isomeric with **18**, whereas **18** was practically absent. The new alcohol gave spectra similar to **18**, and was assigned structure **23** after an investigation of the NMR spectra of both compounds with Eu(DPM)$_3$. The singlet for the vinylic protons at C(2) and C(3) of **18** was split into an AB spectrum by the shift reagent, as expected for the asymmetric relationship between these protons and the OH-group. In contrast, in **23** this singlet remained unsplit under the influence of the shift reagent, indicating that the OH-group has a symmetric position relative to the protons at C(2) and C(3). This is only possible in a 7-membered ring. The other two vinylic protons of the exocyclic $=CH_2$ group showed the expected AB pattern with $J = 1.5$ Hz.

At the present stage, it is difficult to give a consistent interpretation for the formation of all the products of Table 1. However, a few comments can be made. Both the ring contraction in many cases as well as the optical activity in alcohols **18** and **23** point out, that the reactions as a rule do not occur as simple E2 eliminations or via allyl cations. Rather, 1,3-participation is indicated; it is well documented in ring contraction reactions of sulfur heterocycles,[18] and it can explain why optical activity is retained. In our opinion, Scheme 1 gives the most plausible pathways for the observed products, although other possibilities cannot be excluded.

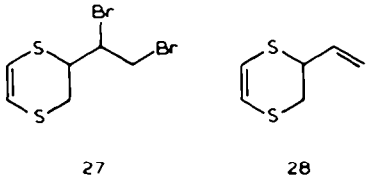
The initial step is formation of the thiiranium ion (**24**), which can react in several ways. Abstraction by base of H(5) and opening of the S–C(6) bond (route A) gives back an 8-membered ring, whereafter direct S_N2 substitution or double substitution via sulfur participation leads to **18** and **22**. As the absolute configuration of **18** (and **23**) is not known, it is not possible to distinguish between these two reactions; however, in view of the generally encountered phenomenon of 1,3-participation, it seems more likely that it is also responsible for the formation of **18** (and **23**; retention of configuration). Abstraction of H(6) and opening of the S–C(5) bond gives a 7-membered ring, which upon substitution yields **23**, as shown in route B.

A third possibility (route C) is attack of a nucleophile at C(5) of **24**, leading to intermediate **25**. Nucleophilic attack at C(6) is probably sterically more hindered than



Scheme 1.

at C(5). Again thiiranium formation, now followed by proton abstraction gives 6-membered ring compounds such as **19** and **20**, whereas, in the absence of base, substitution yields a disubstituted product. Reaction of **13** or **14** with LiBr in acetone gave the dibromo compound (**27**), which upon treatment with $(n\text{-Bu})_3SnH$[19] afforded **28**; no 8-membered ring product was found.

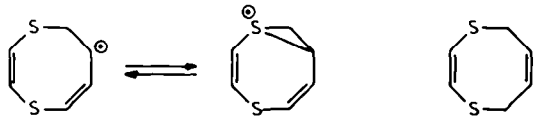


27 28

Scheme 1 does not explain all results. For instance, it is not clear why formation of **23** depends on the leaving group; the difference between a mesylate or tosylate group as leaving group is not so big[20] as to easily explain the exclusive formation of **23** from **14** and not also from **13**. No 6-membered ring product is formed via route B. In this case, apparently 1,3-participation of the S atom which was not involved in the formation of **24** is favoured, as participation of the original S atom would lead to a highly strained 2 - methylene - 1 - thiiranium system. However, in the formation of **19**, **20** and **27** via intermediate **26** the same S atom participates twice. 1,3-Participation of the second S atom in **25** would give an intermediate, which, as molecular models show, is sterically more hindered than **26**. In Scheme 1 only 1,3-participation is used to explain the results. 1,4-Participation cannot be rigorously exluded, but especially formation of **19** and **20** is difficult to explain in this way. Compound **30**, prepared from **12** via **29**, is not an intermediate in the elimination reaction, when MeOH is present. It was unreactive under the same conditions and underwent reaction only with KO-t-Bu in DMSO, to give the previously described mixture of methyl ethers, of which **22** now was only a minor component; no **20** was formed.

DIHYDRO-1,4-DITHIOCINS AS PRECURSORS

Although the elimination reactions from tetrahydro - 1,4 - dithiocins did not afford **1c** directly, the main product **18** seemed to be a promising precursor for **1c**. Two double bonds are in the right position and the OH group offers several possibilities for introducing the third double bond. First we tried dehydration of **18**, but neither reaction with strong acid, nor oxalic acid, nor the mild reagent ethyl(carboxysulfamoyl)triethylammoniumhydroxide[21] afforded **1c**; tar was the only product. Attempts to convert **18** into a chloride with thionylchloride or triphenylphosphine/CCl_4, or into a sulfonate ester failed too. The failure of these reactions must be attributed to the formation of the ions (**31a–b**). A leaving group on C(6) is very reactive because of the allylic position and a sulfur atom in the β-position, so that **31a–b** can be formed easily. That **1c** is not formed from **31a–b** indicates that elimination of H(8) to **1c** is not a reaction that occurs easily; this would not be expected if **1c** had strong aromatic stabilization.

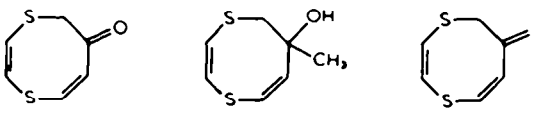


31a 31b 37

The OH group could on the other hand be converted into a less reactive group such as the ester derivatives (32, 33 and 34) in good to moderate yield. Normal pyrolysis of ester derivatives to form a double bond requires high temperatures at prolonged time and seemed to be too rigorous for the synthesis of 1c, in view of the thermal behaviour of 2c, 5c and 7. Flash Vacuum Pyrolysis (FVP)[22] enables the synthesis of thermally unstable compounds and therefore we have tried this method on 32, 33 and 34. The principal reaction product was tar; no 1c could be detected. Pyrolysis of 33 afforded benzene in 30% yield relative to the methanol formed; 32 and 34 gave only minor amounts of benzene. Contrary to these results after pyrolysis of 35, 36 and 37[14] the starting material was recovered without appreciable decomposition.

Elimination of MeOH from 22 with lithium diisopropylamide, by a method developed by Corey *et al.*[23] and successfully applied by Murata *et al.* in the synthesis of 5H-1,4-dithiepin,[24] also failed. Reaction at −78° for 24 hr gave only 22 (75%), whereas reaction at −20° almost and at 0° completely destroyed the ring system; no ether soluble product was found.

Dauben *et al.*[25] obtained several 1,3-dienes from α,β-unsaturated aldehydes and ketones through conversion into the tosylhydrazones followed by elimination with 2 equivalents of MeLi. Oxidation of 18 to 38 could be accomplished with CrO_3 in HMPT[26] in low yield. Activated MnO_2[27] gave still lower yields with much more loss of starting material. Stronger oxidation reagents caused total destruction of 18. Ketone 38 is very unstable towards base. The HMPT used in the oxidation reaction must therefore be completely free of amines, otherwise no ketone could be obtained. The reaction of 38 with tosylhydrazine, followed by MeLi, was not successful; again total destruction of the ring system occurred. Grignard reaction of 38 with MeMgI afforded 39 in moderate yield. Dehydration of 39 might have given the desired endocyclic, or, alternatively, an exocyclic double bond, but just as with 18, these reactions afforded only tar. Wittig reaction of 38 to 40 failed, too.



38 39 40

CONCLUSION

The described failures to synthesize 1c from suitable precursors indicate that in all likelihood 1c will not be strongly stabilized by resonance energy. This is in agreement with the properties of 2c and 3, and is further confirmed by the properties of the 6-acetoxy derivative of 1c.[28] On the other hand, 1c may have been formed as intermediate in those cases, where benzene was obtained; this possibility will also be discussed in the following paper.[28]

EXPERIMENTAL

M.ps are uncorrected. Mass spectra were recorded with a Varian Mat CH5 spectrometer. ^1H NMR spectra were recorded with a Varian A-60 or with a Varian XL-100/12 WG spectrometer (CDCl₃ solutions unless otherwise stated); chemical shifts are given in δ (ppm) from internal TMS. The IR spectra were recorded with a Perkin-Elmer 237 or a Beckman Acculab 4 spectrophotometer (5% in $CHCl_3$ or 0.3% in KBr) and the UV spectra with a Perkin-Elmer 137 spectrophotometer. Preparative TLC was carried out on PSC-Fertig-platten Kieselgel F 254 (Merck) with $CHCl_3$ as eluent unless otherwise stated. Elemental analyses were performed under supervision of Mr. W. J. Buis at the Micro-Analytical Department of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands.

trans - 6,7 - *Dihydroxy* - 6,7 - O - *isopropylidene* - 5,6,7,8 - *tetrahydro* - 1,4 - *dithiocin* (11)

A soln of 10 (69.5 g, 0.25 mol) and KOH (70 g, 1.25 mol) in 1.25 l EtOH (abs) was stirred for 16 hr under N_2. *cis*-1,2-Dichloroethene (21 ml; 0.28 mol) was added and the mixture was refluxed for 20 hr under N_2 with stirring. The solvent was evaporated, the residue dissolved in H_2O and 2x extracted with ether. The combined ether extracts were washed with 2N NaOH and H_2O and dried on $MgSO_4$. Evaporation *in vacuo* followed by short path distillation and crystallization from MeOH gave 21.5 g 11 as colourless crystals (40%). The crystallization residue consisted according to GC–MS mostly of 11 and two other compounds with molecular weights of 160 resp. 192. The NMR spectrum of the residue was very similar to that of pure 11; only the ratio of olefinic to aliphatic protons was lower. Therefore, structures 16 and 15 were assigned to these compounds. M.p. 54°; IR: 1380, 1370, 1230, 1050; NMR: 1.42 (s, 6 H; CH_3), 2.78 (m, 2 H; H_5, H_8), 3.88 (m, 2 H; H_5, H_8), 4.38 (m, 2 H; H_6, H_7), 6.44 (s, 2 H; H_2, H_3). (Found: C, 49.46, H, 6.45, S, 29.25. $C_8H_{14}O_2S_2$ requires: C, 49.50, H, 6.46, S, 29.37%).

trans - 6,7 - *Dihydroxy* - 5,6,7,8 - *tetrahydro* - 1,4 - *dithiocin* (12)

A soln of 11 (21.8 g, 0.1 mol) in 180 ml 80% AcOH was stirred for 3 hr at 80°. After evaporation of the solvent *in vacuo* the residue was 3x flashed off with benzene. The crude product was used without purification for the syntheses of 13 and 14. An analytically pure sample of 12 was obtained by recrystallization from $CHCl_3$–ether. M.p. 70°; IR: 3540, 3380, 1030. NMR: 2.90 (m, 2 H; H_5, H_8), 3.90 (broad s, 2 H; OH), 4.10 (m, 2 H; H_6, H_7), 4.25 (m, 2 H; H_5, H_8), 6.33 (s, 2 H; H_2, H_3): (Found: C, 40.47, H, 5.68, S, 35.80. $C_8H_{10}O_2S_2$ requires: C, 40.42, H, 5.65, S, 35.97%).

trans - 6,7 - *Dihydroxy* - 5,6,7,8 - *tetrahydro* - 1,4 - *dithiocin* - 6,7 - *bismethanesulfonate* (13)

To a stirred soln of 12 (18.0 g, 0.1 mol) in 85 ml pyridine was added dropwise mesyl chloride (19.0 ml, 0.25 mol) at −10° in 1 hr. After standing for 20 hr at 0° the mixture was poured into 260 ml ice-water. The resulting ppt was filtered off, washed with cold H_2O and dried *in vacuo* above P_2O_5. Recrystallization from $CHCl_3$ yielded 21.7 g 13 of pale brown crystals (65%); m.p. 133°; IR: 1350, 1180, 1160; NMR (D_6-DMSO): 3.25 (s, 6 H; CH_3), 3.30 (m, 2 H; H_5, H_8), 4.25 (m, 2 H; H_5, H_8), 5.27 (m, 2H; H_6, H_7), 6.54 (s, 2 H, H_2, H_3). (Found: C, 28.60, H, 4.28, S, 38.00. $C_{10}H_{14}O_6S_4$ requires: C, 28.73, H, 4.22, S, 38.35%).

trans - 6,7 - *Dihydroxy* - 5,6,7,8 - *tetrahydro* - 1,4 - *dithiocin* - 6,7 - *bis* - p - *toluenesulfonate* (14)

Compound 14 was prepared in the same way as 13. When the mixture was poured into ice-water, a viscous oil separated. The aqueous mixture was 2x extracted with benzene; the benzene extracts were washed with 2N HCl and H_2O, dried on $MgSO_4$ and evaporated, yielding 14 (8.4 g, 70%) as colourless, viscous oil. On dissolving in MeOH, partial crystallization occurred. For the elimination reactions both crystals and oil were used, giving identical results; m.p. 117°; IR: 1370, 1190, 1175; NMR: 2.45 (s, 6 H; CH_3), 3.30 (m, 2 H; H_5, H_8), 3.95 (m, 2 H; H_5, H_8), 5.04 (m, 2 H; H_6, H_7), 6.28 (s, 2 H; H_2, H_3), 7.60 (m, 8 H; aromatic protons). (Found: C, 49.39, H, 4.61, S, 26.29. $C_{20}H_{22}O_6S_4$ requires: C, 49.36, H, 4.56, S, 26.25%).

Elimination reactions with **13**.

(a) *With* KO-t-Bu *in* t-BuOH *or DME*. A suspension of **13** (1.0 g, 3 mmol) and KO-t-Bu (0.84 g, 7.5 mmol) in 30 ml t-BuOH or DME was stirred under N_2 for 1 hr at room temp. After dilution with H_2O the mixture was extracted with ether. The ethereal extracts were washed with H_2O, dried on $MgSO_4$ and evaporated. The products were isolated by TLC.

(b) *With* NaOMe *in* MeOH. A soln of **13** (0.67 g, 2 mmol) and NaOMe (216 mg, 4 mmol) in 12 ml MeOH was refluxed with stirring for 1 hr under N_2. The mixture was worked up as described under (a).

(c) *With* KOH *in* DMF–MeOH. To a stirred soln of **13** (1.0 g, 3 mmol) in 24 ml DMF–MeOH 1:1 solid KOH (0.56 G, 10 MMOL) was added. After stirring for 2 hr at room temp. under N_2 the mixture was worked up as described under (a).

(d) *With* KOH *in* DMF–H_2O. To a stirred solution of **13** (1.0 g, 3 mmol) in 24 ml DMF–H_2O 3:1 solid KOH (0.56 g, 10 mmol) was added. After stirring for 2 hr at room temp under N_2 the mixture was worked up as described under (a).

6-*Hydroxy*-5,6-*dihydro*-1,4-*dithiocin* (**18**)

Short-path dist. 85°/0.1 mm. On standing at −20° **18** solidified. Recrystallization from n-hexane/ether yielded pale yellow crystals, m.p. 45°; IR: 3590, 3390, 1020; NMR: 2.49 (dd, 1 H; H_5, $J_{5,5'}$ = 14 Hz, $J_{5,6}$ = 7 Hz), 2.56 (broad s, 1 H; OH), 3.88 (dd, 1 H; $H_{5'}$, $J_{5',6}$ = 5 Hz), 5.05 (m, 1 H; H_6), 6.13 (m, 2 H; H_7, H_8), 6.25 (s, 2 H; H_2, H_3); $[\alpha]_{546}^{20}$ = 102° ($CHCl_3$)), measured on a sample of **18** which was composed mostly of the product obtained from reaction under conditions (c) and (d). (Found: C, 45.19, H, 5.14, S, 40.13. $C_6H_8OS_2$ requires: C, 44.96, H, 5.03, S, 40.02%).

2-(2-*Oxoethyl*)-2,3-*dihydro*-1,4-*dithiin* (**19**)

Short-path dist. 80°/0.1 mm; IR: 2810, 2720, 1710; NMR: 2.96 (dd, 2 H; CH_2, J = 1 and J = 7 Hz), 2.95 (dd, 1 H; H_3, $J_{3,2}$ = 7 Hz and $J_{3,3'}$ = 14 Hz), 3.28 (dd, 1 H; $H_{3'}$, $J_{3',2}$ = 2 Hz), 3.85 (m, 1 H; H_2), 6.10 (s, 2 H; H_5, H_6), 9.81 (t, 1 H; CHO, J = 1 Hz).

2,4-*Dinitrophenylhydrazone of* **19**. M.p. 125°; IR: 3260, 1625, 1590, 1505, 1335; NMR (D_6-DMSO): 2.85 (m, 2 H; CH_2), 3.24 (m, 2 H; H_3, H_3), 3.73 (m, 1 H; H_2), 6.27 (s, 2 H; H_5, H_6), 8.01 (t, 1 H; CH=N, J = 5 Hz), aromatic protons 7.93 (d, 1 H; J = 9 Hz), 8.33 (dd, 1 H; J = 9 Hz and J = 2.5 Hz), 8.83 (d, 1 H; J = 2.5 Hz). (Found: C, 42.57, H, 3.53, N, 16.26, S, 18.78. $C_{12}H_{12}N_4O_4S_2$ requires: C, 42.34, H, 3.55, N, 16.46, S, 18.84%).

2-(trans-2-*Methoxyvinyl*)-2,3-*dihydro*-1,4-*dithiin* (**20**)

Short-path dist. 80°/0.1 mm; IR: 1665, 1645, 1305, 1140, 935; NMR: 3.05 (m, 2 H; H_3, H_3), 3.55 (s, 3 H; CH_3), 3.93 (m, 1 H; H_2), 4.82 (dd, 1 H; CH=, J = 9.5 Hz and J = 12.5 Hz), 6.13 (s, 2 H; H_5, H_6) 6.60 (d, 1-H; =CHOMe, J = 12.5 Hz). (Found: C, 48.44, H, 5.94, 36.65. $C_7H_{10}OS_2$ requires: C, 48.24, H, 5.78, S, 36.79%).

2-(2,2-*Bismethoxyethyl*)-2,3-*dihydro*-1,4-*dithiin* (**21**)

(a) *From* **19**. A soln of **19** (80 mg, 0.5 mmol), 1 ml 2,2-dimethoxypropane and 10 mg *p*-toluenesulfonic acid was refluxed for 4 hr under N_2. After addition of 20 mg K_2CO_3 the mixture was diluted with ether, washed with H_2O, dried on $MgSO_4$ and evaporated. TLC yielded 72 mg **21** (70%).

(b) *From* **20**. A soln of **20** (35 mg, 0.2 mmol) and 5 mg *p*-toluenesulfonic acid in 1 ml MeOH was refluxed for 1 hr under N_2. Working up as above yielded 30 mg **21** (75%). The spectra of the compounds obtained by both reactions were identical. Short-path dist. 80°/0.1 mm; IR: 2835, 1125, 1055; NMR: 2.03 (dd, 2 H; CH_2, J ≈ 6 Hz and J ≈ 7 Hz), 2.90 (dd, 1 H; $J_{3,2}$ = 3 Hz and $J_{3,3'}$ = 13 Hz), 3.25 (dd, 1 H; $H_{3'}$, $J_{3',2}$ = 3 Hz), 3.31 (s, 3 H; CH_3), 3.33 (s, 3 H; CH_3), 3.50 (m, 1 H, H_2), 4.62 (t, 1 H; CH, J = 6 Hz), 6.08 (s, 2 H; H_5, H_6) Mass spectrum: M⁺ calculated 206.0435, found 206.0431.

6-*Methoxy*-5,6-*dihydro*-1,4-*dithiocin* (**22**)

To a stirred suspension of NaH (36 mg, 1.5 mmol) in 4 ml THF at 0° was added **18** (0.24 g, 1.5 mmol). After 0.5 hr 0.1 ml MeI was added and the stirring continued for 4 hr under N_2 at room temp. The mixture was diluted with H_2O and 2x extracted with ether. The ethereal extracts were washed with H_2O, dried on $MgSO_4$ and evaporated. TLC yielded **22** (174 mg, 66%) and **18** (32 mg, 13%).

Short-path dist. 80°/0.1 mm; IR: 3000, 2915, 2815, 1190, 965; NMR: 2.33 (dd, 1 H; H_5, $J_{5,5'}$ = 13 Hz and $J_{5,6}$ = 7.5 Hz), 3.34 (s, 3 H; CH_3), 3.42 (dd, 1 H; $H_{5'}$, $J_{5',6}$ = 5 Hz), 4.55 (m, 1 H; H_6, $J_{6,7}$ = 5 Hz), 5.90 (dd, 1 H; H_7, $J_{7,8}$ = 3 Hz), 6.05 (d, 1 H; H_8), 6.20 (AB, 2 H; H_2, H_3, J = 9 Hz).

Elimination reactions with **14**. These were carried out and worked up in the same way as described for **13**.

5-*Methylene*-6-*hydroxy*-6,7-*dihydro*-5H-1,4-*dithiepin* (**23**)

Short-path dist. 85°/0.1 mm; IR: 3590, 3540, 3360, 1400, 1380, 1060, 1000, 930; NMR: 2.75 (broad s, 1 H; OH), 3.10 (dd, 1 H; H_7, $J_{7,6}$ = 6 Hz and $J_{7,7'}$ = 15 Hz), 3.60 (dd, 1 H; $H_{7'}$, $J_{7',6}$ = 4 Hz), 5.86, 5.95 (AB, 2 H; CH_2 = J = 1.5 Hz), 6.02 (s, 2 H; H_2, H_3)); $[\alpha]_{546}^{20}$ = 81° ($CHCl_3$)), measured on **23** obtained by method c). (Found: C, 44.98, H, 5.23, S, 37.03. $C_6H_8OS_2$ requires: C, 44.96, H, 5.03, S, 40.02%: Mass spectrum: M⁺ calculated 160.0017, found 160.0021).

trans-6-*Methoxy*-7-*hydroxy*-5,6,7,8-*tetrahydro*-1,4-*dithiocin* (**29**)

To a stirred suspension of NaH (192 mg, 8 mmol) in 15 ml DMF was added **12** (1.44 g, 8 mmol) at 0°. After 0.5 hr 0.6 ml MeI was added and the stirring continued for 4 Hr under N_2 at room temp. The mixture was diluted with H_2O and 2x extracted with ether; the ethereal extracts were washed with H_2O, dried on $MgSO_4$ and evaporated. TLC yielded **29** (553 mg, 35%), **12** (0.35 g, 25%) and dimethylether of **12** (291 mg, 17%). NMR: 2.95 (m, 2 H; H_5, H_8), 3.16 (broad s, 1 H; OH), 3.48 (s, 3 H; CH_3), 3.6–4.5 (m, 4 H; $H_{5'}$, $H_{8'}$, H_6, H_7), 6.33 (s, 2 H; H_2, H_3).

trans-6-*Methoxy*-7-*hydroxy*-5,6,7,8-*tetrahydro*-1,4-*dithiocin*-7-*methanesulfonate* (**30**)

To a stirred solution of **29** (553 mg, 2.9 mmol) in 4 ml pyridine was added at −10° mesylchloride (0.265 ml, 3.5 mmol). After stirring for 3 hrs and standing for 16 hr at 0°, the mixture was diluted with ice-water and 2x extracted with benzene. The benzene extracts were washed with 2N HCl and H_2O, dried on $MgSO_4$ and evaporated. Yield 0.78 g colourless, viscous oil (100%). NMR: 2.90–4.15 (m, 5 H; H_5, $H_{5'}$, H_8, $H_{8'}$, H_6), 3.03 (S, 3 H; OSO_2CH_3), 3.40 (s, 3 H; OCH_3), 4.92 (dt, 1 H; H_7, J = 3 Hz and J = 9 Hz), 6.27 (s, 2 H; H_2, H_3).

2-(1,2-*Dibromoethyl*)-2,3-*dihydro*-1,4-*dithiin* (**27**)

A soln of **13** or **14** (3 mmol) and LiBr (1.74 g, 20 mmol) in 20 ml acetone was refluxed for 16 hr under N_2. The solvent was evaporated and the residue dissolved in ether–H_2O. The H_2O layer was extracted with ether and the combined ethereal extracts washed with H_2O, dried on $MgSO_4$ and evaporated. TLC (CCl_4) yielded 606 mg (66%) of a pale yellow solid. GC–MS and NMR showed it to be a mixture of two isomers (4:1), of which (**27**) was the major component. IR: 1550, 1420, 810; NMR: 3.38 (m, 2 H; H_3, $H_{3'}$), 3.70 (m, 1 H; H_2), 3.98 (dd, 1 H; CH_2, J = 3 Hz and J = 11.5 Hz), 4.32 (dd, 1 H; CH_2, J = 4 Hz and J = 11.5 Hz), 4.60 (m, 1 H; CH), 6.05 and 6.15 (AB, 2 H; H_5, H_6, J = 9 Hz). The unidentified isomer showed two singulets at 3.66 and 6.05 (*ca.* 3:1). (Mass spectrum: M⁺ calculated 301.8434, found 301.8434).

2-*Vinyl*-2,3-*dihydro*-1,4-*dithiin* (**28**)

A soln of **27** (304 mg, 1 mmol, mixture of isomers) and (n-Bu)$_3$SnH (582 mg, 2 mmol) in 5 ml ether was refluxed for 4 hr under N_2. After evaporation, TLC (CCl_4) yielded 77 mg **28** (53%). Short-path dist. 40°/0.1 mm; IR: 3090, 1635, 1410, 980, 925; NMR: 3.08 (m, 2 H; H_3, $H_{3'}$), 3.95 (m, 1 H; H_2), 5.10–5.45 (m, 2 H; CH_2=), 5.70 (m, 1 H; CH=), 6.12 (s, 2 H; H_5, H_6). (Mass spectrum: M⁺ calculated 144.0067, found 144.0068).

6-*Acetoxy*-5,6-*dihydro*-1,4-*dithiocin* (**32**)

A soln of **18** (176 mg, 1.1 mmol) in Ac_2O (0.115 ml, 1.1 mmol) and pyridine (0.11 ml, 1.3 mmol) was heated at 90° for 2 hr under N_2. Ice-water was added and the mixture 2x extracted with ether. The ethereal extracts were washed with 2N HCl, $NaHCO_3$ soln

and H_2O, dried on $MgSO_4$ and evaporated. After TLC and sublimation (45°/0.05 mm) 160 mg **32** (80%) was obtained, m.p. 84°; IR: 1740, 1375, 1220, 1025; NMR: 2.08 (s, 3 H; CH_3), 2.55 (dd, 1 H; H_4, $J_{4,5'}$ = 14 Hz and $J_{5,6}$ = 6 Hz), 3.83 (dd, 1 H; H_4, $J_{4',6}$ = 5 Hz), 6.05 (m, 1 H; H_6), 6.10 (m, 2 H; H_7, H_8), 6.28 (s, 2 H; H_2, H_3); $[\alpha]_D^{21}$ = 134° ($CHCl_3$).

6 - *Methoxycarbonyloxy* - 5,6 - *dihydro* - 1,4 - *dithiocin* (**33**)

To a stirred soln of **18** (0.16 (0.16 g, 1 mmol) in 4 ml pyridine was added dropwise in 5 min methyl chloroformiate (0.6 ml, 7.5 mmol). After stirring for 16 hr under N_2 at room temp. the mixture was worked up in the usual way. TLC yielded 80 mg **33** (37%) and **18** (70 mg). IR: 1745, 1445, 1270, 965; NMR: 2.55 (dd, 1 H; H_4, $J_{4,5'}$ = 14 Hz and $J_{5,6}$ = 7 Hz), 3.80 (s, 3 H; CH_3), 3.80 (dd, 1 H; $J_{4',6}$ = 5 Hz), 5.95 (m, 1 H; H_6), 6.11 (m, 2 H; H_7, H_8), 6.28 (s, 2 H; H_2, H_3).

6 - (*Methylthio*)*thiocarbonyloxy* - 5,6 - *dihydro* - 1,4 - *dithiocin* (**34**)

To a stirred suspension of NaH (48 mg, 2 mmol) in 12 ml benzene was added **18** (0.32 g, 2 mmol). After stirring under N_2 for 0.5 hr CS_2 (0.13 ml, 2.15 mmol) was added. After 0.5 hr MeI (0.16 ml, 2.5 mmol) was added and stirring continued for 16 hr. Usual work up yielded 72 mg **34** (12.5%, yellow oil) and **18** (195 mg). IR: 1190, 1055; NMR: 2.59 (s, 3 H; CH_3), 2.71 (dd, 1 H; H_4, $J_{4,5'}$ = 14 Hz and $J_{4,6}$ = 7 Hz), 3.91 (dd, 1 H; H_4, $J_{4',6}$ = 5 Hz), 6.20 (m, 2 H; H_7, H_8), 6.30 (s, 2 H; H_2, H_3), 6.76 (m, 1 H; H_6).

5 - *Methylene* - 6 - *acetoxy* - 6,7 - *dihydro* - 5H - 1,4 - *dithiepin* (**35**)

Prepared in the same way as **32**, yield 85%. Short-path dist. 50°/0.03 mm; IR: 1740, 1370, 1220, 1020; NMR: 2.08 (s, 3 H; CH_3), 3.40 (m, 2 H; H_7, H_7), 5.76 (m, 1 H; H_6), 5.95 (m, 2 H; CH_2=), 6.00 (s, 2 H; H_2, H_3); $[\alpha]_D^{21}$ = 200° ($CHCl_3$).

5 - *Methylene* - 6 - *methoxycarbonyloxy* - 6,7 - *dihydro* - 5H - 1,4 - *dithiepin* (**36**)

Prepared in the same way as **33**, yield 33% **36** and 45% **23**. IR: 1745, 1440, 1265, 945; NMR: 3.37 (dd, 1 H; H_7, $J_{7,7'}$ = 15 Hz and $J_{7,6}$ = 6 Hz), 3.57 (dd, 1 H; H_7, $J_{7',6}$ = 7 Hz), 3.78 (s, 3 H; CH_3), 5.62 (m, 1 H; H_6), 6.01 (AB, 2 H; CH_2=, J = 0.5 Hz), 6.02 (s, 2 H; H_2, H_3).

6-*Oxo*-5,6-*dihydro*-1,4-*dithiocin* (**38**)

A soln of **18** (0.64 g, 4 mmol) in 5 ml HMPT (stored on mol-sieves 10x) was added to a stirred soln of CrO_3 (0.7 g, 7 mmol) and 3 drops H_2O in 10 ml HMPT. After stirring for 16 hr under N_2 the mixture was poured into ether and filtered. The ether solution was washed 4x with H_2O, dried on $MgSO_4$ and evaporated. TLC yielded 10–20% **38** (yellow oil) and 50–60% **18**. Longer reaction times only lowered the yield. Short-path dist. 50°/0.05 mm; IR: 1665; NMR: 4.33 (s, 2 H; CH_2), 6.21 and 6.77 (AB, 2 H; H_2, H_3, J = 9 Hz), 6.68 and 7.10 (AB, 2 H; H_7, H_8, J = 9 Hz); (Found: C, 45.67, H, 3.89, S, 40.53. $C_6H_6OS_2$ requires: C, 45.54, H, 3.82, S, 40.53%).

6-*Hydroxy*-6-*methyl*-5,6-*dihydro*-1,4-*dithiocin* (**39**)

To a soln of MeMgI (0.66 mmol) in 2 ml ether was added dropwise at 0° a soln of **38** (108 mg, 0.68 mmol) in 2 ml ether. After stirring for 10 min under N_2, the mixture was worked up in the usual way. TLC and sublimation (85°/0.1 mm) yielded 60 mg **39** (50%), m.p. 60°; IR: 3560, 3410, 1090, 1050; NMR: 1.48 (s, 3 H; CH_3), 2.69 (broad s, 1 H; OH), 2.85 (dd, 1 H; H_4, $J_{4,5'}$ = 15 Hz and $J_{4',5}$ = 1 Hz), 4.95 (d, 1 H; H_4), 5.78 (d, 1 H; H_8, $J_{8,7}$ = 9 Hz), 5.93 and 6.35 (AB, 2 H; H_2, H_3, J = 9 Hz), 6.71 (dd, 1 H; H_7); (Found: C, 48.34, H, 5.68, S, 36.59. $C_7H_{10}OS_2$ requires: C, 48.24, H, 5.78, S, 36.79%).

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