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SYNTHESIS AND PROPERTIES OF 6-ACETOXY-1,4-DITHIOCIN[1,2]

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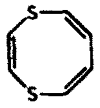
Abstract—The title compound 5 has been prepared from the previously obtained ketone 2 by acetylation of its enolate anion. Spectral properties, reactivity and the results of a crystal structure determination show that 5 is a nonplanar molecule without aromatic character.

In the preceding paper[3] we have discussed in some detail that 1,4-dithiocin 1 is an interesting compound, because it might be expected to be a Hückel 10π electron system and therefore to show aromatic stabilization and properties. Although several derivatives of 1 were known,[4-6] they were too highly substituted to permit a clear answer to the question of its electronic structure. For this reason, preparation of 1 seemed highly desirable.



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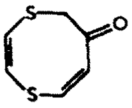

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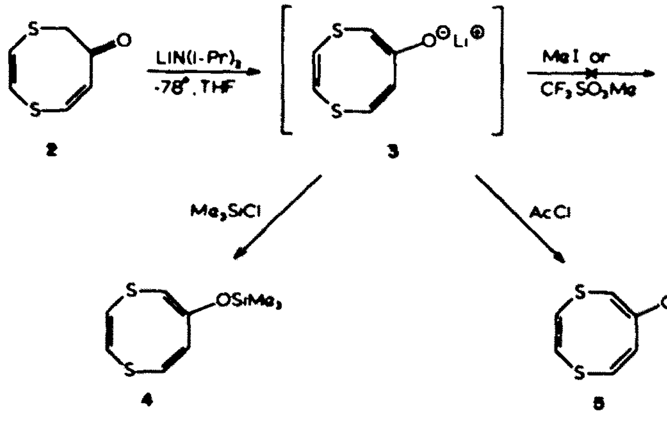
However, all attempts in this laboratory[3] and by Vogel's group[7] to prepare 1 itself were thwarted so far, presumably by the relatively low degree of stability of 1 and its ready decomposition to benzene. It was therefore of interest to synthesize a derivative of 1 which was as simple as possible, so that the effect of the substituents would not obscure the behaviour of the heterocyclic ring proper. Ketone 2, which became available in the course of our synthetic studies directed towards 1,[3] appeared to be a suitable starting material.

Synthesis and properties of 6-acetoxy-1,4-dithiocin (5)

When 2 was reacted with acetic anhydride or isopropenyl acetate in the presence of catalytic amounts of *p*-toluenesulfonic acid, starting material was recovered. Attempts to prepare the enolate 3 of 2 at room temperature invariably led to complete destruction. Only with lithium diisopropylamide in THF at −78°, 3 was obtained as a very unstable species; the deeply brown coloured solution had to be reacted at −78° with the appropriate reagent within one minute, whereupon the colour gradually disappeared.

With methyl iodide or "magic methyl" as reagents, only tar formation was observed. Trimethylchlorosilane gave the trimethylsilyl enol ether 4, as was indicated by the ^{1}H NMR spectrum and by the absence of C=O absorptions in the IR spectrum. However, 4 could not be further purified, as it decomposed to give 2 on distillation (partially) or on tlc. The acetate 5, on the other hand, was a pale yellow, stable, crystalline compound of m.p. 45°; its purification by successively tlc, sublimation and crystallization from hexane posed no particular problems. The spectroscopic data indicated that 5 was not a delocalized, aromatic system.

The ^{1}H NMR spectrum of 5 (Fig. 1) was very similar to that of 4. The chemical shifts of the protons at C(2), C(3), and C(5) were in the same range as those of 5,6-dihydro-1,4-dithiocins such as 7,[3] indicating that a diamagnetic ring current was not present in 5. Also, the vicinal coupling constants of J = 9 Hz are the same as those of 6 and 2; they would be expected to be different if the ring were flat. The UV spectrum of 5 differs from that of 1,4-dioxocin[8] and of cycloocta-1,3,6-triene by the



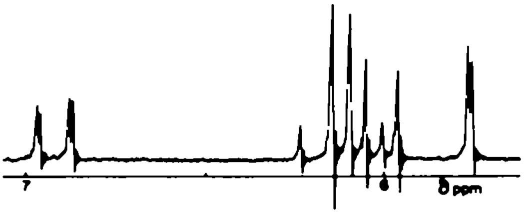
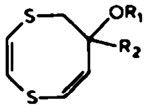


Fig. 1. ^{1}H NMR spectrum of 5 ($CDCl_3$, 100 MHz).

presence of an absorption band at 285 nm ($\epsilon = 3100$); this, however, is due to the auxochromic effect of sulfur and is comparable in the dihydro derivative 7. The spectroscopic evidence for lack of aromaticity, clear though circumstantial, was unambiguously confirmed by an X-ray determination of the molecular structure.



6 $R_1 = H, R_2 = CH_3$

7 $R_1 = Ac, R_2 = H$

Crystal and molecular structure of 5

The crystals of 5 are monoclinic, cell constants $a = 15.42$ (1), $b = 7.173$ (4), $c = 8.386$ (4) Å, $\beta = 93.25$ (1)°, $Z = 4$, space group $P2_1/a$.

By means of a NONIUS CAD 4 diffractometer all reflections with $\theta < 50.0°(CuK_\alpha)$ were measured at room temperature; 911 independent reflections were above 2.5σ. As the investigation was aimed merely at establishing the conformation of the 8-membered ring, no absorption correction was applied.

A Patterson minimum function based on one S–S vector was used to locate the S atoms in the unit cell. Another Patterson minimum function based on the sulfur positions revealed all non-H atoms.

Full matrix refinement with unit weights and anisotropic temperature factors led to an R-index of 0.096. Final parameters are given in Table 1, interatomic distances and bond angles in Fig. 2. The standard deviations in the distances are approximately 0.02 Å, those of the angles around 1°. Figure 3 provides a general view of the molecule; in Fig. 4 the Newman projections are shown.

Table 1. Positional parameters of 5; estimated standard deviations are given in brackets

	x	y	z
S(1)	0.2764(3)	0.3432(6)	.2798(7)
C(2)	0.2448(9)	0.1163(19)	.3279(20)
C(3)	0.1810(9)	0.0074(20)	.2722(21)
S(4)	0.0992(2)	0.0458(5)	.1241(5)
C(5)	0.0358(9)	0.2282(19)	.2013(18)
C(6)	0.0575(8)	0.4116(20)	.1846(17)
C(7)	0.1320(9)	0.4933(19)	.1063(19)
C(8)	0.2155(9)	0.4621(20)	.1307(17)
O(9)	-0.0100(6)	0.5346(12)	.2191(11)
C(10)	0.0058(9)	0.6537(19)	.3455(16)
C(11)	-0.0720(9)	0.7790(20)	.3582(19)
O(12)	0.0715(6)	0.6484(13)	.4262(12)

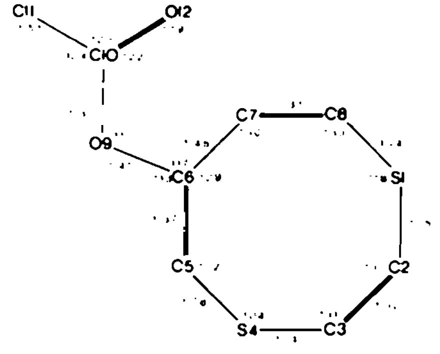


Fig. 2. Interatomic distances and bond angles of 5.

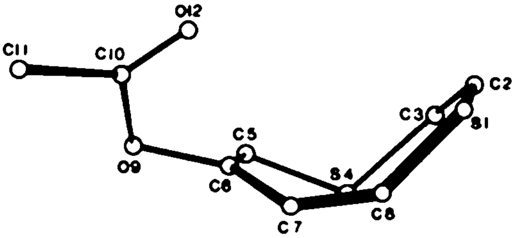
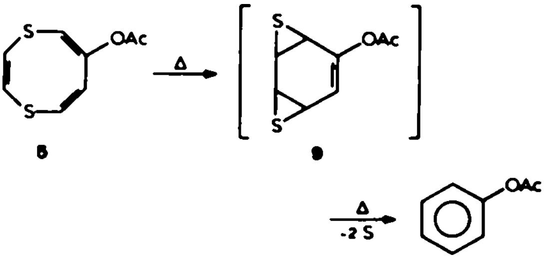


Fig. 3. General view of the molecule of 5.

From Figs. 3 and 4, the nonplanarity of the ring system of 5 is obvious. While five ring atoms (atoms 1–4 and 8) lie in one plane, the rest of the molecule is more or less perpendicular to that plane; even the diene sub-system C(5)–C(8) is far from planar. The ester unit is planar but nearly perpendicular on the C(5)–C(6) double bond. There is considerable correspondence between the structure of 5 and that of its dihydro analog 7;[9] for instance, in both compounds the C(7)–C(8) double bond is not planar (5: 11°!), and the valence angle at S(1) is 13–14° larger than that at S(4). On the other hand, in 7 only four ring atoms lie in one plane (S(1) to S(4)) instead of five, and in general the valence angles are smaller than in 5, indicating the presence of higher strain in the latter. Figure 2 shows that the bond lengths in 5 are clearly either aliphatic or olefinic, and no shortening or lengthening can be observed in comparison with 7.†

Reaction of 5

A few reactions were performed with 5 in order to complement the information obtained from spectra and structure determination. At temperatures above 50°, 5 is thermally unstable and decomposes under extrusion of sulfur to yield phenyl acetate 8. This behaviour is paralleled by that of the unsubstituted parent compound 1; in reactions, especially at higher temperatures, where one might have expected the formation of 1, benzene was found instead.[3] From the investigations of Vogel *et al.*[7] it



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†The full list of observed and calculated structure factors and of the atomic parameters including the temperature parameters has been deposited at the editorial office.

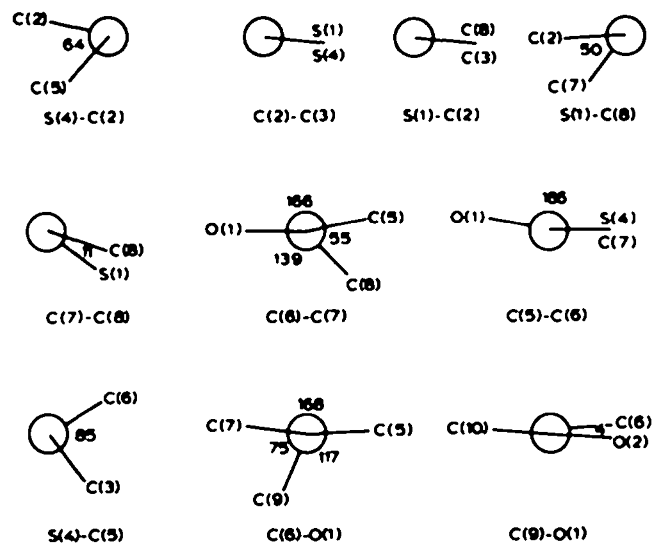
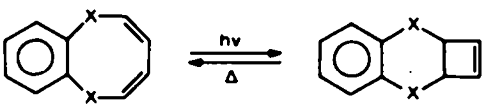


Fig. 4. Newman projections of 5.

is very likely that the extrusion of sulfur is preceeded by isomerization of 5 to its valence isomer 9; the corresponding *syn*-benzenebisepisulfide has been shown to be thermally labile at room temperature, decomposing to benzene.[7] Contrary to the silyl ether 4, the acetate 5 could not be converted to the starting ketone 2. Both acid and base hydrolysis resulted in tar formation, probably due to the instability of 2.

In view of the apparent lack of aromaticity of 5, it was of interest to investigate the ability of its diene subsystem to undergo a Diels–Alder reaction. Because of the thermal lability of 5, these reactions had to be performed at 45°. Under these conditions, no reaction occurred with maleic anhydride, tetracyanoethene or hexafluoro-2-butyne; only with the reactive dienophile 4-phenyl-1,2,4-triazoline-3,5-dione, a reaction took place, but no identifiable product could be isolated. Possibly, this lack of reactivity is caused by the twisted conformation of the diene part.

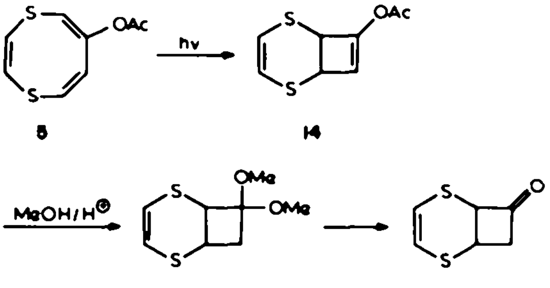
A typical reaction of benzo-1,4-dithiocin 10[9] and of its nitrogen analog 11[10] is the photochemical conversion to their valence isomers 12 and 13; this reaction can be thermally reversed.



10 X=S
11 X=NCH_3

12 X=S
13 X=NCH_3

Irradiation of 5 with a daylight lamp for 24 hr was accompanied by decomposition (25%); 5 was for 55% converted to its bicyclic valence isomer 14. A few percent of phenyl acetate were probably due to thermal decomposition. The mixture of 5 and 14 could not be separated into the components. The structure assignment is based on the analogy of the reaction with that of 10 and 11, on the spectra (Experimental), and on its conversion with methanolic HCl to the acetal 15, which could be hydrolyzed in low yield to the cyclobutanone 16 (IR: 1785 cm^{-1}).



CONCLUSION

According to different and complementary criteria of aromaticity, 5 is not an aromatic compound. Its low thermal stability (decomposition to phenyl acetate), its spectra (no diamagnetic ring current) and, most convincingly, its crystal structure (nonplanar geometry) show that 5 is neither stabilized nor delocalized nor flat. As the 6-acetoxy group of 5 is approximately perpendicular to the ring system, it is very unlikely that it disturbs the cyclic resonance to such an extend, that it is responsible for the lack of resonance and consequently for nonplanarity. It is therefore also unlikely, that 1, if synthesized, will turn out to be aromatic. Possibly two factors are mainly responsible for this lack of aromaticity. Calculations by Hess and Schaad[11] have shown that 1, if planar, would have a resonance energy close to zero; therefore, the electronic driving force to obtain a planar geometry may be expected to be small. Furthermore, and probably more important, sulfur, because of its typically small valence angles (normally around 100°) is less suited to tolerate planarity in an 8-membered ring than carbon, nitrogen or oxygen, so that ring strain in planar 1 may be expected to be considerably larger than in the cyclooctatetraene dianion.[12] In fact, the relatively increased partial planarity of 5 as compared to 7, which is accompanied by an increase of strain, may be an expression of a tendency of 5 to approach the planar state; it is prevented from reaching this state by excessive geometric constraints.

Normally, sulfur is a good substitute for a C=C bond in aromatic and other systems. However, the specific geometric conditions of the medium-sized ring in combination with the favoured small valence angle of sulfur make this atom a poor candidate for an aromatic hetero atom in 1,4-dithiocin, especially as two S atoms have to be incorporated in this case. This does, of course, not exclude that sulfur may function in smaller (thiophene; 1,3-dithia-4,6-cycloheptadienyl anion[13]) or in larger (dimethylbisdehydrothia[13]annulene[14]) ring systems, where angle strain is absent or not prohibitive.

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 ($CDCl_3$ solutions); 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 $CHCl_3$). Preparative TLC was carried out on PSC-Fertigplatten Kieselgel F 254 (Merck) with $CHCl_3$ as eluens. Elemental analyses were performed under the supervision of Mr. W. J. Buis at the Micro-Analytical Department of Institutute for Organic Chemistry TNO, Utrecht, The Netherlands.

6-*Trimethylsilyloxy*-1,4-*dithiocin* (4)

To an icecooled, stirred soln of diisopropylamine (0.215 ml, 1.6 mmol) in 3 ml THF was added 2M n-BuLi (0.58 ml, 1.16 mmol). After stirring for 15 min under N_2 the flask was cooled to −78° and a soln of 2 (186 mg, 1.17 mmol) in 1 ml THF was added, followed within one minute by a soln of 0.4 ml Me_3SiCl in 0.3 ml Et_3N. After 0.5 hr the cooling bath was removed and the mixture slowly warmed up to 0°. The mixture was diluted with 10 ml hexane, filtered and evaporated. Short-path distillation (40°/0.05 mm) yielded 104 mg impure product, whereas partial decomposition to 2 had occurred (NMR before and after distillation). TLC yielded 60 mg 2 (33%). IR: 1570, 1355, 1260, 1185, 970, 850; NMR: 5.08 (d, 1 H; H_5, $J_{5,7} = 0.5$ Hz), 5.88 (d, 1 H; H_8, $J_{7,8} = 9$ Hz), 5.98 and 6.25 (AB, 2 H; H_2, H_3, $J = 9$ Hz), 6.83 (dd, 1 H; H_7).

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

A soln of 2 (252 mg, 1.59 mmol) in 1 ml THF was added to a stirred soln of lithium diisopropylamide (1.58 mmol) in 7 ml THF at −78° under N_2, within one min followed by acetyl chloride (0.24 ml, 3 mmol). The mixture was stirred for 0.5 hr at −78°, then slowly warmed up to 0°, diluted with 15 ml hexane, filtered and evaporated. Tlc yielded 100 mg 5 and 17 mg 2. Short-path distillation (45°/0.1 mm) gave 95 mg oil (30%) which solidified on cooling. Recrystallization from hexane yielded pale yellow crystals, m.p. 45°; IR: 1760, 1585, 1370, 1185, 1110, 1010; NMR: 2.17 (s, 3 H; CH_3), 5.76 (d, 1 H; H_5, $J_{5,7} = 1$ Hz), 6.00 (d, 1 H; H_8, $J_{7,8} = 9$ Hz), 6.05 and 6.19 (AB, 2 H; H_2, H_3, $J = 9$ Hz), 6.92 (dd, 1 H; H_7); UV (cyclohexane): 225 (5380), 249 (sh, 3050), 255 (sh, 2550), 285 (3100); Mass spectrum: M^+ calculated 199.9955, found 199.9965; *m/e*: 200 (2%), 158, 113, 94, 45, 43 (100%); (Found: C, 48.14, H, 4.15, S, 31.93. $C_8H_8O_2S_2$ requires: C, 47.97, H, 4.02, S, 32.03%).

7-*Acetoxy*-2,5-*dithiabicyclo*[4.2.0]*octa*-3,7-*diene* (14)

A stirred soln of 5 (125 mg, 0.62 mmol) in 10 ml cyclohexane was irradiated under N_2 for 24 hr with a SP 500 high pressure Hg lamp (Philips) with benzene filter. After filtration and evaporation 95 mg was obtained. Nor tlc or glc could separate the mixture into its components. Besides the signals of 5 the NMR spectrum of the mixture showed signals at $\delta = 4.27$ and 4.66 (m, 2 H; H_1, H_6, $J_{1,6} = 4.4$ Hz, $J_{1,8} = 0.8$ Hz and smaller couplings with H_3 and H_4), 5.30 (d, 1 H; H_8), 6.75 (m, 2 H; H_3, H_4). The couplings between H_3, H_4 and H_1, H_6 were confirmed by double resonance experiments. The integral ratio between H_3, H_4 of 14 and H_7 of 5 showed that the mixture contained 55% 14. IR: 1775, 1760, 1625, 1370, 1180, 1110, 1020. GC–MS of the mixture showed only one peak with $M^+ = 200$.

7,7-*Bismethoxy*-2,5-*dithiabicyclo*[4.2.0]*octa*-3-*ene* (15)

A soln of 95 mg of the mixture of 5 and 14 (see above) and 5 mg *p*-toluenesulfonic acid in 4 ml MeOH was refluxed for 4 hr under N_2. Evaporation, tlc and short-path distillation (50°/0.1 mm) yielded 51 mg oil (95% relative to 14). IR: 2930, 2810, 1785, 1260, 1105, 1030; NMR: 2.10 (dd, 1 H; H_8, $J_{8,8'} = 12.5$ Hz and $J_{8,1} = 7.5$ Hz), 2.58 (m, 1 H; $H_{8'}$, $J_{8',1} = 7$ Hz, $J_{8',6} = 4$ Hz), 3.18 (s, 3 H; CH_3), 3.22 (s, 3 H; CH_3), 3.50–4.15 (m, 2H; H_1, H_6), 6.75 (m, 2 H; H_3, H_4, $J_{3,4} = 8.5$ Hz). From the absorption at 1785^{-1} cm in the IR spectrum it is clear that some 16 is present.

7-*Oxo*-2,5-*dithiabicyclo*[4.2.0]*octa*-3-*ene* (16)

A soln of 51 mg 15 and 5 mg *p*-toluenesulfonic acid in 3 ml dioxane and 2 ml H_2O was refluxed for 1.5 hr under N_2. Usual working up yielded after tlc 10 mg oil. GC–MS showed it to be a mixture, consisting mostly of 16 ($M^{+\cdot} = 158$), besides 15 ($M^{+} = 204$) and a methyl ether ($M^+ = 172$). IR: 1785; NMR: to 16 the following signals could be attributed: 2.91 (m, 1 H; H_8, $J_{8,8'} = 16$ Hz, $J_{8,1} = 6$ Hz and $J_{8,6} = 3$ Hz), 3.50 (m, 1 H; $H_{8'}$, $J_{8',1} = 8$ Hz, $J_{8',6} = 3.5$ Hz), 4.10 (m, 1 H; H_1, $J_{1,6} = 10$ Hz), 4.70 (m, 1 H; H_6), 6.78 (AB, 2 H; H_3, H_4, $J = 10$ Hz).

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