for the GC analyses, IR, NMR, and mass spectra, respectively.

Registry No.—1, 19220-93-0; 2, 771-61-9.

References and Notes

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(5) Falardeau and Desmarteau[3] reported mp 29.8–30.2 °C, vapor pressure 10.8 mm at 57.21 °C, $\nu_{C=C}$ 1813 cm^{-1} in the gas phase, and ^1H NMR δ 2.05. Collings et al.[4] reported, $\nu_{C=O}$ 1798 and 1792 cm^{-1} in CCl_4 and CH_2Cl_2, respectively.

Facile Preparation of Cyclic Ethylene Thioketals and Thioacetals with 2-Phenyl- and 2-Chloro-1,3,2-dithiaborolanes[1]

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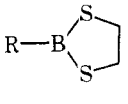
Received June 19, 1978

The importance of cyclic ethylene thioacetals and thioketals in organic synthesis as temporary protecting forms for aldehydes and ketones has been well documented in the literature.[2] The advantages of cyclic ethylene thioacetals and thioketals relative to their oxygenated counterparts include: (1) ease of formation from dithiols and carbonyl substrates; (2) relative resistance to acidic and basic reaction conditions;[2a,3] (3) relative resistance to cleavage by organometallic reagents (e.g., Grignard and alkyllithium reagents);[2a,4] (4) lack of double bond migration with α,β-unsaturated carbonyl substrates;[2a,5] and (5) availability of mild conditions for hydrolysis back to the carbonyl substrate.[3,5,6]

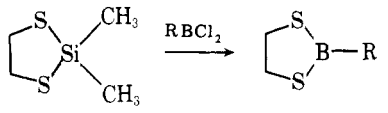
Despite these advantages, however, the formation of cyclic ethylene thioacetals and thioketals from carbonyl substrates generally requires the presence of a strong acid catalyst. As a consequence, their use as carbonyl protecting forms is not always feasible when other acid sensitive functional groups are present in the substrate molecule. Evans has provided an alternative method which circumvents this problem by the use of methylthiotrimethylsilane.[7] Mild methods for effecting thioketallization have also been developed using alkyl orthothioborates;[8-10] however, no work has been reported to date on the use of alkyl orthothioborates as thioketallizing agents for carbonyl substrates with any degree of complexity. Further, no attempts have been made to our knowledge to generate cyclic ethylene thioacetals and thioketals from carbonyl substrates and 2-substituted 1,3,2-dithiaborolanes (e.g., **1**). Accordingly, we have investigated the nature and scope of the reaction of **1a** and **1b** with a variety of carbonyl substrates and report our findings below.



1a, R = C_6H_5
b, R = Cl

Results and Discussion

The dithiaborolanes **1a** and **1b** were synthesized by the methods of Abel et al.[11] Briefly, these reagents were prepared



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by the reaction of an appropriately substituted boron dichloride with 2,2-dimethyl-1,3-dithia-2-silacyclopentane, and the latter compound was synthesized in good overall yield (ca. 90%) from dichlorodimethylsilane.[11b] Although these reagents are quite reactive, they may be conveniently stored at or below room temperature under nitrogen without appreciable decomposition.

The reactions of 2-phenyl-1,3,2-dithiaborolane (**1a**) with a variety of carbonyl substrates are summarized in Table I. In the majority of examples described, the yields of thioacetal or thioketal products are comparable to or better than those reported in the literature for reaction of the carbonyl substrate and ethanedithiol in the presence of an acid catalyst. Simple aromatic aldehydes (e.g., **2** and **8**) react rapidly with **1a** to give the corresponding thioacetal in essentially quantitative yield, and simple dialkyl ketones (e.g., **4**) react to give the thioketal in high yield. Diaryl ketones, on the other hand, are slow to react. Fluorenone (**6**) only affords a thioketal product in poor yield after greater than 12 h at reflux temperature in chloroform. In similar fashion, benzophenone fails to undergo any detectable reaction with **1a**. The reagent **1a** also displays good steric selectivity with multicarbonyl substrates as evidenced by the reactions of **12** and **17**.[21] Further, even though **1a** is rapidly decomposed by water and simple alcohols, it appears to be unaffected by a hindered alcohol (e.g., **15**).

In all of the above cited examples, the boron-containing byproduct formed is triphenylboroxine (**19**),[10a] and this substance is most easily removed by chromatography. In many instances, a quick chromatographic filtration over silica gel is all that is required to purify the reaction mixture. Examination of these reactions in a variety of different solvents at 25 °C revealed that polar solvents enhance the rate of reaction (chloroform > benzene > carbon tetrachloride) while polar solvents containing heteroatoms (e.g., tetrahydrofuran, dioxane, or acetonitrile) appear to act as Lewis bases and reduce the reactivity of **1a** presumably by a complexation phenomenon.

The reactions of 2-chloro-1,3,2-dithiaborolane (**1b**) with three carbonyl substrates are also summarized in Table I. Reagent **1b** is very much more reactive than **1a** as evidenced by the fact that both fluorenone (**6**) and benzophenone (**20**) are quantitatively converted to their thioketals at room temperature. This increased reactivity is also reflected by the observations that **1b** is violently decomposed by water and simple alcohols and that it reacts with multicarbonyl substrates with little or no selectivity (e.g., **12**).

In conclusion, the reactions of **1a** and **1b** with carbonyl substrates to form cyclic ethylene thioacetals and thioketals have been shown to be synthetically useful. Several advantages of the reaction are: (1) the thioacetals and thioketals are formed under mild and anhydrous conditions; (2) the reaction proceeds at room temperature and often at lower temperatures; (3) reagents **1a** and **1b** are readily prepared from commercially available materials and can be kept almost indefinitely in closed containers under nitrogen; (4) the reagent **1a** is selective in its thioketallization capacity for unhindered carbonyls and also displays differential reactivity between aryl and alkyl ketones; (5) the reagent **1b** is extremely reactive toward diaryl ketones and would be useful in the thioketallization of these and other ketones of low reactivity; and (6) the reagent **1a** is mild enough to use with acid sensitive compounds (e.g., furaldehyde and prostaglandins).

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Table I. Reaction Conditions[a] and Products for Reaction of Carbonyl Substrates with 2-Phenyl-1,3,2-dithiaborolane (1a) and 2-Chloro-1,3,2-dithiaborolane (1b)

substrate (S)	registry no.	molar ratio 1a/S[d]	molar ratio 1b/S[e]	product(s) (% yield)[b]	registry no.
benzaldehyde (**2**)	100-52-7	1.3		benzaldehyde ethylene thioacetal (**3**)[12] (98)	5616-55-7
cyclohexanone (**4**)	108-94-1	1.1		cyclohexanone ethylene thioketal (**5**)[13] (98)	177-16-2
fluorenone (**6**)	486-25-9	1.5		fluorenone ethylene thioketal (**7**)[13b] (27)[c]	7049-31-2
2-furaldehyde (**8**)	98-01-1	1.5		2-furaldehyde ethylene thioacetal (**9**)[14] (98)	6008-83-9
17β-acetoxyandrostan-3-one (**10**)	18642-28-9	1.1		17β-acetoxyandrostan-3-one 3-ethylene thioketal (**11**)[15] (87)	68509-55-7
4-pregnene-3,20-dione (**12**) (progesterone)	57-83-0	1.2		4-pregnene-3,20-dione 3-ethylene thioketal (**13**)[16] (89)	63883-02-3
				4-pregnene-3,20-dione,3,20-bis(ethylene thioketal) (**14**)[17] (9)	10417-76-2
17β-hydroxyandrost-4-en-3-one (**15**) (testosterone)	58-22-0	1.0		17β-hydroxyandrost-4-en-3-one 3-ethylene thioketal (**16**)[18] (99)	13947-29-0
17α-hydroxy-21-acetoxy-4-pregnene-3,20-dione (**17**)	640-87-9	1.5		17α-hydroxy-21-acetoxy-4-pregnene-3,20-dione 3-ethylene thioketal (**18**)[19] (99)	68438-23-3
fluorenone (**6**)			1.1	fluorenone ethylene thioketal (**7**)[13b] (99)	
benzophenone (**20**)	119-61-9		1.1	benzophenone ethylene thioketal (**21**)[20] (99)	6317-10-8
4-pregnene-3,20-dione (**12**) (progesterone)			1.1	4-pregnene-3,20-dione 3-ethylene thioketal (**13**)[16] (33)	
				4-pregnene-3,20-dione 3,20-bis(ethylene thioketal) (**14**)[17] (31)	

[a] See Experimental Section for details for a typical procedure. In general, thioketallization in chloroform was complete in less than 2 h at 25 °C, and reactions were easily monitored by TLC of aliquots quenched in brine–ethyl acetate. [b] Isolated yields of reaction product(s). In all cases the product structure was established by comparison of spectral parameters and physical constants with those of authentic material cited in the literature reference. [c] The remaining 73% was recovered starting material. [d] Registry no. 1870-72-0. [e] Registry no. 1870-71-9.

Experimental Section

General. All analytical data, except for NMR spectra, were obtained by the Physical and Analytical Chemistry Department of the Upjohn Co., with IR spectra being obtained either on neat samples (oils) or on mulls (crystalline samples). The NMR spectra were obtained at 60 MHz on chloroform-*d* solutions containing internal tetramethylsilane. Thin-layer chromatography (TLC) was conducted using Analtech (Uniplate) glass plates precoated with silica gel GF (250 μm). The TLC plates were visualized first by UV light (using a UVS-12 lamp) then by spraying with 50% aqueous sulfuric acid, followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck), 70–230 mesh. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reagents were used as purchased and were Reagent Grade where available.

2-Phenyl-1,3,2-dithiaborolane (1a) was prepared by the method of Abel et al.[11]

2-Chloro-1,3,2-dithiaborolane (1b) was prepared by the method of Abel et al.[11]

Typical Procedure for the Reaction of 2-Phenyl-1,3,2-dithiaborolane (1a) with Carbonyl Substrates. 17α-Hydroxy-21-acetoxypregn-4-ene-3,20-dione 3-Ethylene Thioketal (18). A 25-mL flask, equipped with a magnetic stirring bar, was charged with 0.503 g (2.80 mmol) of 2-phenyl-1,3,2-dithiaborolane (**1a**), 9.4 mL of chloroform, and 0.726 g (1.84 mmol) of 17α-hydroxy-21-acetoxypregn-4-ene-3,20-dione (**17**). The reaction mixture was stirred under nitrogen at 25 °C for 21.5 h, diluted with brine, and extracted with ethyl acetate (2×). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give a solid. A 19 mm × 24 in. column was slurry packed with 50 g of silica gel in Skellysolve B. The sample was applied in chloroform and eluted with 250 mL each of 2, 4, 8, and 16% ethyl acetate in Skellysolve B followed by 750 mL of 32% ethyl acetate in Skellysolve B. Fractions were 20 mL each, and based on TLC homogeneity, fractions 49–65 were combined to give 0.856 g (99%) of **18** as a solid. Recrystallization from acetone–water gave colorless plates, mp 208.1–217.0 °C. Further recrystallization from acetone gave colorless prisms: mp 220–222 °C (undepressed on admixture with an authentic specimen of **18**[19]); $[\alpha]_D$ +160° (*c* 0.8645; $CHCl_3$) (lit. $[\alpha]_D$ +154 °C[19]). The NMR showed absorptions at δ 0.70 (s, 3 H), 1.03 (s, 3 H), 0.6–3.0 (m, 19 H), 2.18 (s, 3 H), 2.27 (s, 1 H, OH, exchangeable with D_2O), 3.37 (m, 4 H), 4.60–5.37 (AB mult, 2 H), 5.53 (2, 1 H). Anal. Calcd for $C_{25}H_{36}O_4S_2$: C, 64.62; H, 7.81; S, 13.80. Found: C, 64.77; H, 8.08; S, 13.89.

Typical Procedure for the Reaction of 2-Chloro-1,3,2-dithiaborolane (1b) with Carbonyl Substrates. Fluorenone Ethylene Thioketal (7). A 25-mL flask, equipped with a magnetic stirring bar, was charged with 0.349 g (2.52 mmol) of 2-chloro-1,3,2-dithiaborolane (**1b**), 8.5 mL of chloroform, and 0.413 g (2.29 mmol) of fluorenone (**6**). The reaction mixture was stirred under nitrogen at 25 °C for 26.5 h, diluted with brine, and extracted with ethyl acetate (2×). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give a colorless solid. A 19 mm × 24 in. column was slurry packed with 20 g of silica gel in Skellysolve B. The sample was applied in Skellysolve B and eluted with benzene. Fractions containing pure **12** (by TLC) were combined to give 0.579 g (99%) of a colorless solid. This material was recrystallized from Skellysolve B to give colorless plates, mp 123.0–126.3 °C (lit. mp 125 °C[13b]). The NMR showed absorptions at δ 3.82 (s, 4 H) and 7.37–8.03 (m, 8 H). Anal. Calcd for $C_{15}H_{12}S_2$: C, 70.27; H, 4.72; S, 25.01. Found: C, 70.36; H, 4.75; S, 25.12.

Acknowledgments. The authors gratefully acknowledge Mr. P. A. Meulman and Mr. R. J. Wnuk for their IR and mass spectra. We especially acknowledge helpful discussions with Professor David A. Evans.

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Ascorbic Acid Derivatives. Structure Determinations by Carbon-13 Nuclear Magnetic Resonance

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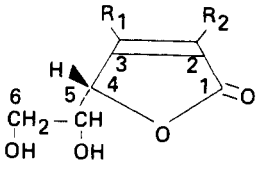
Received August 14, 1978

The well-known susceptibility of L-ascorbic acid toward thermal and oxidative degradation has promoted an interest in derivatives which show increased stability in vitro, while being able to generate antiscorbutic activity in vivo through enzymatic cleavage to free L-ascorbate. In this context the differing chemical reactivities of the two enol groups of L-ascorbic acid were utilized to prepare several monosubstituted, nonreducing derivatives.[1,2] A number of these, including a monosulfate,[3] a monophosphate,[4] and a monomethyl ether,[5,6] were demonstrated to exert vitamin C activity in sensitive species.[7-9] The sulfate is also important as a naturally occurring metabolite of L-ascorbic acid, first found in brine shrimp cysts[10] and since then in the urine of man, monkeys, rats, and guinea pigs.[2]



1 $R_1 = O^-$ $R_2 = SO_4^-$

2 $R_1 = OCH_3$ $R_2 = OH$

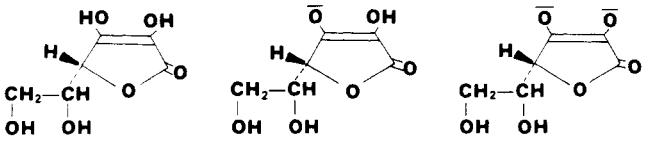
3 $R_1 = HPO_4^-$ $R_2 = O^-$

4 $R_1 = O^-$ $R_2 = HPO_4^-$

For a number of years these and several other monosubstituted analogues were regarded as 3-O-substituted L-ascorbic acid derivatives. Recently the dianion of L-ascorbic acid monosulfate was shown to have structure **1** by X-ray diffraction.[11] On the basis of this result prior assignments of substituents to C-3 in other L-ascorbic acid derivatives have been questioned.[2]

We report here ^{13}C NMR data and other evidence which supports the structures previously assigned to **1** and **2** but indicate that structure **3** proposed for the dianion of L-ascorbic acid monophosphate[4] should be revised to **4**.

^{13}C NMR chemical shifts have previously been reported for L-ascorbic acid[12] and also a study of their pH dependence was published.[13] The data suggest that species **5**, **6**, and **7** exist in solution under conditions of low, neutral, and high pH, respectively.



5 **6** **7**

These conclusions are in accord with accepted views regarding the relative acidity of the ene diol protons of L-ascorbic acid,[1] and they are also consistent with the results of X-ray analyses of L-ascorbic acid[14] and its monosodium salt.[15]

Chemical shifts derived from ^{13}C NMR spectra of compounds **1**, **2**, and **4**–**6**, determined in aqueous solution at the indicated pH, are given in Table I. It is evident that the C-3 chemical shifts noted for **1** and **4** are close to that observed for the ascorbate monoanion (**6**). Thus the presence of an anion at C-3 is indicated for both **1** and **4**. These results support their formulation as 2-O-substituted derivatives. On the other hand the C-3 chemical shift listed for **2** is clearly consistent with the absence of an anion at C-3 in accord with the previously assigned structure.[5,6]

Confirmatory evidence for the structure of **2** was obtained by chemical modification and mass spectrometry. Hydrogenation of **2** in the presence of Pd–C gave a saturated γ-lactone to which the L-manno configuration was assigned on steric grounds. Reduction of the lactone with sodium borohydride under standard conditions,[16] followed by acetylation, yielded a product **9** whose mass spectrum (Table II) was essentially identical with the spectrum of authentic 1,2,4,5,6-penta-*O*-acetyl-3-*O*-methyl-D-glucitol (**8**), thus confirming the structure of the ascorbic acid methyl ether as **2**. The close similarity between the two sets of data in Table II is to be expected on the basis of previous MS studies of stereoisomeric alditol derivatives.[17]

Further support for structure **2** is available from a pK_a determination.[18] The value obtained, 7.8, is significantly higher than the first acid dissociation constant of **5** (4.25)[19] or the pK_a's of **1** (2.0 and 3.1)[2] and it is only consistent with

Table I. ^{13}C NMR Chemical Shifts of 1, 2, and 4–6 in Water at pH 7.0 with Dioxane as Internal Reference

	registry no.	C-1	C-2	C-3	C-4	C-5	C-6
1	68582-35-4	181.0	111.3	176.6	79.7	70.6	63.4
2	13443-57-7	174.3	119.5	155.7	76.9	70.0	63.0
4	68582-36-5	178.0	113.4[a]	176.5	79.4	70.5	63.4
			113.2				
6	63983-49-3	178.2	114.1	176.3	79.3	70.5	63.6
5 (pH 2.7)	50-81-7	174.0	118.8	156.4	77.1	69.9	63.1

[a] The origin of this multiplicity was not determined but it probably results from ^{13}C–^{31}P coupling.

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