Novel 1,2,3-Thiadiazolyl Sulfines from the Reaction of N-Substituted Hydrazones with Thionyl Chloride

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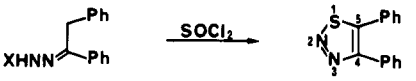
The reaction of 17β-acetoxy-5α-androstan-3-one (ethoxycarbonyl)hydrazone (**5a**) with neat $SOCl_2$ at 65 °C gave (1*Z*)-17β-acetoxy-5α-androst-2-eno[3,2-*d*][1,2,3]-thiadiazole-1-thione *S*-oxide (**6**) in 84% yield. Under similar conditions the corresponding tosyl- and formylhydrazones afforded 17β-acetoxy-5α-androst-2-eno[3,2-*d*]-[1,2,3]thiadiazole (**7**) in 84% and 85% yields, respectively, while the acetylhydrazone gave a mixture of the two products. A single-crystal X-ray of **6** revealed a close (2.66 Å) sulfine-O thiadiazole-S distance suggestive of a weakly attractive interaction. The ethoxycarbonyl hydrazones of a series of cyclohexanone derivatives were similarly reacted with $SOCl_2$. Those substrates having γ-alkyl substituents afforded 1,2,3-thiadiazolyl sulfines in moderate to good yield. The 3,3,5,5-tetramethyl- and 2,5-methanocyclohexanone derivatives gave only the corresponding 1,2,3-thiadiazoles. When **5a** was treated with 2 equiv of $SOCl_2$ at −20 °C, in addition to **6** and **7**, the intermediates 17β-acetoxy-2′-(ethoxycarbonyl)-2′,5′α-dihydro-5α-androstano[3,2-*d*][1,2,3]thiadiazole 1′-oxide (**22**) and 17β-acetoxy-2′-(ethoxycarbonyl)-2′*H*-5α-androst-1-eno[3,2-*d*][1,2,3]thiadiazole (**23**) were isolated. Based on the above and additional mechanistic studies, a mechanism for the formation of **6** and **7** from **5a** is proposed. The general behavior of hydrazones with $SOCl_2$ is rationalized in light of this mechanism.

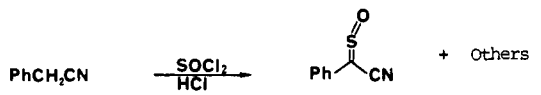
In 1955 Hurd and Mori[1] first reported the preparation of 1,2,3-thiadiazoles (e.g., **2**) from the reaction of α-methylene(or methyl)hydrazones (e.g., **1**, X = $ArSO_2$, CH_3CO, EtOCO) with $SOCl_2$. Representing the most convenient



1 **2**

and general synthesis of the above heterocycle, this method has been used to prepare a wide variety of thiadiazoles, including 4-alkyl,[2] 4- and 5-monoaryl,[1-3] dialkyl,[4] diaryl,[1,3,5] alicyclic,[3,6] and heterocyclic[1,3] derivatives. The chemistry of 1,2,3-thiadiazoles has recently been reviewed.[7]

Sulfines (thione *S*-oxides, $R_2C{=}S{=}O$) have been prepared by a variety of methods, including the thermal or base-induced dehydrohalogenation of sulfinyl chlorides.[8] Sulfinyl chlorides are in turn produced from the reaction of some active methylene and methine compounds and $SOCl_2$.[9] In general, however, such initially formed products are subject to a variety of further transformations in situ, and neither sulfines nor sulfinyl chlorides are the ultimate products of these reactions.[10] One notable exception is the low-yield conversion of phenylacetonitrile into sulfine **3** on treatment with $SOCl_2$/HCl.[9c] A one-step, high-yield conversion of an unactivated methylene group into a sulfine has not previously been reported.



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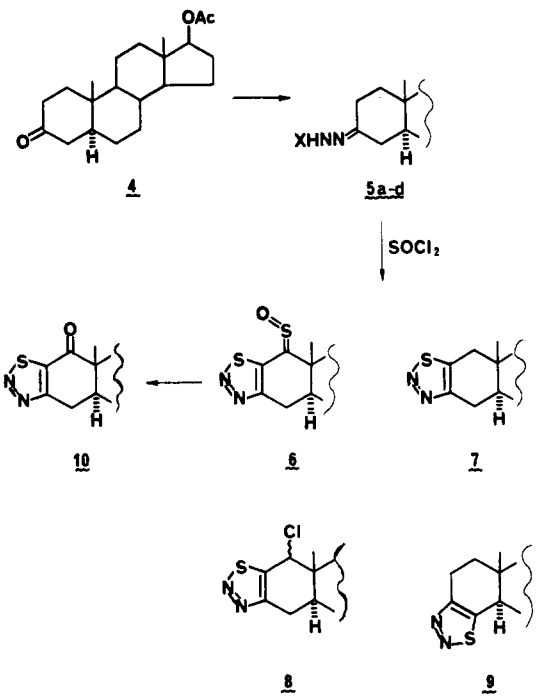
In attempting to prepare novel steroidal [3,2-*d*][1,2,3]-thiadiazoles (e.g., **7**) in support of a program exploring A-ring fused heterocyclic steroids for use as male contraceptives, we found that the reaction of certain N-substituted hydrazones with $SOCl_2$ affords instead thiadiazolyl sulfines (e.g., **6**) in high yield. The partitioning of products between thiadiazoles and their sulfine derivatives was found to be a function of both the acyl and alkylidine moieties of the hydrazone starting material. Herein we report our investigations into the scope, limitations, and mechanism of this reaction.

Chart I



4 **5a-d** **10** **6** **7** **8** **9**

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(8) An excellent review on sulfines, including a comprehensive summary of the methods of synthesis, has recently been published: Zwanenburg, B. *Rec. Trav. Chim. Pays-Bas* **1982**, *39*, 1.
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(10) The reactions of active methylene compounds with $SOCl_2$ have been reviewed. See ref 27.

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Table I. Product Distribution from the Reaction of Hydrazones 5a-d with Neat $SOCl_2$

hydrazone	X	$SOCl_2$, molar equiv	conditions: temp, °C	conditions: time, min	% isolated yield of products: 6	7	8	9
5a	CO_2Et	30	70	20	84	a	a	a
5b	$COCH_3$	45	65	30	34	45	5	a
5c	CHO	43	25	30	0	85	2.7	1.7
5d	p-tosyl	59	70	20	0	84	2	5

[a] None detected. Small amounts (≤2%) may have been present.

Results

When the (ethoxycarbonyl)hydrazone **5a** derived from 5α-dihydrotestosterone acetate (**4**) was dissolved in neat $SOCl_2$ and the resulting red solution heated briefly to 65 °C, instead of the expected product **7**, we obtained an 84% yield of its C-1 (*Z*)-sulfine derivative **6**. Sulfine **6** was a surprisingly stable, off-white solid that could be handled in air, chromatographed on silica gel, and stored at 25 °C in excess of 1 year without noticeable decomposition. However, **6** was partially converted (~8%) to ketone **10**[11] in boiling methyl ethyl ketone.

Scope. The unexpected formation of **6** from **5a** prompted us to systematically explore the effect of hydrazone structure on the reaction (Chart I). Braun and Meier[6] reported that the tosylhydrazones of a series of alicyclic ketones gave high yields of thiadiazoles with $SOCl_2$ while the reaction "failed" with the corresponding acetylhydrazones. This suggested to us that the nitrogen substituent (X) may influence the extent of sulfine formation. To test this idea the acetyl (**5b**), formyl (**5c**), and *p*-tosyl (**5d**) hydrazones of **4** were prepared and similarly reacted with $SOCl_2$. The results (Table I) indicated that X was in fact critical to the reaction course. Compounds **5c** and **5d** both gave high yields of thiadiazole **7** and no sulfine, whereas acetylhydrazone **5d** gave a mixture of **6** and **7**. Small amounts of chlorothiadiazole **8** were also produced in these reactions. In addition, the isomeric 3,4-fused thiadiazole **9** was isolated in low yield from the formyl- and tosylhydrazone substrates. Tosyl chloride was obtained in 96% yield as a byproduct of the latter reaction.

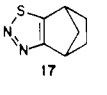
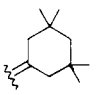
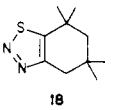
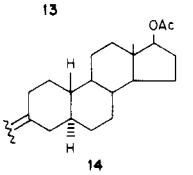
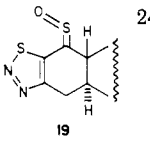
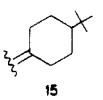
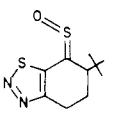
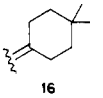
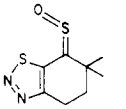
The scope of sulfine formation was studied further by examining the $SOCl_2$ reaction of the (ethoxycarbonyl)-hydrazones of a series of structurally related ketones. In Table II it can be seen that either thiadiazoles or thiadiazolyl sulfines were obtained from all these substrates except the cyclohexanone derivative **11**. The latter afforded a complex mixture of several products which, because of their instability, were not characterized.[12]

The results for hydrazones **11**, **14**, **15**, **16**, and **5a** indicate a general trend of increasing yields of thiadiazolyl sulfines with increasing alkyl substitution γ to the hydrazone ketimine carbon (α to the incipient sulfine). The regiospecificity of sulfine formation for the methylene group α to the sulfur-bearing carbon of the thiadiazole ring is illustrated by the result for substrate **13**. In this case sulfine formation is blocked by dimethyl substitution at the requisite carbon, the reaction affording thiadiazole **18** almost quantitatively even though the adjacent allylic methylene is available for further transformation.

Mechanistic Studies. The fate of the nitrogen substituent (EtOCO) in the (ethoxycarbonyl)hydrazone/$SOCl_2$ reactions was of interest since byproducts, e.g., ethyl chloroformate[13] (ECF), could be involved in the $-CH_2-$ to C=S=O transformation. To that end, **16** was reacted with 4.2 molar equiv of $SOCl_2$ in CH_2Cl_2, and the volatile products were fractionally distilled, resulting in the isolation of ECF, identified by IR and ^1H NMR comparison with authentic material. Similarly, when **5a** was reacted with an excess of $SOCl_2$ in $CDCl_3$ at 25 °C in a tightly capped NMR tube, the only CH_2CH_3 peaks in the resulting 80-MHz ^1H NMR spectrum were shown to be identical with those of ECF by spiking with authentic material.

When thiadiazole **7** was heated to 65 °C for 20 min in $SOCl_2$ containing 1.0 equiv of ECF, no reaction was observed, thereby eliminating **7** as a possible intermediate in the conversion of **5a** to **6**. Intermediates enroute to sulfine **6** were isolated when **5a** was treated with 2.0 equiv of $SOCl_2$ in CH_2Cl_2 at −20 °C, and the reaction was quenched after 70 min by the addition of excess aqueous $NaHCO_3$. The resulting mixture gave the following products (% yield): dihydrothiadiazole *S*-oxide **22** (6%), vinyl sulfide **23** (9%), hydrazone **5a** (57% recovery), ketone **4** (14%),[14] sulfine **6** (4%), and thiadiazole **7** (3%). In

Table II. Reaction of (Ethoxycarbonyl)hydrazones 11-16 with Neat $SOCl_2$

hydrazone ($EtO_2CHNN=$)	$SOCl_2$, molar equiv	conditions: temp, °C	conditions: time, min	product	% yield
 11	24	65	30	unstable mixture	
 12	27	65	30	 17	29
 13	33	65	30	 18	97
 14	55	65	20	 19	24-41
 15	43[a]	25	60	 20	72
 16	39	65	15	 21	82

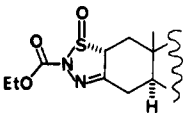
[a] Small amount of CH_2Cl_2 added to facilitate stirring. See Experimental Section.

(11) The conversion of sulfines into the corresponding carbonyl compounds under thermal and photolytic conditions is well documented. See ref 8.

(12) Braun and Meier (ref 6) were similarly unsuccessful in an attempt to prepare a 1,2,3-thiadiazole from the corresponding acetyhydrazone and $SOCl_2$. However, the desired product was obtained in 90% yield from the tosylhydrazone.

(13) It has been suggested (ref 1) that ethyl chloride may be a by product of the reaction of (ethoxycarbonyl)hydrazones and $SOCl_2$. We found no evidence in our studies to support this suggestion.

separate experiments, **22** and **23** were both converted cleanly to sulfine **6** when dissolved in neat $SOCl_2$ at 25 °C. Treatment of a solution of **23** in $CDCl_3$ with only a slight excess of $SOCl_2$ afforded a 3:1 mixture of sulfine **6** and thiadiazole **7**.



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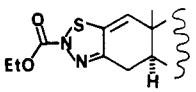
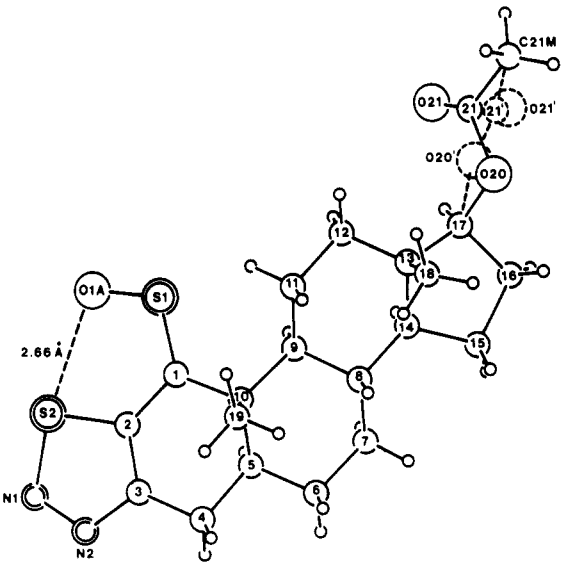


23

The color produced during these reactions has been a reliable indicator of the nature of the products. In all cases studied, sulfine formation was accompanied by a deep red color formed immediately on mixing the reagents and which faded as the reaction neared completion. In contrast, the reactions of those substrates (e.g., **5c**, **5d**, **13**) which did not produce sulfines remained pale yellow initially, although some darkening was generally noted as the reaction neared completion. The single exception to the latter statement is **11**, whose reaction mixture went from red to dark brown and subsequently yielded neither sulfine nor thiadiazole. The possibility that "stable" radicals involved in sulfine formation might be the source of this intense red color prompted us to study the reaction of **5a** with $SOCl_2$ by ^1H NMR and ESR. Neither CIDNP[15] in the ^1H NMR nor an ESR signal was observed.

Determination of Structures. The structure of **6** was unambiguously determined by X-ray crystallography. The details of the X-ray study, including a description of the disorder found in the D-ring substituent, are given in the Experimental Section. Figure 1 shows conformation, numbering, and the fractional atomic coordinates. Bond distances and the bond angle for the sulfine atoms, C1–S1 = 1.64 Å, S1–O1A = 1.49 Å, and C1–S1–O1A = 111°, are in good agreement with values reported by Schaumann et al.[15a] and are within the range of values given in the review on sulfines.[8] The nonbonded sulfine-O thiadiazole-S distance in **6** was found to be 2.66 Å, which is 0.6 Å shorter than the sum of the van der Waals radii for sulfur and oxygen.[16] The sulfine group is almost in the plane of the thiadiazole ring, and the N1–S2 --- O1A angle is 169°. The consensus of opinion among several investigators[17-21] who have observed S---O contacts in the range of 2.64–2.74 Å is that the interaction is weakly attractive. Kalman and Párkányi[20] surveyed 26 structures with close S---O contacts and agree with a previous suggestion by Hamilton and LaPlaca[21] that in a planar environment an almost linear –S---O geometry provides a favorable situation for s, p, and d orbital participation in partial S---O bonding.

The structure of the remaining thiadiazole derivatives was determined by comparison of their physical properties (^1H NMR, IR, UV, MS) with those of **6**. The ^1H NMR



	X	Y	Z
S1	5156 (2)	4567 (1)	1135 (1)
S2	3518 (2)	6735 (1)	1654 (1)
O1A	5884 (4)	5597 (3)	1098 (2)
C1	3311 (6)	4602 (4)	1478 (2)
N1	1761 (6)	7306 (3)	1856 (2)
C2	2578 (6)	5573 (4)	1622 (3)
N2	514 (6)	6691 (3)	1882 (2)
C3	975 (6)	5701 (4)	1753 (3)
C4	245 (7)	4865 (4)	1702 (3)
C5	513 (6)	3952 (4)	1327 (3)
C6	682 (6)	3076 (4)	1327 (3)
C7	3 (7)	2162 (4)	948 (3)
C8	1613 (6)	1835 (4)	1276 (3)
C9	2896 (6)	2695 (4)	1282 (3)
C10	2232 (6)	3680 (3)	1631 (3)
C11	4495 (6)	2286 (4)	1602 (3)
C12	5207 (7)	1388 (4)	1190 (3)
C13	3952 (7)	525 (4)	1164 (3)
C14	2342 (7)	946 (4)	879 (3)
C15	1295 (9)	9 (4)	762 (3)
C16	2581 (9)	795 (5)	516 (3)
C17	4214 (8)	298 (4)	608 (3)
C18	3781 (7)	41 (4)	1911 (3)
C19	2161 (7)	3556 (4)	2453 (3)
C21M	7906 (7)	1952 (4)	690 (3)
O20	5204 (9)	1131 (5)	752 (4)
C21	6906(18)	1000(11)	476 (8)
O21	7223 (8)	327 (5)	108 (3)
O20'	5779(11)	917 (6)	899 (5)
C21'	6635(23)	1301(13)	446 (9)
O21'	6366(16)	1295 (9)	195 (7)

Figure 1. Conformation, numbering, fractional atomic coordinates (×10^4), and standard deviations for **6**. Alternate O20, C21, and O21 atoms are shown with dotted lines.

spectra of **6** and **10** were almost identical, the most characteristic features of which were the low-field position of their 19-CH_3 singlets (δ 1.16 and 1.13, respectively) and the distinctive eight-line pattern (AB portion of ABX system) displayed by their respective C-4 methylene protons in the δ 3.6–2.9 region. The juxtaposition of the ketonic carbonyl and thiadiazole ring in **10** was further indicated by its low-energy ketone absorption (1685 cm^{-1}) and a 15-nm bathochromic shift both of the thiadiazole UV absorptions (λ_{max} 236, 277 nm) relative to those of **7** (λ_{max} 221, 262 nm).

The regiochemistry of thiadiazole annelation for the isomers **7** and **9** was unambiguously determined from the number and coupling patterns of their allylic protons, which were sufficiently deshielded to be readily identified in their 200-MHz ^1H NMR spectra (see Experimental Section).

Similarly, the indicated regiochemistry of the sulfine group and thiadiazole ring in **19** was supported by the low-field position of the 4α, 4β, and 10β protons at δ 3.55, 2.96, and 2.67, respectively, which were identified by their

(14) Some of this ketone was undoubtedly formed by hydrolysis of **5a** during chromatographic separation of the mixture. The partial decomposition of **5a** to ketone **4** on silica gel was verified by two-dimensional TLC experiments.

(15) Chemically Induced Dynamic Nuclear Polarization. See review: Kaptein, R. In "Chemically Induced Magnetic Polarization"; Proceedings of NATO ASI, Series C, Vol. 34; Muus, L. T., Atkins, P. W., McLauchlan, K. A., Pedersen, J. B., Eds.; D. Reidel Co.: Boston, 1977; Chapter 1. (a) Schaumann, E.; Behr, H.; Adiwidjaja, G.; Tangerman, A.; Lammerink, B. H. M.; Zwanenburg, B. *Tetrahedron* **1981**, *37*, 219.

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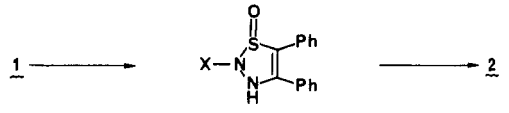
coupling patterns in the 200-MHz ^{1}H NMR. A one-proton singlet at δ 5.25 in the ^{1}H NMR of **8** indicated the presence of an isolated –CHCl– group, thereby establishing the regiochemistry of thiadiazole annelation as well as that of the chlorine substituent.

Intermediates **22** and **23** both gave strong molecular ions in the mass spectrum. The stereochemistry of **22** at C-2 was evident from its ^{1}H NMR, the 2β-H (δ 3.80) exhibiting typical trans–diaxial and axial–equatorial couplings (J = 12.8 and 7.1 Hz, respectively) to the C-1 methylene.[22] The olefinic proton of **23** appeared as a singlet at δ 5.87. The intense UV absorption of **23** at 337 nm (ϵ 15 200) was supportive of a system having extended conjugation. It is interesting to note that while the carbamate C=O of **23** absorbs at 1698 cm^{-1}, typical for this functionality,[23] the corresponding absorption for **22** occurs at 1767 cm^{-1}, presumably shifted to higher wavenumber due to resonance/induction effects of the proximate sulfoxide.[24]

The configuration ("*E*" or "*Z*") of the sulfine groups in **19**, **20**, and **21** have not been rigorously established. In all cases only one isomer was detected. Models indicate that a relatively severe steric interaction would exist between the sulfine oxygen and the adjacent alkyl group of (*E*)-sulfines analogous to **19** and **20**. In view of this, and the potential for sulfine-O thiadiazole-S close contact stabilization for the *Z* isomers, as observed in the X-ray of **6**, the sulfine groups in **19**, **20**, and **21** have similarly been assigned the *Z* configuration (as drawn).

Discussion

A mechanism has been proposed[6,25] for the formation of thiadiazoles from hydrazones and $SOCl_2$ which is based primarily on the work of Hurd and Mori,[1] who isolated the intermediate *S*-oxides **24** and demonstrated their further conversion to **2** under conditions of acid and base catalysis.

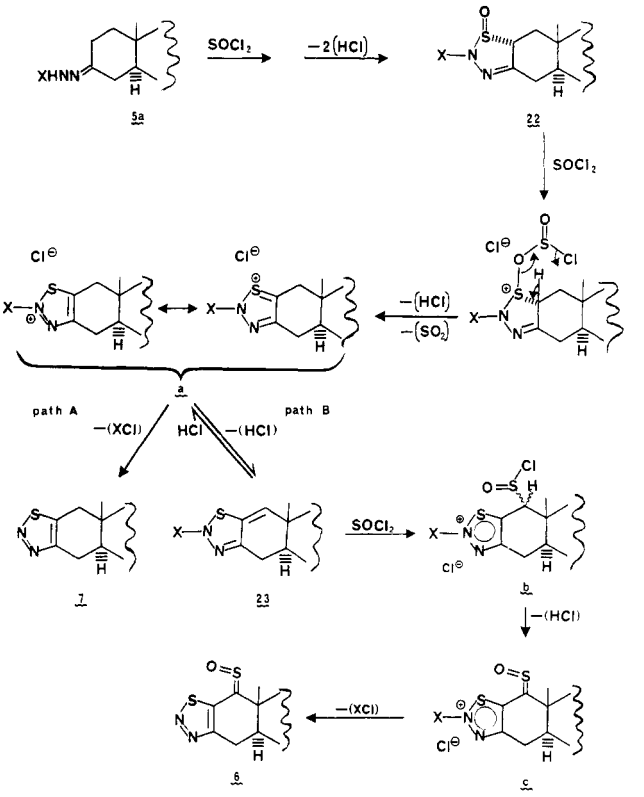


24 (X = COCH$_3$, p-Tosyl)

More recently tosyl chloride has been isolated as a by-product of the reaction with tosylhydrazone substrates[6] and earlier studies[1] suggest that it may be formed via nucleophilic attack by Cl^- on sulfonyl sulfur.

In Scheme I we propose a mechanism for the formation of thiadiazolyl sulfine **6** and thiadiazole **7** from **5a** and $SOCl_2$. A key step in this sequence is the reaction of intermediate **22** (X = CO_2Et) with $SOCl_2$ in a Pummerer-like[26,27] process to yield the resonance-stabilized acyl thiadiazolium chloride a. As the pivotal intermediate, a can give thiadiazole **7** via nucleophilic attack on X by Cl^-.[28]

Scheme I



Alternatively, through a reversible deprotonation, vinyl sulfide **23** (X = CO_2Et) may be generated. Electrophilic attack on the electron-rich double bond in **23** by $SOCl_2$ followed by dehydrohalogenation can then afford the α-sulfinylthiadiazolium chloride c. Loss of ethyl chloroformate (XCl) from c generates the sulfinylthiadiazole **6**.

We believe that the above mechanism also has broader implications in that it provides a rationale for the general behavior of hydrazones in $SOCl_2$. The compatibility of this model with our results and the literature is illustrated below with specific examples.

According to the model, the proportion of thiadiazole formed should relate directly to the ease of loss of the X group from the pivotal intermediate a if the competing process (path B) is not significantly affected. In Table I we see that greater proportions of the thiadiazole are formed as X is varied from CO_2Et to the increasingly more labile, but electronically similar, $COCH_3$ and CHO groups, as predicted by the model. When X is tosyl the formation of the thiadiazole is also favored, a result more difficult to rationalize in view of the general observation that sulfonyl sulfur is less reactive toward nucleophilic attack than carbonyl carbon.[29] However, the tosyl group is also highly electron withdrawing[30] and through a strong negative inductive effect could reduce the reactivity of the vinyl sulfide intermediate (i.e., **23** where X = *p*-tosyl) toward electrophilic attack by $SOCl_2$. This later influence would favor the production of the thiadiazole by slowing down path B.

While the use of an (ethoxycarbonyl)hydrazone in this reaction favors the formation of the sulfine derivative, this tendency can be preempted by unfavorable steric or electronic features which (1) inhibit the formation of the

(22) The analogous couplings to the 1β-H in 2α-bromocholestan-3-one are 13 and 6 Hz, respectively: Bhacca, N. S.; Williams, D. H. "Applications of NMR Spectroscopy in Organic Chemistry"; Holden-Day: San Francisco, 1964; p 47.

(23) Bellamy, L. J. "The Infra-Red Spectra of Complex Molecules"; Wiley: New York, 1954; p 190.

(24) A reduction in electron availability on the carbamate nitrogen either through resonance with the sulfoxide group or by its inductive effect should increase the C=O frequency by interfering with the "amide" (O=C–N) resonance. For a general discussion of factors that influence the C=O absorption frequency, see: Conley, R. T. "Infrared Spectroscopy"; Allyn and Bacon: Boston, 1966; p 136.

(25) Bellesia, F.; Grandi, R.; Pagnoni, U. M.; Trave, R. *Gazz. Chim. Ital.* **1981**, *111*, 289.

(26) Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572.

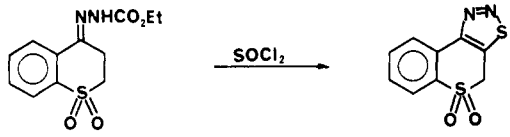
(27) Oka, K. *Synthesis* **1981**, 661.

(28) In the general sense, loss of the X group from b could occur via several alternative mechanisms, e.g., α-elimination to give HCl and CO when X is formyl, or β-elimination to give ketene and HCl when X is acetyl.

(29) (a) March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure"; McGraw-Hill: New York, 1969; p 372. (b) Kice, K. L.; Legan, E. *J. Am. Chem. Soc.* **1973**, *95*, 3912.

(30) Oae, S., Ed. "Organic Chemistry of Sulfur"; Plenum Press: New York, 1977; p 583.

vinyl sulfide intermediate (analogous to **23**) or (2) reduce its reactivity toward $SOCl_2$. For example, the formation of an analogous vinyl sulfide from **12** would be a violation of Bredt's rule.[31] An illustration of the second point can be found in the report by Hurd and Mori[1] that thiadiazole **26** is obtained in 73% yield from the reaction of hydrazone



25 **26**

25 and $SOCl_2$. In this case, the analogous vinyl sulfide intermediate would be greatly deactivated toward electrophilic attack due to the electron-withdrawing influence of the proximate sulfonyl group.[30]

The source of chlorothiadiazole **8** in these reactions (Table I) is unknown. Sulfinyl chlorides are known to give the corresponding chlorides on heating.[9a] However, if **8** were formed from intermediate b (where X = $COCH_3$, CHO, and *p*-tosyl), one would expect it to be accompanied by significant amounts of sulfine **6**, since b is a likely precursor to **6**. The results for hydrazones **5c** and **5d**, therefore, tend to refute this possibility. Alternatively **8** could be formed via electrophilic chlorination of intermediate **23** by a chlorinating agent which is generated in situ.[32]

Experimental Section

Cyclohexanone, *d,l*-norcamphor, 3,3,5,5-tetramethylcyclohexanone, 4-*tert*-butylcyclohexanone, ethyl carbazate, acethydrazide, formic acid hydrazide, and *p*-toluenesulfonhydrazide were purchased from Aldrich and used as received. 4,4-Dimethylcyclohexanone,[33] 17β-acetoxy-3-oxo-5α-estran-17β-ol,[34] and 5α-dihydrotestosterone acetate (**7**)[35] were prepared by standard procedures. Commercial thionyl chloride (Eastman, bp 75–7 °C) was used without further purification.[36] LPLC referes to preparative low-pressure (~30–100 PSIG) liquid chromatography on either prepacked Lobar columns (E. Merck, Lichroprep Si 60) or Michel-Miller columns (Ace Glass, Inc.) packed with silica gel 60 (E. Merck, 230–400 mesh). Solvents (Burdick and Jackson, distilled-in-glass) were driven with an FMI Model RPD pump. Typical column loadings were 0.5–1.0 g/100 g of adsorbant. Fractions were combined based on TLC analysis on Analtech Uniplates (silica). Melting points were obtained in open capillaries on a Thomas-Hoover Unimelt and are uncorrected. IR spectra were recorded with a Digilab Model FTS-14D. ^1H NMR spectra were obtained on either a Varian HFT 80 or XL 200 spectrometer. $W_{1/2h}$ refers to peak width at half-height. ^{13}C NMR spectra were obtained on a Varian CFT 20 instrument. Chemical shifts are expressed in δ (parts per million relative to internal tetramethyl silane). UV spectra were recorded with a Cary 15 spectrometer on solutions in 95% EtOH. Mass spectra (MS) and chemical ionization mass spectra (CI) were obtained on a Varian MAT CH7 instrument. The ionizing gas (either isobutane or NH_3) for CI is indicated in parentheses. Combustion analyses were performed by the Upjohn Physical and Analytical Chemistry Department.

General Procedure for the Preparation of Hydrazones. To a mixture of the ketone and 1.10 equiv of the hydrazine in absolute EtOH (10 mL/g ketone) was added 0.1 equiv of glacial acetic acid. The mixture was stirred at 25 °C for 4 h or optionally refluxed for 5 min. The products, isolated as described below, were used without further purification:

17β-Acetoxy-5α-androstan-3-one (Ethoxycarbonyl)hydrazone (5a). The mixture was diluted with H_2O and cooled with ice. The precipitate was collected, washed with cold EtOH, and dried to give **5a** (95% yield) as a fluffy white solid: mp 197–9 °C (gas evolution); ^1H NMR ($CDCl_3$) δ 7.66 (br s, $W_{1/2h}$ ~5 Hz, 1 H, NH), 4.58 (br t, 1 H, J = 8 Hz, 17α-H), 4.26 (q, 2 H, J = 7 Hz, OCH_2), 2.03 (s, 3 H, CH_3CO_2), 1.30 (t, 3 H, J = 7 Hz, CH_3CH_2), 0.90 (s, 3 H, 19-CH_3), 0.79 (s, 3 H, 18-CH_3). Anal. Calcd for $C_{24}H_{38}N_2O_4$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.90; H, 9.40; N, 6.70.

17β-Acetoxy-5α-androstan-3-one Acetylhydrazone (5b). The mixture was evaporated in vacuo. The residue was dissolved in CH_2Cl_2, and the solution was washed with H_2O, dried ($MgSO_4$), and evaporated. Trituration of the residue with EtOAc afforded **5b** in 95% yield as a white powder: mp 253–6 °C (lit.[37] mp 232–243 °C); ^1H NMR ($CDCl_3$) δ 8.53 and 8.25 (br s, 1 H total, NH), 4.58 (br t, J = 8 Hz, 1 H, 17α-H), 2.24 (s, 3 H, CH_3CON), 2.03 (s, 3 H, CH_3CO_2), 0.91 (s, 3 H, 19-CH_3), 0.79 (s, 3 H, 18-CH_3). Anal. Calcd for $C_{23}H_{36}N_2O_3$: C, 71.10; H, 9.34; N, 7.21. Found: C, 71.15; H, 9.51; N, 7.02.

17β-Acetoxy-5α-androstan-3-one Formylhydrazone (5c). The mixture was cooled (ice) and the precipitate was collected, washed (EtOH), and dried to give **5c** (84% yield) as a white powder: mp 256–9 °C dec; ^1H NMR ($CDCl_3$) δ 9.92 (apparent t which disappeared on D_2O exchange, J = 10 Hz, 1 H, NH), 8.63 (d which collapsed to s on D_2O exchange, J = 10 Hz, 1 H, NCHO), 4.58 (br t, J ~ 8 Hz, 1 H, 17α-H), 2.03 (s, 3 H, CH_3CO_2), 0.91 (s, 3 H, 19-CH_3), 0.79 (s, 3 H, 18-CH_3). Anal. Calcd for $C_{22}H_{34}N_2O_3$: C, 70.55; H, 9.15; N, 7.48. Found: C, 70.43; H, 8.83; N, 7.61.

17β-Acetoxy-5α-androstan-3-one (*p*-Tolylsulfonyl)hydrazone (5d). The mixture was cooled (−20 °C), and the precipitate was collected, washed (cold EtOH), and air-dried to yield **5d** (92%) as a fluffy white solid: mp 108–112 °C (lit.[38] mp 93–5 °C); ^1H NMR ($CDCl_3$) δ 7.83 (apparent d, J = 8 Hz, 2 H, Ar H's), 7.29 (apparent d, J = 8 Hz, Ar H's), 4.57 (br t, J = 8 Hz, 1 H, 17-H), 2.42 (s, 3 H, Ar CH_3), 2.02 (s, 3 H, CH_3CO_2), 0.84 (s, 3 H, 19-CH_3), 0.77 (s, 3 H, 18-CH_3).

Cyclohexanone (Ethoxycarbonyl)hydrazone (11). The mixture was evaporated in vacuo and the viscous residue partitioned between Et_2O and 5% aqueous $NaHCO_3$. The Et_2O phase was washed with saturated aqueous NaCl (×3), dried ($MgSO_4$), and evaporated to give **11** (80%) as a colorless, viscous oil. The sample that was reacted with $SOCl_2$ was quickly chromatographed on alumina [Woelm basic, activity 3, CH_2Cl_2/Et_2O (95:5)] to remove a trace impurity: ^1H NMR ($CDCl_3$) δ 7.86 (br s, $W_{1/2h}$ = 8 Hz, 1 H, NH), 4.26 (q, J = 7 Hz, 2 H, OCH_2), ~2.45–2.10 (m, 4 H, $CH_2(C{=}N)CH_2$), 1.5–1.8 (m, 6 H), 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3). Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.45; H, 8.68; N, 15.19.

***d,l*-Norcamphor (Ethoxycarbonyl)hydrazone (12).** The mixture was evaporated in vacuo and the residual oil partitioned between Et_2O and dilute aqueous NaCl. The Et_2O phase was washed (saturated NaCl), dried ($MgSO_4$), and evaporated to yield **12** (90%) as a white solid: mp 76–9 °C; ^1H NMR ($CDCl_3$) δ 7.38 (br s, $W_{1/2h}$ = 8 Hz, 1 H, NH), 4.27 (q, J = 7 Hz, 2 H, OCH_2), 2.97 (br s, $W_{1/2h}$ = 7 Hz, 1 H), 2.59 (br s, $W_{1/2h}$ = 9 Hz, 1 H), ~2.77–1.47 (m, 8 H), 1.31 (t, J = 7 Hz, 3 H, CH_2CH_3). Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.01; H, 8.05; N, 14.50.

3,3,5,5-Tetramethylcyclohexanone (Ethoxycarbonyl)hydrazone (13). The mixture was diluted with H_2O, and the resulting precipitate was collected, washed with H_2O, and dried to yield **13** (95%) as a fluffy white solid: mp 138–9 °C; ^1H NMR ($CDCl_3$) δ 7.64 (br s, $W_{1/2h}$ = 7 Hz, 1 H, NH), 4.28 (q, J = 7 Hz, 2 H, OCH_2), 2.16 (s, 2 H, syn $CH_2C{=}N$), 1.96 (s, 2 H, anti

(31) Fawcet, F. S. *Chem. Rev.* **1950**, *47*, 219.
(32) Mixtures of sulfoxides and $SOCl_2$ are capable of effecting electrophilic chlorinations of olefins, e.g., cyclohexene. See: Granoth, I. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2166 and ref 30, p 406.
(33) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 1347.
(34) Villotti, R.; Ringold, H. J.; Djerassi, C. *J. Am. Chem. Soc.* **1960**, *82*, 5693.
(35) Ruzicka, L.; Kägi, H. *Helv. Chim. Acta* **1937**, *20*, 1557.
(36) The reaction of **5a** with $SOCl_2$ that was purified immediately prior to use by distillation from quinoline followed by fractionation from linseed oil (Fieser, L. F. "Experiments in Organic Chemistry", 2nd ed.; D.C. Heath and Co.: New York, 1941; p 381) gave a result indistinguishable from that obtained when commercial $SOCl_2$ was used without further purification.
(37) Pitt, C. G. *J. Org. Chem.* **1965**, *30*, 3242.
(38) Cagliot, L.; Gasparrini, F. *Synthesis* **1979**, 207–8.

$CH_2C{=}N$), 1.40 (s, 2 H, $(CH_3)_2CCH_2C(CH_3)_2$), 1.31 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.00 (s, 12 H, $(CH_3)_2CCH_2C(CH_3)_2$). Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.96; H, 10.07; N, 11.66. Found: C, 64.95; H, 9.98; N, 11.85.

17β-Acetoxy-5α-estran-3-one (Ethoxycarbonyl)hydrazone (14). The mixture was diluted with H_2O and cooled (ice), and the precipitate was collected, washed (H_2O), and dried to yield **14** (97%) as a fluffy white solid: mp 170–1 °C; ^1H NMR ($CDCl_3$) δ 7.60 (br s, $W_{1/2h}$ = 4 Hz, 1 H, NH), 4.59 (br t, J = 8 Hz, 1 H, 17α-H), 4.26 (q, J = 7 Hz, 2 H, OCH_2), 2.03 (s, 3 H, CH_3CO_2), 1.31 (t, J = 7 Hz, 3 H, CH_2CH_3), 0.80 (s, 3 H, 18-CH_3). Anal. Calcd for $C_{23}H_{36}N_2O_4$: C, 68.29; H, 8.97; N, 6.93. Found: C, 68.19; H, 9.37; N, 6.91.

4-*tert*-Butylcyclohexanone (Ethoxycarbonyl)hydrazone (15). Worked up as for **11**, **15** was obtained in 98% yield as a colorless oil (solvent removed at 25 °C/≤3 mm) which crystallized on standing at 25 °C for several weeks: mp 98–100 °C (after trituation with hexane); ^1H NMR ($CDCl_3$) δ 7.71 (br s, $W_{1/2h}$ = 7 Hz, NH), 4.26 (q, J = 7 Hz, 2 H, OCH_2), 2.8–1.15 (m with OCH_2CH_3, t (J = 7 Hz) at δ 1.31, 12 H) 0.87 (s, 9 H, $C(CH_3)_3$). Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.96; H, 10.07; N, 11.66. Found: C, 65.04; H, 10.15; N, 11.61.

4,4-Dimethylcyclohexanone (Ethoxycarbonyl)hydrazone (16). Worked up as for **14**, **16** was isolated in 86% yield as a white solid: mp 106–8 °C; ^1H NMR ($CDCl_3$) δ 7.68 (br s, $W_{1/2h}$ = 7 Hz, 1 H, NH), 4.26 (q, J = 7 Hz, 2 H, OCH_2), 2.48–2.15 (apparent p, J = 7 Hz, 4 H, $CH_2(C{=}N)CH_2$), 1.58–1.36 (m, 4 H, $CH_2C(CH_3)_2CH_2$), 1.31 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.00 (s, 6 H, $C(CH_3)_2$). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20. Found: C, 62.26; H, 9.66; N, 13.11.

General Procedure for the Reaction of Hydrazones 5a–d with $SOCl_2$. To the hydrazone was added $SOCl_2$ (30–60 molar equiv, see Table I) in one portion, and the resulting solution was stirred under inert atmosphere and heated as indicated (Table I) after the initial mild exotherm subsided. Excess $SOCl_2$ was evaporated in vacuo, residual traces being removed by azeotropic vacuum distillation with benzene or toluene. The residue was chromatographed (LPLC) on silica gel, eluting with toluene/EtOAc [linear gradient from 95:5 to 9:1] or, for substrate **5a**, CH_2Cl_2/Et_2O (95:5). The following compounds were thus prepared (see yields in Table I).

(1*Z*)-17β-Acetoxy-5α-androst-2-eno[3,2-*d*][1,2,3]thiadiazole-1-thione *S*-oxide (6): off-white solid; mp 260–2 °C dec (acetonitrile); IR (Nujol) 1731 (C=O), 1236, 1216, 1077, 1046, 1020, cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 (br t, 1 H, 17α-H), 3.56–2.88 (2 H, eight-line AB portion of ABX system: 3.39 (4α-H), 3.09 (4β-H), $J_{4\alpha H-4\beta H}$ = 17.8 Hz, $J_{4\beta H-5\alpha H}$ = 11.2 Hz, $J_{4\alpha H-5\alpha H}$ = 4.6 Hz), 2.05 (s, 3 H, CH_3CO_2), 1.16 (s, 3 H, 19-CH_3), 0.88 (s, 3 H, 18-CH_3); ^{13}C NMR ($CDCl_3$) δ 192.3 (C-1), 170.9 (CH_3CO_2), 157.9 (C-3), 137.4 (C-2), 82.3 (C-17), 51.2 (C-14), 49.8 (C-9), 47.2 (C-10), 44.3 (C-5), 42.7 (C-13), 37.6 (C-8), 36.8 (C-12), 29.7 (C-4 and C-7), 28.8 (C-6), 27.5 (C-16), 26.0 (C-11), 23.6 (C-15), 21.1 (CH_3CO_2), 14.8 (C-19), 12.8 (C-18); UV λ_{max} (ε) 231 (7400), 283 (sh, 1650), 342 nm (10000); MS, m/e 420 (M^+). Anal. Calcd for $C_{21}H_{28}N_2O_3S_2$: C, 59.97; H, 6.71; N, 6.66; S, 15.25. Found: C, 60.29; H, 6.78; N, 6.69; S, 15.19.

17β-Acetoxy-5α-androst-2-eno[3,2-*d*][1,2,3]thiadiazole (7): off-white solid; mp 147–9 °C (MeOH); IR (Nujol) 1735 (C=O), 1523 (C=C/C=N), 1246, 1237, 1231, 1043, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.62 (br t, J = 8 Hz, 1 H, 17α-H), 3.36–3.03 (m, 2 H), 2.85–2.30 (m, 2 H), 2.04 (s, 3 H, CH_3CO_2), 0.82 (s, 3 H, 18-CH_3), 0.79 (s, 3 H, 19-CH_3); partial 200-MHz ^1H NMR ($CDCl_3$) δ 3.225 (ddd, $J_{4\alpha H-4\beta H}$ = 17 Hz, $J_{4\alpha H-5\alpha H}$ = 5 Hz, J(?) = 1.2 Hz, 1 H, 4α-H), 3.126 (slightly broadened d, $J_{1\beta H-1\alpha H}$ = 17 Hz, $W_{1/2h}$ = 2 Hz, 1 H, 1β-H), 2.685 (ddm, $J_{4\beta H-4\alpha H}$ = 17 Hz, $J_{4\beta H-5\alpha H}$ = 11.5 Hz, $W_{1/2h}$ = 5 Hz, 1 H, 4β-H), 2.477 (dm, $J_{1\alpha H-1\beta H}$ = 17 Hz, $W_{1/2h}$ = 5 Hz, 1-H); UV λ_{max} (ε) 221 (4800), 262 nm (3600); MS, m/e 346 ($M - N_2^+$, base peak); (CI, isobutane) m/e 375 ($M + H^+$). Anal. Calcd for $C_{21}H_{30}N_2O_2S$: C, 67.34; H, 8.07; N, 7.48; S, 8.56. Found: C, 67.24; H, 8.03; N, 7.60; S, 8.61.

17β-Acetoxy-1-chloro-5α-androst-2-eno[3,2-*d*][1,2,3]thiadiazole (8): white solid; mp 189–189.5 °C (CH_2Cl_2/hexane); IR (Nujol) 1730 (C=O), 1523 (C=C/C=N), 1254, 1042, 1025, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 (s, 1 H, Cl-C-H), 4.63 (br t, J = 7 Hz, 1 H, 17α-H), 3.36 (dd, $J_{4\alpha H-4\beta H}$ = 17.2 Hz, $J_{4\alpha H-5\alpha H}$ = 5.5 Hz, 1 H, 4α-H), 2.69 (dd, $J_{4\alpha H-4\beta H}$ = 17.2 Hz, $J_{4\beta H-5\alpha H}$ = 11.1 Hz, 1 H, 4β-H), 2.04 (s, 3 H, CH_3CO_2), 0.85 (s, 3 H, 19-CH_3), 0.81 (s, 3 H, 18-CH_3); UV λ_{max} (ε) 224 (4900), 264 (3950), 320 nm (sh, 323); MS, m/e 380 ($M - N_2^+$), 345 (base peak); (CI, isobutane) m/e 409 ($M + H^+$, base peak). Anal. Calcd for $C_{21}H_{29}ClN_2O_2S$: C, 61.67; H, 7.15; Cl, 8.67; N, 6.85; S, 7.84. Found: C, 61.30; H, 7.13; Cl, 8.68; N, 6.84; S, 7.93.

17β-Acetoxy-5α-androst-3-eno[3,4-*d*][1,2,3]thiadiazole (9): white solid; mp 171.5–3 °C (acetone/hexane); IR (Nujol) 1739 (C=O), 1512 (C=C/C=N), 1255, 1245, 1239, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.62 (br t, J = 8 Hz, 1 H, 17α-H), 3.5–3.0 (m, 2 H), 2.8–2.5 (m, 1 H), 2.04 (s, 3 H, CH_3CO_2), 0.82 (s, 3 H, 18-CH_3), 0.75 (s, 3 H, 19-CH_3); partial 200-MHz ^1H NMR ($CDCl_3$) δ 3.33 (ddt, $J_{2\alpha H-2\beta H}$ = 17.5 Hz, $J_{2\alpha H-1\alpha H}$ = 7 Hz, J(?) = 1 Hz, 1 H, 2α-H), 3.07 (dddd, $J_{2\beta H-2\alpha H}$ = 17.5 Hz, $J_{2\beta H-1\alpha H}$ = 12 Hz, $J_{2\beta H-1\beta H}$ = 6.6 Hz, J(?) = 2.5 Hz, 1 H, 2β-H), 2.66 (dm, $J_{5\alpha H-6\beta H}$ = 12.5 Hz, $W_{1/2h}$ = 8 Hz, 1 H, 5α-H); UV λ_{max} (ε) 219 (5100), 264 nm (4000); MS, m/e 346 ($M - N_2^+$, base peak); (CI, isobutane) m/e 375 ($M + H^+$). Anal. Calcd for $C_{21}H_{30}N_2O_2S$: C, 67.34; H, 8.07; N, 7.48; S, 8.56. Found: C, 67.29; H, 8.08; N, 7.81; S, 8.56.

17β-Acetoxy-1-oxo-5α-androst-2-eno[3,2-*d*][1,2,3]thiadiazole (10). Chromatographically pure **6** was dissolved in boiling methyl ethyl ketone. The crystals formed on cooling contained, by TLC, a slower moving impurity. This mixture (2.10 g) was chromatographed (LPLC) on silica gel [CH_2Cl_2/Et_2O (95:5)] to give 1.88 g of pure **6** and 0.16 g of pure **10**: white solid; mp 222–4 °C (acetone/hexane); IR (Nujol) 1736 (acetate C=O), 1685 (ketone C=O), 1511, 1241, 1212, 1052, 1032, 1020, cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.62 (br t, J = 8 Hz, 17-H), 3.54–2.86 (2 H, eight-line AB portion of ABX system; 3.35 (4α-H), 3.07 (4β-H), $J_{4\alpha H-4\beta H}$ = 17.8 Hz, $J_{4\beta H-5\alpha H}$ = 10.9 Hz, $J_{4\alpha H-5\alpha H}$ = 4.7 Hz), 2.04 (s, 3 H, CH_3CO_2), 1.13 (s, 3 H, 19-CH_3), 0.84 (s, 3 H, 18-CH_3); UV λ_{max} (ε) 236 (5300), 277 nm (4150); MS, m/e 360 ($M - N_2^+$, base peak); (CI, isobutane) m/e 389 ($M + H^+$, base peak). Anal. Calcd for $C_{21}H_{28}N_2O_3S$: C, 64.92; H, 7.26; N, 7.21; S, 8.25. Found: C, 64.88; H, 7.28; N, 7.15; S, 8.27.

Reaction of Hydrazones 11–16 with $SOCl_2$. The same general procedure was employed. Stochiometry, conditions, and yields are listed in Table II. The products were isolated as described below.

***d*,*l*-4,5,6,7-Tetrahydro-4,7-methano-1,2,3-benzothiadiazole (17)** was isolated by LPLC [silica, hexane/EtOAc (9:1)]. The analytical sample was distilled: colorless liquid; bp 75 °C (0.5 mm); IR (neat) 2973–2877, 1474, 1449, 1426, 1283, 1199, 1171, 1114, 992, 826 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (br s, $W_{1/2h}$ = 8 Hz, 2 H, methine CH's), 2.3–1.7 (m, 4 H), 1.55–1.0 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 175.3 (CN), 157.9 (CS), 53.6 ($CHCH_2CH$), 42.0 (HCCN), 39.6 (HCCS), 27.2, 26.5; UV λ_{max} (ε) 219 (3950), 267 nm (3050); MS, m/e 152 (M^+), 123 (base peak). Anal. Calcd for $C_7H_8N_2S$: C, 55.23; H, 5.30; N, 18.40; S, 21.07. Found: C, 55.10; H, 5.40; N, 18.35; S, 21.30.

5,5,7,7-Tetramethyl-4,5,6,7-tetrahydro-1,2,3-benzothiadiazole (18): isolated by LPLC [silica, hexane/EtOAc (9:1)] and recrystallized from hexane: off-white solid; mp 44–45.5 °C; IR (Nujol) 1503, 1389, 1369, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.93 (s, 2 H, 4-CH_2), 1.67 (s, 2 H, 6-CH_2), 1.42 [s, 6 H, 7-$C(CH_3)_2$], 1.08 (s, 6 H, 5-$C(CH_3)_2$); UV λ_{max} (ε) 221 (4200), 263 nm (3550); MS, m/e 168 ($M - N_2^+$), 167, 153 (base peak); (CI, isobutylene) m/e 197 ($M + H^+$, base peak). Anal. Calcd for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.22; N, 14.27; S, 16.33. Found: C, 60.89; H, 8.33; N, 14.54; S, 16.38.

(1*Z*)-17β-Acetoxy-5α-estr-2-eno[3,2-*d*][1,2,3]thiadiazole-1-thione *S*-oxide (19): isolated initially as a crude oil in 41% yield by LPLC (silica, CH_2Cl_2 followed by CH_2Cl_2/Et_2O (95:5)). Trituration with hexane/EtOAc (7:3) afforded 24% of pure **19**. The analytical sample was recrystallized (hexane/EtOAc): tan solid; mp 190–3 °C dec; IR (Nujol) 1735 (C=O), 1257, 1074, 1063, 1042, 1022 cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 4.67 (dd, J = 7, 9 Hz, 1 H, 17α-H), 3.55 (dd, $J_{4\alpha H-4\beta H}$ = 17 Hz, $J_{4\alpha H-5\alpha H}$ = 4 Hz, 1 H, 4α-H), 2.96 (dd, $J_{4\alpha H-4\beta H}$ = 17 Hz, $J_{4\beta H-5\alpha H}$ = 11 Hz, 1 H, 4β-H), 2.67 (dd, J = 10, 11 Hz, 1 H, 10β-H), 2.05 (s, 3 H, CH_3CO_2), 0.88 (s, 3 H, 18-CH_3); UV λ_{max} (ε) 230 (6800), 285 (sh, 1950), 346 nm (8700); MS, m/e 406 (M^+), 330 (base peak); (CI, NH_3) m/e 424 ($M + NH_3^+$), 407 ($M + H^+$, base peak). Anal. Calcd for $C_{20}H_{26}N_2O_3S_2$: C, 59.08; H, 6.45; N, 6.89; S, 15.77. Found: C, 58.92; H, 6.47; N, 6.94; S, 15.75.

(7*Z*)-6-*tert*-Butyl-5,6-dihydro-1,2,3-benzothiadiazole-7-(4*H*)-thione *S*-Oxide (20). Hydrazone **15** (amorphous glass) was diluted with CH_2Cl_2 (0.2 mL/g of **15**) prior to the addition of the $SOCl_2$ to facilitate stirring. Following workup the crude residue was triturated with EtOAc/hexane and cooled in ice to afford pure **20**. Additional pure **20** was obtained by LPLC [silica, hexane/EtOAc (8:2)] of the triturate liquor. The analytical sample was recrystallized from EtOAc: yellow solid; mp 142.5–5 °C; IR (Nujol) 1480, 1454, 1470, 1429, 1365, 1187, 1080, 1048 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75–1.75 (several complex multiplets, 5 *H*), 0.97 (s, 9 H, $C(CH_3)_3$); the δ 3.75–1.75 region was resolved in the 200-MHz ^1H NMR ($CDCl_3$), 2 H AB quartet (CH_2CN) additionally split by the two vicinal H's, $\delta(A) = 3.542$, $\delta(B) = 3.374$, $J_{AB} = 18.1$ Hz, $J_{A\text{-cis}} = 6.5$ Hz, $J_{A\text{-trans}} = 2.2$ Hz, $J_{B\text{-trans}} = 12.4$ Hz, $J_{B\text{-cis}} = 5.0$ Hz), δ 2.972 (dd, $J_{cis} = 4.9$ Hz, $J_{trans} = 2.7$ Hz, 1 H, $CHC(CH_3)_3$), 2.674 (apparent dp, actual dddd, $J_{gem} = 14.7$ Hz, $J_{B\text{-cis}} = 5.0$ Hz, $J_{A\text{-trans}} = 2.2$ Hz, $J_{5\text{-}6} = 2.7$ Hz, 1 H, $NCCH_2CHHCH$), 2.047 (dddd, $J_{gem} = 14.8$ Hz, $J_{B\text{-trans}} = 12.4$ Hz, $J_{A\text{-cis}} = 6.5$ Hz, $J_{5\text{-}6} = 4.9$ Hz, 1 H, $NCCH_2CHHCH$); UV λ_{max} (ϵ) 234 (7300), 285 (sh, 1900), 343 nm (10 500); MS, *m/e* 242 (M^+), 186 (base peak). Anal. Calcd for $C_{10}H_{14}N_2S_2O$: C, 49.56; H, 5.82; N, 11.56; S, 26.46. Found: C, 49.51; H, 5.97; N, 11.69; S, 26.66.

(7*Z*)-6,6-Dimethyl-5,6-dihydro-1,2,3-benzothiadiazole-7-(4*H*)-thione *S*-oxide (21): isolated by LPLC [silica, benzene/EtOAc (9:1)] and recrystallized from EtOAc/hexane; tan solid; mp 102.5–5 °C; IR (Nujol) 1480, 1460, 1366, 1183, 1171, 1053, 996 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42 (t, $J = 6.3$ Hz, 2 H, 4-CH_2), 2.01 (t, $J = 6.3$ Hz, 2 H, 5-CH_2), 1.49 (s, 6 H, $C(CH_3)_2$); UV λ_{max} (ϵ) 232 (7450), 282 (sh, 1900), 339 nm (10 640); MS, *m/e* 214 (M^+), 138 (base peak). Anal. Calcd for $C_8H_{10}N_2S_2O$: C, 44.83; H, 4.70; N, 13.07; S, 29.92. Found: C, 44.60; H, 4.81; N, 13.19; S, 30.08.

Isolation of Ethyl Chloroformate (ECF). To a stirred solution of 9.00 g (42.4 mmol) of **16** in 7 mL of CH_2Cl_2 cooled to −78 °C under argon was added 13.0 mL (179 mmol) of $SOCl_2$. The solution was warmed slowly until a moderate rate of gas evolution was noted (bath temperature 40–45 °C), held at that temperature until gas evolution subsided (1–1.5 h), refluxed for 0.5–1 h, and then distilled through a small Vigereux column. The fraction distilling at 63–7 °C (760 mm) (1.2 mL) was found by IR, ^1H NMR, and combustion analysis (C, H, Cl) to be ECF containing a trace of CH_2Cl_2.

17β-Acetoxy-2′-(ethoxycarbonyl)-2′,5′α-dihydro-5α-androstano[3,2-*d*][1,2,3]thiadiazole 1′-Oxide (22) and 17β-Acetoxy-2′-(ethoxycarbonyl)-2′*H*-5α-androst-1-eno[3,2-*d*]-[1,2,3]thiadiazole (23). To a stirred solution of 10.0 g (23.9 mmol) of **5a** in CH_2Cl_2 (100 mL) cooled to −70 °C under argon was added dropwise a solution of 3.48 mL (47.9 mmol) of $SOCl_2$ in CH_2Cl_2 (10 mL). The mixture was warmed to −20 °C, becoming red in color. After 70 min at −20 °C excess aqueous 5% $NaHCO_3$ was added and the phases were equilibrated (saturated aqueous NaCl being added to help break the emulsion). The aqueous phase was extracted with CH_2Cl_2. The CH_2Cl_2 phases were combined, dried ($MgSO_4$), filtered through Celite, and evaporated in vacuo. The residue was chromatographed on silica gel (330 g), eluting with a gradient of CH_2Cl_2/EtOAc (95:5 to 8:2). Fractions (50 mL) were pooled based on TLC. The following compounds, listed in order of elution, were obtained (yield): **23** (9%), **7** (3%), **4** (14%), **6** (4%), **22** (6%), and **5a** (57%). Compounds **4**, **5a**, **6**, and **7**, isolated in pure form or as two component mixtures, were identified by ^1H NMR, IR, MS, and TLC comparison with authentic samples.

Crystallization of **23** from EtOAc/hexane afforded the analytical sample: 0.86 g of light-yellow solid; mp 184.5–186.5 °C; IR (Nujol) 3055 (=CH), 1724 (acetate C=O), 1698 (carbamate C=O), 1591, 1582, (C=N/C=C), 1409, 1326, 1257, 1066 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.87 (s, 1 H, =CH), 4.59 (br t, $J = 8$ H z, 1 H, 17α-H), 4.35 (q, $J = 7$ Hz, 2 H, OCH_2), 2.03 (s, 3 H, CH_3CO_2), 1.35 (t, $J = 7$ Hz, ~3 H, CH_2CH_3), 0.93 (s, 3 H, 19-CH_3), 0.80 (s, 3 H, 18-CH_3); UV λ_{max} 337 nm (ϵ 15 200); MS, *m/e* 446 (M^+), 359 (base peak). Anal. Calcd for $C_{24}H_{34}N_2SO_4$: C, 64.54; H, 7.67; N, 6.27; S, 7.18. Found: C, 64.15; H, 7.52; N, 6.44; S, 7.14.

The crude **22** was rechromatographed (LPLC, silica), eluting with hexane/EtOAc (6:4), and crystallized from EtOAc/hexane to give 0.51 g of analytically pure cream colored solid: mp 212–4 °C; IR (Nujol) 1767 (carbamate C=O), 1729 (acetate C=O), 1640 (C=N), 1374, 1288, 1265, 1253, 1237, 1121, 1106, 1093, 1047, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.58 (br t, $J = 8$ Hz, 17α-H), and 4.44 (q, $J = 7$ Hz, OCH_2) (3 H total), 3.80 (dd, $J_{1\alpha H\text{-}2\beta H} = 12.8$ Hz, $J_{1\beta H\text{-}2\beta H} = 7.1$ Hz, 1 H, 2β-H), 2.78 (dm, $J = 15$ Hz, $W_{1/2h} = 6$–7 Hz, 1 H), 2.03 (s, 3 H, CH_3CO_2), 1.40 (t, $J = 7$ Hz, ~3 H, CH_2CH_3), 0.99 (s, 3 H, 19-CH_3), 0.80 (s, 3 H, 18-CH_3); UV λ_{max} (ϵ) 219 (4750), 262 (3150), 335 nm (2800); MS, *m/e* 464 (M^+), 359 (base peak). Anal. Calcd for $C_{24}H_{36}N_2O_5S$: C, 62.04; H, 7.81; N, 6.03; S, 6.90. Found: C, 61.96; H, 8.03; N, 6.02; S, 6.87.

Reaction of 22 and 23 with $SOCl_2$. A solution of 25 mg (54 μmol) of **2** and 250 μL (3.4 mmol) of $SOCl_2$ was kept at 25 °C for 10 min, during which time the initial red color faded to a pale yellow. Excess $SOCl_2$ was evaporated in vacuo. The residue was dissolved in CH_2Cl_2, washed with 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated in vacuo. The residue was found by ^1H NMR and TLC to be identical with authentic **6**. Under the same conditions **23** (25 mg) and $SOCl_2$ (250 μL) afforded the same result.

A solution of **23** (25 mg; 56 μmol) in $CDCl_3$ (~0.6 mL) was treated with 1 drop (10–15 mg; 85–130 μmol) of $SOCl_2$. The reaction as monitored by ^1H NMR (probe temperature 30 °C) was found to be complete within 10 min. Workup as above afforded an approximate 3:1 mixture of **6** and **7**, respectively.

X-ray Study of 6 ($C_{21}H_{28}N_2O_3S_2$). Crystal data for **6** were as follows: orthorhombic; space group $P2_12_12_1$; $Z = 4$; $a = 8.143$ (1) Å, $b = 13.270$ (1) Å, $c = 18.838$ (2) Å; D_{calc} 1.37 g cm^{-3}; μ(CuK) = 24.5 cm^{-1}; 1746 reflections, of which 1647 had intensities greater than one standard deviation. Intensity data for all reflections with $2\theta \leq 120°$ were collected by using the step-scan technique at −150 °C on a Syntex PI diffractometer controlled by a Harris computer using graphite monochromatized CuK radiation (λ = 1.5418 Å). The data were corrected for systematic errors, including absorption.[39] Standard deviations in observed intensities were approximated by the function $\sigma^2(I) = \sigma^2$(counting statistics) + $(0.012I)^2$, where the coefficient of I was calculated from intensities of ten reflections monitored throughout the data collection, considering deviations in intensities which were not explained by counting statistics.[40] The structure was solved by direct methods using DIREC.[41]

Coordinates and thermal parameters were refined minimizing the function $\sum w(F_o^2 - F_c^2)^2$ where weights w were taken as the reciprocals of the variances $\sigma^2(F_o^2)$. Hydrogens were included in the calculations at positions generated by using standard planar or tetrahedral geometry. Methyl hydrogens were rotated to positions observed in a difference Fourier map. The required torsion angle rotations were −26°, −3°, and −11°, about C13–C18, C10–C19, and C21–C21M, respectively. Atomic form factors were from International Tables for X-Ray Crystallography[42] except hydrogen form factors which were taken from Stewart, Davidson, and Simpson.[43]

The final agreement index R [$R = \sum||F_o| - |F_c||/\sum|F_o|$] was 0.055. All calculations were carried out on an IBM 3033 computer using the CRYM system of crystallographic programs.[41] There is disorder in the positions of the O—C=O atoms O20, C21, and O21 of the $OCOCH_3$ group at C17. Two conformers are populated approximately 60% (unprimed numbers) and 40% (primed numbers). The position of the C21 methyl carbon is the same in both conformers. Positions for ring atoms C17, C16, and C15 are different in the two conformers but are too close to resolve; the coordinates reported are intermediate between positions in the alternate conformations, so bond distances and angles for these atoms are somewhat distorted. Anisotropic thermal parameters for C17, C16, and C15 are enlarged in the x direction; the mean squared deviations (msd's) of the principal axes of the thermal ellipsoids were 0.081–0.113 Å for these three atoms (in directions approximately parallel to the a axis); msd's for all other atoms were in the range 0.016–0.073 Å. Temperature factors for the disordered atoms O20, C21, and O21 were kept isotropic. The close intermolecular contacts listed below were all with the

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(41) DIREC, a direct methods program that uses quartets, and the CRYM system of crystallographic programs were written by David J. Duchamp, the Upjohn Company, Kalamazoo, MI 49001.
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molecule related by $x - {}^1/_2, {}^1/_2 - y, -z$.

related atom	atom	distance, Å
O1A	C16	3.35 (1)
O21	S1	3.49 (1)
O21	C1	3.26 (1)
O21	C2	3.29 (1)
O21′	S2	3.31 (1)
O21′	N1	3.42 (1)
O21′	C2	3.02 (1)
O21′	N2	3.30 (1)
O21′	C3	3.06 (1)

The O21 and O21′ contacts with A-ring carbons C1, C2, and C3 are less than the sum of their van der Waals radii.[16] The disorder observed in the O20–C21–O21 atoms is likely related to these close packing interactions.

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Registry No. **4**, 1164-91-6; **5a**, 92720-27-9; **5b**, 3701-62-0; **5c**, 92720-28-0; **5d**, 89396-38-3; **6**, 92720-29-1; **7**, 92720-30-4; **8**, 92762-53-3; **9**, 92720-31-5; **10**, 92720-32-6; **11**, 6971-92-2; (±)-**12**, 92720-33-7; **13**, 92720-34-8; **14**, 92720-35-9; **15**, 92720-36-0; **16**, 92720-37-1; (±)-**17**, 92720-38-2; **18**, 92762-54-4; **19**, 92720-39-3; **20**, 92720-40-6; **21**, 92720-41-7; **22**, 92720-42-8; **23**, 92720-43-9; (±)-norcamphor, 22270-13-9; cyclohexanone, 108-94-1; 3,3,5,5-tetramethylcyclohexanone, 14376-79-5; 17β-acetoxy-5α-estran-3-one, 33767-87-2; 4-*tert*-butylcyclohexanone, 98-53-3; 4,4-dimethylcyclohexanone, 4255-62-3; (ethoxycarbonyl)hydrazine, 4114-31-2; acetylhydrazine, 1068-57-1; formylhydrazine, 624-84-0; tosylhydrazine, 1576-35-8; thionyl chloride, 7719-09-7; ethyl chloroformate, 541-41-3.

Supplementary Material Available: Tables of anisotropic or isotropic thermal parameters, bond lengths, bond angles, and hydrogen coordinates for **6** (4 pages). Ordering information is given on any current masthead page.

Synthesis of 2*H*-1,4-Thiazine-2,6-dicarboxylates and Their Conversion to 3,4-Pyrroledicarboxylates via Sulfur Extrusion

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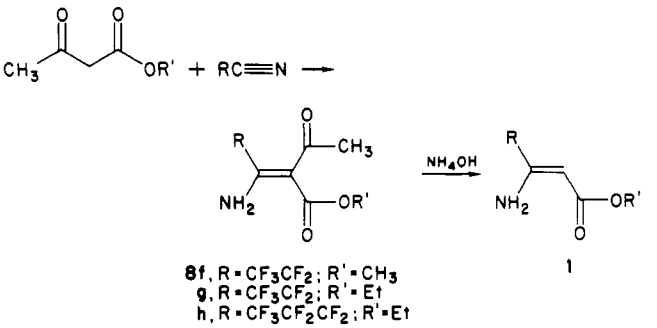
The reactions of 3-aminocinnamates **1c,d** with S_2Cl_2 provided 2,5-diaryl-3,4-pyrroledicarboxylates **7c,d** in 36–52% yields whereas the reactions of 3-(perfluoroalkyl)-3-aminoacrylates **1e–h** with S_2Cl_2 or SCl_2 gave 3,5-bis(perfluoroalkyl)-2*H*-1,4-thiazine-2,6-dicarboxylates **4e–h** as the major products. Further treatments of **4e–g** with triethylamine provided the corresponding pyrroles **7e–g** in good yields (58–77%) via sulfur extrusion. These methods constitute a novel synthesis of 3,4-pyrroledicarboxylates from 3-aminoacrylates.

Although 2*H*-1,4-thiazine was reported[1] in 1948, only limited methods have been developed for the synthesis of this ring system and only a few 2*H*-1,4-thiazinecarboxylates are known.[2] Contrarily, the chemistry of the corresponding dihydro-1,4-thiazines has been well developed.[2] Because several biologically active and naturally occurring compounds contain the 1,4-thiazine ring,[2] we are interested in developing new synthetic methodology for this chemical class, particularly the hitherto unknown 2*H*-1,4-thiazine-2,6-dicarboxylates **4**.

In principle **4** might be prepared by reaction of 3-aminoacrylates **1** with S_2Cl_2 or SCl_2 to form bis(2-aminovinyl) sulfides **2** first, followed by cyclization of **2** to 3-amino-2,3-dihydro-2*H*-1,4-thiazine-2,6-dicarboxylates **3** and loss of ammonia from **3** as shown in Scheme I. The reactions of 3-aminocrotonates with S_2Cl_2 and SCl_2 have been reported[3] to give unsatisfactory results in attempts to prepare the corresponding **2a**. However, **2a** has been obtained from the reaction of methyl 3-aminocrotonate (**1a**) with morpholine-*N*-sulfenyl chloride.[3] No further transformation of **2a** has been reported. We have prepared **2b** from **1b** similarly but have been unable to cyclize **2b** under a variety of conditions. We thought that the cyclization process might be facilitated by replacement of the 3-methyl group in **2b** with an electron-withdrawing group such as an aryl or a perfluoroalkyl group and decided to study the reactions of S_2Cl_2 and SCl_2 with 3-aminoacrylates containing electron-withdrawing substituents.

Results and Discussion

The starting 3-aminocinnamates **1c,d** were prepared from the appropriate Grignard reagent and ethyl cyanoacetate as described previously.[4] The 3-(perfluoroalkyl)-3-aminoacrylates **1e–h** were prepared either by the reaction of the appropriate 3-keto ester with ammonia[5] or by reaction of an acetoacetate with an appropriate perfluoroalkanenitrile[6] followed by treatment of the resulting adduct with ammonium hydroxide.



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