New Imidoyl Isothiocyanates. Chemical Behavior in Polar Solvents. Reaction with Sulfenyl Thiocyanates: Preparation of 1,2-Dihydro-2-thioxo-1,3,5-triazines and 1,3,4,6,6a-Triazadithia(6aS^{IV})pentalenes

Georges Morel, Evelyne Marchand, Catherine Haquin, and André Foucaud*

Groupe de Chimie Structurale associé au CNRS, Université de Rennes, Campus de Beaulieu, 35042 Rennes, France

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The alkylthio (or arylthio) imidoyl isothiocyanates **1** can be isolated when isocyanides are treated with sulfenyl thiocyanates or via the reaction of imino chloro sulfides **3** with ammonium thiocyanate in CCl_4. In a polar solvent, the dissociation of **1e–h** affords the thiocyanate anion and a nitrilium cation which react with **1** to give the dihydrotriazines **7e–h**. The reaction of **1** with sulfenyl thiocyanates in CCl_4 gives the 1,3,4,6,6a-triazadithia-(6aS^{IV})pentalenes **11** or a mixture of **11** and of 1,2-dihydro-4-(methyldithio)-2-thioxo-1,3,5-triazines **10**.

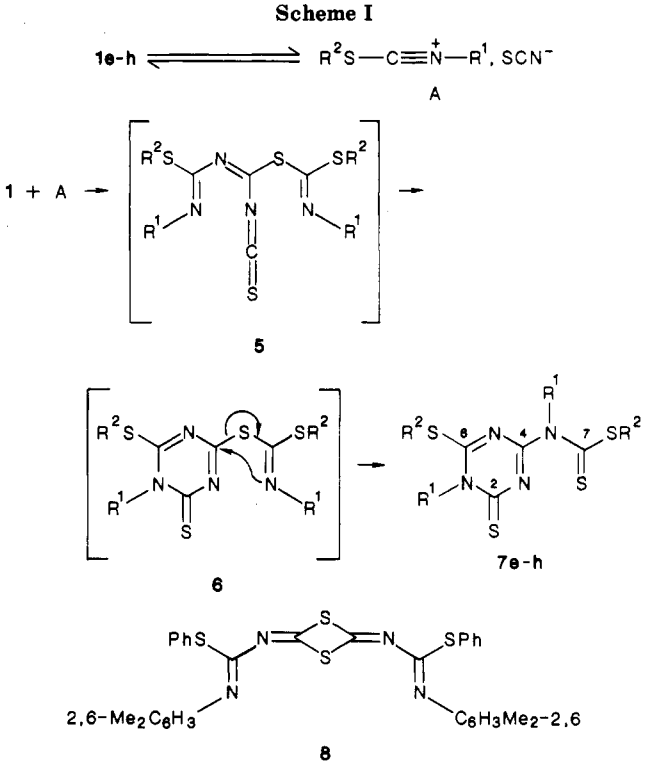
The Diels–Alder reaction of aza dienes is a powerful process for the preparation of six-membered heterocyclic compounds.[1] Imidoyl isothiocyanates have been used as 1,3-diazadiene systems for [2 + 4] cycloadditions with various dienophiles: enamines,[2,3] amidines and imidates,[4] ketene acetal and carbodiimide,[3] ketene,[5] and phenyl isocyanate.[3,6] The dimerization of a number of imidoyl isothiocyanates, in a polar medium, has been described as a formal hetero Diels–Alder reaction.[3,6-9] Some *N*-aryl- and *N*-benzoylimidoyl isothiocyanates have been respectively converted into thioxoquinazoline[3,6,10] and thioxo-oxadiazine[11] by an intramolecular [2 + 4] cycloaddition. The preparation of dithioxotriazines by the reaction of imidoyl isothiocyanates with HNCS has also been investigated.[3,6,7] However, similar reactions with sulfenyl thiocyanates, which can release NCS^- and MeS^+ have yet to be investigated. These reactions can lead to new thioxotriazines. In this paper we describe the syntheses of several (alkylthio)- and (arylthio)formimidoyl isothiocyanates **1** which have been isolated, the investigation of their stability in solution, and their reaction with sulfenyl thiocyanates.

Results and Discussion

Preparation of Imidoyl Isothiocyanates 1. The sulfenyl thiocyanates[12-15] **2a–d** are obtained by reaction of R^2SCl with NH_4SCN in CCl_4. The IR spectra of **2** (neat, ν 2145 cm^{-1}) are consistent with the thiocyanate structure **2**.[16] The thiocyanate group of **2** can be easily displaced by nucleophiles,[15,17-19] for example, by isocyanides.[20] Thus, the formimidoyl isothiocyanates **1** can be prepared by the reaction of R^1NC with the sulfenyl thiocyanates **2a–d**. But **1** reacts with **2** (see the next section); therefore, it is indispensible to slowly add a stoichiometric amount of **2** to a solution of isocyanide in CCl_4 at 0 °C. For this reason, we have prefered the reaction of ammonium thiocyanate with the imino chloro sulfides **3** in CCl_4.

The IR spectra of **1** exhibit a broad intense band at 1960 cm^{-1} (neat or CCl_4 solution).[2,3,9] The thiocyanate isomers are never observed. The formimidoyl isothiocyanates **1**

Scheme I



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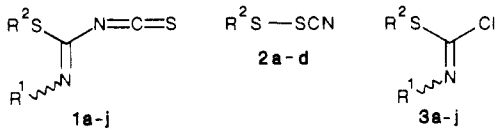
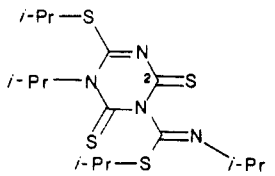


1a-j 2a-d 3a-j

	R^1	R^2
a	t-Bu	Me
b	t-Bu	Ph
c	t-Bu	$2\text{-}NO_2C_6H_4$
d	t-Bu	$4\text{-}MeC_6H_4$
e	$2,6\text{-}Me_2C_6H_3$	Me
f	$2,6\text{-}Me_2C_6H_3$	Ph
g	i-Pr	Me
h	i-Pr	i-Pr
i	$PhCH_2$	Me
j	Ph_2CH	Me

have been generally used in situ, in CCl_4 solution. In these conditions, **1a–j** are stable for several days (except **1f**). This is not the case when the solvent is polar, e.g., acetone or acetonitrile.[9]

Chemical Behavior of 1 in Polar Solvents. It has been suggested that imidoyl isothiocyanates are dimerized by a [2 + 4] cycloaddition reaction.[3,6-9] For example, Goerdeler[9] has reported the formation of the dithioxotriazine **4** when **1h** is prepared in acetonitrile or acetone.



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We have reproduced this reaction: when **1h** is dissolved in CH_3CN at room temperature for a few hours, it is completely transformed into a product which is identical with the compound described by Goerdeler,[9] but the structure cannot be **4**. The ^{13}C NMR data are in agreement with structure **7h** (Scheme I). The signal C-2 of the dithioxotriazine **4** should be a singlet, but the spectrum of the isolated product has no singlet (Table I). In the same way, when **1e** and **1g** are dissolved in acetonitrile, compounds **7e** or **7g** are obtained in almost quantitative yield. Under the same conditions, or slowly in CCl_4 solution, **1f** gives **7f** and the dithietane **8** by a reversible process. When **8** is dissolved in $CDCl_3$, the formation of **7f** is observed by NMR. Similar dimerization reaction into dithietanes has been reported for sulfonyl isothiocyanates.[21] The necessity of a polar solvent to obtain **7** suggests a mechanism involving the ionic dissociation of **1** into an ion pair (A) (Scheme I). A similar ionization pathway dominates the chemistry of imidoyl halides owing to the stabilization of the nitrilium ion formed by the adjacent lone pair.[22] The addition of A to **1** gives the intermediate **5**. In the last step, cyclization of **5** gives the thioxotriazine **6**, which rearranges rapidly into **7** by a [1,3] shift on the triazine ring.

Reaction of 1 with Sulfenyl Thiocyanates 2 in CCl_4. The reaction of R^3SSCN with **1** in CCl_4, at room temperature, for a few minutes, affords the 1,3,4,6,6a-triazadithia(6aS^{IV})pentalene[23] when R^1 = t-Bu. In the other cases, this reaction gives a mixture of **11** and 1,2-dihydro-2-thioxo-1,3,5-triazines **10** (Table II). When R^2 = R^3, the experimental procedure is a simple reaction of R^1NC with a twofold amount of sulfenyl thiocyanate **2**.

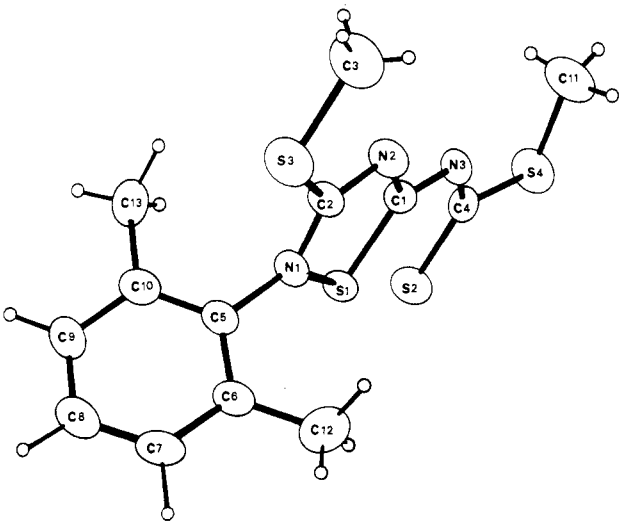

Figure 1. X-ray crystallographic structure of **11e**.

Table I. Selected ^{13}C NMR Shifts for 7

	chem shift, ppm (mult)			
cmpd	C-2	C-6	C-4	C-7
7e	182.2 (s)	174.6 (q)	155.8 (s)	204.9 (q, ^3J = 6 Hz)
7f	182.0 (s)	175.4 (s)	156.4 (s)	204.1 (s)
7g	185.4 (d)	171.1 (qd)	153.6 (d)	211.3 (qd, ^3J = 6 Hz)
7h	185.6 (d)	170.7 (dd)	153.5 (d)	210.0 (t, ^3J = 5 Hz)

Table II. Reaction of Imidoyl Isothiocyanates 1 with Sulfenyl Thiocyanates R^3SSCN

starting material 1	R^3	product	yield,[a] %	selected ^{13}C NMR data[b]
1a	Me	**11a**	79	164.9 (C-2), 177.8 (C-3a), 203.8 (C-5)
1b	Ph	**11b**	60	
1c	Me	**11c**	64	
1d	$4\text{-}MeC_6H_4$	**11d**	54	164.5 (C-2), 178.9 (C-3a), 203.7 (C-5)
1d	Me	**11d′**	85	164.8 (C-2), 178.1 (C-3a), 203.1 (C-5)
1e	Me	**11e**	35	167.4 (C-2), 181.5 (C-3a), 204.0 (C-5)
		10e	52	181.3 (C-2), 175.0 (C-4), 173.5 (C-6)
1g	Me	**11g**	29	165.4 (C-2), 179.2 (C-3a), 205.1 (C-5)
		10g	44	183.8 (C-2), 172.1 (C-4), 172.1 (C-6)
1i	Me	**11i**	46	166.9 (C-2), 179.7 (C-3a), 204.8 (C-5)
		10i	46	183.9 (C-2), 173.8 (C-4), 172.8 (C-6)
1j	Me	**11j**	32	167.2 (C-2), 179.7 (C-3a), 204.2 (C-5)
		10j	32	

[a] Isolated product yield. [b] Chemical shift in ppm.

Structural assignments are based on spectral data and are confirmed by a single-crystal X-ray analysis of **10e** and **11e** (Figures 1 and 2). For structure **11e**, the heterocyclic system is almost planar (dihedral angle between the rings: 179.5°). The short S···S (2.405 Å) together with the long N–S (1.871 Å) and C=S (1.684 Å) bonds indicates a fairly strong S···S bonding interaction, analogous to that in similar systems.[24,25]

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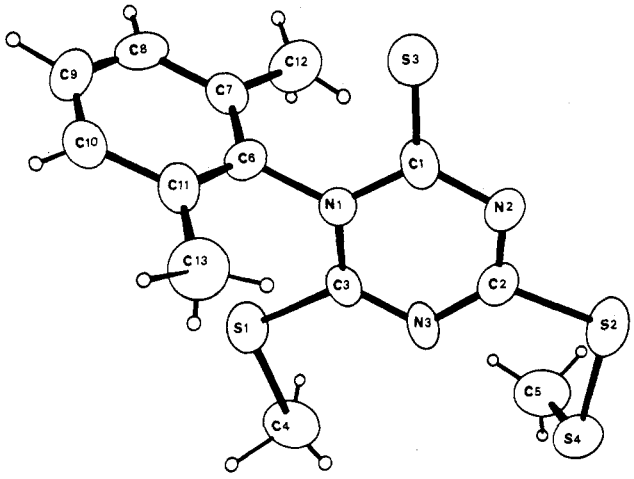
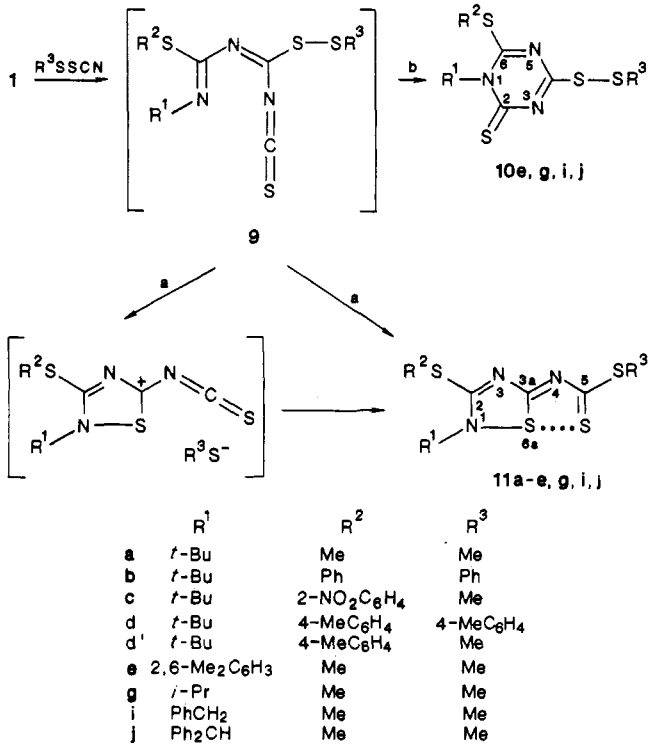


Figure 2. X-ray crystallographic structure of **10e**.

Scheme II



	R^1	R^2	R^3
a	*t*-Bu	Me	Me
b	*t*-Bu	Ph	Ph
c	*t*-Bu	2-$NO_2C_6H_4$	Me
d	*t*-Bu	4-MeC_6H_4	4-MeC_6H_4
d'	*t*-Bu	4-MeC_6H_4	Me
e	2,6-$Me_2C_6H_3$	Me	Me
g	*i*-Pr	Me	Me
i	$PhCH_2$	Me	Me
j	Ph_2CH	Me	Me

The formation of **10** and **11** can be interpreted as follows. In the first step of the reaction, the addition of R^3SSCN on **1** leads to an intermediate **9**. We postulate that the rearrangement of **9** can occur in two ways (Scheme II). The process a is the displacement of the sulfenyl anion R^3S^-. Imidoyl isothiocyanates are known to undergo a similar cyclization in two steps: addition of a primary amine, then oxidation of the formed imidoylthiourea to give 5-imino-1,2,4-thiadiazoline.[26] The process b is the intramolecular nucleophilic attack of the nitrogen atom on the heterocumulenic group. This process b is not observed when R^1 is the *tert*-butyl group, probably for steric reason.

In summary, a series of (alkylthio)- and (arylthio)formimidoyl isothiocyanates **1** are prepared and isolated for the first time. In contrast to the previously reported results, these compounds lead to the thioxotriazines **7** in a polar solvent. The dimerization products (dithioxotriazines **4**) are not observed. A new and easy synthetic route to compounds **11**, which are new examples of compounds with a thiapentalene structure,[24,27] is described.

Experimental Section

Melting points are uncorrected. Mass spectra were obtained on a Varian MAT 311 spectrometer. IR spectra were recorded as suspensions in Nujol, unless otherwise indicated, with a Perkin-Elmer 225 spectrometer. NMR spectra (internal standard Me_4Si) were taken in $CDCl_3$, unless stated otherwise, on Bruker WP 80 and FT WP 80 spectrometers. Elemental analyses were performed by the analytical laboratory Centre National de la Recherche Scientifique.

Preparation of Sulfenyl Thiocyanates 2. General Procedure. Ammonium thiocyanate (1.9 g, 25 mmol) was added to a solution of sulfenyl chloride (20 mmol) in CCl_4. The mixture was stirred under nitrogen for 3 h at room temperature. The ammonium chloride was filtered. The crude sulfenyl thiocyanates were used without further purification after removing of the solvent or directly in this CCl_4 medium.

Methanesulfenyl thiocyanate (2a):[14] ^1H NMR (CCl_4) δ 2.80 (s); ^{13}C NMR δ 22.9, 109.7; IR (neat) ν 2147 cm^{-1}.

Benzenesulfenyl thiocyanate (2b):[19,28] IR (CCl_4) ν 2143 cm^{-1}.

2-Nitrobenzenesulfenyl thiocyanate (2c):[12,18] mp 92 °C; IR (CCl_4) ν 2146 cm^{-1}.

4-Methylbenzenesulfenyl thiocyanate (2d):[19,28] ^1H NMR δ 2.41 (s, 3 H), 7.16–7.62 (m, 4 H); IR (neat) ν 2141 cm^{-1}.

Preparation of Imidoyl Isothiocyanates 1. Method A. To a solution of isocyanide (12 mmol) in CCl_4 (10 mL) was added dropwise with stirring over several minutes at 0 °C a solution of sulfenyl thiocyanate (10 mmol) in CCl_4 (10 mL).

Method B. To a solution of imino chloro sulfide **3**[29,30] (20 mmol) in CCl_4 (30 mL) was added ammonium thiocyanate (2 g, 26 mmol). The mixture was stirred for 3 h (6 h for **3e**, **3f**, and **3j**) at ambient temperature. The ammonium chloride was filtered. The imidoyl isothiocyanates were employed in the CCl_4 solution or isolated as crude product when the solvent was removed in vacuo.

***N*-*tert*-Butyl(methylthio)formimidoyl isothiocyanate (1a):** oil; IR (CCl_4) ν 1957 cm^{-1}; ^1H NMR (CCl_4) δ 1.36 (s, 9 H), 2.37 (s, 3 H); ^{13}C NMR δ 15.5, 29.8, 57.4, 135.5, 144.0.

***N*-*tert*-Butyl(phenylthio)formimidoyl isothiocyanate (1b):** oil; IR (CCl_4) ν 1981 cm^{-1}; ^1H NMR (CCl_4) δ 1.33 (s, 9 H), 7.4 (m, 5 H).

***N*-*tert*-Butyl[(2-nitrophenyl)thio]formimidoyl isothiocyanate (1c):** oil; IR (CCl_4) ν 1955 cm^{-1}; ^1H NMR (CCl_4) δ 1.28 (s, 9 H), 7.5 (m, 4 H).

***N*-*tert*-Butyl[(4-methylphenyl)thio]formimidoyl isothiocyanate (1d):** oil; IR (CCl_4) ν 1992 cm^{-1}; ^1H NMR (CCl_4) δ 1.32 (s, 9 H), 2.45 (s, 3 H), 7.08–7.44 (m, 4 H).

***N*-(2,6-Dimethylphenyl)(methylthio)formimidoyl isothiocyanate (1e):** oil; IR (neat) ν 1960, 1610, 1575 cm^{-1}; ^1H NMR (CCl_4) δ 2.10 (s, 6 H), 2.60 (s, 3 H), 6.9 (s, 3 H).

***N*-(2,6-Dimethylphenyl)(phenylthio)formimidoyl isothiocyanate (1f):** oil; IR (CCl_4) ν 1945 cm^{-1}; ^1H NMR (CCl_4) δ 2.13 (s, 6 H), 6.89 (s, 3 H), 7.3–7.6 (m, 5 H).

***N*-Isopropyl(methylthio)formimidoyl isothiocyanate (1g):** oil; IR (CCl_4) ν 1955 cm^{-1}; ^1H NMR (CCl_4) δ 1.17 (d, 6 H), 2.40 (s, 3 H), 3.95 (m, 1 H).

***N*-Isopropyl(isopropylthio)formimidoyl isothiocyanate[9] (1h):** oil; IR (CCl_4) ν 1960 cm^{-1}; ^1H NMR (CCl_4) δ 1.20 (d, 6 H), 1.41 (d, 6 H), 3.70 (m, 1 H), 3.97 (m, 1 H).

***N*-Benzyl(methylthio)formimidoyl isothiocyanate (1i):** oil; ^1H NMR (CCl_4) δ 2.46 (s, 3 H), 4.65 (s, 1 H), 7.22 (s, 5 H).

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***N*-(Diphenylmethyl)(methylthio)formimidoyl isothiocyanate (1j)**: oil; ^{1}H NMR (CCl_4) δ 2.52 (s, 3 H), 5.92 (s, 1 H), 7.2 (m, 10 H).

Conversion of 1e,g,h into 7e,g,h. A solution of imidoyl thiocyanate (10 mmol) in acetonitrile (25 mL) was left for 20 h at room temperature. After concentration the crude product **7** was crystallized from methanol or ether.

7e (63%): yellow crystals; mp 140 °C and then 176 °C (MeOH); ^{1}H NMR δ 1.91 (s, 3 H), 2.21 (s, 6 H), 2.68 (s, 3 H), 7.20 (m, 6 H). Anal. Calcd for $C_{22}H_{24}N_4S_4$: C, 55.93; H, 5.08; N, 11.86; S, 27.11. Found: C, 55.85; H, 5.10; N, 11.77; S, 27.64.

7g (51%): orange crystals, mp 144 °C (MeOH); ^{1}H NMR δ 1.44 (d, 6 H), 1.70 (d, 6 H), 2.46 (s, 3 H), 2.71 (s, 3 H), 5.25 (m, 1 H), 6.12 (m, 1 H); MS, *m/e* (relative intensity) 348 (M^+, 68), 333 (100), 301 (32), 291 (47), 259 (32), 257 (53), 249 (26), 217 (68), 215 (89), 190 (32). Anal. Calcd for $C_{12}H_{20}N_4S_4$: C, 41.37; H, 5.74; N, 16.09; S, 36.78. Found: C, 41.46; H, 5.87; N, 15.91; S, 36.78.

7h: orange crystals; mp 100 °C (ether); ^{1}H NMR δ 1.44 (d, 6 H), 1.46 (d, 6 H), 1.51 (d, 6 H), 1.73 (d, 6 H), 3.89 (m, 2 H), 5.17 (m, 1 H), 6.10 (m, 1 H); MS, *m/e* (relative intensity) 404 (M^+, 10), 361 (100), 319 (69), 277 (36), 261 (10), 243 (14), 235 (17), 218 (21).

Conversion of 1f into 7f. A solution of imidoyl isothiocyanate **1f** (10 mmol) in acetonitrile (25 mL) was maintained at 20 °C for 20 h. The dimer **8** was filtered. Removal of the solvent under reduced pressure and addition of ether yielded the crystalline product **7f**. The formation of **8** is a reversible process: at room temperature, a solution of **8** in $CDCl_3$ slowly gave the triazine **7f**.

8 (1.35 g, 45%): orange crystals; mp 182 °C ($CHCl_3$/ether); ^{1}H NMR (at 60 °C) δ 1.99 (s, 6 H), 2.15 (s, 6 H), 7.0–7.4 (m, 16 H). Anal. Calcd for $C_{32}H_{28}N_4S_4$: C, 64.43; H, 4.70; N, 9.40. Found: C, 64.20; H, 4.73; N, 9.18.

7f (0.75 g, 25%): yellow crystals; mp 210 °C ($CHCl_3$/ether); ^{1}H NMR δ 2.02 (s, 6 H), 2.35 (s, 6 H), 6.70–7.40 (m, 16 H). Anal. Calcd for $C_{32}H_{28}N_4S_4$: C, 64.43; H, 4.70; N, 9.40. Found: C, 64.17; H, 4.70; N, 9.35.

Reaction of Imidoyl Isothiocyanates 1 with Sulfenyl Thiocyanates. To a solution of imidoyl isothiocyanate **1** (10 mmol) in CCl_4 (30 mL) was added sulfenyl thiocyanate (10 mmol) in CCl_4 (10 mL). The mixture was maintained at 20 °C for 15 min. Concentration of the solvent gave **11** or a mixture of **11** and **10** as yellow crystalline compounds, which were separated by crystallization from ether or methanol.

1-*tert*-Butyl-2,5-bis(methylthio)-1,3,4,6,6a-triazadithia-(6aS^{IV})pentalene (11a): mp 108 °C; ^{1}H NMR δ 1.81 (s, 9 H), 2.74 (s, 3 H), 2.85 (s, 3 H); MS, *m/e* (relative intensity) 293 (M^+, 11), 246 (46), 190 (100). Anal. Calcd for $C_9H_{15}N_3S_4$: C, 36.86; H, 5.11; N, 14.30; S, 43.68. Found: C, 36.84; H, 5.07; N, 14.27; S, 43.20.

1-*tert*-Butyl-2,5-bis(phenylthio)-1,3,4,6,6a-triazadithia-(6aS^{IV})pentalene (11b): mp 195 °C ($CHCl_3$/MeOH); ^{1}H NMR δ 1.81 (s, 9 H), 7.4–8.2 (m, 10 H). Anal. Calcd for $C_{19}H_{19}N_3S_4$: C, 54.67; H, 4.55; N, 10.07; S, 30.69. Found: C, 54.48; H, 4.50; N, 9.93; S, 30.37.

1-*tert*-Butyl-5-(methylthio)-2-[(2-nitrophenyl)thio]-1,3,4,6,6a-triazadithia(6aS^{IV})pentalene (11c): mp 156 °C (MeOH); ^{1}H NMR δ 1.85 (s, 9 H), 2.61 (s, 3 H), 7.4–8.2 (m, 4 H). Anal. Calcd for $C_{14}H_{16}N_4O_2S_4$: C, 42.00; H, 4.00; N, 14.00; S, 32.00. Found: C, 41.69; H, 4.12; N, 13.90; S, 31.41.

1-*tert*-Butyl-2,5-bis[(4-methylphenyl)thio]-1,3,4,6,6a-triazadithia(6aS^{IV})pentalene (11d): mp 162 °C (MeOH); ^{1}H NMR δ 1.79 (s, 9 H), 2.42 (s, 6 H), 7.15–7.55 (m, 8 H). Anal. Calcd for $C_{21}H_{23}N_3S_4$: C, 56.62; H, 5.17; N, 9.43; S, 28.76. Found: C, 56.60; H, 5.10; N, 9.23; S, 28.70.

1-*tert*-Butyl-2-[(4-methylphenyl)thio]-5-(methylthio)-1,3,4,6,6a-triazadithia(6aS^{IV})pentalene (11d′): mp 207 °C ($CHCl_3$/MeOH); ^{1}H NMR δ 1.82 (s, 9 H), 2.40 (s, 3 H), 2.60 (s, 3 H), 7.1–7.5 (m, 4 H). Anal. Calcd for $C_{15}H_{19}N_3S_4$: C, 48.78; H, 5.14; N, 11.38; S, 34.68. Found: C, 48.50; H, 5.05; N, 11.19; S, 34.22.

1-(2,6-Dimethylphenyl)-2,5-bis(methylthio)-1,3,4,6,6a-triazadithia(6aS^{IV})pentalene (11e): mp 190 °C ($CHCl_3$/MeOH); ^{1}H NMR δ 2.14 (s, 6 H), 2.72 (s, 6 H), 7.2 (s, 3 H). Anal. Calcd for $C_{13}H_{15}N_3S_4$: C, 45.74; H, 4.39; N, 12.31; S, 37.53. Found: C, 45.46; H, 4.43; N, 12.13; S, 37.66.

1-Isopropyl-2,5-bis(methylthio)-1,3,4,6,6a-triazadithia-(6aS^{IV})pentalene (11g): mp 143 °C; ^{1}H NMR δ 1.58 (d, 6 H), 2.70 (s, 3 H), 2.81 (s, 3 H), 4.34 (m, 1 H). Anal. Calcd for $C_8H_{13}N_3S_4$: C, 34.40; H, 4.65; N, 15.05; S, 45.87. Found: C, 34.40; H, 4.82; N, 15.09; S, 45.32.

1-Benzyl-2,5-bis(methylthio)-1,3,4,6,6a-triazadithia-(6aS^{IV})pentalene (11i): mp 126 °C ($CHCl_3$/MeOH); ^{1}H NMR δ 2.69 (s, 3 H), 2.75 (s, 3 H), 4.91 (s, 2 H), 7.3 (s, 5 H). Anal. Calcd for $C_{12}H_{13}N_3S_4$: C, 44.03; H, 3.97; N, 12.84; S, 39.14. Found: C, 43.94; H, 4.04; N, 12.64; S, 39.14.

1-(Diphenylmethyl)-2,5-bis(methylthio)-1,3,4,6,6a-triazadithia(6aS^{IV})pentalene (11j): mp 206 °C ($CHCl_3$/MeOH); ^{1}H NMR δ 2.65 (s, 3 H), 2.75 (s, 3 H), 6.38 (s, 1 H), 7.3 (m, 10 H). Anal. Calcd for $C_{18}H_{17}N_3S_4$: C, 53.59; H, 4.21; N, 10.42; S, 31.76. Found: C, 53.30; H, 4.33; N, 10.36; S, 31.61.

1,2-Dihydro-1-(2,6-dimethylphenyl)-4-(methyldithio)-6-(methylthio)-2-thioxo-1,3,5-triazine (10e): mp 200 °C ($CHCl_3$/ether); ^{1}H NMR δ 2.20 (s, 6 H), 2.55 (s, 3 H), 2.64 (s, 3 H), 7.2 (m, 3 H). Anal. Calcd for $C_{13}H_{15}N_3S_4$: C, 45.74; H, 4.39; N, 12.31; S, 37.53. Found: C, 45.64; H, 4.47; N, 12.23; S, 37.21.

1,2-Dihydro-1-isopropyl-4-(methyldithio)-6-(methylthio)-2-thioxo-1,3,5-triazine (10g): mp 100 °C (MeOH); ^{1}H NMR δ 1.72 (d, 6 H), 2.57 (s, 3 H), 2.72 (s, 3 H), 5.93 (m, 1 H); MS, *m/e* (relative intensity) 279 (M^+, 91), 264 (100), 231 (59), 232 (59), 207 (29), 191 (88), 190 (59), 176 (12), 173 (17), 165 (15), 159 (26), 158 (23). Anal. Calcd for $C_8H_{13}N_3S_4$: C, 34.40; H, 4.65; N, 15.05; S, 45.87. Found: C, 34.63; H, 4.49; N, 14.86; S, 45.86.

1-Benzyl-1,2-dihydro-4-(methyldithio)-6-(methylthio)-2-thioxo-1,3,5-triazine (10i): mp 208 °C ($CHCl_3$/MeOH); ^{1}H NMR δ 2.58 (s, 3 H), 2.62 (s, 3 H), 5.87 (s, 2 H), 7.32 (s, 5 H). Anal. Calcd for $C_{12}H_{13}N_3S_4$: C, 44.03; H, 3.97; N, 12.84; S, 39.14. Found: C, 44.22; H, 3.84; N, 12.58; S, 39.20.

1,2-Dihydro-1-(diphenylmethyl)-4-(methyldithio)-6-(methylthio)-2-thioxo-1,3,5-triazine (10j): mp 128 °C ($CHCl_3$/ether); ^{1}H NMR δ 2.47 (s, 3 H), 2.57 (s, 3 H), 7.35 (s, 10 H), 9.07 (s, 1 H). Anal. Calcd for $C_{18}H_{17}N_3S_4$: C, 53.59; H, 4.21; N, 10.42; S, 31.76. Found: C, 53.53; H, 4.16; N, 10.36; S, 31.78.

X-ray Analysis of 11e. Crystal data: orthorhombic, $P2_12_12_1$, a = 7.813 (5) Å, b = 13.992 (5) Å, c = 14.787 (6) Å, V = 1616.4 (8) Å^3, Z = 4, D_x = 1.41 mg m^{-3}, μ = 0.56 mm^{-1}; 1543 reflections with $I \geq \sigma(I)$ collected with a Enraf Nonius CAD-4 diffractometer, monochromatized Mo Kα radiation. The structure was solved by direct methods,[31] and the hydrogen atoms were found between 0.45 and 0.22 e Å^{-3}. The best full-matrix refinement gave R_W = 0.041 and S_W = 1.21 for 227 parameters and 1543 observations.

X-ray Analysis of 10e. Crystal data: orthorhombic, P_{bca}, a = 8.127 (4) Å, b = 13.269 (5) Å, c = 30.242 (6) Å, V = 3261.5 (7) Å^3, Z = 8, D_x = 1.39 mg m^{-3}, μ = 0.55 mm^{-1}; 1029 reflections with $I \geq \sigma(I)$. The structure was solved by direct methods.[31] The hydrogen atoms were located by difference Fourier synthese (between 0.35 and 0.21 e Å^{-3}). The best full-matrix least-squares refinement gave R_W = 0.048 and S_W = 1.13 for 227 parameters and 1029 observations.

All calculations were performed on a PDP 11/60 digital computer with the SDP package.[32] Final coordinates and bond geometry tables are found in the supplementary material.

Acknowledgment. We thank L. Toupet for performing the X-ray analysis.

Registry No. **1a**, 104157-41-7; **1b**, 104157-42-8; **1c**, 104157-43-9; **1d**, 104157-44-0; **1e**, 104157-45-1; **1f**, 104157-46-2; **1g**, 104157-47-3; **1h**, 57182-35-1; **1i**, 104157-48-4; **1j**, 104157-49-5; **2a**, 104157-40-6; **2b**, 3153-52-4; **2c**, 29572-51-8; **2d**, 66067-70-7; **3e**, 94518-64-6; **3f**, 104157-50-8; **3j**, 94518-62-4; **7e**, 104157-52-0; **7f**, 104157-55-3; **7g**, 104172-30-7; **7h**, 104157-53-1; **8**, 104157-54-2; **10e**, 104157-65-5; **10g**, 104157-66-6; **10i**, 104157-67-7; **10j**, 104157-68-8; **11a**,

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104157-56-4; **11b**, 104157-57-5; **11c**, 104157-58-6; **11d**, 104157-59-7; **11d'**, 104157-60-0; **11e**, 104157-61-1; **11g**, 104157-62-2; **11i**, 104157-63-3; **11j**, 104157-64-4; 2-nitrobenzenesulfenyl chloride, 7669-54-7; 4-methylbenzenesulfenyl chloride, 933-00-6; *tert*-butyl isocyanide, 7188-38-7; isopropyl isocyanide, 598-45-8; benzyl isocyanide, 10340-91-7; isopropylsulfenyl thiocyanate, 104157-51-9; methanesulfenyl chloride, 5813-48-9; benzenesulfenyl chloride, 931-59-9.

Supplementary Material Available: Tables of positional parameters, bond distances, and angles of **11e** and **10e** (7 pages). Ordering information is given on any current masthead page.

Improved Preparation of (3β,5α,14α)-3-Hydroxy-14-methylcholest-7-en-15-one. Synthesis of Ergostenone and 20α-(Hydroxymethyl)pregnenone Analogues

Roland E. Dolle* and Lawrence I. Kruse

Department of Medicinal Chemistry, Research and Development Division, Smith Kline & French Laboratories, P.O. Box 7929, Philadelphia, Pennsylvania 19101

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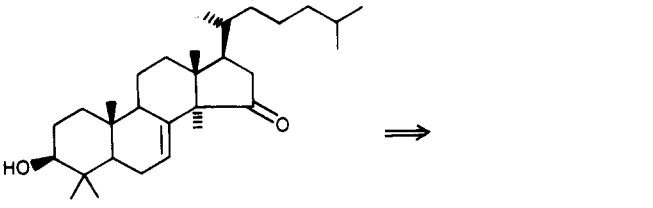
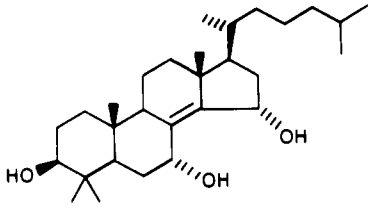
Reexamination of the synthesis of (3β,5α,14α)-3-hydroxy-14-methylcholest-7-en-15-one has led to an improved, large-scale preparation of this ketone. Noteworthy is the controlled outcome of a solvent effect observed during the pinacol-type rearrangement of vinyl epoxide **18** and the use of the ethoxyethyl ether protecting group at the C3 alcohol during alkylation. Preparative-scale routes to ergostenone derivatives **3** and **4** and pregnenone analogue **5** are described.

Certain 15-oxygenated sterol derivatives have been shown to be potent inhibitors of sterol biosynthesis.[1a-h] As a result of our current interest in this area we required multigram quantities of ketones **1**, **3**, **4**, and **5** (Schemes I and III) as synthetic intermediates. Nearly 30 years ago Woodward and co-workers described ketone **2** enroute to the first total synthesis of lanostenol via the chemical modification of cholesterol.[2a,b] The key step in this preparation of **2** was the vinylogous pinacol rearrangement of triol **6** to the corresponding 8(14)-en-15-one,[2c] which was subsequently methylated at C14.



2



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Analogous synthetic strategies have since been employed by others for the construction of **1** with some success.[3,4] Our reinvestigation of these reactions for preparative purposes has led to an improved synthesis of ketone **1**, readily adaptable to large scale. We also report the first synthesis of (3β,5α,14α)-3-hydroxy-14-methylergost-7-en-15-one (**3**), its corresponding 4,4-dimethyl analogue **4**, and on an efficient preparation of the pregnenone analogue **5**.

Results and Discussion

4,4-Dimethylergosterol **10** was conveniently prepared in 55% overall yield via an oxidation, methylation, and reduction sequence on a 500-g scale using modified literature procedures[5,6] employing ergosterol[7] **7** as starting material (Scheme I). Subsequent benzoylation using 2 equiv of benzoyl chloride in pyridine furnished the crystalline benzoate **14** in 97% yield (Scheme I). Similar benzoylations of 7-dehydrocholesterol[7] **11** and ergosterol **7** furnished benzoates **12** and **13** in 95% and 92% yield, respectively. These latter two benzoylations were easily carried out on a kilogram scale, and isolation of the products was straightforward (Scheme I).

The first of several problems arose during initial attempts to generate large quantities of the 7,14-diene **15a** and 7,14,22-trienes **16a** and **17a** as products from the acid-catalyzed migration of the corresponding 5,7-diene congeners **12**–**14** (Scheme I). The literature procedures[4,8,9]

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