After 0.5 h, TLC (S_2) indicated quantitative conversion to **14**. Anhydrous sodium sulfate (1.49 g, 10.5 mmol) and dry methanol (50 μL, 1.25 mmol) were added directly, and the mixture was stirred at room temperature for 72 h. The filtered solution was evaporated to dryness at reduced pressure and the oily residue revealed a single major spot on TLC (S_2). The residue, on preparative TLC with the same solvent system, afforded a syrupy oil which was distilled under high vacuum at 150 °C (4×10^{-3} mm) [lit.[22] 120–140 °C (5×10^{-3} mm)]. NMR data shown in Table III are in accord with literature assignments.[23]

The preparation of an authentic sample of **15** was as follows. To a solution of **13** (0.20 g, 1 mmol) in 5 mL of dry dimethylformamide was added 96 mg (4 mmol) of a 50% mineral oil emulsion of NaH and the reaction mixture was stirred for 15 min at room temperature. Freshly distilled benzyl bromide (243 μL, 2 mmol) was then introduced with careful exclusion of moisture. The mixture was stirred at ambient temperature for 18 h, at the end of which time TLC (S_2) indicated the completion of the reaction. The mixture was poured into ice–water and the clear solution was extracted (3 × 30 mL) with chloroform. The extract was washed with water and dried (Na_2SO_4), and the filtered solution was evaporated to dryness under reduced pressure. The product (0.25 g, 85%) was obtained as a colorless syrup. The compound was further purified by preparative TLC (S_2) and the ^1H NMR spectrum of the product was identical with that (**15**) derived via the rearrangement reaction.

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Registry No. **2**, 70209-11-9; **3a**, 80082-66-2; **3b**, 80082-67-3; **4a**, 80082-68-4; **4b**, 80082-69-5; **5a**, 80082-70-8; **5b**, 80082-71-9; **11**, 64018-52-6; **12**, 23276-32-6; **13**, 4099-85-8; **14**, 70209-12-0; **15**, 33019-63-5; 4-nitroestrone, 5976-74-9; bromoethanol, 540-51-2; 3-bromopropanol, 627-18-9.

Thapsigargin and Thapsigargicin, Two Histamine Liberating Sesquiterpene Lactones from *Thapsia garganica*. X-ray Analysis of the 7,11-Epoxide of Thapsigargin

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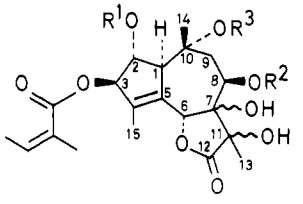
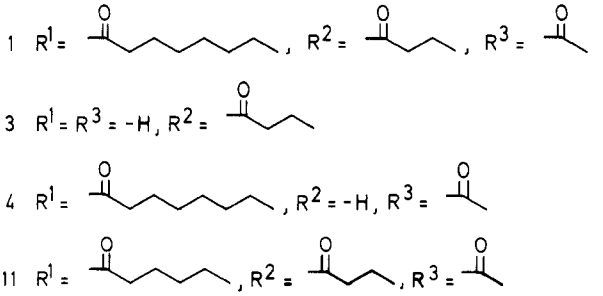
The hydrolysis of thapsigargin (**1**), a very potent histamine-liberating hexaoxygenated 6,7-guaianolide isolated from *Thapsia garganica* L., has been investigated. The procedure developed for selective cleavage of the ester groups in **1** and in the 7,11-epoxide (**2**) have been utilized in the structure elucidation of the closely related thapsigargicin (**11**) isolated from the same plant. X-ray analysis of the epoxide (**2**) has been performed.

The plant *Thapsia garganica* L.[1] (Apiaceae = Umbelliferae), especially the root, contains potent skin irritants.[2,3] Because of this property, described by Hippokrates about 400 B.C., drugs prepared from the plant have been recorded in several pharmacopoieas, most recently the 1937 edition of the French pharmacopoiea. The drugs are still used as ingredients of rheumatic pain releasing ointments in Arabian folk medicine.[2] Two very potent skin irritants, named thapsigargin (yield 0.1% of fresh material) and thapsigargicin (yield 0.02%), have been isolated from an ethanolic extract of the root. The constitution of thapsigargin (**1**) has been reported in a preliminary communication.[4] The stereochemistry of thapsigargin could not be deduced unequivocally from the NMR data, and therefore an X-ray crystallographic investigation was undertaken. The noncrystalline state of the natural product forced this analysis to be performed on the 7,11-epoxide **2**, prepared by treatment of **1** with thionyl chloride. Crystal data are listed in the Experimental Section. Figure 1 is a stereoscopic drawing of the molecule, showing the conformation and the relative configuration of the com-





(1) The morphology, the great population on the Cyrenaica peninsula, and the use of *T. garganica* in folk medicine have lead to the assumption that the plant was the source of the famous antique drug Silphion. This subject, however, is still open for discussion.[2]
(2) U. Rasmussen, "Farmakognostiske Undersøgelser af slaegten *Thapsia* L.", Ph.D. Thesis, Royal Danish School of Pharmacy, Copenhagen, 1979.
(3) U. Rasmussen, S. B. Christensen, and F. Sandberg, *Acta Pharm. Suec.* **15**, 133 (1978); S. A. Patkar, U. Rasmussen, and B. Diamant, *Agents Actions* **9**, 53 (1979).
(4) S. B. Christensen, U. Rasmussen, and C. Christophersen, *Tetrahedron Lett.*, **21**, 3829 (1980).

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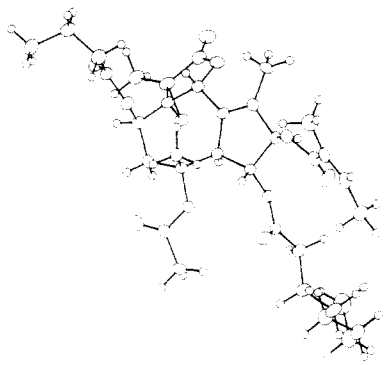
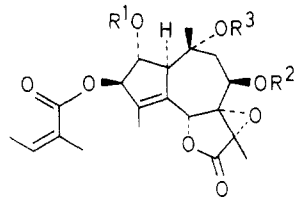
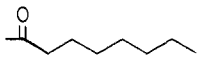
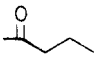


Figure 1. Stereoscopic view of **2**.

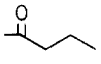
pound. The absolute configuration could not be deduced from the X-ray data.



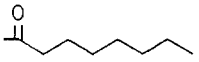
2 R^1 =  , R^2 =  , R^3 = 

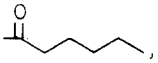
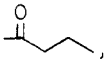
6 $R^1 = R^2 = R^3 = -H$

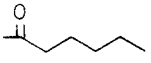
7 $R^1 = R^2 = -H$, R^3 = 

8 $R^1 = R^3 = -H$, R^2 = 

9 $R^1 = -H$, R^2 =  , R^3 = 

10 R^1 =  , $R^2 = -H$, R^3 = 

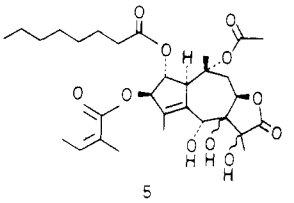
12 R^1 =  , R^2 =  , R^3 = 

13 R^1 =  , $R^2 = -H$, R^3 = 

The ester groups at C(2) and C(10), the H atom at C(1), and the 7,11-epoxide are all α. The lactone ring is fused trans, and the ester groups at C(3) and C(8) and the C(13) methyl group are β. The cycloheptane ring adopts a distorted chair conformation with C(7), C(8), C(1), and C(10) as the central plane. The cyclopentene ring and the lactone ring are slightly puckered but approximate envelopes with C(3) and C(6), respectively, as the flaps. (See paragraph at the end of the paper about supplementary material.)

Unambiguous conclusions with respect to the configurations at C(7) and C(11) of the natural product (**1**) cannot be drawn, because the mechanism of epoxide formation is unkown.

Thapsigargin is a representative of a group of sesquiterpene lactones, which is known to consist of at least eight hexaoxygenated guaianolides only differing in the structures of the attached acyl moieties.[5] In order to facilitate the structure elucidations of these compounds, we undertook a study of the acidic and basic hydrolysis of **1**. Besides unreacted starting material, only **3** was detected in the acidic hydrolysate, whereas **4** and **5** were isolated



5

from the carbonate-catalyzed reaction mixture. An increase in reaction temperature or prolongation of reacton time increased the yield of **5**. Attempts to hydrolyze other ester groups with stronger bases lead to a degradation of the sesquiterpene skeleton. In contrast the nucleus of the epoxide **2**, in which the β-hydroxy γ-lactone is masked, is stable toward bases. Thus, sodium hydroxide catalyzed saponification of **2** at −10 °C for 15 min affords a mixture, from which the five products **6**–**10** were isolated besides starting material. The relative amounts of the products are strongly dependent on the reaction conditions. Attempts to open the epoxide ring afforded either extensive degradation or, in the case of boron trifluoride catalyzed hydrolysis, formation of **9**. The structures of the products **4**–**10** have been established by NMR spectroscopy (Tables I and II).

The NMR spectra of thapsigargicin and the presence of a peak at m/e 623 ($M^+ + 1$) in the FD mass spectrum strongly suggested for this compound structure **11**. The identities of the carboxylic acids were proven by GC–MS investigations of the methyl esters formed by transesterification as described for **1**.[4] Advantage was taken of the knowledge of the chemistry of **1** in the localizations of the acyl moieties. Thus, the presence of two hydroxyl groups at C(7) and C(11) was established by thionyl chloride promoted transformation of **11** into **12**, which according to NMR spectroscopic findings possess the same nucleus as **2**. Acidic hydrolysis of thapsigargicin afforded, besides unreacted starting material, a product, the NMR spectra of which established identity with **3**. The locations of the hexanoyl and the acetyl groups were proven by saponification of the epoxide **12**. The four more polar reaction products were found to be identical with the four compounds (**6**–**9**) obtained by saponification of **2**. In addition saponification of **12** afforded **13**.

Thapsigargin (**1**) and thapsigargicin (**11**) are both very potent noncytotoxic histamine liberators.[3] A number of biological activities including cytostatic,[6-8] antiflammato-

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(6) K. H. Lee, E. S. Huang, C. Piantadosi, J. S. Pagano, and T. A. Geissman, *Cancer Res.*, **31**, 1649 (1971).

Table I. ^{1}H NMR Spectral Data[a,d]

	1/11	2[b]/12[b]	3	4	5	6[c]	7[c]	8[c]	9[c]	10/13
1	4.39	3.78	3.43	4.23	3.48	2.78	3.55	2.82	3.59	3.66
2	5.68	5.53 (dd)	4.27 (dd)	5.45 (dd)	5.36 (dd)	4.21 (dd)	4.06	4.22	4.07	5.53
3	5.49	5.16	5.36	5.70	5.61	5.40[d]	5.51[d]	5.45[d]	5.49	5.48
6	5.68	5.65	5.67	5.81	4.66	5.48[d]	5.48[d]	5.51[d]	5.49	5.64
8	5.68	4.99 (dd)	5.54	4.34	5.09 (bd)	3.81 (dd)	3.89 (dd)	4.94	5.03	4.02 (dd)
9a	3.10 (dd)	2.90 (dd)	2.39 (bd)	2.84 (dd)	2.87 (bd)	2.04 (dd)	2.71 (dd)	2.09	2.88 (dd)	2.93 (dd)
9b	2.3	2.61 (dd)	1.93 (bd)	2.46 (dd)	1.73 (dd)	1.80 (dd)	2.35 (dd)	2.09	n.a.	2.38 (dd)
13	1.39 (s)	1.48 (s)	1.26 (s)	1.44 (s)	1.46 (s)	1.49 (s)	1.49 (s)	1.50 (s)	1.52 (s)	1.55 (s)
14	1.45 (s)	1.64 (s)	1.45 (s)	1.49 (s)	1.65 (s)	1.02 (s)	1.29 (s)	1.00 (s)	1.29 (s)	1.60 (s)
15	1.85	1.82	1.88	1.85	1.87 (s)	1.66	1.65	1.67	1.68	1.82

[a] Recorded at 270 MHz in $CDCl_3$ unless specified otherwise. Shifts in parts per million downfield from Me_4Si. Unmarked signals are broad singlets. [b] Recorded at 89.6 MHz. [c] In Me_2SO-d_6. [d] J values [proton,proton = J (Hz), numeric values] in all compounds except 5: 1,2 = 4-5, 2,3 = 2-3, 8,9a = 3-4, 8,9b = 3, 9a,9b = 14-15. In 5: 1,2 = 2, 3 = 3, 8,9a < 3, 8,9b = 14. The signals due to the acyl moieties appear at the following: acetyl, 1.92; butyryl, 2.3, 1.6, 0.94; angeloyl, 6.17, 1.96, 1.85; octanoyl and hexanoyl, 2.3, 1.6, 1.3, 0.87.

Table II. ^{13}C NMR Spectral Data[a]

	1/11	2[b]/12[b]	3[b]	4[b]	5	6	8	10/13
1	59.1 d	59.9	63.5	58.7	56.5 (d)	64.9	65.5	59.8
2	79.5 (d)[c]	79.1[c]	74.1[c]	79.4	78.3 (d)[c]	78.9 (d)[c]	79.3[c]	79.2[c]
3	85.8 (d)[c]	86.0[c]	88.0[c]	85.7	86.4 (d)[c]	88.6 (d)[c]	89.0[c]	86.1[c]
4	133.1 (s)[d]	133.3[d]	133.7[d]	133.1	134.9 (s)[d]	134.4[d]	134.6	133.7[d]
5	141.4 (s)[d]	143.4[d]	139.6[d]	139.2	137.8 (s)[d]	140.9[d]	n.a.	142.3[d]
6	78.4 (d)[c]	73.8[c]	78.9[c]	77.9	71.3 (d)[c]	74.6[c]	75.0[c]	73.8[e]
7	79.7 (s)[e]	69.4[e]	79.6	80.2	79.8 (s)[e]	71.4[e]	70.1[d]	71.1[d]
8	67.7 (d)[c]	67.0[c]	67.7[c]	69.8	84.3 (d)[c]	65.5[c]	67.7[c]	65.2[c]
9	39.5 (t)	41.2	n.a.	40.5	40.4 (t)	n.a.	n.a.	43.5
10	86.3 (s)	85.6	79.3	86.5	82.3 (s)	74.4	74.5	86.3
11	79.7 (s)[e]	64.8[e]	79.6	80.3	77.3 (s)[e]	63.6[e]	65.1[d]	63.9[d]
12	178.7 (s)	173.1	178.3	177.3	179.6 (s)	174.1	173.3	174.4
13	16.2 (q)[f]	9.6[f]	15.9[f]	16.0	24.5 (q)[f]	9.3[f]	10.6[e]	9.2[e]
14	23.4 (q)[f]	23.7[f]	24.8[f]	22.8	24.0 (q)[f]	25.3[f]	26.0[e]	24.1[e]
15	13.2 (q)[f]	13.0[f]	13.1[f]	12.8	12.8 (q)[f]	13.2[f]	15.2[e]	13.0[e]

[a] Recorded at 67.9 MHz in CD_3OD unless specified. The multiplicities of unmarked signals have not been determined. [b] At 22.3 MHz. [c-f] Assignments interchangeable. The signals due to the acyl moieties appears at the following: acetyl, 172.7, 23.0; angeloyl, 169.2, 128.8, 140.0, 16.4, 20.9; butyryl, 174.4, 37.7, 19.2, 14.7; octanoyl, 174.9, 35.4, 26.1, 30.1, 30.1, 32.9, 23.7, 14.3; hexanoyl, 174.5, 35.4, 25.9, 32.6, 23.6, 14.6.

ry,[9,10] and antimicrobial[7,11] properties have been reported for other sesquiterpene lactones. An α,β-unsaturated carbonyl moiety is present in most of these lactones. This structure is present in the angeloyl group of **1**, **11**, **2**, and **12**, but the abscence of histamine-liberating properties of the epoxides (**2**, **12**) indicates the dihydroxy γ-lactone moiety to be of importance.

Experimental Section

Isolation of 1 and 11. The isolation of **1** and **11** has been described.[3] Compound **1** was obtained as a colorless gum: IR (CCl_4) 1780, 1750–1710 cm^{-1}. Significant peaks in the low-resolution mass spectrum appeared at m/e 446 ($M^+ - C_8H_{16}O_2 - C_2H_4O_2$), 358 ($M^+ - C_8H_{12}O_2 - C_2H_4O_2 - C_4H_8O_2$), 83. Compound **11** was obtained as a colorless gum: IR (CCl_4) 1780, 1750–1710 cm^{-1}. Significant peaks in the low-resolution mass spectrum appeared at m/e 446 ($M^+ - C_6H_{12}O_2 - C_2H_4O_2$), 358 ($M^+ - C_6H_{12}O_2 - C_2H_4O_2 - C_4H_8O_2$), 83. The epoxides **2** and **12** were obtained by addition of thionyl chloride (0.6 mL) to an iced solution of the natural product (200 mg) in pyridine (3 mL). After 15 min water (20 mL) and ether (20 mL) were added. The ether layer was washed with hydrochloric acid (20 mL, 0.5 M), a sodium carbonate solution (20 mL, 0.25 M), and water (20 mL), dried, and concentrated to a crystalline residue. Epoxide **2** was recrystallized from methanol–water: mp 110–111 °C; $[\alpha]^{20}_D$ −8 (c 0.30, MeOH); IR (KBr) 1780, 1770, 1750, 1740, 1720 cm^{-1}. Anal. Calcd for $C_{34}H_{48}O_{11}$: C, 64.54; H, 7.65. Found: C, 64.60; H, 7.64. Epoxide **12** was recrystallized from methanol–water: mp 119–120 °C; $[\alpha]^{20}_D$ −9 (c 0.21, MeOH); IR (KBr) 1780, 1750, 1730, 1720 cm^{-1}. Anal. Calcd for $C_{32}H_{44}O_{11}$: C, 63.56; H, 7.33. Found: C, 63.40; H, 7.28.

Acidic hydrolysis was performed by heating the natural products (30 mg) in a mixture of methanol–water–CF_3COOH (85:15:0.1, 15 mL) to 90 °C for 48 h in a sealed glass vessel. Unreacted starting material and product were isolated as gums by HPLC on Spherisorb S GP ODS [8 μm; eluent, MeOH–H_2O (7:3)]. Basic hydrolysis was performed by treatment of the natural product (35 mg) with a 0.25 M solution of Na_2CO_3 in H_2O MeOH (1:1) at −10 °C for 15 min. The reaction was quenched by addition of CF_3COOH and the products isolated as gums by HPLC over Spherisorb S GP ODS [8 μm; eluent, MeOH–H_2O (3:1), 0.25% CH_3COOH added].

Saponification of the epoxides **2** and **12** was performed by treatment of the compounds (45 mg) with a solution of KOH in MeOH (1 mL, 0.67 M) at −10 °C for 15 min. The reaction mixture was neutralized with Dowex W 50 (H^+). Besides the starting material the five reaction products were isolated as gums by HPLC over Spherisorb S GP ODS [8 μm; eluent, MeOH–H_2O (3:1)]. The four more polar products (**6**–**9**) obtained from **2** and the corresponding compounds obtained from **12** were identical as evidenced by HPLC [Nucleosil C_8, 5 μm, eluent MeOH–H_2O (3:1), 1240 theoretical plates calculated for **9**] and 270-MHz ^{1}H NMR spectroscopy.

X-ray Analysis of 2. Single crystals of the thapsigargin epoxide **2** were prepared by slow crystallization from hexane. The space is group $P2_1$ with a = 16.199 (6) Å, b = 8.040 (3) Å, c = 12.946 (5) Å, β = 100.84 (3)°, and d_{calcd} = 1.269 g cm^{-3} for Z = 2

(7) E. Rodriguez, G. H. N. Towers, and J. C. Mitchell, *Phytochemistry*, **15**, 1573 (1976).
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(9) I. H. Hall, K. H. Lee, C. O. Starnes, Y. Sumida, R. Y. Wu, T. G. Wadell, J. W. Cochran, and K. G. Gerhart, *J. Pharm. Sci.*, **68**, 537 (1979).
(10) I. H. Hall, C. O. Starnes, K. H. Lee, and T. G. Wadell, *J. Pharm. Sci.* **69**, 537 (1980).
(11) K. H. Lee, T. Ibuka, R. Y. Wu, and T. A. Geissman, *Phytochemistry*, **16**, 1177 (1977).

($C_{34}H_{48}O_{11}$, mol wt 632.76). The intensity data were collected on a Picker FACS-1 diffractometer equipped with a graphite monochromator (Mo Kα radiation, λ = 0.71069) and with modified Nonius low-temperature device.[12] A crystal measuring approximately 0.15 × 0.35 × 0.5 mm was used for data collection at 96 K. Cooling was used in order to increase the number of observed reflections, which was very limited at room temperature. A total of 5827 independent reflections were measured (θ < 30°) of which 3889 were considered to be observed [$I > 2.0\sigma(I)$]. The data were not corrected for absorption (μ = 1.01 cm^{-1}).

The structure was solved by direct methods, using the program MULTAN[13] and refined by full-matrix least-squares methods, using the X-RAY system.[14] The 48 H atoms were located in difference maps. In the final refinement anisotropic thermal parameters were used for C and O atoms, and isotropic temperature factors (B = 2.0 Å^2) were used for H atoms, but only positional parameters for the H atoms were refined. The final discrepancy index is R = 0.080 for the 3889 reflections. Unit weights were used for all observed reflections. (See paragraph at the end of the paper about supplementary material.)

Acknowledgment. We are grateful to Professor F. Sandberg for supply of plant material, Dr. Elfinn Larsen for recording the mass spectra, and Dr. K. Schaumburg and Dr. H. Eggert for recording the FT NMR spectra with the Bruker HX-270S and the JEOL FX 90Q spectrometers of the Danish Natural Science Research Council. Dr. S. Larsen and Mr. F. Hansen are thanked for help in X-ray data collection.

Registry No. 1, 67526-95-8; 2, 77521-47-2; 3, 80063-00-9; 4, 80048-99-3; 5, 80063-01-0; 6, 77521-46-1; 7, 77521-45-0; 8, 80049-00-9; 9, 80049-01-0; 10, 77521-43-8; 11, 67526-94-7; 12, 80049-02-1; 13, 80049-03-2.

Supplementary Material Available: Figure 2 giving the notation of the atoms and tables III-VII listing torsion angles, final atomic coordinates and anisotropic thermal parameters, bond lengths, and bond angles (6 pages). Ordering information is given on any current masthead page.

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Competitive Reactivity of Nitrenium and Carbenium Ion Contributors of Purinium Cations with "Soft" Bases[1]

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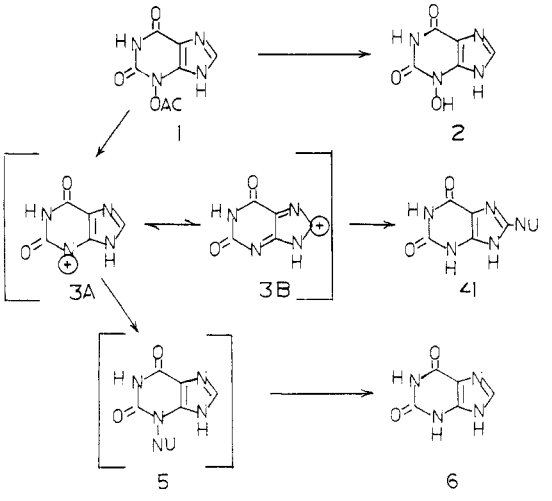
Delocalized cations formed by ionization of "activated" esters of carcinogenic purine N-oxides react with many nucleophiles to yield C-substitution products but afford oxidation-reduction products with others. The present study provides experimental support for the proposals (1) that these two reactivities result from nucleophilic substitutions at different sites of the delocalized cations and (2) that HSAB "hard" bases react only at carbenium ion sites to form C-substitution products, while "soft" bases react preferentially at nitrenium ion contributors to afford adducts that ultimately yield redox products. "Soft" bases showed the following order of reactivity at a purine nitrenium ion: iodide ≈ selenourea ≫ thio amides ≈ thio acids ≈ biselenide > bisulfide ≈ thiols ≈ disulfides > thiosulfate. This order differs significantly from that observed for the double S_N2 displacement reaction of nucleophiles with compounds of the type NH_2-X. This appears to be the first report of differing orders of nucleophilicities of bases involved in S_N1 and S_N2 reactions at electron-deficient nitrogen centers. No evidence was found for radical intermediates formed by electron transfer.

3-Hydroxyxanthine and several related N-oxidized purines are potent carcinogens in rats.[2-7] Studies on the mechanism of tumor induction demonstrated that while the N-oxides undergo few reactions, their O-esters are extremely reactive under mild conditions. Metabolic esterification in vivo is an essential step for tumor development.[8-10] In vitro N-(acyloxy)purines undergo a variety of reactions including hydrolysis, spontaneous reduction, nucleophilic substitution, and an oxidation-reduction reaction with certain nucleophiles.[11-15] Nucleophilic sub-

Scheme I



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