zone by the same procedure as for **8a**: mp 266–268° (lit.[11,12] mp 257°, 260–261°); NMR (DMSO) δ 12.2 (broad s, 1, –NH–), 8.44 (s, 1, PhCH=N–), ten protons of two phenyl rings gave signals at 7.8–7.7 (m), 7.50 (s), and 7.42 (s), 5.52 (s, 1, PhCHS–).

Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.07; H, 4.44; N, 14.23; S, 10.86. Found: C, 65.08, H, 4.65; N, 14.50; S, 11.08.

5-(*p*-Chlorophenyl)-2,4-thiazolidinedione 2-isopropylidenehydrazone (8c) was prepared in 79% yield from *p*-chlorophenyl(trichloromethyl)carbinol[13] as above: mp 227°; NMR (DMSO) δ 12.0 (broad s, 1, –NH–), 7.51 (s, 4, Ph), 5.47 (s, 1, >CH–), 3.73 and 3.71 (s, 6, $-CH_3$).

Anal. Calcd for $C_{12}H_{12}N_3OSCl$: C, 51.15; H, 4.29; N, 14.91; Cl, 12.58. Found: C, 51.42; H, 4.56; N, 14.74; Cl, 12.80.

5-(*p*-Methoxyphenyl)-2,4-thiazolidinedione 2-isopropylidenehydrazone (8d) was prepared in 31% yield from *p*-methoxyphenyl(trichloromethyl)carbinol[13] as above. The material did not melt sharply; after repeated crystallization from aqueous ethanol, it melted at 169–175° when inserted in the melting point bath at 165° and the temperature raised at 2°/min: NMR (DMSO) δ 11.8 (broad s, 1, –NH–), 7.4–6.9 (quartet, 4, Ph), 5.35 (s, 1, >CH–), 3.82 (s, 3, $-OCH_3$), 2.07 and 2.03 (s, 6, $-CH_3$).

Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15; S, 11.56. Found: C, 56.45; H, 5.54; N, 15.05; S, 11.28.

4-Hydroxy-2-methyl-5-phenylthiazole (11). To a solution of 45 g (0.2 mol) of phenyl(trichloromethyl)carbinol and 30 g (0.38 mol) of thioacetamide in 250 ml of ethylene glycol was added 70 g (1.06 mol) of potassium hydroxide pellets in 200 ml of ethylene glycol over an 80-min period at 50°. The mixture was maintained at 50° for an additional 2.5 hr and stirred overnight while cooling to room temperature. The potassium chloride was filtered off, the filtrate and methanol washings were diluted with an equal volume of ice water and extracted with ether to remove neutral material, and the pH of the aqueous solution was adjusted to 9 with hydrochloric acid. The product which precipitated (7.1 g, mp 206–209°, 18% yield) was recrystallized twice from benzene and then weighed 3.3 g and melted at 210–212.5° (same melting point procedure as for **8d**): ir (halocarbon and Nujol oil mulls) 3100–2900, 2700–2000, 1580, 1450, 1425, 1230, 1190, 1030, 995, 865, 755, and 685 cm^{-1}; NMR (DMSO) δ 11.2 (broad s, 1, –OH), 7.8–7.1 (m, 5, Ph); NMR (F_3CCOOH) δ 7.50 (s, 5, Ph), 2.86 (s, 3, $-CH_3$).

Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32; S, 16.77; mol wt, 191. Found: C, 62.92; H, 4.64; N, 7.05; S, 16.80; mol wt (Rast), 182 and 211.

Compound **11** was hydrolyzed by refluxing 0.9 g with 16 ml of aqueous 25% potassium hydroxide for 18 hr. The solution was acidified to pH 7.5 and filtered. An intense purple color developed on adding 3 drops of 5% ferric chloride to the aqueous solution. Air was blown through the solution at room temperature for 3 hr until the purple color was discharged. Dithiobis(phenylacetic acid), mp 208–211°, was isolated which was identical in all respects with an authentic sample.

4-Acetoxy-2-methyl-5-phenylthiazole was prepared by refluxing 1 g of **11** with 10 ml of acetic anhydride for 1 hr. The excess reagents were removed by distillation at 10 mm, and the acetoxythiazole (1 g, 82% of theory) was then distilled, bp 184–190° (10 mm), mp 72–77°. The distillate solidified, and crystallization from ethanol–water raised the melting point to 82°: ir (halocarbon and Nujol oil mulls) 1770, 1540, 1490, 1445, 1375, 1320, 1305, 1275, 1250, 1190, 1040, 1030, 1000, 870, 765, 690, 585, 565, and 550 cm^{-1}; NMR (CCl_4) δ 7.3 (m, 5, Ph), 4.25 (s, 3, ring $-CH_3$), 3.87 (s, 3, acetate $-CH_3$).

Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.76; H, 4.75; N, 6.03; S, 13.74. Found: C, 61.95; H, 5.00; N, 6.12; S, 13.45.

Registry No.—**1**, 2000-43-3; **4**, 55073-89-7; **5**, 55073-90-0; **6**, 55073-91-1; **7**, 55073-92-2; **8a**, 55073-93-3; **8b**, 55073-94-4; **8c**, 55073-95-5; **8d**, 55073-96-6; **11**, 55073-97-7; thiosemicarbazide, 79-19-6; dihydro-4-methyl-6-phenyl-2*H*-1,3,4-thiadiazine-2,5(6*H*)-dione, 55073-98-8; 5-phenyl-2,4-thiazolidinedione, 4695-17-4; acetone thiosemicarbazone, 1752-30-3; benzaldehyde thiosemicarbazone, 1627-73-2; *p*-chlorophenyl(trichloromethyl)carbinol, 5333-82-4; *p*-methoxyphenyl(trichloromethyl)carbinol, 14337-31-6; 4-acetoxy-2-methyl-5-phenylthiazole, 55073-99-9.

References and Notes

(1) This work was supported by the National Science Foundation through their Cooperative Graduate Fellow program, 1965–1967; abstracted in part from the Doctoral Thesis of E. R. Barron, University of Maryland, 1967.
(2) W. Reeve and M. Nees, *J. Am. Chem. Soc.*, **89**, 647 (1967).
(3) W. Reeve and E. Barron, *J. Org. Chem.*, **34**, 1005 (1969).
(4) W. Reeve, R. J. Bianchi, and J. R. McKee, *J. Org. Chem.*, **40**, 339 (1975).
(5) G. W. Stacy in "Heterocyclic Compounds", Vol. 7, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1961, Chapter 10, pp 826–838.
(6) W. Reeve and E. L. Compere, Jr., *J. Am. Chem. Soc.*, **83**, 2755 (1961).
(7) K. Jensen and I. Crossland, *Acta Chem. Scand.*, **17**, 144 (1963).
(8) W. Reeve and L. W. Fine, *J. Org. Chem.*, **29**, 1148 (1964).
(9) H. J. Taverne, *Recl. Trav. Chim. Pays-Bas*, **16**, 34 (1897).
(10) "Sadtler Standard Spectra Catalogue", Sadtler Research Laboratory, Philadelphia, Pa., Spectrum No. 151; "Sadtler NMR Spectra", 1969, Spectrum No. 6359M.
(11) F. J. Wilson and R. Burns, *J. Chem. Soc.*, **123**, 803 (1923).
(12) P. R. Pathan, B. K. Raval, and J. J. Trivedi, *J. Indian Chem. Soc.*, **37**, 355 (1960).
(13) W. Reeve, J. P. Mutchler, and C. L. Liotta, *Can. J. Chem.*, **44**, 575 (1966).

Synthesis of *p*-Methylthiobenzyl Chloride. A Case of Isomer Control in an Electrophilic Substitution[1]

Seemon H. Pines,* Robert F. Czaja, and N. Lee Abramson

Merck Sharp & Dohme Research Laboratories, A Division of Merck & Co., Inc., Rahway, New Jersey 07065

Received December 18, 1974

Reaction of thioanisole and methylal with ~2 mol of aluminum chloride under mild Friedel–Crafts conditions yields 74% *p*-methylthiobenzyl chloride (**1**) accompanied by only ~0.5% of its ortho isomer. Both the yield and isomer ratio change dramatically when 1 mol of aluminum chloride is used. The effect of weaker Lewis acids is reported, and the combined results are rationalized in terms of a mechanism where a thioanisole–Lewis acid complex is proposed as a key to the unique results.

We have devised a superior, direct synthesis of *p*-methylthiobenzyl chloride (**1**) via a new chloromethylation of thioanisole. Besides its immediate practical value,[2] the reaction study provides new information on the behavior of thioanisole in Friedel–Crafts chemistry.[3] For this reason, some of our developmental observations and conclusions are included in this paper.

The title compound is reported to be formed in 23% yield from the chloromethylation of thioanisole with chloromethyl methyl ether[4] in acetic acid.[5] Our scrutiny of that reaction by vapor phase chromatography shows about a 4.5:1 ratio of **1** and its isomer, *o*-methylthiobenzyl chloride (**2**), which are not practicably separable. Attempted monochloromethylation with aqueous formaldehyde and hydrochloric acid gave an even poorer isomer ratio, 7:4.[6] Apparently, the most satisfactory authenticated preparation of **1** is a multistep procedure involving lithium aluminum hydride reduction of *p*-methylthiobenzoic acid, followed by

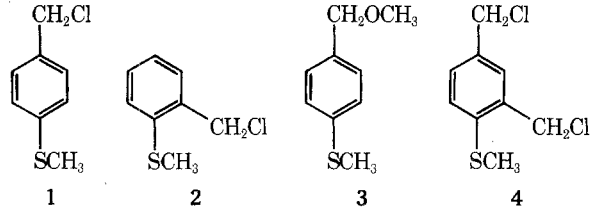
Table I
Chloromethylation of Thioanisole with Methylal and Lewis Acids

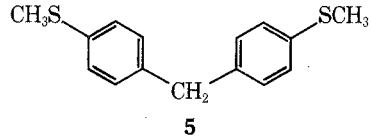
	Yield, %			
	2.2 mol[a]		1.1 mol[a]	
Lewis acid	Para	Ortho	Para	Ortho
$AlCl_3$	74	0.5	27[b]	24[b]
$AlCl_3$, moderated[c]	55	8		
$TiCl_4$	60	5	24	16
$SnCl_4$	47	4.5	19	19
$FeCl_3$	15	0.8	2	15

[a] Moles of Lewis acid per mole of thioanisole. [b] Actually 1.3 mol of $AlCl_3$ in this case. [c] 1 mol of methanol per mole of $AlCl_3$ added before methylal and thioanisole.

thionyl chloride treatment of the resultant purified p-methylthiobenzyl alcohol.[7]

By contrast, we find that reaction of thioanisole with methylal and aluminum chloride in 1,2-dichloroethane (EDC) gives 74% of 1 accompanied by only ca. 0.5% of the ortho isomer, **2**. Some 10–12% of thioanisole remains unreacted. Other constituents of the product include 3–5% of methyl p-methylthiobenzyl ether (**3**), a trace of its ortho isomer, 1–2% of 2,4-bis(chloromethyl)thioanisole (**4**), and up to 0.5% of bis(4-methylthiophenyl)methane (**5**).





5

Methanol-attenuated $AlCl_3$ and some of the weaker common Lewis acids are less effective reactant–catalysts, as can be seen from Table I. Both the product yield and specificity diminish with their use. The optimum mole ratio of Lewis acid is slightly above 2:1, relative to thioanisole. Reaction still occurs with lower catalyst levels, but the outcome is drastically altered. For instance, the almost exclusive para orientation with 2 mol of $AlCl_3$ drops to near 50:50 ortho to para substitution when only 1 mol of $AlCl_3$ is used. The stannic chloride case changes similarly. The ferric chloride reactions give about 15% yield whether 2 or 1 mol of $FeCl_3$ is used; in the former case, para substitution dominates; in the latter case, ortho substitution is found.

It is worthy of note that in the low (overall) yield reactions, the remaining thioanisole is generally not found unreacted, nor is it present as a simple monosubstituted product. Rather, the lack of simple GC-volatile products suggests that higher condensation products result with the less favorable reaction conditions.

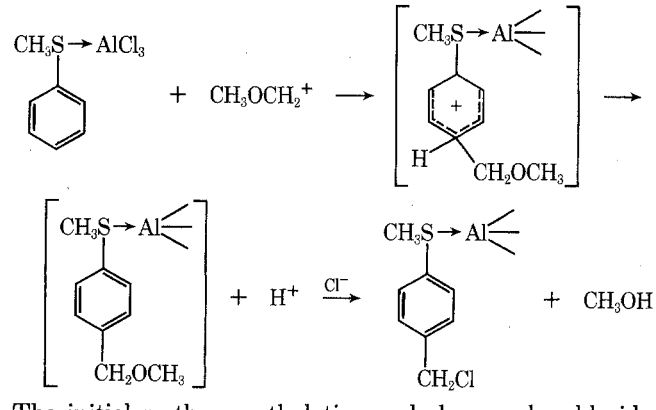
Further inferences concerning the reaction pathway can be drawn from other experiments. The best results are obtained when the thioanisole is added gradually at or below 5–10° to the EDC solution of methylal and $AlCl_3$. If, on the other hand, $AlCl_3$ is slowly added to the other reactants, the yield of 1 drops below 40%, the para:ortho ratio to 30.

The product complex which crystallizes from the reaction mixture has been examined by a number of analytical probes. Since GC and ^1H NMR analyses show that it still contains small amounts of thioanisole and traces of the methoxy methyl analog **3**, and since the solid is extremely susceptible to hydrolysis in atmospheric moisture, we cannot propose a firm structure. From the elemental analysis, we tentatively consider the product complex to be represented by the structure $p\text{-}CH_3SC_6H_4CH_2Cl\cdot(AlCl_2OCH_3)_2$. Zeisel determination shows 10.4% methoxyl (cf. 14.4% for 2 OCH_3's). Raman spectroscopy is quite enlightening.[8a] Bands at 629 and 653 cm^{-1} can be assigned to the in-plane ring bending and CH_3–S stretch modes, respectively. The comparable bands for the uncomplexed **1** are found at 634 and 673 cm^{-1}. The decrease is indicative of bond weakening, and is consonant with the formulation of the material as a Lewis acid–Lewis base pair. Similar shifts are observed in comparing the spectra of thioanisole and the thioanisole–$AlCl_3$ complex. Changes in the ring breathing mode at 1090 cm^{-1} show the same phenomenon. The low-energy region (<200 cm^{-1}) is suggestive of a polymeric lattice; X-ray diffraction methods support crystallinity.[8b]

Table II shows the gas chromatographic analyses of aliquots which were taken to determine the optimum reaction time. The experiment differed slightly in that the thioanisole was added rapidly below 5°, and the reaction was then brought to 20° at which point slurry samples were quenched and injected into the chromatograph. The results are tabulated in *area* percent, normalized to 100. While this disregards other lesser by-products, it provides the desired information.

Critical examination of the data of Table II might suggest that either the ortho isomer rearranges to para (to account for the high initial para:ortho ratio), or that the ortho isomer is formed by some other reaction mechanism (see below). A spiking experiment showed that when ortho isomer, **2**, was added initially to a reaction, it was recovered virtually unchanged in the product. While rearrangements under Lewis acid catalysis are well known, they have not been noted for chloromethyl groups.

All of these results and others are consistent (in the preferred case) with an electrophilic substitution in which the substrate is not thioanisole per se, but a thioanisole–aluminum chloride complex[9] as suggested in the scheme below.[10]



The initial methoxymethylation and cleavage by chloride have precedent in other chloromethylations using chloromethyl ethers.[12] During the course of this reaction, the Friedel–Crafts activity of the Lewis acid becomes markedly diminished, not only by formation of methanol, but more importantly by the nature of the product complex. If it did not, we might expect that the once-formed **1** would alkylate the remaining thioanisole in accord with the results of a benzylation study by Olah and coworkers.[13] In fact, when we applied these same reaction conditions to some other aromatic compounds which do not carry a methylthio substituent, much of the substrate was converted to higher

Table II
$AlCl_3$ (2.2)-Methylal (1.1) Chloromethylation of Thioanisole (1) at 20°[a]

Time, min	Thioanisole	Isomers[b] Para	Ortho
0	94.8	4.4	0.8
10	91.9	7.1	1.0
20	87.2	11.8	1.0
30	79.3	19.5	1.2
70	62.6	35.8	1.6
90	55.0	43.3	1.7
180	32.1	65.9	2.0
300	23.5	74.6	1.9
1320	16.3	82.6	1.1

[a] Parenthetic numbers are mole ratios. All values are GC, area percent normalized to 100. [b] Includes methoxymethyl analogs.

molecular weight products; the initially formed substituted benzyl chloride (i.e., benzyl cation) was too reactive to survive in its environment.

This is not the first example of variable orientation in a chloromethylation. Several reports of dependence upon reaction conditions can be found in the review of Olah and Tolgyesi.[12] The available latitude in isomer control (cf. with ferric chloride) in addition to the ability to achieve greater than 100:1 isomer ratios makes this reaction unique.[14]

Norman and Radda[15] have applied and extended the Hammond postulate[16] to the overall problem of the ortho: para ratio in aromatic substitution. They point out convincingly that with highly reactive electrophiles operating on −I, +R aromatics, the −I effect operates most powerfully on the ortho position, thus increasing the *relative* para position reactivity. Since Lewis acid complexation would be expected to enhance −I character of the methylthio group,[17] we can expect that those Lewis acids forming the strongest complexes would lead to chloromethylation products with the highest para:ortho ratio. This appears to be the case (Table I).

A simple explanation for the case of low Lewis acid mole ratios is harder to construct. If we accept a concept of dynamic exchange[17]

$$C_6H_5SCH_3 + C_6H_5S^*CH_3 \cdot AlCl_3 \rightleftarrows C_6H_5S^*CH_3 + C_6H_5SCH_3 \cdot AlCl_3$$

and equate excess Lewis base with a resultant weaker complex, then at lower mole ratios, competition for the Lewis acid by both thioanisole and methylal would diminish the enhancement of the −I effect noted above. Furthermore, a consequence of this competition would be to allow secondary reactions to occur with uncomplexed thioanisole, lowering overall yields. These arguments are in accord with our observations and also satisfy the results of the experiment in which aluminum chloride is added slowly, where the mole ratio is low during part of the reaction. Likewise, they are consonant with the known condensation of thioanisole with chloromethyl methyl ether in the presence of boron trifluoride etherate (mole ratio 10:1:1) where an 83% yield of bis(4-methylthiophenyl)methane (**5**) is obtained.[18]

Other explanations might be offered to rationalize the different results in terms, e.g., of the timing of the transition state on the reaction coordinate. In any event, the reason for the difference is suggested to be complexation with sulfur.

Experimental Section[19,20]

***p*-Methylthiobenzyl Chloride. Preferred Procedure.** *Caution! This product is a severe skin irritant. Appropriate protection against contact is advised.* To a stirred slurry of 61.4 g (0.46 mol) of anhydrous $AlCl_3$ in 200 ml of 1,2-dichloroethane was added dropwise over 30–35 min 18.2 g (0.24 mol) of methylal while keeping the temperature at 5–10°. Thioanisole (24.8 g, 0.2 mol) was then added similarly over ca. 1 hr. The reaction was brought to and held at 25° with stirring for 6–10 hr. Crystallization commenced during the warm-up to room temperature. The reaction was then quenched by the dropwise addition of 225 ml of water below 25° internal temperature with vigorous agitation.[21] The organic layer was separated, combined with an extract of the aqueous phase, and washed rapidly with 50 ml of water. Evaporation in vacuo gave a concentrate which contained[22] 25.5 g (74%) of *p*-methylthiobenzyl chloride. Present also were 3.1 g (12.6%) of unreacted thioanisole, and the following by-products in the percent indicated: *o*-methylthiobenzyl chloride (0.4%), methyl *p*-methylthiobenzyl ether (4.8%), 2,4-bis(chloromethyl)thioanisole (2.2%), and bis(*p*-methylthiophenyl)methane (0.1%).

Chloromethylation–Inverse Addition. A solution of 16.8 g (0.22 mol) of methylal and 24.8 g (0.2 mol) of thioanisole in 150 ml of EDC was stirred at ca. 10° while a slurry of 58.6 g (0.44 mol) of $AlCl_3$ in 75 ml of EDC was added over a 90-min period. At the end of the addition, the temperature was brought to 24–26°, and held there for 6 hr. After the usual quench and work-up, gas chromatography showed the presence of 13.1 g (37.8%) of **1**, 0.42 g (1.2%) of ortho isomer **2**, and 6.35 g (25.7%) of unreacted thioanisole. The remainder of the substrate was presumably lost to higher molecular weight (less volatile) products.

Isolation of Product Complex. A portion of a reaction was filtered cold immediately after the thioanisole addition, and the filtrate was allowed to crystallize for 4 hr in the usual way. It was filtered and washed with sieve-dried EDC (drybox) and pumped dry for 120 hr.

A portion (350 mg) was suspended in 1 ml of CCl_4, cooled in an ice bath, and quenched by the addition of ice, then concentrated HCl. The CCl_4 layer and an extract of the aqueous layer were dried over $MgSO_4$ and examined by GC and ^1H NMR. The GC showed, area percent relative to **1**: 0.074 thioanisole, 0.018 **2**, 0.002 **3**. The NMR signals were as expected for **1**, but with 6–7% excess aromatic and S–CH_3 signal. Raman (partial) spectrum: 629 (in-plane ring bend), 653 (C–S stretch), 1080–1099 (Ar–S stretch), 1595 cm^{-1} (C=C).

Anal. Found: C, 28.56; H, 3.87; Cl, 39.4; S, 8.37; Al, 12.72; OCH_3, 10.4. These values satisfy the following relationship: $C_{10}H_{16.2}Cl_{4.7}O_{1.9}S_{1.1}Al_2$.

Preparation and Characterization of Pure Substances. Pure samples of all derivatives of thioanisole mentioned were synthesized and purified according to standard methods. Their physical constants (melting point or boiling point and refractive index) agree well with literature values. NMR spectra were unambiguous. One compound is new, methyl *o*-methylthiobenzyl ether, made by reaction of **2** with sodium methoxide in methanol: bp 82–83° (0.35 mm); $n^{23}D$ 1.5680; NMR ($CDCl_3$) δ 2.4 (s, 3, CH_3S), 3.4 (s, 3, CH_3O), 4.5 (s, 2, CH_2), 7.2 (m, 4, aromatic).

Anal. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19; S, 19.06. Found: C, 64.54; H, 7.30; S, 18.93.

Registry No.—**1**, 874-87-3; **2**, 26190-68-1; **3**, 16155-09-2; methylal, 109-87-5; thioanisole, 100-68-5; methyl *o*-methylthiobenzyl ether, 55102-98-2.

References and Notes

(1) Presented at the Northwest Regional Meeting of the American Chemical Society, Cheney, Wash., June 13, 1974.
(2) As part of a multistep synthesis to be published in due course.
(3) A recent report: S. Clementi and P. Linda, *Tetrahedron*, **26**, 2869 (1970). References to prior studies are included therein.
(4) The standards advisory committee on carcinogens of the Occupational Safety and Health Administration have defined this compound as a carcinogen. It may be used only in rigidly defined laboratory facilities. See Federal Register, Vol. 38, No. 173, p 24375, Sept 7, 1973.
(5) N. P. Buu-Hoi and N. Hoán, *J. Org. Chem.*, **17**, 350 (1952).
(6) (a) Unpublished work from these laboratories modeled after the procedure of A. Müller, M. Mészáros, M. Lempert-Sreter, and I. Szára, *J. Org. Chem.*, **16**, 1003 (1951). Bischloromethylation has been achieved in this medium by J. H. Wood, M. A. Perry, and C. C. Tung, *J. Am. Chem. Soc.*, **72**, 2989 (1950). (b) We have repeated the uncatalyzed reaction of ethyl phenyl sulfide with paraformaldehyde and HCl, which is reported[6c] to give 86% of *p*-ethylthiobenzyl chloride. The distilled product shows the same refractive index as reported,[6c] but analysis by GC and NMR clearly shows it to be a ~6:4 ratio of the ortho and para isomers. (c) A. F. Prokof'eva, N. N. Mel'nikov, and I. L. Vladimirova, *Zh. Obshch. Khim.*, **38**, 2355 (1968). We thank Dr. R. Dewey for calling our attention to this paper.
(7) M. W. Goldberg and L. M. Jampolsky, U.S. Patent 2,624,738. This pro-

cedure has been used by (a) R. Grice and L. N. Owen, *J. Chem. Soc.*, 1947 (1963); (b) H. Bohme and G. Lerche, *Chem. Ber.*, **100**, 2125 (1967).

(8) (a) We are deeply indebted to Dr. Alan J. Rein of these laboratories for the Raman experiments and the interpretation of their significance. (b) We thank Dr. J. McCauley for this information.

(9) Complexes of thioanisole with (a) $AlCl_3$ and (b) $SnCl_4$ have recently been reported; see (a) G. H. Smith and F. J. Hamilton, *J. Phys. Chem.*, **72**, 3567 (1967); (b) I. P. Goldshtein, E. N. Kharlamova, and E. N. Guryanova, *Zh. Obshch. Khim.*, **38**, 1925 (1968).

(10) (a) A referee has suggested that if the aluminum chloride–methylal complex is very bulky, steric hindrance may account for the predominant product. We had discounted this possibility since the Sn, Ti, and Fe complexes should be bulkier than the one with aluminum, and should thus give even higher selectivity. Olah[11] has recently relegated steric factors to eighth in a list of eight influences on reactivity and selectivity in Friedel–Crafts chemistry. (b) The same referee has, in questioning the proposed mechanism, pointed out that a good case can be made that the thioanisole–aluminum chloride complex might be meta directing, and that it certainly should be deactivating. His first point probably rests on the well-known predominant meta direction of sulfoxides and sulfonium ions. We agree with the latter point concerning deactivation, and cite it as further evidence for complexation. The reaction is certainly slower (Table II) than would be expected for an aromatic substrate which has been reported to react 2.5 times as fast as mesitylene in electrophilic reaction.[3]

(11) G. A. Olah in "Friedel-Crafts Chemistry", Wiley, New York, N.Y., 1973, p 393.

(12) G. A. Olah and W. S. Tolgyesi in "Friedel-Crafts and Related Reactions", Vol. 2, G. A. Olah, Ed., Wiley, New York, N.Y., 1964, Part 2, Chapter XXI. See also "Aromatic Haloalkylations", Ph.D. Dissertation of D. A. Beal, Case Western Reserve University, 1973.

(13) G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

(14) After our work was completed, we happened upon a reference to the influence of, inter alia, the amount of aluminum chloride used in the chloromethylation of 2-acetyl- and 2-formylthiophene with chloromethyl methyl ether or bis(chloromethyl) ether. Variable orientation was obtained in that case also. The authors ascribed the effect to the influence of complexation with the carbonyl moiety. See L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, *J. Org. Chem. USSR*, **7**, 1809 (1971).

(15) R. O. C. Norman and G. K. Radda, *J. Chem. Soc.*, 3610 (1961).

(16) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(17) Further evidence for a complex comes from the NMR spectrum of 1:1 aluminum chloride–thioanisole solutions. The aromatic protons are shifted selectively downfield, relative to thioanisole alone. The methyl proton singlet is also shifted downfield. The NMR spectrum of a 2:1 mole ratio of thioanisole and aluminum chloride shows chemical shifts intermediate between thioanisole and 1:1 thioanisole–aluminum chloride.

(18) V. A. Topchii and S. V. Zavgorodnii, *Zh. Org. Khim.*, **5**, 130 (1969).

(19) Commercially available reagents and solvents were used as purchased. NMR spectra were obtained on $CDCl_3$ solutions of the compounds with a Varian A-60A or Jeolco C-60HL spectrometer. The Raman spectra were obtained with a Carey Model 82 spectrometer excited with a Spectra-Physics Model 165-03 argon ion laser.

(20) We have been unable to detect the presence of either chloromethyl methyl ether or bis(chloromethyl) ether during reaction or work-up. Nevertheless, in view of the carcinogenicity of these two compounds,[4] considerable care should be exercised in experiments of this type.

(21) Some experiments were quenched *into* a large amount of water, and up to 3–5% hydrolysis of the product to the corresponding carbinol occurred. Rapid quench onto ca. 250 g of ice and water gave satisfactory results.

(22) GC analyses were run on a 6 ft × 0.125 in. S. S. column packed with 10% SP-2401 on 100/120 mesh Supelcoport, programmed from 110 to 170° at 4°/min. Thermal conductivity detection was used. The identity of the individual components was secured not only by mixed chromatograms with the pure substances, but also by GC–mass spectral methods. Quantitation of the thioanisole and **1** was by the internal standard method (tetradecane). The minor components are reported on an area percent rather than weight percent basis. We thank Mr. W. E. Tait for assay support.

Isonucleosides. I. Preparation of Methyl 2-Deoxy-2-(purin-9-yl)arabinofuranosides and Methyl 3-Deoxy-3-(purin-9-yl)xylofuranosides

John A. Montgomery,* Sarah D. Clayton, and H. Jeanette Thomas

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received February 12, 1975

Since the reaction of 6-(methylthio)purine with methyl 2,3-anhydro-5-deoxy-α-D-ribofuranoside in the presence of base gave two products, the desired methyl 2,5-dideoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (**6**) and methyl 3,5-dideoxy-3-[6-(methylthio)-9-purinyl]-α-D-xylofuranoside (**7**), resulting from attack by the purine anion on both C-2 and C-3 of the sugar, an alternative route to **6** and related structures was developed. The best procedure appeared to consist of reaction of 5-amino-4,6-dichloropyrimidine with **4** or **5** followed by ring closure of the resultant diaminopyrimidines to the corresponding purines. Replacement of the chloro group of **22** then gave the desired isonucleosides **23** and **24**.

In naturally occurring nucleosides and nucleotides, the purine ring is attached to C-1 of ribose or 2-deoxyribose, this linkage being part of an aminal structure, which is quite susceptive to both hydrolytic and enzymatic cleavage. The reasons for our interest in analogs of the naturally occuring nucleosides have been adequately discussed.[1] Available data indicate that if N-9 of the purine ring is attached to C-2 rather than C-1 of a pentofuranose, with the hydroxyl group at C-3 trans to the purine ring and the hydroxymethyl group at C-4 cis (see **23**), the resulting sugar derivative, which we have named isonucleoside, is likely to be a substrate for the anabolic enzyme adenosine kinase.[2] If the nucleotide is formed intracellularly by this enzyme, it may be capable of interfering with vital cellular metabolism (e.g., the biosynthesis or function of nucleic acids), and this type of structure would be of great potential interest.

Since one approach to the synthesis of such compounds is the reaction of a purine anion with the appropriate sugar epoxide, the reaction of 6-(methylthio)purine (**1**) with cyclohexene oxide (**2**) in the presence of pyridine was investigated and found to proceed satisfactorily (although the yield was low, no attempt was made to optimize it). That attack occurred as expected at N-9 of **1** to give the desired 9-(*trans*-2-hydroxycyclohexyl)-6-(methylthio)purine (**3**) (Scheme I) was demonstrated by comparing the uv spectrum of **3** with that of 7- and 9-benzyl-6-benzylthiopurine.[3] Since it is well known that epoxides open by rearward nucleophilic attack to give trans products, that aspect of the structural assignment was not open to question.

The success of the reaction of **1** with **2** caused us to study the reaction of **1** with methyl 2,3-anhydro-5-deoxy-α-D-ribofuranoside[4] (**4**), since it had been reported that attack by ammonia on **4** occurred exclusively at C-2 to give the arabino sugar derivate (**9**).[5,6] Attack by the anion of 6-(methylthio)purine on **4** was expected to give the desired arabino sugar **6** with the purine attached at C-2 and the hydroxyl at C-3 trans. The reaction of **1** with **4** proved sluggish, and more drastic conditions had to be employed than in the case with **2**. Less than half of **1** reacted and two sugar-containing products were formed (TLC). Although we original-