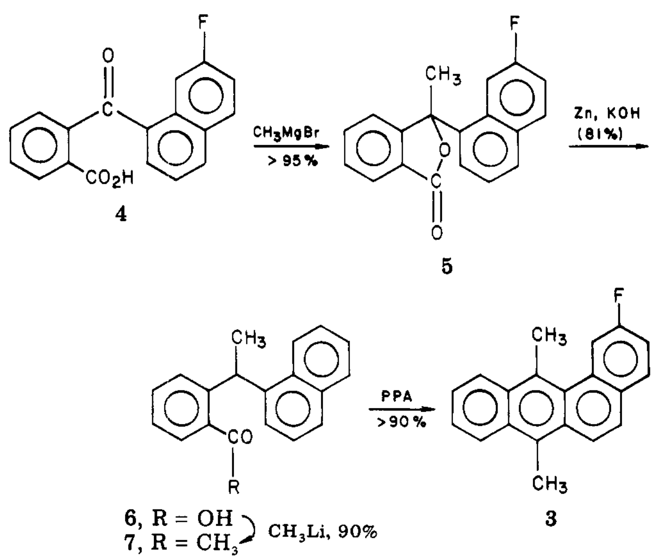
Scheme I



no tumors has appeared in 18 male Fischer rats 20 months after injection.

Randomly tritiated[6] 3 showed decreased bonding to DNA in cell culture[7] which fact correlates with the findings of the Millers (above).

The fact that 3 was noncarcinogenic lends support to the bay region diol epoxide hypothesis in the benz[*a*]anthracene series[8] because the presence of a fluorine atom in the 2-position would be expected to prevent such metabolism, as is the case.

Experimental Section[9]

γ-(*p*-Fluorophenyl)butyric Acid. This was prepared in 75% overall yield by condensation of fluorobenzene with succinic anhydride followed by Clemmensen reduction as described.[10]

1-Amino-7-fluoronaphthalene. Ring closure of the above acid via its acid chloride gave 7-fluoro-3,4-dihydro-1(2*H*)-naphthalenone, bp 120–121 °C (2 mm), in 88% yield. This ketone was converted to the oxime and the latter to 7-fluoro-1-naphthylamine, bp 140–145 °C (3 mm), as described for other similar conversions.[11] This amine was converted to 1-bromo-7-fluoronaphthalene, bp 125–127 °C (3 mm), mp 42–43 °C, in 45% yield.[12]

***o*-(7-Fluoro-1-naphthoyl)benzoic Acid*, 4.** A solution of 13.6 g (60 mmol) of 1-bromo-7-fluoronaphthalene[4] in 100 mL of ether (distilled from butylmagnesium bromide solution), 50 mL of dry benzene, and 0.5 mL of ethylene dibromide[5] was added during 1 h to a stirred mixture of 4 g (167 mmol) of pure sublimed magnesium in 25 mL of ether. After 0.5 h at reflux the clear pale yellow solution was transferred under N$_2$ to an addition funnel and added rapidly to a stirred hot solution of 9.6 g (65 mmol) of phthalic anhydride in 250 mL of benzene. After being held at reflux for 5 h, the acidic product was isolated to yield 16.1 g (91%) of 4, mp 206–208 °C, suitable for the next step. The analytical sample was obtained with little loss by recrystallization from benzene to yield pure colorless 4, mp 212–213 °C.

3-(7-Fluoro-1-naphthyl)-3-methylphthalide*, 5. A solution of 12.5 g (42 mmol) of 4 in 400 mL of dry ether and 100 mL of dry benzene was added to 50 mL of 2.7 M methylmagnesium bromide (Ventron), and the mixture was refluxed for 1 h. From the neutral fraction of the reaction mixture was obtained 12.0 g (96%) of yellowish solid, 5, mp 140–143 °C (IR band at 5.7 μm), pure enough for the next step. Recrystallization from benzene–petroleum ether afforded the analytical sample, mp 152–154 °C, with little loss.

2-[α-(7-Fluoro-1-naphthyl)ethyl]benzoic Acid*, 6. A stirred mixture of 11.5 g (39 mmol) of 5, 70 g of zinc dust (activated by brief treatment with CuSO$_4$), 520 mL of 10% KOH, and 65 mL of pyridine was held at reflux for 26 h. From the acid fraction was obtained 9.3 g (81%) of 6, mp 153–155 °C, good enough for the next step. The colorless analytical sample, mp 155.0–156.5 °C, was obtained by crystallization from aqueous alcohol with little loss.

2-[α-(7-Fluoro-1-naphthyl)ethyl]acetophenone*, 7. To a solution of 9.5 g (32 mmol) of 6 in 650 mL of dry ether was added slowly 50 mL of 1.8 M CH$_3$Li (Ventron), and the mixture was refluxed for 2 h. From the neutral fraction of the reactants was isolated 8.8 g (93%) of 7, mp 116–118 °C, and a small amount of 6 was recovered from the acidic fraction. Recrystallization from benzene–petroleum ether yields pure 7, mp 122–123 °C, with little loss.

3-Fluoro-7,12-dimethylbenz[*a*]anthracene*, 3. To warm (45 °C) stirred polyphosphoric acid (115%) was added 8.4 g (29 mmol) of 7. The mixture was heated to 90–95 °C, kept there for 30 min, cooled, and poured on ice. The product was taken into ether–benzene and isolated to yield 7.7 g (98%) of 3, mp 86–89 °C. The crude mixture was treated with 6.6 g of picric acid in benzene and the crystalline picrate recrystallized to a constant melting point of 130–131 °C. This picrate was then treated with an aqueous solution of diethanolamine to remove the picric acid. Recrystallization of the resulting 3 from benzene–ethanol afforded 4.5 g (57%) of 3, mp 96.5–97.5 °C. Chromatography over alumina and recrystallization yielded (with little loss) the purest 3, mp 97.5–98.5 °C, for testing purposes.

Registry No. 3, 68141-56-0; 3 picrate, 72017-22-2; 4, 71276-91-0; 5, 72017-23-3; 6, 72017-24-4; 7, 72017-25-5; α-(*p*-fluorophenyl)butyric acid, 589-06-0; 1-amino-7-fluoronaphthalene, 13916-95-5; 7-fluoro-3,4-dihydro-1(2*H*)-naphthalenone, 2840-44-0; 1-bromo-7-fluoronaphthalene, 13790-91-5; phthalic anhydride, 85-44-9.

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[6] A new synthesis of 3 has been used. See: Sheikh, Y. M.; Cazer, F. D.; Hart, R. W.; Witiak, D. T., submitted for publication in *J. Org. Chem.*

[7] See: Daniel, F. B.; Wong, L. K.; Oravec, C. T.; Cazer, S. D.; Wang, C.-L. A.; D'Ambrosio, S. M.; Hart, R. W.; Witiak, D. T. "Proceedings of the 3rd International Symposium on Polycyclic Aromatic Hydrocarbons"; Oct 25–27, 1978, in press.

[8] For a review of the development of concepts see: Heidelberger, C. In "Carcinogenesis"; Raven Press: New York, 1976; p 1 and references therein.

[9] All melting and boiling points are uncorrected and are in °C. All new compounds marked with an asterisk gave results within ±0.3% of the correct analytical results by Galbraith or MHW Laboratories. The usual way of working up a reaction mixture was to wash a benzene–ether solution of the products with alkali, to remove the acid portion, or acid. The solvents were then extracted with saturated NaCl solution and dried by passing them over MgSO$_4$.

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Kinetics of Acetylation of Substituted 4-Thianols. Single-Crystal Analysis of *cis*-2,*trans*-6-Diphenyl-*cis*-3-ethylthian-*r*-4-ol and 2,2,6,6-Tetramethyl-4(e)-phenylthian-4(a)-ol

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Received October 17, 1978

The synthesis[1] and ^{13}C NMR analyses[2] of a large number of highly substituted 1-hetera-2,6-diaryl-4-cyclohexanones

Table I. Second-Order Rate Constants of Acetylation of 4-Thianols (Axial Hydroxyl) and the Corresponding 1,1-Dioxides with Acetic Anhydride in Pyridine at 40 °C

4-thianols	10^5k, mol^{-1} s^{-1}	1,1-dioxides	10^5k, mol^{-1} s^{-1}
trans-2,*trans*-6-diphenylthian-*r*-4-ol[a–d] (1)	15.56 ± 0.19 (7.62)[a]	5[a,c,d]	38.37 ± 0.43 (11.32)[a]
trans-2,*trans*-6-diphenyl-*cis*-3-methylthian-*r*-4-ol (2)	7.19 ± 0.18	6	25.10 ± 0.03
trans-2,*trans*-6-diphenyl-*cis*-3-ethylthian-*r*-4-ol (3)	4.23 ± 0.02	7	20.32 ± 0.26
cis-2,*trans*-2-dimethyl-*trans*-6-phenylthian-*r*-4-ol (4)	7.09 ± 0.14	8	15.48 ± 0.12

[a] V. Baliah and T. Chellathurai.[3] [b] C. A. R. Baxter and D. A. Whiting.[5] [c] Present work. [d] Melting points for 1 are 139–140 °C,[a] 140–141 °C,[b] and 144–145 °C,[c] and for 5 are 246–247 °C[a] and 261–262 °C[c].

Table II. Acetylation Rates of 4-Thianols (Equatorial Hydroxyl) and the Corresponding 1,1-Dioxides with Acetic Anhydride in Pyridine at 40 °C

4-thianols	10^5k, mol^{-1} s^{-1}	1,1-dioxides	10^5k, mol^{-1} s^{-1}
cis-2,*cis*-6-diphenylthian-*r*-4-ol[a–d] (9)	45.19 ± 0.48 (33.20)[a]	19[a,c,d]	85.99 ± 0.22 (55.60)[a]
cis-2,*trans*-6-diphenylthian-*r*-4-ol (10)	42.00 ± 0.87 (42.80)[a]	20[a,c,d]	81.27 ± 0.64 (66.40)[a]
cis-2,*cis*-6-diphenyl-*trans*-3-methylthian-*r*-4-ol (11)	50.77 ± 0.26	21	104.53 ± 0.24
cis-2,*trans*-6-diphenyl-*cis*-3-methylthian-*r*-4-ol (12)	19.69 ± 0.19	22	9.43 ± 0.04
cis-2,*cis*-6-diphenyl-*trans*-3-ethylthian-*r*-4-ol (13)	53.68 ± 0.33	23	125.60 ± 0.64
cis-2,*trans*-6-diphenyl-*cis*-3-ethylthian-*r*-4-ol (14)	10.28 ± 0.10	24	6.15 ± 0.05
cis-2,*trans*-2-dimethyl-*cis*-6-phenylthian-*r*-4-ol (15)	32.10 ± 0.38	25	62.23 ± 0.44
4-thianol (16)	22.3 ± 0.39		
cis-2,*trans*-2-dimethylthian-*r*-4-ol (17)	68.65 ± 0.38		
cis-2,6,*trans*-2,6-tetramethylthian-*r*-4-ol (18)	38.56 ± 0.26		

[a] V. Baliah and T. Chellathurai.[3] [b] C. A. R. Baxter and D. A. Whiting.[5] [c] Present work. [d] Melting points for 9 are 149–150 °C,[a] 155–156 °C,[b] and 156–157 °C,[c] for 10 are 139–140 °C,[a] 142–143 °C,[b] and 147–149 °C,[c] for 19 are 237–238 °C[a] and 240–243 °C,[c] and for 20 are 234–235 °C[a] and 185–187 °C.[c]

and the corresponding cyclohexanols were recorded recently from this laboratory. We now report a study of the kinetics of acetylation[3] of the substituted 4-thianols in order to conduct a partial conformational analysis thereof.[4,5] In addition, a single-crystal X-ray diffraction analysis was also performed on *cis*-2,*trans*-6-diphenyl-*cis*-3-ethylthian-*r*-4-ol and on 2,2,6,6-tetramethyl-4(e)-phenylthian-4(a)-ol. To our knowledge, these X-ray studies are the first to be reported on any substituted thianols.

Experimental Section

Materials. The preparation of the thianols 2–4, 6–8, 11–15, and 21–25 has been communicated.[1] Compounds 1,[6] 5,[6] 9,[6] 10,[6] 19,[6] and 20[6] along with 16[7] and 18,[7] found in Tables I and II, were prepared from literature routes. The preparation of 2,2,6,6-tetramethyl-4(e)-phenylthian-4(a)-ol (26) was modeled after that procedure recorded.[6] The crystalline solid melted at 104–105 °C and was subjected to the X-ray analysis described in this paper.

All NMR data were recorded on a Varian XL-100(15) spectrometer equipped with a Nicolet TT-100 PFT accessory as described previously.[1,2]

Crystallographic Experimental Data. Colorless, hexagonally prismatic crystals of thianol 14 were obtained from a solution of ethanol and water. The crystal selected for subsequent diffraction studies had a cross section with dimensions 0.16 × 0.17 × 0.18 mm and a length of 0.62 mm. Preliminary studies revealed a threefold diffraction axis and a systematic extinction, $00l$ ($l \neq 3n$), consistent with space group $P3_1$ or $P3_2$. The $P3_1$ group was chosen initially. After the structure determination and refinement, the Hamilton significance test[8] was performed on the R value ratio of refinements by using positive and negative values of $\Delta f''$. The test results established $P3_1$ as the correct space group at a confidence level of greater than 99.5%.

Crystals of thianol 26 ($C_{15}H_{22}OS$, mol wt 250.4) were obtained from a *tert*-butyl alcohol solution by slow evaporation. The crystal, a hexagonal prism, selected for the diffraction experiments was colorless and had dimensions of 0.34 × 0.28 × 0.46 mm. Diffraction symmetry and systematic extinctions ($0k0$, k odd, and $h0l$, l odd) were consistent with monoclinic space group $P2_1/c$.

Unit cell parameters were determined by a least-squares fit to the positive and negative 2θ values, measured at −135 °C, of 56 reflections for 14 and 52 reflections for 26, distributed throughout reciprocal space, using Cu Kα_1 radiation ($\lambda = 1.54051$ Å). The unit cell constants are $a = 15.756$ (2) Å, $c = 5.596$ (1) Å, $\gamma = 120°$, $\alpha = \beta = 90°$, $V = 1203.1$ Å^3, $Z = 3$, and $D_x = 1.234$ g/cm^3 for 14 and $a = 9.6736$ (5) Å, $b = 12.8580$ (9) Å, $c = 11.5290$ (9) Å, $\beta = 96.172$ (6)°, $V = 1425.7$ Å^3, and $D_x = 1.166$ g/cm^3 for 26.

Intensity data were collected at −135 °C on a CAD-4 automatic diffractometer employing well-collimated, nickel-filtered Cu Kα radiation. Measurements were made on all data within the range $2° < 2\theta < 150°$ by using θ–2θ scans and a maximum time of 90 s per reflection for 14 and 60 s for 26. A total of 1803 individual intensity data were collected for 14 of which 1770 (98.2%) were considered observed on the basis that their intensities were larger than $2\sigma(I)$. The total number of data for 26 was 2930 of which 2774 (94.7%) were considered observed. The intensity of monitor reflections was measured regularly throughout both data collections to monitor changes in experimental conditions; the intensity differences were not significant. An absorption correction[9] was made by using $\mu = 16.96$ cm^{-1} (for 14) and 18.06 cm^{-1} (for 26), for Cu Kα radiation. The data sets were corrected for Lorentz and polarization factors, and each structure factor was assigned a weight.[10]

The structures were solved by using the program MULTAN.[11] All hydrogen atoms were located after initial refinement of the

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Table III. Positional Parameters for Carbon, Oxygen, and Sulfur Atoms for 14[a]

	x	*y*	*z*
S(1)	0.64158 (4)	0.02362 (4)	0.25000
C(2)	0.5545 (1)	0.0042 (1)	0.4895 (4)
C(3)	0.4623 (1)	−0.0987 (2)	0.4733 (4)
C(4)	0.4952 (1)	−0.1742 (1)	0.5231 (4)
C(5)	0.5643 (2)	−0.1749 (2)	0.3340 (5)
C(6)	0.6624 (2)	−0.0785 (2)	0.3090 (5)
C(7)	0.5310 (2)	0.0865 (1)	0.4947 (4)
C(8)	0.5546 (2)	0.1540 (2)	0.3110 (5)
C(9)	0.5295 (2)	0.2270 (2)	0.3257 (5)
C(10)	0.4799 (2)	0.2328 (2)	0.5229 (5)
C(11)	0.4557 (2)	0.1659 (2)	0.7078 (5)
C(12)	0.4823 (2)	0.0939 (2)	0.6946 (5)
C(13)	0.4033 (2)	−0.1194 (2)	0.2423 (5)
O(14)	0.4134 (1)	−0.2720 (1)	0.5309 (4)
C(15)	0.7348 (2)	−0.0601 (2)	0.5096 (5)
C(16)	0.7746 (2)	0.0226 (2)	0.6573 (6)
C(17)	0.8412 (2)	0.0358 (3)	0.8372 (7)
C(18)	0.8705 (2)	−0.0322 (3)	0.8726 (7)
C(19)	0.8339 (2)	−0.1136 (3)	0.7237 (8)
C(20)	0.7672 (2)	−0.1275 (2)	0.5436 (7)
C(21)	0.3353 (2)	−0.0764 (2)	0.2282 (6)

[a] Estimated standard deviations for the last digit are given in parentheses.

nonhydrogen atoms. The full-matrix least-squares method[12] was used for 14, while the block-diagonal least-squares procedure[13] was employed for 26. Anisotropic thermal parameters for the carbon, oxygen, and sulfur atoms, isotropic thermal parameters for the hydrogen atoms, and anomalous dispersion corrections for the sulfur and oxygen atoms, in the case of 14, were used in the final refinement cycles for both compounds. The refinements were terminated when all shifts were small fractions of the corresponding standard deviations. The final *R* value [$R = [(\sum||kF_o| - |F_c||)/\sum|kF_o|]]$ for all data was 0.032 for 14 and 0.043 for 26. In the final difference Fourier maps, the largest residual electron density was 0.35 e/Å^3 for both compounds.

The atomic scattering factors for S, O, and C and the anomalous scattering factors were taken from the literature.[14] The scattering factors for hydrogen atoms were those of Stewart, Davidson, and Simpson.[15] The final positional coordinates for the carbon, oxygen, and sulfur atoms are listed in Table III for 14 and in Table IV for 26. Anisotropic thermal parameters, hydrogen positional and thermal parameters, and tables of final observed and calculated structure factors for both compounds are available.[8]

Kinetics. The procedure employed was that published with subsequent modifications[4a,b] and at 40 ± 0.1 °C in pyridine. In the case of sulfone alcohols, a mixture of carbon tetrachloride and *n*-butyl alcohol was used to dissolve the acetate formed.

Preparation of Thianol 17. To a suspension of $LiAlH_4$ (1.52 g, 0.04 mol) in dry ether (50 mL) was added dropwise a solution of 2,2-dimethyl-4-thianone[16] (12 g, 0.076 mol) in dry ether (100 mL). The mixture was stirred under reflux for 5 h, and excess hydride was destroyed by careful addition of ice-cold water. The resultant mixture was neutralized with hydrochloric acid (5%, 25 mL), and then the final mixture was extracted with ether. The ether extracts were combined and washed with $NaHCO_3$ (3%) and then with water and dried (Na_2SO_4). Removal of ether and vacuum distillation of the residue gave 4.0 g (32.9%) of thianol 17: bp 37–38 °C (1 mm); IR (film) 1040 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.15 (d, 2 H, H(3), J = 6.0 Hz), 1.40 (s, 3 H, CH_3(a)), 1.42 (s, 3 H, CH_3(e)), 1.63–1.68 (m, 2 H, H(5)), 1.80 (t, 2 H, H(6), J = 7.0 Hz), 2.86 (s, 1 H, OH), 3.90–4.16 (m, 1 H, H(4)).

Table IV. Final Positional Parameters for Carbon, Oxygen, and Sulfur Atoms for 26[a]

	x	*y*	*z*
S(1)	0.14254 (3)	0.66236 (3)	0.29259 (3)
C(2)	0.1090 (1)	0.7647 (1)	0.3975 (1)
C(3)	0.2475 (1)	0.8053 (1)	0.4588 (1)
C(4)	0.3490 (1)	0.7257 (1)	0.5205 (1)
C(5)	0.3881 (1)	0.6394 (1)	0.4382 (1)
C(6)	0.2719 (1)	0.5756 (1)	0.3710 (1)
C(7)	0.0400 (2)	0.8525 (1)	0.3216 (1)
C(8)	0.0067 (1)	0.7282 (1)	0.4817 (1)
O(9)	0.2885 (1)	0.67605 (8)	0.61368 (8)
C(10)	0.4852 (1)	0.7801 (1)	0.5687 (1)
C(11)	0.5468 (1)	0.7549 (1)	0.6796 (1)
C(12)	0.6712 (2)	0.8011 (1)	0.7255 (1)
C(13)	0.7364 (2)	0.8728 (1)	0.6612 (2)
C(14)	0.6769 (2)	0.8980 (1)	0.5497 (2)
C(15)	0.5525 (2)	0.8521 (1)	0.5038 (1)
C(16)	0.3338 (2)	0.5154 (1)	0.2738 (1)
C(17)	0.2040 (2)	0.4968 (1)	0.4475 (1)

[a] Estimated standard deviations for the last digit are given in parentheses.

Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.65; S, 21.93. Found: C, 57.59; H, 9.72; S, 21.98.

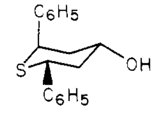
Preparation of Thianol 26. To phenylmagnesium bromide at 0 °C [from magnesium (2.8 g, 0.12 mol)] and bromobenzene (18.2 g, 0.12 mol) in dry ether (150 mL) was added 2,2,6,6-tetramethyl-4-thianone[7] (10 g, 0.06 mol) in dry ether (100 mL), and the mixture was stirred under reflux for 12 h. The reaction mixture was poured onto crushed ice (500 g), a solution of ammonium chloride (50 g in 100 mL of H_2O) was added, and the mixture was stirred well. The ether layer was then separated, washed with water, and dried ($MgSO_4$). Removal of the ether gave thianol 26: 12.5 g (86%); mp 104–105 °C (ethanol); ^1H NMR ($DCCl_3$) δ 1.28 (s, 6 H, 2,6-CH_3(e)), 1.69 (s, 6 H, 2,6-CH_3(a)), 1.74 (s, 1 H, OH), 1.95 (s, 4 H, H(3), H(5)), 7.20–7.54 (m, 5 H, Ar H).

Anal. Calcd for $C_{15}H_{22}OS$: C, 71.95; H, 8.86; S, 12.81. Found: C, 71.83; H, 8.93; S, 12.75.

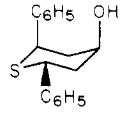
Results and Discussion

All rate constants for the acetylation of 4-thianol, substituted 4-thianols, and the corresponding sulfones are found in Tables I and II together with a few previous results by Baliah and co-workers.[3] Our data agrees well with theirs[3] for *cis*-2,*trans*-6-diphenylthian-*r*-4-ol (**10**) but differs significantly (our rate constants are about 25% higher) for epimeric pairs of 2,6-diphenyl-4-thianol (**1** and **9** in Tables I and II) and the corresponding sulfones (**5** and **19** in Tables I and II). Differences in melting points of these compounds conceivably could reflect the presence of only small amounts of impurities, which may, however, influence the rates of acetylation. All compounds in our study analyzed correctly via ^{13}C NMR, ^1H NMR, and mass spectral techniques.[1,2]

The differences in rates between **1** and **9** and between sulfones **5** and **19** and the large size of the phenyl groups suggest these compounds are likely conformationally biased. Surprising was the greater rate of acetylation of **9** compared to that of **10** (the differences are well outside experimental error) since the reverse order was reported.[3] Assignment of an equatorial hydroxyl group at C(4) in **10** in our work was based on IR, ^1H NMR, and ^{13}C NMR analyses.[1,2] Possibly **10** may not be conformationally homogeneous in solution, with perhaps **10a** making a con-



10



10a

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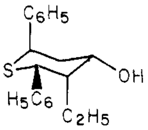
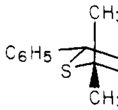
Table V. Torsion Angles (deg) for 14

S(1)-C(2)-C(3)-C(4)	66.1	C(6)-S(1)-C(2)-C(7)	175.1
C(2)-C(3)-C(4)-C(5)	-65.0	S(1)-C(2)-C(3)-C(13)	-60.6
C(3)-C(4)-C(5)-C(6)	62.2	C(4)-C(3)-C(2)-C(7)	-168.2
C(4)-C(5)-C(6)-S(1)	-55.9	C(2)-C(3)-C(4)-O(14)	175.4
C(5)-C(6)-S(1)-C(2)	50.2	C(5)-C(4)-C(3)-C(13)	63.0
C(6)-S(1)-C(2)-C(3)	-58.0	C(13)-C(3)-C(4)-O(14)	-56.6
		C(6)-C(5)-C(4)-O(14)	-175.1
S(1)-C(2)-C(7)-C(8)	13.5	C(4)-C(5)-C(6)-C(15)	74.8
C(3)-C(2)-C(7)-C(12)	67.0	C(2)-S(1)-C(6)-C(15)	-80.3
S(1)-C(6)-C(15)-C(16)	7.0		
C(5)-C(6)-C(15)-C(20)	61.0	C(2)-C(3)-C(13)-C(21)	-79.6
		C(4)-C(3)-C(13)-C(21)	156.7

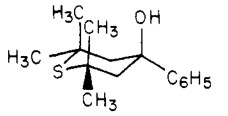
tribution and thereby reducing the rate of acetylation. Also, in view of the observation that crystalline 14 is a chair conformer (with equatorial OH) and the fact that 4 (with axial OH) has been isolated as a solid (mp 64–65 °C),[1] it is clear both equatorial and axial C–OH bonds can exist in these systems with other *axial* substituents present. Moreover, crystalline 26 has the hydroxyl group in an axial position as will be discussed. Finally, steric factors surely would play a role in determining the energy barrier for ring reversal in 10 ⇄ **10a**, and such are difficult to assess. However, Courtauld models show little difficulty for this interconversion of conformers.



14



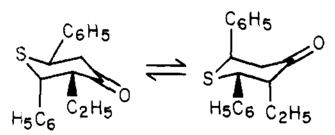
4



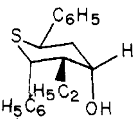
26

Interestingly, comparison of rates of acetylation of the thianols 1 and 5 with the rates for the corresponding 3-alkyl-substituted compounds 2 and 3 and 6 and 7, respectively, reveal a marked retardation effect. Assuming the rings are flattened out (as for 26; 14 slightly flattened), the dihedral angle RC(3)–C(4)OH (R = CH_3, C_2H_5) would be reduced, introducing an increased steric factor. Models support this. In contrast, thianols 9 and 10 as well as 19 and 20 react *slower* than the corresponding 3-alkyl compounds 11, 13 and 12, 14 as is true for 21, 23 and 22, 24, respectively. Here ring flattening would cause the dihedral angle between RC(3) and C(4)OH to *increase* when R = CH_3 and C_2H_5 as compared to when R = H.

Reduction of thianone 27[1] (the crystal analysis proved the conformation for the solid to be that as shown in 27)[1] with $LiAlH_4$ might expectedly yield **14a** via attack by $HAlH_3$ from the top side of 27. However, the single crystalline product isolated in high yield[1] proved to be 14. Intuitively, one could predict reduction of 27 to give **14a** which then could undergo ring reversal to give 14 as observed. Although it is conceivable that 27 ⇄ **27a** occurs, followed by reduction of the latter to 14, hydride transfer from the top side of **27a** would appear to be more hindered than that in 27. That 14 is a chair and the hydroxyl group is equatorial in solution is supported by ^1H NMR analysis which revealed $^3J_{H(2a),H(3e)}$ = 5 Hz and $W_{1/2}$ = 20 Hz for H(4).[1,17] A similar situation exists for 3-methyl analogue 12 [$^3J_{H(2a),H(3e)}$ = 3 Hz and $W_{1/2}$ = 20 Hz], which is presumed to have a geometry like that of 14. Again, a flattening of the ring in 12 or 14 should reduce the dihedral angle RC(3)–C(4)OH (R = CH_3 or C_2H_5) and create increased steric difficulty (compared to that in 10) for acetylation. In addition, some syn-axial 1,3-interactions may be important, involving axial phenyl-hydrogen and axial alkyl-hydrogen groups as indicated from an examination of Courtauld models.



27 27a



14a

Two other aspects of the system 14 ⇄ **14a** need to be considered. Although solid 14 shows only slight flattening of the thiane ring, a simple calculation of the HO–C(15) distance in theoretical **14a** (axial OH) gives a value of 2.95 Å. This is less than the van der Waals distance of 3.0 Å. Consequently, a ring flattening should be present in **14a**. This situation coupled with the gauche interaction with the C_2H_5 group at C(3) could retard acetylation. In the series 10 > 12 > 14, the rate of acetylation decreases as the axial substituent at C(3) increases in size from H to CH_3 to C_2H_5.

A calculation from the X-ray data for 14 reveals an H(4)–C(15) distance of 2.98 Å compared to the van der Waals distance of 2.8 Å. Although there is no contact here, it is clearly recognized that there must exist hindered rotation for the phenyl group because of interaction with H(4). In solution, there may possibly be some flattening of the ring to minimize the interaction unless the rotation is completely retarded, which seems unlikely. If there is any flattening at C(4), the C(4)–H(4) bond may be forced away from the ring axis and may be "bent downward" into a slightly more eclipsed position with the C(3)–C(13) bond. Consequently, this should be reflected in a smaller dihedral angle for C(13)C(3)–C(4)O(14) which is observed to be -56.6° (Table V). Unfortunately there does not appear to be any analogous system of known structure with which a comparison might be made with respect to distortion of the dihedral angle between *syn-oriented*, vicinal substituents in six-membered rings. In view of the other internal molecular restrictions in 14, it does not seem unreasonable that the above arguments might be valid in explaining the reduction in the rate of acetylation.

In view of the $W_{1/2}$ values in the ^1H NMR spectrum for H(4) for 14 (similarly for 12) in solution, we tentatively conclude that it is 14 which undergoes acetylation. To be sure, an equilibrium 14 ⇄ **14a** could provide **14a** for the reaction. One would expect that perhaps the energy barrier for the acetylation would be higher for **14a** with C(2) and C(4) holding two axial groups (C_6H_5 and OH) on the *same side of the ring* compared to 14 which has the axial groups at C(3) and C(6) but on *opposite sides of the ring*. Courtauld models support this contention.

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[17] Compare similar values in glycosides; see: Lemieux, R. U.; Kulling, R. K.; Bernstein, H. J.; Schneider, W. G. S. *J. Am. Chem. Soc.* **1958**, *80*, 6098.

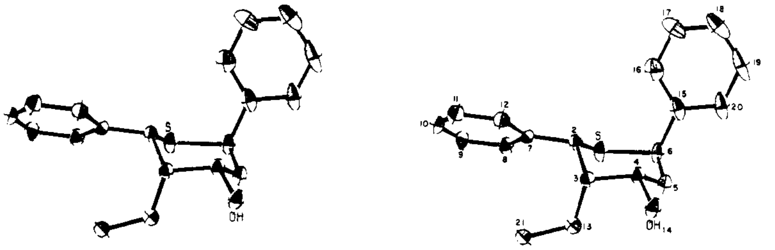

Figure 1. Stereoscopic view of 14.

Rate constants in Tables I and II for the acetylation of the sulfone alcohols **5–8**, **19–21**, **23**, and **25** are larger (by nearly a factor of 2 or greater) than those for sulfide alcohols **1–4**, **9–11**, **13**, and **15**, respectively. It is not unreasonable that the thianol ring of the sulfones[18b] has a larger C–SO_2–C bond angle than is present in the sulfide, and this results in ring flattening. Consequently, nonbonded interactions of the 1,3 type should be relieved, and acetylation rates may increase in sulfones **5–8** (axial OH) compared to those in sulfides **1–4**. In the case of alcohols **9–11**, **13**, and **15** (equatorial OH), a similar enhancement of acetylation rate is detected in the corresponding sulfones **19–21**, **23**, and **25**. Exceptions are sulfone alcohols **22** and **24** which are acetylated at a lower rate than the precursor sulfides **12** and **14**, respectively. Flattening of the rings in **22** and **24** would reduce the dihedral angle RC(3)–C(4)OH (R = CH_3 or C_2H_5 in an axial position), thus imposing a greater steric effect that could retard acetylation To be sure, one axial oxygen atom on the sulfur could also be involved in a syn-axial interaction with the alkyl group at C(3), forcing the latter toward the hydroxyl group and causing it to be more hindered. Some ring distortion may occur too since the ^{1}H NMR spectra (Me_2SO-d_6) for **22** and **24** displayed $W_{1/2}$ values of 11 and 10 Hz, respectively.[18]

Isomeric alcohols **4** (axial OH) and **15** (equatorial OH) were included to assess the influence of the axial CH_3 at C(2). Thianol **15** reacted 4.5 times faster than **4** while the corresponding sulfone **25** was acetylated 4.0 times faster than **8**. Moreover, the rate constant for **15** is smaller than that for **9**, suggesting the axial CH_3 of the former may distort the ring somewhat. Of course, such distortion is probably greater in **4** which is supported by ^{13}C NMR studies.[2]

An interesting observation also is found in the series **16–18**. Introducing the 2,2-dimethyl group resulted in a rate increase for **17** (compared to that for **16**) by a factor of 3. A similar rate-accelerating effect has been reported in the comparison of acetylation of 3,3-dimethylcyclohexanol with that of cyclohexanol.[4b] With the tetramethylated analogue **18**, the rate was 1.7 times *slower* than that for **17**. Steric factors of the type described for systems **15** and **25** could be operating in **18**. Ring distortion or perhaps a boat form is not totally untenable in **18** in solution. It was reasoned that a system such as **26** should possess a geometry that could test the hypothesis as to whether a boat form could exist since it has *three* axial substituents. Thus, an X-ray analysis was performed on a single crystal of **26** which clearly shows it to be a flattened *chair* form, at least in the solid state. Consequently, although there appear to be severe nonbonded interactions, alleviation of the strain requires ring flattening primarily near the sulfur atom and not a conversion to a boat form. The extent to which such heterocyclohexane systems may contain severe internal nonbonded interactions and remain a chair form is under investigation.

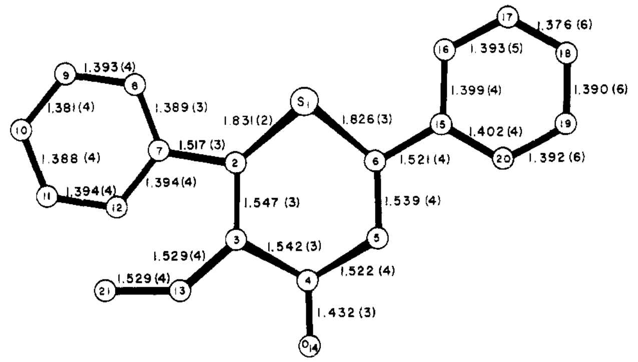

Figure 2. Bond distances in 14.

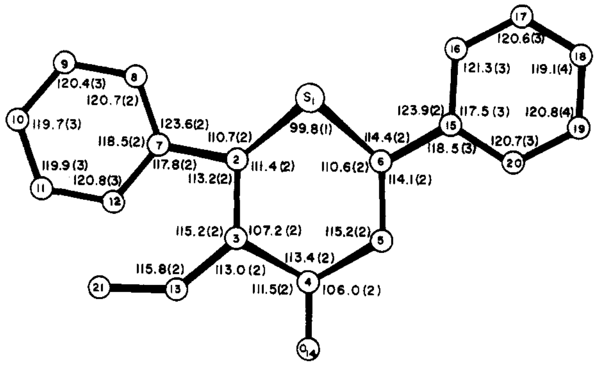

Figure 3. Bond angles in 14.

Single-Crystal Analysis of 14 and 26

A stereoscopic view of *cis*-2,*trans*-6-diphenyl-*cis*-3-ethylthianol-*r*-4-ol (**14**) is shown in Figure 1. The bond distances and angles are shown in Figures 2 and 3, and selected torsion angles are listed in Table V. Figure 1 and the values in Table V show that the phenyl group at C(2) and the hydroxyl group are equatorial while the phenyl group at C(6) and the ethyl group at C(3) are axial.

When the internal torsion angles in the heterocyclic ring of **14** are compared with those found in the corresponding ketone **27**,[1] it is noticed that the angles around C(3)–C(4) and C(4)–C(5) have increased by 13 and 8°, respectively, as may be expected from the change in substitution of C(4). Also, the average value of the internal torsion angle has increased by 4.5°. It is also interesting that the absolute values of the internal torsion angles for C(2)–C(3) and C(5)–C(6) differ by 10° and the ones for S(1)–C(2) and S(1)–C(6) by 8°, while those angles, in pairs, were essentially the same in the corresponding ketone **27**.

From the values in Table V, it can also be concluded that the two phenyl rings are approximately coplanar with their

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(18) (a) Sutton, L. E. "Tables of Interatomic Distances"; The Chemical Society: London, 1965; p 122s. (b) Although an X-ray analysis of thiapyrane 1,1-dioxide could not be found in the literature, several dihydro derivatives gave C–S–C bond angles of 101.9–103.1°; see: Bolema, E.; Visser, G. L.; Vos, A. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1275. Pagani, G. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1184. Ealick, S. E.; van der Helm, D.; Ramalingam, K.; Thyvelikakath, G. X.; Berlin, K. D. *J. Heterocycl. Chem.* **1977**, *14*, 387.

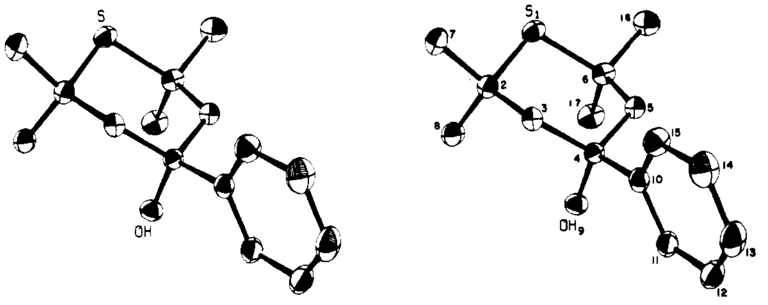

Figure 4. Stereoscopic view of **26**.

Table VI. Torsion Angles (deg) for **26**

S(1)-C(2)-C(3)-C(4)	-55.0	C(6)-S(1)-C(2)-C(7)	162.5
C(2)-C(3)-C(4)-C(5)	56.7	C(6)-S(1)-C(2)-C(8)	-80.6
C(3)-C(4)-C(5)-C(6)	-55.4	C(4)-C(3)-C(2)-C(7)	-168.2
C(4)-C(5)-C(6)-S(1)	52.4	C(4)-C(3)-C(2)-C(8)	71.1
C(5)-C(6)-S(1)-C(2)	-45.1	C(4)-C(5)-C(6)-C(16)	165.7
C(6)-S(1)-C(2)-C(3)	46.4	C(4)-C(5)-C(6)-C(17)	-74.0
C(3)-C(4)-C(10)-C(11)	137.3	C(2)-C(1)-C(6)-C(16)	-161.4
C(3)-C(4)-C(10)-C(15)	-44.7	C(2)-C(1)-C(6)-C(17)	82.0
O(9)-C(4)-C(10)-C(11)	15.4	C(2)-C(3)-C(4)-O(9)	-62.9
O(9)-C(4)-C(10)-C(15)	-166.6	C(2)-C(3)-C(4)-C(10)	176.0
		C(6)-C(5)-C(4)-O(9)	66.4
		C(6)-C(5)-C(4)-C(10)	-176.4

adjacent C–S bonds. The angles are 13.5° for the phenyl ring at C(2) and 7.0° for the one at C(6). In the corresponding ketone, only the phenyl ring at C(6) was approximately coplanar (30°), while the one at C(2) was perpendicular to the S(1)–C(2) bond (90°). In the ketone **27**, the two C–S bond distances showed a significant difference [1.811 (4) and 1.835 (5) Å], while those two distances are the same in the thianol **14** [1.826 (3) and 1.831 (2) Å]. The average is slightly longer than 1.817 (5) Å given by Sutton[18a] as the mean for a paraffinic C–S distance, and 1.816 Å observed for trithiane.[19] The bond distances, in general, seem normal, although there is a significant difference between the C(3)–C(4) and C(4)–C(5) distances which may be caused by the substitution on C(3), while the C(2)–C(7)–C(8) and C(6)–C(15)–C(16) bond angles [123.6 (2) and 123.9 (2)°] are significantly larger than 120° and the C(2)–C(17)–C(12) and C(6)–C(15)–C(20) bond angles of 117.8 (2) and 118.5 (2)°. The latter may possibly be correlated with the approximate coplanarity of the phenyl rings with the adjacent C–S bonds.

An interesting intermolecular hydrogen bonding scheme, in which the oxygen atom serves as both donor and acceptor atom, is observed in the structure **14**. Linked by these hydrogen bonds, the molecules form an infinite right-handed helix around the 3_1 screw axis. The oxygen–oxygen distance is 2.720 (3) Å, the O···H distance is 1.87 (3) Å, and the O–H···O angle is 163 (3)°.

Thianol **14** crystallizes in a polar space group, $P3_1$, but is prepared from a racemic mixture, and crystals of the enantiomer in space group $P3_2$ are equally likely. This selective crystallization of the enantiomers is possibly caused by the hydrogen bonding described above.

A stereoscopic view of thianol **26** is shown in Figure 4. The bond distances and angles are given in Figures 5 and 6. Selected torsion angles are listed in Table VI.

The thiane ring is in a chair conformation with the substituent phenyl ring in an equatorial position and the hydroxyl group in an axial position. The torsion angles, listed in Table VI, show that the thiane ring at the sulfur position is substantially flattened in comparison to representative cyclohexane systems.[20] This flattening is

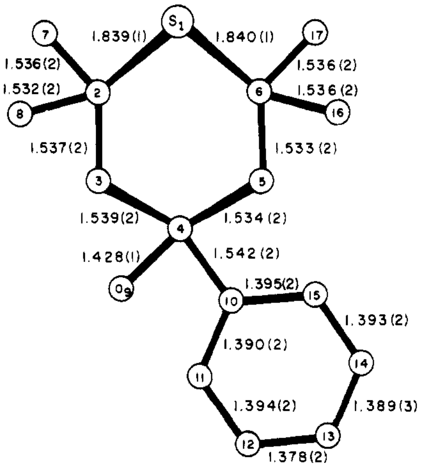

Figure 5. Bond distances in **26**.

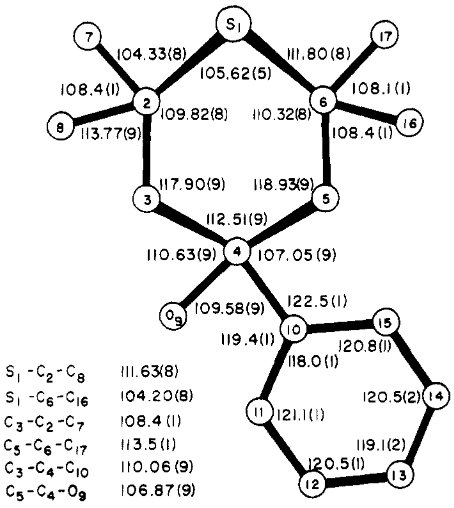

Figure 6. Bond angles in **26**.

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(19) Fleming, J. E.; Lynton, H. *Can. J. Chem.* **1967**, *45*, 353. Valle, G.; Bussetti, V.; Mammi, M.; Carazzolo, G. *Acta Crystallogr., Sect. B* **1969**, *25*, 1432.

significant even when compared to other thiane structures.[1] This flattening is not unexpected if the steric requirements of the nonbonded electrons on sulfur and the four bulky methyl groups at positions C(2) and C(6) are considered. On one side of the ring there are close intramolecular contacts between H(8b) and H(17a) (2.42 Å) and of S(1) with H(8b) (2.91 Å) and H(17c) (2.90 Å). Moreover, on the other side there are close contacts between S(1) with H(7b) (2.87 Å), H(7c) (2.86 Å), H(16a) (2.82 Å), H(16c) (2.86 Å), H(3a) (2.95 Å), and H(5a) (2.98 Å), all smaller than the expected van der Waals distance of 3.00 Å for a sulfur–hydrogen atom contact. The phenyl group is tilted out of the possible mirror plane through S(1), C(4), O(9), and C(10). The angle between this plane and the phenyl group is 16.6°, and the tilt is such that C(15) is closer to C(3) than to C(5), with the shortest contact between H(15) and H(3a) (2.16 Å). This distance cannot be increased without decreasing the already close contact between O(9) and H(11) (2.35 Å), the other phenyl ortho-hydrogen atom. The phenyl group is therefore locked in the conformation which is observed. Other close intramolecular contacts of O(9) are H(8a) (2.48 Å) and H(17a) (2.46 Å). The strain which exists in the molecule can also be seen by the significant increase of the bond angles at C(3) and C(5), when compared to the normal tetrahedral value and by an increase of the bond angle at S(1) compared to that in other thiane ring systems.[1]

The bond distances appear quite normal and are self-consistent within similar bond types. The average of the C–S bond distances (1.840 ± 0.001 Å) is slightly longer than that observed in thianol 14 (average 1.829 Å) and also longer that the 1.817 (5) Å given by Sutton[18] as the mean for a parafinnic C–S distance and the 1.816 Å observed for trithiane.[21] The *gem*-dimethyl substitution at C(2) and C(6) is probably the cause for this small elongation of the C–S bonds.

The hydroxyl group forms one hydrogen bond with S(1) ($x, {}^3/_2 - y, {}^1/_2 + z$). The contact distance between the sulfur and hydrogen atom is 2.48 Å, about 0.5 Å smaller than the sum of van der Waals radii if 1.75 Å is accepted to be the radius of the sulfur atom.[22] The S(1)···O(9) distance is 3.346 Å and the S(1)···O(9) angle is 168 (2)°.

Acknowledgment. This investigation was supported in part by a grant from the National Institutes of Health, the Cancer Institute, Grant No. CA 17562 (to D.v.d.H.). The authors wish to thank Professor D. K. P. Varadarajan, Principal, PSG College of Arts and Science, Coimbatore, India, and Professor G. R. Damodaran, Director, PSG Institutions, Coimbatore, India, for constant encouragement and financial support. Thanks are also due to Professor D. Sethu Rao for providing facilities. N.S. wishes to thank the University Grants Commission, New Delhi, India, for the award of a Fellowship. K.D.B. also gratefully acknowledges partial funding from the National Science Foundation for departmental grants for the purchase of the XL-100(15) NMR spectrometer (GP 17641) and the TT-100 PFT accessory (CHE 76-05571). K.D.B. thanks the College of Arts and Sciences Office of Research for partial support in the form of salary. We (K.D.B.) also gratefully acknowledge partial support by the National Institutes of Health through a grant from the National Cancer Institute, Grant No. CA 22770.

Registry No. 1, 18456-46-7; **2**, 68296-31-1; **3**, 68296-37-7; **4**, 68226-25-5; **5**, 32428-23-2; **6**, 68296-48-0; **7**, 68296-49-1; **8**, 72121-27-8; **9**, 18456-47-8; **10**, 18456-50-3; **11**, 68226-14-2; **12**, 68296-39-9; **13**, 68226-23-3; **14**, 68296-40-2; **15**, 68226-24-4; **16**, 29683-23-6; **17**, 68600-05-5; **18**, 20931-54-8; **19**, 32510-65-9; **20**, 32428-18-5; **21**, 68226-69-7; **22**, 68296-52-6; **23**, 68226-70-0; **24**, 68296-53-7; **25**, 72121-28-9; **26**, 20931-56-0; 2,2-dimethyl-4-thianone, 2323-13-9; 2,2,6,6-tetramethyl-4-thianone, 22842-41-7.

Supplementary Material Available: Anisotropic thermal parameters, hydrogen positional and thermal parameters, and a listing of observed and calculated structure factor amplitudes (for 14 and 26) (25 pages). Ordering information is given on any current masthead page.

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(20) Geise, H. J.; Buys, H. R.; Mijlhoff, F. C. *J. Mol. Struct.* **1971**, *9*, 447.

(21) (a) Valle, G.; Busetti, V.; Mammi, M.; Carazzolo, G. *Acta Crystallogr., Sect. B* **1969**, *25*, 1432. (b) Fleming, J. E.; Lynton, H. *Can. J. Chem.* **1967**, *45*, 353.

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Halogenation of Pentaphenylethane[1]

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Received August 3, 1979

Recently we have attempted to prepare the reportedly "stable" pentaphenylethyl free radical by the method of Schlenk and Mark.[2] Since no useful yield of the radical has been achieved by their method, we turned to the more conventional method of radical generation by metal–halogen abstraction from the corresponding pentaphenylethyl halides. These we had hoped to generate by the photochemical halogenation of the ethane since they are unreported in the literature.

Bachmann[3] reported the treatment of pentaphenylethane with bromine in dibromoethane at 100 °C to give triphenylmethyl bromide (55%). The rational assumption was made that he was observing the bromination of thermal dissociation fragments of the ethane. We have observed by ESR spectroscopy that pentaphenylethane starts to dissociate above 80 °C. However, there is no perceptible dissociation with visible light at room temperature in carbon tetrachloride.

The bromination of pentaphenylethane in carbon tetrachloride was carried out at room temperature with visible light and 1 or 2 equiv of halogen. Since the triphenylmethyl halides and the diphenylmethyl dihalides are sensitive to both heat and moisture, the reaction products were analyzed by carbon-13 NMR. The chemical shifts of the appropriate model compounds are given in Table I. These parameters for pentaphenylethane and related hydrocarbons have been reported previously.[4]

When 2 equiv of bromine was used, only the carbon-13 absorptions of triphenylmethyl bromide and diphenylmethyl dibromide were found in the product. Peak intensities indicated these to be in equal amounts. Since the dibromide could arise from the prior formation and bromination of benzhydryl bromide, a similar experiment was carried out with 1 equiv of bromine. The results in this instance showed about one-half of the starting ethane remaining and only the two halides noted before as

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[1] Presented in part at the EUCHEM Conference on Organic Free Radicals, Cirencester, England, September, 1979.

[2] W. Schlenk and H. Mark, *Ber.* **55**, 2285 (1922).

[3] W. E. Bachmann, *J. Am. Chem. Soc.*, **55**, 3005 (1933).

[4] T. W. Proulx and W. B. Smith, *J. Magn. Reson.*, **23**, 477 (1976).