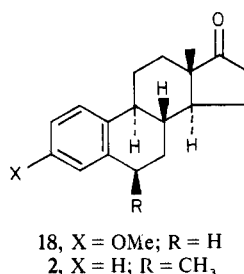
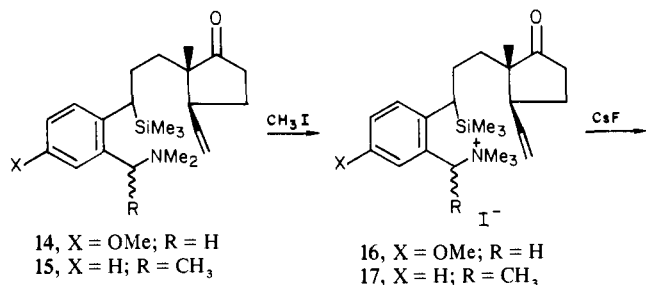


generated by the present method, since their precursors are readily accessible from *o*-tolualdehyde.⁵

In a parallel line of experiments, cyclopentanone moiety **13** was prepared in an almost stereoisomerically pure form, starting from 2-methyl-2-cyclopentenone (**12**) by modification⁸ of the reported method.^{1c,d,f}

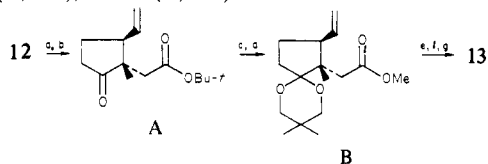
The assembly of the bromide **13** with **3** was carried out by adding **13** to the benzylic carbanion **5** at -75°C to room temperature, which had been generated in situ from **3**, according to the procedure described above. In the assembly of the bromide **13** with **4**, HMPA was added to the carbanion **6**, generated in situ prior to the alkylation. Deketalization of the coupling products **7** and **8** afforded the crucial precursors **14** and **15**¹⁰ as stereoisomeric mixtures [**14**, 2:1;¹¹ **15**, 1:2 (the former is less polar)] in 94% and 95% yields, respectively, after preparative TLC [**14**: TLC on silica gel, R_f 0.60 (6:4 AcOEt-C₆H₆); **15**: TLC on silica gel, R_f 0.59 and 0.38 (6:4 AcOEt-C₆H₆)].

The final intramolecular cyclization of **14** and **15** via the corresponding *o*-quinodimethanes was exemplified with the estrone synthesis. To an acetonitrile solution (20 mL) of a diastereo-



isomeric mixture of **16**, which had been prepared by quaternization of **14** (1.1 mmol) with CH₃I at 0°C , was added a suspension of

(8) The bromide **13**⁹ was prepared stereoselectively in 47% overall yield from 2-methyl-2-cyclopentenone **12** via the keto ester A (>96% stereochemical purity) as shown. **13**: [bp 115–117 $^{\circ}\text{C}$ (0.3 mmHg); mp 53–54 $^{\circ}\text{C}$, recrystallization from hexane]; IR (KBr disk) 1642, 1105, 921 cm^{-1} ; ¹H NMR (CCl₄ with Me₄Si) δ 0.73 (s, 3 H), 0.82 (s, 3 H), 1.19 (s, 3 H), 1.4–2.7 (m, 7 H), 3.0–3.9 (m, 6 H), 4.7–5.9 (m, 3 H).



(9) All attempts to prepare the ethylene glycol ketal corresponding to the bromide **13** from its precursor tosylate and alcohol by conventional methods provided the desired bromide in low yields with several products.

(10) **14**: IR (neat) 1738, 1639, 1246, 862, 838 cm^{-1} ; ¹H NMR (CD₃CN with Me₄Si as an external reference) δ -0.25 (s, 9 H), 0.52 and 0.55 (s, 3 H), 1.1–2.6 (m, 10 H), 2.02 (s, 6 H), 3.08 (s, 2 H), 3.50 (s, 3 H), 4.5–5.0 (m, 2 H), 5.1–5.9 (m, 1 H), 6.3–6.8 (m, 3 H). **15**: IR (neat) (two stereoisomers show almost same spectrum) 1734, 1634, 1242, 856, 831 cm^{-1} ; ¹H NMR (CD₃CN with Me₄Si as an external reference) (less polar isomer) δ -0.26 (s, 9 H), 0.50 (s, 3 H), 0.96 (d, 3 H), 1.2–2.6 (m, 10 H), 1.85 (s, 6 H), 3.20 (q, 1 H), 4.5–4.9 (m, 2 H), 5.0–5.8 (m, 1 H), 6.6–7.2 (m, 4 H); (polar isomer) δ -0.24 (s, 9 H), 0.56 (s, 3 H), 1.07 (d, 3 H), 0.9–2.7 (m, 10 H), 1.99 (s, 6 H), 3.44 (q, 1 H), 4.4–5.0 (m, 2 H), 5.1–5.8 (m, 1 H), 6.6–7.3 (m, 4 H).

(11) The ratio of the stereoisomers was determined by NMR spectrum.

CsF (2.2 mmol) in 10 mL of acetonitrile at once at reflux; the mixture was heated for 1.5 h. The reaction mixture was evaporated in vacuo, triturated with CH₂Cl₂, and filtered to remove the insoluble materials. The filtrate was evaporated and chromatographed on silica gel with chloroform solvent (TLC, R_f 0.45) to afford estrone methyl ether (**18**)¹² in 86% yield based on **14**, which was identified by comparison of its spectral data with those of the authentic sample. The similar treatment of **15** gave rise to 6 β -methylstra-1,3,5(10)-trien-17-one (**2**)¹⁴ in 95% yield. It was identified by comparison of the spectral data with those of the authentic sample, which was independently prepared via hydrogenation on Pd/C of 6-methylstra-1,3,5(10),6-tetraen-17-ol, starting with estradiol 17-monoacetate.^{15,16}

The simplicity and versatility of the present methodology for the generation of *o*-quinodimethane intermediate have been demonstrated by the stereoselective syntheses of estrone and 6 β -methylstra-1,3,5(10)-trien-17-one. Furthermore, the generation of *o*-quinodimethanes with appropriate substituents on the aromatic nucleus and the α and α' carbons is expected in our methodology, which makes derivatization of steroidal skeleton possible.¹⁷ Further extensions of the methodology are now in progress in our laboratory.

Acknowledgment. We are grateful to Shin-etsu Chemical Industry Co., Ltd., for the generous gift of trimethylchlorosilane. We also thank Teikoku Horm. Manufacturing Company for providing estradiol 17-monoacetate, which was used to prepare the authentic sample of 6 β -methylstra-1,3,5(10)-trien-17-one.

(12) Estrone methyl ether thus obtained contained ca. 7–8% of C(9) epimer, but recrystallization from AcOEt afforded pure estrone methyl ether, mp 183.5–185 $^{\circ}\text{C}$ (lit.¹³ 183.2–184 $^{\circ}\text{C}$).

(13) Johnson, W. S.; Banerjee, D. K.; Schneider, W. P.; Gutsche, C. D.; Shelberg, W. E.; Chinn, L. J. *J. Am. Chem. Soc.* **1952**, *74*, 2832.

(14) **2**: mp 89.5–91.5 $^{\circ}\text{C}$, recrystallization from AcOEt; IR (neat) 1738, 758 cm^{-1} ; ¹H NMR (CDCl₃ with Me₄Si) δ 0.84 (s, 3 H), 1.25 (d, 3 H), 1.1–3.2 (m, 17 H), 6.9–7.3 (m, 4 H). ¹³C NMR (CDCl₃ with Me₄Si) δ 13.60, 21.32, 24.29, 25.15, 31.35, 31.71, 33.06, 33.55, 35.48, 44.29, 47.75, 50.13, 124.62, 125.65 (2 C), 128.44, 139.27, 141.52, 220.05.

(15) Japanese Patent Publication 4071, 1963; Teikoku Horm. Manufacturing Company.

(16) (a) Douglas, G. H.; Buzby, G. C., Jr.; Walk, C. R.; Smith, H. *Tetrahedron* **1966**, *22*, 1019. (b) Velarde, E.; Iriarte, J.; Ringold, H. J.; Djerassi, C. *J. Org. Chem.* **1959**, *24*, 311.

(17) We have been informed through a private communication from Professor P. Magnus of The Ohio State University that he has developed a synthetic route to 11 α -hydroxyestrone [*J. Am. Chem. Soc.* **1980**, *102*, 6885] on the basis of our methodology for generation of *o*-quinodimethane intermediates.

Directional Preferences of Nonbonded Atomic Contacts with Divalent Sulfur in Terms of Its Orbital Orientations. 2. S...S Interactions and Nonspherical Shape of Sulfur in Crystals

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Our earlier studies¹ of nonbonded atomic contacts with divalent sulfur in crystals revealed that electrophiles tend to approach sulfur roughly 20° from the perpendicular to the plane through atoms Y–S–Z, whereas nucleophiles tend to approach approximately along the extension of one of the covalent bonds to S, indicating

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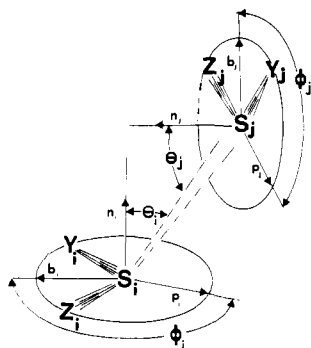


Figure 1. The approach of S_j relative to the plane of $Y_i-S_i-Z_i$ and S_i relative to that of $Y_j-S_j-Z_j$. The polar angles θ_i, θ_j measured so that $0^\circ \leq \theta \leq 90^\circ$ and azimuthal angles ϕ_i, ϕ_j ($0 \leq \phi \leq 80^\circ$) 180° are spherical polar coordinates specifying the direction of the vector $S_i \cdots S_j$ with respect to the planes $Y_i-S_i-Z_i$ and $Y_j-S_j-Z_j$. Vectors n_i, n_j are normal to the sulfide planes, b_i, b_j bisect angles $\alpha_i(Y_i-S_i-Z_i)$ and $\alpha_j(Y_j-S_j-Z_j)$, and p_i, p_j show the direction of $S_i \cdots S_j$ projected onto the sulfide planes.

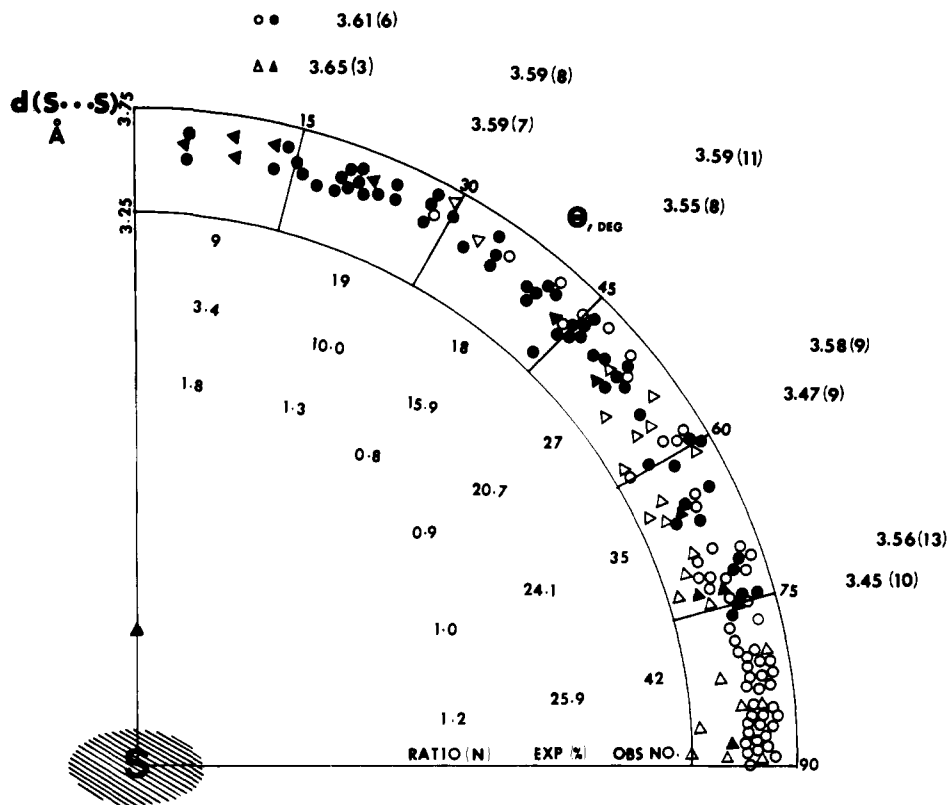


Figure 2. Polar graphs of $d(S \cdots S)$ vs θ . Of the two values of θ for each $S_i \cdots S_j$ contact, the lower one is denoted as θ_i (filled circles) and the higher one as θ_j (open circles). Triangles define type III contacts ($\theta_i = \theta_j$); open triangles have $\phi_i \approx \phi_j$ (within 5°) and closed triangles have $\phi_i \neq \phi_j$. The number of observed and expected contacts in each angular range of 15° and the normalized value of their ratio are given on the inner edge of the arcs. Deviation from unity for the ratio represents deviation from random distribution. Overlapping symbols are slightly displaced for clarity. The mean values of the $S \cdots S$ distances for type III (Δ, \blacktriangle) and type I-II (\circ, \bullet) contacts are shown along the outer edge of the arcs. These values are calculated for 30° ranges in θ and are marked at the middle of each range.

the preferred directions of electrophilic and nucleophilic attack on divalent sulfur. We have now extended these studies to include $S \cdots S$ interactions in crystals, which show that a majority of these interactions may also be regarded as the incipient formation of an attractive electrophile-nucleophile pairing. If one sulfur (S_1) in this pair approaches the sulfide plane of the other sulfur (S_2) along specific directions corresponding to an electrophile, the direction of approach of S_2 relative to the sulfide plane of S_1 is also specific and complementary and corresponds to a nucleophile.

A sulfur atom S_i , not covalently bonded to a particular S_j , was considered to make a "nonbonded contact" if the $S_i \cdots S_j$ distance was not greater than 3.7 Å, which is twice the traditional² van der Waals radius of sulfur. We searched for such nonbonded contacts in crystal structures, using the Cambridge crystallographic

data base and related programs for automatic retrieval of such contacts.³ Of the 18 648 structures in the data base (up to 1978), 2784 contained divalent sulfur (bonded to two ligands, neither one being H), and 57 of these structures contained 151 nonbonded $S \cdots S$ intermolecular contacts. Each $S_i \cdots S_j$ contact is associated with two sets of angles (θ_i, ϕ_i) and (θ_j, ϕ_j), corresponding to the approach S_j relative to the plane of $Y_i-S_i-Z_i$ and S_i relative to that of $Y_j-S_j-Z_j$, respectively (Figure 1). The two sets of values of θ, ϕ for each contact were calculated automatically by using a computer program. Of the two values of θ for each contact, the lower one is denoted as θ_i and the other as θ_j ; θ_i and θ_j are plotted in Figures 2 and 3. As Figures 2 and 3 imply, a majority of θ_i and θ_j values (filled and open circles, respectively) fall into two classes, corresponding to type I for θ_i 's (electrophile) and type II for θ_j 's (nucleophile). The ratio of the expected to observed number of contacts⁴ for a given range in θ was calculated (Figure 2). It shows that there is a preference for θ to be $<30^\circ$ (type I) or $>75^\circ$ (type II). Figure 3 shows that type II contacts tend to lie along the extension of a sulfur bond. Figure 4, which illustrates the correlation of θ_i vs. θ_j for each of the contacts, shows

a preference for values around $\theta_i \approx 30^\circ$ and $\theta_j \approx 75^\circ$ for type I-II contacts. Thus, the two sets of θ, ϕ values for each contact reveal a complementarity: if one sulfur, S_j , is regarded as an

(2) Pauling, L. "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press: Ithaca, NY, 1960; p 260.

(3) MurrayRust, P.; Motherwell, W. D. S. *Acta Crystallogr., Sect. B* **1978**, *B34*, 2518-2526. Kennard, O.; Watson, D. G.; Allen, F. H.; Motherwell, W. D. S.; Town, W. G.; Rodgers, J. *Chem. Br.* **1975**, *11*, 213-216.

(4) Assuming that the vectors $S_i \cdots S_j$ have a purely random relation to each other, the number of contacts occurring in the angular range θ and $\theta + d\theta$ is proportional to $\sin \theta d\theta$. The ratio of the observed to expected number of contacts for each angular range of 15° was calculated by counting the observed contacts in each grid (Figure 2) and normalizing this count to the number of the expected contacts in each range.

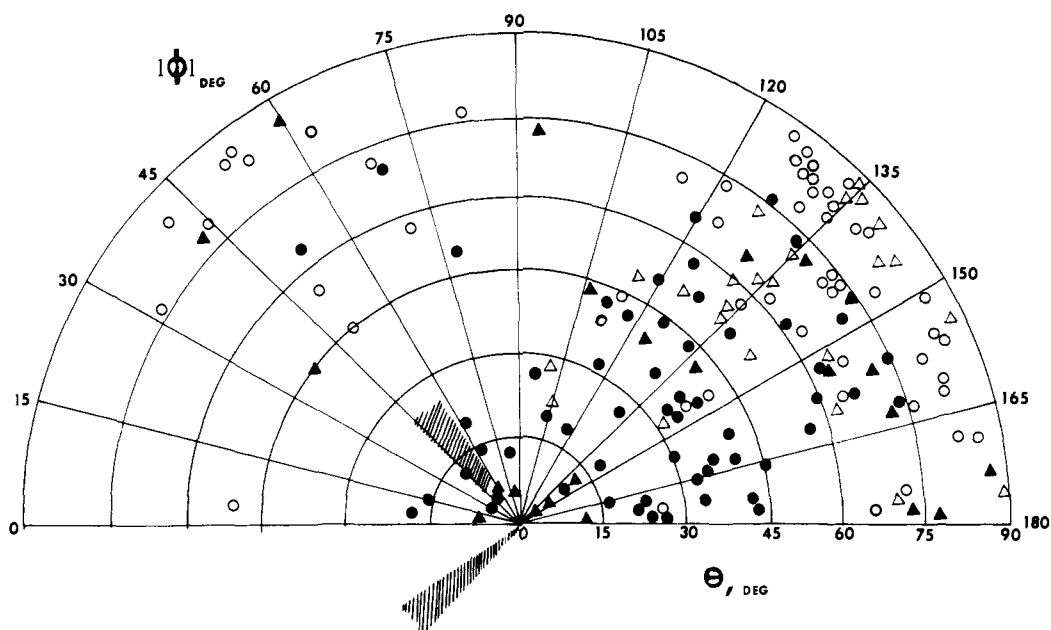


Figure 3. Polar graph of θ vs. $|\phi|$, the absolute value of ϕ , indicates spatial distribution of $S\cdots S_j$ contacts. No distinction is made here between contacts above or below the sulfide planes or between S-Y and S-Z. Shaded areas represent the sulfide plane in Figure 2 and the S-Y and S-Z bonds in Figure 3.

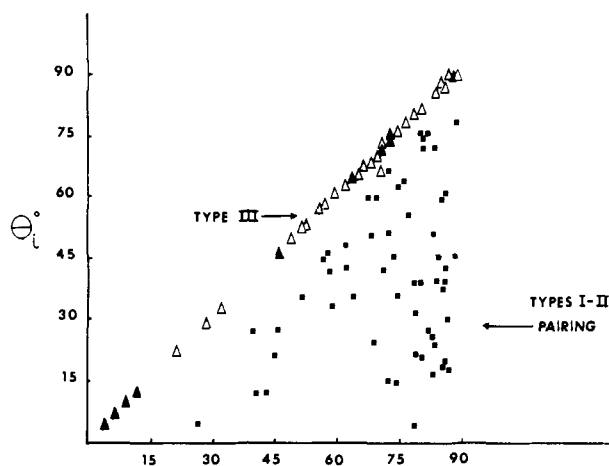


Figure 4. Shows correlation of θ_i vs. θ_j for each of the contacts. The squares show type I-II contacts.

electrophile (filled circles) in terms of its θ_i , ϕ_i values which define its approach to the plane $Y_i-S_i-Z_i$, the θ_j , ϕ_j values for the approach of the other sulfur, S_j , to the $Y_j-S_j-Z_j$ plane correspond to a nucleophile (open circles).

Some contacts (36), denoted by triangles, do not follow the above pattern and form a third group (type III) by themselves; for most of these contacts, $\theta_i = \theta_j$ due to a crystallographic center of symmetry. For the others, $\theta_i \sim \theta_j$ even without any such crystallographic symmetry requirement. These contacts are further subdivided into two classes, those with $\phi_i \sim \phi_j$ (within 5°) (open triangles, type IIIa) and those with $\phi_i \neq \phi_j$ (filled triangles, type IIIb). All type III contacts, in general, are shorter than type I and type II contacts,⁵ especially for $\theta > 45^\circ$, indicating nonspherical effective shapes⁶⁻⁸ for sulfur (see Figure 3). Type IIIa contacts may be interpreted as a nucleophilic attack of one sulfur on another; since both the sulfurs approach each other in

plane, there is no electrophile-nucleophile pairing.

The "frontier-orbital" model^{1,9} provides a convenient frame for discussing the directional preferences of the nonbonded atomic contacts with divalent sulfur. The majority of the $S\cdots S$ contacts correspond to electrophile-nucleophile (type I-type II) pairing; their mutual approach directions indicate¹ interaction of the highest occupied molecular orbital (HOMO), which is essentially a sulfur lone-pair orbital extending nearly perpendicular to the Y-S-Z plane, with the lowest unoccupied molecular orbital (LUMO), which is a $\sigma^*(S-Y)$ or $\sigma^*(S-Z)$ orbital. For type IIIa contacts, there is no such electrophile-nucleophile pairing and no HOMO-LUMO interaction; one sulfur approaches the other along the $\sigma^*(S-Y)$ or $\sigma^*(S-Z)$ of the other (see, however, ref 7).

These results indicate that there are preferred and complementary directions of electrophilic and nucleophilic attack on one divalent sulfur by another divalent sulfur in the incipient stages of chemical reactions, and these regularities display features of orbital distribution around sulfur. It is quite remarkable that these regularities due to orbital interactions are evident in the environment around sulfur in crystals and are the basis of some of the strongest intermolecular forces in these crystals.

Acknowledgment. We thank the National Institutes of Health (Grant CA 23704) for financial support.

(5) Type III contacts clearly show an anisotropic shape for sulfur atoms in crystals. The difference of the means of type III contacts at $\theta = 15^\circ$ and $\theta = 75^\circ$ was tested for significance using Student's *t* distribution. The mean contact distances at $\theta = 15^\circ$ and 75° are different at the 0.005 significance level. Similarly, the mean $S\cdots S$ contact distances for type III and type I-II contacts at $\theta = 75^\circ$ but not at $\theta = 15^\circ$ are significantly different at a level of 0.005.

(6) Rosenfield, R. E. Jr.; Parthasarathy R. *J. Am. Chem. Soc.* **1974**, *96*, 1925-1930.

(7) Boyd, D. B. *J. Phys. Chem.* **1978**, *82*, 1407-1416.

(8) Nyburg, S. C. *Acta Crystallogr. Sect. A* **1979**, *A35*, 641-645.

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