groups and is equal to 1.43 $D$. Using a value[14,15] of 2.8 $D$ for the semipolar P–O bond acting from P to the unattached oxygen, one obtains on adding up vectorially the three different vertical components, a value of 3.03 $D$ for the molecule.

Diethyl sulfite was assumed to have a pyramidal structure by analogy to thionyl chloride.[16] The mean moment due to the free rotation of the two ethoxy groups was calculated by Eqn. 1 to be 1.42 $D$. A value[13] of 1.0 $D$, based on electronegativities, was used for the S–O single link moment and a value[15] of 3.0 $D$ was used for the semipolar S–O bond. A value[16] of 1.45 for the S–O bond distance was assumed for evaluation of other desired data in the pyramid. Following a procedure similar in principle to the one used in the triethyl phosphate calculation, one calculates the value 3.08 $D$ for the molecule.

(14) Lister and Sutton, *Trans. Faraday Soc.*, **35**, 495 (1939). These authors quote this value from unpublished work of J. S. Hunter and argue in its favor because of similarity to the C–O and S–O bonds.

(15) Smyth, Lewis, Grossman and Jennings, THIS JOURNAL, **62**, 1223 (1940). These authors assign a value of 3.5 $D$ to the P–O semi-polar bond. This value would lead to a calculated moment of 3.73 $D$ for the molecule.

(16) Palmer, THIS JOURNAL, **60**, 2360 (1938).

Reference to Table II will show that the agreement between experiment and theory, assuming free rotation, is as good as can be reasonably expected, considering the assumptions made. Reference to atomic models indicates the possibility of a large amount of rotation before steric hindrance becomes important. In the case of ethyl orthocarbonate, steric hindrance is much more important than in the case of tetraethyl silicate and thus the moments of these compounds will differ from one another regardless of apparent similarity in structure.

## Summary

1. The dipole moments of diethyl sulfite, triethyl phosphate and tetraethyl silicate were determined in benzene and were found to be 2.96, 3.07 and 1.70 $D$, respectively.

2. Vectorial derivations of equations assuming free rotation of groups in a molecule are given.

3. The measured moments are in reasonably good agreement with those calculated assuming free rotation.

COLLEGE PARK, MARYLAND      RECEIVED JULY 29, 1948

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# Cleavage of the Carbon–Sulfur Bond. The Action of Acid Catalysts, Especially Aluminum Bromide, on Benzyl Phenyl Sulfide

BY DONALD P. HARNISH[1] AND D. S. TARBELL

In spite of the increasing importance of sulfur compounds in organic chemistry and in biological processes, there is little definite information available about many fundamental aspects of the chemistry of the carbon–sulfur bond. A survey of the literature dealing with cleavage of the carbon–sulfur bond in sulfides, which was carried out in connection with some projected syntheses, disclosed a number of qualitative observations,[2] indicating that the carbon–sulfur bond is cleaved by acidic reagents much more slowly than the corresponding carbon–oxygen bond, but no systematic quantitative information was found.[3]

The present paper reports a quantitative study of the cleavage of the carbon–sulfur bond in benzyl phenyl sulfide (BPS) by acidic substances,

(1) Beaunit Mills Fellow, 1947–1948; present address, Department of Chemistry, Columbia University, New York, N. Y.

(2) Auwers and Arndt, *Ber.*, **42**, 537 (1909); Arndt, Loewe and Ozansoy, *ibid.*, **72**, 1860 (1939); Stevens and Gustus, THIS JOURNAL, **55**, 378 (1933).

(3) The usefulness of the reductive cleavage of S-benzyl groups by sodium and liquid ammonia (Sifferd and du Vigneaud, *J. Biol. Chem.*, **108**, 757 (1935), and later papers) and of the Raney nickel desulfuration reaction (Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943)) has been abundantly demonstrated. The cleavage of sulfides by chlorine is described by Zincke and Rose, *Ann.*, **406**, 127 (1914); Lee and Dougherty, *J. Org. Chem.*, **5**, 81 (1940), and Baker, Dodson and Riegel, THIS JOURNAL, **68**, 2636 (1946), among others.

principally aluminum bromide, according to the equation

$$C_6H_5SCH_2C_6H_5 \xrightarrow[\text{2. } H_2O]{\text{1. } AlBr_3} C_6H_5SH + C_6H_5CH_2Br$$
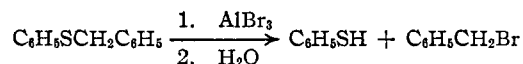
Numerous preliminary experiments, some of which are given in Table I, showed that aqueous halogen acids did not produce any thiophenol from BPS, although complete decomposition sometimes occurred. This behavior is in striking contrast to the facile cleavage of analogous oxygen ethers. Glacial acetic acid containing hydrogen bromide (about 30%) was studied in detail as a cleavage agent[4]; it was found that under optimum conditions about 15% of free thiophenol was formed, and about an equal amount of phenyl thiolacetate ($C_6H_5SCOCH_3$) formed by the reaction of acetic acid with thiophenol. The evidence all indicated that a maximum of 30–35% of thiophenol, free and esterified, could be formed by cleavage of BPS with acetic acid–hydrogen bromide. Analysis of a reaction mixture obtained by heating 1.0 g. of BPS with 4 cc. of acetic acid–hydrogen bromide at 100° for twenty-four hours gave 14.2% thiophenol, 17.8% phenyl thiolacetate and 76.2%

(4) Cf. Pinck and Hilbert, *ibid.*, **68**, 751 (1946).

BPS, a total of 108.2%.[4a] Longer heating or higher temperatures did not increase the amount of thiophenol. Other cleavage agents are tabulated in Table I.

TABLE I

CLEAVAGE OF BPS BY VARIOUS REAGENTS

| Reagent | Solvent | Temp., °C. | Time, hr. | $C_6H_5SH$, % | $C_6H_5$-SCOR, % |
|---|---|---|---|---|---|
| HBr | $H_2O$ | 200 | 6 | ..[a] | |
| HI | $H_2O$ | 170 | 3 | ..[a] | .. |
| HBr | HOAc | 50 | 24 | 2.7 | ..[b] |
| HBr | HOAc | 100 | 24 | 10.5 | ..[b] |
| HBr | HOAc | 150 | 24 | 14.9 | ..[b] |
| HBr | HOAc | 100 | 48 | 9.1 | ..[b] |
| HBr | HOAc | 100 | 168 | 11.5 | ..[b] |
| $CH_3COCl$ | ... | 100 | 24 | 0.5 | |
| $CH_3COBr$ | ... | 100 | 24 | dec | |
| $CH_3COBr$ | ... | Reflux | 4 | 0.5 | 0.5 |
| $AlCl_3$ | None | 50 | 24 | 21.3 | .. |
| $SnCl_4$ | None | 50 | 11 | 5.6 | .. |
| $AlCl_3$ | $C_6H_5COCl$ | 50 | 11 | 3.8 | 23.0 |
| $ZnCl_2$ | $C_6H_5COCl$ | 50 | 11 | 0.8 | 26.7 |
| $C_6H_5SO_2Cl$ | $C_6H_6$ | 28 | 24 | None | 3–4[c] |
| $C_2H_5MgI$ | $C_6H_6$ + ether | 28 | 24 | 3.0 | .. |
| $POCl_3$ | $C_6H_6$ | 28 | 24 | None | .. |
| $C_6H_5SO_2Cl$ | Petroleum ether (90–100°) | Reflux | 3 | None | 2[c] |

[a] These runs, and several others not reported, were usually accompanied by decomposition and hydrogen sulfide formation. [b] Blank runs showed that there is appreciable esterification of thiophenol to form phenyl thiolacetate under these conditions, and that there is probably an amount of esterified thiophenol about equal to the free thiophenol. [c] As the benzenesulfonate ester.

Aluminum bromide was chosen for extensive quantitative study because of its solubility in organic solvents, and because it gave a clean reaction with BPS with the formation of a high yield of thiophenol. The fact that the reaction quoted above actually occurred with aluminum bromide and BPS was shown by isolation of thiophenol (and its disulfide) in good yield from the cleavage in benzene or chlorobenzene solution, and by isolation of benzyl bromide as dibenzylphenylsulfonium bromide.

The effects of variation in the ratio $r$ (moles aluminum brominde/moles BPS) on the per cent. cleavage showed that slightly over one mole of aluminum bromide was required to cleave one mole of BPS (Table II).[5]

A plot (not given) of the data in Runs A and B (Table II) gave a straight line, which, however, did not go through the origin. The fact that the molar ratio $r$ was not exactly one-to-one indicated that the effective concentration of the aluminum

(4a) The excess over 100% may have been due to the presence of some diphenyl disulfide, which according to the analytical method used, would be equivalent to five moles of BPS.

(5) The fact that the low per cent. cleavage at small values of $r$ was not due to incomplete reaction was shown by three series of runs (not given), which indicated that the reaction was complete within five hours under the conditions used.

TABLE II

EFFECT OF ALUMINUM BROMIDE/BPS RATIO, AND OF OXYGEN ON PER CENT. CLEAVAGE

| | Per cent. cleavage | | | Per cent. cleavage |
|---|---|---|---|---|
| $r$[a] | Run A[b] | Run B[b] | $r$[c] | Run C |
| 0.143 | 2.0 | 4.8 | 0.125 | 3.1 |
| .429 | 21.4 | 24.1 | .250 | 9.7 |
| .858 | 66.0 | 65.4 | .500 | 29.6 |
| 1.000 | 74.2 | 75.8 | .625 | 40.7 |
| 1.286 | 92.1 | 95.2 | 1.250 | 91.0 |
| 1.429 | 98.6 | 97.2 | 1.875 | 93.7 |

[a] $r$ = moles aluminum bromide/moles BPS; the $r$ values in this column apply to Runs A and B. [b] Benzene was the solvent in Run A; chlorobenzene in Run B. Concentrations about 0.025 mole; runs let stand about twenty-three hours at room temperature. [c] Oxygen was bubbled through these solutions; the $r$ values in this column refer to Run C only.

bromide was not equal to the calculated one. The most obvious explanation, that small amounts of water were picked up by the reaction mixtures while they were being made up, was supported by experiments (Table III) showing that added water did decrease the per cent. cleavage.

TABLE III

EFFECT OF ADDED WATER ON PER CENT. CLEAVAGE

| Moles $H_2O$/moles $AlBr_3$[a] | Cleavage,[b] % |
|---|---|
| 0.2 | 84.5 |
| 0.6 | 78.0 |
| 1.0 | 68.5 |
| 2.0 | 48.5 |
| 3.0 | 28.8 |

[a] Calculated on the basis that benzene saturated with water contains $1.17 \times 10^{-4}$ mole of water per cc. of benzene (Herz, Ber., 31, 2669 (1898)). [b] Solutions were about 0.025 molar, using benzene, and were left at room temperature for twenty-four hours.

The decrease in percentage of cleavage was linear with the amount of added water, and it required several moles of water to deactivate one mole of aluminum bromide. It is perhaps significant that aluminum bromide forms a hexahydrate[6]; experiments with BPS and finely powdered aluminum bromide hexahydrate in benzene and chlorobenzene showed that it was ineffective in cleaving BPS at room temperature. Samples of the hexahydrate were heated in boiling benzene and chlorobenzene for some time, liberating an acidic gas, but the cooled mixtures showed no ability to cleave BPS. Apparently the hexahydrate cannot be dehydrated to anhydrous aluminum bromide.[6]

To determine the effect of oxygen on the cleavage of BPS by aluminum bromide,[7] dry oxygen was bubbled for several minutes through a benzene solution of aluminum bromide, which was then

(6) Mellor, "Treatise," Vol. V, p. 324–325.

(7) Effects of oxygen, water, halogen acids and olefins on the catalytic activity of aluminum bromide in isomerizing paraffins have been observed by Leighton and Heldman, THIS JOURNAL, 65, 2276 (1943); Pines and Wackher, ibid., 68, 595, 599 (1946); Oblad and Gorin, Ind. Eng. Chem., 38, 822 (1946).

added in various amounts to benzene solutions of BPS. The data in Table II show that the oxygen had no appreciable affect on the per cent. cleavage. If oxygen or water do have a strong catalytic affect on the cleavage, under our conditions there was apparently always more than the threshold amount of these agents present. However, considering the one to one ratio of the reactants and the apparent mechanism of the cleavage reaction, it would not be expected to be similar to the paraffin isomerization in sensitivity to traces of extraneous substances.

Frequently in runs where $r$ was less than unity, a white precipitate was observed, which appeared to be dibenzylphenylsulfonium bromide. Since the cleavage of BPS requires an equimolar amount of aluminum bromide, the formation of the sulfonium salt at low ratios of aluminum bromide to BPS is easy to understand; unchanged BPS could be alkylated by benzyl bromide or by some material which acted as a source of benzyl bromide.[8] Much time was spent on analytical

$$C_6H_5SCH_2C_6H_5 + C_6H_5CH_2Br \xrightarrow{AlBr_3} C_6H_5S^+(CH_2C_6H_5)_2Br$$
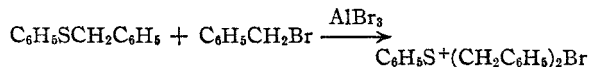
methods in an attempt to show that the amount of sulfonium compound increased as $r$ decreased, but the results were not conclusive.

A kinetic study of the cleavage by aluminum bromide was carried out to obtain information about the mechanism of the reaction, and to determine the activation energy. It was found that the rate was first order in BPS, and independent of the aluminum bromide concentration as long

### TABLE IV

FIRST ORDER CHARACTER OF REACTION BETWEEN BPS AND ALUMINUM BROMIDE[a]

Part A

| Time, min. | Cleavage, % | First order constant,[b] $k \times 10^{-3}$ min.$^{-1}$ | Second order constant,[c] liters/mole/min. |
|---|---|---|---|
| 60 | 24.4 | 4.66 | 0.090 |
| 120 | 50.9 | 5.92 | .124 |
| 180 | 67.5 | 6.24 | .140 |
| 240 | 79.5 | 6.60 | .157 |
| 300 | 85.5 | 6.43 | .159 |
| 420 | 93.1 | 6.36 | .168 |

[a] [BPS]$_{initial}$ = 0.0250 mole/l.; $r$ = 2.2; solvent, chlorobenzene; temperature, 27.5°. [b] From equation $k$ = $(2.303/t)$ log $a/(a - x)$ where $a$ = [BPS]$_{initial}$. [c] From equation $k$ = $(2.303/t(a - b))$ log $[b(a - x)/a(b - x)]$.

Part B[a]

| Time, hr. | Cleavage, % | | |
|---|---|---|---|
| | $r$ = 1.95 | $r$ = 3.40 | $r$ = 4.86 |
| 0.5 | 9.5 | 8.4 | 10.0 |
| 3.0 | 47.5 | 47.3 | 47.9 |
| 4.0 | 60.3 | 62.4 | 60.8 |
| 6.0 | 77.5 | 79.2 | 78.8 |

[a] Conditions: $4.99 \times 10^{-3}$ mole BPS and $4.99 \times 10^{-3}$ $r$ mole aluminum bromide in 20.0 cc. of chlorobenzene at room temperature.

(8) Cf. Lee and Dougherty, J. Org. Chem., 4, 48 (1939).

as the latter was in excess.[9] This is evident from Part A of Table IV, in which the first order constants are seen to be much more satisfactory than the constants calculated assuming a bimolecular process, involving BPS and aluminum bromide, each to the first power. Conclusive evidence is given by the data in Part B, showing that the rate of cleavage was unchanged when $r$ was varied from 1.95 to 4.86. Larger changes in $r$ were found to change the rate slightly, probably due to the effect of changes in the medium.

Further evidence for the first-order dependence of the rate was given by two runs in which the concentration of BPS was 0.0166 and 0.0250 molar ($r$ being 10.2 in both cases); the time for 50% reaction was nearly the same in both cases, as it should be. Other runs (using chlorobenzene as solvent) showed that the rate was unaffected by the addition of benzyl bromide; this experiment was tried because there was some evidence, from runs in benzene, of an induction period. There was no sign of this in the chlorobenzene runs, however.

The data in Table V were obtained for a calculation of the activation energy. From the plot of

### TABLE V

RATES OF CLEAVAGE AT DIFFERENT TEMPERATURES[a]

| Temp., °C. | $r$ | $k$[b] |
|---|---|---|
| 0.0 | 1.50 | 0.000123 |
| 25.5 | 4.00 | .00378 |
| 27.5 | 2.20 | .00680 |
| 32.5 | 1.81 | .01645 |
| 35.5 | 1.72 | .0262 |

[a] Conditions: solvent, chlorobenzene; [BPS]$_{initial}$ = 0.0250 molar in all runs. [b] Constants for first order dependence on [BPS], obtained graphically.

log $k$ vs. $1/T$, as shown in Fig. 1, the activation energy for the cleavage of BPS by aluminum bromide in chlorobenzene was found to be 25.8 kcal./mole.
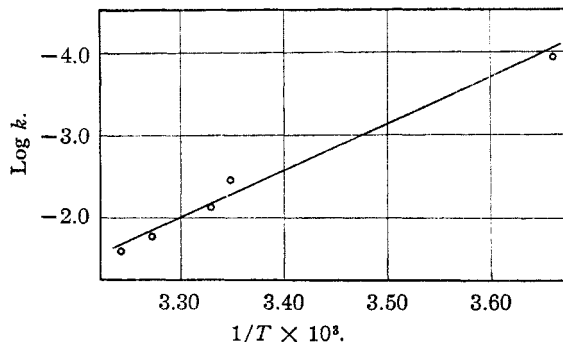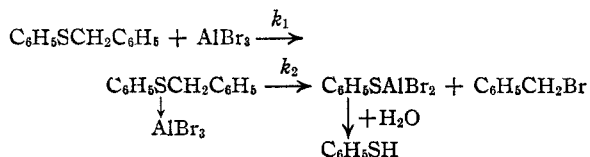


Fig. 1.—Plot of the logarithm of the first order reaction rate constants vs. the reciprocal of the temperature for the reaction of benzyl phenyl sulfide with aluminum bromide in chlorobenzene solution.

(9) It would have been desirable to have measured the rate using $r$ less than unity; this situation, however, was the one which favored sulfonium salt formation by a secondary reaction, as shown above, and it was considered unlikely to yield useful data.

**Mechanism of the Reaction.**—The observed facts agree with the following mechanism for the cleavage. The cleavage of the complex is consid-

$$C_6H_5SCH_2C_6H_5 + AlBr_3 \xrightarrow{k_1}$$

$$\begin{array}{ccc} C_6H_5SCH_2C_6H_5 & \xrightarrow{k_2} & C_6H_5SAlBr_2 + C_6H_5CH_2Br \\ \downarrow & & \downarrow +H_2O \\ AlBr_3 & & C_6H_5SH \end{array}$$

ered to be the rate-determining step (*i. e.*, $k_1 \gg k_2$), which accounts for the first-order rate in BPS and the independence of the rate of aluminum bromide.[10] The idea that the rate-determining step is the break-up of the complex is in agreement with numerous qualitative observations on the cleavage of oxygen ethers by aluminum bromide.[11]

Indirect evidence for the necessity of coördination between BPS and the aluminum bromide was found in the effects of oxygenated solvents on the cleavage. In diethyl ether, nitrobenzene, nitromethane, nitroethane or absolute alcohol as solvent, no cleavage of BPS by aluminum bromide occurred. The effect of water has already been mentioned. This indicates that oxygenated solvents coördinate preferentially with the aluminum bromide, to prevent it from coördinating and cleaving BPS. These results were extended by studying the effect of small amounts of alcohol, glacial acetic acid, diethyl ether and ethyl acetate
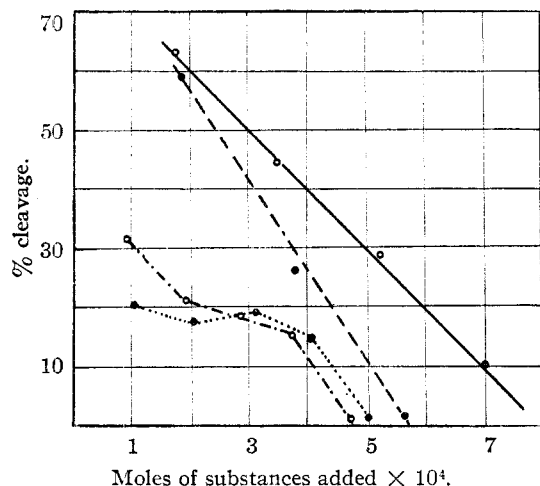


Moles of substances added × 10⁴.

Fig. 2.—Plot of per cent. cleavage *vs.* moles of substances added for the cleavage of benzyl phenyl sulfide (0.000499 mole) with aluminum bromide (0.00055 mole) in benzene solution; substances added: O—O, glacial acetic acid; ●— — — —●, 95% ethyl alcohol; O——·——·—O, ethyl ether; ●·······●, ethyl acetate.

(10) The aluminum bromide is considered to function as aluminum bromide, although it is well known that it is dimeric in organic solvents (*e. g.*, Kohler, *Am. Chem. J.*, **24**, 389 (1900); Ulich, *Z. physik. Chem.*, Bodenstein Festband, 1931, p. 427. The form AlBr₃ is presumably in mobile equilibrium with Al₂Br₆.

(11) Menzel, *Ber.*, **75**, 1060 (1942); Pfeiffer and Haack, *Ann.*, **460**, 156 (1928); Pfeiffer and Loewe, *J. prakt. Chem.*, **147**, 293 (1936).

on the cleavage in benzene. The results, shown in Fig. 2, indicated that the presence of any of these compounds in molar amount equal to the aluminum bromide prevented cleavage almost completely, and that 20% of this amount of oxygenated compound cut the per cent. of cleavage very sharply.

The accelerating effect of acetyl bromide on the cleavage of BPS by aluminum bromide in benzene[12] is shown in Table VI. The runs were carried out by adding either moist ether or acetyl bromide to solutions of BPS and aluminum bromide in benzene, which had stood for the stated time, allowing the mixture to set for thirty seconds, then adding water and analyzing as usual.

TABLE VI

EFFECT OF ACETYL BROMIDE ON CLEAVAGE[a]

| Time, hr. | Cleavage, % | | |
|---|---|---|---|
| | Run A[b] | | Run B[c] |
| 0.25 | 10.9 | 1.3 | 58.8 |
| 0.75 | 36.3 | 1.3 | 69.5 |
| 1.5 | 73.5 | 1.0 | 67.1 |
| 3.0 | 94.1 | 1.4 | 82.3 |

[a] Conditions: Aliquots of a solution of 7.70 g. of aluminum bromide and 2.50 g. of BPS in 250 cc. of benzene. Temperature, 32°. [b] Treated with moist ether. [c] Treated with acetyl bromide; the first column indicates the thiophenol titrated, and the second the thiol ester titrated.

**Experimental**

**Preparation of Materials.**—BPS was made by the literature method[13]; aluminum bromide was obtained from Westvaco Chlorine Products Corporation, through the kindness of Mr. F. von Bergen. Thiophenol and 30% hydrogen bromide in glacial acetic acid were Eastman products. Chlorobenzene was generously supplied by the Dow Chemical Company.

**Reactions with Halogen Acids.**—For these experiments 1.00 g. of benzyl phenyl sulfide was placed in the reaction vessel, and 5–10 cc. of the acid was added. Sealed tube reactions were carried out in an oven thermostatically controlled to ±3° at 100°. At the end of the reaction time, the reaction mixture was cooled and diluted with water. The mixture was then extracted with ether and the ether extracts washed with water and dilute sodium bicarbonate solution. The ether layer was then analyzed by the titration methods described in the previous paper.[14]

**Reactions with Aluminum Bromide.**—For these experiments, two stock solutions were prepared, one of the sulfide and one of the aluminum bromide. The two solutions were brought to the desired temperature. Then, by means of the glass pump system described in the preceding paper,[14] measured amounts of each stock solution were transferred to glass stoppered flasks. The flasks were then placed into a bath, thermostatically controlled to ±0.5°. Zero reaction time was taken as the time the two aliquots of the stock solutions were mixed. At the completion of the reaction time, the contents of the flask were hydrolyzed immediately with water. Ether extracts of the hydrolyzed mixture were taken as before, and analyzed by the titration methods.[14]

**Isolation of Dibenzylphenylsulfonium Bromide.**—In reactions wherein the ratio of aluminum bromide to benzyl phenyl sulfide was less than unity, an oil could be detected at the bottom of the flask. On hydrolysis, this oil gave a white solid. The solid was collected by filtration,

(12) This type of reaction is being investigated further by Mr. H. F. Wilson of this Laboratory.

(13) Shriner, Struck and Jorison, THIS JOURNAL, **52**, 2060 (1930).

(14) Harnish and Tarbell, *Anal. Chem.*, in press.

washed with anhydrous ether, and dried *in vacuo*. The material obtained melted at 82–84° with decomposition. Several other sulfonium compounds were found to decompose at the same point. The compound was very unstable and could not be recrystallized; hence, analyses were unsatisfactory. The compound burned without leaving a residue, and therefore did not contain aluminum.

*Anal.* Calcd. for $C_{20}H_{19}SBr$: C, 64.69; H, 5.18. Found: C, 63.80; H, 5.50.

Isolation of Thiophenol.—Ten grams of the sulfide was allowed to react at room temperature for forty-one hours with a solution of 15.33 g. of aluminum bromide in benzene (80 cc.). The ether extracts of the hydrolyzed reaction mixture were diluted to 100 cc. with ether. One cc. of the resulting solution was titrated for mercaptan, and indicated 91% cleavage of the sulfide had occurred. The remaining ether extracts were dried and distilled *in vacuo*. A total of 4.1 cc. of thiophenol (b. p. 89–95° (51 mm.)) was obtained, corresponding to 80.3% cleavage of the benzyl phenyl sulfide.

Isolation of Diphenyl Disulfide.—The washed ether extracts of the reaction mixture were extracted with 10% aqueous sodium hydroxide solution. The alkaline extracts were acidified and extracted with ether. Alcoholic iodine was added to the ether solution until the iodine was no longer decolorized. Evaporation of the ether and recrystallization of the residue from alcohol gave white crystals, m. p. 59–60°, which did not depress the melting point of a known sample of diphenyl disulfide.

## Summary

1.   Under optimum conditions, benzyl phenyl sulfide (BPS) can be cleaved to thiophenol to the extent of about 30% by hydrogen bromide–glacial acetic acid. Aqueous halogen acids are virtually ineffective in this reaction.

2.   Aluminum bromide in benzene or chlorobenzene cleaves BPS rapidly and smoothly; the reaction requires one mole of bromide per mole BPS. It is retarded by water or oxygen-containing solvents.

3.   The rate is first order in BPS, and practically independent of the aluminum bromide concentration if this is in excess. The reaction is not affected by molecular oxygen.

The mechanism is believed to involve a rapid coördination of aluminum bromide with BPS, followed by a slow cleavage of the complex.

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# The Hexahydro Derivatives of meso-Hexestrol[1]

BY A. L. WILDS AND WILLIAM B. MCCORMACK[2]

In attempts to rationalize the high activity of the synthetic estrogens diethylstilbestrol (I) and hexestrol (II), the superficial resemblance of these compounds (as written in the accompanying formulas) to the natural hormone estradiol (III) has frequently been pointed out. While several objections can be raised to this hypothesis, nevertheless, in harmony with it, the more active of the two possible stereoisomers in each case (*trans* I and *meso* II) is that which corresponds more closely to the probable configuration of estradiol. For some time we have been interested in preparing for estrogenic testing the hexahydro derivatives of *meso*-hexestrol (IV) in which one ring is reduced, since these resemble the phenolic alcohol estradiol (III) even more closely than does the diphenol hexestrol (II).

Preliminary attempts in 1940–1941[3] to hydrogenate one ring of *meso*-hexestrol or its monobenzoate did not appear promising, leading to mixtures containing fully hydrogenated as well as unchanged material. A second approach (by A. L. W.) through a synthesis involving the Friedel–Crafts condensation with anisole of α-(4-acetoxycyclohexyl)-butyric acid,[4] obtained by hydrogenation of the readily available ethyl α-(4-hydroxyphenyl)-butyrate,[5,6] was carried as far as the crystalline carbinol (V) when the work had to be discontinued in 1942.
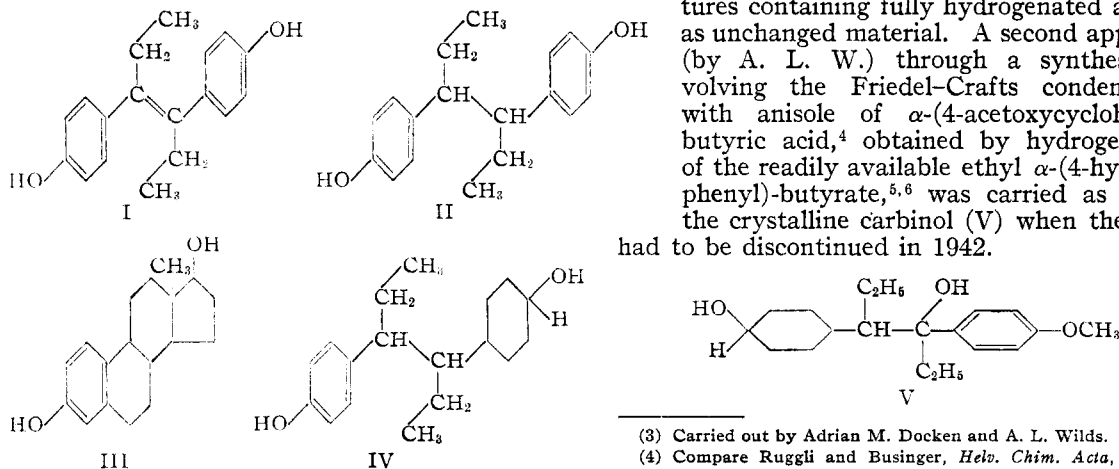




(1)   For a preliminary communication see Wilds and McCormack, THIS JOURNAL, 70, 884 (1948).

(2)   Wisconsin Alumni Research Foundation Research Assistant, 1945–46; American Chemical Society Predoctoral Fellow, 1946–1948.

(3)   Carried out by Adrian M. Docken and A. L. Wilds.

(4)   Compare Ruggli and Businger, *Helv. Chim. Acta*, 24, 346, 1112 (1941).

(5)   Wilds and Biggerstaff, THIS JOURNAL, 67, 789 (1945).

(6)   Recently the reduction of this compound was carried out independently by Ungnade and Morriss [THIS JOURNAL, 70, 1898 (1948)].