

TABLE I
 PREPARATION AND PROPERTIES OF ACRYLIC ESTERS

Acrylate	Yield, %		Boiling point, °C.		n_D^{20}	d_4^{20}	Mol. refraction		Carbon, %		Hydrogen, %		Cl, Br or N, %		Brittle pt. of polymer, °C.
	Calcd.	Found	Calcd.	Found			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
2-Bromoethyl	74	53	5		1.4770	1.4774	34.24	34.24	33.6	33.5	3.9	4.0	44.6	44.2	-12 ^a
3-Bromopropyl	70	96	18		1.4786	1.4106	38.86	38.78	37.3	37.1	4.7	4.6	41.4	41.1	
2,3-Dibromopropyl	94	105	6		1.5220	1.7803	46.63	46.60	26.5	26.2	3.0	2.9	58.7	57.9	
1-Bromo-2-propyl	80	69	10		1.4712	1.3885	38.86	38.86					41.4	41.2	
3-Chloropropyl	95	79	14		1.4522	1.1122	35.96	36.05					23.9	23.7	-14
2,3-Dichloropropyl	94	58	0.5		1.4765	1.2603	40.83	41.00					38.7	38.5	-10
1,3-Dichloro-2-propyl		50	1		1.4725	1.2592	40.83	40.76	39.4	38.9	4.4	4.5	38.7	38.6	5
2,2,2-Trichloroethyl ^b	56	55	1		1.4718	1.3264	45.70	45.90					48.8	48.4	90
2,2,2-Trichloro- <i>t</i> -butyl ^b	83	31	1		1.4657	1.2469	54.57	54.92	39.1	38.6	4.5	4.8	43.3	42.8	75 ^a
2-Cyanoethyl	81	108	12		1.4409	1.0619	30.84	31.10	57.6	57.1	5.6	6.0	11.2	11.6	
2-Methyl-2-nitro-1-propyl ^c	94	95	5		1.4470	1.1162	41.33	41.45	48.5	48.3	6.4	6.6	8.1	7.9	32
2-Nitrobutyl ^c	73	63	1		1.4480	1.1172	41.33	41.49	48.5	48.0	6.4	6.8	8.1	7.7	
2-Phenylethyl	87	104	5		1.5111	1.0369	50.59	50.93	75.0	74.8	6.9	6.9			-2

^a Polymer appeared to be of low molecular weight. ^b Methacrylate. ^c These compounds were reported by Marans and Zelinski, *THIS JOURNAL*, **72**, 2125 (1950), after the present work had been completed. The properties reported for the monomeric esters are in substantial agreement with ours. Our 2-methyl-2-nitro-1-propyl polyacrylate was hard and brittle at room temperature, whereas Marans and Zelinski reported theirs to be softer than methyl polyacrylate (which has a brittle point of about 0°).

raised slightly by halogen substituents, moderately by the phenyl group, and considerably by the nitro group.

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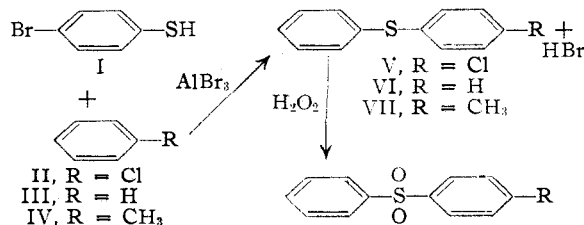
RECEIVED MAY 29, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Action of Aluminum Bromide on Some Halogenated Thiophenols and Benzyl Phenyl Sulfides

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During a continuation of some investigations² on the cleavage of benzyl phenyl sulfides by aluminum bromide, it was noted that 4-bromothiophenol (I), in chlorobenzene solution containing a molar equivalent of aluminum bromide, showed a rapid disappearance of the thiol group, as determined by iodine titration. The product, which was formed in high yield, was found to be 4-chlorodiphenyl sulfide (V), and was characterized by oxidation to the crystalline sulfone, which was shown to be identical with an authentic sample.³



(1) du Pont Fellow, 1949-1950.

(2) Harnish and Tarbell, *THIS JOURNAL*, **70**, 4123 (1948).

(3) Beckurts and Otto, *Ber.*, **11**, 2066 (1878). The position of the chlorine atom is shown by other syntheses not involving the Friedel-Crafts reaction (Meyer, *Ann.*, **433**, 337, 345 (1923)).

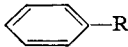
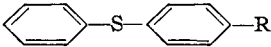
It was found that a similar reaction occurred in benzene and in toluene solution, leading to good yields of diphenyl sulfide (VI) and 4-methyl-diphenyl sulfide (VII), respectively. 2-Bromothiophenol behaved similarly in chlorobenzene and benzene solution, but 3-bromothiophenol did not give any evidence of reaction even under conditions much more drastic than those required with 2- and 4-bromothiophenol. 4-Chlorothiophenol did not react under these conditions. The detailed data are in Table I.

The reaction of the 4-bromo compound (I) with chlorobenzene was investigated in most detail. It was found that, when the molar ratio r of aluminum bromide to thiophenol was one or greater, the rate of the reaction was first-order in the thiophenol, as shown in Table II; an increase in r from 1 to 1.5 increased the rate about fourfold, but a further increase in the ratio caused a slight decrease in rate.

Hydrogen bromide was shown to be a product of the reaction by an experiment in which the reaction mixture was swept out with dry nitrogen; the evolved gases were passed into standard base, and about 75% of the theoretical amount

TABLE I

REACTION OF BROMOTHIOPHENOLS WITH AROMATIC COMPOUNDS

ArSH + 		AlBr ₃			
Ar	R	Temp., °C.	Time, min.	Unreacted thiophenol, % ^a	Yield of sulfone, % ^b
4-BrC ₆ H ₄	Cl	25.2°	6	69.5	65
			12	45.3	
			21	24.5	
	H	25.2 ^d	30	94.7	61
			105	53.7	
			180	17.2	
CH ₃	33.1 ^e		10	88.4	55
			32	50.9	
			69	11.8	
			69	11.8	
2-BrC ₆ H ₄	Cl	0 ^f	3	86.7	40
			15	61.2	
			36	38.4	
	H	29 ^g	3	79.7	60
			12	35.2	
			22	21.5	
3-BrC ₆ H ₄	Cl	57.4	1500	79 ^h	
4-IC ₆ H ₄	Cl	0 ⁱ	3	51.7	55 ^j
			6	14.5	
			6	15.7	
			6	15.7	
4-ClC ₆ H ₄	Cl	75.7 ^m	90	71.0 ^k	25 ^l
			420	34.0	
			420	34.0	

^a Determined by iodine titration. ^b Yield of crystalline material obtained from a preparative run under similar conditions. ^c $r = (\text{AlBr}_3 / \text{bromothiophenol}) = 2.0$; $a = (\text{bromothiophenol}) \text{ initial} = 0.0198 \text{ m./l.}$ For run at 0°, see Table II. ^d $r = 1.8$; $a = 0.0189 \text{ m./l.}$ ^e $r = 2.3$; $a = 0.187 \text{ m./l.}$ ^f $r = 1.55$; $a = 0.0192 \text{ m./l.}$ ^g $r = 1.5$; $a = 0.0253 \text{ m./l.}$ ^h Hydrogen sulfide evolved, indicating decomposition. ⁱ $r = 2.1$; $a = 0.00695 \text{ m./l.}$ ^j Yield of diphenyl disulfide isolated. ^k $r = 1.65$; $a = 0.0128 \text{ m./l.}$ ^l Yield of diphenyl sulfone isolated. ^m $r = 2.3$; $a = 0.0328 \text{ m./l.}$

TABLE II

KINETICS OF REACTION BETWEEN 4-BROMOTHIOPHENOL AND CHLOROBENZENE^a AT 0°

Time, min.	Unreacted thiophenol, %	$k \times 10^2$ min. ^{-1b}
12	85.9	1.27
20	80.0	1.12
40	63.6	1.14
60	49.7	1.17
85	37.0	1.17

^a $r = (\text{AlBr}_3) / (4\text{-bromothiophenol}) = 1.44$; initial (4-bromothiophenol) = 0.0135 m./l. ^b First-order constant, from equation $k = 2.3/t \log a/(a-x)$, where $a = (4\text{-bromothiophenol}) \text{ initial}$.

TABLE III

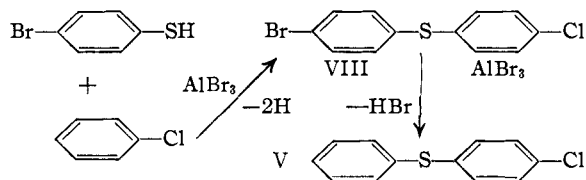
EFFECT OF CHANGE IN RATIO r ON RATE^a

r	0.48	0.94	1.44	2.5	7.0
$k \times 10^2, \text{min.}^{-1b}$	0	2.32	11.7	8.7	8.7

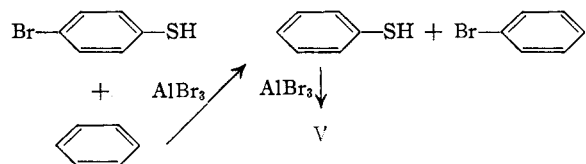
^a In chlorobenzene at 0°. a varied from 0.0134–0.0138 m./l. ^b First order constant.

of acid (bromide ion was shown to be present by qualitative test) was obtained.

The following experiments showed that the loss of hydrogen bromide was simultaneous with the attack of the thiol group on chlorobenzene. 4-Bromo-4'-chlorodiphenyl sulfide (VIII) was prepared, and was recovered unchanged in 65% yield after standing in chlorobenzene for fifteen minutes with aluminum bromide; under these conditions the reaction of 4-bromothiophenol with chlorobenzene to form V was complete. This rules out the one course for the reaction



The other possibility given below was ruled out by showing that thiophenol reacted too slowly with bromobenzene to account for the reaction of 4-bromothiophenol in benzene.⁴ It has been shown that thiophenol does not react with chlorobenzene under these conditions.²



In spite of the fact that chlorobenzene reacted faster than benzene with 4-bromothiophenol, diphenyl sulfide was the only product obtained from the action of 4-bromothiophenol on an equimolar mixture of benzene and chlorobenzene. It was shown that 4-chlorodiphenyl sulfide was stable under these reaction conditions, and therefore the benzene must be attacked preferentially. The effect of solvent composition on the rate of reaction of 4-bromothiophenol is shown in Table IV; the faster rate in chlorobenzene may be due to the higher dielectric constant of this solvent. A contributing factor may be that aluminum

TABLE IV

REACTION OF 4-BROMOTHIOPHENOL IN BENZENE-CHLOROBENZENE MIXTURES AT 25°

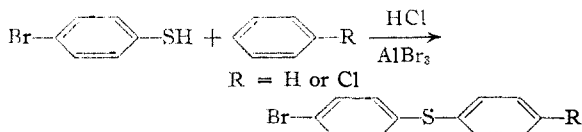
Solvent	Time, min.	Unreacted thiophenol, %
Benzene	180	17.2
Benzene-5 mole % chlorobenzene	160	22.0
1:1 Molar ratio	90	11.2
Chlorobenzene-5 mole % benzene	21	23.8
Chlorobenzene	21	24.5

(4) Thiophenol forms diphenyl sulfide and thianthrene when treated with aluminum chloride in ligroin (Deuss, *Rec. trav. chim.*, **27**, 145 (1908)). Under the same conditions, 2- and 4-methylthiocresol split out hydrogen sulfide to form the diaryl sulfides (Deuss, *ibid.*, **28**, 136 (1909)). The activity of aluminum halides in catalyzing hydrogen transfer is well known.

bromide forms complexes with benzene and toluene to a greater extent than with chlorobenzene, and hence its effective concentration is lowered more in these solvents. Brown and Brady⁵ have found that the solubility of hydrogen chloride in aromatic compounds increases with increasing nucleophilic character of the nucleus, in the order chlorobenzene-benzene-toluene-mesitylene. In the present work, aluminum bromide was found to form a separate phase when dissolved in triethylbenzene, which was probably a complex.⁶

No solvent was found in which kinetic studies could be carried out using a low concentration of the aromatic compound (chlorobenzene, benzene or toluene); all solvents investigated showed some reaction with the bromothiophenol-aluminum bromide combination, which made them unsuitable for kinetic work.

The reaction of 4-bromothiophenol and aluminum bromide with benzene or chlorobenzene was catalyzed by water, hydrogen bromide and hydrogen chloride; benzene saturated with the latter gave a five-fold increase in rate. The product of this reaction, which was impure and isolated with difficulty, was 4-bromodiphenyl sulfide; 4-bromo-4'-chlorodiphenyl sulfide was obtained from the reaction in chlorobenzene saturated with dry hydrogen chloride.



The behavior of 4-iodothiophenol in benzene and chlorobenzene is indicated in Table I. Several substituted thiophenols (2-thionaphthol, 4-phenylthiophenol, thiosalicylic acid) were found to be decomposed by aluminum bromide, with evolution of hydrogen sulfide,⁷ and 4-nitrothiophenol was precipitated largely unchanged by aluminum bromide in benzene.

The effect of other acidic reagents on 4-bromothiophenol in chlorobenzene was investigated briefly: aluminum chloride caused no reaction, probably due to low solubility, and stannic chloride, boron fluoride etherate or boron fluoride likewise failed to catalyze the reaction.

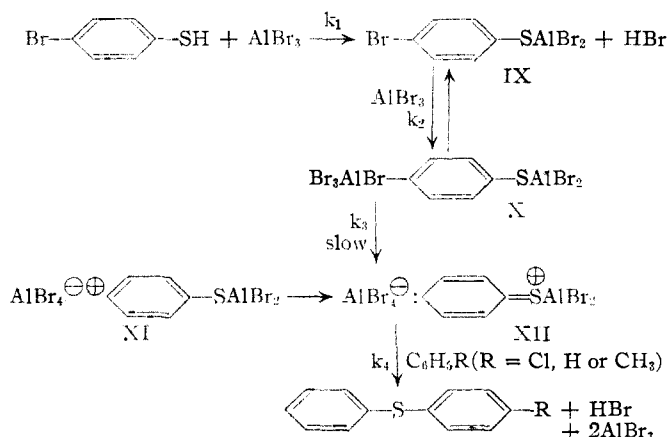
Mechanism.—A consideration of the facts described above suggests the following as the most reasonable mechanism for the reaction.

The formation of IX would be rapid, and the subsequent coordination with aluminum bromide would probably be an equilibrium reaction. The rate-determining step would be the breaking of the carbon-bromine bond to form XI, which would be stabilized by resonance among several

(5) Brown and Brady, *THIS JOURNAL*, **71**, 3573 (1949).

(6) Norris and Rubinstein, *THIS JOURNAL*, **61**, 1163 (1939).

(7) Harnish and Tarbell, unpublished.



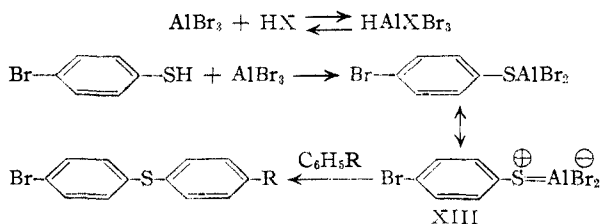
forms, such as XII; this would then react rapidly with the aromatic solvent with the sulfur as an electrophilic group to form the diaryl sulfide. Reactions 3 and 4 may be a concerted process, in which the solvent molecule approaches the sulfur while the bromine is being removed from the 4-position.

The suggested scheme would make the reaction first-order in the thiophenol, as long as the aluminum bromide was present in excess; if it was a concerted process, the concentration of the solvent should enter the rate expression to the first power, but, as stated above, experimental conditions for testing this were not found.

The rate of formation of XI and XII should be increased by an increase in the dielectric constant; hence reaction was faster in chlorobenzene ($E = 5.9$) than in benzene or toluene ($E = 2.3$ and 2.4). The electrophilic reagent XII would attack the more nucleophilic solvent, and thus reacts preferentially with benzene in benzene-chlorobenzene mixtures. With 3-bromothiophenol there could be no stabilization of the carbonium ion XI by contributions from forms like XII; this explains its failure to react.

The carbon-chloride bond requires more energy to be broken, and hence step 3 does not occur; thus 4-chlorothiophenol does not give the same reaction as the bromo compound. The carbon-iodine bond in 4-iodothiophenol is very easily broken, but gives only 25% yield of diphenyl sulfide in benzene; in chlorobenzene, iodine is apparently liberated, which oxidizes the thiophenol to diphenyl disulfide.

The effect of hydrogen chloride (see above) on the reaction may be explained by the scheme



Enough of the aluminum bromide is tied up by the halogen acid so a second molecule does not coordinate with the 4-bromine atom and remove it.

The observation that 4-chloro- and 3-bromothiophenols were stable to aluminum bromide in chlorobenzene at room temperature allowed the determination of the rate of cleavage of the corresponding benzyl sulfides. The results, which are summarized in Table V, were not as accurate as those obtained with benzyl phenyl sulfide,² and there was evidence of an initial rapid reaction of the 3-bromo compound for the first few per cent. of the reaction. The rate then settled down to first-order kinetics.

From the data at 0° in Table V, it appears that electron-attracting groups speed up the cleavage of aryl benzyl sulfides by aluminum bromide, the order being as follows: 3-bromophenyl > 4-chlorophenyl > phenyl. This is consistent with the mechanism previously suggested.²

TABLE V

RATE OF CLEAVAGE OF $\text{ArSCH}_2\text{C}_6\text{H}_5$ BY ALUMINUM BROMIDE IN CHLOROBENZENE

Ar	Temp., °C.	k , ^a m./l.	$10^3 \times k$, min. ^{-1b}
C_6H_5	0	0.0250	0.123 ^c
4- ClC_6H_4	0	.0242	0.998
	24.6	.0336	27.2
	26.5	.0242	38.4
3- BrC_6H_4	0	.178 ^d	4.86

^a Symbols have same meaning as in previous tables; $r = 1.5$. ^b Constants for first-order dependency (on sulfide). ^c Taken from ref. 2. ^d $r = 3.5$.

The data also allow calculation of the ρ values for the reaction from Hammett's equation⁸

$$\log k - \log k_0 = \rho\sigma$$

Using the σ values given⁸ for 4-chloro (0.227) and 3-bromo (0.391), and taking k_0 from the rate of cleavage of benzyl phenyl sulfide, the ρ value from the 4-chlorophenyl rate is +4.05, and from the 3-bromophenyl rate is +4.08.⁹

Experimental¹⁰

4-Bromothiophenol was prepared by reduction of 4-bromobenzenesulfonyl chloride with stannous chloride-hydrogen chloride in glacial acetic acid,^{11a} and melted after recrystallization from ethanol (87% over-all yield) at 74–75°, as reported,^{11a,b}

Several unreported derivatives were prepared:

The acetate was prepared by the action of acetyl chloride in glacial acetic acid, and melted, after recrystallization from hexane, at 51.5–52°.

Anal. Calcd. for $\text{C}_8\text{H}_7\text{BrOS}$: C, 41.57; H, 3.05. Found: C, 41.38; H, 2.90.

(8) Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, Chap. VII.

(9) Schwarzenbach and Rudin, *Helv. Chim. Acta*, **22**, 360 (1939), have shown that the Hammett equation is followed by the dissociation constants for substituted thiophenols.

(10) Analyses by Mrs. O. C. Sauvage; all melting points are corrected.

(11) (a) Amstutz, Fehnel and Woods, *This Journal*, **69**, 1922 (1947); (b) Hubner and Alsborg, *Ann.*, **156**, 327 (1870); (c) Suter and Scrutcheff, *This Journal*, **58**, 54 (1936).

The benzoate was obtained from benzoyl chloride in pyridine, and melted, after crystallization from hexane, at 84–84.5°.

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{BrOS}$: C, 53.25; H, 3.09. Found: C, 53.17; H, 3.07.

Benzhydryl 4-Bromophenyl Sulfide.¹²—To a solution of 30 g. of benzhydryl in 150 cc. of glacial acetic acid was added 60 cc. of concentrated sulfuric acid: the solution was warmed on the steam-bath for fifteen minutes and then poured on ice. The product was crystallized from heptane, yielding 38 g. (67%) of material, m. p. 105–106°. Recrystallization from alcohol gave material of m. p. 106–107°.

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{BrS}$: C, 64.23; H, 4.25. Found: C, 64.01; H, 4.14.

Benzyl 4-bromophenyl sulfide was prepared from the thiophenol by the usual method,¹³ and melted at 64–65° as reported by Taboury,¹⁴ instead of 48°, as reported by Reid.¹⁵

3-Bromothiophenol.¹⁶—*m*-Bromoaniline (51.5 g.) was diazotized at 5°, and the excess nitrous acid destroyed with urea. The diazonium solution was then added over a fifty-minute period to a stirred solution of 70 g. of potassium ethyl xanthate in 90 cc. of water, at 40–50°. The mixture was heated for an additional half hour, then cooled, the red oil which separated was isolated, and the aqueous layer extracted twice with ether. The red oil was added to the ether extracts, the combined extracts were washed with 10% sodium hydroxide and twice with water. The ether solution was dried, the solvent removed, 300 cc. of alcohol was added and the solution heated to boiling. Potassium hydroxide was added slowly, the solution refluxed for seven hours, and then concentrated by distillation. Water was added, the alkaline solution was extracted twice with ether, and then acidified with 6 *N* sulfuric acid. The acid solution was steam distilled, and the product collected from the distillate by ether extraction; the solution was dried, the solvent was removed, and the residue distilled, yielding 28.0 g. (50%) of 3-bromothiophenol with the following properties; b. p. 119–121° (20–22 mm.), n_D^{25} 1.6310.¹⁷

Anal. Calcd. for $\text{C}_6\text{H}_4\text{BrS}$: C, 38.11; H, 2.67; mol. wt., 189.08. Found: C, 38.06; H, 2.53; mol. wt. (iodine titration), 189.1.

3,3'-Dibromodiphenyl disulfide was prepared by oxidizing 3-bromothiophenol with alcoholic iodine. The solution was taken up in ether, washed twice with aqueous alkali, twice with water, the solution dried, and the solvent was removed. The residue was distilled, yielding the disulfide, b. p. 187–190° (0.4 mm.).

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{Br}_2\text{S}_2$: C, 38.32; H, 2.14. Found: C, 38.42; H, 1.98.

Benzyl 3-bromophenyl sulfide was prepared from the thiophenol and benzyl chloride by the usual method,¹³ and melted, after crystallization from pentane, at 40–41°.

Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{BrS}$: C, 55.92; H, 3.97. Found: C, 56.16; H, 3.80.

3'-Bromo-4-nitrodiphenyl sulfide was prepared from 3-bromothiophenol and *p*-nitrochlorobenzene by the usual procedure,¹⁸ and melted, after crystallization from alcohol, at 72.5–73°.

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{BrNO}_2\text{S}$: C, 46.46; H, 2.58. Found: C, 46.76; H, 2.72.

4-Bromo-4'-aminodiphenyl Sulfide.—A solution of 4-bromo-4'-nitrodiphenyl sulfide^{11a} (5.9 g.) in 200 cc. of

(12) Cf. Finzi and Bellavita, *Gazz. chim. ital.*, **62**, 699 (1932).

(13) Shriner, Struck and Jorison, *This Journal*, **52**, 2060 (1930).

(14) Taboury, *Bull. soc. chim.*, [3] **31**, 1183 (1904).

(15) Holt and Reid, *This Journal*, **46**, 2329 (1924).

(16) Cf. "Organic Syntheses," **27**, 81 (1947).

(17) This compound is mentioned by Schwarzenbach and Egli, *Helv. Chim. Acta*, **17**, 1176 (1934), and by Reinboldt, *Ber.*, **59**, 1311 (1926) but no description is given.

(18) Tarbell, Todd, Paulson, Lindstrom and Wystrach, *This Journal*, **70**, 1381 (1948).

benzene was heated to boiling in a 3-necked flask fitted with a dropping funnel, stirrer and condenser, and 50 g. of activated iron filings added.¹⁹ The mixture was stirred and refluxed, while 20 cc. of water was added, over a seven-hour period; after stirring and heating for an additional hour, the iron filings were separated by filtration, and hydrogen chloride was bubbled into the benzene solution. The amine hydrochloride was collected and dissolved in aqueous alcohol, from which the free amine (3.7 g.) was precipitated by the addition of aqueous alkali. The amine, after purification by chromatography on alumina, melted at 75.5–76°.

Anal. Calcd. for $C_{12}H_{10}BrNS$: C, 51.43; H, 3.60. Found: C, 51.71; H, 3.60.

The *N*-acetyl derivative was crystallized from benzene, m. p. 165–165.5°.

Anal. Calcd. for $C_{14}H_{12}BrNOS$: C, 52.18; H, 3.76. Found: C, 52.40; H, 3.79.

4-Bromo-4'-chlorodiphenyl Sulfide (VIII).—This compound was prepared by the bromination of 4-chlorodiphenyl sulfide,²⁰ and also by the following process, in order to establish the position of the bromine conclusively. 4-Bromo-4'-aminodiphenyl sulfide hydrochloride was obtained in finely divided form by dissolving 3.35 g. in hot acetic acid and pouring into 100 cc. of cold water containing 9 cc. of concentrated hydrochloric acid. The solution was diazotized with 1.4 g. of sodium nitrite in 8 cc. of water, and added to a solution of cuprous chloride prepared in the usual way from 7.5 g. of copper sulfate.²¹ After mixing at 0°, the solution was allowed to warm up to room temperature, and heated at 60°. The mixture was then cooled, extracted with benzene, the extract dried and the solvent was removed. The product was dissolved in 1:1 hexane-benzene and purified by chromatography on alumina. Several crystallizations from alcohol yielded 0.70 g. of product, m. p. 106–107°, identical with that obtained by bromination. The reported m. p. is 110°.

2-Bromothiophenol²² was prepared by essentially the above xanthate procedure from 2-bromoaniline in 55% yield; b. p. 117–118° (18 mm.); n_D^{20} 1.6321.

It was characterized by preparation²³ of the solid **2,2'-dibromodiphenyl disulfide** by oxidation with alcoholic iodine; this product melted, after crystallization from alcohol, at 97.5–98°.

Anal. Calcd. for $C_{12}H_8Br_2S_2$: C, 38.31; H, 2.14. Found: C, 38.47; H, 1.86.

Reactions of Thiophenols with Aromatic Solvents.—Chlorobenzene²⁴ was purified by washing with concentrated sulfuric acid, followed by steam distillation; it was then dried over potassium carbonate and distilled, taking the middle fraction. The aluminum bromide²⁵ was distilled before use, and was kept in a tightly stoppered bottle; the aluminum bromide solutions were prepared just before use, because they darkened noticeably after standing for a day. The stock solutions of the thiophenol and aluminum bromide were brought to temperature, and aliquots were transferred to a glass-stoppered flask by the glass pump previously described.²⁶ At the completion of the reaction time the contents of the flask were hydrolyzed by water, and extracted with ether. A few drops of pyridine were added, and the amount of the thiophenol present was determined by iodine titration.²⁶ After determination of the optimum reaction time by titration experiments, a larger run was made to allow isolation of the reaction products. After hydrolysis and extraction with ether, the organic layer was washed

with 10% alkali, then with water. The ether layer was dried, the solvent removed and the residual sulfide oxidized to the sulfone for identification.

Preparation of the Sulfones.—The sulfides were oxidized to the sulfones in acetic acid solution on the steam-bath for several hours by an excess of 30% hydrogen peroxide. The mixture was poured onto ice, the solid was collected and was crystallized from alcohol. The data on the m. p. and the literature references are given in Table VI; each sample was identified by a mixed m. p. with an authentic sample.

TABLE VI

PHYSICAL CONSTANTS OF SULFONES, $ArSO_2Ar'$

A. Prepared by method described in the literature.
B. Prepared by oxidation of the sulfide isolated.

Ar	Ar'	m. p., °C.	m. p., °C.
C_6H_5	C_6H_5	124 ^a	124–125
C_6H_5	4- ClC_6H_4	91–92 ^a	91–92
C_6H_5	4- BrC_6H_4	107–107.5 ^b	104–105
C_6H_5	4- $CH_3C_6H_4$	120–121 ^a	119–120
4- BrC_6H_4	4- ClC_6H_4	156–157 ^b	157–158

^a Beckurts and Otto, *Ber.*, 11, 2066 (1878). ^b Böeseken, *Rec. trav. chim.*, 30, 139 (1911).

Experiments on the Reaction Mechanism.—A solution of aluminum bromide in chlorobenzene was placed in a dry flask fitted with a nitrogen inlet and gas outlet. Nitrogen was bubbled through to sweep out any hydrogen bromide formed by hydrolysis. The gas outlet tube was then connected to a gas washing bottle containing standard sodium hydroxide solution. A solution of 4-bromothiophenol in chlorobenzene was added, and nitrogen was bubbled through for three hours, sweeping any gas evolved over into the alkali solution. At the end of this time, the alkali solution was back titrated with standard acid solution. Based upon 4-bromothiophenol, 0.75 mole of acid was evolved. In a separate experiment, elementary analysis of the alkaline solution indicated bromine was present.

Benzene (20 cc.) and chlorobenzene (23 cc.) were mixed to give an equimolar mixture; to this was added 1.95 g. of aluminum bromide and 0.34 g. of 4-bromothiophenol. After three hours at room temperature, the contents were hydrolyzed and extracted with ether; the ether extract was dried over Drierite and the solvent was removed. The liquid obtained was oxidized to the sulfone. Elementary analysis indicated no halogen was present. After one crystallization from alcohol, the compound melted at 122–123° and showed no depression when mixed with diphenyl sulfone.

A chlorobenzene solution (60 cc.) of aluminum bromide (1.5 g.) and 4-chloro-4'-bromodiphenyl sulfide, m. p. 106–107° (220 mg.) was prepared and allowed to stand in an ice-bath for forty-five minutes. The contents were hydrolyzed and extracted with ether, the ether extracts were dried and after removal of the solvent a solid was obtained. This was dissolved in benzene and passed over a column of activated alumina. After one crystallization from alcohol, 131.7 mg. (60%) was obtained, m. p. 105–106°, which showed no depression when mixed with 4-chloro-4'-bromodiphenyl sulfide.

A solution of 4-chlorodiphenyl sulfide (0.75 g.) in benzene (20 cc.) was added to a solution of 2.8 g. of aluminum bromide in 70 cc. of benzene. After three hours the contents were hydrolyzed, extracted with ether and the ether extracts were combined and dried. The solvent was removed and the liquid obtained oxidized as usual to yield a sulfone m. p. 89–90°. When mixed with 4-chlorodiphenyl sulfone, it melted at 90–92°.

Cleavage of the Benzyl Halophenyl Sulfides.—These rate runs were carried out by the general methods already described.² The treatment of 1.17 g. (4.9 mmol.) of benzyl 4-chlorophenyl sulfide with 1.92 g. (7.2 mmol.) of aluminum bromide in chlorobenzene at room tempera-

(19) Hazlet and Dornfeld, *THIS JOURNAL*, 66, 1781 (1944).

(20) Loth and Michaelis, *Ber.*, 27, 2547 (1894).

(21) "Organic Syntheses," Coll. Vol. I, p. 170.

(22) Van Hove, *Bull. acad. roy. Belg.*, [5] 12, 929 (1926); Schwarzenbach and Egli, *Helv. Chim. Acta*, 17, 1176 (1934).

(23) We are indebted to Mr. G. W. Wick for this experiment.

(24) Generously supplied by the Dow Chemical Company.

(25) Obtained from Westvaco Chlorine Products Corporation through the kindness of Mr. F. VonBergem.

(26) Harnish and Tarbell, *Anal. Chem.*, 21, 968 (1949).

ture resulted in the isolation of 0.56 g. (70%) of 4-chlorothiophenol, m. p. 51.5–53°, and a neutral oil which was similar to that isolated from the cleavage of benzyl phenyl sulfide.

Summary

1. 4-Bromothiophenol has been found to react rapidly with toluene, chlorobenzene and benzene in the presence of aluminum bromide, to form 4-methyl-, 4-chloro- and unsubstituted diphenyl sulfide, respectively, with loss of hydrogen bromide. 2-Bromothiophenol behaves similarly, but

the 3-bromo and the 4-chloro compounds do not give this reaction. Numerous kinetic and other experiments on the reaction are reported, leading to a proposed mechanism.

2. The rate of cleavage of benzyl 4-chlorophenyl and 3-bromophenyl sulfides by aluminum bromide has been measured, and the ρ value (Hammett) for the reaction has been determined.

3. Numerous new compounds incidental to the work have been prepared and characterized.

ROCHESTER, NEW YORK

RECEIVED MAY 20, 1950

[FROM THE DIVISION OF STEROID BIOCHEMISTRY, THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Preparation of Deuterated Steroids¹

BY DAVID K. FUKUSHIMA, SEYMOUR LIEBERMAN AND BERNADETTE PRAETZ

In recent years there has been increasing recognition of the important role steroid hormones play in the function and regulation of various physiological processes. Because of the extraordinary success of the isotope tracing technique in clarifying other biochemical and physiological problems, there is also great interest in the application of this tool to the problems of steroid biochemistry.² With this in mind, two methods for the incorporation of deuterium atoms on C₇ of Δ^5 -unsaturated steroids have been developed. These methods are general and can be applied to a variety of steroid hormones or related compounds. They possess the advantage that the deuterium is introduced in a known and stable position in compounds which still retain the 5,6-double bond and which therefore may readily be converted to α,β -unsaturated 3-ketones. Moreover, another desirable property of the deuterated steroids is that the presence of a carbon-deuterium bond in the steroid molecule can be detected easily by its specific absorption maximum in the infrared at about 2100 cm.⁻¹. This property not only facilitates the isolation of deuterated steroids, but also provides a method for the semiquantitative analysis of the deuterium content of isotopically labeled substances.

The report of Henbest, *et al.*,³ on the preparation

(1) Presented before the 33rd Meeting of the Federation of American Societies for Experimental Biology, Detroit, Michigan, March, 1949; *Fed. Proc.*, **8**, 200 (1949).

(2) A number of isotopically labeled steroids have already been reported: (a) cholestenone and testosterone with C¹⁴ in ring A, Turner, *Science*, **106**, 248 (1948); *THIS JOURNAL*, **69**, 726 (1947); (b) C¹⁴-methyl-labeled methyltestosterone, MacPhillamy and Scholz, *J. Biol. Chem.*, **178**, 37 (1949); (c) C¹⁴-methyl-labeled progesterone, Riegel and Prout, *J. Org. Chem.*, **13**, 933 (1938); MacPhillamy and Scholz, *J. Biol. Chem.*, **178**, 37 (1949); (d) dehydroisoandrosterone with C¹³ in ring D, Hershberg, Schwenk and Stahl, *Arch. Biochemistry*, **19**, 300 (1948); (e) deuterated cholesterol, Bloch and Rittenberg, *J. Biol. Chem.*, **149**, 505 (1943); Anker, *THIS JOURNAL*, **66**, 1752 (1944); (f) progesterone and testosterone with deuterium at C₁₁ and C₁₃, Koehlin, Kritchevsky and Gallagher, *J. Biol. Chem.*, **184**, 393 (1950).

(3) Henbest, Jones, Bide, Peever and Wilkinson, *Nature*, **158**, 169 (1946).

of 7-bromocholesterol acetate by N-bromosuccinimide bromination of cholesterol acetate suggested to us the possibility of employing such Δ^5 -7-bromo-derivatives as intermediates. As illustrated in Fig. 1, the replacement of the halogen of these derivatives (II) with deuterium affords tagged steroids containing the isotope in the stable position on C₇.

The procedure described⁴ for the allylic bromination of cholesterol acetate with N-bromosuccinimide yielded in our hands an uncrystallizable oil⁶ which, after chromatography on magnesium silicate: Celite, afforded 3 β -acetoxy- Δ^5 -cholestene-4 β ,7 α -diol, a compound which will be described in detail in the following paper.⁶ For our deuteration experiments, therefore, we have employed 7-bromocholesterol benzoate which can easily be obtained crystalline.⁷ We have also brominated Δ^5 -androstene-3 β ,17 β -diol 3-acetate-17-benzoate (Ib) with N-bromosuccinimide and obtained a crystalline 7-bromo-derivative (IIb) in 40% yield. The position of the bromo group in IIb was proved by replacing the halogen with hydroxyl on an alumina column and oxidizing the resulting alcohol to the 7-keto derivative, 3 β -acetoxy-17 β -benzoxy- Δ^5 -androstene-7-one (IV). This 7-keto compound was also prepared by the direct chromic acid oxidation of Ib, following the method of Windaus, Lettré and Schenck.⁸

A variety of methods for the reduction of the 7-bromo group of these derivatives was explored. Reduction of 7-bromocholesterol benzoate (IIa) with deuterium was best accomplished by using "deuterized" Raney nickel in ethyl acetate to give 63% of 7-d-cholesterol containing 1.55 atom per cent. excess deuterium. 7-Bromo- Δ^5 -androstene-

(4) British Patent 574,432.

(5) In a more recent publication, the isolation of crystalline 7-bromocholesterol acetate has been reported in detail: Bide, Henbest, Jones, Peever and Wilkinson, *J. Chem. Soc.*, 1783 (1948).

(6) Lieberman and Fukushima, *THIS JOURNAL*, **72**, 5211 (1950).

(7) Bulsman, Stevens and van der Vliet, *Rec. trav. chim.*, **66**, 83 (1947); Bernstein, *et al.*, *J. Org. Chem.*, **14**, 433 (1949).

(8) Windaus, Lettré and Schenck, *Ann.*, **520**, 98 (1935).