Although XV is unstable at room temperature, it can be kept in the refrigerator for several weeks. XV is very soluble in acetone, soluble in alcohol, ethyl acetate and benzene, poorly soluble in ether and insoluble in water and pentane.

The alcohol mother liquor from the crystallization was concentrated, dissolved in ether and extracted with four 30-cc. portions of 3 *M* hydrochloric acid. Ether extraction of the neutralized solution gave 0.51 g. of tan crystals. Crystallization from ethyl acetate afforded 0.45 g. (0.19%) of **α-(4-pyridyl)-cyclohexanone (XVI)**, m.p. 107.0–108.5°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.23; H, 7.53; N, 8.24.

Soluble in the common organic solvents and insoluble in water and pentane, XVI dissolves in 3 *M* hydrochloric acid and 10% aqueous sodium hydroxide.

Oxidation of α-(1-Benzoyl-1,4-dihydro-4-pyridyl)-cyclohexanone (XV) with Iodine.—The reaction mixture obtained by refluxing 46.5 g. (0.165 mole) of XV and 84.0 g. (0.33 mole) of iodine in 600 cc. of benzene for three hours was shaken with 500 cc. of saturated sodium sulfite solution. The sulfite solution was acidified with 125 cc. of 12 *M* hydrochloric acid and used in five portions to extract the benzene solution, following which two more extractions with 75 cc. each of 9 *M* hydrochloric acid were carried out.

A tarry material, filtered from the benzene solution, was triturated with 10% sodium hydroxide solution which was filtered and used to neutralize the combined acid extracts. The ether extracts (five 200-cc. portions) of the neutralized solution were washed with water, dried, treated with Norit and concentrated by distillation ultimately *in vacuo*. The residual oil (15.6 g.) solidified and was fractionally crystallized from 95% alcohol to give 9.8 g. (33.9%) of colorless prisms of **α-(4-pyridyl)-cyclohexanone** (XVI), m.p. 107.0–108.5°, showing no depression of m.p. in admixture with XVI obtained above.

Extraction of the benzene solution above with 5% aqueous sodium bicarbonate gave 6.21 g. (30.8%) of benzoic acid. The benzene solution was then mixed with 10 cc. of aniline and evaporated to dryness to give 12.25 g. (37.7%) of benzanilide, m.p. 160–161°.

Reactions of α-(4-Pyridyl)-cyclohexanone (XVI). (a) Oxidation with Potassium Permanganate.—A mixture of 6.1 g. of potassium permanganate, 1.00 g. of XVI and 50 cc. of water was refluxed 90 minutes. Decolorized by sodium bisulfite, the reaction mixture was filtered, acidified with concentrated hydrochloric acid to *p*H 6, and concentrated to 40 cc. The addition of aqueous copper acetate produced an immediate precipitate which was washed with hot water, suspended in 50 cc. of water and decomposed with hydrogen sulfide. Filtration of the copper sulfide and evaporation to dryness afforded 0.43 g. (63%) of **isonicotinic acid**, m.p. 314–315°, showing no depression on admixture with authentic isonicotinic acid.

(b) **Fusion with Potassium Hydroxide.**—One gram of XVI was added to a molten mixture of 5 drops of water and 10.0 g. of potassium hydroxide in a nickel crucible and fused at 250° for ten minutes. The cooled mixture was dissolved in 100 cc. of water, partially neutralized with concentrated hydrochloric acid and then made acidic with acetic acid. To the hot solution, 300 cc. of saturated copper acetate was added followed by sodium bicarbonate in small portions until a green precipitate appeared. The filtered and washed copper salt was suspended in water and decomposed with hydrogen sulfide. The filtrate remaining after removal of the copper sulfide was evaporated to dryness leaving 0.41 g. (31.4%) of **ε-(4-pyridyl)-caproic acid dihydrate (XVII)**, m.p. 197.8–198.8° after several crystallizations from absolute ethanol.

Anal. Calcd. for $C_{11}H_{15}N_2 \cdot 2H_2O$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.81; H, 7.93; N, 6.23.

XVII is very soluble in and crystallizable from cold water, is moderately soluble in hot, absolute ethanol and insoluble in ether. The ultraviolet absorption spectrum of XVII in water showed a maximum at 252 mμ (log ε 3.55) as compared with 256 mμ (log ε 3.5) for pyridine hydrochloride in water.[17]

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[17] Landolt-Börnstein, "Physikalisch-chemische Tabellen," 5th ed., 3rd suppl., part 2, J. Springer, Berlin, p. 1416.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

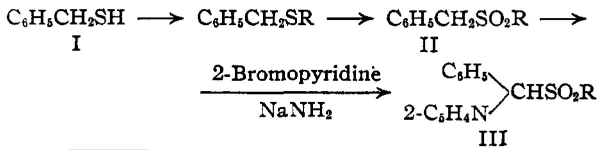
Alkyl Phenyl-(2-pyridyl)-methyl Sulfones. Sulfonium Salts as Alkylating Agents

BY T. R. LEWIS AND S. ARCHER

A series of alkyl phenyl-(2-pyridyl)-methyl sulfones were prepared by condensing alkyl benzyl sulfones with 2-bromopyridine and its homologs in the presence of sodium amide. The yields ranged from poor to moderate, due mainly to the failure of the condensation to proceed to completion. Complicating side-reactions, such as the formation of stilbenes from the unalkylated benzyl sulfones, were noticed. Methylation of benzyl mercaptan with methyl iodide furnished the expected product and a small amount of dibenzyl sulfide. An explanation of the formation of the symmetrical sulfide is offered which requires the intermediate formation of benzyldimethylsulfonium iodide. That a sulfonium salt may act as an alkylating agent was demonstrated by the behavior of trimethylsulfonium mesitoate on gentle heating. The ester, methyl mesitoate, was isolated from the reaction.

A few years ago we prepared a series of alkyl dialkylaminoalkylbenzohydryl sulfones for pharmacological testing.[1] In view of the interesting properties shown by this group of compounds, we thought it desirable to extend our work in the sulfone field to cover a series of alkyl phenyl-(2-pyridyl)-methyl sulfones.

The compounds were prepared according to the general equations



$$\underset{\text{I}}{C_6H_5CH_2SH} \longrightarrow C_6H_5CH_2SR \longrightarrow \underset{\text{II}}{C_6H_5CH_2SO_2R} \longrightarrow$$

$$\xrightarrow[\text{NaNH}_2]{\text{2-Bromopyridine}} \underset{\text{III}}{\left.\begin{matrix} C_6H_5 \\ 2\text{-}C_5H_4N \end{matrix}\right\rangle CHSO_2R}$$

Originally, we planned to prepare a number of sulfones, III, in which the alkyl group (R) was varied considerably. Consequently the sulfides (I) were prepared from the benzyl mercaptans and the alkyl halides rather than by the reverse procedure. The substituted benzyl mercaptans were obtained in good yield by means of the thiourea synthesis.[2] They were not obtained analytically pure but were suitable for further work. Alkylation of the sodium salts was accomplished by warming in alcohol solution with the requisite alkyl halide. The crude sulfides were oxidized to the nicely crystalline, readily purified sulfones, II, with the aid of 30% hydrogen peroxide.[3] The properties of the alkyl benzyl sul-

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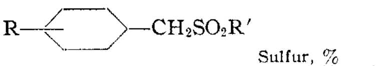
[1] M. M. Klenk, C. M. Suter and S. Archer, THIS JOURNAL, **70**, 3846 (1944).

[2] G. G. Urquhart, J. W. Gates, Jr., and R. Connor, *Org. Syn.*, **21**, 36 (1941).

[3] Superoxol (Merck and Co., Inc.) was used throughout this work.

Table I

Properties of the Substituted Alkyl Benzyl Sulfones

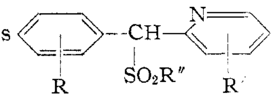


Sulfone R	R′	M.p., °C. (uncor.)	Solvent	Yield, %	Formula	Sulfur, % Calcd.	Sulfur, % Found
H	CH_3	125–127	EtOH–H_2O	50	$C_8H_{10}O_2S$		
H	C_3H_7	88–89.5	EtOH–H_2O	82	$C_{10}H_{14}O_2S$	16.17	16.32
H	C_4H_9	95–97	EtOH	83	$C_{11}H_{16}O_2S$	15.10	15.32
2-Cl	CH_3	92–93.5[a]	EtOH	79	$C_8H_9ClO_2S$	15.66	15.79
3-Cl	CH_3	83.5–85.5[a]	MeOH	65	$C_8H_9ClO_2S$	15.66	15.73
4-Cl	CH_3	120–122	EtOH	63	$C_8H_9ClO_2S$	15.66	15.80
4-Cl	C_2H_5	91.9–93.1[a]	EtOH	81	$C_9H_{11}ClO_2S$	14.65	14.80
3,4-diCl	C_2H_5	110.4–112.4[a]	EtOH–H_2O	87	$C_9H_{10}Cl_2O_2S$	12.66	12.77
4-CH_3	C_2H_5	73.8–75.6[a]	EtOH	57	$C_{10}H_{14}O_2S$	16.17	16.13
4-CH_3O	C_2H_5	103–104[a]	EtOH–H_2O	80	$C_{10}H_{14}O_3S$	14.96	15.08

[a] M.p.'s are corrected.

Table II

Properties of the Substituted Alkyl Phenyl-(2-pyridyl)-methyl Sulfones



Sulfone R	R′	R″	Method	M.p., °C. (cor.)	Solvent	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
H	H	CH_3[a]	A	122.5–124.5	Benzene–ligroin	14[b]	$C_{13}H_{13}NO_2S$	5.67	5.64	12.98	13.14
H	H	C_2H_5[a]	B	151–151.6	EtOH–H_2O	41	$C_{14}H_{15}NO_2S$	5.37	5.42	12.27	12.16
H	H	C_3H_7	A	121.6–122.8	EtOH–H_2O	13	$C_{15}H_{17}NO_2S$	5.09	5.15	11.64	11.77
H	H	C_4H_9	A	101.4–102.6	Benzene–ligroin	30	$C_{16}H_{19}NO_2S$	4.85	4.75	11.08	11.10
4-Cl	H	C_2H_5	A	121.6–122.9	EtOH–H_2O	31	$C_{14}H_{14}ClNO_2S$	11.99[c]	11.82[c]	10.84	10.92
3-Cl	H	CH_3	B	116.2–117.0	MeOH	10	$C_{13}H_{12}ClNO_2S$	12.58[c]	12.36[c]	11.38	11.49
2-Cl	H	C_2H_5	B	196.5–198.5	EtOH	38	$C_{14}H_{14}ClNO_2S \cdot HCl$	22.28[c]	21.80[c]	10.08	9.76
4-Cl	2-CH_3	CH_3	B	98.4–99.6	MeOH–pet. ether	11	$C_{14}H_{14}ClNO_2S$	4.74	4.88	10.84	10.83
4-Cl	4-CH_3	CH_3	B	209.0–210.0	EtOH	30	$C_{14}H_{14}ClNO_2S \cdot HCl$	4.22	4.12	9.65	9.77
3,4-diCl	H	C_2H_5	A	121.0–122.4	EtOH	25	$C_{14}H_{13}Cl_2NO_2S$	4.24	4.12	9.71	9.78
3,4-diCl,	4-CH_3	C_2H_5	B	201–205	EtOH	18	$C_{15}H_{15}Cl_2NO_2S \cdot HCl$	3.68	3.57	8.42	8.30
4-Cl	4-CH_3	C_2H_5	B	208–210	EtOH	26	$C_{15}H_{16}ClNO_2S \cdot HCl$	4.04	3.90	9.20	9.20
4-CH_3	H	C_2H_5	B	195.6–198	EtOH	32	$C_{15}H_{17}NO_2S \cdot HCl$	4.49	4.37	10.28	10.01
4-CH_3O	H	C_2H_5	A	138.8–140.8	MeOH–H_2O	14	$C_{15}H_{16}NO_3S$	4.82	4.68	11.01	11.07

[a] Benzyl methyl sulfone and benzyl ethyl sulfone have been prepared by E. Fromm and J. de Seixas Palma, *Ber.*, **39**, 3308 (1906). [b] When Method B was used the yield was only 10%. [c] Chlorine analysis.

fones are presented in Table I. The yields for the two steps ranged from 50 to 87%.

The condensation of 2-bromopyridine and the 2-bromopicolines with the sulfones, II, to furnish III was accomplished in toluene suspension with the aid of sodium amide in poor to moderate yield. Despite variations in reaction time and the use of large excesses of benzyl sulfone and sodium amide with respect to the bromopyridines it was usually possible to recover starting materials at the end of the reaction.

In one experiment sodium amide and ethyl *p*-chlorobenzyl sulfone were heated together for thirteen hours in order to ensure complete conversion to the sodio derivative, before the bromopyridine was added. We were unable to isolate any of the desired product. Examination of the neutral fraction revealed the presence of 4,4′-dichlorostilbene. In another case, the reaction between 3,4-dichlorobenzyl ethyl sulfone and 2-bromo-4-methyl pyridine, the desired sulfone was isolated. 3,4,3′,4′-Tetrachlorostilbene was isolated from the neutral fraction. Waldron and Reid obtained presumably dinitrostilbene from the reaction between hot sodium hydroxide and an alkyl *p*-nitrobenzyl sulfone.[4]

In some of our earlier experiments we used equimolecular proportions of sulfone, sodium amide and 2-bromopyridine. Since the sulfone III also possessed an active hydrogen it, too, would form a sodio derivative and compete with the benzyl sulfone II for the sodium amide. However, even when the amount of sodium amide was increased to take care of the demands of both sulfones no startling improvement in yield was observed.

Separation of the pyridyl sulfones III from the unreacted 2-bromopyridine required considerable manipulation. To minimize this, advantage was taken of the fact that a number of the sulfones, III, formed hydrochlorides which were very slightly soluble in cold ethanol. On the other hand, the corresponding salts of the bromopyridines were freely soluble in this solvent. Unfortunately this favorable solubility relationship did not hold in all cases and the method could not be applied generally. The pyridyl sulfones are listed in Table II.

In the preparation of methyl benzyl sulfide from benzyl mercaptan and methyl iodide the desired compound I (R = CH_3) was secured in 64% yield, accompanied by a higher-boiling substance which proved to be dibenzyl sulfide. On oxidation, the latter furnished dibenzyl sulfoxide. When methyl bromide was employed as the alkylating agent the

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(4) W. R. Waldron and E. E. Reid, This Journal, **45**, 2399 (1923).

yield of I (R = CH_3) rose to 80% and none of the dibenzyl sulfide was encountered. The following scheme accounts for the formation of the symmetrical sulfide

$$\begin{tikzcd} C_6H_5CH_2SCH_3 + CH_3I \arrow[r] & {[C_6H_5CH_2S(CH_3)_2]^+I^-} \arrow[d, "C_6H_5CH_2S^-"] \\ & C_6H_5CH_2SCH_2C_6H_5 + (CH_3)_2S + I^- \end{tikzcd}$$

Since methyl bromide does not form sulfonium salts as readily as the corresponding iodide this type of reaction does not occur when the less reactive halide is used.

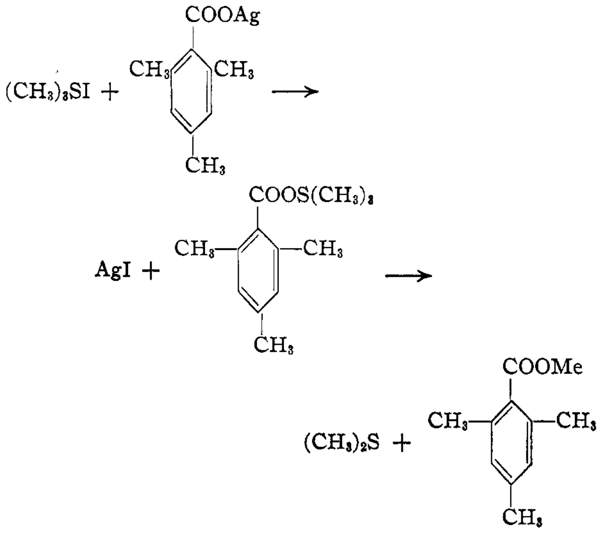
Benzyl dimethylsulfonium picrate was prepared and treated with *o*-chlorobenzyl mercaptan in sodium ethylate solution. A small amount of methyl-*o*-chlorobenzyl sulfide was isolated along with the major product, benzyl-*o*-chlorobenzyl sulfide. Both sulfides were identified by oxidation to the corresponding sulfones and direct comparison of the latter with authentic samples.

$$\begin{tikzcd} {C_6H_5CH_2\overset{+}{S}(CH_3)_2 + 2\text{-}ClC_6H_4CH_2S^-} \arrow[r] & 2\text{-}ClC_6H_4CH_2S\text{—}CH_2C_6H_5 \arrow[d] & + \; 2\text{-}ClC_6H_4CH_2SCH_3 \arrow[d] \\ {2\text{-}ClC_6H_4CH_2SH + C_6H_5CH_2Cl} \arrow[r, "\text{2 steps}"] & 2\text{-}ClC_6H_4CH_2SO_2CH_2C_6H_5 & 2\text{-}ClC_6H_4CH_2SO_2CH_3 \end{tikzcd}$$

Ray and Levine[5] have shown that certain sulfonium halides may reversibly dissociate to an alkyl halide and a dialkyl sulfide. The latter may react with a different alkyl halide to form a new sulfonium salt. When benzyl methyl sulfide and methyl iodide were allowed to react trimethylsulfonium iodide and a highly lachrymatory oil, presumably benzyl iodide, were formed. The products may easily be accounted for by employing the concepts of Ray and Levine.

$$C_6H_5CH_2SCH_3 + CH_3I \longrightarrow [C_6H_5CH_2S(CH_3)_2]^+ I^- \longrightarrow C_6H_5CH_2I + (CH_3)_2S \xrightarrow{CH_3I} (CH_3)_3SI$$

On the basis of this scheme it is quite possible that the benzyl sulfonium salt, although an intermediate in the alkylation of the mercaptans, actually first decomposes to either benzyl iodide or benzyl picrate,[6] which are the true alkylating agents. Trimethylsulfonium iodide and *o*-chlorobenzyl mercaptan were refluxed in sodium ethylate solution. *o*-Chlorobenzyl sulfide was obtained. Of much greater significance, however, was the fact that methyl mesitoate was formed when a suspension of silver mesitoate and trimethylsulfonium iodide in methanol was refluxed for a few hours. In this case the very insoluble silver iodide was produced, leaving trimethylsulfonium mesitoate. The latter decomposed to furnish the ester. Clearly, the unavailability of the iodide ion renders the formation of methyl iodide extremely unlikely. The trimethylsulfonium ion must be the true alkylating agent.



In this connection some work of Bost and Schultze[7] is of interest. These authors found that certain *p*-phenylphenacylsulfonium salts furnished *p*-phenylphenacyl mercaptan when treated with hydrogen sulfide in the presence of silver ion. This may be considered another example of a sulfonium salt acting as an alkylating agent.

Experimental[8]

***p*-Methylbenzyl Bromide.**—Five hundred and thirty-one grams of bromine was added dropwise beneath the surface of 270 g. of *p*-xylene previously heated to 125°. After the addition which required 2.5 hours, the mixture was cooled and stored over potassium hydroxide to remove the last traces of hydrogen bromide. The solidified mass was transferred to a 500-ml. distilling flask and distilled. The main fraction, b.p. 54–58° (0.5 mm.) weighed 166.3 g.: A slightly less pure cut, b.p. 58–64° (0.5 mm.), weighed 31.7 g., making the total yield of usable bromide 198 g. (42%). The first fraction solidified on standing.[9]

The residue was purified by crystallization from benzene. This dibromo derivative weighed 103 g. and melted at 142–144°.[9]

***m*-Chlorobenzyl Chloride.**—A mixture of 115 g. of *m*-chlorotoluene, 123 g. of sulfuryl chloride and 0.4 g. of benzoyl peroxide[10] was heated on the steam-bath for ten hours and then distilled at 21 mm. The first fraction, b.p. 60–103°, n^{25} 1.5221, consisted mainly of recovered *m*-chlorotoluene. The second fraction, b.p. 103–106°, n^{25} 1.5510, weighed 84.0 g. The chloride was suitable for use in the next step.

6-Bromo-2-methylpyridine.—6-Amino-2-methylpyridine was converted to the corresponding bromide by the procedure of Craig.[11] The yield of the product, b.p. 85–92° (16 mm.), n^{25} 1.5590, was 66% of the theoretical. This is a more convenient method than the one previously used.[12]

2-Bromo-4-methylpyridine.—This substance was secured in 70% yield.[11] It boiled at 121–129° (45 mm.).[13]

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[5] F. D. Ray and I. Levine, *J. Org. Chem.*, **2**, 267 (1937).

[6] E. Hertel and J. vanCleef, *Ber.*, **61**, 1545 (1928), found that methyl picryl ether and dimethylaniline furnished trimethylphenylammonium picrate.

[7] R. W. Bost and H. C. Schultze, THIS JOURNAL, **64**, 1165 (1942).

[8] The analyses were carried out under the supervision of Messrs. M. E. Auerbach and K. D. Fleischer of this Laboratory.

[9] E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **91**, 1687 (1907), obtained *p*-methylbenzyl bromide, b.p. 210–220°, m.p. 35.5°, in 46% yield. Their *p*-xylidene dibromide melted at 143.5°.

[10] M. S. Kharasch and H. C. Brown, THIS JOURNAL, **61**, 2142 (1939).

[11] L. C. Craig, THIS JOURNAL, **56**, 232 (1934); *Org. Syntheses*, **26**, 18 (1940).

[12] H. D. T. Willink and J. P. Wibaut, *Rec. trav. chim.*, **53**, 417 (1934), report the b.p. 205.5–207° (772 mm.).

[13] F. H. Case, THIS JOURNAL, **68**, 2574 (1946), gives b.p. 223–224°.

Substituted Benzyl Mercaptans.—The thiols listed below were prepared by the method described in "Organic Syntheses."[2] Analysis of representative samples indicated a purity of about 95%.

***p*-Chlorobenzyl Mercaptan.**—From 342 g. of *p*-chlorobenzyl chloride there was secured 270 g. of the mercaptan, b.p. 66–67° (0.4 mm.).

The 3,5-dinitrobenzoate, prepared in the usual way, melted at 153.5–155° (uncor.), after crystallization from benzene–ligroin.

Anal. Calcd. for $C_{14}H_8ClN_2O_2S$: N, 7.94; S, 9.09. Found: N, 8.03; S, 8.86.

***p*-Methoxybenzyl Mercaptan.**—The compound was obtained in 80% yield, b.p. 89–94° (2.5 mm.), n^{25} 1.5660.

The 3,5-dinitrobenzoate separated from dilute ethanol in beautiful yellow needles, m.p. 100–102° (uncor.).

Anal. Calcd. for $C_{15}H_{12}N_2O_6S$: S, 9.21; OCH_3, 8.90. Found: S, 9.50; OCH_3, 8.70.

***p*-Methylbenzyl Mercaptan.**—This thiol boiled at 116–118° (35 mm.), yield 83%.

3,4-Dichlorobenzyl Mercaptan.—The compound obtained in 79% yield boiled at 87–90° (0.5 mm.).

***o*-Chlorobenzyl Mercaptan.**—This thiol was secured in 85% yield, b.p. 126–128° (28 mm.), n^{25} 1.5840.

***m*-Chlorobenzyl Mercaptan.**—The substance boiled at 120–121° (19 mm.), n^{25} 1.5810; yield 77%.

Methylation of Benzyl Mercaptan (A) Methyl Iodide.—A solution of 89.5 g. of benzyl mercaptan and 16.6 g. of sodium in 400 ml. of absolute ethanol was cooled to 8°. Then 102 g. of methyl iodide was added dropwise to the stirred solution over a 90-minute period. The temperature rose to 53° during the addition. After two hours the mixture was heated on the steam-bath with the condenser set for downward distillation. After 300 ml. of ethanol had distilled, the residue was poured into ice-water. The oil was separated and the aqueous layer washed with benzene. The combined organic fractions were washed with water, dilute sodium hydroxide and again with water. The benzene was removed on the steam-bath and the residue was distilled. After a small forerun the benzyl methyl sulfide came over at 52–54° (1.8 mm.), n^{25} 1.5550. The pressure was reduced and another fraction, b.p. 111–115° (0.3 mm.), wt. 9.0 g. was collected. The oil soon solidified. After crystallization from petroleum ether it melted at 46–50°. It was dibenzyl sulfide.[14] Oxidation with 30% hydrogen peroxide in acetic acid furnished the sulfoxide, m.p. 132–134° after recrystallization from dilute ethanol.[15]

(B) Methyl Bromide.—A solution of 58.0 g. of benzyl mercaptan and 6.9 g. of sodium in 250 ml. of ethanol was cooled to −5° and kept at that temperature during the dropwise addition of a solution of 32.8 g. of methyl bromide in 100 ml. of ethanol. The cooling-bath was removed and the mixture was stirred for three hours as the temperature rose gradually to 25°. After being left overnight the whole was processed as above to furnish 33 g. (80%) of benzyl methyl sulfide, b.p. 120–121° (48 mm.), n^{25} 1.5560. The sulfides used in this work were prepared by this method or a minor variant thereof. Oxidation to the sulfones was carried out on the undistilled sulfides.

Benzyl Butyl Sulfone.—The following general procedure was employed for the preparation of the sulfones listed in Table I. The crude benzyl butyl sulfide obtained from 74.5 g. of benzyl mercaptan and 82.2 g. of butyl bromide was dissolved in 200 ml. of glacial acetic acid. To this stirred solution 170 ml. of Superoxol was added in 90 minutes. During the first part of the addition the evolved heat served to maintain the temperature at 85–90° but during the second half the mixture was heated on the steam-bath to keep the temperature at 95°. After all the hydrogen peroxide had been added the clear solution was held at 95° for 30 minutes. It was poured into water and allowed to stand. The crystalline solid was collected on a filter, washed with water and recrystallized from dilute ethanol with the aid of charcoal. There was obtained 105 g., m.p. 95–97° (uncor.).

***p*-Chlorophenyl (2-Pyridyl)-methyl Ethyl Sulfone (Method A.).**—A suspension of 50 g. (0.228 m.) of *p*-chlorobenzyl ethyl sulfone, 11 g. (0.282 m.) of sodium amide and 375 ml. of dry toluene was placed in a three-necked flask equipped with a nitrogen inlet tube. The mixture was refluxed under nitrogen for 90 minutes before a solution of 36 g. (0.228 m.) of α-bromopyridine in 250 ml. of toluene was added dropwise in 80 minutes. Refluxing and stirring was continued for two hours before the mixture was cooled. The mixture was treated carefully with water to destroy excess sodium amide and then was washed with three 200-ml. portions of water. The toluene was removed *in vacuo* and the residue was extracted with four 150-ml. portions of 10% hydrochloric acid. The first extract yielded an oil when made basic but the next three gave a crystalline solid. The crops were combined and re-dissolved in dilute hydrochloric acid, clarified with Darco and the solution then made basic with sodium hydroxide. A gummy solid was obtained which crystallized completely when triturated with a small amount of ethanol. The crystals were filtered and dried; wt. 20.8 g. (31%), m.p. 113–118° (uncor.). After three recrystallizations from dilute ethanol the substance melted at 121.6–122.9° (cor.).

When the reaction was run in the same way but the sodium amide and *p*-chlorobenzyl ethyl sulfone mixture was heated for 13.5 hours before the addition of the α-bromopyridine none of the desired basic sulfone was isolated. However, the toluene layer on evaporation yielded a crystalline substance which after two recrystallizations from ethanol and one from chloroform melted at 172–173° (uncor.). It was 4,4′-dichlorostilbene.[16] The substance was dissolved in chloroform and treated with excess bromine. The product that separated melted at 224–226° (uncor.).

Ethyl 2-Pyridyl(*p*-tolyl)-methyl Sulfone Hydrochloride (Method B).—The experiment described below illustrates both the method of isolation of the basic sulfone as the hydrochloride and the use of 2 moles each of benzyl sulfone and sodium amide to about one of the α-bromopyridine. Seventy grams of ethyl *p*-methylbenzyl sulfone (0.35 m.) and 13.8 g. (0.35 m.) of sodamide were suspended in 400 ml. of toluene and refluxed two hours. Then 27.9 g. (0.177 m.) of 2-bromopyridine in 100 ml. of toluene was added in 3.5 hours. After the addition was complete the heating was continued for 30 minutes. The mixture was cooled and treated with water to destroy excess sodamide. The toluene layer was separated and washed successively with two 100-ml. portions of water and then with 350 ml. of 6 *N* hydrochloric acid. The aqueous layer was made basic and the oil was taken up in benzene. The solvent was removed and the residue dried by azeotropic distillation with benzene and alcohol. The residue was dissolved in absolute ethanol and treated with alcoholic hydrogen chloride. The crystals that separated were collected and recrystallized from 200 ml. of absolute alcohol with the aid of charcoal; wt. 18.9 g. On further recrystallization there was obtained 17.9 g. of the hydrochloride, m.p. 195.6–198.0° (cor.).

3,4-Dichlorobenzyl Ethyl Sulfone and 2-Bromo-4-methylpyridine. The isolation of 3,4,3′,4′-Tetrachlorostilbene.—The reaction was run as above. The toluene solution that remained after the acid extraction was concentrated to dryness to leave a solid residue. The latter was extracted with hot ethanol. An insoluble crystalline substance was obtained which after crystallization from chloroform melted at 188.4–189.6° (cor.). From 63.6 g. of 3,4-dichlorobenzyl ethyl sulfone, 7.7 g. of the stilbene was isolated.

Anal. Calcd. for $C_{14}H_8Cl_4$: C, 52.87; N, 2.54; Cl, 44.59. Found: C, 53.00; H, 2.53; Cl, 45.00.

Benzyl 2-Chlorobenzyl Sulfone.—A solution of 7.9 g. of 2-chlorobenzyl mercaptan and 1.1 g. of sodium in 100 ml. of ethanol was treated with 6.3 g. of benzyl chloride. The mixture was refluxed for four hours and poured in ice. The oil which separated was extracted with benzene. The solvent was removed and the residue dissolved in acetic acid and oxidized with 13.5 ml. of Superoxol at 90°. After one-half hour the whole was poured in ice-water and allowed to stand. The crystals were filtered, washed with water and recrystallized from ethanol, wt. 8.4 g. (60%). After one more crystallization there was obtained 7.3 g. of the pure sulfone, m.p. 120.5–122° (uncor.).

Anal. Calcd. for $C_{14}H_{13}ClO_2S$: S, 11.42. Found: S, 11.42.

Benzyl Methyl Sulfide and Methyl Iodide. Isolation of Trimethylsulfonium Iodide.—A mixture of 12.8 g. of benzyl methyl sulfide, 71 g. of methyl iodide and 50 ml. of methanol was allowed to stand at room temperature. Crystals

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(14) S. Smiles, *J. Chem. Soc.*, **121**, 1404 (1922), reported m.p. 49–50°.

(15) Lewin, *J. prakt. Chem.*, [2] **119**, 213 (1928), reported m.p. 133–134.6°.

(16) E. Späth, *Monatsh.*, **35**, 473 (1914), reported 177° as the m.p. of the 4,4′-chlorostilbene and 226–227° for the dibromide.

started to separate within the first few hours. After 40 hours the crystals were collected, washed with ether and dried; wt. 10.0 g. The trimethyl sulfonium iodide had no definite melting point. A portion was suspended in ethanol and treated with aqueous sodium picrate. A new salt appeared which was filtered and recrystallized from ethanol. The trimethylsulfonium picrate melted at 194–196° (uncor.).[17]

o-Chlorobenzyl Methyl Sulfide from Trimethylsulfonium Iodide and o-Chlorobenzyl Mercaptan.—To a solution of 3.9 g. of *o*-chlorobenzyl mercaptan (0.024 m.) and 0.6 g. (0.027 m.) of sodium in 60 ml. of ethanol there was added 6.9 g. (0.0335 m.) of trimethyl sulfonium iodide. The mixture was refluxed for three hours and was then poured in water. The oil was dissolved in benzene. The solution was dried and distilled to yield 2.6 g. of crude sulfide, b.p. 52–62° (0.1 mm.).

The sulfide was dissolved in 25 ml. of acetic acid and oxidized with 3 ml. of Superoxol at 90°. On pouring the reaction mixture in ice-water a solid was formed which after filtration and recrystallization from ethanol melted at 92–95°. When admixed with an authentic specimen of *o*-chlorobenzyl methyl sulfone there was no melting point depression.

Benzyldimethylsulfonium Picrate.—To a solution of 7.1 g. of dimethyl sulfide in 25 ml. of methanol there was added 19.7 g. of benzyl bromide in 75 ml. of methanol. The whole was allowed to stand for 12 days. Then 5 volumes of ether was added and the supernatant solvent was decanted from the gum. The latter was washed several times with ether and then dissolved in water. The solution was added to a solution of 26.4 g. of picric acid in 350 ml. of water containing 4.6 g. of sodium hydroxide. The yellow solid which separated was crystallized from 300 ml. of ethanol. The total yield of the sulfonium picrate was 23 g. (52%); m.p. 134.4–136° (cor.).[18]

Anal. Calcd. for $C_9H_{13}S\cdot O\cdot C_6H_2(NO_2)_3$: S, 8.41. Found: S, 8.52.

Reaction between Benzyldimethylsulfonium Picrate and o-Chlorobenzyl Mercaptan.—To a solution of 1.2 g. of sodium in 100 ml. of absolute alcohol there was added 7.9 g. of *o*-chlorobenzyl mercaptan. Then 19 g. of the sulfonium picrate was added in one portion and the resulting mixture was heated with stirring for one hour. The red solution was poured into ice-water and the oil which separated was collected in benzene. The extract was thoroughly washed with 0.5 *N* sodium hydroxide, water and once with dilute hydrochloric acid. The benzene solution was then dried and distilled. A small forerun was obtained, followed by a fraction, b.p. 77–80° (1.4 mm.); wt. 0.8 g. This was oxidized in acetic acid solution with Superoxol. A crystalline solid, m.p. 78–82° after recrystallization from dilute ethanol, was obtained. A mixed melting point determination with a known specimen of *o*-chlorobenzylmethyl sulfone, m.p. 91–93°, melted at 89–92°.

The residue which weighed 7.8 g. (56%) was dissolved in 70 ml. of glacial acetic acid and oxidized with 15 ml. of Superoxol. Crystals were obtained on pouring the mixture in water. After recrystallization from ethanol the benzyl-2-chlorobenzyl sulfone melted at 121–123° (uncor.) and did not depress the m.p. of an authentic specimen.

Methyl Mesitoate.—A suspension of 5.7 g. of silver mesitoate and 9.3 g. of trimethylsulfonium iodide in 50 ml. of methanol was refluxed for six hours. The mixture was filtered through Filter-cel and the methanol was removed under reduced pressure. A few ml. of dilute ammonia was added to the residue and the whole was steam distilled. The oil that came over was extracted with ether, dried and distilled. The fraction, b.p. 86–87° (2 mm.), weighed 1.4 g. (38%).[19]

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[17] D. Strömholm, *Ber.*, **33**, 827 (1900), reported 193° as the m.p. of trimethyl sulfonium picrate.

[18] J. W. Baker and W. G. Moffett, *J. Chem. Soc.*, 1728 (1930), report m.p. 134°.

[19] M. S. Newman, THIS JOURNAL, **63**, 2434 (1941), reported the b.p. 114.8–115.2° (7–7.5 mm.).

[CONTRIBUTION FROM THE LABORATORY OF PATHOLOGY AND PHARMACOLOGY, EXPERIMENTAL BIOLOGY & MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Derivatives of Bis-(4-aminophenyl) Sulfone and Related Compounds

BY HUGO BAUER

Seven different types of substituted diphenyl sulfones were synthesized for evaluation in the chemotherapy of experimental tuberculosis. They included derivatives of sulfamic and amidopyrophosphoric acids, of nicotinic acid and of glycine, methoxysubstituted sulfones, an amidine and an aminoethylamine derivative. These compounds were tested for therapeutic effectiveness upon the chorioallantois of the developing chick embryo or in guinea pigs infected with *Mycobacterium tuberculosis*.

A series of derivatives of bis-(4-aminophenyl) sulfone has been prepared for evaluation in the chemotherapy of experimental tuberculosis. This paper deals with the chemical aspects of the problem[1] as related to seven different types of substituted diphenyl sulfones.[2]

Sulfamic and amidopyrophosphoric acid derivatives of bis-(4-aminophenyl) sulfone were prepared by three routes. Reduction of bis-(4-nitrophenyl) sulfone with sodium dithionite (sodium hydrosulfite) gave 4-amino-4′-sulfaminodiphenyl sulfone (I) and its sodium salt (II). The action of chlorosulfonic acid upon 4-nitro-4′-aminodiphenyl sulfone in the presence of pyridine afforded 4-nitro-4′-sulfaminodiphenyl sulfone which was isolated as the pyridine (III) and the mono-(IV) and disodium (V) salts. An attempt to prepare the chloride and the amide of the 4-nitro-4′-sulfaminodiphenyl sulfone gave an unexpected result. By the action of phosphorus pentachloride upon III, the sulfonic acid group was replaced by a phosphorus-containing group. Subsequent treatment with ammonium hydroxide yielded a diamidopyrophosphoric acid derivative which was isolated as a sodium salt (VI).

A similar compound (VII) was obtained by the action of phosphorus pentachloride on 4-nitro-4′-aminodiphenyl sulfone and subsequent treatment with ammonium hydroxide and aqueous sodium hydroxide. The following formulas are suggested for the anhydrous compounds.

Two derivatives of nicotinic acid were prepared. Nicotinyl chloride acted upon bis-(4-aminodiphenyl) sulfone with formation of the disubstituted bis-(nicotinyl-4-aminophenyl) sulfone (VIII), previously prepared by E. H. Stuart.[3]

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[1] The biological part of this work has been reported in a series of papers from this Laboratory by M. I. Smith and co-workers.

[2] Foregoing papers: THIS JOURNAL, **61**, 617 (1939); **67**, 591 (1945); **70**, 2254 (1948).

[3] E. H. Northey, "The Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1948, p. 355.