2-Isopropyl-1,3-butadiene.—Pyrolysis of 87 g. of 2-isopropyl-3-acetoxy-1-butene as previously described[2] gave 29 g. (54%) of 2-isopropyl-1,3-butadiene, b. p. 85–87°, n^{20}_D 1.4337. This material polymerized readily and gave an infrared spectrum related to that of isoprene. This sample of 2-isopropyl-1,3-butadiene gave the same crystalline maleic anhydride adduct, m. p. 86–86.5°, which was reported earlier.[2]

Diene prepared by dehydration of 2-isopropyl-3-hydroxy-1-butene over either potassium acid sulfate or alumina boiled over a wide range, had a variable index of refraction depending on the fraction examined, and did not polymerize in the GR-S system. A considerable fraction of ketone was always obtained in the attempted dehydration.

3-Methyl-1,3-pentadiene.—This diene was prepared by the method of Nichol and Sandin.[5] Its maleic anhydride adduct was prepared in 61% yield by the procedure used for the adduct of 2-ethyl-1,3-butadiene instead of by the sealed tube method previously described.[6] The product melted at 67–68° as reported.[6]

Summary

Dehydration of 2-alkyl-3-hydroxy-1-butenes produced dienes of uncertain purity. Thermal cracking of the corresponding acetates gave pure 2-alkyl-1,3-butadienes in case of the ethyl, isopropyl and 2-*n*-amyl derivatives.

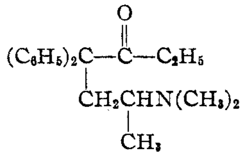
URBANA, ILLINOIS RECEIVED AUGUST 19, 1948

[CONTRIBUTION FROM THE LABORATORIES OF THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation and Properties of Some Benzohydryl Sulfones

BY MABEL M. KLENK, C. M. SUTER AND S. ARCHER

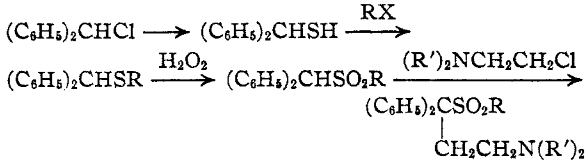
Reports which emanated from Germany at the end of the war[1] and later confirmed in this country[2] revealed that the ketone, I, known as methadone or 10,820 was an analgesic more potent than morphine. As part of an analgesic program under way in these laboratories it was decided to prepare a series of aminoalkyl benzohydryl sulfones.



$$(C_6H_5)_2C(CH_2CH(CH_3)N(CH_3)_2)-C(=O)-C_2H_5$$

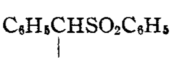
I

The compounds were prepared according to the equations



$$(C_6H_5)_2CHCl \longrightarrow (C_6H_5)_2CHSH \xrightarrow{RX} (C_6H_5)_2CHSR \xrightarrow{H_2O_2} (C_6H_5)_2CHSO_2R \xrightarrow{(R')_2NCH_2CH_2Cl} (C_6H_5)_2C(SO_2R)CH_2CH_2N(R')_2$$

Eisleb[3] alkylated benzyl phenyl sulfone with diethylaminoethyl chloride with the aid of sodium amide and obtained the sulfone, II. Later,[4] it was shown that sulfones such as methyl phenyl sulfone could also be alkylated with sodium amide as the condensing agent.



$$C_6H_5CH(SO_2C_6H_5)CH_2CH_2N(C_2H_5)_2$$

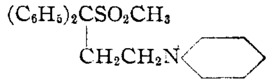
II

Benzohydryl mercaptan was previously prepared by Staudinger from diphenyldiazomethane and hydrogen sulfide.[5] We obtained this thiol in quantity by employing the thiourea synthesis.[6] Iodometric titration after distillation indicated that the thiol was about 85% pure. This material was satisfactory for the next step. It was smoothly alkylated in sodium ethylate solution with alkyl halides to yield the corresponding sulfides of approximately the same purity as the starting thiol. When the sulfides were oxidized with hydrogen peroxide in acetic acid solution, the resulting alkyl benzohydryl sulfones were readily isolated in crystalline form and could be purified easily. It was subsequently found that best results were realized when the distillations of the intermediate thiol and sulfides were avoided. When undistilled mercaptan and sulfide were employed in the preparation of ethyl benzohydryl sulfone the over-all yield based on benzohydryl chloride was 81%.

9-Fluorenyl mercaptan, a nicely crystalline solid, was converted to ethyl 9-fluorenyl sulfone by the procedures used in the benzohydryl series. Benzohydryl *p*-tolyl sulfone was prepared from sodium *p*-toluenesulfinate and benzohydryl chloride.[7]

Alkylation of the sulfones was effected in toluene solution in the presence of sodium amide. Details of the procedure are given in the Experimental Part.

Since the methyl group in methyl phenyl sulfone underwent alkylation under conditions similar to ours,[4] it was necessary to prove that the entering aminoalkyl group replaced the benzohydryl hydrogen rather than the hydrogen of the alkyl group in the alkyl benzohydryl sulfones. The product obtained from the reaction between pi-



III

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[1] Report No. PB-981, Office of the Publication Board, Dept. of Commerce, Washington, D. C., p. 91.

[2] Scott and Chen, *J. Pharmacol. Exptl. Therap.*, **87**, 63 (1946).

[3] Eisleb, *Ber.*, **74B**, 1433 (1941).

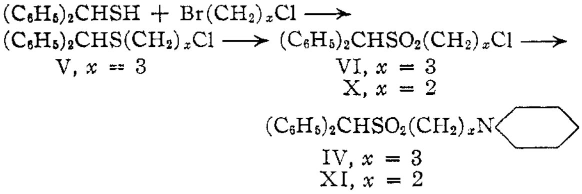
[4] German patent 735,866; *C. A.*, **38**, 4101 (1944).

[5] Staudinger and Stewart, *Ber.*, **49**, 1918 (1916).

[6] "Organic Syntheses," **21**, 36 (1941).

[7] Balfe, Doughty, Kenyon and Poplett, *J. Chem. Soc.*, 605 (1942).

peridylethyl chloride and methyl benzohydryl sulfone was a crystalline base, m. p. 122–123°. It must be either III or IV. Benzohydryl γ-piperidylpropyl sulfone was prepared according to the equations

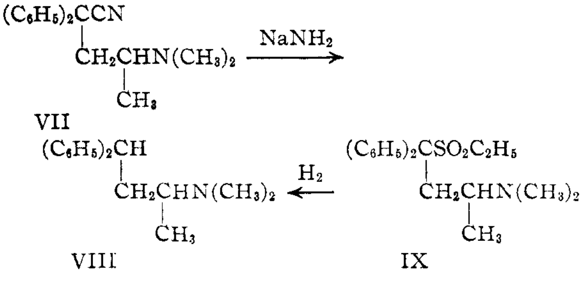


$$(C_6H_5)_2CHSH + Br(CH_2)_xCl \longrightarrow$$
$$\underset{V,\ x\ =\ 3}{(C_6H_5)_2CHS(CH_2)_xCl} \longrightarrow \underset{VI,\ x\ =\ 3;\ X,\ x\ =\ 2}{(C_6H_5)_2CHSO_2(CH_2)_xCl} \longrightarrow$$

IV, $x = 3$
XI, $x = 2$

The chlorosulfide, V, was not isolated but converted directly to the sulfone, VI. When treated with piperidine, VI gave a basic sulfone which melted at 120–121°. Despite the proximity of melting points of the two basic sulfones, admixture of the two specimens resulted in a large melting point depression. Therefore, the alkylation product must be III.

Only one crystalline base was obtained from the reaction between ethyl benzohydryl sulfone and dimethylaminoisopropyl chloride. The configuration of the side chain was the same as in methadone, indicating that a rearrangement occurred in this case also.[8] Sprague[8] and later Stevens[9] have demonstrated that methadone nitrile is represented by formula VII. When this substance was heated with excess sodium amide in boiling toluene the nitrile group was replaced by hydrogen to give the base VIII,[1] it formed a nicely crystalline hydrochloride, which melted at 156–158° after recrystallization from acetone. When the sulfone, IX, was refluxed in ethanol with Raney nickel catalyst hydrogenolysis occurred at the carbon-sulfur bond.[10] A high-boiling basic oil was obtained which yielded a hydrochloride identical with the one prepared from VIII. Since neither step in the degradations involved the side-chain the evidence is conclusive that IX has the indicated structure. Confirmatory evidence was supplied by pharmacological investigation. Preliminary data on animals indicated that IX was equal to methadone in analgesic effect.[11]



$$(C_6H_5)_2C(CN)CH_2CH(CH_3)N(CH_3)_2 \xrightarrow{NaNH_2}$$

VII

$$(C_6H_5)_2CHCH_2CH(CH_3)N(CH_3)_2 \xleftarrow{H_2} (C_6H_5)_2C(SO_2C_2H_5)CH_2CH(CH_3)N(CH_3)_2$$

VIII IX

The basic sulfone obtained from dimethylaminoisopropyl chloride and benzohydryl *n*-propyl sulfone was obtained crystalline as the tartrate. On the other hand little difficulty was experienced in obtaining crystalline bases from the reaction between dimethylaminoisopropyl chloride and methyl benzohydryl sulfone and from piperidylisopropyl chloride and ethyl benzohydryl sulfone. As a matter of convenience only, we have written the structures as the methadone type since we have no degradative evidence to support the formulations except by analogy.

The properties of some β-substituted ethyl benzohydryl sulfones were examined briefly. Benzohydryl mercaptan and piperidylethyl chloride gave β-piperidylethyl benzohydryl sulfide, but in preliminary experiments we were unable to obtain any useful products when the latter was oxidized with either hydrogen peroxide or potassium permanganate. The sulfone, XI, was prepared without difficulty from X. β-Dimethylaminoethyl benzohydryl sulfone (XII) was prepared from the chloro sulfone, X, and alcoholic dimethylamine. When the sulfones, XI and XII were treated with ethyl iodide and sodium amide in boiling toluene solution and after a short time, worked up in the usual manner with the aid of ethanol, two nitrogen free products were obtained. One of these (XIII) was quite insoluble in toluene and melted at about 223°. The other was very soluble and melted at 99–100°.

When β-acetoxyethyl benzohydryl sulfone, prepared according to the equations

$$(C_6H_5)_2CHSH + ClCH_2CH_2OH \xrightarrow{\text{2 steps}} (C_6H_5)_2CHSO_2CH_2CH_2OH \longrightarrow (C_6H_5)_2CHSO_2CH_2CH_2OAc$$

was subjected to the same treatment apparently the same pair of substances was formed. The low-melting compound proved to be identical with the sulfone prepared from the chlorosulfone, X, and aqueous-alcoholic potassium hydroxide and from benzohydryl mercaptan and ethoxyethyl bromide followed by oxidation. It was β-ethoxyethyl benzohydryl sulfone (XIV).

When the sulfone, XIV, was treated with ethyl iodide and sodium amide in toluene, a high melting substance, similar in behavior to XIII, was formed. The substance was quite insoluble in most organic solvents but could be crystallized from pyridine containing a small amount of water. The analytical data were in fair agreement with the formula, $C_{22}H_{32}S_2O_5$. Elucidation of its structure will require further work.

It seems probable that the β-substituted ethyl benzohydryl sulfones were first being converted to

$$(C_6H_5)_2CHSO_2CH_2CH_2R \longrightarrow \underset{XV}{(C_6H_5)_2CHSO_2CH{=}CH_2} \xrightarrow{C_2H_5OH} \underset{XIV}{(C_6H_5)_2CHSO_2CH_2CH_2OC_2H_5}$$

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[8] Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188, 2454 (1947).

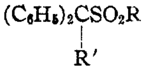
[9] Easton, Gardner and Stevens, *ibid.*, **69**, 2941 (1947).

[10] Mozingo, Spencer and Folkers, *ibid.*, **66**, 1859 (1944).

[11] A more detailed report on the pharmacology of the compounds listed in Table I will be given in a forthcoming publication from the Department of Pharmacology of this Laboratory.

TABLE I

PROPERTIES OF THE AMINOALKYL BENZOHYDRYL SULFONES



$(C_6H_5)_2C(R')SO_2R$

R =	R' =	M. p. (cor.), °C.	Formula[a]	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity[b]
CH_3	$C_5H_{10}NCH_2CH_2$	122.6–123.6	$C_{21}H_{27}NO_2S$	3.94	3.84	8.97	8.77			++
CH_3	$(CH_3)_2NCH(CH_3)CH_2$	148.6–150	$C_{19}H_{25}NO_2S$	4.23	4.15	9.67	9.71			++
C_2H_5	$(CH_3)_2NCH_2CH_2$	202.8–204.8	$C_{19}H_{25}NO_2S \cdot HCl$			8.71	8.56	9.64	9.59	++
C_2H_5	$C_5H_{10}NCH_2CH_2$	117.5–119	$C_{22}H_{29}NO_2S$	3.77	3.79	8.63	8.49			++
C_2H_5	$(C_2H_5)_2NCH_2CH_2$	166.5–168	$C_{21}H_{29}NO_2S \cdot HCl$	3.54	3.47	8.10	8.00			++
C_2H_5	$C_5H_{10}NCH_2CH_2CH_2$	112–113.5	$C_{23}H_{31}NO_2S$	3.63	3.68	8.32	8.25			
C_2H_5	$(CH_3)_2NCH(CH_3)CH_2$	205–206.5	$C_{20}H_{27}NO_2S \cdot HCl$	3.71	3.67			9.57	9.28	+++
C_2H_5	$C_5H_{10}NCH(CH_3)CH_2$	160–161.6	$C_{23}H_{31}NO_2S$[c]	3.63	3.43					+++
C_3H_7	$(CH_3)_2NCH(CH_3)CH_2$	148.2–151	$C_{21}H_{29}NO_2S \cdot C_4H_6O_6$[d]	2.75	2.92					+
p-C_7H_7	$(CH_3)_2NCH(CH_3)CH_2$	191.8–192.3	$C_{25}H_{29}NO_2S \cdot HCl$			7.22	7.00	7.99	7.93	0
p-C_7H_7	$C_5H_{10}NCH_2CH_2$	223.5–223.9	$C_{27}H_{31}NO_2S \cdot HCl$			6.82	6.75	7.58	7.72	0

[a] The hydrochlorides were prepared by Method A, whereas the bases were prepared according to Method B. See Experimental Part. [b] +++ = approximately equal to methadone; ++ = approximately equal to meperidine (Demerol); + = approximately equal to Pyramidon. All the bases were tested in aqueous solution as hydrochlorides. [c] Calcd.: C, 71.65; H, 8.10. Found: C, 71.70; H, 8.04. [d] *d*-Tartrate salt. Calcd.: C, 58.92; H, 6.92. Found: C, 58.60; H, 7.23.

a common intermediate, benzohydryl vinyl sulfone (XV), which then added the ethanol introduced to destroy the sodium amide.

The compounds listed in Table I were assayed for their analgesic effectiveness by a modified Ercoli–Lewis method.[11] The aminoalkyl ethyl benzohydryl sulfones were more active than either the higher or lower members in the series. Maximum activity was reached when the side chains were β-dimethylaminoisopropyl or β-piperidylisopropyl. Compound IX was about equal to methadone in analgesic potency but was only about half as toxic (LD_{50}).

Acknowledgments.—We wish to thank the Department of Pharmacology of this Institute for permission to use their data. We are also indebted to Dr. B. Elpern and Dr. A. Larsen of this Laboratory for some of the aminoalkyl halides used in this work.

Experimental

Preparation of the Benzohydryl Sulfones

Benzohydryl Mercaptan.—A solution of 254 g. of benzohydryl chloride and 97.5 g. of thiourea in 500 ml. of ethanol was refluxed for two hours. Then a solution of 76 g. of sodium hydroxide in 600 ml. of water was added and the boiling then continued for an additional two hours. The whole was allowed to cool to room temperature and the oil which had separated was removed. After the addition of dilute sulfuric acid (10 ml. of concentrated sulfuric acid in 100 ml. of water) the aqueous suspension was extracted thoroughly with ether. The extracts were combined with the first oil layer, dried and distilled to give 209 g. of a fraction boiling mainly at 135° at 1.5 mm. The pale blue[12] liquid was suitable for the next step.

In one experiment the benzohydrylisothiouronium chloride was isolated. When a solution of 365 g. of benzohydryl chloride and 137 g. of thiourea was refluxed for two hours and then cooled there was obtained 440 g. (88%) of a white crystalline solid in the first crop. After recrystallization from ethanol it melted at 196° (uncor.).

Anal. Calcd. for $C_{14}H_{15}ClN_2S$: N, 10.05. Found: N, 9.90.

Benzohydryl Methyl Sulfone.—To a cooled, stirred solution of 6.9 g. of sodium in 400 ml. of absolute alcohol there was added 60 g. of crude benzohydryl mercaptan. Then 19 ml. of methyl iodide was added dropwise to the solution and the mixture then refluxed for five hours. At the end of this time, the alcohol was removed by distillation and the residue poured into cold water. The oil was gathered in ether, dried and distilled to give 52 g. of the sulfide, b. p. 108–111° at 1 mm. To a solution of 28.3 g. of the above sulfide in 78 ml. of acetic acid held at 80° there was added dropwise with stirring 78 ml. of 30% hydrogen peroxide over a period of thirty minutes. After stirring for an additional thirty minutes at this temperature the solution was poured onto ice-water and the solid that separated collected on a filter. After recrystallization from dilute ethanol there was obtained 29 g. of the sulfone, m. p. 127–128.5° (uncor.).

Anal. Calcd. for $C_{14}H_{14}O_2S$: S, 13.02. Found: S, 12.60.

Benzohydryl *n*-Propyl Sulfone.—The crude sulfide, which was obtained from 0.2 *M* of crude benzohydryl mercaptan and an equivalent amount of sodium and *n*-propyl bromide in 200 ml. of absolute alcohol, was not distilled but dissolved in 75 ml. of acetic acid and oxidized with 60 ml. of 30% hydrogen peroxide at 80–90°. There was obtained 37.7 g. of sulfone, m. p. 111–113° (uncor.), after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{16}H_{18}O_2S$: S, 11.65. Found: S, 11.46.

Benzohydryl Ethyl Sulfone.—In the best preparation of this sulfone the isolation of the intermediates by distillation was avoided. The mercaptan was prepared as described above except that chloroform rather than ether was used to extract the aqueous mixture. The crude mercaptan was dried by azeotropic distillation, and alkylated in an alcohol solution (1 liter) containing 26.4 g. of sodium with 86 ml. of ethyl bromide. After four hours of reflux the alcohol was boiled off and the residue was then poured into water and the oil taken up in chloroform. The solvent was then removed and the sulfide dissolved in 560 ml. of acetic acid. To the stirred solution 300 ml. of 30% hydrogen peroxide was added at such a rate that the temperature was kept between 60 and 80°. The solution was then stirred for an additional hour during which time the temperature rose to 100°. The mixture was allowed to cool, poured into ice-water, filtered, washed with dilute sodium bisulfite and finally with water. After drying there was obtained 238 g. (81% based on benzohydryl chloride) of the sulfone, m. p. 132–134°. After recrystallization from 70% ethanol, from which it separated as long, flat blades, the compound melted at 136–138° (uncor.).

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[12] The blue color was probably due to the presence of some thiobenzophenone; *cf.* ref. 7.

Anal. Calcd. for $C_{15}H_{16}O_2S$: S, 12.32. Found: S, 12.12.

9-Fluorenyl Mercaptan.—To a gently boiling solution of 20 g. of 9-hydroxyfluorene in 50 ml. of dry toluene there was added dropwise 8.1 ml. of thionyl chloride. After refluxing for one hour the solution was taken to dryness *in vacuo*. The residue was dissolved in 50 ml. of ethanol and treated with 8.0 g. of thiourea. After three hours of refluxing 60 ml. of 10% sodium hydroxide was added and heating continued for two more hours. The mixture was cooled and the solid that separated was removed by filtration. The filtrate was made slightly acid with dilute sulfuric acid and chilled. The solid that separated was combined with the first crop and crystallized twice from methanol containing a small quantity of acetic acid. The mercaptan, which separated as shining white plates, melted at 105–106° (uncor.).

Anal. Calcd. for $C_{13}H_{10}S$: S, 16.18. Found: S, 16.21.

Ethyl 9-Fluorenyl Sulfone.—Twenty grams of the above mercaptan was converted to the ethyl sulfide in the usual way. The latter was oxidized in 100 ml. of acetic acid with 55 ml. of 30% hydrogen peroxide at 80–90°. The sulfone was recrystallized from ethanol, m. p. 168° (uncor.), wt. 9.2 g.

Anal. Calcd. for $C_{15}H_{14}O_2S$: S, 12.41. Found: S, 12.11.

Benzohydryl *p*-Tolyl Sulfone.—A solution of 100 g. of benzohydryl chloride in one liter of acetone was mixed with 120 g. of sodium *p*-toluenesulfinate in 350 ml. of water and allowed to stand for eighteen hours. The acetone was removed *in vacuo* and the residue poured onto ice. The solid that separated was filtered and recrystallized from acetic acid, m. p. 186–187° (uncor.).

Anal. Calcd. for $C_{20}H_{18}O_2S$: S, 9.99. Found: S, 9.85.

Aminoalkylation of the Sulfones

The first two experiments are typical examples of the alkylation procedures. In the first (Method A) the amino sulfone was isolated as the hydrochloride. In Method B the free base was obtained.

Ethyl 9-N-Piperidylethyl-9-fluorenyl Sulfone Hydrochloride (Method A).—A mixture of 9.2 g. of ethyl 9-fluorenyl sulfone, 4.2 g. of N-piperidylethyl chloride and 1.5 g. of pulverized sodium amide in 40 ml. of dry toluene was stirred under reflux for five hours. A small amount of alcohol was added to the cooled mixture before the whole was poured onto water. The layers were separated and the toluene solution then extracted with 10% hydrochloric acid. The acid extracts were made basic and the oil that separated could not be induced to crystallize. It was dissolved in ether, dried and concentrated. The residue was dissolved in dry ether and treated with a small amount of alcoholic hydrogen chloride. The gum that separated solidified on scratching and cooling. It was filtered and recrystallized from methanol–ether; yield, 7.8 g., m. p. 194.8–196.8° (cor.). The compound had slight analgesic action.

Anal. Calcd. for $C_{22}H_{26}NO_2S \cdot HCl$: N, 3.50; S, 8.02. Found: N, 3.22; S, 7.85.

1,1-Diphenyl-3-N-piperidylpropyl Ethyl Sulfone.—(Method B).—A suspension of 39 g. of ethyl benzohydryl sulfone, 22.2 g. of piperidylethyl chloride and 6.0 g. of pulverized sodium amide in 150 ml. of dry toluene was refluxed for five hours and then worked up as above. However, after treatment of the acid extracts with sodium hydroxide the gum that separated was removed from the supernatant liquor by decantation and then triturated with a small amount of alcohol. The resulting crystalline solid was collected on a filter and recrystallized from alcohol.

Miscellaneous Reactions

Benzohydryl γ-Chloropropyl Sulfone.—Forty grams of crude benzohydryl mercaptan was added to a cold solution of 4.6 g. of sodium in 100 ml. of absolute alcohol. This solution cooled to 5° was added dropwise with stirring to 31.4 g. of trimethylene chlorobromide cooled to zero degrees. An exothermic reaction occurred which resulted in a temperature rise to 50°. After stirring for thirty minutes the mixture was poured onto ice-water. The sulfide was taken up in toluene and the latter removed at the pump at 70°. The sulfide was dissolved in 100 ml. of acetic acid and oxidized at 80° with the aid of 90 ml. of 30% hydrogen peroxide. After stirring for one hour the mixture was diluted with ice-water, the sulfone filtered, and then recrystallized from alcohol; wt. 37.7 g., m. p. 112–113° (cor.).

Anal. Calcd. for $C_{16}H_{17}ClO_2S$: Cl, 11.48; S, 10.38. Found: Cl, 11.31; S, 10.49.

Benzohydryl γ-Piperidylpropyl Sulfone.—A mixture of 32.2 g. of the above chloro sulfone, 60 ml. of alcohol and 27 g. of piperidine was refluxed overnight. The alcohol was removed *in vacuo* and the residue warmed with dilute hydrochloric acid. The mixture was filtered and the filtrate made basic. The oil that separated solidified on scratching. It was crystallized twice from alcohol to yield 19 g. of the desired product, m. p. 119–120° (uncor.). When admixed with a sample of 1,1-diphenyl-3-N-piperidylpropyl methyl sulfone, m. p. 122.6–123.6°, a clear melt resulted before the temperature reached 105°.

Anal. Calcd. for $C_{21}H_{27}NO_2S$: S, 8.97; N, 3.84. Found: S, 8.96; N, 3.89. It formed a hydrochloride which after crystallization from dry ethanol melted at 210–212° (uncor.).

Anal. Calcd. for $C_{21}H_{27}NO_2S \cdot HCl$: S, 8.14; Cl, 9.00. Found: S, 8.14; Cl, 8.93.

2-Dimethylamino-4,4-diphenylbutane Hydrochloride. By Cleavage of 4-Dimethylamino-2,2-diphenylbutane Nitrile (Methadone Nitrile).[13]—A mixture of 27.8 g. of methadone nitrile, 15.6 g. of sodium amide and 150 ml. of dry toluene was refluxed with stirring for twelve hours. Excess sodium amide was destroyed with alcohol and the mixture then poured into water. The toluene layer was shaken with dilute hydrochloric acid and the acid extract then made basic. The oil that separated was extracted with ether and then dried over sodium sulfate. The solvent was removed and the residue converted to the hydrochloride, which after two recrystallizations from acetone, melted at 156–158° (cor.).

Anal. Calcd. for $C_{18}H_{22}N \cdot HCl$: C, 74.59; H, 8.35; Cl, 12.23. Found: C, 74.62; H, 8.20; Cl, 12.00.

By Cleavage of 3-Dimethylamino-1,1-diphenylbutyl Ethyl Sulfone (XI).—Ten grams of the sulfone dissolved in 300 ml. of ethanol was heated under reflux with approximately 200 g. of Raney nickel catalyst for six hours. The metal was then removed and the filtrate concentrated to dryness. The residue was covered with 30 ml. of Skellysolve B and cooled. The gummy solid that did not dissolve was removed by filtration and the filtrate extracted with dilute hydrochloric acid. The extracts were made basic and the oil was extracted with ether and dried. The solvent was removed and the residue distilled to give 3.0 g. of a colorless oil, b. p. 138–140° at 1 mm. This was dissolved in ether and treated with alcoholic hydrogen chloride. A gum separated which solidified on trituration with acetone. After two recrystallizations from acetone the salt melted at 155–157° (cor.) and did not depress the m. p. of the hydrochloride obtained by the cleavage of methadon nitrile.[14]

Benzohydryl β-Chloroethyl Sulfone.—The compound was prepared as its higher homolog except that 29 g. of ethylene chlorobromide was used instead of 31.4 g. of trimethylene chlorobromide. After oxidation of the crude sulfide with 30% hydrogen peroxide in the usual manner there was obtained 31.2 g. of the chlorosulfone, X, m. p. 109–110° (uncor.).

Anal. Calcd. for $C_{15}H_{15}ClO_2S$: S, 10.87; Cl, 12.03. Found: S, 10.70; Cl, 11.43.

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(13) We are indebted to Miss Mary Jackman for carrying out this experiment.

(14) The two specimens were examined microscopically by Dr. R. L. Clarke of this Laboratory, who reported that they had identical optical and crystallographic properties.

Benzohydryl β-Dimethylaminoethyl Sulfone.—A solution of 30 g. of X in 150 ml. of absolute ethanol was treated dropwise with 115 ml. of 1.73 *N* dimethylamine in absolute ethanol. A mildly exothermic reaction occurred and the mixture was allowed to stand for two hours. The solution was poured into water and the solid collected and crystallized from dilute ethanol; m. p. 114.8–115.8° (cor.), wt. 27.8 g.

Anal. Calcd. for $C_{17}H_{21}NSO_2$: N, 4.62; S, 10.57. Found: N, 4.37; S, 10.46.

Benzohydryl β-Piperidylethyl Sulfone.—This was prepared in an analogous fashion to its higher homolog, IV. From 51.2 g. of chlorosulfone there was obtained 50 g. of XI after recrystallization from alcohol; m. p. 118–119° (cor.).

Anal. Calcd. for $C_{20}H_{25}NO_2S$: N, 4.08; S, 9.34. Found: N, 4.01; S, 9.42.

Benzohydryl β-Hydroxyethyl Sulfone.—A solution of 40 g. of benzohydryl mercaptan in 100 ml. of absolute ethanol containing 4.6 g. of sodium was treated with 14.2 ml. of ethylene chlorohydrin. The temperature rose to 65° and heating under reflux was continued for one hour and the mixture was poured into water. The crude sulfide was removed with the aid of ether and after removal of the solvent was dissolved in 150 ml. of acetic acid and oxidized at 80° with an equal volume of 30% hydrogen peroxide. The sulfone, isolated in the usual manner, melted at 125° (uncor.) after crystallization from ethanol; wt. 27 g.

Anal. Calcd. for $C_{15}H_{16}O_2S$: S, 11.60. Found: S, 11.09.

The **acetate** was formed in the usual way. After crystallization from ethanol it melted at 103–104° (uncor.).

Anal. Calcd. for $C_{17}H_{18}O_4S$: S, 10.07. Found: S, 9.93.

Benzohydryl Ethoxyethyl Sulfone. A. From Benzohydryl β-Acetoxyethyl Sulfone.—A mixture of 12.0 g. of the sulfone, 2.5 ml. of ethyl iodide, 1.6 g. of sodium amide and 50 ml. of toluene was heated at 90° for about two hours. At the end of this time 10 ml. of ethanol was added and after stirring for about one-half hour longer the mixture was poured onto water. The insoluble material was filtered off. This was a high melting solid, soluble only in pyridine and could be recrystallized from this solvent after dilution with water; m. p. 223° (uncor.). The toluene solution was concentrated to dryness and the residue recrystallized twice from ethanol; m. p. 99–101° (uncor.), wt. 6.7 g.

Anal. Calcd. for $C_{17}H_{20}SO_3$: C, 67.07; H, 6.62. Found: C, 66.87; N, 6.61.

The same mixture of products was obtained when either benzohydryl β-piperidylethyl sulfone or benzohydryl β-dimethylaminoethyl sulfone were used in place of the acetoxyethyl sulfone in the above reaction. When 3.0 g. of benzohydryl β-chloroethyl sulfone in 5 ml. of ethanol was added to 2.0 g. of 50% potassium hydroxide and the mixture then heated on the steam-bath for thirty minutes, XIV was formed; wt. 2.0 g.

Anal. Calcd. for $C_{17}H_{20}SO_3$: S, 10.52. Found: S, 10.58.

B. From Ethoxyethyl Bromide and Benzohydryl Mercaptan.—A solution of 20 g. of benzohydryl mercaptan and 2.3 g. of sodium in 100 ml. of ethanol was refluxed for three hours with 15.3 g. of ethoxyethyl bromide. After isolation in the usual way the sulfide was oxidized with 30% hydrogen peroxide in acetic acid. The sulfone, XIV, was isolated in the customary way and after repeated recrystallization from ethanol melted at 100–100.5° (uncor.).

The identity of all the specimens was confirmed by the method of mixed melting points.

Attempted Alkylation of Benzohydryl β-Ethoxyethyl Sulfone.—When a suspension of 13 g. of the sulfone, XIV, was heated at 90° for three hours with 1.7 g. of sodium amide and 6.7 g. of ethyl iodide in 50 ml. of toluene a heavy precipitate separated during the course of the reaction. The solid was filtered off, suspended in alcohol and refiltered; wt. 10 g. It was recrystallized from dilute pyridine and melted at about 223° (uncor.).

Anal. Calcd. for $C_{32}H_{32}S_2O_5$: C, 68.54; H, 5.75; S, 11.23. Found: C, 69.15; H, 5.78; S, 11.52.

Summary

1. The preparation of some alkyl benzohydryl sulfones, *p*-tolyl benzohydryl sulfone and ethyl 9-fluorenyl sulfone has been described.

2. The alkylation of these compounds with dialkylaminoalkyl chlorides has been carried out using sodium amide as the condensing agent.

3. It has been shown that the product obtained from dimethylamino isopropyl chloride and ethyl benzohydryl sulfone is the sulfone analog of methadone or that rearrangement preceded the alkylation.

4. Several β-substituted ethyl benzohydryl sulfones have been synthesized. When alkylation with ethyl iodide and sodium amide was attempted, the β-substituent was lost and replaced by an ethoxyl group which came from the ethanol used to destroy excess condensing agent.

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