tions is about 10^{-9} atmosphere, the rate constant of the reverse reaction would have to be enormous. While the process of equation (3) cannot be excluded, it seems unlikely. In any case it could not proceed by the reverse of Beeck's mechanism for olefin hydrogenation.[16] In this a molecule of alkane striking the catalyst would lose two hydrogen atoms and rebound as olefin. The racemized alkane would then contain two and only two deuterium atoms contrary to our experimental results.

The results on nickel–kieselguhr catalysts should not at present be extrapolated to other catalysts. Preliminary experiments in this Laboratory indicate different behavior for cracking catalysts and chromium oxide–alumina catalysts.

Thermomagnetic analysis[17] shows that the ferromagnetism of nickel–kieselguhr as supplied is nearly tripled upon reduction. The ferromagnetism of both forms declines steadily with temperature and reaches low values by 360°. The absence of a Curie point at 357° indicates the absence of any substantial amount of pure, bulk, metallic nickel, but suggests, rather, the presence of a heterogeneous system.

de Lange and Visser[18] report that unreduced nickel–kieselguhr catalysts (20% nickel) possess a layer lattice and that, upon reduction, no X-ray lines characteristic of bulk metallic nickel appear.

It appears desirable to extend these studies to other catalysts known to activate hydrocarbon molecules and particularly to other types of nickel catalysts.

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE COLLEGE]

The Synthesis of Some Tertiary Amine Derivatives of Mixed Phenyl Alkyl Sulfides

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The properties and syntheses of a series of hydrochlorides of tertiary amine derivatives of mixed phenyl alkyl sulfides, ω-(N,N-disubstituted amino)-alkylphenyl sulfides, are described.

As part of a study of sulfur-containing compounds of pharmacological interest, some tertiary amine derivatives of mixed phenyl alkyl sulfides, $C_6H_5S(CH_2)_nNR_2$ (I), were prepared because of the interesting activity possessed by the corresponding ether analogs.

In one of the two reported cases of an investigation of the physiological action of compounds of this type Buchel and Tchoubar[2] compared β-diethylaminoethylphenyl sulfide and β-diethylaminoethyl *o*-tolyl sulfide with their corresponding oxygen ethers. In the other investigation Kohler[3] reported a comparison of the physiological actions of β-ethylaminoethylphenyl sulfide and β-ethylaminoethyl *o*-tolyl sulfide with β-dimethylaminoethylphenyl ether and bis-(β-*o*-toloxyethyl)-methylamine. However, in neither of these limited investigations were a sufficient number of sulfur compounds prepared to allow a complete physiological study to be made of them.

The aminoalkyl phenyl sulfides of the present investigation were prepared by the following sequence of reactions

$$C_6H_5SH + Cl(CH_2)_nOH \xrightarrow{NaOH} C_6H_5S(CH_2)_nOH \quad (II)$$

$$C_6H_5S(CH_2)_nOH \xrightarrow[C_5H_5N]{SOCl_2} C_6H_5S(CH_2)_nCl \quad (III) \xrightarrow[C_6H_5CH_3]{R_2NH} (I)$$

The ω-hydroxyalkylphenyl sulfides (II) with two to six carbon atoms in the alkyl chain, including a branched alkyl chain of three carbon atoms, were prepared by the interaction of thiophenol and the corresponding chlorohydrin, extending the procedure developed by Kirner and Richter[4] for the preparation of β-hydroxyethyl and γ-hydroxypropylphenyl sulfides.

The ω-hydroxylalkylphenyl sulfides were further characterized by the preparation of the 3,5-dinitrobenzoate and *p*-nitrobenzoate derivatives. The properties of those derivatives which have not previously been reported are listed in Table II.

The ω-chloroalkylphenyl sulfides (III) were obtained from the corresponding ω-hydroxyalkylphenyl sulfides by a modification of the method of Darzens.[5]

In an effort to shorten the synthetic scheme shown above, by preparing the ω-chloroalkylphenyl sulfides directly from thiophenol, the use of ω-

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TABLE I

TERTIARY AMINE DERIVATIVES OF MIXED PHENYLALKYL SULFIDE HYDROCHLORIDES $C_6H_5—S(CH_2)_nN\langle^{R}_{R}$ HCl

Phenyl sulfide hydrochlorides	M.p., °C.	Formula	Yield, %	Nitrogen, % Calcd.	Found	Sulfur, % Calcd.	Found
β-Piperidylethyl[a]	185–186	$C_{13}H_{20}SNCl$	50	5.44	5.44	12.45	12.36
β-Morpholylethyl[c]	123–125	$C_{12}H_{18}OSNCl$	69	5.39	5.38	12.35	12.36
γ-Piperidyl-*n*-propyl[a]	149–150	$C_{14}H_{22}SnCl$	90	5.16	5.15	11.81	11.85
γ-Morpholyl-*n*-propyl[c]	142–143	$C_{13}H_{20}OSNCl$	85	5.12	5.10	11.72	11.58
β-Piperidyl-*n*-propyl[b]	128–130	$C_{14}H_{22}SNCl$	90	5.16	5.17	11.81	11.50
β Morpholyl-*n*-propyl[c]	146–148	$C_{13}H_{20}OSNCl$	55	5.12	5.07	11.72	11.34
δ-Piperidyl-*n*-butyl[c]	137–138	$C_{15}H_{24}SNCl$	90	4.90	4.97	11.23	11.05
δ-Morpholyl-*n*-butyl[c]	113–114	$C_{14}H_{22}OSNCl$	60	4.87	4.83	11.15	11.10
ε-Piperidyl-*n*-amyl[c]	118–122	$C_{16}H_{26}SNCl$	88	4.67	4.24	10.70	10.10
ε-Morpholyl-*n* amyl[c]	117–120	$C_{15}H_{24}OSNCl$	60	4.64	4.67	10.63	10.67
ω Piperidyl-*n*-hexyl[c]	119–121	$C_{17}H_{28}SNCl$	57	4.47	4.66	10.22	9.96
ω-Morpholyl-*n*-hexyl[c]	112–114	$C_{16}H_{26}OSNCl$	41	4.44	4.52	10.16	9.83
β-Dimethylaminoethyl[c]	114–115	$C_{10}H_{16}SNCl$	40	6.44	6.55	14.74	14.74
γ-Diethylamino-*n*-propyl[c]	131–132	$C_{13}H_{22}SNCl$	81	5.46	5.13	12.36	12.80

Crystallized from [a] isopropyl alcohol; [b] benzene; and [c] 1,4-dioxane.

TABLE II

p-NITROBENZOATES AND 3,5-DINITROBENZOATES OF ω-HYDROXYALKYLPHENYL SULFIDES

Phenyl sulfide[b]	Ester[a]	M.p., °C.	Formula	Sulfur, % Calcd.	Found
β-Hydroxyethyl	D.N.B.	112–113	$C_{15}H_{12}O_6SN_2$	9.21	9.38
β-Hydroxyethyl	P.N.B.	58–59	$C_{15}H_{13}O_4SN$	10.58	10.68
β-Hydroxy-*n*-propyl	D.N.B.	108–110	$C_{16}H_{14}O_6SN_2$	8.85	8.72
β-Hydroxy-*n*-propyl	P.N.B.	63–64	$C_{16}H_{15}O_4SN$	10.17	10.35
γ-Hydroxy-*n*-propyl	D.N.B.	84–85	$C_{16}H_{14}O_6SN_2$	8.85	8.86
γ-Hydroxy-*n*-propyl	P.N.B.	59–60	$C_{16}H_{15}O_4SN$	10.17	10.43
δ-Hydroxy-*n*-butyl	D.N.B.	85–86	$C_{17}H_{16}O_6SN_2$	8.53	8.75
δ-Hydroxy-*n*-butyl	P.N.B.	59–60	$C_{17}H_{17}O_4SN$	9.69	9.92
ε-Hydroxy-*n*-amyl	D.N.B.	73–74	$C_{18}H_{18}O_6SN_2$	8.22	8.50
ε-Hydroxy-*n*-amyl	P.N.B.	54–55	$C_{18}H_{19}O_4SN$	9.29	9.39
ω-Hydroxy-*n*-hexyl[c]	D.N.B.	136–140	$C_{19}H_{20}O_6SN_2$	7.93	8.06
ω-Hydroxy-*n*-hexyl[c]	P.N.B.	104–109	$C_{19}H_{21}O_4SN$	8.93	8.37

[a] D.N.B. = 3,5-dinitrobenzoate; P.N.B. = *p*-nitrobenzoate; [b] crystallized from ethyl alcohol; and [c] crystallized from a mixture of ethyl and *n*-propyl alcohol.

chloroalkyl benzenesulfonate as a chloroalkylating agent for thiophenol was investigated. Clemo and Perkin[6] reported good results were obtained in an analogous preparation of β-chloroethylphenyl ether from phenol and β-chloroethyl benzenesulfonate.

The interaction of thiophenol and β-chloroethyl benzenesulfonate gave β-chloroethylphenyl sulfide in a low yield along with 1,2-bis-(thiophenyl)-ethane. The low yield of the β-chloroethylphenyl

$$C_6H_5SNa + C_6H_5OSO_2(CH_2)_2Cl \longrightarrow C_6H_5SO_3Na + (C_6H_5SCH_2)_2 + C_6H_5S(CH_2)_2Cl$$

sulfide, which possesses a reactive halogen, was due to its easy conversion to 1,2-bis-(thiophenyl)-ethane by further reaction with sodium thiophenolate. The 1,2-bis-(thiophenyl)-ethane was identified by comparison with an authentic sample of this material.[7]

The tertiary amine derivatives of the mixed phenyl alkyl sulfides were obtained from the ω-chloroalkylphenyl sulfides by treatment with a two molar excess of the corresponding secondary amines which included piperidine, morpholine, dimethylamine and diethylamine. The reactions were carried out in toluene as a solvent and varied with respect to time, temperature and experimental technique, depending on the nature of the secondary amine and the reactivity of the particular ω-chloroalkylphenyl sulfide used. The over-all yields of the morpholine derivatives were in general lower than the dialkyl and piperidine derivatives, presumably because of the lower basicity of the morpholine. Altogether, fourteen new tertiary amine derivatives of mixed alkyl phenyl sulfides where prepared. Some of their properties are summarized in Table I.

The pharmacological studies on these substances did not include the hydrochlorides of ε-piperidyl-*n*-amyl, ε-morpholyl-η-amyl and γ-diethylamino-η-propyl phenyl sulfides. The other ω-(N,N-disubstituted amino)-alkylphenyl sulfide hydrochlorides were tested as local anesthetics by the rabbit cornea method and the guinea pig intracutaneous test. In the cornea test, most of the materials were inactive with the ω-piperidyl-η-hexyl and ω-morpholyl-η-hexyl compounds showing the maximum effect. These compounds at 1% concentration give about 30 minutes of anesthesia with mild irritation. This is in the "Butyn" range of activity. In the intracutaneous test all the compounds studied showed some effect with the γ-piperidyl-η-propyl and γ-morpholyl-η-propyl hav-

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ing an activity in the range of performance of procaine.

Experimental

Materials.—Thiophenol, ethylene chlorohydrin, propylene chlorohydrin, trimethylene chlorohydrin, morpholine, piperidine, diethylamine and dimethylamine as a 25% aqueous solution were obtained from Matheson Chemical Corporation. A generous sample of tetrahydrofuran was supplied by the Electro Chemical Division of the du Pont Company.

ω-Hydroxyalkylphenyl Sulfides.—These compounds were prepared in yields of 65 to 90% by the direct interaction of thiophenol with the corresponding chlorohydrin in aqueous sodium hydroxide.[4]

Benzoate Derivatives.—The 3,5-dinitro- and *p*-nitrobenzoate derivatives were prepared by known methods.

ω-Chloroalkylphenyl Sulfides.—These chlorides were obtained by treating the corresponding ω-hydroxyalkylphenyl sulfides with thionyl chloride following a method already described[8] except that pyridine was used as a reaction medium.

β-Chloroethylphenyl Sulfide and 1,2-Bis-(thiophenyl)-ethane.—To 30 ml. of water in a three-neck flask fitted with a reflux condenser and stirrer was added 17 g. (0.425 mole) of sodium hydroxide and 45.5 g. (0.413 mole) of thiophenol. To the rapidly stirred solution was added quickly 91 g. (0.413 mole) of β-chloroethylbenzene sulfonate.[6] A vigorous exothermic reaction took place causing the temperature to rise to 100° with the formation of insoluble sodium benzene sulfonate. At this point an additional 70 ml. of water was added to the reaction mixture; the sodium salt was broken up and stirring continued for a half hour. The contents of the flask were filtered and the sodium benzene sulfonate washed several times with ether. The ether layer was separated from the filtrate, and washed several times with water and dried over anhydrous sodium sulfate. After removal of the ether the β-chloroethyl phenyl sulfide was distilled using a heat jacketed column, 30 cm. in height, 12 mm. in diameter and packed with 1/3" glass helices to yield 18 g. (25%), b.p. 115–117° (9 mm.).

The light brown oily residue solidified on cooling to room temperature. It was recrystallized from ethyl alcohol after treatment with Norite B to give a white solid; m.p. 66–67°. There was no depression in the melting point of this substance when mixed with an authentic sample of 1,2-bis-(thiophenyl)-ethane.[7]

ω-(N,N-Disubstituted Amino)-alkylphenyl Sulfides.—Two methods were employed for the preparation of these compounds, depending on the nature of the secondary amine used. With dimethyl and diethyl amine the reactions were carried out in a sealed tube while with piperidine and morpholine ordinary equipment was employed.

Method A.—In a typical experiment 27.5 g. (0.32 mole) of piperidine dissolved in 25 ml. of dry toluene was placed in a three-neck flask fitted with a dropping funnel, reflux condenser and stirrer. To this, was added dropwise 18.5 g. (0.107 mole) of β-chloroethylphenyl sulfide dissolved in 25 ml. of toluene. The reaction mixture was maintained at a slow reflux, 100°, for an hour and a half at which time there was no further precipitation of piperidine hydrochloride. This was taken to indicate completeness of reaction. The reaction mixture was then neutralized by the addition of 4.28 g. (0.107 mole) of sodium hydroxide dissolved in 60 ml. of water, whereupon a yellow oil separated. The solvent and excess piperidine were removed by steam distillation. Application of the Simmons[9] color test to the steam distillate indicated when the excess secondary amine had been completely removed. The reaction mixture was dissolved by a slight excess of concentrated hydrochloric acid, followed by extraction with ether to remove any unreacted β-chloroethylphenyl sulfide. Excess sodium hydroxide solution was added, and the resulting oil was separated and combined with a benzene extract of the aqueous layer. After washing with water, the benzene solution was dried over anhydrous sodium sulfate. The benzene was removed on a steam-bath and the oily free amine (13.0 g., 50%) was taken up in 400 ml. of dry ether. Gaseous hydrogen chloride gas was used to convert the amine to its hydrochloride, which was recrystallized twice from dry isopropyl alcohol being decolorized each time with Norite. The product crystallized in needles, m.p. 185–186°.

Anal. Calcd. for $C_{13}H_{20}SCl$: N, 5.44; S, 12.45. Found: N, 5.44; S, 12.36.

Method B.—A mixture of 16 g. (0.1 mole) of β-chloroethylphenyl sulfide and 52 g. of a 25% by weight aqueous solution of dimethylamine (equivalent to 13 g. or 0.29 mole of amine) in 135 ml. of 1,4-dioxane as a solvent was placed in a heavy walled Pyrex tube, after which it was sealed. The tube was put in a Carius oven and slowly brought to a temperature of 130° over a 22-hour period. After cooling overnight it was removed from the oven and opened. The tertiary amine was isolated in the manner described in method A. The yield of amine hydrochloride was 40%, and after recrystallization from 1,4-dioxane melted at 114–115°.

Anal. Calcd. for $C_{13}H_{22}SnCl$: N, 6.44; S, 14.74. Found: N, 6.55; S, 14.74.

Tetramethylene Chlorohydrin.—This material was prepared from tetrahydrofuran by treatment with gaseous hydrogen chloride using the method of Starr and Hixon.[10]

Pentamethylene Chlorohydrin.—This chlorohydrin was obtained from the corresponding glycol and gaseous hydrogen chloride employing the procedure developed by McElvain and Carney.[11]

Hexamethylene Chlorohydrin.—This substance was obtained by treating hexamethylene glycol with gaseous hydrogen chloride following the method employed by Muller and Vanc.[12]

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