$$\begin{array}{ccccc} & & \overset{\text{(fast)}}{\rightleftharpoons} & & \\ \text{Oleic} + Se_2 & & \text{Oleic}\cdot Se_2(\pi) & \longrightarrow & \text{Oleic}\cdot Se_2(\sigma) \\ & & \uparrow\downarrow \text{(slow)} & & \\ \text{Elaidic} + Se_2 & & \underset{\text{(fast)}}{\rightleftharpoons} \text{Elaidic}\cdot Se_2(\pi) & \longrightarrow & \text{Elaidic}\cdot Se_2(\sigma) \end{array}$$

The pseudo first-order rate dependence on substrate means that the active catalytic species is remaining essentially constant at any particular initial concentration of selenium during the major portion of the isomerization reaction. The dissociation of selenium and the establishment of the equilibrium concentration of complexed selenium must be fast. The rate-determining isomerization of one π-complex to the other continues until the selenium is consumed by conversion to the σ-complex. The essential constancy of concentration of complexed selenium at any particular initial concentration of selenium can be determined experimentally and such work is in progress.

The complete rate equation shows the selenium dependence. The known occurrence of an Se_8 species and its dissociation to Se_2 lend credence to the fractional exponent in the rate equation. Also the specificity of the crystalline modification of selenium indicates the necessity of having a special form of selenium available. The increase in rate with increasing concentration of initial selenium is explained by the increased concentration of the π-complex which is essential in order to satisfy the equilibrium constant for the π-complex.

The above "mechanism" does not detail the exact nature of the bonding either in the π- or the σ-complex. The π-complex possibly involves the π-orbital of the olefin and the anti-bonding π-orbital of selenium, but this is conjecture and until further evidence is available it is felt that discussion of the exact bonding in the complexes would not be fruitful.

Acknowledgment.—The authors wish to thank Emery Industries, Inc., for a generous fellowship which made this work possible.

CINCINNATI 21, OHIO

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH DEPARTMENT, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Synthesis of Certain 3-Hydroxy-3-phenylpropylsulfonium Salts. Sulfonium Analogs of Artane (Trihexyphenidyl) and Pathilon (Tridihexethyl Iodide)

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Sulfonium analogs (I) of the antispasmodic Artane (trihexyphenidyl) and the gastric secretion inhibitor Pathilon (tridihexethyl iodide) have been prepared by condensation of several 3-alkylmercapto-1-phenylpropan-1-ols (IV) with methyl, ethyl, allyl, propargyl and benzyl halides. 1-Cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V), which reacts "normally" with the above halides, unexpectedly gave (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium iodide (VIa) when treated with propyl, butyl or amyl iodide. Other anomalous results are reported. The antispasmodic and gastric secretion inhibitory activities are given.

In the search for more useful pharmaceutical agents, sulfonium salts are interesting as analogs of pharmacologically active ammonium derivatives. Sulfonium salts are not only analogs of the quaternary ammonium compounds, but they also may be considered analogs of the tertiary amines, insofar as the pharmacological activity of the amines is mediated by their protonated derivatives, the tertiary ammonium salts. Various sulfonium analogs of pharmacologically active ammonium compounds and amines have been reported. These include analogs of the muscle contracting agent, tetramethylammonium iodide,[1,2] of acetylcholine,[3,4] of the curare-like succinylcholine[5] and decamethonium (decamethylene bistrimethylammonium iodide),[6a] of the hypotensive agents pentamethonium (pentamethylene bistrimethylammonium iodide)[6a] and hexamethonium (hexamethylene bistrimethylammonium iodide),[6b] of the antispasmodics Trasentine[6c] (β-diethylaminoethyl diphenylacetate hydrochloride)[7,8a] and Pavatrine[8b] (β-diethylaminoethyl fluorene-9-carboxylate),[7,8a] of the antihistaminic Benadryl[8c] [dimethyl-(2-benzhydroloxyethyl)-amine][9] and of the sympathomimetic β-hydroxy-β-phenylethylamines.[10,11]

We wish to report the preparation of sulfonium compounds of the type represented by structure I. These compounds are analogs of the gastric

(1) H. R. Ing and W. M. Wright, *Proc. Royal Soc. (London)*, **B114**, 48 (1933).

(2) R. Hunt and R. R. Renshaw, *J. Pharmacol. Exptl. Therap.*, **25**, 315 (1925).

(3) V. Prelog, *et al.*, *Helv. Chim. Acta*, **25**, 907 (1942).

(4) H. R. Ing, *et al.*, *Brit. J. Pharmacol.*, **7**, 112 (1952).

(5) M. Protiva, J. Pliml and P. Finglova, *Coll. Czech. Chem. Comm.*, **19**, 619 (1954).

(6) (a) J. Walker, *J. Chem. Soc.*, 193 (1950); (b) R. B. Barlow and J. R. Vane, *Brit. U. Pharmacol.*, **11**, 198 (1956); (c) Trasentine is the registered trademark of Ciba Pharmaceutical Products for adiphenine.

(7) M. Protiva and O. Exner, *Coll. Czech. Chem. Comm.*, **19**, 524 (1954).

(8) (a) O. Exner, M. Borovicka and M. Protiva, *ibid.*, **18**, 270 (1953); (b) Pavatrine is the registered trademark of G. D. Searle and Co. for carbofluorene aminoester.

(9) M. Protiva and O. Exner, *Coll. Czech. Chem. Comm.*, **16**, 689 (1952).

(10) V. Prelog, *et al.*, *Helv. Chim. Acta*, **27**, 1209 (1944).

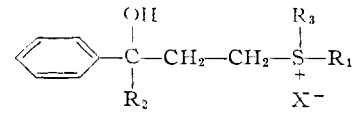
(11) Other reports of interest include certain sulfonium salts with germicidal activity,[12] a highly toxic analog of quinuclidine[13] and certain phenacylsulfonium salts prepared as potential tumor necrotizing agents.[14]

(12) R. Kuhn and O. Dann, *Ber.*, **73B**, 1092 (1940).

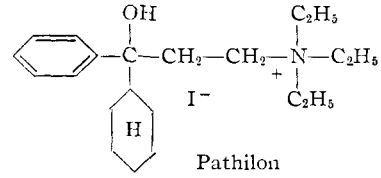
(13) V. Prelog and D. Kohlbach, *ibid.*, **72B**, 672 (1939).

(14) H. Rutter, THIS JOURNAL, **73**, 5905 (1951).

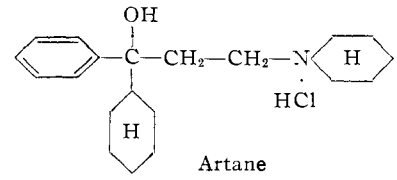
secretion inhibitor Pathilon[15] (tridihexethyl iodide) and of the antispasmodic Artane[19] (trihexyphenidyl).



I



Pathilon



Artane

The compounds were prepared by the sequence.

$$CH_2{=}CH{-}CN + R_1SH \longrightarrow R_1{-}S{-}CH_2{-}CH_2CN$$

II

$$\xrightarrow{C_6H_5MgBr} R_1{-}S{-}CH_2{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 \xrightarrow{R_2MgBr}$$

III

$$R_1{-}S{-}CH_2{-}CH_2{-}\overset{\overset{OH}{|}}{\underset{\underset{R_2}{|}}{C}}{-}C_6H_5 \xrightarrow{R_3X} I$$

IV

β-Methyl- and β-ethylmercaptopropionitrile were obtained in good yields by cyanoethylation of the appropriate mercaptans[21] and were converted by reaction with phenylmagnesium bromide to the corresponding β-alkylmercaptopropiophenones (III) in yields of 50–60%. Much mercaptan was evolved during the latter reaction and considerable quantities of polymeric material were formed. Evidently, treatment of the β-alkylmercaptopropionitrile II with the Grignard reagent resulted in some β-elimination of alkylmercaptan with the concomitant generation of the easily polymerized acrylonitrile. Both β-methyl- and β-ethylmercaptopropiophenone have been prepared previously by Bohme and Heller[22] from β-chloropropiophenone and the required sodium alkyl mercaptide.

Reaction of the β-alkylmercaptopropiophenones III with the appropriate Grignard reagent afforded the desired tertiary carbinols IV: these are listed in Table I. The product from the reaction with butylmagnesium bromide apparently was contaminated with a considerable quantity of precursor ketone.

Finally, the sulfonium salts I were obtained from the alkylmercapto substituted tertiary carbinols of Table I by treatment with alkyl or other halides; these sulfonium salts are listed in Table II. Methyl and ethyl iodide and the reactive halides, allyl iodide, propargyl bromide and benzyl bromide generally reacted smoothly to give the expected sulfonium salts. Thus, 1-cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V) reacted with methyl iodide (to give VIa), allyl iodide, propargyl bromide and benzyl bromide to give in each case the anticipitated sulfonium derivative and except for the benzyl bromide reaction, where the yield was 30% the yields were good (58–77%). Treatment of V with ethyl iodide gave an oil from which a crystalline product could not be isolated. The desired product, (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-ethylmethylsulfonium iodide (I, R_1 = methyl, R_2 = cyclohexyl, R_3 = ethyl), was obtained by a reverse procedure in 46% yield from the reaction of methyl iodide with the ethylmercapto substituted carbinol (IV, R_1 = ethyl, R_2 = cyclohexyl).

Surprisingly, when the sulfide V was treated with propyl, butyl or amyl iodide, the dimethylsulfonium derivative, (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium iodide (VIa), was obtained in each instance as the only isolable product in yields of 32, 43 and 56%, respectively.

$$2\ C_6H_5{-}\overset{\overset{OH}{|}}{\underset{\underset{C_6H_{11}}{|}}{C}}{-}CH_2{-}CH_2{-}S{-}CH_3 + RX \longrightarrow$$

V

$$C_6H_5{-}\overset{\overset{OH}{|}}{\underset{\underset{C_6H_{11}}{|}}{C}}{-}CH_2{-}CH_2{-}\overset{\overset{CH_3}{|}}{S}{-}CH_3\ X^-$$

VI

a series: X = I; b series: X = Br

R = $CH_3CH_2CH_2$, $CH_3(CH_2)_3$ or $CH_3(CH_2)_4$

Similar phenomena have been observed by other workers[10,23–25] and may be interpreted as proceeding according to the mechanism schematically illustrated as

$$R{-}S{-}CH_3 + R'X \xrightarrow{(1)} R{-}\overset{\overset{CH_3}{|}}{S}{-}R'\ I^-$$

VII VIII

$$VII + VIII \xrightarrow{(2)} R{-}\overset{\overset{CH_3}{|}}{S}{-}CH_3\ X^- + R{-}S{-}R'$$

IX

(15) Pathilon is the registered trademark of the American Cyanamid Co., Lederle Laboratories Division, for tridihexethyl iodide. Pathilon is a useful agent for the treatment of peptic ulcers.[16] The bromide salt is reported by Denton and Lawson.[17] The antigastric secretion properties of Pathilon have been reported by Osterberg and Cunningham.[18]

(16) S. A. Schwartz and H. G. Bauer, *Rev. Gastroenterology*, **20**, 913 (1953).

(17) J. J. Denton and V. A. Lawson, THIS JOURNAL, **72**, 3279 (1950).

(18) A. C. Osterberg and R. W. Cunningham, *J. Pharmacol. Exptl. Therap.*, **113**, 41 (1955).

(19) Artane is the registered trademark of the American Cyanamid Co., Lederle Laboratories Division, for trihexyphenidyl. Artane is an important therapeutic agent for the treatment of Parkinsonism (*paralysis agitans*). The chemistry and *in vitro* activity of Artane and related compounds is reported in a series of papers by Denton and co-workers (see THIS JOURNAL, **72**, 3795 (1950), and preceding papers). The pharmacology of Artane and related compounds has been reported by Cunningham and co-workers.[20]

(20) R. W. Cunningham, *et al.*, *J. Pharmacol. Exptl. Therap.*, **95**, 151 (1949).

(21) C. Hurd and L. Gershbein, THIS JOURNAL, **69**, 2328 (1947).

(22) H. Bohme and P. Heller, *Ber.*, **86**, 443 (1953).

(23) T. R. Lewis and S. Archer, THIS JOURNAL, **73**, 2109 (1951).

(24) F. D. Ray and I. Levene, *J. Org. Chem.*, **2**, 267 (1937).

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

TABLE I

3-ALKYLMERCAPTO-1-PHENYLPROPAN-1-OLS, $R_1—S—CH_2—CH_2—\underset{\displaystyle R_2}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}—C_6H_5$

Substituents		B.p.[a]		Yield,	Empirical	Analyses, %					
						Calcd.			Found		
R_1	R_2	°C.	Mm.	%	formula	C	H	S	C	H	S
CH_3	C_6H_{11}	150[b]	0.9	32	$C_{16}H_{24}OS$	72.7	9.09	12.1	72.8	8.83	11.8
CH_3	n-C_4H_9	130[c]	0.25	50	$C_{14}H_{22}OS$	70.5	9.31	13.5	67.7	8.84	13.5
CH_3	C_6H_5	M.p. 109[d]		44	$C_{16}H_{18}OS$	74.4	6.98	12.4	74.2	6.79	12.4
C_2H_5	$C_6H_5CH_2$	157–158	0.3	29	$C_{18}H_{22}OS$	75.5	7.70	11.2	75.7	7.70	11.1
C_2H_5	C_6H_{11}	182–185	2	34	$C_{17}H_{26}OS$	73.4	9.36	11.5	73.4	9.49	11.1

[a] Of analytical material. [b] Fractions within the refractive index range of 1.5454–1.5519 were satisfactory for further use. [c] Impure product, probably contaminated with ketone. [d] Product obtained, without distillation, after distilling combined ether extracts.

TABLE II

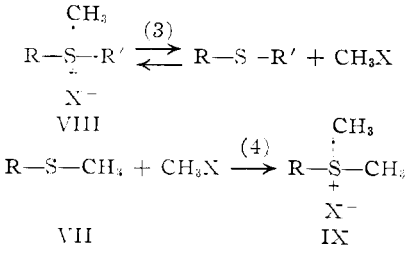
SULFONIUM SALTS, $R_1—\overset{\displaystyle R_3}{\overset{|}{\underset{|}{\overset{+}{S}}}}—CH_2—CH_2—\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}—C_6H_5$ X^- R_2

	R_3X	R_1	R_2	Yield, %	M.p.,[a] °C.	Formula	Carbon, %		Hydrogen, %		Sulfur, %		Halide, %		Pharmacol. act. Gastric secretion inhib.		Pharmacol. act. Anti-spasmodic
							Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	5 mg./kg.[b]	10 mg./kg.[b]	
1	CH_3I[c]	CH_3	C_6H_{11}	77	138–140[d]	$C_{17}H_{27}IOS$	50.2	49.5	6.70	6.37	7.89	7.68	31.2	31.4	D[i]	2	3
2	CH_3I[e]	C_2H_5	C_6H_{11}	46	116.5[f]	$C_{18}H_{29}IOS$	51.4	51.6	6.91	6.69	7.62	7.55	30.2	30.2	0	3	3
3	$H_2C{=}CHCH_2I$[e]	CH_3	C_6H_{11}	70	107–108[d]	$C_{19}H_{29}IOS$	52.8	52.9	6.76	6.67	7.42	7.34	29.4	29.5	2	5	3
4	$HC{\equiv}CCH_2Br$[g]	CH_3	C_6H_{11}	58	118–118.5[f,h] 145	$C_{19}H_{27}BrOS$	59.6	59.7	7.06	6.74	8.36	8.15	20.9	21.4	2		
5	C_2H_5I[e]	C_2H_5	C_6H_{11}	77	112–113[j]	$C_{19}H_{13}IOS$	52.5	52.6	7.20	7.20	7.38	7.19	29.2	28.9	3		3
6	$C_6H_5CH_2Br$[k]	CH_3	C_6H_{11}	30	121.5[l]	$C_{23}H_{31}BrOS$	63.4	63.5	7.18	7.06	7.36	7.14	18.4	18.8	0	3	2
7	$HC{\equiv}CCH_2Br$[e]	C_2H_5	C_6H_{11}	21	104–106[m]	$C_{20}H_{29}BrOS$	60.5	60.7	7.32	7.32	8.06	8.21	20.1 (Br)	20.0 (Br)			
8	p-$ClC_6H_4COCH_2Br$[n]	CH_3	C_6H_{11}	27	120-122[d]	$C_{24}H_{30}BrClO_2S$	57.9	57.9	6.07	5.88	6.44	6.82	16.1 (Cl) 7.12	16.5 (Cl) 7.39	0		
9	CH_3I[k]	CH_3	C_6H_5	81	142[o]	$C_{17}H_{21}IOS$	51.0	51.0	5.30	5.30	8.00	7.90	31.7	31.9	0	0	2
10	CH_3I[c]	C_2H_6	$C_6H_5CH_2$	71	115.5[f]	$C_{19}H_{25}IOS$	53.3	52.2	5.84	5.87	7.48	7.59	29.7	29.8	0	0	2

[a] Of the analytical sample. In most cases the melting points varied with the rate of heating. [b] Dose level in the rat. The candidate drug was administered subcutaneously in a 2% aqueous starch suspension. [c] Reaction was carried out in excess methyl iodide. [d] Recrystallized from absolute ethanol. [e] Reaction was carried out in ether. [f] Product was dissolved in methanol and reprecipitated with ether. [g] No reaction solvent was used. [h] The two melting points represent different polymorphic forms. Polymorphism was demonstrated by infrared analysis and microscopic examination. [i] D = doubtful activity at this dose level. [j] Recrystallized from methyl ethyl ketone. [k] Reaction was carried out in acetone. [l] Product was dissolved in acetone and reprecipitated with ether. [m] Product was dissolved in ethanol and reprecipitated with ether. [n] Reaction was carried out in methanol. [o] Product was recrystallized from methanol.

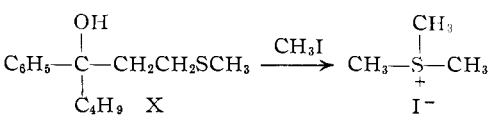
Thus, the formation of the "normal" sulfonium salt VIII may be considered to occur to a limited extent (equation 1). This salt then functions as an alkylating agent, in competition with R'X, to produce the observed dimethylsulfonium derivative IX and a new thioether, R–S–R' (equation 2). This is essentially the mechanism used by Lewis and Archer to explain the formation of dibenzyl sulfide (R–S–R') from the reaction of benzyl mercaptan with methyl iodide.[23]

An alternative explanation by Ray and Levine[24] likewise postulates the initial formation of the desired sulfonium salt VIII which, however, is considered to be in equilibrium with the thioether, R–S–R', and methyl halide (equation 3). The methyl halide so formed reacts with the original thioether VII to give the observed dimethylsulfonium derivative IX (equation 4).



The dimethylsulfonium salt VIb was also obtained (10% yield) as the only isolable product when the sulfide V was treated with phenacyl bromide; whereas when *p*-chlorophenacyl bromide was used, the "normal" sulfonium derivative was obtained in 27% yield. The failure to obtain the "normal" product from the former reaction may not necessarily indicate a basic difference in reaction pattern between these two phenacyl halides, since in each instance the yield of isolated product was very low. A similar difference has been observed by Bost and Schultze who found that butyl methyl sulfide reacted with *p*-phenylphenacyl bromide to give the anticipated *p*-phenylphenacylsulfonium salt but with phenacyl bromide to give the "abnormal" butyldimethylsulfonium salt.[25] On the other hand, Rutter has found that phenacyl bromide reacts "normally" with butyl ethyl, dipropyl and dibutyl sulfides.[14]

When 1-butyl-3-methylmercapto-1-phenylpropan-1-ol (X) was treated with methyl iodide, only trimethylsulfonium iodide could be isolated (33% yield). Because a crude preparation of X was employed, there may be some doubt as to whether the trimethylsulfonium iodide did actually result from the reaction of methyl iodide with X. However, it should be noted that the main contaminant of X is probably its precursor, β-methylmercaptopropiophenone, which does form a "normal" sulfonium derivative.[22]



The formation of trimethylsulfonium iodide in this reaction can be explained by either of the mechanisms described above.

Pharmacological Activities.—For the determination of the pharmacological activities of these compounds we wish to express our indebtedness to Dr. A. C. Osterberg, Dr. R. W. Cunningham and their assistants of the Experimental Therapeutics Section of these laboratories.

The gastric secretion inhibition activities were determined in an 8-hr. pylorus-ligated rat and are rated quantitatively with 5 representing the highest activity.[18] These ratings are listed in Table II. The most active compounds in this test were (3-cyclohexyl-3-hydroxy-3- phenylpropyl)- diethylsulfonium iodide (entry 5) which has a rating of 3 at a dose level of 5 mg./kg. and allyl-(3-cyclohexyl-3-hydroxy-3-phenylpropyl)-methylsulfonium iodide (entry 3) which has a rating of 2 at 5 mg./kg. and 5 at 10 mg./kg. In this test, Pathilon has an activity rating of 5 at 5 mg./kg.

The antispasmodic activities are based on the relaxing effect of the compound on a section of isolated rabbit intestine made spastic with furfuryltrimethylammonium iodide (Furmethide).[20] A rating of 4 represents the highest activity. The activities are listed in Table II. Four of the sulfonium salts tested had a rating of 3 and three of the compounds had a rating of 2. In this test, Artane has an activity rating of 4, Pathilon a rating of 3 and Trasentine a rating of 2.

In connection with the pharmacological studies it was of interest to test dimethyl-(1,1-diphenyl-1-hydroxyethyl)-sulfonium iodide, a compound with one less methylene group between the sulfur atom and the carbinol carbon (compare entry 9, Table II). This compound, previously reported by Prelog and co-workers,[10] was prepared by their procedure and was found to be inactive as an antispasmodic or as a gastric secretion inhibitor.

Further sulfonium analog studies will be reported at a later date.

Acknowledgment.—The authors are grateful to Mr. O. Sundberg and his staff for microanalyses and to Messrs. L. Yogodzinski and E. K. Norton for certain preparations.

Experimental[26]

β-Alkylmercaptopropionitriles (II).—The known β-methylmercaptopropionitrile, b.p. 112–115° (35 mm.), and β-ethylmercaptopropionitrile, b.p. 100–110° (20 mm.), were prepared in 47 and 43% yield, respectively, by the procedure of Hurd and Gershbein.[21]

β-Methylmercaptopropiophenone (III, R_1 = Methyl).—A solution of β-methylmercaptopropionitrile (101 g., 1.0 mole) in 400 ml. of anhydrous ether was added dropwise to a stirred solution of phenylmagnesium bromide, prepared from bromobenzene (197 g., 1.25 moles) and magnesium (28 g., 1.15 g. atoms) in 500 ml. of anhydrous ether. A solid precipitated as the nitrile was added. After the addition was complete (1 hr.), 300 ml. of ether was added and the suspension stirred for 18 hr. A chilled 6 *N* hydrochloric acid solution was then added dropwise. Much heat was evolved and the ether was allowed to boil out. The two liquid phases were stirred and warmed on the steam-bath for 1 hr. and then cooled and extracted several times with ether. A considerable quantity of ether-insoluble gum (probably acrylonitrile polymer) was present and much mercaptan odor was noted. After drying the combined ether extracts over anhydrous sodium sulfate, the solvent was removed and the residual oil distilled *in vacuo*. Following a short forerun, β-methylmercaptopropiophenone was collected as a colorless oil boiling at 112–117° at 1.6 mm. The yield was 93 g. (52%). Redistillation gave material

(26) Melting points and boiling points are uncorrected.

boiling at 110–115° at 1.1 mm. (n^{29}D 1.5687) (reported[22] b.p. 153–155° at 15 mm., m.p. 35–36°).

Anal. Calcd. for $C_{10}H_{12}OS$: C, 66.6; H, 6.71; S, 17.8. Found: C, 66.4; H, 6.43; S, 18.3.

β-Ethylmercaptopropiophenone (III, R_1 = Ethyl).—This compound, b.p. 156–163° at 12 mm., was obtained in 60% yield from β-ethylmercaptopropionitrile by the procedure described above, dibutyl ether being used as solvent. On standing, the product crystallized. Recrystallization from methanol afforded platelets, melting at 47.0–47.5° (reported[22] b.p. 145° at 2 mm., m.p. 45–46°).

Anal. Calcd. for $C_{11}H_{14}OS$: C, 68.0; H, 7.30; S, 15.7. Found: C, 67.6; H, 6.95; S, 16.6.

Tertiary Carbinols (IV) (Table I).—The various tertiary carbinols listed in Table I were prepared by the procedure that follows.

1-Cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (IV; R_1 = Methyl, R_2 = Cyclohexyl).—A solution of β-methylmercaptopropiophenone (60 g., 0.33 mole) in 200 ml. of anhydrous ether was added dropwise to a stirred solution of cyclohexylmagnesium bromide, prepared in the usual manner from cyclohexyl bromide (65 g., 0.40 mole) and magnesium (9.3 g., 0.38 mole) in 400 ml. of anhydrous ether. Heat was evolved and the rate of addition was adjusted so that the ether refluxed gently. Within a few minutes a gray solid precipitated. Addition was complete in 70 minutes and stirring was then continued for 18 hr.

A solution of ammonium chloride (45 g.) in 150 ml. of water was added (heat evolution). The ether phase was separated and combined with an ether extract of the aqueous phase. After drying the combined ether solutions over anhydrous sodium sulfate, the solvent was distilled off and the residual oil distilled *in vacuo* to give, after a considerable forerun, 28 g. (32%) of 1-cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol boiling at 156–165° at 1.2 mm. Redistillation of a sample gave material boiling at 150° at 0.9 mm.

Sulfonium Salts (I) (**Table II**). **General Considerations.**—The sulfonium salts were prepared by treating at room temperature an alkylmercapto substituted tertiary carbinol (IV, Table I) with an alkyl or other halide, usually in large excess. The solvent was either excess halide, ether, acetone or methanol. The particular reaction solvent is indicated in Table II. **The methylpropargylsulfonium** derivative (entry 4), however, was prepared from equivalent amounts of the carbinol and propargyl bromide without any solvent. Also an equivalent amount of ***p*-chlorophenacyl bromide** (entry 8) was used.

Usually the reaction was allowed to stand for 24 **hr.** However, the acetone solution of 1-cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol and ***p*-chlorophenacyl bromide** (entry 8) was allowed to stand for one week and then freed of solvent. The residual oil was redissolved in acetone and precipitated with ether. The supernatant solvent was decanted, the oil was scratched and rubbed and after several days it solidified. Recrystallization from ethanol was slow.

Reaction of **1-cyclohexyl-3-ethylmercapto-1-phenylpropan-1-ol with ethyl iodide** (entry 5) gave the diethylsulfonium derivative in 43% yield after one month and in 70% total yield after an additional month. The reaction period of this carbinol with **propargyl bromide** (entry 7) was five days.

Except for the ***p*-chlorophenacyl salt** (entry 8) all the sulfonium salts precipitate from the reaction solution. The work-up for this product is described above. In general, the sulfonium salts are not very soluble in water; some not even to the extent of forming 1% solutions. The salts are, however, usually quite soluble in methanol or ethanol. The products were either recrystallized from alcohol, acetone or methyl ethyl ketone or dissolved in alcohol and reprecipitated with ether. The purification procedure for each salt is indicated in Table II. Melting points of the salts often varied with the rate of heating.

The preparation which follows is illustrative:

(3-Cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium Iodide (**VIa**) (Entry 1).—1-Cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V) (40 g., 0.15 mole) was dissolved in 100 ml. of methyl iodide. Within a short time crystals began to form. After 24 hr. at room temperature the brownish colored product was filtered, washed with acetone and ether and air-dried. The acetone wash very effectively removed the color. The yield of (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium iodide, melting at 134–139° with gas evolution, was 48 g. (77%). One recrystallization from about 85 ml. of absolute ethanol gave crystals (42 g.) melting at 138–140°.

1-Cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V) **and Propyl Iodide. Formation of (3-Cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium Iodide** (**VIa**).—A solution of 1-cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V) (6.0 g., 0.023 mole) and *n*-propyl iodide (25 ml.) in 50 ml. of anhydrous ether was placed in a stoppered flask and stored at room temperature in the dark. Crystals slowly formed from this solution and after 40 days 1.5 g. (32%) of (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium iodide, melting at 133–138°, was collected. A mixed melting point with an authentic sample showed no depression. Recrystallization from absolute ethanol gave platelets.

Anal. Calcd. for $C_{17}H_{27}IOS$: C, 50.2; H, 6.70; S, 7.89. Found: C, 50.3; H, 6.64; S, 7.95.

1-Cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V) **and Butyl Iodide. Formation of (3-Cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium Iodide** (**VIa**).—A solution of 1-cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V) (6.0 g., 0.023 mole) in *n*-butyl iodide (24 ml.) was placed in a stoppered flask and stored at room temperature in the dark. Within a few days crystals were noted. After 6 weeks, the brownish colored crystals were collected and washed free of color with ether to give 2.0 g. (43%) of (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium iodide, melting at 141–144°. A mixed melting point with an authentic sample (simultaneous m.p. 142–146°) did not show any depression. Recrystallization of the product from absolute ethanol gave beautiful platelets melting at 139–143°.

Anal. Calcd. for $C_{17}H_{27}IOS$: C, 50.2; H. 6.70; I, 31.2; S, 7.89. Found: C, 50.1; H, 6.81; I, 30.6: S, 8.33.

1-Cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V) **and Amyl Iodide. Formation of (3-Cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium Iodide** (**VIa**).—A solution of 1-cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V) (6.0 g., 0.023 mole) in *n*-amyl iodide (35 ml.) was placed in a stoppered flask and stored at room temperature in the dark. A crystalline product slowly precipitated. After 45 days the product was collected and washed free of color with ether to give 2.5 g. (56%), melting at 137–139°. A mixed melting point with an authentic sample of (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium iodide showed no depression. Recrystallization from absolute ethanol gave platelets melting at 139–143°.

Anal. Calcd. for $C_{17}H_{27}IOS$: C, 50.2; H, 6.70; I, 31.2; S, 7.89. Found: C, 50.1; H, 6.93; I, 30.9; S, 8.04.

1-Cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (V) **and Phenacyl Bromide. Formation of (3-Cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium Bromide** (**VIb**).—An acetone solution of 1-cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol (18.5 g., 0.07 mole) was treated with phenacyl bromide (13.1 g., 0.07 mole) for 72 hr. at room temperature. The crystalline product which precipitated was dissolved in acetone and reprecipitated with ether to yield 2.5 g. (10%) of crude product, melting at 170° dec. Recrystallization from methanol gave pure (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-dimethylsulfonium bromide, melting at 179° dec.

Anal. Calcd. for $C_{17}H_{27}BrOS$: C, 56.9; H, 7.52; **Br**, 22.3; S, 8.91. Found: C, 56.9; H, 7.50; **Br**, 22.7; S, 8.75.

1-Butyl-3-methylmercapto-1-phenylpropan-1-ol (**X**) **and Methyl Iodide. Formation of Trimethylsulfonium Iodide.**—A solution of crude 1-butyl-3-methylmercapto-1-phenylpropan-1-ol (X) (7.0 g., 0.03 mole) in methyl iodide (20 ml.) was kept for three days at room temperature. The oily crystals which precipitated were collected, washed with ether and then dissolved in 200 ml. of water. After decolorization with Darco, the aqueous solution was evaporated to dryness *in vacuo* to yield 2.0 g. of trimethylsulfonium iodide (33%) which decomposed at 203°.[27,28]

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Anal. Calcd. for C_3H_9IS: C, 17.7; H, 4.4; I, 62.3; S, 15.7. Found: C, 17.8; H, 4.3; I, 60.5; S, 15.2.

β-Methylmercaptopropiophenone and Methyl Iodide. Formation of (2-Benzoylethyl)-dimethylsulfonium Iodide.—β-Methylmercaptopropiophenone (III, $R_1 = CH_3$) (5.0 g., 0.029 mole) was dissolved in methyl iodide (10 ml.). Crystals began to form almost immediately. After 18 hr., the solids were filtered and air-dried to give 9.3 g. (100%) of (2-benzoylethyl)-dimethylsulfonium iodide as platelets melting at 131–132° (gas evolution). Several recrystallizations did not change the melting point. The corresponding bromide salt, prepared from β-methylmercaptopropiophenone and methyl bromide in 53% yield, has been reported.[22]

Anal. Calcd. for $C_{11}H_{15}IOS$: C, 41.0; H, 4.69; I, 39.4; S, 9.95. Found: C, 41.1; H, 4.71; I, 38.4; S, 10.1.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF COLUMBIA UNIVERSITY]

Organic Reactions Under High Pressure. I. The Polymerization of Styrene[1]

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The free radical polymerization of styrene has been studied under hydrostatic pressures up to 6000 kg./cm.^{2}. By measuring the effect of pressure on the rate of polymerization of styrene emulsions, $\Delta V^{\ddagger}_p$ (the volume change in going from reactants to transition state in chain propagation) has been obtained as -11.5 cc./mole. Comparison of this pressure coefficient with literature data on benzoyl peroxide initiated bulk polymerization indicates that here the increase in k_p with pressure accounts for most of the acceleration but that k_t is also slightly decreased. In the thermally initiated reaction, there also appears to be an increase in the rate of chain starting. The chain transfer constant for styrene–carbon tetrachloride is almost pressure independent, and it is concluded that, in the peroxide-initiated reaction at high pressures, $\bar{P}$ is determined by chain transfer with initiator and monomer, the transfer constants again having almost their atmospheric pressure values.

The application of high pressures, roughly 1000 kg./cm.^{2} and above, provides an additional degree of freedom in controlling the rate and direction of chemical reactions, which, since the initial observation by Roentgen[3] that the acid-catalyzed inversion of sucrose is retarded by pressure, has received rather sporadic but increasing attention in laboratories throughout the world.[4]

A theoretical interpretation of the effect of pressure on reaction velocity was first given by Van't Hoff, in 1901,[5] who proposed the relation

$$\mathrm{d} \ln k/\mathrm{d}P = -\Delta V_c/RT \qquad (1)$$

where ΔV_c represents the volume change in going from reactants to the active molecules at the moment of reaction. The equivalent expression in the more specific terms of transition-state theory

$$\mathrm{d} \ln k/\mathrm{d}P = -V^{\ddagger}/RT \qquad (2)$$

where $\Delta V^{\ddagger}$ represents the volume change in going from reactants to transition state was introduced by Evans and Polanyi,[6] in 1935, and is the form in which the relation is usually expressed. Evans and Polanyi pointed out that the value of $\Delta V^{\ddagger}$ depends upon volume changes both of the reactants and the surrounding solvent. Recent work, notably by Hamann[7] and Laidler,[8] has shown that in reactions between ions or in reactions involving ionic transition states the latter effect is very important. In general, reactions in which the transition states are more ionic than the reactants show large negative values of $\Delta V^{\ddagger}$ (and thus are strongly accelerated by pressure) due to the electrostriction of solvent produced by ion solvation. Because of this complication and because of our interest in non-polar processes, our investigations of reactions under high pressures have been directed initially at radical and "molecular" processes where solvation is relatively unimportant.

The accelerating effect of pressure on (what is now recognized as the free radical) polymerization of olefins was first noted by Bridgman and Conant[9] and has subsequently proved to be a rather general phenomenon. Styrene, as a tractable monomer which undergoes a well-understood and reproducible polymerization at atmospheric pressure, has received particular study. Its thermal polymerization under pressure has been investigated by several groups.[9–12] The benzoyl peroxide initiated reaction has been described by Merrett and Norrish[13] in an important paper which is considered further below. These workers found that the polymerization rate rises almost exponentially with pressure, increasing approximately 12-fold at 5000 kg./cm.^{2}. Polymer molecular weight also increases with pressure, but levels off at about 3000 kg./cm.^{2}. These high pressure polymers have subsequently been investigated by Trementozzi and Buchdahl,[14] who concluded from light scattering measurements that they show no detectable dif-

(1) Taken from a portion of the dissertation of Joseph Pellon, submitted in partial fulfillment of the requirements for the Ph.D. degree, 1957.

(2) Union Carbide and Carbon Corp. Fellow, 1955–1956.

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