The Preparation of Alkyl Sulfonyl Chlorides from Isothioureas. II

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at 40° with 1 or 2% soluble potato starch, made 0.01 *M* in acetate, is obtained at *p*H 5.0 in the presence of 0.02, 0.05 or 0.10 *M* sodium chloride, or at *p*H 5.3 to 5.5 when no sodium chloride is added. These conditions hold for amylase preparations of widely different degrees of concentration and purification, including crude commercial and highly purified products.

The significance of the data summarized here is evident when it is remembered that each step in the purification of enzyme material and every study of its properties, to be of real value, must be accompanied by quantitative activity measurements which in turn depend upon the chemical environment of the enzyme.

Whether the slight differences in the conditions which favor the two kinds of activity indicate that more than one amylase is present can only be decided by future work.

Summary

The conditions which favor the action of the amylase of *Aspergillus Oryzae*, both saccharogenic and amyloclastic, have been established and are reported briefly.

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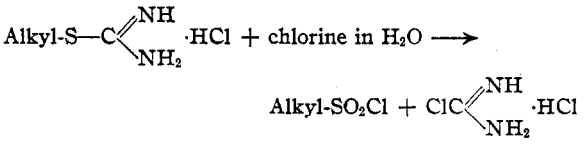
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Preparation of Alkyl Sulfonyl Chlorides from Isothioureas. II

BY JAMES M. SPRAGUE[1] AND TREAT B. JOHNSON

A study of the action of chlorine gas on salts of isothioureas in aqueous solution has opened up a new and practical method of preparing alkyl sulfonyl chlorides. A number of applications of this method of synthesis were described in our first paper,[2] and the complete change may be expressed tentatively according to the equation



The question of the true mechanism of this interesting reaction will be discussed in a future paper from this Laboratory.[3]

Our method of synthesis has now been applied successfully with several other alkyl isothioureas, and the corresponding sulfonyl chlorides prepared without difficulty. Three of the sulfonyl chlorides previously reported have been prepared in much larger quantities and the technique described for practical work. Also the new applications of the chlorination reaction have necessitated the synthesis of several new representatives of the isothiourea type, thereby increasing our knowledge of the chemistry of this class of sulfur compounds. It is of interest to note here that in the chlorination of *s*-butyl and also cyclohexyl isothioureas, there was a partial elimination of the sulfur as sulfate, while in the case of *t*-butyl isothiourea, the sulfur was eliminated completely as sulfate and no sulfonyl chloride was obtained. Several of these isothiourea combinations promise to prove of future physiological interest and their pharmacological study will receive immediate attention.

(1) Sterling Professorship of Chemistry Research Assistant, 1936–37.

(2) Paper I, Johnson and Sprague, THIS JOURNAL, **58**, 1348 (1936); see also *Science*, **83**, 528 (1936).

(3) In our previous paper[2] an error occurs, which we desire to correct at this time. In Table II on page 1350 the data recorded for the *n-butyl* radical are the results of experimentation with *iso-butyl*, and the data for *n-butyl* (recorded below) were omitted entirely.

R	Hours	Yield, %	B. p., °C.	Mm.	$n^{25}D$
n-C_4H_9	24	68	81–82	10	1.4524
	48	76			
	72	82			
	120	80			

Experimental Part

If not otherwise described the S-alkyl isothiourea hydrohalides were prepared by the general procedure previously outlined.[2] The sulfonyl chlorides, recorded in Table I,

TABLE I

FORMATION OF SULFONYL CHLORIDES

R—(SO_2Cl)	Yield, %	Procedure	B. p. or m. p., °C.	Mm.
$C_{12}H_{25}$	75–85	A	M. 42–43	
$C_{16}H_{33}$	70–80	A	M. 52–53	
s-C_4H_9	50	A	B. 86–88	18
	56	B		
s-C_8H_{17}	65	A	B. 110–112	4
C_6H_{11}	40	A	B. 122–123	14
	43–55			
p-$NO_2C_6H_4CH_2$	90	A	M. 91–92	
C_2H_5	66	A	B. 71–72	20
n-C_4H_9	75–83	B	B. 94–96	18
$C_6H_5CH_2$	81	A	M. 91–92	

were prepared by the chlorination of an aqueous solution of the respective salts (Procedure A), or by the chlorination of the product formed by interaction of an alcohol, thiourea and hydrogen chloride[2] (Procedure B). The method used for the isolation and purification of the sulfonyl chlorides was the same as previously reported, and is illustrated by the technique described in this paper for the preparation of ethyl sulfonyl chloride.

Some of the isothioureas were characterized further by the preparation of their picrates. The sulfonamides were prepared from the sulfonyl chlorides and analyzed whenever these derivatives were obtained as solids. The melting points and analytical data of these compounds together with those of other new compounds are recorded in Table II.

S-Dodecyl Isothiourea Hydrohalides.—The hydrochloride and hydrobromide were prepared from thiourea by interaction with dodecyl chloride and bromide, respectively. For a one-tenth mole run the preparation of the isothiourea hydrobromide was complete after heating for about ten hours, but in order to obtain the corresponding hydrochloride, it was necessary to digest dodecyl chloride with thiourea in alcohol solution for four days. After removing the alcohol, the salts were purified by crystallization from a mixture of alcohol and ether. The dodecyl isothiourea hydrochloride was obtained in quantitative yield by dissolving the corresponding hydrobromide in hot water and adding an equal volume of concentrated hydrochloric acid, when the hydrochloride separated in a crystalline form.

Dodecyl Sulfonyl Chloride.—Fourteen grams of the S-dodecyl isothiourea hydrochloride was dissolved in 450 cc. of warm water and chlorine gas passed rapidly into the solution after cooling quickly to 20–25°. The oil which separated finally changed to a solid. The chlorination was productive of a good yield when applied at temperatures below 40°. This solid sulfonyl chloride was dissolved in ether and dried with anhydrous sodium sulfate. On evaporating the ether the sulfonyl chloride was obtained in a yield of 11–13 g. After recrystallizing from petroleum ether, it melted at 42–43°.

S-Hexadecyl Isothiourea Hydrochloride.—This was prepared from hexadecyl chloride and thiourea by refluxing an alcohol solution for three to four days. It was purified easily by crystallization from alcohol.

S-Hexadecyl Sulfonyl Chloride.—Five grams of S-hexadecylisothiourea hydrochloride was dissolved in 850 cc. of warm water and chlorinated at 20–40°. The crude sulfonyl chloride was isolated as described for dodecyl sulfonyl chloride, yield 4.5 g. It was purified by recrystallization from petroleum ether, m. p. 52–53°. The chlorination of this isothiourea salt was also performed successfully in methanol solution (5 g. in 200 cc.) below 20°. After the solution was thoroughly saturated with chlorine, the product was precipitated by the addition of cracked ice. The yield was 4.2–4.6 g. melting at 46–49° without further purification.

***s*-Butyl Sulfonyl Chloride.**—S-*s*-Butyl isothiourea hydrobromide, which was always obtained as an oil, was converted into this sulfonyl chloride by chlorination in aqueous solution, after removal of hydrobromic acid by treatment with the required amount of silver nitrate. The yield was 50%. The sulfonyl chloride was also prepared according to procedure B, using either hydrogen chloride gas or concentrated hydrochloric acid. However, qualitative tests showed unreacted thiourea present after ten days of digestion. Thirty-eight grams of thiourea and 200 cc. of *s*-butyl alcohol containing 40–55 g. of hydrogen chloride were digested on a steam-bath for ten days. After removal of the excess of alcohol, the residue was dissolved in 800 cc. of water and subjected to the chlorination process at 10°. The yield of sulfonyl chloride was 44 g. boiling at 86–88° at 18 mm.; $n^{25}D$ 1.4570.

***s*-Octyl Sulfonyl Chloride.**—*s*-Octyl bromide and thiourea interact to form the desired isothiourea derivative, but it could not be obtained in a solid form. *s*-Octyl chloride failed to react completely with thiourea after digestion in alcohol solution for ten days. The *s*-octyl sulfonyl chloride was prepared by chlorination of the crude isothiourea hydrochloride, b. p. 119–121° at 8 mm., $n^{25}D$ 1.4598.

S-Cyclohexyl Isothiourea Hydrohalides.—On account of the unreactivity of cyclohexyl chloride, and the tendency of the corresponding bromide to dissociate with formation of hydrobromic acid, it was not possible to prepare isothioureas by interaction of these halides with thiourea. Digestion of cyclohexyl bromide with thiourea in ethyl alcohol gave a mixture of S-cyclohexyl isothiourea and S-ethyl isothiourea hydrobromides. Both isothiourea salts were obtained in good yield, however, by heating the cyclohexanol (75 cc.) with thiourea (7.6 g.) in the presence of hydrobromic acid (27 g. of 40%) or hydrochloric acid (10 cc.), respectively, for several days until the ammoniacal silver nitrate test showed very little unreacted thiourea. After removal of the excess cyclohexanol, the S-cyclohexyl isothiourea hydrobromide and hydrochloride were purified by crystallization from dilute hydrobromic and hydrochloric acids, respectively. Cyclohexene was identified as the volatile material which refluxed during the preparation of these hydrohalides.

Cyclohexyl Sulfonyl Chloride.—A 40% yield of this sulfonyl chloride was obtained from S-cyclohexyl isothiourea hydrobromide after removal of the bromine.

Four hundred cubic centimeters of cyclohexanol containing 50 cc. of concentrated hydrochloric acid and 50 g. of hydrogen chloride gas was heated on a steam-bath for eight to ten days with 76 g. of thiourea. The residue obtained on removal of the excess of cyclohexanol was chlorinated as described for ethyl and *n*-butyl sulfonyl chlorides. The yield of crude cyclohexyl sulfonyl chloride from the ether extract was 102 g.; $n^{21}D$ 1.4970.

This sulfonyl chloride when prepared in small amounts may be distilled without appreciable decomposition, b. p. 122–123° at 13 mm.; $n^{25}D$ 1.4960. However, with the large preparations, distillation is impractical because of decomposition with evolution of sulfur dioxide.

S-*p*-Nitrobenzyl Isothiourea Hydrochloride.—This was obtained as an insoluble product from the interaction of *p*-nitrobenzyl chloride and thiourea in alcohol. It may be recrystallized from water or dilute hydrochloric acid.

***p*-Nitrobenzyl Sulfonyl Chloride.**[4]—Forty-four grams of *p*-nitrobenzyl chloride, 20 g. of thiourea and 100 cc. of 95% alcohol were treated on a steam-bath for thirty

(4) Mohr, *Ann.*, **221**, 218 (1883).

TABLE II

ANALYTICAL DATA

Compound	B. p. or m. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
S-Dodecyl isothiourea hydrobromide	M. 112–114	8.61	8.58	24.57	24.48	...	...
S-Dodecyl isothiourea hydrochloride	M. 132–135	9.97	9.98	12.63	12.56	...	...
Dodecyl sulfonyl chloride	M. 42–43	...	...	13.19	13.37	...	...
Dodecyl sulfonamide	M. 93–94	5.61	5.53	...	...	12.86	13.04
S-Hexadecyl isothiourea hydrochloride	M. 126–128	8.31	8.19	10.53	10.61	...	...
Hexadecyl sulfonyl chloride	M. 52–53	...	...	10.91	10.83	9.87	9.81
Hexadecyl sulfonamide	M. 96.5–97.5	4.59	4.63	...	...	...	...
s-Butyl sulfonyl chloride	B. 89–90.5 at 19 mm.	...	...	22.63	22.43	...	...
S-Cyclohexyl isothiourea hydrobromide	M. 202–203	11.71	11.79	33.42	33.47	...	...
S-Cyclohexyl isothiourea hydrochloride	M. 230–231	14.38	14.25	18.22	18.31	...	...
S-Cyclohexyl isothiourea picrate	M. 173–174	18.12	18.00	...	...	...	...
Cyclohexyl sulfonyl chloride	B. 123–124 at 16 mm.	...	...	19.41	19.16	...	...
Cyclohexyl sulfonyl sulfonamide	M. 94–95	8.58	8.64	...	...	19.65	19.87
S-*s*-Octyl isothiourea picrate	M. 130–131	16.78	16.85	...	...	...	...
s-Octyl sulfonyl chloride	B. 110–111 at 4 mm.	...	...	16.67	16.72	...	...
t-Butyl isothiourea hydrochloride	M. 162	16.60	16.50	21.02	20.88	...	...
t-Butyl isothiourea picrate	M. 160–161	19.42	19.36	...	...	...	...
Isobutyl isothiourea picrate	M. 167–168	19.42	19.28	...	...	...	...
s-Butyl isothiourea picrate	M. 164.5–165.5	19.42	19.17	...	...	...	...
p-Nitrobenzyl isothiourea hydrochloride	M. 225–228	16.96	16.83	14.32	14.33	...	...
p-Nitrobenzyl sulfonyl chloride	M. 92–93	5.94	5.72	15.04	14.92	...	...
p-Nitrobenzyl sulfonamide[4]	M. 205	12.96	12.98	...	...	...	...
S-α-Naphthylmethyl isothiourea hydrochloride	M. 238	11.09	11.02	14.03	14.13	...	...
α-Naphthylmethyl sulfonamide	M. 171–172	6.33	6.30	...	...	...	...

minutes. Water was added and the solution diluted to 1500 cc. Chlorination was carried out below 10°. The yield was 57 g. melting at 89–90°. This was purified by recrystallizing from benzene, 48 g. of m. p. 92–93°. The amide[4] melted at 205°.

t-Butyl Isothiourea Hydrochloride.—*t*-Butyl chloride undergoes dissociation when digested with thiourea in alcohol solution, giving S-ethyl isothiourea hydrochloride. When *t*-butyl alcohol was substituted for ethyl alcohol, we also had no success in obtaining the isothiourea. The formation of the desired hydrochloride was finally accomplished by heating a *t*-alcohol solution (75 cc.) containing 12–13 g. of hydrogen chloride and 7.6 g. of thiourea to its boiling point for thirty hours. Isobutylene was generated during this digestion process and was recovered as its dibromide. The *t*-butyl isothiourea hydrochloride (13–14 g.) separated in crystalline condition and was purified by crystallization from a mixture of alcohol and acetone.

That this product was the desired *t*-butyl compound, and not an isobutyl derivative resulting by rearrangement or by interaction of the generated isobutylene with hydrogen chloride, was shown by a comparison of the picrates of the respective isothioureas. We were unable to prepare *t*-butyl sulfonyl chloride by chlorination of this isothiourea hydrochloride, all the sulfur of the isothiourea being oxidized to a sulfate.

S-α-Naphthylmethyl Isothiourea Hydrochloride.—This compound separated as a crystalline solid from the interaction of α-naphthylmethyl chloride[5] and thiourea in alcohol. It may be recrystallized from water.

Five grams of this hydrochloride in 400 cc. of water was chlorinated and the semi-solid precipitated taken up in ether. All attempts to isolate a sulfonyl chloride from this ether solution resulted in the evolution of sulfur dioxide. However, a small amount of material having the properties and composition of α-naphthyl sulfonamide was obtained by treating the ether extract with ammonia gas and extracting the residue obtained upon removal of the ether with hot water. The sulfonamide separated from the aqueous extract, 0.4 g. of m. p. 171–172°.

Ethyl Sulfonyl Chloride.[2]—This compound was obtained easily in quantity according to the following technique: thiourea (76 g.) and diethyl sulfate (85 g.) were heated together in an oil-bath when the mixture slowly liquefied, and at 130–140° a vigorous reaction occurred. If the temperature was allowed to rise above 180°, there resulted much decomposition. Heating at 170–180° was then continued for two hours to complete the reaction. After trituration with a mixture of alcohol and ether to remove excess of diethyl sulfate, one obtained uniformly about 110 g. of the S-ethyl isothiourea sulfate.

For the preparation of ethylsulfonyl chloride 200 g. of this isothiourea sulfate was dissolved in 800 cc. of water and placed in a three-necked flask fitted with a stirrer, a thermometer, an outlet tube leading to a hood, and an inlet tube connected with the chlorine supply. After cooling to 0° and adding 500 g. of cracked ice, chlorine was passed into the solution at a temperature below 10° until the decomposition of the isothiourea sulfate was complete. The sulfonyl chloride separated as an oil and was siphoned off in three portions during the chlorination. This was taken up in ether, washed, dried and purified by distillation; yield 110 g.

***n*-Butyl Sulfonyl Chloride.**[2]—*n*-Butyl alcohol (400 cc.) containing 55–70 g. of hydrogen chloride was digested on a

(5) Rupe and Brentano, *Helv. Chim. Acta*, **19**, 58 (1936).

steam-bath for five days with thiourea (76 g.). After removal of the excess of alcohol under diminished pressure the residue was then dissolved in 800 cc. of water and chlorination applied below 10° as described for ethyl sulfonyl chloride. The yield was 117–130 g.

Benzyl Sulfonyl Chloride.[2]—Thiourea (76 g.), benzyl chloride (126 g.) and alcohol (150 cc.) were heated under reflux on a steam-bath for thirty minutes. The vigorous reaction was controlled by cooling in water. Water (1 liter) was added and the solution chlorinated as described for ethyl sulfonyl chloride. The solid product was filtered off in several portions during the chlorination. The yield was 155 g., m. p. 90–92°. This was recrystallized from benzene, m. p. 91–92°.

Summary

1. The utilization of thiourea as a key reagent for the preparation of sulfonyl chloride has been extended.

2. The preparation of three sulfonyl chlorides on a laboratory scale is described.

3. The branching of the alkyl group in the alkyl isothiourea salts favors the elimination of sulfur as sulfate, thereby limiting the yield of sulfonyl chloride obtainable.

4. No sulfonyl chloride was obtained on chlorination of *t*-butyl isothiourea hydrochloride, the sulfur being oxidized to sulfate.

5. S-Cyclohexyl and S-*t*-butyl isothiourea hydrohalide were prepared by a modified procedure.

NEW HAVEN, CONN. RECEIVED JULY 1, 1937

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE AND THE PARKE, DAVIS & CO. RESEARCH LABORATORIES]

Sterols. XIX. *epi*-Ergosterol and *epi*-α-Ergostenol

BY RUSSELL E. MARKER, OLIVER KAMM, JOSEPH F. LAUCIUS AND THOMAS S. OAKWOOD

Due to the fact that lumisterol, an irradiation product of ergosterol, failed to precipitate digitonin, it was considered that lumisterol might be *epi*-ergosterol and that the primary action of irradiation on ergosterol was therefore an inversion of the configuration of carbon atom 3. Dimroth[1] on the contrary has suggested that irradiation resulted in the inversion of the methyl group on carbon atom 10, which change would prevent digitonin precipitation. From dehydration studies of lumisterol and ergosterol, Heilbron, Spring and Stewart[2] considered that Dimroth's postulation was correct, but recent studies on the dehydration of *epi*-cholesterol and cholesterol,[3] in which different hydrocarbons were obtained, seem to cast doubt upon the validity of Heilbron's inference.

We have prepared *epi*-ergosterol by the reduction of ergostatrienone[4] with aluminum isopropylate and separation of the resulting ergosterol from *epi*-ergosterol by means of digitonin. That there is no shift in the double bonds in the preparation of ergostatrienone by the aluminum *t*-butylate oxidation of ergosterol is shown by the fact that upon reduction with aluminum isopropylate, ergosterol is recovered from the insoluble digitonide.

epi-α-Ergostenol was prepared in the same manner by the aluminum isopropylate reduction of α-ergostenone, giving α-ergostenol and *epi*-α-ergostenol which were separated by means of their digitonides.

A comparison of the properties of *epi*-ergosterol, as prepared by us, with those reported for lumisterol shows conclusively that the two compounds are dissimilar. Appended is a list of compounds derived from ergosterol with their properties.

TABLE I

	Melting point, °C.	$(\alpha)_D$	Acetates melting point, °C.	$(\alpha)_D$
Ergosterol	163	−133	172	−87.4
epi-Ergosterol	152	+ 50	126	
α-Ergostenol	131	+ 17.8	111	+ 5.1
epi-α-Ergostenol	188.5	+ 5.3	119.5	
α-Ergostanol	184	− 20	166	− 7.5
epi-α-Ergostanol	207	+ 13.5		
Lumisterol	118	+191.5	100	+130.5

Experimental

***epi*-Ergosterol.**—Ergostatrienone was prepared by the aluminum *t*-butylate oxidation of ergosterol according to the method of Oppenauer.[4]

A mixture of 10 g. of ergostatrienone (m. p. 132°) and 4.5 g. of aluminum isopropylate in 60 cc. of dry isopropyl alcohol was heated for four hours at reflux and then 45 cc. of solvent was distilled slowly during an additional four hours. To the residue, a hot solution of 5 g. of potassium hydroxide in 75 cc. of methyl alcohol was added and the mixture allowed to stand for thirty minutes. The solution was poured into 250 cc. of water and the precipitate filtered

(1) Dimroth, *Ber.*, **69**, 1123 (1936).

(2) Heilbron, Spring and Stewart, *J. Chem. Soc.*, 1221 (1935).

(3) H. E. Staveley and Werner Bergmann, *J. Org. Chem.*, **1**, 575 (1937).

(4) Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).