ANALYTICAL DATA

Compounds: 2,4-Diketohexahydropyrimidines	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Alkoxyl, % Calcd.	Alkoxyl, % Found	Chlorine, % Calcd.	Chlorine, % Found
5-Chloro-5-methyl-6-methoxy-	221–222	14.54	14.58	16.12	16.20	18.42	18.80
5-Chloro-5-methyl-6-β-chloroethoxy-	200–201	11.62	11.65	...	...	29.43	29.80
5-Chloro-5-methyl-6-ethoxy-	223–224	13.56	13.55	21.81	21.50	17.16	17.26
5-Chloro-5-methyl-6-*n*-butoxy-	193–194	11.94	11.92	...	...	15.12	15.12
5,5-Dichloro-6-methoxy-	225–226	13.09	13.16	14.50	14.53	33.30	33.34
5,5-Dichloro-6-ethoxy-	234–235	12.34	12.36	19.34	19.40	31.24	31.18
5,5-Dichloro-6-β-chloroethoxy-	195–196	10.71	10.78	...	...	40.70	40.73
5,5-Dichloro-6-*n*-butoxy-	172–173	10.98	11.04	...	...	27.81	27.65
5-Chloro-5-nitro-6-methoxy-	216–217(dec.)	18.79	18.60	13.88	13.83	...	...
5-Chloro-5-bromo-6-methoxy-	216–217	10.88	11.26	12.05	12.45	...	...
5,5-Dichloro-6-methyl-6-methoxy-	265–270(dec.)	12.33	12.30	13.67	13.63	31.24	31.15
5,5-Dichloro-6-acetoxy-	174–175	11.62	11.57	...	...	29.42	29.60

to dryness at ordinary temperature in a vacuum over sulfuric acid and soda lime. The chlorination product was best recrystallized by dissolving in a small amount of warm acetic anhydride and adding carbon tetrachloride to incipient crystallization; yield 1.25 g.; m. p. 174–175°. 5-Chlorouracil on similar treatment gave the same product.

B. A solution of 5,5-dichloro-6-hydroxy-2,4-diketohexahydropyrimidine (II, Y = Cl) in acetic anhydride was allowed to stand for thirty hours and the product isolated as described above; m. p. 174–175°.

C. A solution of 5,5-dichloro-6-methoxy-2,4-diketohexahydropyrimidine (IV, R = CH_3, Y = Cl) in equal volumes of acetic anhydride and acetic acid gave on standing two or three days, the same reaction product, melting at 174–175°.

With barium hydroxide, this compound gave a heavy purple precipitate. On standing for eighteen hours in a methanol–hydrogen chloride solution, the acetoxy group was replaced by a methoxy group, giving the 5,5-dichloro-6-methoxy compound (IV, R = CH_3, Y = Cl) melting after crystallizing from water at 226–227°.

Anal. Calcd. for $C_6H_6O_4N_2Cl_2$: N, 13.09; OCH_3, 14.50. Found: N, 13.07; OCH_3, 14.56.

Summary

1. 2,4-Diketotetrahydropyrimidines are attacked immediately by chlorine in different solvents, giving hexahydropyrimidines.

2. Chlorination of the 2,4-diketopyrimidines in alcohols leads to the formation of 6-alkoxyhexahydro derivatives.

3. Chlorination in acetic anhydride solution yields the corresponding 6-acetoxy-hexahydropyrimidines.

4. 6-Hydroxyhexahydropyrimidines are converted easily to the corresponding alkoxy derivatives by interaction with alcohols in the presence of hydrochloric acid.

5. The 6-alkoxyhexahydropyrimidines easily undergo introconversion reactions, when warmed with alcohols, with interchange of alkoxy groups.

6. The halogenated hexahydropyrimidines are converted easily to 2,4-diketotetrahydropyrimidines by reducing agents.

7. The study of hexahydropyrimidines will be continued in this Laboratory.

NEW HAVEN, CONN. RECEIVED SEPTEMBER 18, 1937

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Action of Chlorine on Isothioureas. III

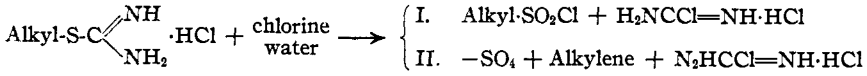
BY JAMES M. SPRAGUE[1] AND TREAT B. JOHNSON

In this short paper the authors present further data obtained by chlorination of isothioureas. The results of our previous experiments on the chlorination of isothioureas[2] showed low yields of alkyl sulfonyl chlorides by the action of chlorine on isopropyl, isobutyl, *s*-butyl and cyclohexylisothioureas. In each of these cases, a large part of the sulfur of the respective isothiourea was split off during the chlorination process and was oxidized to sulfate ($-SO_4$). With *t*-butyl isothiourea this was the sole reaction; no sulfonyl chloride was obtained. These results indicate that branched aliphatic groups attached to the sulfur of isothioureas favor the elimination of the sulfur as sulfate and, thereby, limit the yield of sulfonyl chloride. These two competing reactions are expressed below.

---

[1] Sterling Professorship of Chemistry Research Assistant, 1936–1937.

[2] (a) Johnson and Sprague, THIS JOURNAL, **58**, 1348 (1936); (b) Sprague and Johnson, *ibid.*, **59**, 1837 (1937).



$$\text{Alkyl-S-C}\begin{matrix}\nearrow\text{NH}\\ \searrow\text{NH}_2\end{matrix}\cdot\text{HCl} + \begin{matrix}\text{chlorine}\\ \text{water}\end{matrix} \longrightarrow \begin{cases}\text{I.} & \text{Alkyl}\cdot\text{SO}_2\text{Cl} + \text{H}_2\text{NCCl}{=}\text{NH}\cdot\text{HCl}\\ \text{II.} & -\text{SO}_4 + \text{Alkylene} + \text{N}_2\text{HCCl}{=}\text{NH}\cdot\text{HCl}\end{cases}$$

The further study of the action of chlorine upon some new S-substituted isothioureas in aqueous solution has emphasized this influence of the structure of the S-substituent upon the course of the chlorination reaction. A number of derivatives of methylisothiourea in which a hydrogen atom of the methyl radical was replaced by different groups ($RCH_2SC(NH_2){=}NH$) have been subjected to chlorination in aqueous solution. Where R was a furyl, alkoxyl (methoxy, *n*-butoxy, isoamoxy, carboxy or a carbethoxy group) no sulfonyl chloride was obtained. With tetrahydrofurfuryl isothiourea the corresponding sulfonyl chloride was obtained. In marked contrast to these results, is the excellent yield of sulfonyl chloride[2a] obtained by chlorination of benzylisothiourea ($R{=}C_7H_7$), and the apparent instability of the sulfonyl chloride formed from α-naphthylmethylisothiourea.[2b]

With the B-substituted ethylisothioureas ($RCH_2CH_2SC(NH_2){=}NH$) prepared from β-chloroethyl acetate and β,β'-dichlorodiethyl ether, good yields of the corresponding sulfonyl chlorides were obtained. Similar results were obtained by chlorination of β-phenylethyl-isothiourea.[2a] In fact, all our results clearly demonstrate the effect of the S-substituent, and reveal the limitation which an alteration of structure imposes upon the practical preparation of sulfonyl chlorides by chlorination of isothioureas.

2,4-Dinitrophenyl-sulfonyl chloride was prepared by chlorination of S-2,4-dinitrophenyl-isothiourea, but the reaction did not proceed smoothly and the yield was low.

Experimental Part

The general experimental procedure for conversion of isothioureas into sulfonyl chlorides has been described in a previous paper.[2a]

S-Carboxymethyl- and S-Carbethoxymethyl-isothiourea Hydrochlorides.[3]—The sulfoacetic acid obtained on chlorinating these two isothioureas in aqueous solution was isolated as the barium salt[4] and identified through the aniline salt.

Tetrahydrofurfuryl Sulfonyl Chloride.—Tetrahydrofurfuryl chloride[5] (13 g.) and thiourea (7.6 g.) were refluxed in alcohol (20 cc.) on a steam-bath. The thiourea dissolved completely, but the reaction was not complete after heating for four days. After distilling off the excess of alcohol, the reaction product was dissolved in water and the solution decolorized with norite. This solution gave an immediate precipitate of the picrate of tetrahydrofurfuryl-isothiourea (m. p. 153–154°). On chlorination of this compound, a 25–35% yield of the above sulfonyl chloride was obtained; b. p. 115–116° at 5 mm.; $n^{25}D$ 1.4915. The corresponding sulfonamide melted at 81.5–82.5°.

S-Furfuryl-isothiourea Hydrochloride.—A solution of thiourea and furfuryl chloride[6] in acetone was refluxed on a water-bath until the reaction product had crystallized completely. The yield of the isothiourea hydrochloride was 90%. It was purified by crystallization from a mixture of alcohol and acetone and melted at 142–143°. The picrate melted at 162°. No furfuryl sulfonyl chloride was produced by chlorinating this salt in aqueous solution. The sulfur was attacked by the chlorine and oxidized to sulfate (SO_4).

S-Methoxymethyl-, S-Isoamoxymethyl-, and S-*n*-Butoxymethyl-isothiourea Hydrochlorides.—These were prepared by the action of the required monochloromethyl ether on thiourea in cold acetone solution.[7] The yields of the respective hydrochlorides were 90%. They melted with decomposition. Their aqueous solutions on standing slowly deposited amorphous, colorless solids, and the resulting solution gave an immediate precipitate of silver sulfide with ammoniacal silver nitrate solution.

When treated with chlorine in aqueous solution, these salts gave insoluble chlorination products of the alcohol corresponding to the alkoxy group of the isothiourea salt used. No sulfonyl chloride of type $CH_3OCH_2SO_2Cl$ was produced in any case, and all the sulfur of the isothiourea combination was converted quantitatively to sulfate (SO_4).

Diethyl Ether-β,β'-disulfonyl Chloride $O(CH_2CH_2SO_2Cl)_2$.—Seventy-six grams of thiourea, 70 cc. of β,β'-dichloroethyl ether and 100 cc. of alcohol were heated on a steam-bath until qualitative tests showed no unreacted thiourea (twelve hours). After removal of the excess of alcohol under diminished pressure, the crude salt residue was dissolved in water and chlorination applied under the usual conditions. The yield of crude disulfonyl chloride was 135.5 g. and it separated in the form of a pale yellow oil, which could not be distilled without decomposition. *Anal.* Calcd. for $C_4H_8O_5S_2Cl_2$: chlorine, 26.16%. Found: chlorine, 27.0 to 27.4; $n^{20}D$ 1.503. The picrate of the isothiourea melted at 209–210°. The corresponding diethyl ether-β,β'-disulfonamide melted at 125–126°.

β-Acetoxyethyl Isothiourea Hydrochloride $CH_3CO_2CH_2CH_2SC(NH_2){=}NHHCl$.—Thiourea (22.8 g.) and β-chloroethyl acetate (38 cc.) were heated on a steam-bath with mechanical stirring until the mixture had liquefied and finally set to a crystalline solid (five hours). The yield was practically quantitative. The salt may be crystallized from a mixture of alcohol and acetone and melts at 136–137°. The picrate melted at 174–175°.

β-Acetoxyethyl Sulfonyl Chloride, $CH_3CO_2CH_2CH_2SO_2Cl$.—The crude hydrochloride from the preceding prepa-

---

[3] Ray and Fernandes, *J. Chem. Soc.*, **105**, 2159 (1914).

[4] Stillich, *J. prakt. Chem.*, **73**, 538; **74**, 53 (1906).

[5] Kirner, THIS JOURNAL, **52**, 3251 (1930).

[6] Kirner, *ibid.*, **50**, 1958 (1928).

[7] Favre, *Bull. soc. chim.*, [3] **11**, 881, 1097 (1894); Hill and Keach, THIS JOURNAL, **48**, 257 (1926).

ANALYTICAL DATA

Compound prepared	M. p. or b. p., mm., °C.	Nitrogen, %		Halogen, %		Sulfur, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
Tetrahydrofurfuryl sulfonyl chloride	B. p. 112–113^4	...	...	19.22	19.38	...	...
Tetrahydrofurfuryl sulfonamide	M. p. 81.5–82.5	8.48	8.37	...	...	19.42	19.65
S-Tetrahydrofurfuryl-isothiourea picrate	M. p. 153–153.5	17.98	17.93	...	...	...	...
S-Furfuryl-isothiourea hydrochloride	M. p. 142–143	14.54	14.50	18.40	18.43	16.64	16.97
S-Furfuryl-isothiourea picrate	M. p. 162	18.13	18.04	...	...	...	...
S-Methoxymethyl-isothiourea hydrochloride	M. p. 112	17.88	17.78	22.63	22.60	20.48	20.70
S-Methoxymethyl-isothiourea picrate	M. p. 163	20.00	19.82	...	...	...	...
S-Isoamoxymethyl-isothiourea hydrochloride	M. p. 134–135	13.16	13.08	16.67	16.36	15.07	15.20
S-*n*-Butoxymethyl-isothiourea hydrochloride	M. p. 118–120	14.09	13.95	...	...	...	...
S-Carbethoxymethyl-isothiourea hydrochloride	M. p. 112–113	14.10	14.15	17.85	17.75	...	...
S-β-Acetoxyethyl-isothiourea hydrochloride	M. p. 137–137.5	14.10	14.13	17.85	17.84	...	...
S-β-Acetoxyethyl-isothiourea picrate	M. p. 174.5–175.5	17.89	17.82	...	...	...	...
B-Acetoxyethyl sulfonyl chloride	B. p. 101–103^4	...	...	19.01	19.00	...	...
S-β-Oxidodiethyl-isothiourea picrate	M. p. 209–210	20.58	20.45	...	...	...	...
Diethylether-β,β′-disulfonamide	M. p. 125–126	12.06	12.00	...	...	...	...

ration was chlorinated in 700 cc. of water below 10°. The yield of this sulfonyl chloride was 39.5 g. (70%); b. p. 112–114° at 6 mm.; $n^{25}\text{D}$ 1.4633.

2,4-Dinitrobenzenesulfonyl Chloride.[8]—By chlorinating a dilute aqueous solution of freshly prepared 2,4-dinitrophenyl isothiourea hydrochloride[9] (10 g.), we obtained the above sulfonyl chloride melting at 101–102°. It was purified by crystallization from a mixture of benzene and petroleum ether. The corresponding sulfonamide melted at 156–157°.

Summary

1. The method of preparing sulfonyl chlorides by chlorination of isothiourea in aqueous solution has been investigated further.

2. The practical application of this method of synthesis is influenced by the structure of the grouping attached to sulfur in the isothiourea.

3. Branched aliphatic substituents favor a competing reaction during chlorination leading to dissociation of the alkyl grouping substituted in the isothiourea, and oxidation of the sulfur to sulfate.

4. Isothioureas containing ether groupings and furfuryl attached to the sulfur failed to give the corresponding sulfonyl chlorides.

NEW HAVEN, CONN. RECEIVED SEPTEMBER 20, 1937

[8] Mohr, *J. prakt. Chem.*, [2] **34**, 123 (1886).

[9] Taylor and Dixon, *J. Chem. Soc.*, **125**, 243 (1924).

[COMMUNICATION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Allylic Rearrangements. VI. Effect of Solvent and Metal on the Coupling Reaction of Butenyl Bromides

BY WILLIAM G. YOUNG, JOHN FERO LANE, ABE LOSHOKOFF AND SAUL WINSTEIN

In previous papers from this Laboratory it was shown that the butene mixtures obtained from the formation and decomposition of butenylmagnesium bromides[1] and those obtained from the reaction of butenyl bromides on zinc in ethanol,[2] had similar but definitely different compositions. It was not certain whether those differences were due to the effect of solvent, metal or temperature on the allylic rearrangement. In order to settle this question it was essential to obtain butene mixtures by preparing and decomposing the Grignard reagent in several different ethers and by allowing various metals to react with the butenyl bromides in 80% ethanol. Before this work could be undertaken it was necessary to overcome the well-known tendency for alkenyl halides to undergo a coupling reaction of the Wurtz type.

It is the purpose of this paper to present work on the effect of metal, solvent and experimental conditions on the above-mentioned coupling reaction of butenyl bromides.

The Coupling Reaction During the Formation of Butenylmagnesium Bromides in Different Ethers.—Several investigators[3] have found that the coupling reaction may be eliminated partially by using a large excess of magnesium which is

[1] Young, Winstein and Prater, THIS JOURNAL, **58**, 289 (1936).

[2] Young and Winstein, *ibid.*, **58**, 441 (1936).

[3] (a) Gilman and McGlumphy, *Bull. soc. chim.*, **43**, 1322 (1928); (b) Gilman and Kirby, THIS JOURNAL, **51**, 3475 (1929); (c) Gilman and Zoellner, *ibid.*, **52**, 3984 (1930); (d) Gilman and Harris, *Rec. trav. chim.*, **50**, 3475 (1931); (e) Young, Prater and Winstein, THIS JOURNAL, **55**, 4908 (1933).