less rapid pace than do the cells, and as a result the small cells characteristic of the later growth stages have relatively larger nuclei and less cytoplasm than the large cells found in the plumular and young seedling meristems. Thus the changes in cell/nucleus ratio may be concerned in bringing about the cessation of growth.

Summary.—Ontogenetic changes in the apical meristems of three species of *Lycopersicon* are described. Meristem volume tends to increase during development. The size of the meristem is correlated with the size of the determinate organs which it produces. Apical cells and their nuclei show a progressive diminution in size, a constant minimal size being attained with the onset of maturity. This change is evidently related to the annual growth cycle of the plants.

[1] Rössler, P., *Planta*, 5, 28–69 (1928).

[2] Murneek, A. E., and Gomez, E. T., *Mo. Agr. Exp. Sta. Res. Bull. 242* (1936).

THE SYNTHESIS OF SULFONYL CHLORIDES BY CHLORINATION OF SULPHUR COMPOUNDS

BY TREAT B. JOHNSON

STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY

Communicated July 19, 1939

Introduction.—Reference is being made daily by scientific and technical journals and the public press to the organic compounds—*sulfanilamide* and *sulfanilylaminopyridine*—whose introduction in medicine is one of the most valuable contributions by chemistry to this profession in recent years. The therapeutic side of the sulfanilamide type of sulphur compounds is now in a primitive state of development, and we are really at the beginning of a new chemotherapy today calling for close collaboration between chemists, biologists and clinicians. This discovery of the therapeutic value of these sulphur constructions emphasizes once more how the organic synthetic products of our research institutions and chemical industry are influencing the lives of our people.

The evolution of chemical reactions applicable for the practical synthesis of organic sulfonyl chlorides and amides has been receiving the attention of workers in this laboratory since the publication of a paper by James M. Sprague and the author, in 1935, describing the action of chlorine-water on certain 2-mercaptopyrimidines.[1] In a footnote inserted in that publication (p. 2253) the authors wrote as follows: "the mechanism of these transformations is being investigated and the results will be discussed in a future paper." Within this period of time ten publications have been contributed to the press on this subject from this laboratory,[1] and three United States Patents have been granted, which are based on the results of our investigations in this field.[2]

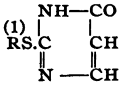
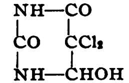
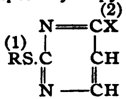
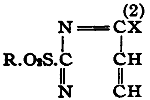
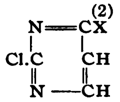
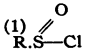
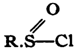
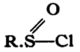
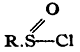
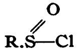
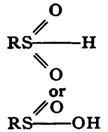
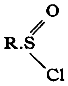
Chlorination Reactions.—The synthetic operations that have received chief attention in our researches on the oxidation of sulphur compounds have been confined to experimentation designed to determine the reactivity of chlorine with sulphur compounds characterized constitutionally by an isothiourea or related structure. The classification of sulphur compounds on which we will report briefly in this paper embraces three types of organic compounds, namely, isothioureas, 2-mercaptopyrimidines or isothioureas in cyclic combination and thiocyanates. In order to conserve space by omitting quotation of experimental data previously published, a condensed tabulation of the results of our experiments on chlorination of these three types of sulphur compounds is recorded in table 1. A knowledge of the many details and the technique of experimentation can be acquired by consulting the series of publications registered in the literature.[1]

An inspection of table 1 will suggest the fact that we are dealing apparently in all these oxidation changes brought about by the action of chlorine water with a common reaction mechanism. The outstanding results obtained are (*a*) that a sulfonyl chloride (RSO_2Cl) is the characteristic end-product containing sulphur of the chlorination reaction, and (*b*) that the nitrogen-containing nucleus of the original sulphur compound exposed to the action of chloride retains a constitution which is easily identified. In fact, it has been our experience that the yields of sulfonyl chlorides from both isothioureas and thiocyanates are good, and that either type of sulphur compound may serve as practical key reagents for the synthesis of aliphatic sulfonyl chlorides.

Mechanism of Reaction.—It is our conclusion that the first reaction step in this chlorination operation is the addition of oxygen to sulphur to form a sulphoxide intermediate as expressed by formula (I). This applies to all three types (*A*, *B* and *C*) represented in table 1. We have practically no knowledge of the chemical properties of sulphur constructions of this type, but it would be predicated, however, that such a sulphur configuration with a sulphur valency of 4 would be unstable in the presence of a strong oxidizing agent like hypochlorous acid. Such a sulphur grouping would be expected to undergo a structural change by interaction with chlorine water to give either (*a*) a sulphone (II) by further oxidation or (*b*) undergo hydrolysis with cleavage of the linkage between sulphur and carbon with production of a sulfinic acid (III) or a sulfinyl chloride (IV), and a stable nitrogen-containing nucleus. It is well known that sulfinic acids are easily oxidized by chlorine water to sulfonic acids and interact with hypochlorous acid to form sulfonyl chlorides (V).[3] The sulfinyl compounds (IV) are characterized by their instability and easily undergo oxida-

TABLE 1

CHLORINATION OF ORGANIC SULPHUR COMPOUNDS IN THE PRESENCE OF WATER

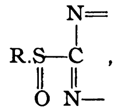
TYPES OF SULPHUR COMPOUNDS CHLORINATED	TYPES OF ORGANIC SULPHUR COMPOUNDS FORMED I	II	ORGANIC NITROGEN RESIDUE FORMED	INTERMEDIATES
A 2-MERCAPTOPYRIMIDINES  (2-Mercaptodihydropyrimidines)	(1) $R.SO_2OH$ (Sulfonic acid)		 (Hexahydropyrimidine compound)	
 (2-Mercaptopyrimidines)	 (2-Sulfone-pyrimidine)	(1) $R.SO_2Cl$		 (Sulfinyl chloride)
B ISOTHIOUREAS				
1. (1) $RS.C(NH_2):NH.HCl$ (*N*-unsubstituted)		$R.SO_2Cl$	 $Cl.\overset{\overset{NH_2}{\vert}}{C}:NH.HCl$ or $NH_2CN.2HCl$ (Cyanamide dihydrochloride)	
2. $RSC(NHCH_3):NH.HCl$ (*N*-monosubstituted)		$R.SO_2Cl$	$CH_3NHCN.HCl$ (Methylcyanamide hydrochloride)	
3. $RSC(NHCH_3):NCH_3.HCl$ (*N,N'*-disubstituted)		$R.SO_2Cl$	$CH_3NHCONHCH_3$ (Dimethylurea)	
4. $RSCN(CH_3)_2:NCH_3.HCl$ (*N,N,N'*-trisubstituted)		$R.SO_2Cl$	$(CH_3)_2N.CONHCH_3$ (Trimethylurea)	
C THIOCYANATES (1) $R.SCN$	 (Sulfinic acid)	$R.SO_2Cl$	$CN.Cl$ (Cyanogen chloride)	

(1) R = alphyl or aryl radicals. The alkylated isothioureas are all expressed as methyl derivatives (CH_3) for simplicity, and this does not mean that only methylated ureas undergo the changes represented. The only intermediates represented are the sulfinylchlorides which undergo oxidation very easily to form sulfonylchlorides, $R.SO_2Cl$.

(2) X = H, halogen, alkyl, $—OCH_3$, NH_2, etc.

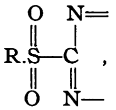
tion even in contact with air to give the corresponding sulfonyl chlorides (V).[4] An inspection of table 1 will reveal the fact that representatives of the three types of sulphur degradation products (II), (III) and (V) are recorded under the heading "types of organic sulphur compounds formed."

The experimental results, therefore, furnish evidence in support of the postulation that the sulfinyl chlorides (IV) are intermediate products of these oxidation reactions, and serve as the precursors of the sulfonyl chlorides (IV) obtained as final reaction products. It is particularly important to note here that sulfonic acids do not interact with hypochlorous acid to form sulfonyl chlorides.[5]



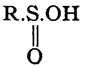
$\mathrm{R.\underset{\underset{O}{\|}}{S}{-}\overset{\overset{N=}{|}}{\underset{\underset{N-}{\|}}{C}}}$,

(I)



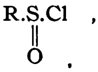
$\mathrm{R.\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}\overset{\overset{N=}{|}}{\underset{\underset{N-}{\|}}{C}}}$,

(II)



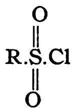
$\mathrm{R.\underset{\underset{O}{\|}}{S}.OH}$,

(III)



$\mathrm{R.\underset{\underset{O}{\|}}{S}.Cl}$,

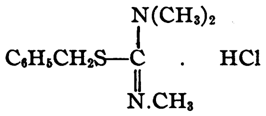
(IV)



$\mathrm{R.\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}.Cl}$.

(V)

Attention is called to the striking difference in behavior of 2-mercaptodihydropyrimidines and 2-mercaptopyrimidines, so far examined, towards chlorine water leading to the formation of a hexahydro-pyrimidine and free sulfonic acid, and true sulfone derivatives, respectively. These characteristic reactions serve as a clean-cut method for differentiating between these types of 2-mercaptopyrimidine structures. No reference has been made in any of our previous publications to the behavior of *N,N,N'*-trisubstituted isothioureas towards chlorine water. We wish to report here that the hydrochloride of the isothiourea (VI) interacts



$\mathrm{C_6H_5CH_2S{-}\overset{\overset{N(CH_3)_2}{|}}{\underset{\underset{N.CH_3}{\|}}{C}}\ .\ HCl}$

(VI)

smoothly to yield benzylsulfonyl chloride and trimethylurea (m. p. 74–75°).

---

[1] *Sequence of publications on Chlorination:* Sprague, J. M., and Johnson, T. B., *Jour. Amer. Chem. Soc.*, **57**, 2252–2255 (1935); Johnson, T. B., and Sprague, J. M., *Science*, **83**, 528–530 (1926); Sprague, J. M., and Johnson, T. B., *Jour. Amer. Chem. Soc.*, **58**, 423–426 (1936); Johnson, T. B., and Sprague, J. M., *Ibid.*, **58**, 1348–1352 (1936); Sprague, J. M., and Johnson, T. B., *Ibid.*, **59**, 1837–1840 (1937); Douglass, I. B., and Johnson, T. B., *Ibid.*, **60**, 1486–1489 (1938); Johnson, T. B., and Sprague, J. M., *Ibid.*, **60**, 1622–1624 (1938); *Ibid.*, **61**, 176–179 (1939); Johnson, T. B., and Douglass, I. B., *Jour. Amer. Chem. Soc.* (unpublished).

[2] *United States Patents:* No. 2,146,744 (Feb. 14, 1939), "Process of preparing sulfonyl halides and sulfonic acids from pseudothioureas"; No. 2,147,346 (Feb. 14, 1939), "Sulfonic halides"; Serial No. 201,728, Filed in U. S. Patent Office Apr. 13, 1938; Application allowed March 7, 1939.

[3] List, R., and Stein, M., *Ber.*, **31**, 1648–1672 (1898); Otto, R., and Tröeger, J., *Ibid.*, **24**, 478–488 (1891); Otto, R., *Ann.*, **145**, 317–329 (1868); Otto, R., and Ostrop, H., *Ibid.*, **141**, 365–377 (1867).

[4] Hilditch, T. B., and Smiles, S., *Ber.*, **41**, 4113–4116 (1908); Spring, W., and Winsinger, C., *Ibid.*, **15**, 445–448 (1882); *Ibid.*, **17**, 537–540 (1884); *Bull. Soc. Chim.*, (2) **49**, 68–74 (1887).

[5] Spring, W., and Winsinger, C., loc. cit.

*HYBRIDIZATION AND TUMOR FORMATION IN MICE**

By C. C. Little

Roscoe B. Jackson Memorial Laboratory

Communicated July 20, 1939

The object of this paper is to record the incidence of tumors in a species cross in mice and to discuss their frequency in that cross in relation to their frequency in the parent strains.

The two strains used differed from one another in size, rate of growth, fertility and tumor incidence. One strain was the inbred descendants of wild *Mus bactrianus* obtained from China in 1926 and reported on by Green in a series of papers (1931) (1935).

Mus bactrianus

	TOTAL MICE	MICE WITH TUMORS	% WITH TUMORS	NO. OF TUMORS	TOTAL TUMORS / TOTAL ANIMALS	NO. OF MICE WITH EPITHELIAL TUMORS	% EPITHELIAL TUMORS	NO. OF MICE WITH NON-EPITHELIAL TUMORS	% NON-EPITHELIAL TUMORS
Males	20	2	10.0	2	10.0	2	10.0	0	0.0
Females	139	4	2.9	4	2.9	4	2.9	0	0.0
Combined Sexes	159	6	3.8	6	3.8	6	3.8	0	0.0

It will be noted that all six tumors were epithelial in origin.

It is also worth mentioning that no animal had more than one tumor. This will be in marked contrast with the other material.

The second parent strain, C57 black, is an inbred derivative of *Mus musculus*. This strain has been extensively used in cancer research and has been described by several investigators (Murray and Little, 1935) (Little, Murray and Cloudman, 1939).

The animals of this strain are large and fertile. They mature more rapidly than do *Mus bactrianus*. Their tumor incidence is as follows: