However, it appeared likely that Ia had been formed as a precursor to II and our experience with the chloromethylation reaction led us to believe that Ia could be obtained in good yield by properly adjusting the reaction conditions.

When 2,5-dimethoxytoluene was slowly added to a chloromethylation mixture at 55–60°, yields of Ia from 55–65% were obtained. This mode of addition of reagent differs from those generally applied[2] in which either all reactants are mixed at once or formalin is added slowly to the reaction mixture.[1] The position of the chloromethyl group was shown by converting Ia to the known 2,5-dimethoxy-*p*-xylene (III).[3]

This technique of chloromethylation, when applied to *n*-octylhydroquinone dimethyl ether gave Ib in comparably good yield, and it is reasonable to assume that other alkyl- or aryl-substituted hydroquinone dimethyl ethers can be chloromethylated with similar ease.

EXPERIMENTAL[4]

5-Chloromethyltoluhydroquinone dimethyl ether (Ia). Gaseous hydrogen chloride was bubbled into a well-stirred mixture of 200 ml. of 35% formaldehyde, 100 ml. of concd. hydrochloric acid, and 400 ml. of dioxane for 15 min. at such a rate that the temperature of the mixture remained between 55–60° with no external heating. To this mixture 152 g. (1.0 mole) of 2,5-dimethoxytoluene was added, dropwise, over a period of 20 min., while the temperature was maintained between 55–60°. When the addition was completed, the passage of hydrogen chloride was stopped. The mixture was cooled and poured into 2 l. of ice water and 300 ml. of ethyl ether. The aqueous layer was extracted twice more with 250-ml. portions of ether. The combined ether extracts were washed with cold water until the washings were neutral to litmus, then dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was distilled through a 4-in. Vigreux column to give 110–130 g. (55–65%) of colorless liquid, b.p. 144–153°/14–16 mm., which solidified on cooling. Recrystallization from acetonitrile gave white crystals, m.p. 61.5–62.5°.

Anal. Calcd. for $C_{10}H_{13}ClO_2$: C, 59.9; H, 6.5; Cl, 17.7. Found: C, 59.8; H, 6.5; Cl, 17.5.

A portion of the residue from the distillation flask was recrystallized from 95% ethanol to give II, m.p. 147–148°.[1]

2,5-Dimethoxy-p-xylene (III). A mixture of 1.0 g. of Ia in 150 ml. of ethyl acetate containing 1.0 g. of 10% palladium on charcoal catalyst was hydrogenated at 45 p.s.i. and 25°. After 1 hr., the mixture was filtered to remove the catalyst and the filtrate evaporated to give a white solid which, after recrystallization from hexane, gave 0.5 g. of white crystals, m.p. 108–109° (lit.[3] m.p. 108°). A mixed melting point with authentic III was not depressed and the infrared spectra of the two were identical.

5-n-Octylhydroquinone dimethyl ether. To a mixture of 2 g. of 10% palladium on charcoal catalyst in 150 ml. of acetic acid was added 26.4 g. (0.1 mole) of 2-*n*-caprylylhydroquinone dimethyl ether.[5] The mixture was hydrogenated at 50 p.s.i. at 25° and hydrogenation was complete overnight. The catalyst was filtered and the acetic acid removed under reduced pressure. The residue was distilled to give 21.3 g. (85%) of slightly yellow liquid, b.p. 128–132°/1 mm., n_D^{25} 1.4979.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.8; H, 10.4. Found: C, 76.5; H, 10.3.

2-Chloromethyl-5-n-octylhydroquinone dimethyl ether (Ib). The reaction was performed exactly as described for the preparation of Ia. From 100 g. (0.4 mole) of *n*-octylhydroquinone dimethyl ether there was obtained, after distillation, 75 g. (62%) of colorless liquid, b.p. 170–173°/0.4 mm., which solidified on cooling. Recrystallization from acetonitrile gave white crystals, m.p. 51–52°.

Anal. Calcd. for $C_{17}H_{27}ClO_2$: C, 68.3; H, 9.1; Cl, 11.9. Found: C, 68.5; H, 9.0; Cl, 11.8.

KODAK RESEARCH LABORATORIES
ROCHESTER 4, N. Y.

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2-Aminothiazolesulfonamides

CARL ZIEGLER, ELEANOR K. KUHL, AND JAMES M. SPRAGUE

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The sulfonation of 2-acetamidothiazoles with chlorosulfonic acid has been reported by several investigators, but the structure of the resulting sulfonyl chlorides has been a subject of controversy.[1-3]

Backer and co-workers[4,5] considered the products that they obtained from 2-acetamidothiazole and 2-acetamido-4-methylthiazole to be 5-sulfonyl chlorides (I). This assignment of structure by these investigators was based on previous work which proved the point of attack of electrophilic agents, such as nitric acid and bromine, to be the 5 position of the thiazole ring.

However, Postovskii and Belaya,[3] who carried out the reaction under similar conditions, interpreted the reaction as occurring on the acetamido group to yield the acetylsulfamyl chlorides (II). Postovskii[6] later concluded, on the basis of infrared absorption spectra, that this interpretation was in error and that the products were thiazole-5-sulfonyl chlorides.

The amides derived from these sulfonyl chlorides afford a ready solution to the problem. Hydrolysis of the acetyl derivatives that arise from the reaction

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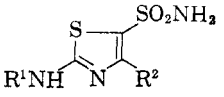
TABLE I

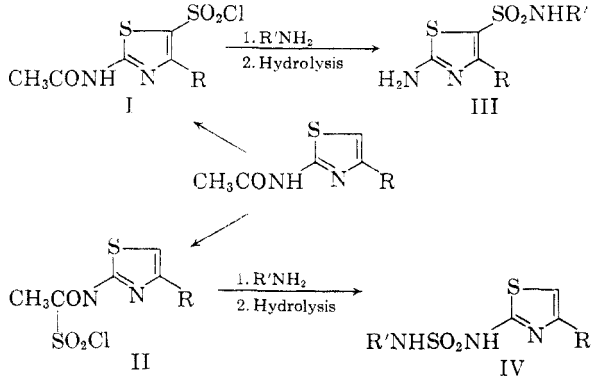


R¹	R²	M.P.° uncorr.	Formula	Analysis[c] Calcd. C, %	Calcd. H, %	Calcd. N, %	Found C, %	Found H, %	Found N, %	Yield, %
p-$HO_2CC_6H_4SO_2$	H	297–298	$C_{10}H_9N_3O_6S_3$	33.05	2.50	11.56	32.60	2.70	11.42	50[a]
p-$HO_2CC_6H_4SO_2$	CH_3	298–300	$C_{11}H_{11}N_3O_6S_3$	35.00	2.94	11.14	35.09	3.22	11.06	19[a]
$C_6H_5SO_2$	CH_3	201–203	$C_{10}H_{11}N_3O_4S_3$	36.03	3.33	12.61	36.27	3.49	12.60	54[a]
p-NCC_6H_4CO	CH_3	260–262	$C_{12}H_{10}N_4O_3S_2$	44.70	3.13	17.38	44.89	3.08	17.36	76[a]
C_6H_5—CH=CHCO	CH_3	244–245	$C_{13}H_{12}N_3O_3S_2$	48.27	4.05	12.98	48.34	4.07	12.96	52[a]
C_6H_5—CH=$CHSO_2$	CH_3	239–240	$C_{15}H_{21}N_3O_5S_3$[b]	43.05	4.82	10.04	43.51	4.90	10.07	24[a]
C_3H_7CO	CH_3	166–167	$C_8H_{13}N_3O_3S_2$	36.49	4.98	15.96	36.36	4.83	15.95	33
CH_3CO	C_6H_5[d]	301–303	$C_{11}H_{11}N_3O_3S_2$	44.43	3.73	14.13	44.94	3.90	13.6	30
H	C_6H_5[d]	271 dec.	$C_9H_9N_3O_2S_2$	42.34	3.55	16.46	42.95	3.85	16.17	72

[a] From the amine and the appropriate acid chloride. [b] Solvated with isopropanol. [c] We are indebted to Mr. K. B. Streeter and his associates for the microanalyses. [d] *Cf.* ref. 8.

of the sulfonyl chlorides with ammonia or amines would, in one case, lead to a 2-thiazolylsulfamide (IV), and in the other to a 2-aminothiazole-5-sulfonamide (III). As 2-aminothiazoles can be diazotized and coupled with α-naphthyldimethylamine to give characteristic dyes,[7] III would be expected to undergo this reaction but IV would not.

The work of the previous investigators was repeated in our laboratories and the products subjected to the diazo test. Acid hydrolysis of the acetyl derivatives in all instances (R = H, CH_3 or C_6H_5) yielded products that gave a diazo color; therefore, these products must have the 5-sulfonamide structure III and not the sulfamide structure IV.



In addition to the compounds prepared by Backer *et al.*, the 4-phenyl derivative (R = C_6H_5) was also prepared and found to possess structure III; this compound has been reported by Bas and Rout.[8] Several sulfonyl and acyl derivatives of the aminosulfonamides (III) were prepared through reaction with the appropriate sulfonyl or acyl chloride. The formation of these derivatives under the conditions employed also supports structure III. These compounds are recorded in Table I.

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EXPERIMENTAL

Sulfonyl chlorides. The method of Backer *et al.*[4] was used, except that prolonged heating of the chlorosulfonic acid solutions was found unnecessary. Heating longer than 2 hr. on the steam bath did not increase the yield of product.

Sulfonamides. Crude, moist sulfonyl chloride was added to a large excess of liquid ammonia according to the method of Roblin and Clapp.[9] Hydrolysis to the 2-aminothiazole-5-sulfonamides was carried out in acidic medium by the method of Backer.[4] The diazotization and coupling test was carried out as previously described.[7]

Derivatives. Of the compounds listed in Table I, most were prepared by the reaction of a 2-aminothiazole-5-sulfonamide with the appropriate acyl chloride or sulfonyl chloride in pyridine solution.

2-Methylamino-4-methylthiazole, prepared by the method of Burtles *et al.*,[10] was acetylated with acetic anhydride. Subsequent treatment with chlorosulfonic acid gave a crude sulfonyl chloride. This was treated with liquid ammonia to give a low yield (<1%) of 2-acetylmethylamino-4-methylthiazole-5-sulfonamide, m.p. 204–206°.

Anal. Calcd. for $C_7H_{11}N_3O_2S_2$: C, 33.72; H, 4.45; N, 16.86. Found: C, 34.20; H, 4.80; N, 16.84.

MERCK SHARP AND DOHME
RESEARCH LABORATORIES
WEST POINT, PA.

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Potential Anticancer Agents.[1] XXXV. Nonredox Analogs of Riboflavin. II. Synthesis of 3,4-Dihydro-4,4,6,7-tetramethyl-1-(1-D-ribityl)carbostysil

ELMER J. REIST, HARLAN P. HAMLOW, IRENE G. JUNGA, R. M. SILVERSTEIN, AND B. R. BAKER

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A recent program in these laboratories devoted to the synthesis of antagonists of riboflavin, such as