[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

The Cleavage of Sulfonamides[1]

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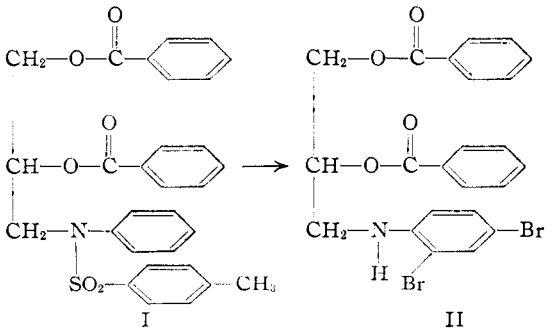
Treatment of sulfonamides with 30% hydrogen bromide in acetic acid in the presence of a phenol at room temperature rapidly cleaves the sulfonamide to give the amine in high yield. In the absence of phenol brominated products are obtained.

In many instances it is advantageous to block primary or secondary amino groups by conversion to the sulfonamide. In this manner changes may be performed in other parts of the molecule without interference from the reactive groups. The use of this method of blocking amino groups was restricted since the removal of the sulfonyl group was often difficult to accomplish except under vigorous conditions. The most widely used method of cleavage is acid hydrolysis which requires a high concentration of mineral acid at elevated temperatures for extended periods of time.[2a,b] The use of acid chlorides, sodium in alcohol or ammonia and in certain cases strong alkali for cleavage of sulfonamides also has been described.[2a] The limitation of these reactions as applied to labile molecules of a polyfunctional nature is self evident.

Recently Snyder and Heckert described an improved procedure for the acid hydrolysis of sulfonamides in which the sulfonamide was heated under reflux in a solution of 48% hydrobromic acid and phenol.[2b] Although this is the first disclosure of the use of 48% hydrobromic acid for the cleavage of sulfonamides, Ohle and co-workers previously have described the cleavage of sulfonamides with 30% hydrogen bromide in acetic acid.[3] They reported that, when N-2,3-dibenzoxypropyl-*p*-tolylsulfonanilide (I) was treated at room temperature with 30% hydrogen bromide in acetic acid, a 90% yield of N-(2,3-dibenzoxypropanyl)-2,4-dibromoaniline (II) was formed. In addition to II a 72% yield of di-*p*-tolyl disulfide also was isolated. In a

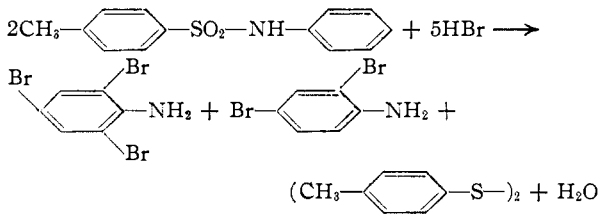


I II

similar experiment the reaction of tetraacetyl-6-desoxy-6-(N-*p*-tosylsulfonanilino)-β-D-glycopyranose[4] with hydrogen bromide in acetic acid gave tri-acetyl-6-desoxy-6-(2,4-dibromoanilino)-α-D-glycopyranosyl bromide.

Ohle pointed out that this reaction is an example of the reductive cleavage of a sulfonamide with hydrogen bromide in acetic acid. The reducing properties of hydrogen bromide in acetic acid are well known. Hinsberg describes the reduction of disulfoxides to disulfides[5] and Krohnke and Timmler describe the disproportionation of sulfur dioxide to sulfuric acid and sulfur by the same reagent.[6] The reduction of α-bromoketones by hydrogen bromide also has been reported.[7]

The method of reductive cleavage as described by Ohle was repeated in this Laboratory with *p*-toluenesulfonanilide. The equation for this reaction using Ohle's scheme is



By pouring the reaction mixture of *p*-toluenesulfonanilide and 30% hydrogen bromide in acetic acid into anhydrous ether there was isolated a mixture of bromoaniline hydrobromides in approximately a 50% yield. In one experiment the free amine was recrystallized several times to give a small amount of pure *p*-bromoaniline. In another experiment the crude mixture of hydrobromides was benzoylated and by fractional crystallization a 15% yield of the benzoyl derivative of *p*-bromoaniline and a 2% yield of the benzoyl derivative of 2,4-dibromoaniline were isolated. In neither reaction was there evidence of tribromoaniline. In addition to the basic fraction there was isolated from the neutral fraction two compounds, the one being identified as di-*p*-tolyl disulfide, while the other, present in larger amounts, proved to be N-tosyl-2,4-dibromoaniline.

Similarly the detosylation of ethyl N-tosyl-*p*-aminobenzoate with hydrogen bromide in acetic acid gave a mixture which contained 13.7% bromine. This material was not further investigated.

The addition of phenol to the reaction mixture prevented the formation of the undesired bromination products due to its rapid rate of bromination. Phenol also increased the solubility of the sulfonamides in the reaction mixture. The cleavage of *p*-toluenesulfonanilide in 30% hydrogen bromide in acetic acid containing phenol gave 70% of aniline

(1) Presented in part before the Division of Biological Chemistry at the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., Sept. 10 to 13, 1951.

(2) (a) C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 581. (b) H. R. Snyder and R. E. Heckert, THIS JOURNAL, **74**, 2006 (1952). See also D. I. Weisblat, B. J. Magerlein and D. R. Myers, U. S. Patent 2,562,222 (issued July 31, 1951).

(3) H. Ohle, H. Friedeberg and G. Haeseler, *Ber.*, **69B**, 2311 (1936); H. Ohle and G. Haeseler, *ibid.*, 2324 (1936).

(4) The term "tosyl" refers to the *p*-toluenesulfonyl group.

(5) O. Hinsberg, *Ber.*, **41**, 4294 (1908).

(6) F. Krohnke and H. Timmler, *ibid.*, **69B**, 1140 (1936).

(7) F. Krohnke and H. Timmler, *ibid.*, **69B**, 614 (1936); M. S. Newman, THIS JOURNAL, **73**, 4993 (1951).

hydrobromide. No evidence of brominated amines was noted. Subsequently other phenols, such as catechol and β-naphthol, were found to be satisfactory bromine acceptors, although phenol is preferred due to its marked solubility effect on the sulfonamides.

It is possible to cleave *p*-toluenesulfonanilide in good yield with 30% hydrogen iodide in acetic acid. However, due to the difficulty of preparing this reagent, hydrogen bromide in acetic acid is preferred. The use of hydrogen bromide in pelargonic acid was also satisfactory, except that the solubility of the sulfonanilides in this solvent was limited.

Table I lists the sulfonamides cleaved using 30% hydrogen bromide in acetic acid containing phenol. The sulfonanilides were treated with 30% hydrogen bromide in acetic acid containing a phenol at room temperature for the intervals of time shown. The reaction was quenched with anhydrous ether which precipitated the hydrobromide of the amine. Treatment of the hydrobromide with alkali gave the amine which was identified by melting point if a solid or by conversion to a solid derivative if a liquid. The compounds listed in Table I were chosen to test the versatility of this novel method of cleavage of sulfonamides but no effort was made to obtain optimum yields. Ethyl N-carboxymethyl-*p*-aminobenzoate, the detosylation product of ethyl N-(tosyl)-N-(carboxymethyl)-*p*-aminobenzoate, was also prepared by the alkylation of ethyl *p*-aminobenzoate with bromoacetic acid.

TABLE I

Sulfonamide	Time, hr.	Hydrobromide isolated	Yield of hydrobromide, %
p-Toluenesulfonanilide	1.5	Aniline·HBr	42
	3		71
	6		88
	6.5		81[a]
	4		77[b]
N-Tosyl-*o*-toluidine	24	*o*-Toluidine·HBr	84
N-Methyl-*p*-toluenesulfonanilide	3	N-Methylaniline·HBr	34
	7		65
	5		49[c]
	5		53[d]
β-Naphthylenesulfonanilide	3 days	β-Naphthylamine·HBr	32[e]
m-Nitrobenzenesulfonamide	3	*m*-Nitroaniline·HBr	19
	7		40
p-Nitrobenzenesulfonamide	7	*p*-Nitroaniline·HBr	68
Ethyl N-tosyl-*p*-aminobenzoate	5 days	Ethyl *p*-aminobenzoate·HBr	97
Diethyl N-tosyl-N-*p*-aminobenzoyl-L-glutamate[f]	16	Diethyl N-(*p*-aminobenzoyl)-L-glutamate[g]·HBr	42
Ethyl N-tosyl-N-carboxymethyl-*p*-aminobenzoate[10]	5	Ethyl N-(carboxymethyl)-*p*-aminobenzoate·HBr	92
Methanesulfonanilide	6.5	Aniline·HBr	7
	15		21
N,N-Dimethyl-*p*-tolylsulfonanilide	6	Dimethylamine·HBr	52

[a] 30% HBr–pelargonic acid. [b] 30% HI–acetic acid. [c] β-Naphthol used as Br_2 acceptor. [d] Catechol used as Br_2 acceptor. [e] Very insoluble in HBr–acetic acid. [f] D. I. Weisblat, B. J. Magerlein, A. R. Hanze, D. R. Myers and S. T. Rolfson, THIS JOURNAL, **75**, 3625 (1953). [g] Isolated as the free amine.

The reported unsuccessful hydrolysis of the sulfonamide linkages in 3-(N-γ-diethylaminopropyl - (*p* - toluenesulfonamido) - 4 - (N - *n* - propyl-*p*-toluenesulfonamido)-anisole[8] prompted us to study its reactivity with 30% hydrogen bromide in acetic acid containing phenol.[9] When this compound was treated for 5.5 hours at room temperature, an oil was isolated which on the basis of its elementary analysis contained only one sulfonamide group. However, when treated with the same reagent for 3.5 days the resulting oil showed the complete absence of sulfonamide groups, probably being the desired 3-(N-γ-diethylaminopropyl)-4-(N-*n*-propyl)-anisole.

The effect of water and of a more dilute solution of hydrogen bromide in acetic acid also was studied using *p*-toluenesulfonanilide as the model compound. These data are summarized in Table II. Both variations decreased the amount of hydrobromide isolated.

TABLE II

Variation	Time, hr.	Hydrobromide, %
Standard	3	71
Standard	6	88
15% HBr–HOAc	3	24
15% HBr–HOAc	6	43
Standard + 2 ml. H_2O	3	29
Standard + 2 ml. H_2O	6	37

It should be stressed that this method of sulfonamide cleavage is the result of an effort to develop a mild method which could be applied to the synthesis of relatively unstable compounds such as pteroylglutamic acid (folic acid).[10] For this reason the reductive cleavage of sulfonamides with hydrogen bromide in acetic acid containing phenol was studied exclusively at room temperature. With more stable compounds higher yields of amine may be obtained at an elevated temperature using shorter reaction periods.

Experimental

Detosylation of *p*-Toluenesulfonanilide in the Absence of Phenol.—A solution of 5.0 g. of *p*-toluenesulfonanilide in 40 ml. of 30% hydrogen bromide in acetic acid was permitted to stand at 25° for 6 hours. The red solution was poured into 700 ml. of anhydrous ether. The insoluble hydrobromides were collected by filtration, washed with a small amount of ether and dried. The yield was 2.20 g., m.p. 208–210°. After shaking with 20 ml. of 5% NaOH for 10 minutes, there was isolated 0.75 g. of free amine, m.p. 55–60°. Several recrystallizations from dilute ethanol and also from Skellysolve B gave 0.07 g. of *p*-bromoaniline, m.p. 65–66°.[11] When mixed with an authentic sample of *p*-bromoaniline there was no depression of the melting point. The infrared absorption curve of the compound isolated was identical with that of an authentic sample of *p*-bromoaniline.

The ether solution from above was extracted with water several times to remove any acid soluble fraction; however, none was obtained on neutralization and ether extraction of the aqueous phase. The ether extract was washed with dilute NaOH and evaporated to dryness. The oily residue was crystallized from dilute ethanol to give 1.7 g. of crystals, m.p. 30–34°. Fractional crystallization of this material from dilute ethanol and then 2-propanol gave 0.05 g. of di-*p*-tolyl

(8) M. J. Weiss and C. R. Hauser, THIS JOURNAL, **71**, 2268 (1949).

(9) The authors are indebted to Prof. C. R. Hauser for a generous sample of 3-(N-γ-diethylaminopropyl-*p*-toluenesulfonamido)-4-(N-*n*-propyl-*p*-toluenesulfonamido)-anisole.

(10) D. I. Weisblat, B. J. Magerlein, D. R. Myers, A. R. Hanze, E. I. Fairburn and S. T. Rolfson, THIS JOURNAL, **75**, 3625 (1953).

(11) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 197.

disulfide, m.p. 44–46°.[3] There was no depression in melting point when mixed with an authentic sample of di-*p*-tolyl disulfide.

A less soluble fraction, m.p. 132–134°, was also obtained. It weighed 0.250 g. Several recrystallizations from 2-propanol gave an analytical sample, m.p. 132–132.5°.

Anal. Calcd. for $C_{12}H_{11}Br_2NSO_2$: C, 38.45; H, 2.74; Br, 39.45; S, 7.91. Found: C, 38.89, 38.92; H, 2.92, 2.92; Br, 39.73, 39.46; S, 7.95, 8.02.

This compound gave no depression of melting point when mixed with N-tosyl-2,4-dibromoaniline prepared by the tosylation of the amine in pyridine.[12] The infrared absorption curves of the two compounds are identical.

In a similar experiment the ether precipitate of hydrobromides was benzoylated by the method of Schotten–Baumann to give, after recrystallization, 0.84 g. of N-benzoyl-*p*-bromoaniline, m.p. 200–201.5°. This material gave no depression of melting point when mixed with an authentic sample. Infrared data confirmed the identity of this derivative. There was also isolated 0.13 g. of N-benzoyl-2,4-dibromoaniline, m.p. 135–136°,[11] which gave no depression of melting point when mixed with an authentic sample of the benzoyl derivative of 2,4-dibromoaniline.[12] Infrared data confirmed the identity of this compound.

Detosylation of *p*-Toluenesulfonanilide in the Presence of Phenol.—A solution of 0.01 mole (2.5 g.) of *p*-toluenesulfonanilide and 0.02 mole (2.0 g.) of phenol in 23 g. of 30% hydrogen bromide in acetic acid was permitted to stand at 26° for 16 hours. The reaction mixture was poured into 150 ml. of anhydrous ether. The precipitate was filtered, washed with 100 ml. of ether and dried. It weighed 1.48 g. (86% yield), m.p. 283° (dec.).

Acetylation of the hydrobromide by the method of Schotten–Baumann gave 85% yield of acetanilide, m.p. 112.5–113.5°. There was no depression of melting point when this material was mixed with an authentic sample of acetanilide.

(12) We are indebted to Prof. H. R. Snyder, of the University of Illinois, for a sample of 2,4-dibromoaniline.

Detosylation of the other sulfonamides described in Table I was done in identical fashion.

Ethyl N-Carboxymethyl-*p*-aminobenzoate.—A solution of 8.25 g. (0.05 mole) of ethyl *p*-aminobenzoate, 7.45 g. (0.05 mole) of bromoacetic acid and 8.4 g. (0.10 mole) of sodium bicarbonate in 75 ml. of water and 25 ml. of ethanol was warmed on a steam-bath for 90 minutes. The mixture was cooled, filtered and the alcohol removed under reduced pressure. The *p*H of the aqueous solution was adjusted to 5.0 and the solution filtered to give 6.5 g. of product, m.p. 138–149°. An additional 1.5 g. of crystals, m.p. 136–147°, was collected when the *p*H was lowered to 2.0. The total yield was 72%. Two recrystallizations from dilute ethanol raised the melting point to 160–162°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 59.2; H, 5.9; N, 6.3; neut. equiv., 223.2. Found: C, 59.6, 59.7; H, 6.2, 6.2; N, 5.7, 6.0; neut. equiv., 225.2.

Detosylation of 3-(N-γ-Diethylaminopropyl-*p*-toluenesulfonamido)-4-(N-*n*-propyl-*p*-toluenesulfonamido)-anisole. (a).—A solution of 1.0 g. of 3-(N-γ-diethylaminopropyl-*p*-toluenesulfonamido)-4-(N-*n*-propyl-*p*-toluenesulfonamido)-anisole[9] and 0.9 g. of phenol in 7 ml. of 30% hydrogen bromide in acetic acid after 5.5 hours at 26° was poured into 250 ml. of anhydrous ether. The precipitate which formed was dried under vacuum and then dissolved by stirring with two 35-ml. portions of 0.05% hydrochloric acid. Neutralization, followed by extraction, gave a yellow oil, a portion of which rapidly darkened when exposed to the air. After drying at 0.1 mm. for 2 hours at 60° it weighed 0.58 g.

Anal. Calcd. for $C_{24}H_{37}N_3O_3S$: C, 64.39; H, 8.33; S, 7.16. Found: C, 64.70, 64.03; H, 8.03, 8.21; S, 7.23.

(b).—A similar experiment was permitted to stand at 26° for 3.5 days. When worked up as described above there was isolated 0.44 g. of a brown oil. Distillation of this material gave 0.21 g., b.p. 170–176° (0.7 mm.).

Anal. Calcd. for $C_{17}H_{31}N_3O$: C, 69.58; H, 10.65. Found: C, 70.27; H, 10.60; S, 0.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Alkaloid Studies. I. The Isolation of Pilocereine from the Cactus *Lophocereus schottii*[1]

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The isolation of a crystalline alkaloid $C_{30}H_{42}O_4N_2$, termed pilocereine, from the cactus *Lophocereus Schottii* and its occurrence in the plant tissues is described. The alkaloid has been characterized by a number of derivatives and the nature of the functional groups has been investigated. Both nitrogen atoms are tertiary, one forming part of a heterocyclic ring, while of the four oxygen atoms, two are present as methoxyl groups, one as a phenolic hydroxyl group and the fourth appears to be present in an ether linkage.

The hallucinatory principle (mescaline) present in certain *Lophophora* species first stimulated research on cactus alkaloids[4] and a whole series of closely related alkaloids has subsequently been isolated and identified, all of them possessing a rather simple structure based on a single phenylethylamine or tetrahydroisoquinoline nucleus. According to Britton and Rose's classification,[5] the genus *Lophophora* (also referred to as *Anhalonium*) belongs to the subtribe *Echinocactanae* of the *Cactaceae* family and with few exceptions, it has only been this particular genus which has occupied the attention of alkaloid chemists. The giant cacti, which occur so widely in the southwestern United States and particularly in the semi-arid regions of Mexico, Central and South America, are encompassed in 38 genera[5] of the subtribe *Cerenae*. With one exception (*vide infra*), the few chemical studies of this subtribe have been limited to one species each of the genera *Pachycereus*[6] and *Carnegiea*[7] and to Reti's[4,8] investigations of Argentinian *Trichocereus* species; in all instances, the alkaloids isolated were found to belong to the β-phenylethylamine or isoquinoline group.

In view of the fact that the giant cacti of the subtribe *Cereanae* are comparatively readily accessible since many of them are indigenous to Mexico, a

(1) This work has been supported by a grant from the American Heart Association, Inc., to which we are greatly indebted.

(2) Postdoctorate Fellow, 1952–1953.

(3) Predoctorate Fellow, 1952.

(4) An excellent review on cactus alkaloids has been published by L. Reti in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. VI, Springer, Vienna, 1950, pp. 242–289.

(5) N. L. Britton and J. N. Rose, "The Cactaceae," Vols. I–IV, Carnegie Institution of Washington, Washington, D. C., 1919–1923.

(6) G. Heyl, *Arch. Pharm.*, **239**, 451 (1901).

(7) G. Heyl, *ibid.*, **266**, 668 (1928).

(8) L. Reti and J. A. Castrillon, THIS JOURNAL, **73**, 1767 (1951).