CLEAVAGE AND REARRANGEMENT OF SULFONAMIDES

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I. INTRODUCTION

The cleavage of sulfonamides has been utilized frequently since the famous Hinsberg reaction was discovered (18). In this reaction primary, secondary, and tertiary amines may be distinguished by observing the mode of reaction with a sulfonyl chloride and aqueous alkali, the primary amine giving an alkali-soluble sulfonamide, the secondary amine giving an alkali-insoluble sulfonamide, and the tertiary amine giving no reaction. In the Hinsberg method for the separation of amines, the sulfonamides thus formed and separated by means of differences in their solubility in alkali must be cleaved, regenerating the amines. This last step, however, is generally difficult by the usual methods, since sulfonamides are very stable and very difficult to hydrolyze. Consequently, con-

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siderable study has been given to this step. The rearrangement of aromatic sulfonamides to *o*-aminosulfones was discovered in this connection.

The same problems arise in the Hinsberg synthesis of secondary amines from primary amines (7, 51), which is based on the reaction of alkali salts of sulfonamides with alkyl halides or sulfates, followed by cleavage (19, 20). The method has found wide application because of its simplicity and the high yields in the first phase.

A wide variety of reagents and techniques were brought to bear on the problem of cleaving sulfonamides so as to generate the parent amines, and by 1925 a number of much improved methods had been discovered. Later, the effort was applied more to developing alternative methods of separation and synthesis, in order to avoid altogether the problem of sulfonamide cleavage, but recently very promising new methods have been developed. Also, it is now recognized that there are special cases, such as the synthesis of azetidine, where the Hinsberg method seems to be preferred. Thus, it may well be that the general importance of sulfonamides as intermediates in the synthesis and separation of amines is about to be revived.

Another recent trend in the field has been the study of the actual course of some of the interesting reactions that were discovered in the earlier work. The nature of the products other than the amines and the mechanisms involved have received further attention. It is now recognized that causes of low yields of amines may be due to rearrangements and to carbon–nitrogen and carbon–sulfur bond cleavage competing with or accompanying the desired fission of the sulfur–nitrogen bond.

This review covers the methods of cleaving sulfur–nitrogen, carbon–sulfur, and carbon–nitrogen bonds in sulfonamides of all types. Since no previous review of this subject was found,[2] the literature has been reviewed from the first work done by Hinsberg in 1890 through the June 1959 issues of most of the principal journals and *Chemical Abstracts*. No attempt has been made, of course, to find every application of sulfonamide cleavage in the literature; it has been utilized in so many syntheses that such a compilation would be very lengthy and somewhat repetitious, and it would certainly be difficult to locate many of the applications. It is believed, however, that all of the different methods of sulfonamide cleavage are included with references to all of the principal studies and to many of the reports of other synthetic work, showing the scope of compounds that have been studied to date.

II. Hydrolysis of Sulfonamides

A. Catalysis by hydrochloric acid

Heating with concentrated hydrochloric acid in a sealed tube at 150–170°C. was the original method of hydrolyzing sulfonamides, reported by Hinsberg

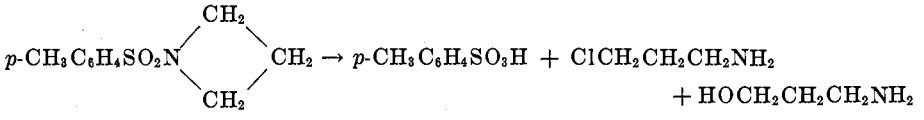
[2] Except for an interesting, brief, historical survey of the period up to 1913 (25), in which it is pointed out that benzenesulfonamides were known, but their potential importance not realized, many years prior to Hinsberg's work (12a).

(18), and has been one of the standard procedures for hydrolyzing aromatic amines (4, 7, 21, 27). Various minor modifications have been employed, of course,

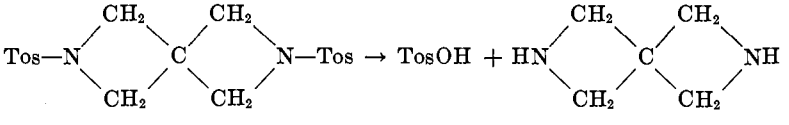
$$ArSO_2NRR' + H_2O \xrightarrow{H^+} ArSO_3H + RNHR'$$

such as addition of glacial acetic acid to the concentrated hydrochloric acid (3.5:10 v./v.) in the case of 2-methylaminonaphthalene, which was obtained thus in 70 per cent yield (51). Adaptation of the method for analytical purposes has been described, whereby the hydrolysis was carried out with 1 *N* hydrochloric acid at 100–120°C. and the products chromatographed on an ion-exchange resin (23, 24).

The method has the disadvantages that optically active compounds may be racemized (11) and acid-sensitive amines usually cannot be obtained. Thus, in the hydrolysis of *p*-toluenesulfonazetidide the azetidine ring was cleaved also, so that 3-chloropropylamine and 3-hydroxypropylamine were the products (44). It appears, however, that the azetidine ring in 2,6-diazaspiro[3,3]heptane



survives the treatment, at least to some extent, since this compound was obtained after its *p*-toluenesulfonyl derivative had been heated with hydrochloric acid



at 140°C. for 6 hr. (41). A further disadvantage of the method is its failure to work in some instances. For example, α-toluenesulfonamides of aromatic amines are not cleaved by heating in hydrochloric acid at 130–150°C. (45), nor are the *p*-toluenesulfonamides of the higher aliphatic amines (33).

Another difficulty is found in the application of the method to the synthesis of amino acids, the isolation of these being greatly complicated by the presence of the sulfonic acid also formed by hydrolysis (25, 56). To avoid this trouble, α-toluenesulfonamides may be employed, for α-toluenesulfonic acid is hydrolyzed under the conditions, forming toluene and sulfuric acid (25). The success of the method depends on the unusual lability of the sulfonamides of amino acids, similar to that of sulfonamides of benzylamine, towards hydrolysis (25).

The milder conditions and simpler procedure of refluxing in 25 per cent hydrochloric acid under atmospheric pressure for 10–36 hr. have been used successfully for a variety of substituted benzenesulfonanilides, as shown in table 1. In this study both the amine and the aromatic sulfonic acid were isolated in good yield, except where electronegative substituents or steric hindrance were present in the sulfonic acid moiety. The former greatly reduced the rate so that very little reaction occurred, while the latter gave rise to cleavage of the carbon–sulfur

TABLE 1

Hydrolysis of substituted benzenesulfonanilides catalyzed by hydrochloric acid (64)

Benzenesulfonanilide	Yield of Amine	Yield of Sulfonic Acid	Yield of Substituted Benzene	Recovery
	per cent	*per cent*	*per cent*	*per cent*
$C_6H_5SO_2NHC_6H_5$	91	82	0	0
$4\text{-}CH_3C_6H_4SO_2NHC_6H_5$	90	72	0	0
$2,4\text{-}(CH_3)_2C_6H_3SO_2NHC_6H_5$	90	56	9.4	0
$2,4,6\text{-}(CH_3)_3C_6H_2SO_2NHC_6H_5$	92	0	89.0	0
$4\text{-}O_2NC_6H_4SO_2NHC_6H_5$	0	0	0	98
$3\text{-}O_2NC_6H_4SO_2NHC_6H_5$	0	0	0	96
$2\text{-}O_2NC_6H_4SO_2NHC_6H_5$	0	0	0	99
$C_6H_5SO_2N(CH_3)C_6H_5$	94	78	0	0
$4\text{-}CH_3C_6H_4SO_2N(CH_3)C_6H_5$	93	80	0	0
$2,4\text{-}(CH_3)_2C_6H_3SO_2N(CH_3)C_6H_5$	91	70	11.3	0
$2,4,6\text{-}(CH_3)_3C_6H_2SO_2N(CH_3)C_6H_5$	95	0	92.0	0
$4\text{-}O_2NC_6H_4N(CH_3)C_6H_5$	31	20	0	61
$3\text{-}O_2NC_6H_4N(CH_3)C_6H_5$	87	64	0	6
$2\text{-}O_2NC_6H_4N(CH_3)C_6H_5$	17	6	0	71

bond, as well as the nitrogen–sulfur bond (64). Similar results have been obtained with *N*-substituted *p*-toluenesulfonamides (33).

These results may be rationalized in terms of a recently proposed mechanism in which the conjugate acid of the sulfonamide is pictured as dissociating into amine and an intermediate sulfonylonium ion (34). Electron-withdrawing groups

$$ArSO_2NR_2 + H^+ \rightarrow ArSO_2\overset{+}{N}HR_2 \rightarrow ArSO_2^+ + HNR_2$$

on the benzene ring of the sulfonamide reduce the basicity of the sulfonamide, decreasing the ease of formation of the conjugate acid and thus inhibiting the cleavage. The effect of the nitro group decreases in the series ortho, para, meta position, because of strongest inductive and resonance effects at the ortho position, weaker effects at the para position, and only the inductive effect at the meta position.

The effect of polymethyl substitution at the ortho and para positions seems related to the fate of the sulfonylonium-ion intermediate. Probably this reacts with water to give an intermediate similar to that obtained in aromatic sulfonation or desulfonation which would decompose into either sulfonic acid or aromatic hydrocarbon. It has been observed that desulfonation is facilitated by the presence of ortho methyl groups (9), probably by a mechanism analogous to that deduced for the decarboxylation of sterically hindered aromatic acids (58).

$$ArSO_2^+ + H_2O \rightarrow \left[\begin{array}{c} H \\ \diagup \\ Ar \\ \diagdown \\ SO_3H \end{array}\right]^+ \rightarrow ArSO_3H + H^+$$

$$\downarrow$$

$$ArH + HSO_3^+ \xrightarrow{H_2O} H_2SO_4 + H^+$$

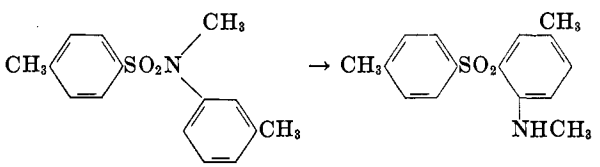
B. CATALYSIS BY SULFURIC ACID: REARRANGEMENT TO SULFONES

Sulfuric acid has been commonly used for cleaving sulfonamides (26), following a report in 1902 of the synthesis of *o*-aminobenzophenone in nearly quantitative yield by warming its *p*-toluenesulfonyl derivative with concentrated sulfuric acid (53, 72).

Difficulties were encountered, however, in the application of this method to aromatic sulfonanilides not possessing negative substituents in the aniline moiety, owing to ease of sulfonation and rearrangement. For example, treatment of benzenesulfonanilide with concentrated sulfuric acid, even in the cold, resulted in cleavage, accompanied by sulfonation (57).

$$C_6H_5SO_2NHC_6H_5 + H_2SO_4 \rightarrow C_6H_5SO_3H + p\text{-}H_2NC_6H_4SO_3H$$

Concentrated sulfuric acid was found to bring about rearrangement of *N*-alkylated aromatic sulfonanilides to *o*-alkylaminodiphenyl sulfones (13, 14, 15, 78, 79), as in the following example,



which proceeded in 83 per cent yield at water bath temperatures.

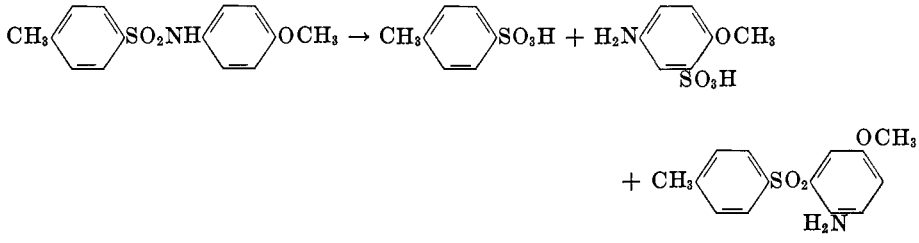
Substituents on the benzene ring of the sulfonic acid moiety seemed to have little effect on sulfone formation, but those on the aniline moiety were found to be very influential. The yields of the sulfones from *N*-ethyl-*p*-toluenesulfon-*p*-toluidide, and from *N*-methyl-*p*-nitrobenzenesulfon-*p*-toluidide were reported as being "nearly quantitative" and 83 per cent, respectively (79).

Substituents on the aniline ring appear to promote rearrangement to sulfone when they are electron-donating and to inhibit it, as well as sulfonation, of course, when electron-withdrawing. The *N*-methylsulfonanilides of aniline, *p*-toluidine, *p*-anisidine, and, to a lesser extent, *p*-chloroaniline were rearranged easily to the corresponding sulfones on treatment with concentrated sulfuric acid, while the corresponding compounds of *p*-nitroaniline and *p*-sulfanilic acid were only hydrolyzed, giving the secondary amines in good yields (14). The same tendency was also found in the reaction of sulfuric acid with the *p*-toluenesulfonamides of diphenylamine, phenyl-*p*-tolylamine, and di-*p*-tolylamine, the ease of rearrangement product markedly increasing in the order of listing (15).

The compounds of the last series possess additional interest because they are *N*,*N*-diarylsulfonamides instead of *N*-alkyl-*N*-aryl, and so give insight into the effects of *N*-substitution. Treatment of the *p*-toluenesulfonamide of diphenylamine with hot concentrated sulfuric acid at 120–145°C., followed by quenching in water (conditions commonly used), resulted only in hydrolysis to diphenylamine, and it was necessary to use special conditions to bring about rearrangement to sulfone; room temperature for 4 days gave a 52 per cent yield of sulfone

and a 23 per cent yield of diphenylamine. Thus the second phenyl group on nitrogen retards the ease of rearrangement. The effect is overcome, however, by *p*-methyl groups on the phenyl rings, as the *p*-toluenesulfonamides of di-*p*-tolylamine and phenyl-*p*-tolylamine rearrange in 85 per cent yield or better when heated at 60–80°C. for 2–4 hr. From the latter were isolated both sulfones resulting from ortho migration of the arenesulfonyl group to the ortho positions of the phenyl and the *p*-tolyl groups (13).

Sulfonanilides of primary aromatic amines were reported generally not to undergo rearrangement to sulfone, suffering cleavage with sulfonation as described previously (78). Substitution by the strongly electron-donating *p*-methoxyl group, however, brought about partial rearrangement of the following primary sulfonamide (13).



To avoid the formation of sulfone and the sulfonation, use of dilute sulfuric acid has been investigated. It was found that sulfuric acid of greater than 80 per cent concentration caused mainly rearrangement of *N*-alkylsulfonanilides, whereas acid of less than 40 per cent concentration gave no reaction. The maximum amount of secondary amine was obtained by using 60 per cent sulfuric acid in the case of *N*-methyl-*p*-toluenesulfon-*p*-anisidide (13). For *N*-alkyl-*p*-toluenesulfonanilides with *N*-alkyl groups up to butyl, the use of 85 per cent sulfuric acid is reported to be best (33).

Methanesulfonamides have been found to be hydrolyzed readily by aqueous sulfuric acid without any of the foregoing complications, and an alternative method of separating amines based on this has been considered (46). The methanesulfonamides were cleaved easily into the corresponding amines by boiling them with 60 per cent sulfuric acid for 6 hr., and the yields must have been good, as 50–60 per cent recovery of amines from a known mixture was accomplished. Methanesulfonyl chloride reacted readily with primary and secondary amines, forming amides that could be separated on the basis of akali solubility, but it was not a satisfactory general reagent for amine separations, because an excess of reagent needed to be used—otherwise the tertiary amine fraction was always contaminated with unchanged primary and secondary amine—and this excess reacted with the primary sulfonamide, giving the disulfonylamine, which precipitated with the secondary sulfonamide (46).

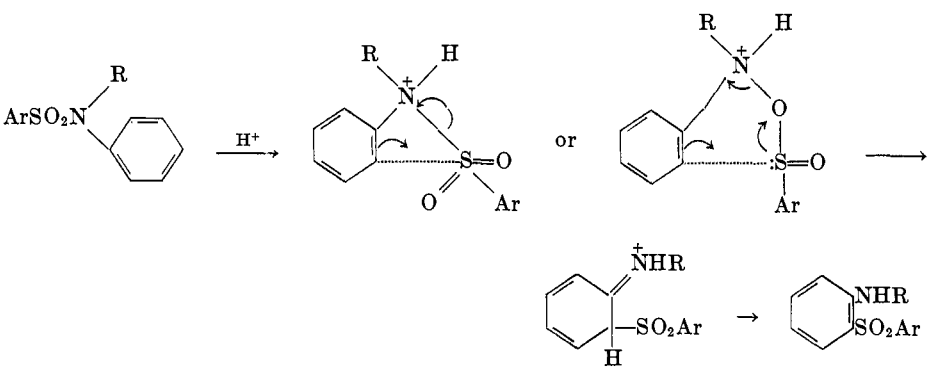
The mechanism for the rearrangement of aromatic sulfonamides to sulfones apparently has not received attention, but the similarity of conditions and general characteristics to the well-known rearrangement of phenylsulfamic acid to orthanilic acid is marked. The mechanism may be similar to that postulated

TABLE 2

Cleavage of benzenesulfonanilides by sulfuric acid (3)

Substituent in Sulfonic Acid	$k \times 10^4$ sec.$^{-1}$		E	log PZ	Substituent in Sulfonic Acid	$k \times 10^4$ sec.$^{-1}$		E	log PZ
	At 100°C.	At 80°C.				At 100°C.	At 80°C.		
			kcal./mole					*kcal./mole*	
4-CH_3O	1.64	0.489	15.8	5.46	4-Cl	0.688	—	—	—
4-CH_3	1.50	0.379	18.0	6.39	4-NH_2	0.298	—	—	6.57
2,4-$(CH_3)_2$	1.88	0.428	18.9	7.28	3-NO_2	0.204	0.0467	19.3	—
2,4,6-$(CH_3)_3$	—	1.19	—	7.23	4-NO_2	0.145	—	—	—
H	1.02	0.235	19.2	—	2-NO_2	0.0149	—	—	—

for the latter (22) with the nitrogen migrating to oxygen followed by shift of electrons in a cyclic process, or, more simply, it may involve attack of the benzene ring electrons on the sulfur atom, the function of the acid being to withdraw electrons from the sulfur, weakening the sulfur–nitrogen bond. The observed effects of substituents then can be accounted for in terms of their effect on the basicity of the sulfonamide, electron-donating groups or atoms on the nitrogen or *N*-phenyl ring enhancing the ease of formation of the conjugate acid.



The sulfuric acid-catalyzed hydrolysis of benzene sulfonanilides in aqueous ethanolic 56 per cent sulfuric acid is reported to be of pseudo-first-order kinetics. The effects of substituents on the rate constants (3) are the same as had been determined qualitatively for the hydrochloric acid-catalyzed hydrolysis, as shown in table 2, and presumably the mechanism is the same.

C. CATALYSIS BY SALTS

The hydrolysis of sulfonamides may be catalyzed by pyridine salts, such as pyridine hydrochloride or hydrobromide (34). The action of the former appears to be similar to that of hydrochloric acid, except that somewhat more vigorous conditions are required, reflecting of course the lower acidity. In table 3 are given the results of heating a variety of sulfonamides with a two- to three-fold excess of pyridine hydrochloride in water for 4–9 hr. at 150–180°C. The method has obvious utility for regenerating acid-sensitive amines, but appears to be not

TABLE 3

Cleavage of p-toluenesulfonanides by pyridinium salts (34)

Group in p-$CH_3C_6H_4SO_2NRR'$		X in $C_5H_5N^+X^-$	Yield of Amine	Group in p-$CH_3C_6H_4SO_2NRR'$		X in $C_5H_5N^+X^-$	Yield of Amine
R	R′			R	R′		
			per cent				*per cent*
C_2H_5	C_6H_5	Cl	80.0	n-C_8H_{17}	C_2H_5	Cl	7.9
n-C_4H_9	C_6H_5	Cl	38.2	C_2H_5	C_6H_5	Br	10.0
n-C_8H_{17}	C_6H_5	Cl	3.4	n-C_4H_9	C_6H_5	Br	8.5
C_2H_5	C_2H_5	Cl	79.7				

feasible for compounds with higher alkyl groups. Pyridine hydrobromide gave similar results, except that the yields were lower, owing to formation of tarry products.

The possibility of getting rearrangement to sulfone as a side reaction, as in the case of catalysis by sulfuric acid, appears to have been demonstrated. Under the extreme conditions of heating with pyridine hydrochloride without water, *N*-ethyl-*p*-toluenesulfonanilide was converted into a noncrystalline product which, according to its analysis and general properties, was a mixture of the *o*- and *p*-ethylaminophenyl *p*-tolyl sulfones (34).

Zinc chloride, aluminum chloride, and stannic chloride are very effective cocatalysts for the hydrolysis of sulfonamides with hydrochloric acid in aqueous acetic acid. For example, a 94 per cent yield of *N*-ethylaniline was realized after heating 0.05 mole of *N*-ethyl-*p*-toluenesulfonamide in a solution of 35 ml. of concentrated hydrochloric acid, 100 ml. of acetic acid, and 0.5 mole of zinc chloride for only 5 min. at 110°C. (34).

D. OTHER ACID CLEAVAGES

Chlorosulfonic acid has been used to cleave various *N*,*N*-dialkyl-*p*-toluenesulfonamides, forming *p*-toluenesulfonyl chloride and the corresponding *N*,*N*-

$$CH_3C_6H_4SO_2N(C_2H_5)_2 + ClSO_3H \rightarrow CH_3C_6H_4SO_2Cl + (C_2H_5)_2NSO_3H$$

dialkylsulfamic acid (33, 44). The conditions are heating for 2–3 hr. at 130–150°C., and the yields of cleavage products are generally 70 per cent or better. The secondary amine may be subsequently liberated and isolated by alkaline hydrolysis and steam distillation.

Acetolysis of sulfonamides in anhydrous acetic acid and in acetyl chloride has been carried out. An acetic acid solution of *N*-ethyl-*p*-toluenesulfonanilide, saturated with hydrogen chloride is cleaved to *N*-ethylaniline in 71 per cent yield after 20 hr. at room temperature (33). Sulfuric acid-catalyzed acetolysis of *N*-methyl- and *N*-ethyl-*p*-toluenesulfonamides gave the corresponding amines (33, 71) in 58–80 per cent yields after 4 hr. at 120°C. Cleavage of *p*-toluenesulfonylglycine and *p*-toluenesulfonylalanine may be accomplished by merely warming with acetyl chloride or chloroacetyl chloride, the toluenesulfonyl group splitting off as *p*-toluenesulfonyl chloride (56a).

Acetolysis catalyzed by zinc, aluminum, and stannic chlorides also has been studied (34). Treatment of *N*-ethyl-*p*-toluenesulfonanilide with acetic acid containing two molecular proportions of zinc chloride or aluminum chloride for 12–14 hr. at 110–116°C. gave 19 and 60 per cent yields, respectively, of *N*-ethylaniline. The unreacted amide was recovered in amounts such as to account quantitatively for all the starting materials; hence there were apparently no side reactions. No reaction took place when pure acetic acid or acetic acid containing sodium chloride was used (34).

In the preceding cases of acetolysis, the sulfonamide was presumably cleaved to amine and the sulfonic acetic anhydride, which is hydrolyzed by the subsequent treatment with water. The mechanism would seem to be similar to that for hydrolysis. It is interesting, therefore, that the opposite type of cleavage may occur when sulfonamides are heated to a temperature of about 230°C.

$$RCOOH + C_6H_5SO_2NR'R'' \rightarrow RCONR'R'' + C_6H_5SO_3H$$

with carboxylic acids in the absence of catalyst. This type of amide interchange, which has been patented as a method of preparation of carboxylic amides (61), is exemplified by the reaction of benzoic acid with *N*,*N*-dimethylbenzenesulfonamide to form *N*,*N*-dimethylbenzamide, and by that of nicotinic acid (or preferably its benzenesulfonate) with *N*,*N*-diethylbenzenesulfonamide to form *N*,*N*-diethylnicotinamide in yields up to 80 per cent. A similar reaction has also been carried out with an ester, ethyl chloroacetate (58).

Since *N*-acylations thus can be carried out on sulfonamides by carboxylic acids and esters, it is interesting that treatment with acetyl chloride in the presence of metal chlorides gives principally cleavage to amine. *N*-Methyl-*p*-toluenesulfonanilide was cleaved into *N*-methylaniline (61 per cent) and *p*-toluenesulfonyl chloride (54 per cent), with a small amount of *N*-methylacetanilide (7 per cent), by heating with aluminum chloride and acetyl chloride in nitrobenzene solution at 90–100°C. for 5 hr., followed by washing with water. *N*-Ethyl-*p*-toluenesulfonanilide was cleaved by zinc chloride in acetyl chloride, after refluxing for 4 hr., into *N*-ethylaniline (11 per cent) and *p*-toluenesulfonyl chloride (35 per cent) (33).

E. CARBON–NITROGEN BOND CLEAVAGE

Usually sulfonamides are cleaved at the sulfur–nitrogen bond by acid hydrolysis, but when the nitrogen atom is substituted by an alkyl group that forms a stable carbonium ion, the cleavage takes place at the carbon–nitrogen bond, and dealkylated sulfonamides are obtained.

$$ArSO_2NHR \xrightarrow{H^+} ArSO_2NH_2R \rightarrow ArSO_2NH_2 + R^+$$

Heating *N*-α-phenethyl-*p*-toluenesulfonamide with hydrochloric acid gave *p*-toluenesulfonamide, α-phenethyl chloride, styrene, and its polymer.

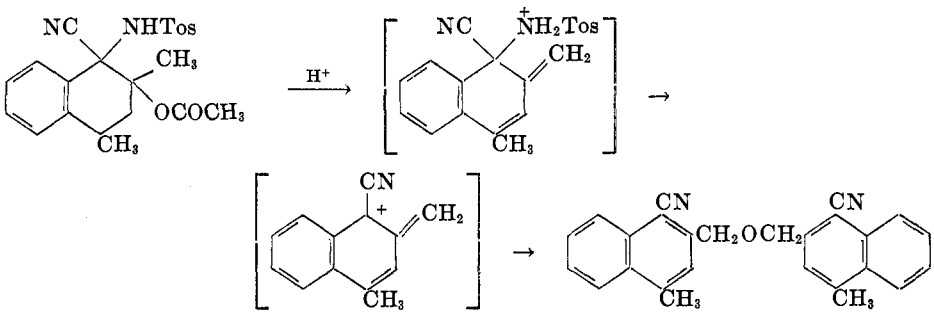
$$\underset{\substack{|\\ C_6H_5}}{CH_3CH}NHSO_2C_6H_4CH_3\text{-}p \xrightarrow{HCl} p\text{-}H_2NSO_2C_6H_4CH_3\text{-}p$$
$$+ CH_3CHClC_6H_5 + CH_2{=}CHC_6H_5 \text{ (+ polymer)}$$

The reaction of *N-tert*-butyl-*p*-toluenesulfonamide with hydrochloric acid gave *tert*-butyl chloride,

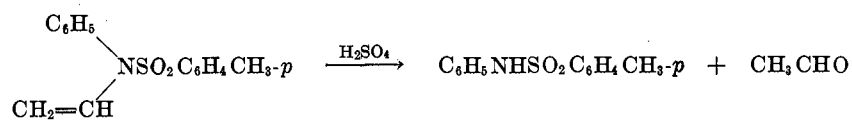
$$C(CH_3)_3NHSO_2C_6H_4CH_3\text{-}p \xrightarrow{HCl} H_2NSO_2C_6H_4CH_3\text{-}p + (CH_3)_3CCl$$

while *N*-isopropyl-*p*-toluenesulfonamide was not affected by hydrochloric acid (5).

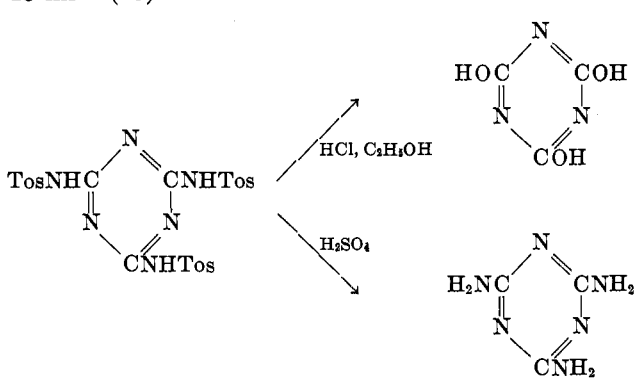
Treatment of 2-acetoxy-1-cyano-2,4-dimethyl-1-*p*-toluenesulfonamide-1,2-dihydronaphthalene with cold sulfuric acid gave 1,1′-dicyano-4,4′-dimethyl-2,2′-dinaphthobenzyl ether in an 84 per cent yield (1). This may go through an allylic carbonium ion as shown:



When the nitrogen atom is substituted by an unsaturated group, attack of water or alcohol on the double bond influences the cleavage of sulfonamide. Treatment of *N*-vinyl-*p*-toluenesulfonanilide with 50 per cent sulfuric acid gave *p*-toluenesulfonanilide and acetaldehyde (8).



Tri(*p*-toluenesulfonyl)melamine gave a 75 per cent yield of cyanuric acid when it was treated with hydrogen chloride in absolute ethyl alcohol, whereas melamine was produced in 84 per cent yield by treatment with concentrated sulfuric acid at 70°C. for 15 min. (40).



F. CATALYSIS BY BASES

1. Carbon–sulfur bond cleavage

Sulfonamides are extremely stable with respect to alkaline hydrolysis, and there are many reports in the literature of the failure to cleave them (62, 63, 82). The positively charged sulfur atom is apparently shielded very well by the negatively charged oxygen and nitrogen atoms, from nucleophilic attack by hydroxide. Even nucleophilic attack on carbon, similar to that involved in the alkaline hydrolysis of sodium benzenesulfonates, is generally very unfavorable. Benzenesulfonanilide, for example, is said to be unattacked by fusion with 80 per cent sodium hydroxide at 250°C.

TABLE 4

Hydrolysis of substituted benzenesulfonanilides (62, 63) by fusion with 80 per cent sodium hydroxide

Substituent	Yield of $C_6H_5NH_2$ from $XArSO_2NHC_6H_5$	Yield of $C_6H_5NHCH_3$ from $XArSO_2N(CH_3)C_6H_5$	Substituent	Yield of $C_6H_5NH_2$ from $XArSO_2NHC_6H_5$	Yield of $C_6H_5NHCH_3$ from $XArSO_2N(CH_3)C_6H_5$
	per cent	*per cent*		*per cent*	*per cent*
2-NO_2	61	60	2,4-Br_2	0.8	0.6
4-NO_2	38	39	2,4,6-Br_3	5.3	3.4
2,4-$(NO_2)_2$	79	71	2,4,6-$(CH_3)_3$	0	0
3-NO_2	14	—	None	0	0

When electronegative groups are present on the benzene ring bearing the sulfonyl group, cleavage can be carried out on both primary and secondary sulfonamides (62, 63). The best conditions found involved fusion in 80 per cent sodium hydroxide and heating at such a temperature that the amine formed distilled out. The results of this study are listed in table 4. It was noted that the nitro group, particularly in the ortho position, is the most effective in labilizing the carbon–sulfur bond, just as in the hydrolysis of nitrochlorobenzenes and nitroanilines, but just opposite to its effect on acid-catalyzed hydrolysis (table 1). It was found that these nitrobenzenesulfonanilides could not be cleaved by sulfuric or phosphoric acid in various concentrations, so that in such cases alkaline hydrolysis could have synthetic value.

In view of the effects of substituents and the lack of any indication of sodium benzenesulfonates formed by the reaction, it was assumed that the hydrolysis involved carbon–sulfur bond cleavage followed by hydrolysis of the sodium sulfonate (63). In possible contradiction to this mechanism, however, is the report that phenylsulfamic acids are very stable to hot concentrated sodium hydroxide (75).

$$ArSO_2NHC_6H_5 + 2NaOH \rightarrow ArONa + C_6H_5NHSO_3Na + H_2O$$

$$C_6H_5NHSO_3Na \xrightarrow{NaOH} C_6H_5NH_2 + Na_2SO_3$$

2. *Carbon–nitrogen bond cleavage*

It is reported that treatment with sodium hydroxide converts *N*-(2-carboxyethyl)-*p*-toluenesulfonanilide into *p*-toluenesulfonanilide in 62 per cent yield (70).

$$p\text{-}CH_3C_6H_4SO_2N(C_6H_5)CH_2CH_2COOH + H_2O \xrightarrow{NaOH} p\text{-}CH_3C_6H_4SO_2NHC_6H_5\ (+\ HOCH_2CH_2COOH)$$

3. *Sulfur–nitrogen bond cleavage*

This type of cleavage, which is the usual one with acid catalysis, does not seem to have been reported for the base-catalyzed hydrolysis of arenesulfonamides, but it has been observed with arenesulfamic acids (75). Sodium *p*-phenetylsulfamate is said to be cleaved easily by heating with 50 per cent sodium hydroxide, giving *p*-phenetidine in excellent yield. The salts of phenyl-

$$p\text{-}CH_3OC_6H_4NHSO_3Na + NaOH \rightarrow p\text{-}CH_3OC_6H_4NH_2 + Na_2SO_3$$

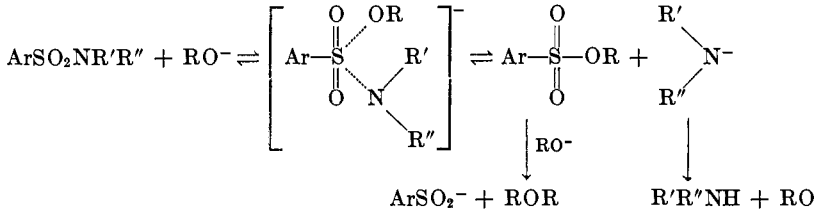
sulfamic acid and *p*-tolylsulfamic acid were much more stable; the latter, however, could be cleaved to *p*-toluidine by fusion with sodium hydroxide at 280°C. It is interesting that electron-donating groups markedly facilitate this reaction.

III. Alcoholysis of Sulfonamides

A. Sulfur–nitrogen bond cleavage

Strangely enough, the base-catalyzed alcoholysis of sulfonamides was not reported until a few years ago, although it might have been anticipated that it would be more successful than basic hydrolysis because of the more basic reagent and the higher temperatures possible. Such has proven to be the case, and normal amide-type hydrolysis was realized under moderate conditions. The work has been limited to secondary sulfonamides, as primary sulfonamides form salts, which are more stable.

A method which has been extensively used is to heat the sulfonamide with 40–50 per cent sodium isoamoxide in isoamyl alcohol at 150–200°C. for 3–6 hr. (29, 30). The products isolated were the secondary amine, the sodium sulfonate, and diisoamyl ether. It therefore appears that the alkoxide ion attacked the sulfur atom, forming the amide ion and a sulfonate ester, which reacted with an additional alkoxide ion in the well-known manner:



Sulfonamides of primary amines could not be cleaved under such conditions. Such form anions in the basic medium, and the resulting negative charge on

TABLE 5

Cleavage of p-$CH_3C_6H_4SO_2NRR'$ *by sodium isoamoxide**

R	R′	Yield of RR′NH	R	R′	Yield of RR′NH
		per cent			*per cent*
CH_3	C_6H_5	92.5	$-(CH_2)_5-$†		0
C_2H_5	C_6H_5	87.0	$-(CH_2)_4-$		92.5
n-C_8H_{17}	C_6H_5	76.3	$-(CH_2)_5-$		80.7
C_2H_5	β-$C_{10}H_7$	99.9	$-(CH_2)_6-$		70.2
CH_3	α-$C_{10}H_7$	68.3	$-(CH_2)_2O(CH_2)_2-$		46.5
C_6H_5	C_6H_5	92.5	$-(CH_2)_2NH(CH_2)_2-$		37.0
CH_3	CH_3	80–85	C_2H_5	p-$CH_3OC_6H_4$	49.4
C_2H_5	C_2H_5	29.2	C_2H_5	p-$CH_3C_6H_4$	71.6
n-C_4H_9	n-C_4H_9	0	C_2H_5	p-ClC_6H_4	91.6
C_2H_5	n-C_8H_{17}	0	C_2H_5	p-$O_2NC_6H_4$	100.0
n-$C_{12}H_{25}$	n-$C_{12}H_{25}$	0			
C_2H_5	Cyclo-C_6H_{11}	53.4			
Cyclo-C_6H_{11}	Cyclo-C_6H_{11}	67.0			

* With 51 per cent sodium isoamoxide in isoamyl alcohol for 6 hr. at 175-180°C. (29, 30).
† Reference 59.

nitrogen no doubt shields the sulfur atom from nucleophilic attack and strengthens the sulfur–nitrogen bond by increasing its polarity.

The yields of secondary amines from a series of twenty-three p-toluenesulfonamides are given in table 5. As the sum of the yield of amine and the recovery of unreacted sulfonamide was 85–100 per cent, it may be concluded that the main deterrent to the yields was lack of reactivity.

The yield of aromatic amines was much better than that of aliphatic amines, probably because of inductive effects. Electronic effects of p-substituents on aromatic amines were observed in the manner expected from the above mechanism, electron-withdrawing groups aiding cleavage and electron-donating groups inhibiting it. Steric factors also were quite evident. The yield of diethylamine was less than half that of dimethylamine, and the higher N, N-dialkylsulfonamides were not affected. Cyclic amines were formed more readily than open-chain amines, and the smaller the ring, the more readily, except for the four-membered ring. (In the latter case the failure to obtain any azetidine is probably due to cleavage of the ring, and the same would doubtless occur also with the ethylenimine derivative.) The easier formation of ethyl-β-naphthylamine than of methyl-α-naphthylamine must be ascribed to the greater steric hindrance at the α-position, for the latter is the weaker base and hence its cleavage would be the more favored by electronic factors.

p-Toluenesulfonamides having one or two benzyl groups on the nitrogen atom have been cleaved under the relatively mild conditions of heating with potassium ethoxide in refluxing toluene (69). Sodium ethoxide could not be substituted for potassium ethoxide. It would seem that the benzyl group enhances the ease of cleavage, since a related allyl compound was cleaved only slightly, but there are no comparable data for compounds of the type listed in table 6.

Very striking enhancement of ease of cleavage was observed when benzoylmethyl, carbethoxymethyl, and carbomethoxymethyl groups were present

TABLE 6

Yields of p-toluenesulfonate salt from p-$CH_3C_6H_4SO_2NRR'$ and potassium ethoxide or sodium ethoxide (69)

R	R′	In Ether		In Toluene	
		C_2H_5OK	C_2H_5ONa	C_2H_5OK	C_2H_5ONa
		per cent	*per cent*	*per cent*	*per cent*
Phenyl	Allyl	0	0	10	0
Methyl	Benzyl	0	0	80	0
Phenyl	Benzyl	0	0	77	0
Benzyl	Benzyl	0	0	90	0
Methyl	Carbethoxymethyl	85	95	70	93
Phenyl	Carbethoxymethyl	77	95	72	95
Phenyl	Benzoylmethyl	80	90	75	85
Carbomethoxymethyl	Carbomethoxymethyl	85	95	70	80

on the nitrogen atom, for such compounds could be cleaved in excellent yields by potassium ethoxide or sodium ethoxide in either toluene or ether (69). The ease of cleavage could be due to the electron-withdrawing properties of the groups.

Unfortunately, isolation of the amine was not reported in any of these last cases, and the criterion of cleavage was the yield of *p*-toluenesulfonate salt isolated. This is a good indication, however, of sulfur–nitrogen cleavage, as carbon–nitrogen cleavage would have given instead a primary sulfonamide which would not have been cleaved further.

Another example of easy alcoholysis of a sulfonamide is the reaction of tri(*p*-toluenesulfonyl)amine with methanolic sodium methoxide; refluxing for 30 min. gives a 72 per cent yield of di(*p*-toluenesulfonyl)amine plus a 28 per cent yield of di(*p*-toluenesulfonyl)methylamine (68). The latter presumably arises from methylation of the former by the methyl *p*-toluenesulfonate, which is the other

$$(Tos)_3N + CH_3O^- \rightarrow TosOCH_3 + Tos_2N^- \rightarrow TosO^- + Tos_2NCH_3$$

product of cleavage. The similar reaction with sodium ethoxide gave an 86 per cent yield of di(*p*-toluenesulfonyl)amine and a 14 per cent yield of its *N*-ethyl derivative.

B. CARBON–NITROGEN BOND CLEAVAGE

The single instance of this type of cleavage is the reaction of *N*-(2-carbomethoxyethyl)-*p*-toluenesulfonanilide with sodium methoxide, to give an 89 per cent yield of *p*-toluenesulfonanilide (70). This is analogous to the cleavage of the corresponding carboxylic acid, mentioned earlier (Section II,F,2).

C. SEPARATION OF AMINES

The original Hinsberg method of separation of amines, which depends on the solubility of primary sulfonamides in aqueous alkali, is generally not satisfactory with sulfonamides of high-molecular-weight primary amines. A number of workers have resorted to using methanolic potassium hydroxide to effect the solubility and separation of sulfonamides.

TABLE 7

Separation of p-toluenesulfonamides A and B by sodium amoxide (30)

N-Substituents in		Recovery of A	Amine from B
A	B		
		per cent	*per cent*
β-$C_{10}H_7$, H	β-$C_{10}H_7$, C_2H_5	100 (?)	97
$(C_6H_{11})_2$	$(C_6H_5)_2$	99	84
$(C_8H_{17})_2$	$(C_6H_5)_2$	100	92
C_2H_5, C_8H_{17}	C_2H_5, C_6H_5	81	84

A very good separation of primary and secondary amines has been recently proposed, utilizing the difference in ease of cleavage of the different classes of sulfonamides by the sodium isoamoxide–isoamyl alcohol reagent (31). For example, treatment of a mixture of the *p*-toluenesulfonamides of β-naphthylamine and ethyl-β-naphthylamine with this reagent gave a 97 per cent yield of the secondary amine and quantitative recovery of the primary sulfonamide.

Satisfactory separation of secondary aromatic amines from dialkylamines can be made likewise, on the basis of the low reactivity of *N*, *N*-dialkylsulfonamides towards the reagent. Examples of this application are summarized in table 7. Each case required a study of the optimum conditions, including concentration of alkoxide, temperature, and reaction time.

IV. Aminolysis of Sulfonamides

Cleavage of sulfonamides by aminolysis is also a development of the last decade, but already many examples of it have been studied (32, 34, 36, 37).

It is ordinarily carried out by heating a sulfonamide with a primary or secondary amine in the presence of the hydrochloride of the latter. In this way amine

$$ArSO_2NRR' + R''R'''NH \rightleftharpoons ArSO_2NR''R''' + RR'NH$$

exchange was effected between aniline and *p'*-nitro-*p*-toluenesulfonanilide, giving *p*-nitroaniline and *p*-toluenesulfonanilide. The temperature in this case was 200–220°C. (36).

In certain cases involving aliphatic amines, acid catalysis may not be required (32). Tri(*p*-toluenesulfonyl)amine and piperidine reacted when heated in benzene for 1 hr. to form 1-*p*-toluenesulfonylpiperidine and di(*p*-toluenesulfonyl)amine in good yields (68).

In table 8 are presented data on a large number of amine exchange reactions that were carried out by heating the sulfonamide with two equivalents of amine hydrochloride at 145–210°C. for 30–120 min. (32, 34). Theoretically the reaction should reach an equilibrium state, and in one case—*p*-toluenesulfonanilide and diethylamine versus *N*, *N*-diethyl-*p*-toluenesulfonamide and aniline—this seems to have been realized. In the two other cases where the reaction was tried in both directions, however, there was insufficient conversion to reach equilibrium, and so it is probable that the majority of the results are not representative of the position of equilibrium.

TABLE 8

Amine exchange of p-toluenesulfonamides (32, 34)

p-Toluenesulfonamides	Amines	Exchanged Sulfonamides	Unreacted Sulfonamides
		per cent	*per cent*
p-Toluenesulfonanilide	Diphenylamine	26.0	68.3
	N-Ethylaniline	10.2	88.6
	Diethylamine	0.0	97.4
N-Ethyl-*p*-toluenesulfonanilide	Aniline*	64.8	34.6
	N-*n*-Dodecylaniline	46.2	45.5
	Ethylamine	3.1	94.3
	Ammonia	0.23	99.7
p-Toluenesulfonamide	Aniline	93.3	0.0
	N-Ethylaniline	12.3	71.8
	Ethylamine	0.0	98.9
	Diethylamine	0.0	98.8
N-Ethyl-*p*-toluenesulfonamide	Aniline	73.2	24.1
	Diphenylamine	66.8	32.0
	N-Ethylaniline	18.1	77.0
	Diethylamine	3.5	96.0
N,*N*-Diethyl-*p*-toluenesulfonamide	Aniline	98.	2.0
	N-Ethylaniline	61.2	38.8
	Ethylamine	17.0	72.0
p-Toluenesulfonepyrrolidide	Aniline	81.4	16.2
p-Toluenesulfonepiperidide	Aniline	86.2	13.7
p-Toluenesulfonehexamethylenimide	Aniline	93.3	4.9
N-Ethyl-*p*-toluenesulfone-β-naphthylamide	Aniline	41.4	57.5
N-Methyl-*p*-toluenesulfone-α-naphthylamide	Aniline	82.4	16.3
N-Ethyl-*p*′-nitro-*p*-toluenesulfonanilide	Aniline	69.1	30.8
	Piperidine	5.8	57.8
N-Ethyl-*p*′-chloro-*p*-toluenesulfonanilide	Aniline	89.9	10.6
	Piperidine	9.8	82.9
N-Ethyl-*p*-toluenesulfonanilide	Aniline*	90.7	7.3
	Piperidine	12.5	84.3
N-Ethyl-*p*′-methyl-*p*-toluenesulfonanilide	Aniline	93.0	5.7
	Piperidine	13.5	85.8
N-Ethyl-*p*′-methoxy-*p*-toluenesulfonanilide	Aniline	93.7	5.0
	Piperidine	14.9	79.9
N-Ethylbenzenesulfonanilide	Aniline	55.6	43.1
N-Ethyl-*p*-toluenesulfonanilide	Aniline*	59.8	39.3
N-Ethyl-β-naphthalenesulfonanilide	Aniline	46.9	52.9
N-Ethyl-α-naphthalenesulfonanilide	Aniline	52.0	47.7

* Different experiments under slightly different conditions.

Nevertheless, it is possible to conclude from these data, on a kinetic basis, that the relative ease of breaking the sulfur–nitrogen bond in sulfonamides increases in the following series: sulfonanilide < *N*-phenylsulfonanilide < *N*-ethylsulfonanilide < sulfamide < *N*-ethylsulfonamide < *N*,*N*-diethylsulfonamide.

The susceptibility of sulfonamides in amine exchange seems to depend largely on basicity, alkyl groups increasing the reactivity and aryl groups decreasing it. The effect of *p*-substituents on an *N*-phenyl group also affects the reactivity in the same way as the basicity.

The tendency of amines to undergo amine exchange seems to depend largely on the acidity of the hydrochlorides, those which are weakest having the most acidic hydrochlorides and exchanging most completely. Under equilibrium conditions, the stability of the resulting sulfonamides also would favor the exchange

with weaker bases. There does not seem to be much evidence for any great steric factors.

The stability of sulfonamides towards amine hydrochlorides is also influenced by substituents on the benzene ring of the sulfonic acid. *N*-Ethyl-*p*-toluenesulfonanilide is exchanged faster than the benzenesulfonic acid derivative, owing to the $+I$ and hyperconjugative effects of the *p*-methyl group, which increase the basicity of the sulfonamide. Naphthalenesulfonanilides are less reactive, owing to the strong electron-withdrawing effect of naphthalene.

These facts, then, suggest that the amine exchange occurs by a dissociative mechanism, involving the conjugate acid of the sulfonamide, rather than a displacement mechanism, although that may be involved with the uncatalyzed reaction of amines with sulfonamides. It is thus related to hydrolysis.

$$\begin{aligned} ArSO_2NR_2 + R'_2NH_2^+ &\rightleftharpoons ArSO_2NHR_2^+ + R'_2NH \\ &\Updownarrow \\ &ArSO_2^+ + HNR_2 + R'_2NH \\ &\Updownarrow \\ ArSO_2NR'_2 + R_2NH_2^+ &\rightleftharpoons ArSO_2NHR'^+_2 + R_2NH \end{aligned}$$

Dealkylation may occur in the course of amine exchange, as in acid hydrolysis. For example, the reaction of *p'*-chloro-*N*-ethyl-*p*-toluenesulfonanilide with aniline hydrochloride gave *p'*-chloro-*p*-toluenesulfonanilide and ethylaniline, as well as the normal products. This dealkylation side reaction proceeded to

$$p\text{-}CH_3C_6H_4SO_2N(C_2H_5)C_6H_4Cl\text{-}p + C_6H_5NH_3^+Cl^- \rightarrow p\text{-}CH_3C_6H_4SO_2NHC_6H_4Cl\text{-}p + (C_6H_5NH_2C_2H_5)^+Cl^-$$

the extent of about 15 per cent of the total reaction, the ethyl group being transferred quantitatively to this extent from the sulfonamide to the amine (32). Somewhat more dealkylation was observed with *p'*-nitro-*N*-ethyl-*p*-toluenesulfonanilide, accompanied, however, by more tar formation (32). Heating with pyridine hydrochloride at 200°C. caused partial dealkylation of *N*-allyl-, *N*-propargyl-, and *N*-propyl-*p*-toluenesulfonamides (80). Also, in the acid-catalyzed aminolysis of sulfonamides by noncyclic tertiary amines, one alkyl group was cleaved (37).

The general occurrence of such dealkylation, even when neither amine involved is not labelled by a substituent, was demonstrated by studying the reaction of *N*-ethyl-*p*-toluenesulfonyl-[1-^{14}C]-anilide with aniline hydrochloride (32). Under the usual conditions, practically all the activity resided in the unchanged ethylanilide and in the ethylaniline formed, but a small activity was found in the *p*-toluenesulfonanilide, indicating 2 per cent dealkylation. Apparently the extent of dealkylation is small unless electron-withdrawing groups are present in the aniline moiety.

The dealkylation is probably mechanistically associated with aminolysis, for in the conjugate acid of the sulfonamide the carbon–nitrogen bonds are neces-

sarily weakened, permitting loss of an alkyl carbonium ion:

$$ArSO_2NR_2 + R'NH_3^+ \rightleftharpoons [ArSO_2NHR_2]^+ + R'NH_2$$
$$\downarrow$$
$$ArSO_2NHR + R^+$$
$$R^+ + R'NH_2 \rightarrow RR'NH_2^+$$

Dealkylation of *N*-alkylacetanilides and even of *N*-alkylanilines has been observed under similar conditions (80).

Amine exchange of sulfonamides has recently been utilized for synthetic purposes. The preparation of sulfanilylguanidine from sulfanilamide and guanidine in cyclohexanol at 140°C. has been patented (73), as has also a preparation of calcium cyclohexyl sulfamate from calcium sulfamate and cyclohexylamine at about 175°C. under pressure (42).

A slightly different method of effecting amine exchange has been used for the synthesis of *N*-butyl-*N'*-*p*-toluenesulfonylurea. The sulfonamide was heated with the *N*-nitroamine (in this case, *N*-butyl-*N'*-nitrourea) in nitrobenzene with some sodium carbonate at 130–160°C. (48). In this case nitrogen and water are split off instead of ammonia. This method of preventing the reverse reaction might be a good way of increasing the yield of transamination products.

V. Reductive Cleavage of Sulfonamides

A. Catalytic Hydrogenation

Sulfonamides are stable to catalytic hydrogenation. Hydrogenolysis of *p*-toluenesulfonazetidide with hydrogen over Raney nickel at 500 p.s.i. did not proceed and the starting material was recovered (38). An attempt using copper chromite as a catalyst was also unsuccessful (54).

B. Reduction by Lithium Aluminum Hydride

Sulfonamides are very resistant to reduction by lithium aluminum hydride, as well as by other anionic reducing agents. The same reason used to explain the resistance to alkali cleavage may be invoked: namely, the shielding of the sulfur atom by the negatively charged oxygen and nitrogen atoms from nucleophilic attack. Here, too, primary sulfonamides are so resistant that they have not been cleaved by lithium aluminum hydride, but secondary sulfonamides have been cleaved by using unusually vigorous conditions for this reagent. Some examples are: *N*-ethyl-*p*-toluenesulfonanilide at 120°C. for 4 hr. in dibutyl ether, to give a 41 per cent yield of *N*-ethylaniline and *p*-thiocresol (28); *N*, *N*-diethylbenzenesulfonamide, heated for 7 days in refluxing tetrahydrofuran (with sodium aluminum hydride) to give a 57 per cent yield of benzenesulfinic acid and a 10 per cent yield of thiophenol (10); p-toluenesulfonylazetidide, heated for 18 hr. in refluxing ether, to give a 10 per cent yield of azetidine (38).

Xylene solutions of Grignard reagents are reported to bring about similar reductive cleavage of sulfonamides (28).

C. REDUCTION BY HYDROBROMIC ACID

One of the most frequently used reagents for the cleavage of sulfonamides is hydrobromic acid in a mildly acidic organic solvent, and sometimes hydriodic acid is used likewise. Not uncommonly it is assumed that these acids serve as catalysts for the hydrolysis or solvolysis of sulfonamides, like hydrochloric acid. Actually, their mode of action, however, is as reducing agents rather than as catalysts for hydrolysis.

Treatment of *N*-(2,3-dibenzoylpropyl)-*p*-toluenesulfonanilide with a mixture of hydrobromic acid and acetic acid at room temperature for 2 hr. produced a 90 per cent yield of 2,4-dibromophenyl(2,3-dibenzoxypropyl)amine and a 72 per cent yield of ditolyl disulfide (17). A mixture of hydrobromic acid and glacial acetic acid at 20°C. gave an optically active 2,3,4-triacetyl-6-(2,4-dibromophenylamino)-*α*-*d*-chinopyranosyl-1-bromide from its *p*-toluenesulfonyl derivative (50). Other reports of treatment of sulfonamides of aromatic amines with hydrobromic acid showed a brominated amine to be a product (33).

Addition of phenol to prevent the bromination of the amines formed has been employed by several workers (65, 66, 76, 77). This method is a good way to obtain the amine from sulfonamides (49).

Comparison of the hydrobromic acid–phenol method with the hydrochloric acid method is shown in table 9. The low yields of amines in the case of the cleavage of tetramethyl-, pentamethyl-, and dimethoxybenzenesulfonanilides by hydrochloric acid are due to their low solubility in an aqueous acid. Phenol acts

TABLE 9

Cleavage of sulfonanilides of the structure $XC_6H_nSO_2NHC_6H_5$*

X	25 Per Cent Hydrochloric Acid		48 Per Cent Hydrobromic Acid-Phenol	
	Time	Amine	Time	Amine
	hours	*per cent*	*minutes*	*per cent*
H	7	26	20	69
2,4,6-$(CH_3)_3$	7	61	20	93
2,3,5,6-$(CH_3)_4$	7	6	20	92
$(CH_3)_5$	7	1	20	94
2,4-$(CH_3O)_2$	7	0	20	89

* At refluxing temperature (66).

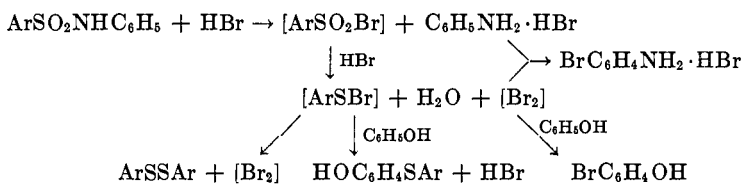
TABLE 10

Cleavage of sulfonamides with hydrogen bromide and phenol (63)

Groups in RSO_2NHR'		Amine	Groups in RSO_2NHR'		Amine
R	R'		R	R'	
		per cent			*per cent*
C_6H_5	H	50	C_6H_5	*o*-$O_2NC_6H_4$	22
CH_3	C_6H_5	83	C_6H_5	*p*-$O_2NC_6H_4$	90
C_6H_5	$C_6H_5CH_2CH_2$	55	*p*-$O_2NC_6H_4$	C_6H_5	90
C_6H_5	*α*-$C_{10}H_7$	84			

as a solvent for these sulfonamides, and the hydrobromic acid–phenol method gave an excellent yield of amines. The method also cleaves electronegatively substituted sulfonanilides which are not affected by hydrochloric acid (table 10). It is less affected by electron availability and steric factors at the reaction point than other common methods. The low yield of *o*-nitroaniline may be due to stabilization of the sulfonamide by chelate ring formation with the *o*-nitro group.

With regard to the mechanism, it has been proposed that the sulfonyl bromide and sulfenyl bromide are intermediates in this reaction (64). The sulfenyl bromide (ArSBr) produces diaryl disulfide in the absence of phenol, and reacts with phenol to form hydroxyphenyl sulfide. The formation of hydroxyphenyl sulfide and bromophenol is rapid, and by use of a high enough concentration



of phenol (10 g. of phenol for 10 g. of benzenesulfonanilide) the formation of disulfide and bromoaniline can be prevented (68).

D. REDUCTION BY HYDRIODIC ACID

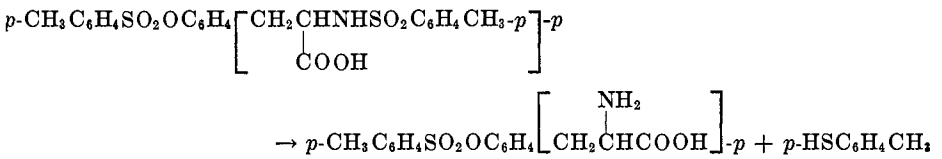
Hydriodic acid also reduces aromatic sulfonamides, forming thiophenols and ammonium iodide or amine hydroiodides. This reaction is illustrated by the following equation; in this example the yield of *p*-thiocresol was 85 per cent (11).

$$p\text{-}CH_3C_6H_4SO_2NH_2 + 7HI \rightarrow p\text{-}CH_3C_6H_4SH + NH_4I + 3I_2 + H_2O$$

When the reaction is used with *N*-substituted sulfonamides, it is necessary to remove the iodine formed in order to prevent iodination or oxidation. The reducing agent, phosphonium iodide, has been used successfully for this. Since it regenerates the hydrogen iodide, it serves as the apparent reducing reagent

$$PH_4I + 3I_2 + 3H_2O \rightarrow H_3PO_3 + 7HI$$

with the hydriodic acid present as a catalyst. Treatment of active *N*-*p*-toluenesulfonyl-*d*-phenylalanine ($[\alpha]^{17} = +35.08$ in 2 per cent aqueous solution) with concentrated hydriodic acid containing 1.5 molecular proportions of phosphonium iodide, for 30 min. at 95°C., gave *d*-phenylalanine ($[\alpha]^{17} = +33.4°$, 2 per cent solution) and thiocresol in practically quantitative yields (11). The same technique has been applied to the preparation of the dipeptides glycyl-*dl*-alanine, glycyl-*dl*-leucine, *dl*-alanylglycine, *dl*-leucylalanine, and *d*-alanyl-*l* leucine, which were obtained in about 90 per cent yields (55). *p*-Toluenesulfonanilide has been cleaved to *p*-thiocresol and aniline by the hydriodic acid–phosphonium iodide reagent at 75–80°C. for 30 min. (10). Di(*p*-toluenesulfonyl)tyrosine was reduced only at the sulfonamide linkage and gave *O*-*p*-toluenesulfonyltyrosine and *p*-thiocresol (11).



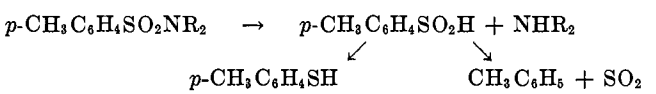
The sulfonamide linkage is especially sensitive to hydrogen halogenide reduction and can be cleaved without affecting the sulfonate group or carboxylic amide group (55). Carboxylic amide groups are hydrolyzed slowly by hydriodic acid but are not reduced. This offers an interesting contrast to the sodium amalgam reagent, which reduces the carboxylic amide function but does not affect the sulfonamide group.

A procedure has been developed in which elemental phosphorus (red or yellow) is substituted for the phosphonium iodide (47). This is possible because elemental phosphorus reduces free iodine to form phosphorus triiodide, which is converted to phosphonium iodide. Thus, elemental phosphorus is made the effective reducing reagent, with hydriodic acid the catalyst. *p*-Toluenesulfonamide and *p*-toluenesulfonanilide were reduced by treating with a solution of potassium iodide (0.3 mole) in concentrated phosphoric acid, containing phosphorus in about 100 per cent excess, under reflux for 4–6 hr. *p*-Thiocresol, apparently the only product sought, was isolated in yields of 87 and 84 per cent, respectively.

The reaction mechanism is considered to be the same as in the case of hydrobromic acid, and the intermediate sulfonyl iodide has actually been isolated (33).

E. REDUCTION BY ZINC AND ACID

Zinc and hydrochloric acid reduce sulfonamides to amines and thiophenols or hydrocarbons (34). The particle size of the zinc and the nature of the acid used



are important factors in determining the results of this type of reduction, but there has not been sufficient study of this method to warrant many generalizations. The work that has been done is summarized in table 11 (35).

TABLE 11

Reductive cleavage of sulfonanilides with zinc and acid

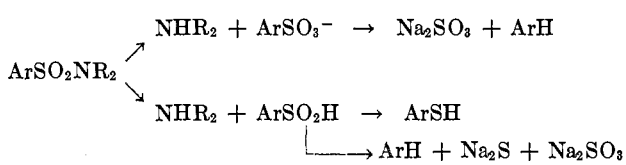
Sulfonanilide	Zinc	Acid Used (v./v.)		Yields		Recovered Amide
		Concentrated HCl	Acetic acid	Amine	Thiocresol	
				per cent	*per cent*	*per cent*
N-Ethyl-*p*-toluenesulfonanilide	Granular	100	0	6.6	4	81.5
	Granular	36.8	63.2	77.8	3.2	18.5
p-Toluenesulfonanilide	Dust	30.2	69.8	2.7	4.8	89
N-Dodecyl-*p*-toluenesulfonanilide	Dust	10	90	87	74	—
N-Methyl-*p*-toluenesulfonanilide	Dust	0	100	9.4	10	78

F. REDUCTION BY A METAL AND AN ALCOHOL OR AN AMINE

Reductive cleavage with sodium and an alcohol has found some use in the past to generate amines from the corresponding sulfonamides in cases where acid cleavages were unsatisfactory and alkaline hydrolysis was not feasible. An example of this application is the preparation of azetidine from *p*-toluenesulfonazetidide. The latter may be obtained rather easily and is an attractive intermediate for the difficultly accessible azetidine. Reductive cleavage of *p*-toluenesulfonazetidide with sodium in amyl alcohol was originally reported to give azetidine almost quantitatively (42), but according to most subsequent reports, the method did not give satisfactory results. A 14 per cent yield of azetidine (26), a 36 per cent yield of azetidine and 3-hydroxypropylamine and di(3-hydroxypropyl)amine as by-products (81), a 42 per cent yield of volatile amine (52), an 8 per cent yield of azetidine (60), and a 78 per cent yield of 2-methylazetidine from tosyl-2-methylazetidide (38) have been reported. (The yields reported are to a large degree dependent on the purity, including dryness, of the product, for it is difficult to avoid mechanical losses in handling this volatile, hygroscopic compound.)

Disadvantages of the method are the large amount of amyl alcohol (25 times the quantity of *p*-toluenesulfonazetidide (43)) and the large excess of sodium (about 20 atoms of sodium to 1 mole of *p*-toluenesulfonazetidide) required (38, 43).

The mechanism of the reaction was studied by Klamann and Hofbauer (35). *n*-Octyl-*p*-toluenesulfonanilide gave *n*-octylaniline, hydrogen sulfide, and sodium sulfite in yields of 78.2 per cent, 42 per cent, and 31.6 per cent, respectively, by treatment with sodium and isoamyl alcohol at 70°C. for 1 hr. Sodium sulfite and *p*-thiocresol were not affected by isoamyl alcohol and sodium. *p*-Toluenesulfonic acid gave sodium sulfite in yields of 77.5 and 72.6 per cent, and *p*-toluenesulfinic acid gave a mixture of sulfide and sulfite. Reductive cleavage and alcoholysis proceed at the same time. An appreciable amount of sodium *p*-toluene-



sulfonate was isolated in the cleavage of *N*-substituted *p*-toluenesulfonanilides by sodium and isoamyl alcohol (35), as shown in table 12.

A study of the reductive cleavage of various *p*-toluenesulfonamides by sodium and isomyl alcohol showed that the reaction was not greatly affected by electronic factors and steric factors of the substituents. The data on this study are summarized in table 13.

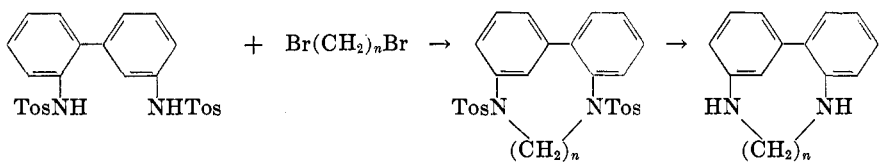
Use of *n*-butyl alcohol and sodium to reduce the products from *N*, *N*-di(*p*-toluenesulfonyl)-2,2′-diaminobiphenyl and polymethylene dibromides to the

TABLE 12

Reductive cleavage of sulfonanilides with sodium and isoamyl alcohol (35)

Sulfonanilide	Amine	Sodium *p*-Toluenesulfonate
	per cent	*per cent*
p-Toluenesulfonanilide	6.6	0
N-Methyl-*p*-toluenesulfonanilide	92	76.3
N-Ethyl-*p*-toluenesulfonanilide	82.5	72.2
N,*N*-Diphenyl-*p*-toluenesulfonamide	88.3	69.8

corresponding cyclic diamines has been reported. The yields were 79.3, 84.7, and 88.8 per cent for tri-, tetra-, and pentamethylene derivatives, respectively (67).



Reduction with sodium and ammonia or amines is a promising method of sulfonamide cleavage. *p*-Toluenesulfonazetidide was reduced by sodium and ammonia, forming azetidine in 30 per cent yield (5). A comparison of these agents in reductive cleavage is shown in table 14 (59).

Ethylenediamine and sodium at 90°C. gave an 18.3 per cent yield of azetidine and a 49.5 per cent yield of toluene from *p*-toluenesulfonazetidide, a 22.2 per cent yield of azetidine and a 42.9 per cent yield of benzene from benzenesulfonazetidide, and a 9.4 per cent yield of azetidine and a 13.7 per cent yield of naphthalene from β-naphthalenesulfonazetidide (59).

VI. Oxidative Cleavage of Sulfonamides

Oxidation of sulfonamides is not a good general method to obtain amines because sulfonamides are quite stable to oxidation and usually amines are easily oxidized.

It can be used, however, with sulfonamides of amines which are resistant to oxidation. An example here is the oxidation of *N*-*tert*-butyl-*p*-toluenesulfonamide with alkaline permanganate, which gives *tert*-butylamine and 2-methyl-2-nitropropane as minor products, the major one being *N*-*tert*-butylsulfamylbenzoic acid (5). The last-named compound is apparently an intermediate in the formation of the first two, since further treatment with the reagent produces them, and so the first step must have been oxidation of the *p*-methyl group to a carboxyl group, which facilitated cleavage of the sulfonamide linkage. It is not clear by what path this occurred, but the nitro compound undoubtedly arose from oxidation of the *tert*-butylamine, as it has recently been shown that it can be synthesized in 83 per cent yield in this way (39).

Dealkylation of *N*-alkyl groups often occurs in oxidation of sulfonamides. *N*-Alkyl-*p*-toluenesulfonamides are reported to be oxidized by boiling alkaline

TABLE 13

*Reductive cleavage of sulfonamides with sodium and isoamyl alcohol**

Groups in p-$CH_3C_6H_4SO_2NRR'$		Amine	Groups in p-$CH_3C_6H_4SO_2NRR'$		Amine
R	R'		R	R'	
		per cent			*per cent*
H	C_6H_5	81.3	n-C_8H_{17}	C_6H_5	78.2
C_2H_5	C_6H_5	93.5	n-$C_{12}H_{25}$	C_6H_5	91.4
n-C_4H_9	C_6H_5	81.0	n-C_8H_{17}	C_2H_5	83.7
n-C_5H_{13}	C_6H_5	80.6			

* Heated 1 hr. under reflux (34).

TABLE 14

Reductive cleavage of N,N-diethyl-p-toluenesulfonamide (59)

N,N-Diethyl-p-toluenesulfonamide	Reducing agent	Time	Temperature	Diethylamine
grams		*hours*	°C.	*per cent*
22.7	17 g. NH_3 + 23 g. Na	0.7	−35	31.5
22.7	70 g. EDA* + 9.2 g. Na	2	90	52.0
22.7	60 g. EDA + 2.8 g. Li	1.5	90	42.4
22.7	60 g. EDA + 2.8 g. Li	7	35	30.8

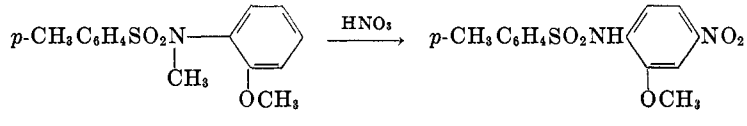
* EDA = ethylenediamine.

potassium permanganate solution to p-toluenesulfonamide and p-sulfamylbenzoic acid (2), while cold permanganate converted N-methyl-o-toluenesulfonamide to

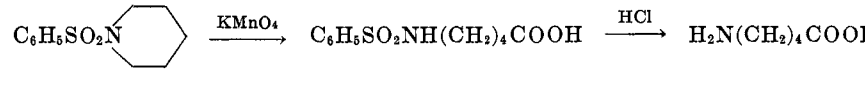
$$p\text{-}CH_3C_6H_4SO_2NHR \xrightarrow{KMnO_4} p\text{-}CH_3C_6H_4SO_2NH_2 + p\text{-}HOOCC_6H_4SO_2NH_2$$

R = CH_3, C_2H_5, C_3H_5.

o-sulfamylbenzoic acid (52). N-Methyl-p-toluenesulfon-o'-anisidide was converted into p-toluenesulfon-p'-nitro-o'-anisidide by treatment with 10 per cent nitric acid at 80°C. (74).



An example showing the fate of an alkyl group cleaved is the reaction of potassium permanganate with N-isopropyl-p-toluenesulfonamide, yielding acetone, p-toluenesulfonamide, and p-sulfamylbenzoic acid (5). An interesting case where the oxidized fragment was not lost is the Schotten–Schlomann synthesis of δ-aminovaleric acid (56). Here benzenesulfonylpiperidine was treated with potassium permanganate to yield δ-benzenesulfonamidovaleric acid, which was hydrolyzed by heating with concentrated hydrochloric acid at 180°C., forming the amino acid.



VII. Cleavage of Sulfonamides with Methyl Iodide

In an extension of a study of the cleavage of cyclic sulfides and cyclic ethers by methyl iodide, it was discovered that sulfonamides, as well as benzamides, could be cleaved by this reagent under severe conditions. The reaction was studied with only four sulfonamides, all of them of cyclic imines, and the cleavage was accomplished by heating for 24–50 hr. at 150–160°C. with a large excess of methyl iodide dissolved in acetone (47a). In this manner, *p*-toluenesulfonpiperidide was converted into *p*-toluenesulfonyl iodide and 1,1-dimethylpiperidinium iodide in 38 per cent yield.

Application of the method to *p*-toluenesulfonyl derivatives of small-ring and large-ring imines resulted in cleavage of the ring as well as the *p*-toluenesulfonyl group. *p*-Toluenesulfonazetidide was converted into *p*-toluenesulfonyl iodide in 95 per cent yield, 1,1-dimethylazetidinium iodide (17 per cent), and 1,3-diiodopropane, isolated as 1,3-di(β-naphthoxy)propane in 49 per cent yield; tetramethylammonium iodide was also formed. The di-*p*-toluenesulfonyl derivatives of 1,5-diazocycloöctane and 1,10-diazocycloöctadecane were converted by this treatment into tetramethylammonium iodide (53 per cent and 43 per cent yields, respectively) and to 1,3-diiodopropane and 1,8-diiodoöctane, respectively, which were isolated as their di-β-naphthyl ethers in 49 per cent and 38 per cent yields.

VIII. References

(1) Adams, R., and DeYoung, E. L.: J. Am. Chem. Soc. **79**, 705 (1957).
(2) Ash, A. S. F., Challenger, F., and Greenwood, G.: J. Chem. Soc. **1951**, 1877.
(3) Berkman, Ya. P., and Lushina, N. P.: Ukrain. Khim. Zhur. **24**, 320 (1958); Chem. Abstracts **53**, 1215 (1959).
(4) Braun, J. von, and Weismantel, J.: Ber. **55**, 3165 (1955).
(5) Briscoe, P. A., Challenger, F., and Duckworth, P. S.: J. Chem. Soc. **1956**, 1757.
(6) Burg, A. B., and Good, C. D.: J. Inorg. & Nuclear Chem. **2**, 237 (1956).
(7) Carothers, W. H., Brickford, C. F., and Hurwitz, G. J.: J. Am. Chem. Soc. **49**, 2908 (1927).
(8) Clemo, C. R., and Perkin, W. H., Jr.: J. Chem. Soc. **1924**, 1808.
(9) Crafts, J. M.: J. Am. Chem. Soc. **23**, 236 (1901).
(10) Field, L., and Grundwald, F. A.: J. Org. Chem. **16**, 946 (1951).
(11) Fischer, E.: Ber. **48**, 93 (1915).
(12) Geissman, T. A.: *Principles of Organic Chemistry*, p. 497. W. H. Freeman and Co., San Francisco (1959).
(12a) Gerhardt, C., and Chiozza, L.: Ann. **87**, 299 (1853).
(13) Halberkann, J.: Ber. **54**, 1665 (1921).
(14) Halberkann, J.: Ber. **54**, 1833 (1921).
(15) Halberkann, J.: Ber. **55**, 3074 (1922).
(16) Heinz, O., Friedeberg, H., and Haeseler, G.: Ber. **69**, 2311 (1936).
(17) Heinz, O., and Haeseler, G.: Ber. **69**, 2324 (1936).
(18) Hinsberg, O.: Ber. **23**, 2962 (1890).
(19) Hinsberg, O.: Ann. **265**, 178 (1891).
(20) Hinsberg, O., and Strupler, A.: Ann. **287**, 220 (1895).
(21) Houben, J.: *Die Methoden der organischen Chemie*, Vol. IV, p. 479. Geo. Thieme, Liepzig (1924).
(22) Ingold, C. K.: *Structure and Mechanism in Organic Chemistry*. Cornell University Press, Ithaca, New York (1953).

(23) JINDRA, A., AND SIPOS, F.: Chem.Listy **44**, 235 (1950); Chem. Abstracts **45**, 5569 (1951).
(24) JINDRA, A., AND SIPOS, F.: Časopis českého lékárnictva **63**, 211 (1950); Chem. Abstracts **46**, 7000 (1952).
(25) JOHNSON, T. B., AND AMBLER, J. A.: J. Am. Chem. Soc. **36**, 372 (1914).
(26) JONES, G. D.: J. Org. Chem. **9**, 484 (1944).
(27) KARRER, P.: *Organische Chemie*, 4th English edition, p. 128. Elsevier, Amsterdam (1950).
(28) KLAMANN, D.: Monatsh. Chem. **84**, 651 (1953).
(29) KLAMANN, D., AND BERTSCH, H.: Ber. **91**, 212 (1958).
(30) KLAMANN, D., AND BERTSCH, H.: Ber. **91**, 1427 (1958).
(31) KLAMANN, D., AND BERTSCH, H.: Ber. **91**, 1688 (1958).
(32) KLAMANN, D., AND FABIENKE, E.: Ber. **92**, 712 (1959).
(33) KLAMANN, D., AND HOFBAUER, G.: Monatsh. Chem. **84**, 62 (1953).
(34) KLAMANN, D., AND HOFBAUER, G.: Ann. **581**, 182 (1953).
(35) KLAMANN, D., AND HOFBAUER, G.: Ber. **86**, 1246 (1953).
(36) KOGAN, I. M., AND DZIOMKO, V. M.: Zhur. Obshcheĭ Khim. **21**, 1891 (1951); Chem. Abstracts **46**, 6608 (1952).
(37) KOGAN, I. M., AND DZIOMKO, V. M.: Zhur. Obshcheĭ Khim. **93**, 1234 (1953); Chem. Abstracts **47**, 12280 (1953).
(38) KOLONOWSKI, R. S.: Ph.D. Dissertation, University of Michigan (1959).
(39) KORNBLUM, N., CLUTTER, R. J., AND JONES, W. J.: J. Am. Chem. Soc. **78**, 4003 (1956).
(40) KURZER, F., AND POWELL, J. R.: J. Chem. Soc. **1953**, 2536.
(41) LITHERLAND, A., AND MANN, F. G.: J. Chem. Soc. **1938**, 1588.
(42) LODER, D. J.: U. S. patent 2,804,472; Chem. Abstracts **52**, 8191 (1958).
(43) MARKWALD, W., AND HOWARD, C. C.: Ber. **32**, 2031 (1899).
(44) MARKWALD, W., AND PORSTE-HUELSCHOFF, A. F. VON: Ber. **31**, 3261 (1898).
(45) MARVEL, C. S., AND GILLESPIE, H. B.: J. Am. Chem. Soc. **48**, 2943 (1926).
(46) MARVEL, C. S., HELFRICK, M. D., AND BELSLEY, J. P.: J. Am. Chem. Soc. **51**, 1272 (1929).
(47) MIESCHER, K., AND BILLETER, I. R.: Helv. Chim. Acta **29**, 601 (1939).
(47a) MÜLLER, A., FUNDER-FRITZSCHE, E., KONAR, W., AND RINTERSBACHER-WLASAK, E.: Monatsh. Chem. **84**, 1206 (1953).
(48) MUKHERJEE, S. L., AND ALBERT DAVID LTD.: Indian patent 59,251; Chem. Abstracts **53**, 1158 (1959).
(49) NOLLER, C. R.: *Chemistry of Organic Compounds*, p. 472. W. B. Saunders Company, Philadelphia (1957).
(50) OHLE, H., FRIEDEBERG, H., AND HAESELER, G.: Ber. **69**, 2311 (1936).
(51) PSCHORR, R., AND KARO, W.: Ber. **39**, 3140 (1906).
(52) REMSEN, I., AND CLARK, F. E.: J. Am. Chem. Soc. **30**, 281 (1903).
(53) REVERDIN, F., AND CREPIEUX, P.: Ber. **35**, 1441 (1902).
(54) SCHAEFER, F. C.: J. Am. Chem. Soc. **77**, 5928 (1955).
(55) SCHONHEIMER, R.: Z. physiol. Chem. **154**, 203 (1926).
(56) SCHOTTEN, C., AND SCHLÖMANN, W.: Ber. **24**, 3687 (1891).
(56a) SCHROETER, G.: Angew. Chem. **39**, 1460 (1926).
(57) SCHROETER, G., AND ESLIEB, O.: Ann. **367**, 157 (1909).
(58) SCHUBERT, W. M.: J. Am. Chem. Soc. **71**, 2639 (1949).
(59) SEARLES, S., AND NUKINA, S.: Manuscript in preparation.
(60) SEARLES, S., TAMRES, M., BLOCK, F., AND QUARTERMAN, L. A.: J. Am. Chem. Soc. **78**, 4917 (1956).
(61) SHORT, W. F., AND OXLEY, P.: British patent 587,810; Chem. Abstracts **43**, 689 (1949).
(62) SHRINER, R. L., AND SCHREIBER, R. S.: J. Am. Chem. Soc. **56**, 114 (1934).
(63) SHRINER, R. L., SCHREIBER, R. S., AND PEZOLD, M. P.: J. Am. Chem. Soc. **56**, 696 (1934).
(64) SHRINER, R. L., AND SCHREIBER, R. S.: J. Am. Chem. Soc. **56**, 1618 (1934).

(65) SNYDER, H. R., AND GELLER, H. C.: J. Am. Chem. Soc. **74**, 4864 (1952).
(66) SNYDER, H. R., AND HECKERT, R. E.: J. Am. Chem. Soc. **74**, 2006 (1952).
(67) STETTER, H.: Ber. **86**, 380 (1953).
(68) STETTER, H., AND HANSMANN, H.: Ber. **90**, 2728 (1957).
(69) TAKATA, Y.: J. Pharm. Soc. Japan **71**, 1474 (1951); Chem. Abstracts **46**, 8036 (1952).
(70) TAKATA, Y.: J. Pharm. Soc. Japan **72**, 321 (1952); Chem. Abstracts **47**, 2129 (1953).
(71) ULLMANN, F.: Ann. **327**, 110 (1903).
(72) ULLMANN, F., AND BLEIER, H.: Ber. **35**, 4273 (1902).
(73) VEB FARBENFABRIK WOLFEN: German patent (East) 10,969: Chem. Abstracts **53**, 2097 (1959).
(74) VERKADE, P. E., AND BOSMA, G. S. K.: Rec. trav. chim. **67**, 241 (1948); Chem. Abstracts **43**, 167 (1949).
(75) WEIL, H., AND MOSER, E.: Ber. **55**, 732 (1922).
(76) WEISBLAT, D. I., MAGERLEIN, B. J., AND MYERS, D. R.: U. S. patent 2,562,222; Chem. Abstracts **46**, 3093 (1952).
(77) WEISBLAT, D. I., MAGERLEIN, B. J., AND MYERS, D. R.: British patent 676,037; Chem. Abstracts **46**, 9600 (1952).
(78) WITT, O. N., AND UERMENYI, D.: Ber. **46**, 296 (1913).
(79) WITT, O. N., AND TRUTTWIN, H.: Ber. **47**, 2786 (1914).
(80) WOLF, V., AND RAMIN, D.: Ann. **610**, 67 (1957).
(81) YANBIKOV, YA. M., AND DEM'YANOV, N. YA: Zhur. Obschcheĭ Khim. **8**, 1545 (1938); Chem. Abstracts **33**, 4538 (1939).
(82) YANORA, N. M., KOSTOVA, A. G., AND SUSHKO, Z. N.: Zhur. Obshcheĭ Khim. **26**, 2855 (1956); Chem. Abstracts **51**, 8026 (1957).