(11) M. S. Norn, *Acta Ophthalmol.*, **45**, 347(1967).
(12) P. D. Joyce, *Ir. J. Med. Sci.*, **6**, 359(1967).
(13) T. Matsumato, R. M. Hardaway, and C. A. Heisterkamp, *Arch. Surg. (Chicago)*, **94**, 794(1967).
(14) C. M. Papa and A. M. Kligman, *J. Invest. Dermatol.*, **46**, 193(1966).
(15) E. I. Korobkova and I. V. Liskina, *Fed. Proc. Transl. Suppl.*, **22**, 1227(1963).
(16) J. Convit and J. M. Goihman, *Arch. Dermatol.*, **88**, 350 (1963).
(17) L. B. Goss, R. R. Franklin, and W. C. Hunter, *Amer. J. Obstet. Gynecol.*, **87**, 493(1963).
(18) L. B. Goss, *Med. Rec. Ann.*, **57**, 342(1964).
(19) F. G. Papkess, *Ann. Allergy*, **22**, 42(1964).
(20) E. Gurr, "Staining—Practical and Theoretical," 2nd ed., Williams and Wilkins, Baltimore, Md., 1962, p. 303.
(21) W. F. Kocholaty and B. D. Ashley, *Toxicon*, **3**, 184(1966).
(22) W. F. Kocholaty, B. D. Ashley, and J. A. Billings, *ibid.*, **5**, 43(1967).
(23) W. F. Kocholaty, *ibid.*, **3**, 175(1966).
(24) M. Brin and R. H. Yonemato, *J. Biol. Chem.*, **230**, 307 (1958).
(25) Q. H. Gibson, *Biochem. J.*, **42**, 13(1948).
(26) T. P. Stossel and R. B. Jennings, *Amer. J. Clin. Pathol.*, **45**, 600(1966).
(27) H. J. Conn, "Biological Stains," 7th ed., Williams and Wilkins, Baltimore, Md., 1961.
(28) K. Bergmann and C. T. O'Konski, *J. Phys. Chem.*, **67**, 2169 (1963).
(29) G. S. Singhal and E. Rabinowitch, *ibid.*, **71**, 3347(1967).
(30) R. D. Lillie, *Stain Technol.*, **18**, 1(1943).
(31) W. C. Holmes, *ibid.*, **3**, 45(1928).
(32) W. C. Holmes and E. F. Snyder, *ibid.*, **4**, 7(1929).
(33) F. C. Schaefer and W. D. Zimmerman, *Nature*, **220**, 66 (1968).
(34) H. Dreser, *Z. Biol.*, **21**, 41(1885).
(35) F. Muller, *Deut. Arch. Klin. Med.*, **53**, 130(1899).
(36) K. Elsner, *ibid.*, **59**, 47(1901).
(37) P. Herter, *Amer. J. Physiol.*, **12**, 128(1904).
(38) F. Underhill and O. Closson, *ibid.*, **13**, 358(1905).
(39) A. R. DiSanto and J. G. Wagner, *J. Pharm. Sci.*, to be published.
(40) *Ibid.*, to be published.
(41) P. Mukerjee and A. K. Ghosh, *J. Phys. Chem.*, **67**, 2169 (1963).

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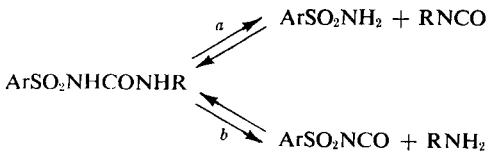
# Thermal Dissociation of Sulfonylureas II: Dissociation of Four *N*- and *N'*-Substituted Sulfonylureas in Different Media

FRANCESCO BOTTARI, BORIS GIANNACCINI, ENRICO NANNIPIERI▲, and MARCO F. SAETTONE

**Abstract** □ *N-n*-Butyl-*N'*-tosylurea (tolbutamide), *N-n*-butyl-*N'*-methyl-*N'*-tosylurea, *N,N*-pentamethylene-*N'*-tosylurea, and *N,N*-pentamethylene-*N'*-methyl-*N'*-tosylurea were heated at different temperatures in a series of solvents, and the reaction products were submitted to quantitative analysis. The outcome of these experiments, which had the aim of elucidating the mechanism by which sulfonylureas undergo a breakdown when heated in reactive solvents, may contribute to a better understanding of the stability of sulfonylureas in pharmaceutical preparations. The results of the reactions in alcoholic media were in good agreement with a mechanism involving dissociation of the urea into isocyanate and amine, followed by reaction of the isocyanate with the alcohol. The behavior of the four sulfonylureas in water was also in good agreement with the dissociation hypothesis. The breakdown of these compounds in amines seems to follow a more complicated pattern, the reactivity being influenced, among other factors, by the basicity of the amine. Although dissociation seems to be operative at the lower temperature, the occurrence of aminolysis at higher temperatures could not be excluded. The present results point to dissociation, rather than solvolysis, as the most likely mechanism by which sulfonylureas undergo breakdown in alcohols and in water, as well as in amines at relatively low temperatures.

**Keyphrases** □ Sulfonylureas—thermal dissociation in alcohols, water, and amines, mechanism □ Tolbutamide and related sulfonylureas—thermal dissociation in alcohols, water, and amines, mechanism □ Dissociation, thermal, tolbutamide and related sulfonylureas—in alcohols, water, and amines, mechanism

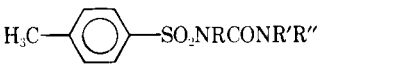
Sulfonylureas, a class to which belong some important oral hypoglycemic agents, are known to undergo a breakdown under various experimental conditions. Although a hydrolytic process is most frequently observed in such decompositions (1–4), cases of thermal dissociation were reported (5, 6). Symmetrically substituted sulfonylureas such as tolbutamide (I) can theoretically yield on dissociation either an alkyl (path *a*) or an arylsulfonyl isocyanate (path *b*), as indicated in Scheme I. A quantitative dissociation of I to *p*-toluenesulfonamide and *n*-butyl isocyanate (path *a*) was recently reported (5) to take place in inert solvents at 160–180°. Evidence for the dissociation of I in alcohols at 80° according to the alternative path *b* was given in the first paper of this series (6). The purpose of the present work was to provide additional information on the




*Scheme I*

dissociation of sulfonylureas in reactive[1] solvents, a subject which seems to have received little attention until now. In particular, it was of interest to ascertain: (*a*) whether other reactions such as solvolysis compete with dissociation, and (*b*) what experimental conditions favor either type (*a* or *b*) of dissociation for compounds of type I.

The sulfonylureas used for this study were *N*-*n*-butyl-*N'*-tosylurea (tolbutamide) (I), *N*-*n*-butyl-*N'*-methyl-*N'*-tosylurea (II), *N*,*N*-pentamethylene-*N'*-tosylurea (III), and *N*,*N*-pentamethylene-*N'*-methyl-*N'*-tosylurea (IV). The four compounds were chosen so that each one




| | R | R' | R'' |
|---|---|---|---|
| I: | —H | —H | —$C_4H_9$ |
| II: | —$CH_3$ | —H | —$C_4H_9$ |
| III: | —H | —$(CH_2)_5$— | |
| IV: | —$CH_3$ | —$(CH_2)_5$— | |

would display a different type of reactivity on dissociation. Indeed, I may dissociate according to paths *a* and *b;* but II and III, being *N*- (or *N'*-) disubstituted, can dissociate only in a single fashion (*a* and *b*, respectively). Compound IV, being completely *N*,*N'*-substituted, is unable to dissociate. Therefore, were dissociation to play a predominant (or exclusive) role in their breakdown, a rather definite behavior might reasonably be anticipated. Conversely, in the case of solvolysis, the reactivity of the ureas and the structure of the reaction products, although not exactly predictable, should be less dependent on substitution on either N atom, and even Compound IV might show some degree of reactivity.

## EXPERIMENTAL[2]

**Materials**—*p*-Toluenesulfonamide[3], butyl isocyanate[4], *n*-octadecyl alcohol[4], *N*-methyl-*p*-toluenesulfonamide (7), ethyl and *n*-octadecyl *N*-tosylcarbamate (6), *N*,*N'*-dibutylurea (8), *N*-butyl-*N'*-phenylurea (9), *N*-butyl-*N'*-cyclohexylurea (10), *N*,*N*-pentamethylene-*N'*-phenylurea (11), *N*,*N'*-diphenylurea (8), *N*-phenyl-*N'*-tosylurea (12), and *N*,*N'*-dicyclohexylurea (13) were either obtained from commercial sources or prepared by known methods; they were purified to constant melting point or boiling point.

Tolbutamide (I) was the medicinal grade drug; it was crystallized several times from benzene to a constant melting point (127–129°). *N*-*n*-Butyl-*N'*-methyl-*N'*-tosylurea (II) was prepared in 70% yield from *N*-methyl-*p*-toluenesulfonamide and butyl isocyanate at 100° in the presence of a catalytic amount of pyridine. The crude reaction product was chromatographed over alumina and melted at 50–52° after crystallization from petroleum ether[5]; IR: 3400 (NH) and 1690 (CO) cm.$^{-1}$.

*Anal.*—Calc. for $C_{13}H_{20}N_2O_3S$: C, 54.92; H, 7.04; N, 9.85; S, 11.26. Found: C, 54.70; H, 7.12; N, 9.90; S, 11.38.

*N*,*N*-Pentamethylene-*N'*-tosylurea (III) was prepared in 69% yield from ethyl *N*-tosylcarbamate and piperidine, according to the general method of Marshall and Sigal (14). The product, purified by dissolution in cold methanol and reprecipitation with water, melted at 146–148° [lit. (15) m.p. 145–147°].

*N*,*N*-Pentamethylene-*N'*-methyl-*N'*-tosylurea (IV) was prepared in 74% yield by methylation of III in dimethylformamide by the sodium hydride–methyl iodide method of Fones (16). The crude reaction product was chromatographed over alumina and melted at 62–64° after crystallization from petroleum ether; IR: 1680 (CO) cm.$^{-1}$; no NH absorption.

*Anal.*—Calc. for $C_{14}H_{20}N_2O_3S$: C, 56.75; H, 6.75; N, 9.45; S, 10.81. Found: C, 56.80; H, 6.82; N, 9.10; S, 11.00.

All four sulfonylureas were shown by TLC to be free from contaminants or decomposition products.

The following salts were prepared, using standard methods:

1. *n*-Butylamine salt of I, m.p. 115–125° (dependent on heating rate) after crystallization from absolute ethanol.

*Anal.*—Calc. for $C_{16}H_{29}N_3O_3S$: N, 12.28; S, 9.35. Found: N, 12.02; S, 9.40.

2. Piperidine salt of III, m.p. 98–102° after crystallization from ether.

*Anal.*—Calc. for $C_{18}H_{29}N_3O_3S$: N, 11.44; S, 8.71. Found: N, 11.15; S, 8.52.

3. Piperidine salt of ethyl *N*-tosylcarbamate, m.p. 126–128° after crystallization from absolute ethanol.

*Anal.*—Calc. for $C_{15}H_{24}N_2O_4S$: N, 8.53; S, 9.75. Found: N, 8.80; S, 9.74.

*n*-Octadecyl *N*-*n*-butylcarbamate was prepared by heating for 90 min. at 100° a mixture of *n*-octadecyl alcohol (2.0 g.), butyl isocyanate (0.89 g., 20% molar excess), and pyridine (0.2 g.). The product melted at 67–68° after crystallization from petroleum ether; IR: 3350 (NH) and 1680 (CO) cm.$^{-1}$.

*Anal.*—Calc. for $C_{23}H_{47}NO_2$: C, 74.74; H, 12.82; N, 3.79. Found: C, 74.80; H, 12.59; N, 3.85.

**Methods**—*Reactions with Alcohols*—The dissociation of the four sulfonylureas and of the salts of I and of III in ethyl and in *n*-octadecyl alcohol at 80° was investigated by the procedure described in the previous paper (6). Mixtures containing 50 mg. of sulfonylurea and 450 mg. of alcohol were heated for 1 hr. in 5-ml. sealed ampuls. The reaction products were estimated spectrophotometrically after separation by quantitative TLC with the solvent system described previously (3).

The sulfonylurea III was very reactive; even a brief (5–10 min.) heating in ethanol, followed by evaporation of the solution at low temperature, caused its conversion into the piperidine salt of ethyl *N*-tosylcarbamate.

The reactions at higher temperature were carried out by heating for 5 hr. at 150° mixtures containing 10 mmoles of the urea and 11 mmoles of *n*-octadecyl alcohol. The reaction products were first evaluated qualitatively and semiquantitatively by TLC. Then they were separated using different methods—*viz.*, quantitative TLC, column chromatography, solvent extraction, and fractional crystallization. As an example, the procedure followed in the case of I is described. A mixture of I (2.70 g., 10 mmoles) and of *n*-octadecyl alcohol (3.0 g., 11 mmoles) was heated for 5 hr. at 150° in a sealed ampul in an electrically controlled oil bath. After cooling, the mixture was extracted several times with cold petroleum ether. Evaporation of the solvent afforded pure *n*-octadecyl *N*-butylcarbamate (VII, 0.48 g.). The insoluble residue was chromatographed over silica gel. A mixture of petroleum ether and benzene (50:50) eluted 1.70 g. of unreacted alcohol. Benzene eluted *n*-octadecyl *N*-tosylcarbamate (X, R = *n*-$C_{18}H_{37}$, 1.26 g.), m.p. 96–98° [lit. (6) m.p. 97–98°]. A mixture of benzene and ethyl ether (90:10) eluted

[1] The term "reactive" indicates a potential reactivity either toward the undissociated sulfonylurea or toward one of the dissociation products.

[2] A Beckman DU spectrophotometer was used for all determinations. IR spectra were recorded in mineral oil mulls with a Perkin-Elmer Infracord 137 spectrophotometer. TLC separations were carried out on Merck $F_{254}$ silica gel plates. Melting points were determined on a Kofler hot stage and are uncorrected. "Petroleum ether" refers to the fraction of boiling range 60–80°.

[3] Aldrich Chemical Co., Inc.

[4] Fluka AG.

[5] The same product was obtained by methylation of I with dimethyl sulfate, according to the method described by K. Sabih and K. Sabih [*J. Pharm. Sci.*, **59**, 782(1970)] for the preparation of their "methyl derivative of tolbutamide," m.p. 33°. The structure of the compound (*N'*- rather than *N*-methyl) is unequivocally established by the preparation from *N*-methyl-*p*-toluenesulfonamide and butyl isocyanate.

Table I—Breakdown of Sulfonylureas I, II, III, and IV in Ethanol and in *n*-Octadecyl Alcohol

| Compound | Experiment[a] | Sulfonylurea, % Recovered | (mmoles Found/mmoles of Sulfonylureas Introduced in Reaction) × 100 — Ethyl or *n*-Octadecyl *N*-Tosylcarbamate | *n*-Octadecyl *N*-Butylcarbamate | *N,N'*-Dibutylurea | *p*-Toluenesulfonamide or *N*-Methyl-*p*-toluenesulfonamide |
|---|---|---|---|---|---|---|
| I | A | 59 | 40 | — | — | — |
| | B | 60 | 40 | — | — | — |
| | C | 25 | 27 | 13 | 27 | 42 |
| I, butylamine salt | A, B | 100 | — | — | — | — |
| II | A | 100 | — | — | — | — |
| | B | 100 | — | — | — | — |
| | C | 90 | — | 9 | — | Trace amount |
| III | A | 0 | 98 | — | — | — |
| | B | Trace amount | 94 | — | — | — |
| | C | 0 | 99 | — | — | — |
| III, piperidine salt | A, B | 100 | — | — | — | — |
| IV | A | 100 | — | — | — | — |
| | B | 100 | — | — | — | — |
| | C | 100 | — | — | — | — |

[a] A = 10% w/w solution of sulfonylurea in absolute ethanol, heated 1 hr. at 80°. B = 10% w/w solution of sulfonylurea in *n*-octadecyl alcohol, heated 1 hr. at 80°. C = sulfonylurea, 1 mole, and *n*-octadecyl alcohol, 1.1 moles, heated 5 hr. at 150°.

1.4 g. of a mixture shown by quantitative TLC to consist of 48.5% unreacted I and 51.5% *p*-toluenesulfonamide (V). Finally, a mixture of benzene and ethyl ether (50:50) eluted 0.47 g. *N,N'*-dibutylurea (VIII), m.p. 68–70° [lit. (8) m.p. 70.5–71°].

*Reactions with Water*—Aqueous 1.0% suspensions (50 ml.) of the sulfonylureas (solutions in the cases of the salts of I and of III) were heated for 15 hr. to boiling in flasks connected with reflux condensers. The mixtures were then acidified with 10% hydrochloric acid and extracted with chloroform. The products were estimated as follows:

1. Compound I and the butylamine salt of I—evaporation of the chloroform extract yielded a mixture of I and of *p*-toluenesulfonamide (V), which was quantitatively analyzed by TLC.

2. Compound II—evaporation of the chloroform yielded a mixture shown by IR and TLC to consist of *N*-methyl-*p*-toluenesulfonamide (XIII), m.p. 77–78° [lit. (7) m.p. 78–79°] and *N,N'*-dibutylurea (VIII). A treatment of the mixture with 10% NaOH, which left the urea undissolved, allowed a quantitative estimation of the products.

3. Compound III and piperidine salt of III—the analysis was carried out as described for I.

4. Compound IV—evaporation of the extract yielded quantitatively the starting material.

*Reactions with Amines*—In all cases, 20% w/w solutions of the sulfonylureas (5 mmoles) in the amines were heated in small flasks connected with reflux condensers. A description of the workup procedures follows.

1. Reactions with aniline, 1 hr. at 80°—Compound I: the reaction mixture yielded a solid on acidification with 10% HCl. This was collected and triturated with a little 10% NaOH. The insoluble portion (Na salt) was dissolved in water; acidification of this solution caused precipitation of *N*-phenyl-*N'*-tosylurea (XII), m.p. 166–168° [lit. (12) m.p. 166–169°]. The NaOH solution was acidified to yield unreacted I. Compounds II and IV: the starting material was recovered quantitatively. Compound III: acidification of the reaction mixture caused separation of pure *N*-phenyl-*N'*-tosylurea (XII).

2. Reactions with aniline, 5 hr. at 150°—Compound I: acidification of the mixture caused separation of a solid (A). The mother liquors from A were extracted with ethyl acetate. Evaporation of the extract gave a solid residue (B). Trituration of B with 5% NaOH left undissolved *N,N'*-dibutylurea (VIII). Acidification of the NaOH solution followed by extraction with ethyl acetate yielded *p*-toluenesulfonamide (V). A similar treatment of A gave, as the portion insoluble in NaOH, a mixture of *N*-butyl-*N'*-phenylurea, m.p. 129–130° [lit. (9) m.p. 129–130°], and *N,N'*-diphenylurea, m.p. 232–234° [lit. (8) m.p. 235°], which was separated by fractional crystallization from chloroform. Acidification of the NaOH solution gave additional *p*-toluenesulfonamide. Compound II: the reaction mixture was acidified and extracted several times with chloroform. The organic solution, after thorough extraction with 5% NaOH, gave on concentration *N,N'*-diphenylurea and then unreacted II. After acidification, the NaOH solution gave on extraction *N*-methyl-*p*-toluenesulfonamide. Compound III: the acidified reaction mixture was extracted with ethyl acetate. Evaporation of the organic extract gave a solid residue, which was triturated with 5% NaOH. An undissolved portion was shown by TLC and fractional crystallization from chloroform to consist of a mixture of *N,N*-pentamethylene-*N'*-phenylurea (65%), m.p. 168–169° [lit. (11) m.p. 168°], and *N,N'*-diphenylurea (35%). The NaOH solution gave pure *p*-toluenesulfonamide on acidification and extraction with ethyl acetate. Compound IV: the starting material was quantitatively recovered from the acidified reaction mixture.

3. Reactions with cyclohexylamine, 1 hr. at 80°—Compounds I, III, and IV: the compounds were recovered quantitatively from the reaction mixtures. Compound II: the reaction mixture was diluted with chloroform, washed with 10% hydrochloric acid, and extracted with 5% NaOH. Evaporation of the chloroform gave *N*-butyl-*N'*-cyclohexylurea, m.p. 104–106° [lit. (10) m.p. 105°]. Acidification of the NaOH solution gave *N*-methyl-*p*-toluenesulfonamide.

4. Reactions with cyclohexylamine, 5 hr. at reflux (134°) temperature—Compound I: acidification of the mixture gave a precipitate (A). The mother liquors from A were extracted with ethyl acetate; evaporation of the solvent gave a solid (B). Trituration of A with 5% NaOH left undissolved *N,N'*-dicyclohexylurea, m.p. 227–229° [lit. (13) m.p. 229–230°]. Acidification of the NaOH solution followed by extraction with ethyl acetate gave pure *p*-toluenesulfonamide. A similar treatment of B gave *N*-butyl-*N'*-cyclohexylurea and additional *p*-toluenesulfonamide. Compound II: acidification of the mixture gave a precipitate (A). Extraction of the mother liquors from A with ethyl acetate gave *N*-methyl-*p*-toluene-

Table II—Breakdown of Sulfonylureas I, II, III, and IV in Water after 15 hr. at Reflux Temperature[a]

| Compound | Sulfonylurea, % Recovered | (mmoles Found/mmoles of Sulfonylureas Introduced in Reaction) × 100 — *p*-Toluenesulfonamide or *N*-Methyl-*p*-toluenesulfonamide | *N,N'*-Dibutylurea |
|---|---|---|---|
| I | 44 | 54 | — |
| I, butylamine salt | 74 | 24 | — |
| II | 0 | 98 | 49 |
| III | 15 | 84 | — |
| III, piperidine salt | 74 | 25 | — |
| IV | 100 | — | — |

[a] Initial concentration of compounds was 1% w/w.

Table III—Breakdown of Sulfonylureas I, II, III, and IV in Aniline and in Cyclohexylamine

| Compound | Experiment[a] | Sulfonylurea, % Recovered | (mmoles Found/mmoles of Sulfonylureas Introduced in Reaction) × 100 — *p*-Toluenesulfonamide or *N*-Methyl-*p*-toluenesulfonamide | Other Compounds Present in the Reaction Mixture |
|---|---|---|---|---|
| I | A | 22 | — | *N*-Phenyl-*N'*-tosylurea, 71 |
| | B | 0 | 97 | *N*-Butyl-*N'*-phenylurea, 67; *N,N'*-diphenylurea, 26; *N,N'*-dibutylurea, 13 |
| | C | 100 | — | — |
| | D | 0 | 95 | *N,N'*-Dicyclohexylurea, 87; *N*-butyl-*N'*-cyclohexylurea, 7 |
| II | A | 100 | — | — |
| | B | 96 | 3.0 | *N,N'*-Diphenylurea, 2.5 |
| | C | 0 | 98 | *N*-Butyl-*N'*-cyclohexylurea, 90 |
| | D | 0 | 97 | *N,N'*-Dicyclohexylurea, 99 |
| III | A | 0 | — | *N*-Phenyl-*N'*-tosylurea, 96 |
| | B | 0 | 93 | *N,N*-Pentamethylene-*N'*-phenylurea, 65; *N,N*-diphenylurea, 33 |
| | C | 100 | — | — |
| | D | 0 | 98 | *N,N'*-Dicyclohexylurea, 97 |
| IV | A | 100 | — | — |
| | B | 100 | — | — |
| | C | 100 | — | — |
| | D | 80 | 14 | *N,N'*-Dicyclohexylurea, 13 |

[a] A = 20% w/w solution of sulfonylurea in aniline, heated 1 hr. at 80°. B = same solution as in A, heated 5 hr. at 150°. C = 20% w/w solution of sulfonylurea in cyclohexylamine, heated 1 hr. at 80°. D = same solution as in C, heated 5 hr. under reflux (134°).

sulfonamide. Treatment of A with 5% NaOH, as already described, gave *N,N'*-dicyclohexylurea and additional sulfonamide. Compound III: the treatment just described gave pure *p*-toluenesulfonamide and *N,N'*-dicyclohexylurea in practically quantitative yield. Compound IV: acidification of the reaction mixture gave a precipitate (A). The mother liquors from A yielded *N*-methyl-*p*-toluenesulfonamide on extraction with ethyl acetate. Extraction of A with petroleum ether left undissolved *N,N'*-dicyclohexylurea; evaporation of the solvent gave unreacted starting material.

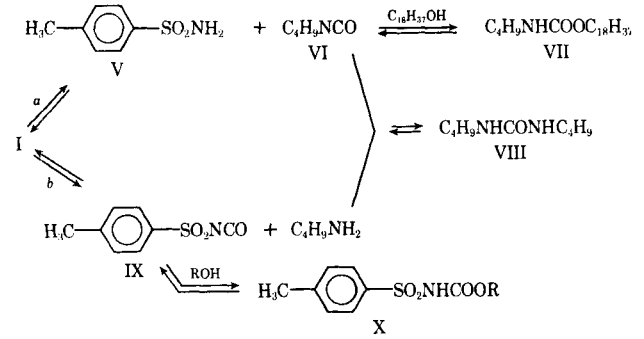
## RESULTS AND DISCUSSION

The results obtained after heating the four sulfonylureas (I, II, III, and IV) at different temperatures in alcohols, water, and amines are summarized in Tables I, II, and III, respectively. In all experiments, the qualitative and the quantitative estimation of the reaction products was carried out with the greatest care. The amount of reaction products found satisfactorily accounted for the amounts of sulfonylureas which disappeared.

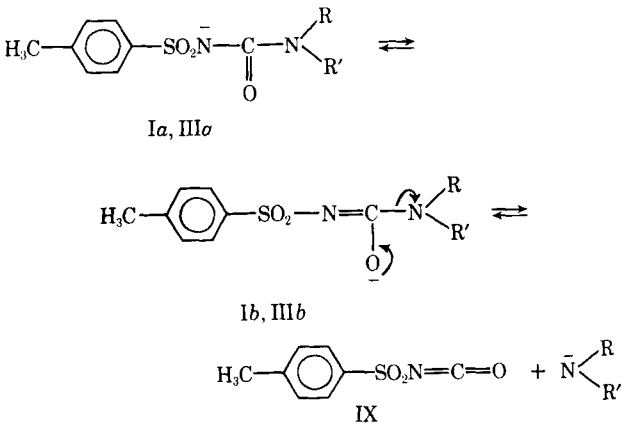
**Breakdown in Alcohols**—Because of the high reactivity of isocyanates toward alcohols, alkyl carbamates should be expected as final products of the dissociations carried out in alcoholic media. As shown in Table I, tolbutamide (I) gave *N*-tosylcarbamates at the lower temperature, while an *N*-butylcarbamate also was formed when the reaction was carried out in *n*-octadecyl alcohol at 150°. The results obtained with the other sulfonylureas seem to be in line with the dissociation hypothesis; II gave only a butylcarbamate, III only tosylcarbamates, and IV did not react. A tentative rationalization for the preferential dissociation of I at low temperature to *N*-tosylisocyanate was given in a previous paper (6). The formation of a butylcarbamate from I (and II) at higher temperature is consistent with the findings of Ulrich and Sayigh (5), who found butyl isocyanate (besides *p*-toluenesulfonamide) as the main product of the dissociation of I under pyrolysis conditions.

A possible pathway for the formation of *N,N'*-dibutylurea (VIII) among the products of the dissociation of I in *n*-octadecyl alcohol at 150° is given in Scheme II. By taking into account the amounts of all substances found at equilibrium in this experiment, it would seem that about 60% of reacted I dissociates according to path *a* and about 40% according to path *b*. In the comparative experiments carried out at 80°, quite analogous results were obtained in ethyl and in *n*-octadecyl alcohols. This seems to provide further evidence for the dissociation mechanism. Indeed, if alcoholysis were responsible for the formation of the carbamates, some influence of solvent polarity should have been observed. The observation that conversion of I and III into the butylamine and piperidine salt, respectively, results in noticeably increased stability is noteworthy. An enhanced stability of sulfonylureas in basic solution, where they exist in a salt form, was reported by Wiseman *et al.* (17). The observed effect might be rationalized assuming that the tautomeric salt form of I (or of III), I*b* (or III*b*), would resist conversion into the isocyanate (IX), since the conversion would require a transfer of charge on a basic nitrogen (Scheme III).

**Breakdown in Water**—The behavior of the four sulfonylureas in water (Table II) is also in good agreement with the dissociation hypothesis. The extent of the dissociation may have been limited by the very low solubility of the compounds. Ureas I and III gave a 54 and 84% yield, respectively, of *p*-toluenesulfonamide (V), whose formation can be assumed to occur by the intermediacy of the isocyanate (IX). Indeed, the latter is known to react readily with water as indicated in Reaction 1 of Scheme IV (18). The urea II, which




*Scheme II*




*Scheme III*

$$IX + H_2O \longrightarrow V + CO_2 \quad \text{(Reaction 1)}$$

$$VI + H_2O \longrightarrow C_4H_9NH_2 + CO_2 \quad \text{(Reaction 2)}$$

$$VI + C_4H_9NH_2 \rightleftharpoons VIII \quad \text{(Reaction 3)}$$

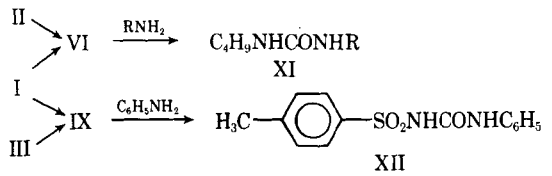
*Scheme IV*

can only dissociate to butyl isocyanate (VI) and XIII, gave a quantitative yield of XIII and *N,N'*-dibutylurea (VIII). As proved by a separate experiment, VIII originated in good yield when butyl isocyanate was heated in water at 100°, the formation occurring in all probability by Reactions 2 and 3 of Scheme IV. An enhanced stability of the water-soluble amine salts of I and III was observed also in this case.

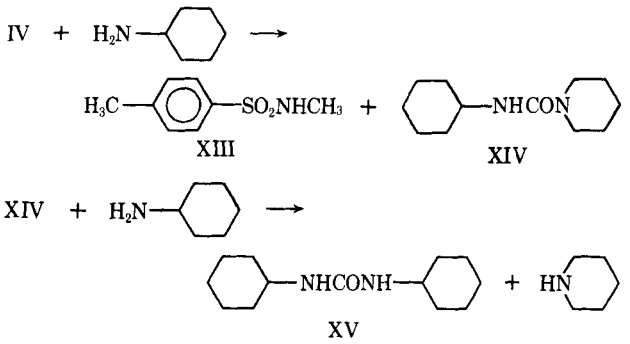
**Breakdown in Amines**—Two amines, aniline and cyclohexylamine, endowed with different basicity (pKa 4.58 and 10.64, respectively) were selected for this study. Amines as solvents were used in other instances for investigation on the dissociation of ureas (8). In the case of dissociation, *e.g.*, in aniline, I was expected to yield *N*-phenyl-*N'*-tosylurea (XII) and, depending on the reaction conditions, *N*-butyl-*N'*-phenylurea (XI, R = Ph); accordingly, II was expected to yield only XI, and III only XII, as shown in Scheme V. Analogous cyclohexyl-substituted ureas were expected from the reactions in which cyclohexylamine was used as the solvent. As shown in Table III, the results of the reactions carried out at 80° did not disagree with the dissociation theory. However, I and III did not dissociate in cyclohexylamine, while II was far more reactive in the latter solvent than in aniline. The lack of reactivity of I and III might be explained by assuming the unreactive salt forms I*b* and III*b* to be present in the basic solvent.

The reactions at higher temperature offer a more complicated picture. Aminolysis was certainly operative in one case, since IV underwent partial breakdown to *N*-methyl-*p*-toluenesulfonamide (XIII) and *N,N'*-dicyclohexylurea (XV) when heated in cyclohexylamine. A possible sequence of reactions leading to XIII and XV is given in Scheme VI. As shown, *N*-cyclohexyl-*N',N'*-pentamethyleneurea (XIV), formed by aminolysis of IV, would further react with cyclohexylamine to yield XV. A separate experiment proved indeed that XV was formed quantitatively when XIV was heated in cyclohexylamine. In view of this result, an individual discussion of the other reactions seems inappropriate. In fact, hydrolysis and dissociation might concur in the breakdown of the sulfonylureas at high temperature, particularly when cyclohexylamine is used as solvent.

In conclusion, the present results point to dissociation as the most likely mechanism by which sulfonylureas undergo a breakdown in alcohols and in water, as well as in amines at a comparatively low (80°) temperature. Solvolysis seems to occur in amines at high temperature and is probably favored by a high basicity of the amine, as shown by the lack of reactivity of IV with aniline. A temperature dependence of the type of dissociation of I was also apparent, the




*Scheme V*




*Scheme VI*

dissociation *b* being preferred at lower temperature and the dissociation *a* at higher temperature (*cf.*, Schemes I and II). Further studies of this effect of temperature on type of dissociation are now being carried out on other pharmacologically active sulfonylureas in view also of the preparative interest of the reactions involved.

## REFERENCES


(1) H. Vogt, *Pharm. Zentralh.*, **98,** 651(1959).

(2) A. Häussler and P. Hajdú, *Arch. Pharm.*, **295,** 471(1962).

(3) K. K. Kaistha and W. N. French, *J. Pharm. Sci.*, **57,** 459 (1968).

(4) K. K. Kaistha, *ibid.*, **58,** 235(1969).

(5) H. Ulrich and A. A. R. Sayigh, *Angew. Chem. Int. Ed. Engl.*, **5,** 724(1966).

(6) F. Bottari, M. Mannelli, and M. F. Saettone, *J. Pharm. Sci.*, **59,** 1663(1970).

(7) F. Reverdin, *Ber.*, **42,** 1523(1909).

(8) T. L. Davis and K. C. Blanchard, *J. Amer. Chem. Soc.*, **45,** 1816(1923).

(9) T. L. Davis and N. D. Constan, *ibid.*, **58,** 1800(1936).

(10) F. Cramer and M. Winter, *Ber.*, **92,** 2761(1959).

(11) W. Gebhardt, *ibid.*, **17,** 3033(1884).

(12) R. Tull, R. C. O'Neill, E. P. McCarthy, J. J. Pappas, and J. M. Chemerda, *J. Chem. Soc. C*, **1967,** 701.

(13) A. Skita and H. Rolfes, *Ber.*, **53,** 1242(1920).

(14) F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23,** 927 (1958).

(15) Wellcome Foundation Ltd., Brit. pat. 896,303 (May 16, 1962); through *Chem. Abstr.*, **57,** 11110b(1962).

(16) W. S. Fones, *J. Org. Chem.*, **14,** 1099(1949).

(17) E. H. Wiseman, J. Chiaini, and R. Pinson, Jr., *J. Pharm. Sci.*, **53,** 766(1964).

(18) H. Ulrich, *Chem. Rev.*, **65,** 369(1965).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