Sulfamoyl Azides. Hydrolysis Rates and Hypotensive Activity

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The synthesis, hydrolysis, and hypotensive properties of a series of sulfamoyl azides are described. The monosubstituted compounds cause significant lowering of blood pressure in anesthetized dogs at 0.03 to 0.01 of the dose required for the disubstituted compounds. This difference in hypotensive activity appears to be due to rapid release of azide ion from the monosubstituted derivatives in neutral aqueous media, but not in acidic solutions. The mechanism and kinetics of their hydrolysis are discussed. The rate of N_3^- release from these compounds is compared with that from other hypotensive azides. Disubstituted sulfamoyl azides are extremely resistant to hydrolysis, and their hypotensive action may be due to the intact molecular structure or to release of N_3^- by *in vivo* activation.

Sodium azide and certain organic azides have been reported to be potent, but toxic, hypotensive agents.[1-5] Werle and Fried[3] proposed that organic azides must release azide ion to cause hypotension and should, therefore, have a similar therapeutic index to sodium azide. Recent reports of aromatic sulfonyl azides[6,7] as effective hypotensive agents, with a high therapeutic index, are surprising on the basis of Werle's theory. Arylsulfonylazides are extremely resistant to hydrolysis[8] and should not release N_3^- readily. On the assumption that the sulfonyl azide grouping may have inherent biological activity, we synthesized, and investigated, a series of sulfamoyl azides of general structure $R_1R_2NSO_2N_3$, where R_1 and R_2 are alkyl, aryl, H, or connected to form a piperazine ring (Table I). We also prepared some related sulfamide derivatives, **25** to **33** (Table II), to compare their hypotensive effects.

Chemistry. Synthesis. The sulfamoyl azides (Table I) were prepared by reaction of the corresponding sulfamoyl chlorides with NaN_3[9] (eq 1), or by reaction of a primary or secondary amine with chlorosulfonyl azide[10] (eq 2). This

$$R_1R_2NSO_2Cl + NaN_3 \longrightarrow R_1R_2NSO_2N_3 + NaCl \quad (1)$$

$$2R_1R_2NH + ClSO_2N_3 \longrightarrow R_1R_2NSO_2N_3 + R_1R_2NH \cdot HCl \quad (2)$$

reagent is conveniently generated *in situ* by the reaction of NaN_3 with an equimolar amount of SO_2Cl_2 in MeCN solution. Neat chlorosulfonylazide is extremely shock sensitive and should not be isolated! A sample exploded violently with slight mechanical shock.

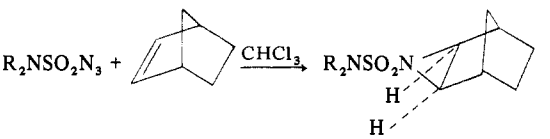
The mono- and dialkyl and piperazine compounds were prepared by the first method, since the corresponding sulfamoyl chlorides (Table II) could be prepared readily from the appropriate amine·HCl and SO_2Cl_2 in boiling MeCN.[11] It was not necessary to use a Lewis acid catalyst for this reaction. This method was not suitable for N-aromatic compounds, since SO_2Cl_2 rapidly chlorinates and oxidizes aromatic amines.[12] These compounds were prepared exclusively by the second method.

The sulfamoyl hydrazides **25** and **28** were prepared by the reaction of a sulfamoyl chloride with hydrazine hydrate. These hydrazides condensed with aldehydes to form the corresponding hydrazones **26**, **27**, and **29** (Table II).

As with arylsulfonyl azides,[13] both the mono- and disubstituted sulfamoyl azides add to the strained olefin norbornene in $CHCl_3$ to form the aziridines **30-33** (Table II).

$$R_2NSO_2Cl \xrightarrow{NH_2NH_2} R_2NSO_2NHNH_2 \xrightarrow{R'CHO} R_2NSO_2NHN{=}CHR'$$

These compounds have the exo configuration as shown by their nmr spectra.[13] Their formation occurs slowly at 25° but is complete after 6 hr at 61°.



Hydrolysis of Sulfamoyl Azides. The mono- and disubstituted sulfamoyl azides are quite stable to aqueous acid. Thus, *N*-methyl-*N*-phenylsulfamoyl azide was recovered unchanged after treatment with 3 *N* aqueous HCl in MeCN at 25° for 3 days. Under the same conditions, *p*-toluenesulfamoyl azide was unchanged after 3 hr but, after 5 days, a 75% yield of *p*-toluidine was isolated.

The disubstituted sulfamoyl azides are little affected by 10% NaOH. After stirring a MeCN solution of *N*-methyl-*N*-phenylsulfamoyl azide with 10% NaOH solution for 3 days at 25°, starting material was recovered in 70% yield. The monosubstituted compounds, however, are extremely reactive toward aqueous base, and a MeCN solution of *p*-toluenesulfamoyl azide is converted rapidly to sodium *p*-toluenesulfamate on treatment with 5% NaOH solution. In aqueous media, these compounds produce two equiv of acid per equiv of sulfamoyl azide consumed, according to eq 3.

$$RNHSO_2N_3 + H_2O \longrightarrow RNHSO_3H + HN_3 \quad (3)$$

Their rate of hydrolysis in aqueous dioxane solution is proportional to the concentration of sulfamoyl azide at a given pH value (Table III).

Dependency of the first-order rate constant (k_{obsd}) on pH was examined using *n*-propylsulfamoyl azide. A plot of log k_{obsd} against pH (from Table III) is linear, with a slope close to unity, indicating that the rate is inversely proportional to the H^+ concentration.

Two mechanisms, consistent with the kinetic data for hydrolysis of the monosubstituted compounds, may be written

$$\text{(A)}\ RNHSO_2N_3 + OH^- \xrightarrow{\text{slow}} RNHSO_3H + N_3^-$$

$$\text{(B)}\ RNHSO_2N_3 + H_2O \underset{K_A}{\rightleftharpoons} \dot{R}N\dot{S}O_2N_3 + H_3O^+$$

$$\dot{R}N\dot{S}O_2N_3 \xrightarrow{-N_3^-,\ \text{slow } k} [RN{=}SO_2] \xrightarrow[+H_2O]{\text{fast}} RNHSO_3H$$

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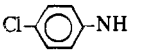
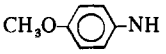
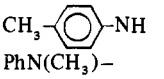
In the rate-determining step of mechanism A, OH^- directly attacks the S atom with expulsion of N_3^-. However, this

reaction should not be much more rapid than the hydrolysis of disubstituted sulfamoyl azides, which could occur only by this mechanism.

In mechanism B, the rate-determining step is elimination of N_3^- from the conjugate base of the sulfamoyl azide. The resulting sulfonylamine (**34**) is then rapidly hydrolyzed to a sulfamic acid.

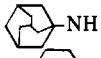
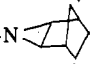
In agreement with mechanism B, the monosubstituted sulfamoyl azides react with amines in aprotic solvents to form stable salts. Thus, **14** (Ar = *p*-tolyl) reacts with Et_3N (1

Table I. Sulfamoyl Azides $R_1R_2NSO_2N_3$

Compound No.	R_1R_2N	Mp or bp (mm), °C	Recrystn solvent[e] or $n^{25}D$	Method	Yield, %	Formula[f]
1[a]	$(CH_3)_2N$			1	66	$C_2H_6N_4O_2S$
2	$PhCH_2N(CH_3)-$		1.5340	1	93	$C_8H_8N_4O_2S$
3[b]	CH_3N(piperazine)$N-$	130–130.5° dec	A–C	1	67	$C_5H_{12}ClN_5O_2S$
4	$-N$(piperazine)$N-$	151 dec	B	1	91	$C_4H_8N_8O_4S_2$
5	CH_3NH	87–88 (0.25)	1.4680	1	50	$CH_4N_4O_2S$[g]
6	*n*-PrNH	100–120 (0.05–0.8)	1.4625	1	67	$C_3H_8N_4O_2S$
7	$(CH_3)_2CHNH$	56–58 (0.05)	1.4580	1	65	$C_3H_8N_4O_2S$
8	$(CH_3)_2CHCH_2NH$	120–130 (0.1–3.0)		1	45	$C_4H_{10}N_4O_2S$
9	$(CH_3)_3CNH$	62–63 (0.03–0.05)	1.4612	1 2	93 30	$C_4H_{10}N_4O_2S$
10		74–75	D	1	65	$C_{10}H_{16}N_4O_2S$
11[c,d]	PhNH	47.5–48.5	E	2	26	$C_6H_6N_4O_2S$
12[c,d]		54–55	E–F	2	36	$C_6H_5ClN_4O_2S$
13		48–49	E–F	2	35	$C_7H_8N_4O_3S$
14[c]		39.5–40	E	2	22	$C_7H_8N_4O_2S$
15	$PhN(CH_3)-$	62–63	C	2	40	$C_7H_8N_4O_2S$

[a]See ref 9. [b]HCl salt. [c]See ref 10. [d]The corresponding diarylsulfamide was also isolated in 10–15% yield by column chromatography on silica gel. [e]A, MeOH; B, acetone; C, *i*-Pr_2O; D, hexane; E, petr ether (bp 60–80°); F, Et_2O. [f]All compounds were analyzed for C, H, and N. [g]C: calcd 41.17; found 40.62. Also analyzed for S.

Table II. Sulfamoyl Chlorides and Derivatives $R_1R_2NSO_2X$

Compound No.	R_1R_2N	X	Mp or bp (mm), °C	Recrystn solvent[d] or $n^{25}D$	Yield, %	Formula[f]
16	$PhCH_2N(CH_3)-$	Cl	155–159 (8.0)	1.5355	19[e]	$C_8H_{10}ClNO_2S$
17[a]	CH_3-N(piperazine)$N-$	Cl	182–188 dec	A	74	$C_5H_{12}Cl_2N_2O_2S$
18	$-N$(piperazine)$N-$	Cl	236.5–250 dec	B	71	$C_4H_8Cl_2N_2O_4S_2$
19[b]	CH_3NH	Cl	54 (0.2)		80	$C_4H_{10}ClNO_2S$
20[b]	$CH_3(CH_2)_2NH$	Cl	73–74 (0.05)		30	$C_3H_8ClNO_2S$
21[b]	$(CH_3)_2CHNH$	Cl	59–61 (0.25–0.3)		59	$C_3H_8ClNO_2S$
22[b]	$(CH_3)_2CHCH_2NH$	Cl	74–75 (0.03)		78	$C_4H_{10}ClNO_2S$
23	$(CH_3)_3CNH$	Cl	55–57 (0.03–0.05)[c]	1.4600	73	$C_4H_{10}ClNO_2S$
24		Cl	104–106	D	68	$C_{10}H_{16}ClNO_2S$
25	$-N$(piperazine)$N-$	$-NHNH_2$	147 dec	G	93	$C_4H_{14}N_6O_4S_2$
26	$-N$(piperazine)$N-$	$-NHN=CH(CH_3)_2$	170–171 dec	A	90	$C_{12}H_{26}N_6O_4S_2$
27	$-N$(piperazine)$N-$	$-NHN=CH-$ 	139–141 dec		95	$C_{16}H_{20}N_8O_4S_2$
28[a]	$PhCH_2N(CH_3)-$	$-NHNH_2$	110–110.5 dec	H–C	75	$C_8H_{14}ClN_3O_2S$
29	$PhCH_2N(CH_3)-$	$-NHN=CH-$ 	108.5–110 dec	J	83	$C_{14}H_{16}N_4O_2S$
30	$PhCH_2N(CH_3)-$	$-N$ 	102–104.5 dec	D	74	$C_{14}H_{18}N_2O_2S$
31[a]	CH_3-N(piperazine)$N-$	$-N$ 	186.5–188.5 dec	K	73	$C_{12}H_{22}ClN_3O_2S$
32	$CH_3(CH_2)_2NH$	$-N$ 	57.5–60	D	57	$C_{10}H_{18}N_2O_2S$
33	$(CH_3)_2N$	$-N$ 	69–71	D–C	58	$C_9H_{16}N_2O_2S$

[a]HCl salt. [b]See ref 11. [c]Mp 28–30.5°. [d]A, MeOH; B, acetone; C, *i*-Pr_2O; D, hexane; G, H_2O; H, EtOH; J, *i*-PrOH; K, MeCN. [e]Considerable decompn occurred during distn. [f]All new compds were analyzed for C, H, and N.

Table III. Observed First-Order Rate Constants (k_{obsd}) for Hydrolysis of $RNHSO_2N_3$ in Aqueous Dioxane at 29°

Compound No.	R	10^2k_{obsd}, min^{-1}	pH	Half-life, min
5	CH_3	2.40	6.0	29.0
6	$CH_3(CH_2)_2$	2.03	6.0	34.0
		9.20	6.5	7.5
		18.9	6.8	3.6
		32.2	7.0	2.2
7	$(CH_3)_2CH$	1.87	6.0	37.2
8	$(CH_3)_2CHCH_2$	2.20	6.0	31.3
9	$(CH_3)_3C$	4.80	6.0	14.3
11	Ph	8.75	6.0	8.0
12	*p*-ClPh	6.68	6.0	10.4
13	*p*-MeOPh	8.68	6.0	8.0

equiv) in PhH to afford a salt **35**, which is converted slowly to the sulfamate ester **36** in the presence of *i*-PrOH.

Similarly, **14** (Ar = *p*-tolyl) reacts with *p*-toluidine (1 equiv) in MeCN solution to form the salt **37**, which reacts

$$\underset{\mathbf{14}}{ArNHSO_2N_3} \xrightarrow[\text{benzene}]{Et_3N} \underset{\mathbf{35}}{ArN^-SO_2N_3Et_3NH^+} \xrightarrow{i\text{-PrOH}} \underset{\mathbf{36}}{ArNHSO_3CH(CH_3)_2}$$

$$\underset{\mathbf{37}}{ArN^-SO_2N_3ArNH_3^+} \xrightarrow{ArNH_2} \underset{\mathbf{38}}{ArNHSO_2NHAr}$$

with a second equiv of *p*-toluidine at 25° to afford the sulfamide **38** in 80% yield.

These reactions probably proceed *via* the same sulfonylamine intermediate (**34**) as proposed for the hydrolysis reaction. This type of species has been generated by reacting ethylsulfamoyl chloride with Et_3N at low temp in toluene.[14] The same type of intermediate has been postulated in the photolytic conversion of benzenesulfonyl azide to phenylsulfamic esters in the presence of alcohols.[15] The formation of unsymmetrical *N,N'*-diarylsulfamides and arylsulfamic esters from arylsulfamoyl azide salts constitutes a useful synthetic route to these types of compounds.

Biology. Sulfamoyl azides cause a rapid, dose-dependent, lowering of systolic and diastolic blood pressure when they are administered iv to anesthetized, normotensive dogs. The monosubstituted derivatives elicit a significant hypotensive response at a minimally effective dose of 0.005–0.01 mg/kg, iv. In contrast, the disubstituted compounds reduce blood pressure at higher minimally effective doses of 0.3–1.25 mg/kg. At doses which cause hypotension, these azides have little direct effect on heart rate or right ventricular contractile force.

The potential oral effectiveness of sulfamoyl azides in lowering blood pressure has been evaluated in anesthetized dogs by intraduodenal administration of **2**, **3**, **10**, and **12**. The disubstituted sulfamoyl azides **2** and **3** are essentially inactive at doses of 1 and 10 mg/kg. In contrast, the monosubstituted compounds **10** and **12** cause a rapid lowering of blood pressure within 1–2 min of drug administration (1 mg/kg id). A maximum reduction in blood pressure of about 45% occurs 7–27 min later. The duration of this hypotensive response is about 1 hr. The fall in systemic blood pressure is accompanied by a decrease in aortic blood flow (cardiac output minus coronary blood flow). At the same dose, **10** and **12** lower hind-limb perfusion pressure by 34% at constant blood flow, which reflects an increase in hind-limb vascular conductance. The hypotensive response appears, therefore, to be due to a reduction in both total peripheral resistance and aortic blood flow.

The monosubstituted derivatives are more toxic than their disubstituted congeners. LD_{50} values are 100–500 mg/kg and >2000 mg/kg, respectively, po in mice, for these two series of azides.

The sulfamoyl derivatives **25–33**, which do not contain the azide moiety, show little hypotensive activity in the normotensive, anesthetized dog.

Table IV. Rates of Hydrolysis of Azides

No.	Compound	k_{obsd}, min^{-1} [c]	Half-life at pH 7.0, min
15	$PhN(Me)SO_2N_3$		>2880
39			>2880
40[a]		1.32×10^{-3}	522
41[b]	$PhNHCON_3$	1.06×10^{-1}	6.5
6	$CH_3(CH_2)_2NHSO_2N_3$	3.22×10^{-1}	2.2
11	$PhNHSO_2N_3$	8.75×10^{-1}	0.8

[a] See ref 16. [b] The hydrolysis rate was detd by the same method as for the sulfamoyl azides. [c] Observed or calcd first-order rate constants at pH 7.0.

Discussion

The monosubstituted sulfamoyl azides are 30–100 times more potent in reducing blood pressure than the disubstituted compounds or arylsulfonyl azides.[6,7] Their greater potency appears due to the rapid liberation of N_3^- in neutral solution (see Table III). On oral administration, these compounds should be relatively stable in the stomach (pH 1–5); however, they should release azide ion rapidly after passage through the stomach into the alkaline medium of the duodenum (pH >7) and/or after absorption into the blood stream (pH 7.4). Iv administration of the monosubstituted derivatives should result in a rapid liberation of azide ion directly in the blood stream.

In Table IV, the rates of release of N_3^- from several types of organic azides are compared.

The potent blood pressure lowering properties of monosubstituted sulfamoyl azides and of **40**[4] and **41**[17] (Table IV) appear to depend upon the release of N_3^-. The most rapidly hydrolyzed compounds cause significant hypotensive effects at much lower doses than more slowly hydrolyzed compounds such as nicotinoyl azide.[4] Azide ion, therefore, appears to be the species responsible for the hypotensive effects of these compounds, although a direct causal relationship between N_3^- concentration in the blood and a decrease in blood pressure has not been established.

Since it has been shown that disubstituted sulfamoyl azides and arylsulfonyl azides are very resistant to hydrolysis, their hypotensive activity may be due to enzymatic breakdown to azide ion *in vivo*, or to an inherent property of these molecules.

Experimental Section†

Sulfamoyl Azides. The compds in Table I were prepd by adaptations of previously reported methods.[9,10]

Method 1. The primary or secondary amine hydrochloride (0.3 mole) was added in portions to a stirred soln of SO_2Cl_2 (80 ml, 1 mole) in MeCN (150 ml). After stirring and refluxing the mixt for 24 hr,‡ it was concd *in vacuo* to a viscous oil,§ which was extd with Et_2O. The Et_2O-soluble material was then isolated and crystd, or distd under reduced pressure, to yield the sulfamoyl chloride (Table II).

†Nmr spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as internal standard. Melting points, determined with a Thomas-Hoover capillary apparatus, are corrected.

‡In the prepn of 18 and 23, additional SO_2Cl_2 (0.3 mole) was added at this stage and refluxing was contd for a further 24 hr.

§Compds 17 and 18 crystd at this stage.

A soln of the latter (0.1 mole) in dry MeCN# (150 ml) was stirred with NaN_3 (0.11 mole) for 48 hr at 25°. Insoluble inorganic material was removed by filtration and the filtrate was concd *in vacuo*. The residue yielded the pure sulfamoyl azide on crystn or distn under reduced pressure.

Method 2. Chlorosulfonyl azide was prepd *in situ* by stirring a suspension of NaN_3 (1 mole) in MeCN (500 ml) with SO_2Cl_2 (80 ml, 1 mole) for 48 hr at 25°. Insol NaCl was removed and the filtrate was dild to 1 l. with MeCN. This soln of chlorosulfonyl azide (approx 1 *M*) was used without further purification. It may be stored at 25° for several months without appreciable decompn. **Neat chlorosulfonyl azide is extremely shock sensitive and should not be isolated!**

A soln of the appropriate primary or secondary amine (0.2 mole), in MeCN (200 ml), was added dropwise with stirring to the 1 *M* soln of chlorosulfonyl azide in MeCN (110 ml, ~0.1 mole), cooled to 0–10°. The mixt was then stirred at 25° for 8 hr. Pptd amine HCl was removed by filtration and the filtrate was concd *in vacuo*. After extg the residue with anhyd Et_2O, unreacted amine was pptd from the Et_2O soln with Et_2O–HCl and the Et_2O soln was concd *in vacuo*. The pure sulfamoyl azide was isolated from the residue by distn under reduced pressure, by crystn, or by column chromatog on silica gel.

Sulfamoyl Hydrazides (25 and 28, Table II). A soln of the sulfamoyl chloride (0.05 mole) in abs EtOH (10 ml) was added dropwise to a stirred soln of hydrazine (64%, 0.5 mole) in abs EtOH (25 ml). External cooling was required to keep the temp of the mixt below 30°. After stirring the mixt for 1–2 hr, it was concd *in vacuo* and dild with water to ppt the product.

Sulfamoyl Hydrazones (26, 27, 29, Table II). A soln or suspension of the sulfamoyl hydrazide (0.02 mole) and an aldehyde (0.02 mole) in EtOH (100 ml) was refluxed for 10–30 min. Cooling caused the corresponding hydrazone to sep.

Addition of Sulfamoyl Azides to Norbornene. The sulfamoyl azide (0.02 mole) in $CHCl_3$ (200 ml) was stirred with norbornene (0.03 mole) at 25° for 4 days (or at reflux for 6 hr). Solvent and excess norbornene were removed *in vacuo* and the residue was crystd to obtain the corresponding N-substituted sulfamoyl-3-azatricyclo-[3.2.1.$0^{2,4}$ exo]octane **(30–33, Table II)**.

Rate Measurements. The rates of hydrolysis of the monosubstituted sulfamoyl azides (Table III) were measured by continuous titrn of the acid produced in the reaction. The general procedure was as follows.

A mixt of spectral grade dioxane (95 ml), distd H_2O (90 ml), and 0.1 *N* HCl (10 ml) was adjusted to the desired pH with 0.1 *N* NaOH. The pH was detd with a Sargent pH meter. The sulfamoyl azide (~10^{-3} mole) in dioxane (5 ml) was added in one lot and the vol of 0.1 *N* NaOH, which had to be added from a burette to maintain the pH of the soln, was recorded against time. The temp of the soln was kept at 29° (±0.5).

If V_F = total vol of 0.1 *N* NaOH required to neutralize liberated acid, V_t = vol of 0.1 *N* NaOH required to neutralize acid at time *t* (min) then, for first-order kinetics

$$t = -\frac{2.303}{k_{obsd}} \log \frac{V_F - V_t}{V_F} = -\frac{2.303}{k_{obsd}} \log (V_F - V_t) + \text{constant}$$

The rate constant (k_{obsd}) was obtained from the slope of a plot of log ($V_F - V_t$) *vs. t*.

Reactions of *N*-Methyl-*N*-phenylsulfamoyl Azide (15). Solns of **15** (0.005 mole) in MeCN (20 ml) were stirred with (i) 3 *N* HCl (5 ml), (ii) 10% NaOH (5 ml), (iii) Et_2NH (0.01 mole), and (iv) *p*-toluidine (0.01 mole), respectively, at 25° for 3 days. After concg each soln *in vacuo*, Et_2O (50 ml) was added and the soln was extd with 3 *N* HCl. Concn of the dried ($MgSO_4$) Et_2O solns *in vacuo* afforded unreacted starting material in yields of (i) 96%, (ii) 68%, (iii) 90%, (iv) 89%, resp.

Reactions of *p*-Toluenesulfamoyl Azide (14). (a) With Acid. A soln of 14 (0.005 mole) in MeCN (20 ml) was stirred with 3 *N* HCl (5 ml) for 3 days. After concg the soln *in vacuo* and adding Et_2O (50 ml), the org layer was sepd and dried ($MgSO_4$). Evapn of the solvent yielded only a trace of unreacted starting material. The acidic fraction was made basic with 10% NaOH and the pptd oil was extd with Et_2O. After drying (K_2CO_3), the ext was concd to afford *p*-toluidine (0.42 g, 76%).

When 14 reacted with acid under the same conditions for 3 hr, starting material was recovered in 92% yield.

(b) With NaOH. A soln of **14** (0.005 mole) in MeCN (20 ml) was stirred for 15 min with 5% NaOH (5 ml) and then concd *in vacuo*. The colorless residue crystd from 95% EtOH to afford sodium *p*-toluenesulfamate[18] (0.8 g, 76%).

(c) With Et_3N. A soln of 14 (0.005 mole) and Et_3N (0.01 mole) in dry C_6H_6 was kept at 25° for 15 min. The soln was concd *in vacuo* to a viscous oil, which was identified as the Et_3NH^+ salt of *p*-toluenesulfamoyl azide **(35)** by its ir and nmr spectra.

A soln of the salt in *i*-PrOH was kept at 25° for 3 hr and then refluxed for 5 min. After evapg the solvent, H_2O was added to the residue and the mixt was extd with Et_2O to give a 75% yield of the isopropyl *p*-toluenesulfamate ester **(36)** identified by its ir and nmr spectra.

(d) With *p*-Toluidine. A soln of **14** (0.005 mole) in MeCN (10 ml) was stirred with *p*-toluidine (0.005 mole) for 15 min at 25°. Evapn of the solvent left a viscous oil, which was identified as the salt 37 by its ir and nmr spectra.

A second equiv of *p*-toluidine in MeCN (10 ml) was added to the oil and the soln was kept at 25° for 48 hr. Evapn of the solvent left a gummy residue which was dissolved in Et_2O and washed with 3 *N* HCl and water. Addn of 10% NaOH to the Et_2O soln pptd an oil, which was sepd and combined with the aq layer. Acidification of the mixt with 3 *N* HCl pptd a solid, which was extd with Et_2O, washed (H_2O), and dried ($MgSO_4$). Evapn of the solvent afforded 1,3-di(4-tolyl)sulfamide **(38)**[19] as a pale yellow solid (1.1 g, 80%), mp 96–97°.

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#Aq acetone or EtOH may be used for the disubstituted compds.