Potter.[12] A solution of *cis*-3-aminocyclopentanecarboxylic acid[7] (200 mg, 1.55 mmol) in 1 ml of acetic anhydride was refluxed for 0.5 hr. After removal of the solvent *in vacuo*, dichloromethane was added and the solution was filtered. Evaporation of dichloromethane afforded *N*-acetyl-2-azabicyclo[2.2.1]heptan-3-one as a colorless oil (185 mg, 78%): ir (neat) 1750 (lactam C=O) and 1690 cm^{-1} (amide C=O); pmr (CCl_4) δ 1.4–2.1 (m, 6, 3 CH_2), 2.31 (s, 3, CH_3), 2.8 (m, 1, CH), 4.7 (m, 1, CH); mass spectrum (70 eV) *m/e* 153 (M^+).

A portion of this oil (168 mg) was heated at 30–40° with 0.5 g of 10% potassium hydroxide for 20 min. The solution was extracted with ether (2 × 25 ml), and the extract was dried ($MgSO_4$) and concentrated *in vacuo*, giving 26 mg (*ca.* 21%) of 4 as a colorless oil, identical with the compound described above by ir, pmr, and glc retention time.

From the water layer, an additional product, *cis*-3-acetylaminocyclopentanecarboxylic acid, was obtained by acidifying the water layer with concentrated hydrochloric acid and, thereafter, extracting with dichloromethane (50 ml). The extract was dried ($MgSO_4$) rapidly and concentrated to *ca.* 3 ml and the white precipitate (92 mg, 46%) was collected, mp 136–139°. An analytical sample, mp 144–146°, was obtained from ethanol-ether-petroleum ether: ir (KBr) 3350 (NHCO), 3000–2200 (COOH), 1705 (COOH), 1615 (amide I), 1560 cm^{-1} (amide II); pmr ($CDCl_3$) δ 1.5–2.3 (m, 9, CH_3, 3 CH_2), 3.0 (br, 1, CH), 4.4 (br, 1, CH), 6.2 (br, 1, NH), 8.8 (br, 1, COOH).

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.1; H, 7.7; N, 8.4.

***cis*-3-Aminocyclopentanecarboxylic Acid Hydrochloride (5).** A solution of lactam 4 (45 mg, 0.40 mmol) in 10 ml of 5% hydrochloric acid was, after standing for 3 days at room temperature, concentrated *in vacuo*. Addition of acetone to the yellow oil gave 55 mg (82%) of 5 as a white solid, mp 142–145° (lit.[7] mp 145–146°), which was identical with an authentic sample[7] by mixture melting point, ir, and pmr: ir (KBr) 3300–2500 (v br, $-CO_2H$ and $-NH_3^+$), 1700 cm^{-1} (C=O); pmr (CD_3OD) δ 1.4–2.6 (m, 6, 3 CH_2), 3.0 (t-like m, 1, CH), 3.7 (t-like m, 1, CH).

Registry No. 1a, 19158-51-1; **1b,** 24225-00-1; **1c,** 49805-26-7; **2a,** 49805-27-8; **2b,** 49805-28-9; **2c,** 49805-29-0; **3,** 49805-30-3; **4,** 24647-29-8; **5,** 24647-29-8; cyclopentadiene, 542-92-7; *cis*-3-aminocyclopentanecarboxylic acid, 49805-32-5; *N*-acetyl-2-azabicyclo-[2.2.1]heptan-3-one, 49805-33-6; *cis*-3-acetylaminocyclopentanecarboxylic acid, 49805-34-7.

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(2) The reaction mixture obtained at 380° from cyanogen bromide and perfluoro-1,3-cyclohexadiene is reported[3] to contain, in addition to perhalopyridine, the primary adduct 3-bromo-1,4,5,6,7,7,8,8-octafluoro-2-azabicyclo[2.2.2]bicycloocta-2,5-diene in low yield (9%). This, together with a similar result from 1,3-dicyanoperfluoropropane,[3] is the only exception that has come to our knowledge.

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(6) The reaction is complete after 60 hr, providing[5a] 4,5-dimethyl-2-tosylpyridine (24%) and 3,6-dihydro-4,5-dimethyl-2(1*H*)-pyridone (55%).

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(17) Glc analysis (SE-30, 6 ft × 0.125 in.) of this oil at 150 and 200° showed one single peak; no impurities were detected by pmr and ir either.

Trifluoroacetic Acid Cleavage of *N*-*tert*-Butylamides. A New Synthesis of Primary Sulfamides

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During the preparation of some sulfamides, we observed cleavage of the *tert*-butyl group from *tert*-butylsulfamides on treatment with trifluoroacetic acid at room temperature. Since *tert*-butylsulfamides are readily available from *tert*-butylsulfamoyl chloride[1] and amines, their dealkylation with trifluoroacetic acid would constitute an attractive route to primary sulfamides. We have also investigated the use of the *tert*-butyl group as a blocking group for sulfamides, sulfonamides, and benzamides.

Known methods[2,3] of synthesis of primary sulfamides include reaction of sulfamoyl chloride with amines, heating sulfamide or *o*-nitrophenylsulfamide with amines, and treating substituted sulfamoyl chlorides with ammonia. These methods have serious limitations; *e.g.*, both the sulfamide and sulfamoyl chloride methods quite often give poor yields of the desired products, the use of sulfamide and *o*-nitrophenylsulfamide usually requires drastic conditions, and many substituted sulfamoyl chlorides, particularly aromatic ones, are unknown.

Although *tert*-butyl and benzyl groups have been used previously as blocking groups for sulfonamides and benzamides, hot methanesulfonic acid or concentrated sulfuric acid[4,5] has generally been required for their removal. Similarly, hot concentrated hydrochloric acid has been used to cleave the alkyl group from *N,N*-di-*tert*-butylsulfamide.[6] However, these conditions are quite vigorous and can cause N–S bond cleavage in sulfamides.[7]

We have prepared various *tert*-butylsulfamides in good yields (Table I, compounds 3–8) from *tert*-butylsulfamoyl chloride[1] (1) and amines *via* the sulfonylamine 2[8] (eq 1). Generation of 2 *in situ* by adding 1 to an ether solution of triethylamine and the appropriate amine at −50° provides better yields of sulfamides than with prior formation of 2.[8] The dimethylsulfamide 14 was prepared by exhaustive methylation of 5.

$$t\text{-}C_4H_9NHSO_2Cl \xrightarrow{Et_3N} [t\text{-}C_4H_9{=}SO_2] \xrightarrow{RNH_2} t\text{-}C_4H_9NHSO_2NHR \quad (1)$$

1 2 3–8

Treatment of the *tert*-butylsulfamides with trifluoroacetic acid at room temperature gave the dealkylated products 9–13 and 15 in high yields (Table I). Similarly, compound 8 gave a nearly quantitative yield of sulfamide.

The mechanism (eq 2) for the cleavage probably involves rapid protonation of the nitrogen bearing the *tert*-

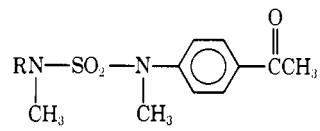
$$(CH_3)_3\overset{+}{C}NHSO_2NHR \rightleftharpoons \begin{matrix}(CH_3)_3C\\ |\\ H\end{matrix}\!\!NHSO_2NHR$$

$$NH_2SO_2NHR + [(CH_3)_3C^+] \xrightarrow{CF_3CO_2^-} CF_3CO_2C(CH_3)_3 \quad (2)$$

24

butyl group followed by loss of the *tert*-butyl carbenium ion to give the primary sulfamide. The *tert*-butyl carbenium ion then combines with trifluoroacetate anion to give *tert*-butyl trifluoroacetate (24). This ionic reaction would be favored by the strongly ionizing trifluoroacetic acid solvent.[9] Support for this mechanism was obtained from the nmr spectra where the only change observed was a 15 Hz downfield shift of the *tert*-butyl peak, which is consistent

Table I

No.	R	R′	R″	% yield	Mp, °C	Cryst solvent	Formula[a]	$t^{1/2}$,[b] min
				$RNHSO_2NHR'$				
3	*t*-C_4H_9	C_6H_5		72	132–134.5	C_6H_6	$C_{10}H_{16}N_2O_2S$	4.3
4	*t*-C_4H_9	C_6H_4-4-OCH_3		63	103–104	*i*-PrOH	$C_{11}H_{18}N_2O_3S$	4.3
5	*t*-C_4H_9	C_6H_4-4-$COCH_3$		78	175.5–177	*i*-PrOH	$C_{12}H_{18}N_2O_3S$	27.5
6	*t*-C_4H_9	C_6H_3-3,4-Cl_2		100	153.5–155	*i*-PrOH	$C_{10}H_{14}Cl_2N_2O_2S$	12.5
7	*t*-C_4H_9	$CH_2CH_2C_6H_5$		60	93–95.5	*i*-Pr_2O	$C_{12}H_{20}N_2O_2S$	6.4
8	*t*-C_4H_9	H		76	57–59	Skelly F	$C_4H_{12}N_2O_2S$	4.0
9	H	C_6H_5		85	108–110[c]	C_6H_6	$C_6H_8N_2O_2S$	
10	H	C_6H_4-4-OCH_3		71	135–136[d]	C_6H_6	$C_7H_{10}N_2O_3S$	
11	H	C_6H_4-4-$COCH_3$		95	160–162	EtOH	$C_8H_{10}N_2O_3S$	
12	H	C_6H_4-3,4-Cl_2		87	104.5–108[e]	C_6H_6	$C_6H_6Cl_2N_2O_2S$	
13	H	$CH_2CH_2C_6H_5$		63	62–63[g]	C_6H_6	$C_8H_{12}N_2O_2S$	
								
14	*t*-C_4H_9			67	79.5–81	Et_2O	$C_{14}H_{22}N_2O_3S$	<0.5
15	H			87	119.5–121.5	C_6H_6	$C_{10}H_{14}N_2O_3S$	
				$RNSO_2R''$ | R'				
16	*t*-C_4H_9	H	CH_3	23	43–45[f]	*i*-Pr_2O	$C_5H_{13}NO_2S$	2.6
17	*t*-C_4H_9	H	C_6H_4-4-CH_3	40	106–112[g]	*i*-PrOH	$C_{11}H_{17}NO_2S$	3.4
18	*t*-C_4H_9	CH_3	C_6H_4-4-CH_3	43	54–54.5	Heptane	$C_{12}H_{19}NO_2S$	<0.5
19	*t*-C_4H_9	H	C_6H_5	5	73–77[h]	Cyclohexane	$C_{10}H_{15}NO_2S$	4.3
20	*t*-C_4H_9	H	C_6H_4-4-NO_2	44	108.5–110	C_6H_6	$C_{10}H_{14}N_2O_4S$	10.8
21	*i*-C_3H_7	$SO_2C_6H_4$-4-CH_3	C_6H_4-4-CH_3	30	125.5–126.5	*i*-PrOH	$C_{17}H_{21}NO_4S_2$	
22	$C_6H_5CH(CH_3)$	CH_3	C_6H_4-4-CH_3	52	77–78	Skelly F	$C_{16}H_{19}NO_2S$	<0.5
23		*t*-$C_4H_9N(CH_3)COC_6H_5$		50	78.5–80.5	*i*-Pr_2O	$C_{12}H_{17}NO$	2.1

[a] Satisfactory analytical results (±0.4% for C, H, N) were obtained for all new compounds. [b] Half-lives at 37° in trifluoroacetic acid. [c] Lit.[3] mp 102–103°. [d] Lit. mp 135–136°: V. M. Cherkasov and T. A. Dashevshaya, *Ukr. Khim. Zh.*, **32**, 486 (1966); *Chem. Abstr.*, **65**, 5314*b* (1966). [e] Lit. mp 68°: J. J. Lafftery and B. Loev, U. S. Patent 3,143,549 (1964); *Chem. Abstr.*, **62**, 489*e* (1965). [f] Lit.[10] mp 40–41°. [g] Lit. mp 110–112°: W. Bradley and R. F. Maisey, *J. Chem. Soc.*, 247 (1954). [h] Lit.[10] mp 77–78°.

with the formation of *tert*-butyl trifluoroacetate. No loss of the *tert*-butyl group as isobutylene was observed.

Half-lives (Table I) of the *tert*-butylsulfamides in trifluoroacetic acid at 37° were determined by nmr. The cleavage rates are consistent with first-order reactions. The half-life of **3** was determined at 10^{-1} and 10^{-2} *M* and found to be independent of concentration, also consistent with a first-order reaction.

The effect of aromatic substituents on the cleavage rates is surprising since the N adjacent to the aromatic ring would not be expected to participate in the cleavage process. In the case of the methoxy and acetyl substituents, these groups are probably protonated in the strongly acidic medium in preference to the sulfamide.

An unexpected finding was the rate enhancement produced by methylation of the nitrogen bearing the *tert*-butyl group. For example, while compound **5** has a half-life of 27.5 min, compound **14** is cleaved in less than 30 sec. This is about the minimum time in which a reading can be taken with the nmr spectrometer. This rate enhancement is no doubt due to increased steric factors.

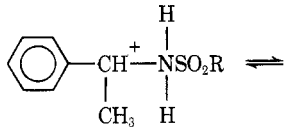
Following the study of sulfamides, we prepared several sulfonamides (Table I, compounds **16–22**) to determine if they would cleave similarly. In general, the sulfonamides were prepared by standard methods and no effort was made to optimize yields. Compounds **18** and **22** were prepared by methylation of the corresponding N-H compounds with methyl iodide. Compound **21** was prepared by adding tosyl chloride to the sodium salt of *N*-isopropyl-*p*-toluenesulfonamide (**25**).

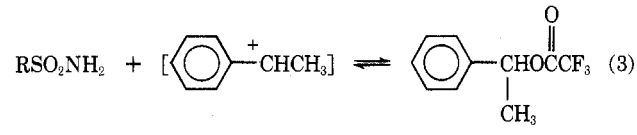
The *tert*-butylsulfonamides, like the *tert*-butylsulfamides, are readily cleaved by treatment with trifluoroacetic acid at room temperature. Removal of the *tert*-butyl group from aromatic sulfonamides appears to be favored by electron-donating substituents and hindered by electron-withdrawing groups, *e.g.*, compounds **17**, **19**, and **20**. The enhanced rate of cleavage of the *tert*-butyl group from tertiary sulfonamides compared to secondary sulfonamides is demonstrated by the much faster cleavage of **18** than **17**.

As would be expected for a carbenium ion mechanism, *N*-isopropyl-*p*-toluenesulfonamide (**25**) and its *N*-methyl derivative **26** were not cleaved by trifluoroacetic acid at room temperature. Similarly, the bissulfonyl compound **21** does not cleave, but it may be too weakly basic to be protonated by trifluoroacetic acid.

N-Methyl-*N*-benzyl-*p*-toluenesulfonamide (**27**) did not cleave, but *N*-α-methylbenzyl-*p*-toluenesulfonamide (**28**) and the corresponding methanesulfonamide **29** were cleaved, although more slowly than the *tert*-butyl compounds. Once again, the *N*-methyl compound **22** was cleaved much faster than the corresponding N-H compound. The half-lives of compounds **28** and **29** could not be determined accurately. Initially, the α-methylbenzyl group cleaved rapidly, but the reaction gradually slowed until an equilibrium was attained with just slightly more than half the compound reacted. This equilibrium is probably due to the reversibility of the cleavage process as shown in (eq 3). Once the equilibrium was attained, the slow appearance of a broad peak in the aromatic region of the nmr spectrum was observed. The unsaturated impurity was probably a polymer, formed from the α-methylbenzyl carbenium ion. It is not surprising that an equilibrium was attained in the cleavage of these compounds, since

N-alkylsulfonamides such as **19** have been prepared in low yield in concentrated sulfuric acid from primary sulfonamides and alcohols.[10]





In the case of benzamides, the scope of the dealkylation reaction is more limited and only tertiary benzamides cleave under our reaction conditions. Although no cleavage was observed overnight with *tert*-butylbenzamide (**30**), its *N*-methyl derivative **23**, prepared by methylation of **30** with methyl iodide, has a half-life of 2.1 min in trifluoroacetic acid at 37°.

Experimental Section

All new compounds were identified by nmr and ir spectra on Varian A-60A and Beckman IR-18A spectrometers, respectively. Corrected melting points were determined for all new compounds on a Thomas-Hoover capillary apparatus. Elemental analyses were determined with an F & M 185 analyzer by the Physical-Analytical Department, Mead Johnson & Co.

Rate Measurements. Cleavage rates of the amides were measured with a Varian T-60 nmr spectrometer. A sample of the amide was added to prewarmed (37°) trifluoroacetic acid, and this solution was immediately inserted into the pretuned instrument. Scans of the *tert*-butyl region were taken every 30 sec for the first 5 min and every 1 min thereafter until the cleavage was 95% complete. The concentration of starting amide [a] at time t is proportional to the area under the peak due to the *tert*-butyl group in the nmr spectrum. The half-life, $t^{1/2}$, was obtained from the slope of a plot of $-\log$ [a] *vs.* t.

$$t^{1/2} = \log 2/\text{slope}$$

The following experiments represent typical experimental procedure.

Sulfamoylation. *N*-(4-Acetylphenyl)-*N'*-*tert*-butylsulfamide (5). *tert*-Butylsulfamoyl chloride (3.4 g, 0.02 mol) was added dropwise to a solution of 4'-aminoacetophenone (2.7 g, 0.02 mol) and triethylamine (2.0 g, 0.02 mol) in 1.5 l. of ether at −50°. The mixture was stirred for 3 hr during which time it was allowed to warm to room temperature. The mixture was made acidic with ethanolic hydrogen chloride, and the insolubles were collected. The insolubles were washed with water and recrystallized from isopropyl alcohol to give 4.2 g (78%) of **5**.

Sulfonylation. *N*-*tert*-Butyl-4-nitrobenzenesulfonamide (20). A solution of 4-nitrobenzenesulfonyl chloride (22.1 g, 0.10 mol) in CH_2Cl_2 was added dropwise with cooling to a solution of *tert*-butylamine (7.3 g, 0.10 mol) in 50 ml of pyridine. The mixture was stirred overnight at room temperature and then concentrated *in vacuo*. Ether was added to the residue and the mixture extracted with dilute hydrochloric acid. The ether solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from benzene to give 11.2 g (44%) of **20**.

Trifluoroacetic Acid Cleavage. *N*-4-Methoxyphenylsulfamide (10). A solution of **4** (3.0 g, 0.011 mol) in 50 ml of trifluoroacetic acid was stirred for 5 hr at room temperature. The solution was concentrated *in vacuo* and the residue recrystallized from ethanol to give 1.5 g (71%) of **10**.

Methylation. *N*-(4-Acetylphenyl)-*N'*-*tert*-butyl-*N,N'*-dimethylsulfamide (14). A mixture of **5** (2.7 g, 0.01 mol), methyl iodide (4.3 g, 0.03 mol), and potassium carbonate (8 g) in 30 ml of acetone was refluxed for 48 hr. Additional methyl iodide was added after 20 hr and 44 hr (0.01 and 0.005 mol, respectively). The insolubles were removed, and the solution was concentrated *in vacuo*. Ether was added, and the insolubles were removed. Cooling furnished pure **14**, 2.2 g (67%).

Registry No.—3, 49689-92-1; **4**, 49689-93-2; **5**, 49689-94-3; **6**, 49689-95-4; **7**, 49689-96-5; **8**, 49689-97-6; **9**, 15959-53-2; **10**, 10539-83-0; **11**, 49690-00-8; **12**, 49690-01-9; **13**, 710-15-6; **14**, 49690-03-1; **15**, 49690-04-2; **16**, 2512-23-4; **17**, 2849-81-2; **18**, 49690-07-5; **19**, 2512-24-5; **20**, 49690-09-7; **21**, 49690-10-0; **22**, 49690-11-1; **23**, 49690-12-2; $RNHSO_2Cl$, 33581-95-2 (R = *t*-C_4H_9), 7778-42-9 (R = H); NH_2R', 62-53-3 (R' = C_6H_5), 104-94-9 (R' = C_6H_4-4-OCH_3), 99-92-3 (R' = C_6H_4-4-$COCH_3$), 95-76-1 (R' = C_6H_3-3,4-Cl_2), 64-04-0 (R' = $CH_2CH_2C_6H_5$), 7664-41-7 (R' = H); $RNHR'$, 75-64-9 (R = *c*-C_4H_9, R' = H), 14610-37-8 (R = *t*-C_4H_9, R' = CH_3), 21230-07-9 (R = *i*-C_3H_9, R' = $SO_2C_6H_4$-4-CH_3), 32512-24-6 (R = $C_6H_5CH(CH_3)$, R' = CH_3); $ClSO_2R''$, 124-63-0 (R'' = CH_3), 98-59-9 (R'' = C_6H_4-4-CH_3), 98-09-9 (R'' = C_6H_5), 98-74-8 (R'' = C_6H_4-4-NO_2); trifluoroacetic acid, 76-05-1.

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Central Nervous System Depressants. 12. The Reaction of Chlordiazepoxide with Methyl Isocyanate

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Although the reaction of isocyanates with other benzodiazepines is in the literature,[1,2] the reaction of 7-chloro-2(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (chlordiazepoxide) (**1**) with isocyanates does not seem to have been reported. We have investigated this reaction and its unexpected course prompts us to report the results.

Treatment of chlordiazepoxide[3] (**1**) with an excess of methyl isocyanate yielded essentially one product as shown by tlc. This contained two isocyanate moieties and was assigned the structure **2**. The oxadiazolo compound **3** was isolated as a minor component from another run. The product ratio suggests that the 1,3 addition of the isocyanate to the nitrone is more rapid than the reaction with the $-NHCH_3$ group. The opposite may be true of the 2-NH_2 analog. Meguro, *et al.*,[1] report only the simple *N*-methylurea derivative from the reaction of methyl isocyanate with 7-chloro-2-amino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, but they gave no yield.

Compound **2** proved to be unstable. Repeated crystallization lowered the melting point, but a run, quickly crystallized from CH_2Cl_2–cyclohexane, gave material with an essentially correct analysis. On standing for many months, the elements of $MeNH_2$ and CO_2 split out and the cyclic urea **4** was formed essentially quantitatively. This conversion seemed to take place faster in a bottle than in an open dish and $CH_3NHCOO^-CH_3NH_3^+$ sublimed into the upper part of the bottle. That this conversion is base catalyzed was shown by adding Et_3N to the reaction of **1** with CH_3NCO, giving an increased yield of **4**, and **5** as a minor product. It is believed that the reason the conversion into **4** took place more rapidly in the bottle was due to the $MeNH_2$ being retained in the mixture.