the latter has also superior handling features, such as crystallinity of the chloride and the ester derivative, higher yield in the synthesis of the chloride, and higher rotation of the ester derivative.

The present results render the pentamethylbenzenesulfonate group the least reactive sulfonate group known; they also extend the reactivity spread of sulfonate leaving groups from the known 8 × 10^4-fold range—from trifluoromethanesulfonates to *p*-toluenesulfonates[2]—up to a 7 × 10^5-fold range, from trifluoromethanesulfonates to pentamethylbenzenesulfonates.[3]

Several uses of "poor" sulfonate leaving groups can be envisaged. Among them, one can mention some of those for which this study was undertaken. Thus, *e.g.*, the use of the pentamethylbenzenesulfonate ester of (+)-*threo*-3-*p*-anisyl-2-butanol has rendered possible the measurement of the polarimetric rate of formolysis of this system, which was not possible for its *p*-toluenesulfonate ester since its formolysis was very rapid even near the freezing point of formic acid.[6] Similarly, the polarimetric rate of trifluoroacetolysis of the same ester of (+)-*threo*-3-phenyl-2-butanol could be measured more conveniently and accurately at temperatures above zero, *e.g.*, 8°,[6] as compared to the difficult and very inconvenient rate measurements conducted earlier with the *p*-toluenesulfonate derivative at −8°.[7]

It is of interest to assess the effect of successive substitution by methyl and methoxy groups on the reactivity of arenesulfonates. For this purpose, the unsubstituted benzenesulfonate ester itself was also studied. Comparison with this derivative (Table II) indicates that introduction of one methyl group in the para position slows down the solvolysis by a factor of only 1.31, whereas the fully methylated derivative solvolyzes 11.21 times slower. Introduction of a *p*-methoxy group decelerates the reaction by 2.52-fold, whereas the 2,4,6-trimethoxybenzenesulfonate derivative solvolyzes 10.47 times slower.

Other sulfonate leaving groups are under study and will be reported subsequently.

Experimental Section

The melting points reported are corrected. A Perkin-Elmer Model 141 photoelectric polarimeter was used for the measurement of polarimetric rates. The temperatures inside the polarimeter cell were measured with the use of thermistors and a thermistor actuated differential thermometric bridge allowing differential reading between these temperatures and the corresponding ones of the bath used to thermostat the polarimeter cell (jacket). The bath temperatures were corrected against factory calibrated (Thermoschneider, W. Germany) standard thermometers. The temperatures in the kinetic runs were maintained constant to within ±0.002°.

Arenesulfonyl Chlorides. *p*-Methoxybenzenesulfonyl chloride was prepared as previously reported.[8] The pentamethylbenzenesulfonyl chloride and the 2,4,6-trimethoxybenzenesulfonyl chloride were prepared from pentamethylbenzene and 2,4,6-trimethoxybenzene, respectively, by a known general procedure for the synthesis of arenesulfonyl chlorides.[9]

The following is a typical synthesis. A 0.09*M* solution of chlorosulfonic acid in dry chloroform was added dropwise over a period of about 30 min to a stirred 0.03 *M* solution of pentamethylbenzene in dry chloroform kept at about −5° during the addition. The reaction mixture was then allowed to reach room temperature and was poured into 5% aqueous sodium carbonate containing crushed ice. The chloroform layer was washed with cold 5% aqueous sodium bicarbonate followed by saturated aqueous sodium chloride and was dried over magnesium sulfate. The solvent was removed under reduced pressure. The solid residue, mp 79–81° (53%), was recrystallized twice from hexane giving the pure product, mp 80–81°. Analytical data are given in Table I.

Arenesulfonate Esters of (+)-*threo*-3-*p*-Tolyl-2-butanol. These were prepared by reaction of (+)-*threo*-3-*p*-tolyl-2-butanol[10] with the appropriate arenesulfonyl chloride (methanesulfonyl chloride in the synthesis of the methanesulfonate) by the usual procedure.[11] Room temperature and 2–3 days of reaction time were used for the preparation of the pentamethyl and the trimethoxy derivatives. The pure esters were obtained in about 75% yield. Physical and analytical data of these esters are given in Table I.

Kinetic Measurements. Polarimetric rates of solvolysis were measured by following the change in the optical rotation, at 436 mμ, of the appropriate solutions of the esters placed in a thermostated 1-dm cell of a photoelectric polarimeter. The solvolysis medium, 65% (wt/wt) aqueous ethanol, contained an excess of sodium acetate used to react with the arenesulfonic acid liberated during reaction. Neither the resulting acetic acid nor sodium acetate had any measurable effect on observed rates of such ethanolysis reactions at the molarities involved (0.03 *M*), as concluded from earlier studies in our laboratory.[6] The polarimetric rates were followed from 12 to about 83% completion and showed good first-order kinetics. The pseudo-first-order rate constants were obtained from a least-squares treatment of the data.

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References and Notes

(1) Author to whom inquiries should be directed.

(2) T. Gramsted and R. N. Haszeldine, *J. Chem. Soc.*, 4069 (1957); R. L. Hansen, *J. Org. Chem.*, **30**, 4322 (1965); R. K. Crossland, W. E. Wells, and V. J. Shiner, Jr., *J. Amer. Chem. Soc.*, **93**, 4217 (1971).

(3) (a) Comparison of polarimetric rates, as against of titrimetric ones, avoids the obscuring influence of a possible change in the extent of internal return with different leaving groups. Nevertheless, and because of this possibility, in order to render more meaningful a comparison of the present results with those based on overall reaction rates (*e.g.*, those in ref 2), titrimetric or conductimetric, the question of a change in k_α/k_t with leaving group has been taken into consideration. This change, however, should be relatively small for the reactivity range of the sulfonate derivatives studied, as deduced from earlier work in our laboratory (ref 3b, 6), hence should not hinder the aforementioned comparison. (b) At the suggestion of a referee we are including some of our earlier work (ref 6) referred to above. The k_α/k_t ratio has been found to vary only from 1.54 to 1.44 and to 1.31, respectively, in going from *threo*-3-phenyl-2-butyl tosylate to the brosylate and to the nosylate in 65% aqueous ethanol at 60° (ref 6). It should be noted that the reactivity range of these esters, given by $k_{\mathrm{RONs}}/k_{\mathrm{ROTs}}$, is about 16 as compared to the smaller range from the tosylate to the pesylate, $k_{\mathrm{ROTs}}/k_{\mathrm{ROPmes}}$, which is 8.5. More pertinent to the present study, the k_α/k_t ratio for the *threo*-3-*p*-tolyl-2-butyl arenesulfonates in 65% ethanol is both small and varies little with the leaving group; k_α/k_t is (ref 6) 1.3 for the tosylate (at 55°), and 1.3 and 1.4, respectively, for the pentamethylbenzenesulfonate and the trimethoxybenzenesulfonate esters (at 66 5°).

(4) R. E. Robertson, *Progr. Phys. Org. Chem.*, **4**, 213 (1967).

(5) Since the relative reactivities of leaving groups should be influenced by, in addition to the leaving group itself, the structure of the reacting system and by the particular reaction studied and its conditions, inclusion of the methanesulfonate derivative in our study was of interest in order to assess properly the significance of the retarding effects of the new reported groups.

(6) F. S. Varveri, M. R. Velkou, and G. A. Gregoriou, unpublished data.
(7) S. L. Loukas, M. R. Velkou, and G. A. Gregoriou, *Chem. Commun.*, 1199 (1969); 251 (1970).
(8) M. S. Morgan and L. H. Cretcher, *J. Amer. Chem. Soc.*, **70**, 375 (1948).
(9) E. E. Gilbert, *Synthesis*, **1**, 3 (1970).
(10) S. L. Loukas, F. S. Varveri, M. R. Velkou, and G. A. Gregoriou, unpublished synthetic work.
(11) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

Reaction Kinetics of Furansulfonyl Chlorides with Anilines in Methanol and Reactivities of Benzene-, Thiophene-, and Furansulfonyl Chlorides

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The side-chain reactivity of pentatomic heterocycles toward nucleophiles is affected by opposite effects. Thiophen and furan are, in fact, electron withdrawing by inductive effect[1] and electron donating by resonance effect.[2,3] In the latter case, moreover, the conjugation between the furan ring and the side chain can be greater or smaller than that of the thiophene ring, depending on the electron de-

Table I
Second-Order Rate Constants and Activation Parameters for the Reactions of Furansulfonyl Chlorides with Anilines in Methanol[a]

$C_4H_3O-SO_2Cl$ C_4H_3O =	Registry no.	$H_2N-C_6H_4-X$ *p*-X =	Registry no.	*T*, °C	$k_2 \times 10^3$, l. mol^{-1} sec^{-1}	No. of runs	Δ*H* *, kcal mol^{-1}	-Δ*S**, cal mol^{-1} $°K^{-1}$
2-Furyl	52665-48-2	H	62-53-3	15	2.81 (0.08)	3	11.6 (0.4)	29.9 (1.4)
				25	6.07 (0.22)	4		
				35	12.1 (1.4)	3		
				45	20.6 (2.0)	4		
2-Furyl		CH_3	106-49-0	15	6.87 (0.18)	3	10.6 (0.4)	31.4 (1.3)
				25	14.4 (1.7)	3		
				35	25.7 (0.2)	3		
				45	44.2 (2.4)	3		
2-Furyl		OCH_3	104-94-9	15	21.6 (0.3)	3	9.6 (0.4)	32.8 (1.2)
				25	39.4 (2.7)	4		
				35	72.9 (0.6)	3		
				45	112.8 (0.4	3		
2-Furyl		Cl	106-47-8	15	0.986 (0.001)	3	12.4 (0.5)	29.3 (1.7)
				25	2.23 (0.17)	4		
				35	4.03 (0.17)	3		
				45	8.53 (0.53)	4		
3-Furyl	52665-49-3	H		15	4.04 (0.12)	3	10.8 (0.6)	31.7 (2.0)
				25	8.54 (0.63)	5		
				35	14.0 (1.0)	4		
				45	27.9 (1.8)	3		

[a] Standard deviations in parentheses.

mand.[4] The balance between these effects can determine different reactivity sequences.[5,6]

Recently the reaction kinetics of some aromatic sulfonyl chlorides (benzenesulfonyl chloride,[7] 2- and 3-thiophenesulfonyl chlorides[8-10]) with anilines in methanol has been investigated.

Following this research, in this work we report a kinetic study of the reaction between 2-furansulfonyl chloride and some para-substituted anilines and between 3-furansulfonyl chloride and aniline in methanol solution, in order to correlate the reactivity data with those obtained before.

Results and Discussion

The reaction of furansulfonyl chlorides with anilines in methanol takes place quantitatively according to equation

$$C_4H_3O-SO_2Cl + 2H_2N-C_6H_4-X \longrightarrow C_4H_3O-SO_2NH-C_6H_4-X + X-C_6H_4-N^+H_3Cl^-$$

C_4H_3O = 2-furyl and X = H, *p*-CH_3, *p*-CH_3, *p*-OCH_3, and *p*-Cl; C_4H_3O = 3-furyl and X = H

The reaction is second order overall, first order with respect to each reactant, and was followed by continuous titration of the acid produced.[8]

The second-order rate constants, reported in Table I together with the activation parameters, were calculated from the plot of k_{psI} against aniline concentrations.[9,10]

The data show that electron-donating substituents in the aniline increase the rate, while electron-withdrawing groups decrease the rate.

The slope value of the Hammett plot ($\rho = -2.4 + 0.3$) is equal, within experimental errors, to that calculated for the analogous reactions of benzenesulfonyl chloride[8] and 2- and 3-thiophenesulfonyl chlorides,[8,10] indicating the same sensitivity of the reaction to substituents in the aniline.

The Brønsted plot for the reaction of 2-furansulfonyl chloride, obtained using the pK_a of anilines in methanol,[11] is linear with a slope $\beta = 0.51$. This value, which is related to the degree of S–N bond formation in the transition state,[12] is equal to those found for benzenesulfonyl chloride, 0.51,[7] for 2-thiophenesulfonyl chloride, 0.53,[8] and for 3-thiophenesulfonyl chloride, 0.54;[10] the transition state structure, then, ought to be the same in all four reactions.

These results, in connection with previous studies on the halogen mobilities in the reaction of 2-thiophenesulfonyl halides[13] and benzenesulfonyl halides[14] with aniline and on the salt effect in the reaction of benzenesulfonyl chloride with *N*-methylaniline,[15] suggest that the reaction proceeds following a two-step addition–elimination mechanism, where the rate-determining step is the aniline nucleophilic attack to the substrate.

The reaction rate constants can then be expected to depend not only on the nucleophile basicity but also on the substrate reactivity.

Comparing the reaction rate constants of furansulfonyl chlorides with those of benzene- and thiophenesulfonyl chlorides, reported in Table II, the following reactivity order is observed: benzene > 3-thiophene > 3-furan > 2-furan ≃ 2-thiophene.

This sequence follows the order of the mesomeric interaction between the aromatic ring and the sulfonyl group.

A measure of this interaction could be provided by E_t, which is the electronic transition energy, related to the structure $Ar^+-SO_2^-$–, calculated from λ_{max} values in the uv spectra of sulfonyl chlorides (see Table II). E_t values are, in fact, in agreement with the free activation energy values.

Moreover, the mesomeric interaction in pentatomic heterocycles at the 3 position is lower than at the 2 position;[16] hence 3-sulfonyl derivatives are more reactive than the corresponding 2 isomers.

The reaction rate constants for 2- and 3-substituted furan derivatives are not remarkably different ($k_{3f-SO_2Cl}/k_{2f-SO_2Cl} = 1.4$), while the analogous ratio for the thiophene derivatives is greater ($k_{3t-SO_2Cl}/k_{2t-SO_2Cl} = 3.7$).

The correlation between kinetic (ΔG^*) and spectroscopic data (E_t) can be regarded as satisfactory ($r = 0.95$), be-

Table II
Comparison between the Electronic Transition Energies and the Free Activation Energies for the Reaction of Ar-SO_2-Cl with Aniline in Methanol at 25°

Ar–SO_2Cl Ar =	Registry no.	λ_{max},[a] nm	E_t, kcal mol^{-1}	$k_2 \times 10^3$ at 25°, l. mol^{-1} sec^{-1}	ΔG*, kcal mol^{-1}
Phenyl	98-09-9	233	123	68.6 (4.4)[b]	18.4
3-Thienyl	51175-71-4	240	119	20.8 (0.7)[b]	19.8
3-Furyl		244	117	8.54 (0.63)[c]	20.2
2-Furyl		254	113	6.07 (0.22)[c]	20.5
2-Thienyl	16629-19-9	253, 272	114, 105	5.62 (0.22)[c]	20.5

[a] In methanol solutions. [b] Maximum error. [c] Standard deviation.

Table III
Melting Points and Spectroscopic Characteristics of Furansulfonanilides[a,b]

		C_4H_3O–SO_2NH–C_6H_4X				Ultraviolet spectra		Infrared spectra, cm^{-1}		
								ν_{NH}	ν_{SO_2} stretch	
No.	Registry no.	C_4H_3O =	X =	Mp, °C	Formula	λ_{max}	log ε	stretch	Asym	Sym
1	52665-43-7	2-Furyl	H	87	$C_{10}H_9NO_3S$	233 230[c]	4.09 4.07	3240	1350	1155
2	52665-44-8	2-Furyl	p-CH_3	95	$C_{11}H_{11}NO_3S$	225	4.18	3255	1345	1150
3	52665-45-9	2-Furyl	p-OCH_3	85	$C_{11}H_{11}NO_4S$	228	4.18	3225	1340	1155
4	52665-46-0	2-Furyl	p-Cl	93	$C_{10}H_8ClNO_3S$	228 235[c]	4.18 4.16	3260	1380	1155
5	52665-47-1	3-Furyl	H	57–58	$C_{10}H_9NO_3S$	225	4.05	3290	1345	1140

[a] All the compounds were crystallized from aqueous ethanol. [b] Satisfactory combustion analytical data for C, H, and N (±0.3%) were found for these compounds. [c] Inflection.

cause the spectroscopic process, chosen as a model for the kinetic one, cannot closely resemble the reaction activation process.

The presence of other kinds of interactions cannot, in fact, be excluded, also if resonance effects seem to play the most important role.

Experimental Section

Sodium 2-Furansulfonate. It was synthesized following the procedure described by Scully and Brown,[17] by direct sulfonation of anhydrous furan using the pyridine-SO_3 complex. The reagents were mixed in a 1:1 molar ratio to prevent disulfonation and heated for 12 hr between 95 and 100° in a sealed Carius tube.

2-Furansulfonyl Chloride. Anhydrous sodium 2-furansulfonate (5 g) was treated with 20 ml of $POCl_3$ and refluxed for 3 hr. The mixture was poured dropwise into crushed ice and extracted with ether. The organic layer, after distillation, gave, in low yields, 2-furansulfonyl chloride, bp 74–76° (6 mm). The uv spectrum in 95% ethanol shows a max at 254 nm (log ε 3.86). The ir absorption frequencies, characteristic of the sulfonyl asymmetric and symmetric stretching, measured in KBr disks, are located respectively at 1385 and 1165 cm^{-1}. The nmr peaks (CCl_4, δ) occur at 6.70 (1 H, dd, H_4), 7.33 (1 H, dd, H_3), and 7.77 ppm (1 H, dd, H_5).

Ammonium 3-Furansulfonate. It was synthesized following the indications reported in the literature,[18,19] but, as the exact reaction conditions are not available, we report here briefly the synthesis method adopted by us. To 52 ml of oleum, kept at 0–10°, 6 g of 5-bromo-2-furoic acid[20] was added slowly and the mixture was allowed to react at room temperature for 12 hr. The mixture was then poured into crushed ice, neutralized with $BaCO_3$, and filtered hot. The filtrate was concentrated and to the cold suspension an aqueous solution of bromine was added until there was no further CO_2 evolution. The solution was concentrated to one-half volume and, after addition of Zn and NH_4OH, refluxed for 12 hr. Zinc dust was eliminated by filtration and the residue, evaporated to complete dryness, gave ammonium 3-furansulfonate.

3-Furansulfonyl Chloride. Ammonium salt (5 g) was suspended in 30 ml of $POCl_3$ and refluxed for 5 hr. The mixture was poured into crushed ice and extracted with ether. The organic layer was distilled and gave, in low yield, 3-furansulfonyl chloride, bp 54–56° (0.2 mm). The uv spectrum in 95% ethanol shows a max at 244 nm (log ε 3.80). The ir absorption frequencies, characteristic of the sulfonyl asymmetric and symmetric stretching, measured in KBr disks, are located respectively at 1370 and 1160 cm^{-1}. The nmr peaks (CCl_4, δ) occur at 6.85 (1 H, dd, H_4), 7.62 (1 H, dd, H_5), and 8.17 ppm (1 H, dd, H_2).

Furansulfonanilides. Furansulfonanilides were synthesized by adding 0.03 mol of furansulfonyl chloride in methanol (10 ml) to a methanol solution (50 ml) containing 0.065 mol of aniline, following the procedure previously described for thiophenesulfonanilides.[8-10] The products were characterized by C, H, and N analysis and uv and ir spectroscopy. In Table III are reported the melting points and the spectroscopic characteristics. The anilines used were commercial products, purified by several crystallizations or distillations. Methanol used for the kinetic runs was RS Carlo Erba.

Kinetic Procedure. Rate measurements were done by a digital pH meter Amel 333 by continuous titration of the acid produced with 0.1 N sodium hydroxide. In a typical kinetic run a solution containing ca. 3 × 10^{-4} mol of furansulfonyl chloride in methanol (10 ml) was added to a methanol solution (90 ml) containing ca. 1.10^{-2} mol of aniline.

The pseudo-first-order rate constants were calculated from conventional plots of log $a - x$ against time from the slope obtained using the least-squares method.

The second-order rate constant was calculated from the slope of the line obtained by plotting the pseudo-first-order rate constants against aniline concentrations. At least three kinetic runs, at different aniline concentrations, were carried out at the established temperature.

The activation energies and log A values were calculated from the Arrhenius equation, while the activation entropies were computed for 25° using the suitable equation.[21]

Spectroscopy. The uv spectra were recorded on a Hitachi Perkin-Elmer Model EPS 3T spectrometer in ethanol solutions (1 × 10^{-5} mol $l.^{-1}$). The ir spectra were recorded in KBr disks on a Perkin-Elmer Model 237 spectrometer. The nmr spectra were obtained with a Varian A-60 spectrometer in carbon tetrachloride, using TMS as internal standard.

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References and Notes

(1) P. A. Ten Thije and M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, **84**, 1169 (1965).

(2) N. N. Magdesieva, *Advan. Heterocycl. Chem.*, **12**, 26 (1970), and references therein.

(3) G. Marino, *Advan. Heterocycl. Chem.*, **13**, 239 (1971).
(4) L. W. Deady, R. A. Shanks, and R. D. Topsom, *Tetrahedron Lett.*, 1881 (1973).
(5) A. Arcoria and S. Fisichella, *Gazz. Chim. Ital.*, **103**, 813 (1973).
(6) A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, work in progress.
(7) O. Rogne, *J. Chem. Soc. B*, 1855 (1971).
(8) A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *J. Org. Chem.*, **38**, 2457 (973).
(9) A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *Ann. Chim.* (*Roma*), **63**, 281 (1973).
(10) A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *J. Org. Chem.*, **39**, 1689 (1974).
(11) M. Kilpatrick and C. A. Arenberg, *J. Amer. Chem. Soc.*, **75**, 3812 (1953).
(12) L. Senatore, E. Ciuffarin, and A. Fava, *J. Amer. Chem. Soc.*, **92**, 305 (1970), and references therein.
(13) E. Maccarone, G. Musumarra, and G. A. Tomaselli, *J. Org. Chem.*, **39**, 3286 (1974).
(14) E. Ciuffarin, L. Senatore, and M. Isola, *J. Chem. Soc., Perkin Trans. 2*, 468 (1972).
(15) S. D. Ross, M. Filkenstein, and F. S. Dunkl, *J. Org. Chem.*, **39**, 134 (1974).
(16) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 13 (1963).
(17) J. F. Scully and E. V. Brown, *J. Org. Chem.*, **19**, 897 (1954).
(18) R. O'Cinneide, *Nature* (*London*), **160**, 260 (1947).
(19) Hill and Palmer, *Amer. Chem. J.*, **10**, 413 (1888).
(20) Z. N. Nagarova and I. G. Gakh, *Zh. Obschch. Khim.*, **30, 2322 (1960);** *Chem. Abstr.*, **55**, 8376 (1961).
(21) M. Simonetta, "Chimica Fisica," Vol. I, Manfredi, Milano, 1966, p 278.

Reaction of 2,3-Dialkylpyrazines and Methyllithium. Indirect Evidence for Ring Metalation

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The widespread occurrence of simple alkylpyrazines in roasted or browned foodstuffs,[1] *e.g.*, coffee, cocoa, peanuts, etc., has prompted considerable interest in the chemistry of these compounds. Certain of the trialkylpyrazines, *e.g.*, 2,5-dimethyl-3-ethylpyrazine are commonly synthesized by adding organolithiums to more readily available 2,5-dialkylpyrazines.[2] With 2,3-dialkylpyrazines and methyllithium, nuclear addition does not readily occur, instead side-chain and ring metalation take place.[2,3] In view of the contemporary importance of these compounds, we decided to examine the metalation of 2,3-dialkylpyrazines under various conditions.

The extent of 2,3-dimethylpyrazine (1) metalation was estimated by reaction with methyllithium in ether (diethyl ether) followed by D_2O quenching and high resolution mass spectrographic analysis of the deuterated products, Table I. The mass fragmentation pattern did not permit a distinction to be made between ring or chain metalated species. The absence of a *m/e* 95 fragment ion (predictable *via* normal methyl loss from $C_6H_6N_2D_2$) excluded the possibilities of CHD_2-containing species, ring dimetalation, or ring plus methyl dimetalation. Previously, both monomethyl metalated and vicinally dimethyl metalated 1 were shown to be present by alkylation with dimethyl sulfate.[3] *No evidence for ring alkylation was found with dimethyl* sulfate obviating ring metalation under these conditions.

Table I
Deuterated Species from D_2O Quenching of Metalated 2,3-Dimethylpyrazine

Reaction conditions[a]	Relative %[b]			
	$C_6H_8N_2$	$C_6H_7N_2D$	$C_6H_6N_2D_2$	$C_6H_5N_2D_3$
1.1, 0.5, 0	39	54	6.8	0.9
1.7, 0.5, 0	3.2	83	12	1.3
m/e calcd	108.069	109.075	110.080	111.087
m/e obsd[c]	108.067	109.073	110.078	111.083

[a] Mole ratio of MeLi/1, time in hr, temp (°C). [b] Values corrected for ^{13}C and ^{15}N content. [c] Precision *ca.* ±0.003 amu.

Evidence for pyrazine ring metalation was sought by quenching reaction products of 2-ethyl-3-methylpyrazine (2) and MeLi with D_2O, Table II. Pmr was used to determine the extent of metalation/deuteration of more acidic hydrogens relative to the presumably unmetalated terminal methyl in the ethyl side chain. Conditions which led to 54% monometalation of 1 produced 30% methyl metalation and a maximum of 1.1% ring metalation in **2**. Treatment of **2** with a sixteenfold excess of MeLi at 25° for 24 hr gave 50% methyl metalation apparently resulting in a mixture of CH_2D and CHD_2 species. Under the more forcing conditions, 15% of available ring positions also underwent metalation. In accord with reported hydrocarbon metalation data,[4] less metalation occurred at the methyl substituted ring CH_2 (31%) than at the ring CH_3 (50%) of **2**.

Table II
Metalation and D_2O Quenching of 2-Ethyl-3-methylpyrazine

Reaction conditions			Per cent substitution of D for H[a]		
MeLi/2 ratio	°C	hr	Ring H's	Ring CH_2	Ring CH_3
1.0	0	1.0	1.0	1.0	30
16	25	24	15	31	50

[a] Determined by pmr using ethyl group methyl (3.00 H) as internal standard, precision *ca.* ±10% of values shown.

A similar effect led to apparent retardation of methyl substitution in the metalation/methylation of methylpyrazine with sodamide and methyl iodide in liquid ammonia, Table III. The yields of isopropylpyrazine and *tert*-butylpyrazine were low relative to ethylpyrazine even in the presence of excess alkylating reagents. The lowered total alkylpyrazine yields in experiments designed to flavor *tert*-butylpyrazine formation possibly resulted from competitive N methylation and loss of quaternary salts during work-up. Since no ring methylated pyrazines were detected, we concluded that ring metalation by sodamide either did not occur or that it was slow relative to isopropylpyrazine side-chain metalation.

Table III
Methylation of Methylpyrazine in Liquid Ammonia

Mol of $NaNH_2$ and CH_3I/mol of methylpyrazine	Pyrazine yield, %[a]			
	Methyl	Ethyl	Isopropyl	*tert*-Butyl
1.0	4.9	77.6	2.6	trace
2.0	3.6	31.8	42.0	4.3
4.0	0.5	2.4	9.9	24.6

[a] Absolute yields based on 1 equiv of methylpyrazine as determined by glc on vacuum distilled products; no other products were detected.

Experimental Section[5]

Metalation/Deuteration of 1. To a stirred mixture of ether (5 ml) and 3.5 ml of 1.6 *M* MeLi in ether (5.6 mmol) at 0° was added