Table I—Accuracy and Reproducibility of GLC Analysis of I Added to Human Plasma

Added, μg/ml	Mean Recovered Amount (Range)	Recovery, %[a]
0.1	0.101 (0.097–0.103)	101
0.5	0.49 (0.480–0.51)	98
1	1.03 (0.95–1.31)	103
5	4.81 (4.74–5.33)	96.2
10	10.35 (9.84–10.72)	103.5
15	15.50 (14.68–15.96)	104

[a] Mean ± *SD* = 100.95 ± 2.92; number of analyses = 4.

The results (Table I) show the accuracy and reproducibility of the GLC analysis of I in clinical samples. The response factor was calculated using the ratio of peak areas for similar concentrations of I and II (1.22 ± 0.12). The method has been used in laboratories to determine the amount of I in rat blood compared with radioisotopic methods (18, 19). It also has been used for the determination of I in plasma and urine of humans and in pharmacokinetic studies (18).

Recently, a simple and fast high-performance liquid chromatographic method (20) was developed in which derivatization was not necessary. However, the sensitivity was not as good as that using GLC electron-capture detection.

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Synthesis, Structure, and Features of Anilinium Anilinomethanesulfonates

MIGUEL G. NEUMANN and ROBERT A. M. C. DE GROOTE ˣ

Received September 11, 1980, from the *Instituto de Física e Química de São Carlos, USP, C.P. 369, 13560 São Carlos, SP, Brazil.* Accepted for publication January 6, 1981.

Abstract □ Two series of anilinomethanesulfonate derivatives, the anilinium and *p*-toluidinium anilinomethanesulfonates, were synthesized. They present interesting spectroscopic features and can be used as characteristic derivatives of the parent compounds. These series allow the easy study of the N–H stretching frequencies of the secondary amine whereas difficulties are encountered with the parent compounds due to the occurrence of O–H stretching bands in the same frequency range. All three compounds present a common fragmentation pattern in mass spectral analysis. Through these analyses, the salt structure of the anilinium anilinomethanesulfonates is demonstrated in opposition to a sulfonamide structure, giving further support to the salt structure of other series previously reported.

Keyphrases □ Anilinomethanesulfonates, derivatives—synthesis and structure elucidation by elemental, IR, and mass spectral analyses □ Mass spectrometry—analysis, anilinomethanesulfonate derivatives, synthesis and structure elucidation □ IR spectroscopy—analysis, anilinomethanesulfonate derivatives, synthesis and structure elucidation

Methanesulfonation of the amine groups of pharmacologically active drugs is used to increase their solubility (1) and to control their hydrolysis in biological media (2). Some common examples are *p*-phenetidinomethanesulfonate[1], dihydroergotamine[2], and dipyrone[3]. On the other hand, some researchers have studied aminomethanesulfonic compounds as potential antiviral (3) or carcinogenic agents (4, 5) since their structures are analogous to the carboxylic amino acids. As part of research into the properties of aminomethanesulfonates, the kinetics of formation of substituted anilinomethanesulfonates were studied recently (6). The inherent difficulties of analyzing IR spectra of substituted aromatic aminomethanesulfonates with regard to the O–H stretching bands also were discussed (7).

Little work has been reported concerning the analysis of the anilinomethanesulfonates, their chemical structure, and the different products that form, depending on the synthetic method. To find appropriate methods of analysis and identification of these products, a new series of derivatives was prepared by the reaction of equimolar

[1] Nevralteine.
[2] Diergotan, dihydergot, ergotex.
[3] Conmel, novalgin, sulpyrin.

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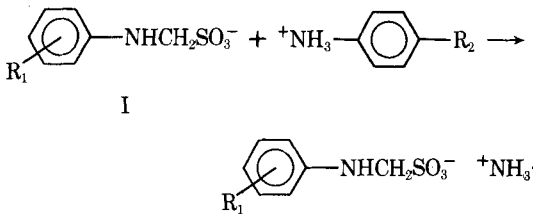


I

IIa: R_2 = H
IIb: R_2 = CH_3

Scheme I

amounts of the anilinomethanesulfonate (I) with anilinium or *p*-toluidinium chloride in water at room temperature to form the anilinium or *p*-toluidinium anilinomethanesulfonates (II) (Scheme I).

EXPERIMENTAL

Anilinomethanesulfonate Sodium Salts—All anilinomethanesulfonates were synthesized from the corresponding anilines and sodium hydroxymethanesulfonate and were purified by previously described methods (6).

Anilinium and *p*-Toluidinium Anilinomethanesulfonates—These compounds were prepared by mixing equimolar amounts of the parent anilinomethanesulfonate with anilinium or *p*-toluidinium chloride at room temperature in a minimal amount of water under strong agitation. After precipitation, which was almost instantaneous, the compound was filtered, washed with cold ethanol and ether, and dried under vacuum at room temperature.

Recrystallization was performed using 50% ethanol–water. Special care was required because the anilinium compounds may be affected by light.

Elemental analysis values for all compounds were within 0.5% of those calculated from the theoretical structure of II.

The melting points for the anilinium- and *p*-toluidinium-substituted anilinomethanesulfonates, respectively, were: R = H, 118–120 and 123–124°; R = *m*-Cl, 119–120 and 123–124°; R = *p*-Cl, 129–134 and 139–142°; R = *p*-CH_3, 122–124 and 131°; and R = *p*-OCH_3, 121–123 and 134–136°. All compounds melted with decomposition.

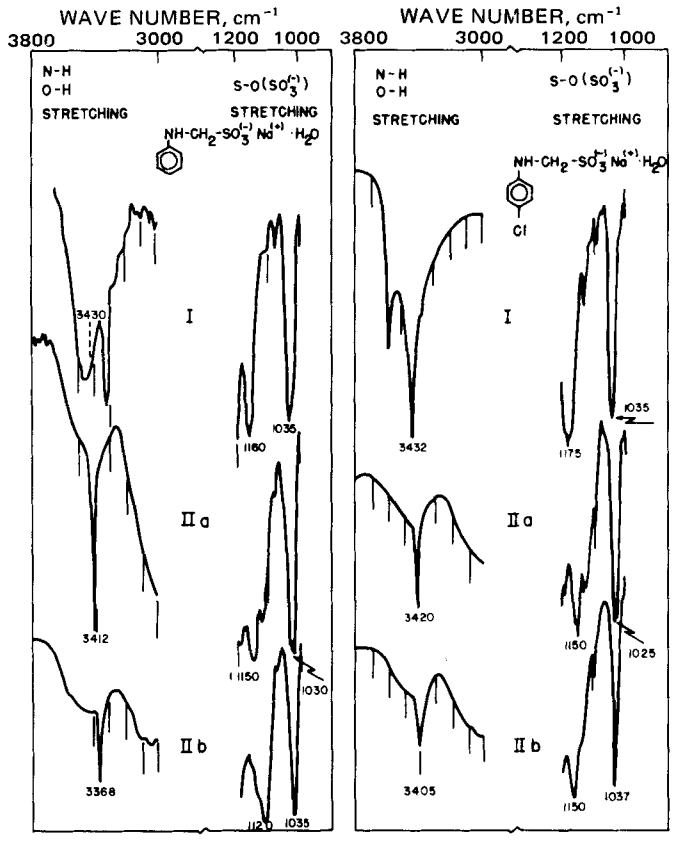


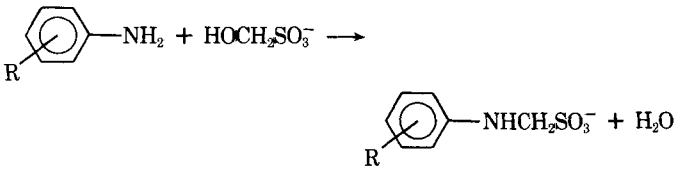
Figure 1—*IR spectra of sodium anilinomethanesulfonate (I), anilinium anilinomethanesulfonate (IIa), and* p*-toluidinium anilinomethanesulfonate (IIb) and its* p*-chloro-substituted derivatives.*

Instrumentation—IR spectra were measured on a high-resolution double-beam spectrophotometer[4]. All spectra were taken from solid pellets with 0.5% of the product in potassium bromide.

Mass spectra were taken at various temperatures with a quadrapole spectrometric system[5].

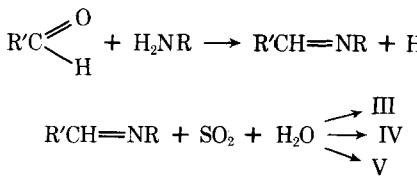
RESULTS AND DISCUSSION

The classic synthesis of substituted anilinomethanesulfonates (I) involves the reaction of equimolar amounts of the substituted aniline hydroxymethanesulfonate in a suitable solvent (6) (Scheme II).



Scheme II

Another common method for aliphatic and, in particular, C-substituted compounds is based on the addition of sulfur dioxide to the corresponding Schiff base dissolved or suspended with enough water to form the hydrogen sulfate ion (HSO_3^-). Depending on the aldehyde and the amine, three products (III–V or a mixture of them) might be formed when using the Schiff base method (8) (Scheme III).



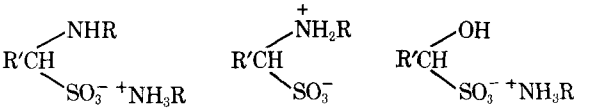
Scheme III

Structure III is obtained with aromatic amines, IV is obtained with aliphatic amines, and V is obtained when either the starting amine is very bulky (steric hindrance) or the aromatic aldehyde is substituted with strong withdrawing groups. In both cases for V, hydrolysis of the Schiff base is faster than the reaction with the bisulfite reagent. Considering the experimental procedure, it might be assumed that the proportion in which III and IV are formed is a function of the difference of the pKa values between aliphatic and aromatic amines.

This method cannot be used for formaldehyde derivatives (R′ = H) since a mixture of bis(phenylamino)methane and resinous material is formed (9).

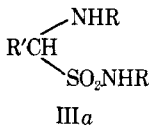
IR Spectral Analysis—The anilinium salt structure of V was confirmed by its IR spectra. The characteristic derivatives, IIa and IIb, present very characteristic N–H and S–O (SO_3^-) stretching bands (10). The N–H stretching frequencies for these compounds were presented elsewhere (7). If the structure of V is sulfonamide-like, as was suggested (11), the N–H stretching frequency for the *sec*-amine group and for the sulfonamide group should be different. Therefore, two narrow stretching bands around 3400 cm^{-1} should be expected for a IIIa (R′ = H) structure.

As can be seen from Fig. 1, only one sharp N–H stretching band appeared at this frequency range, well separated from the characteristic N–H (NH_3^+) broad band at 3200–2600 cm^{-1}. However, the sulfonamide S–O (SO_2) stretching bands appear around 1335 (asymmetric) and 1175 (symmetric) cm^{-1}. The main absorptions in this region for I, IIa, and IIb



III: R′ = aryl IV: R′ = alkyl V: R′ = $C_6H_4NO_2$, R = alkyl, aryl; R′ = alkyl, aryl, R = *tert*-butyl

[4] Perkin-Elmer model 180.
[5] Finnigan model 1015.



IIIa

were at 1175 (asymmetric) and 1050 (symmetric) cm^{-1}, which are typical of sulfonic acid salts.

Mass Spectral Analysis—The mass spectra of the sodium anilinomethanesulfonates (I) and their anilinium (IIa) and *p*-toluidinium (IIb) derivatives (Tables I–III) are consistent with the fragmentation pattern shown in Scheme IV. This pattern provides additional support for the anilinium salts *versus* the sulfonamide structure for two reasons: (*a*) the fragments found in the mass spectra of the anilinium (IIa) and *p*-toluidinium (IIb) derivatives were similar to those found in the mass spectra of the parent anilinomethanesulfonates; and (*b*) no fragments corresponding to the mass of the sulfonamides were apparent.

Some characteristics of these mass spectra should be mentioned.

1. The similarity of the mass spectra of I and II together with the lack of the parent peak, as would be expected for any salt (12), justifies a common fragmentation pattern for all three types of compounds.

2. The abundance of the Schiff base peaks (A and B), the cationic aniline peaks (E), and the characteristic SO_2 and SO peaks suggest successive or alternative fragmentations through C–S and N–C cleavages, followed by hydrogen losses.

3. The substituted phenyl fragments (C) may rearrange to other structures in accordance with the patterns for substituted aromatic compounds (13), as in the case of *p*-toluidinomethanesulfonate where peaks corresponding to the tropylium and cyclopentadienyl cations appear with 100 and 34% frequency, respectively.

4. For the halogen-substituted compounds, important fragments arise from the cleavage of the halogen atom from the aromatic ring, followed by decomposition of the latter. This pattern can be seen in Table II for the anilinium *p*-bromoanilinomethanesulfonate, for which the base peak corresponds to the cyclopentadienyl cation.

5. For the methoxy-substituted compounds, important fragments are found corresponding to CH_3–O cleavage, typical of aromatic ethers (14). That is, the base peak for the *p*-methoxyanilinomethanesulfonate is the $O\text{-}C_6H_5\text{-}N{=}CH_2$ fragment.

The mass spectra of the characteristic derivatives taken at tempera-

Table I—Mass Spectra of the Substituted Sodium Anilinomethanesulfonates

Fragment	Substituent						
	H	*p*-CH_3	*p*-CH_3O[a]	*o*-Cl	*m*-Cl	*p*-Cl	*p*-Br
A	11	17	2	95	35	48	69
B	2	1	1	1	4	3	1
C	100	100	5	40	55	50	38
D	57	50	90	100	100	100	100
SO_2	25	30	22	58	28	21	38
SO	11	10	10	15	6	5	14

[a] The base peak corresponds to the *m/z* 120 fragment.

Table II—Mass Spectra of Substituted Anilinium Anilinomethanesulfonates

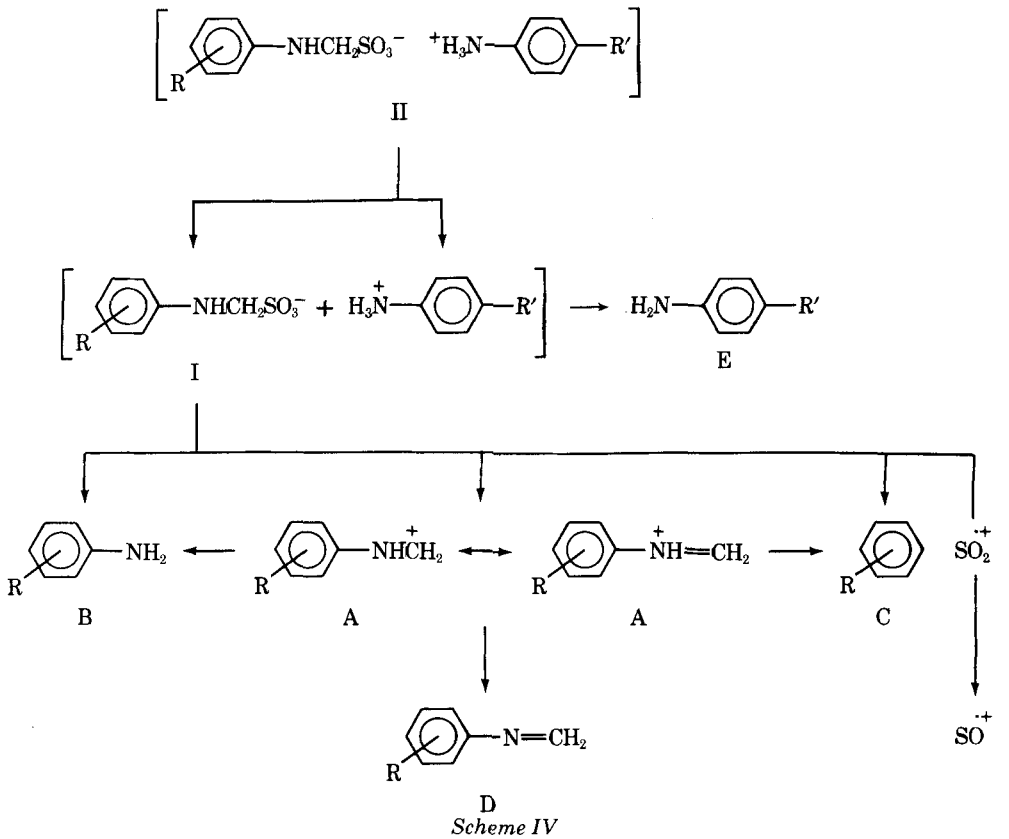
Fragment	Substituent						
	H	*p*-CH_3	*p*-CH_3O	*o*-Cl	*m*-Cl	*p*-Cl	*p*-Br[a]
A	28	7	65	5	10	15	7
B	100[b]	(100)[c]	87	100	100	100	49
C	23	58	1	2	3	10	3
D	4	56	75	5	4	18	7
E	100[b]	69	100	58	17	23	36
SO_2	25	40	41	51	13	10	37
SO	14	10	11	16	2	2	15

[a] Base peak corresponds to the cyclopentadienyl fragment (*m/z* 56). [b] Fragments B and E are indistinguishable. [c] Corresponds to (M − 1).

Table III—Mass Spectra of Substituted *p*-Toluidinium Anilinomethanesulfonates

Fragment	Substituent						
	H	*p*-CH_3	*p*-CH_3O[a]	*o*-Cl	*m*-Cl	*p*-Cl	*p*-Br
A	100	7	5	4	11	21	26
B	69	100[b]	52	100	100	67	25
C	15	64	90[c]	2	16	34	14
D	9	61	45	5	27	60	38
E	78	100[b]	90[c]	58	80	(100)[d]	(100)[d]
SO_2	20	4	50	67	61	49	42

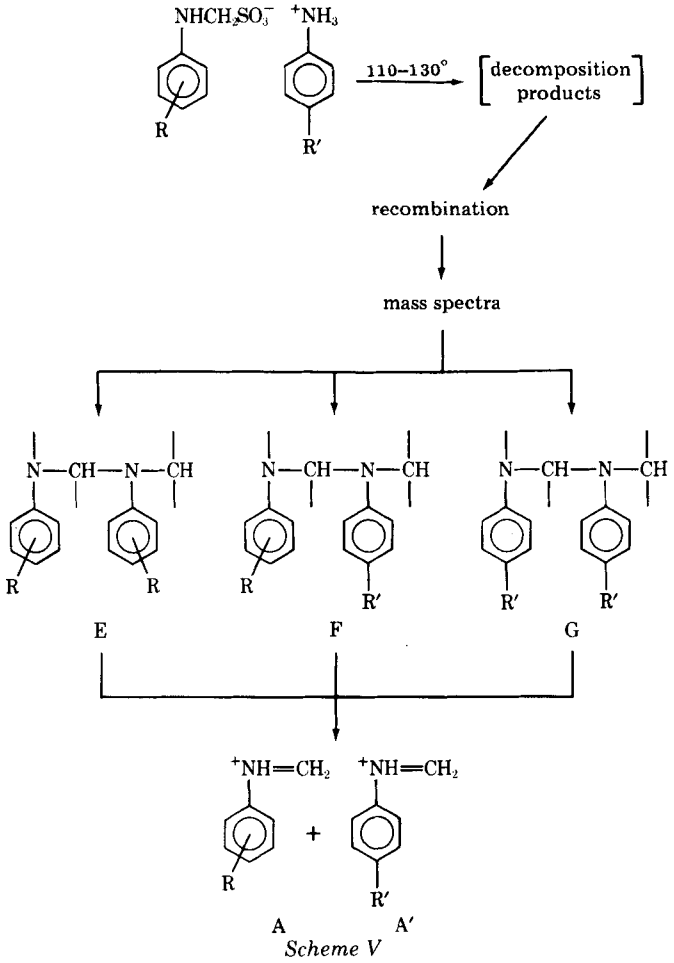
[a] Base peak corresponds to ($C_6H_5{}^+NH{=}CH_2$). [b] Fragments B and E are indistinguishable. [c] Fragments C and E are indistinguishable. [d] Corresponds to (M − 1).



Scheme IV

Table IV—Additional Fragments Originating from Polymer Formation

Compound	Fragment A′ Relative Intensity	Fragment A′ *m/z*	Fragment G Relative Intensity	Fragment G *m/z*	Fragment F Relative Intensity	Fragment F *m/z*	Fragment E Relative Intensity	Fragment E *m/z*	Sample Temperature	Melting Point
II*a*	29	106	41	207	G		G		130°	120°
p-CH_3·II*a*	100	106	11	207	15	221	8	236	170°	122°
m-^{35}Cl·II*a*	20	106	30	207	19	242	4	276	130°	119°
II*b*	26	121	11	207	48	221	41	236	120°	124°
p-CH_3O·II*b*	15	126	15	236	20	252	18	268	150°	134°



Scheme V

tures near their melting points (110–130°) showed significant amounts of higher molecular weight fragments. These fragments arise from dimers formed by recombination of the decomposition products of the initial compounds. The corresponding data are shown in Table IV, and the probable products are shown in Scheme V.

CONCLUSIONS

The formation of the characteristic anilinium and *p*-toluidinium derivatives from the parent anilinomethanesulfonates displaces the water molecule of crystallization of the latter, as may be seen from elemental and IR analyses. This displacement is due to the exchange of sodium by the anilinium or *p*-toluidinium counterion. These derivatives are studied more easily than the parent compounds by mass spectra due to their lower melting points. Thus, the mass spectra must be monitored at low temperatures since polymerization occurs in the melting range of these derivatives, leading to the detection of dimer fractions and unexpected Schiff bases. This polymerization did not occur in the ionization chamber since there was no significant difference in the relative intensity of the dimer fragments when the initial compounds were monitored at different temperatures above the melting points.

The experimental method used in the present study together with the elemental, IR, and mass spectral analyses demonstrate the salt structure of V and furnishes new arguments for the salt structure of these compounds as opposed to the sulfonamide structure suggested previously (11).

The easy synthesis, low melting point, and unambiguous IR spectra suggest that these compounds can be used advantageously as characteristic derivatives for anilinomethanesulfonates.

Preliminary data[6] obtained by X-ray crystallography show that the distance between O–N ($SO_3^-H_3N^+$) is ~2.8 Å, which indicates that no covalent bonds are present in the characteristic derivatives II*a* and II*b*.

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