Relationship between Acid Dissociaiton Constants of N_1-Arylsulfanilamides and the Hammett Equation*

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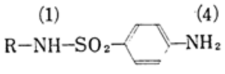
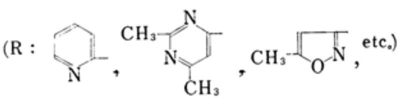
It has been known that there are close and important relationships between acid dissociation constants of sulfa drugs and such chemotherapeutic properties as bacteriostatic activity[1], absorption[2], excretion[2], and so on. The general formula of the drugs is as follows:





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* Presented in part at the Symposium on the Electronic States of the Molecule, Sapporo, August, 1960, and in part at the Symposium on the Mechanism of Organic Reactions, Sendai, October, 1961.

[1] P H. Bell and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **64**, 295 (1942).

[2] L. S. Schanker, "Annual Review of Pharmacology", Vol. I, Annual Reviews. Inc. California (1961), p. 29.

where R are usually heterocyclic substituents.

Therefore, it seems very important to investigate in detail a effect of the substituent R on the acid dissociation constant. In the case of heterocyclic compounds, a quantitative investigation of the effect would involve various, complicated problems. On the other hand, in the case of N_1-arylsulfanilamides (R: Ar; $ArNHSO_2C_6H_4NH_2$), such an investigation could be carried out by applying the Hammett equation (Eq. 1).

$$\log (k/k_0) = \rho \sigma \qquad (1)$$

In this equation k and k_0 are equilibrium (or rate) constants for a meta or para-substituted and for the unsubstituted aromatic compounds respectively. σ is the substituent constant, which depends solely on the substituent, and ρ is the reaction constant, which depends on the specific reaction. A different substituent constant, σ^-, for a para electron-attracting group has been used on dissociations (or reactions) of anilines and phenols. Little examination of dissociation of anilides, however, has been made so it is not clear whether or not σ^{-} [3] should be used with the dissociation of sulfanilamides which belong to the anilides[4]. The purpose of this paper is to clear up this point and to make a quantitative examination of a relationship between the acid dissociation constants of N_1-arylsulfanilamides and the Hammett equation.

Experimental

Materials.—N_1-Arylsulfanilamides were prepared by known procedures[5] and were purified by repeated recrystallizations from aqueous alcohol.

Dissociation Constant Determination.—Bell and Roblin[1] have reported that all the sulfanilamides used in their study, except for the very acidic ones, are in the "non-zwitter ion" form. Accordingly, acid dissociation of the sulfanilamides used here can be expressed by Eq. 2:

$$\underset{BH^+}{Ar\cdot NH\cdot SO_2C_6H_4NH_2} + H_2O \rightleftharpoons \underset{B}{Ar\cdot N^-\cdot SO_2C_6H_4NH_2} + H_3O^+ \qquad (2)$$

The acid dissociation constant, K_{NH}[6], can be given by Eq. 3:

$$K_{NH} = [Ar\cdot N^-\cdot SO_2C_6H_4NH_2][H_3O^+]/ Ar\cdot NH\cdot SO_2C_6H_4NH_2] = [B][H_3O^+]/[BH^+] \qquad (3)$$

Equation 4 can be obtained easily by applying Lanbert and Beer's law to Eq. 3:

$$pK_{NH} = pH - \log \frac{E_{BH^+} - E_{obs}}{E_{obs} - E_B} \qquad (4)$$

where E_{BH^+}, E_B and E_{obs} are optical densities of BH^+, B, and a mixture at a given pH, in the same concentration at a wavelength. Therefore, we can accurately determine pK_{NH} ($-\log K_{NH}$) values by the spectrophotometric method. The ultraviolet spectra of N_1-phenylsulfanilamide and determination of its pK_{NH} value by applying Eq. 4 are shown in Figs. 1 and 2 as typical examples.

A stock solution (2 cc.) of sulfanilamides in an aqueous 0.001 N sodium hydroxide solution or in

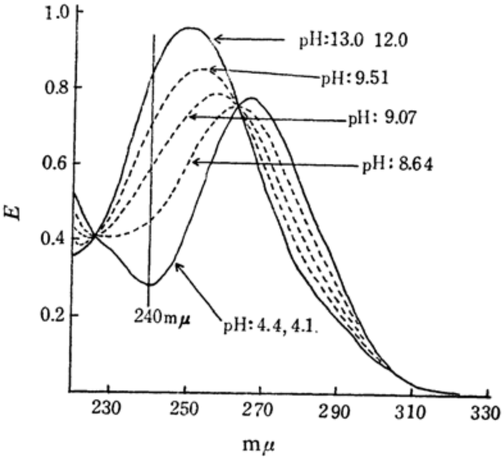

Fig. 1. Ultraviolet spectra of N_1-phenylsulfanilamide at various pH in 4.74×10^{-5} M solution.

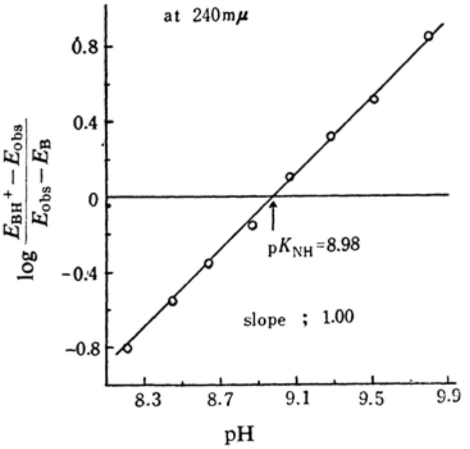

Fig. 2. Determination of the pK_{NH} value of N_1-phenylsulfanilamide at 240 mμ: The mean value of pK_{NH} values at 240, 243, 246 and 249 mμ, is given to be 8.97.

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[3] This constant, σ^-, is the same as Jaffé's σ^*[4].

[4] H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

[5] A. E. Senear et al., *J. Org. Chem.*, **11**, 378 (1946); H. Kaplan and G. W. Leubner, *J. Am. Chem. Soc.*, **67**, 1076 (1945); J. H. Gorrin, *J. Chem. Soc.*, **1945**, 734.

[6] There is another dissociation constant of the sulfanilamides, $K_{NH_3^+}$, as is shown in the following equations:

$$ArNHSO_2\cdot C_6H_4\cdot NH_3^+ + H_2O \rightleftharpoons ArNHSO_2\cdot C_6H_4\cdot NH_2 + H_3O^+$$

$$K_{NH_3^+} = [ArNHSO_2\cdot C_6H_4\cdot NH_2][H_3O^+]/[ArNHSO_2\cdot C_6H_4\cdot NH_3^+]$$

Examination of this dissociation will appear elsewhere.

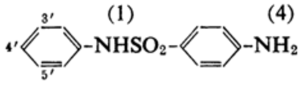
an aqueous 0.033 N ethanolamine solution[7] was diluted to 25 cc. with Britton-Robinson's universal buffer solutions[8], the ionic strength of which had been adjusted to 0.2 by adding sodium chloride. The pH values of sample solutions were measured with a Beckman model G pH meter at 25±2°C, and the spectra were recorded with a Hitachi model EPS-2 recording spectrophotometer at 27±2°C, using a 1 cm. cell. An improved spectrophotometric method[9] was applied for the pK_{NH} determination of the sulfanilamides with a SO_2NH_2 group, because they have overlapping dissociation constants (pK_{NH} and p$K_{SO_2NH_2}$).

Results and Discussion

Acid Dissociation Constants and Melting Points of Sulfanilamides. — The dissociation constants, pK_{NH}, and the melting points are listed in Table I. The elementary analysis of each compound listed here agrees well with the corresponding formula unless otherwise stated.

TABLE I. pK_{NH} AND MELTING POINTS OF N_1-ARYLSULFANILAMIDES

Substituent[a]	pK_{NH}	M. p. °C
3',5'-$(NO_2)_2$	6.19	206.0~209.0
3'-NO_2, 5'-Cl	6.92	201.0~202.0
4'-NO_2	6.97	167.0~169.0
3'-NO_2, 4'-Cl	7.16	159.0~161.0
4'-CN	7.36	176.7~177.5
4'-SO_2NH_2	7.45	119.0~121.0[b]
3',5'-Cl_2	7.54	147.0~148.5
3'-NO_2	7.67	172.5~174.0
4'-$COCH_3$	7.61	193.5~194.5
3'-SO_2NH_2	7.81	122.5~124.5[c]
3'-CN	7.83	188.0~191.5
3'-Cl	8.28	133.0~134.0
3'-$COCH_3$	8.34	187.5~189.0
4'-Cl	8.56	199.0~199.5
3'-OCH_3	8.72	162.0~164.0
H	8.97	195.0~196.5
3'-CH_3	9.05	132.0~133.0
4'-CH_3	9.25	188.5~191.0
4'-OCH_3	9.34	195.0~197.0
3'-$N(CH_3)_2$	9.01	152.0~154.0
4'-$N(CH_3)_2$	9.46	227.0~228.5 (decomp.)

a) 

b) The analysis fits the formula $C_{12}H_{13}O_4 \cdot N_3S_2 \cdot {}^1/_2H_2O$

c) The formula $C_{12}H_{13}O_4N_3S_2 \cdot {}^1/_2C_2H_5OH$ was indicated by analysis.

Substituent Constants (σ and σ⁻). — Since Jaffé's[4] evaluation of normal substituent constants (σ values), they have been re-evaluated by McDaniel, and Brown[11] and by Bekkum et al.[12] We have examined their papers and have selected McDaniel's σ values[11] except for the *m*- and *p*-substituents of SO_2NH_2 and NMe_2, because McDaniel's values have been evaluated from dissociation constants of substituted benzoic acids and so seem to be most reliable and reasonable. It seems to us that McDaniel made a mistake in evaluating the σ values of *m*- and *p*-SO_2NH_2, so Zollinger's original values[13] are adopted for them. At present, the σ values for *m*- and *p*-NMe_2 are quite complicated. McDaniel has given −0.83 for *p*-NMe_2, whereas Jaffé and Bekkum respectively, have given −0.60 and −0.266[14] for it. McDaniel's values for NMe_2 were evaluated from dissociation constants of dimethylaminobenzoic acids, which exist to some extent as the zwitterions. Jaffé's value for *p*-NMe_2 is an average of seventeen values ranging from −1.049 to −0.206. Bekkum calculated the σ value of *p*-NMe_2 from equilibria involving anilines. Therefore, Bekkum's value for *p*-NMe_2 is most reliable and his values for *p*- and *m*-NMe_2 are selected here.

As for σ⁻ values, Jaffé's estimates are adopted for *p*-NO_2, *p*-CN and *p*-$COCH_3$ and

TABLE II. SELECTED SUBSTITUENT CONSTANTS

Subst.	σ	σ⁻
p-NO_2	0.778	1.270
m-NO_2	0.710	
p-CN	0.660	1.000
m-CN	0.56	
p-SO_2NH_2	0.62	0.94
m-SO_2NH_2	0.60	
p-$COCH_3$	0.502	0.874
m-$COCH_3$	0.376	
p-Cl	0.227	
m-Cl	0.373	
p-OCH_3	−0.268	
m-OCH_3	0.115	
p-CH_3	−0.170	
m-CH_3	−0.069	
p-NMe_2	−0.266	
m-NMe_2	−0.049	

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[7] The ethanolamine solution was used for preparation of a stock solution of the compounds having a CN group, because this group is hydrolzyed easily in an alkaline solution.

[8] H. T. S. Britton and R. A. Robinson, *J. Chem. Soc.*, **1931**, 1457.

[9] M. Yoshioka, K. Hamamoto and T. Kubota, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **83**, 229 (1962).

[10] Melting points were measured on a micro hotstage and were not corrected.

[11] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958).

[12] H. V. Bekkum, P. E. Verkade and B. M. Wepster, *Rec. trav Chim.*, **78**, 815 (1959).

[13] H. Zollinger and C. Wittmer, *Helv. Chim. Acta*, **39**, 351 (1956).

[14] A σ value from equilibria involving anilines.

Zollinger's estimate is adopted for p-SO_2NH_2, because there is no other value for these groups.

Table II lists the substituent constants (σ and σ^-) we have selected.

Plot of log K_{NH} ($-$pK_{NH}) against σ (or σ^-). —Figure 3 represents a relation of the dissociation constants of sulfanilamides with the substituent constants. A good, linear relationship between log K_{NH} and σ is obtained except for p-NO_2, p-CN, p-$COCH_3$ and p-SO_2NH_2. For these electron-attracting groups, neither σ values nor σ^- values give a good fit. This result clearly indicates that neither σ nor σ^- for these groups may be applicable to the dissociation of sulfanilamides.

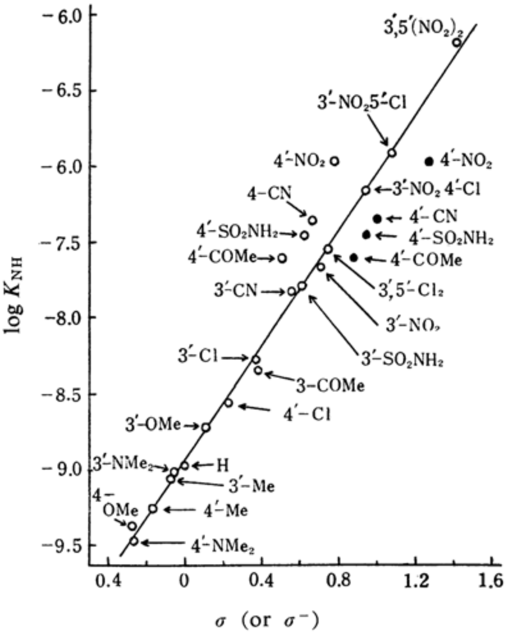


Fig. 3. Plot of log K_{NH} against substituent constants. Open circles, σ; Closed circles, σ^-

A Modified Hammett Equation. — The only other known irregular relationship of this kind for electron-attracting groups in nucleophilic reactions ($\rho > 0$) is in the case of thiophenols[4]. In electrophilic reactions ($\rho < 0$), however, a similar irregular relationship for such electron-releasing groups as p-NH_2, p-OCH_3 and p-CH_3 has been observed in many reactions and equilibria. Yukawa and Tsuno have proposed the following modified Hammett relationship (Eq. 5); this relationship has been applied successfully to many electrophilic reactions[15] ($\rho < 0$).

$$\log (k/k_0) = \rho(\sigma + r\Delta\sigma_R^+)$$
$$\Delta\sigma_R^+ \equiv \sigma^+_{\text{Brown and Okamoto}} - \sigma \qquad (5)$$

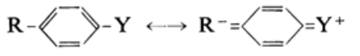
where r is a reaction constant describing the degree of the transition state resonance and $\Delta\sigma_R^+$ is a substituent constant suggesting the resonating capacity of an electron-releasing substituent at the para-position

A similar modification could be made in nucleophilic reactions[16], and a modified Hammett equation can be expressed by Eq. 6 for nucleophilic reactions and equilibria ($\rho > 0$):

$$\log (k/k_0) = \rho(\sigma + r'\Delta\sigma_R^-)$$
$$\Delta\sigma_R^- \equiv \sigma^- - \sigma \qquad (6)$$

Here r' (a resonance reaction constant), $\Delta\sigma_R^-$ (a resonance substituent constant of an electron-attracting p-substituent), and σ^- for nucleophilic reactions correspond to r, $\Delta\sigma_R^+$, and σ^+ Brown and Okamoto respectively for electrophilic reactions.

This modified equation (Eq. 6) may be connected with mesomeric para interactions in nucleophilic reactions (or equilibria), as is shown in the following limiting structures:



R: NO_2, CN, etc. Y: NH_2, SH, etc.

Consequently, Eq. 6. can be applied to the acid dissociation of sulfanilamides. In this case, the ρ value should be calculated only from the data of the m-substituted sulfanilamides. However, the data for such p-substituents as CH_3O, CH_3 and Cl may be used also, for in these groups the mesomeric para interactions are very weak for the sulfanilamides discussed here. On the other hand, the data for such substituents as m-SO_2NH_2, m-NMe_2 and p-NMe_2 should be excluded from the calculation of the ρ value, because σ values for these groups[17] have not been determined definitely and are less reliable than for other groups. Thus, the ρ value was calculated by means of the least square method, using the data for m-substituents of NO_2, CN, and CH_3CO, m- and p-substituents of Cl, CH_3, and CH_3O and H. The calculated values of ρ, log $K_{0,NH}$, S[18], and the correlation

TABLE III. $\Delta\sigma_R^-$ VALUES

Subst.	$\Delta\sigma_R^- \equiv \sigma^- - \sigma$
p-NO_2	0.492
p-CN	0.340
p-SO_2NH_2	0.32
p-$COCH_3$	0.372

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[15] Y. Yukawa and Y. Tsuno, This Bulletin, 32, 971 (1959).

[16] Y. Yukawa and Y. Tsuno, "Progress in Organic Reaction Mechanisms", Vol. I, Maki-shoten, Tokyo (1958), p. 1 (in Japanese).

[17] It is worth noting that the selected values for these groups in Table II give a good fit, as is shown clearly in Fig. 3.

[18] The standard deviation of experimental results from the regression line.

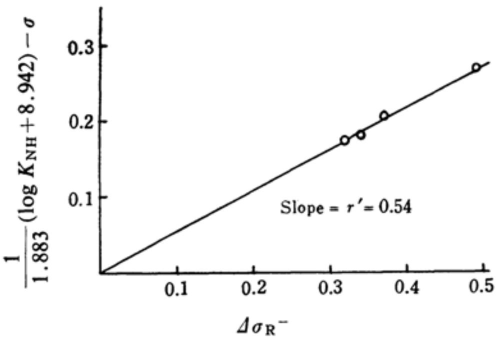

Fig. 4. Determination of r' for the dissociation of N_1-arylsulfanilamides.

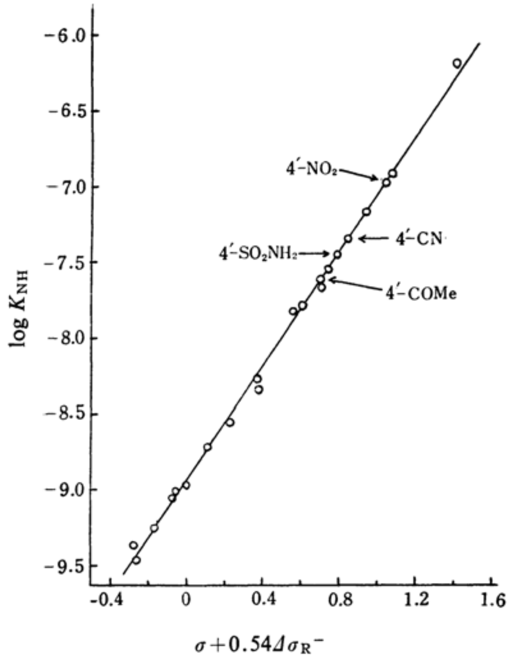

Fig. 5. Correlation of the dissociation of N_1-arylsulfanilamides with the modified Hammett equation.

coefficient are 1.883, −8.942, 0.07 and 0.998 respectively. In Table III are given the $\Delta\sigma_R^-$ values calculated from the substituents constants listed in Table II. From the plot of $[(1/\rho)\log(K_{NH}/K_{0,NH})-\sigma]$ against $\Delta\sigma_R^-$, as shown in Fig. 4, r' is given as 0.54. As is seen in Fig. 5, the acid dissociation of N_1-arylsulfanilamides is expressed well by Eq. 7:

$$\log K_{NH}=1.883(\sigma+0.54\ \Delta\sigma_R^-)-8.942 \qquad (7)$$

Dissociation of *N*-Arylbenzenesulfonamides ($ArNHSO_2C_6H_5$). — Willi[19] has reported a relationship between dissociation constants of *N*-arylbenzenesulfonamides and the Hammett equation. He has concluded that σ^- should be applied for the electron-attracting groups at the para-position in the case of these sulfonamides. These compounds have a –NH– group of the same type as that of the N_1-arylsulfanilamides discussed above, so the modified Hammett equation (Eq. 6) may be applied also to the dissociation of *N*-arylbenzenesulfonamides. Willi's data were treated as in the case of sulfanilamides. The σ values[12] selected for p-COO⁻, and p-NH_2 are 0.120 and −0.423, and the σ^- value for p-COO⁻ is 0.367[20]. The ρ value, $\log K_0$, S[18], and the correlation coefficient are calculated to be 1.833, −8.285, 0.059 and 0.998 respectively, using the data for m-NO_2, p-Cl, H, p-CH_3, p-OCH_3 and p-NH_2. From Fig. 6, r' is given as 0.68.

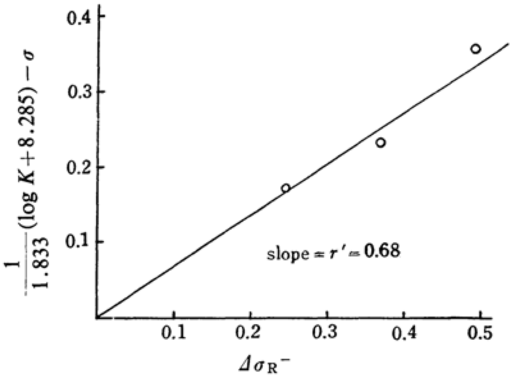

Fig. 6. Determination of r' for the dissociation of *N*-arylbenzenesulfonamide.

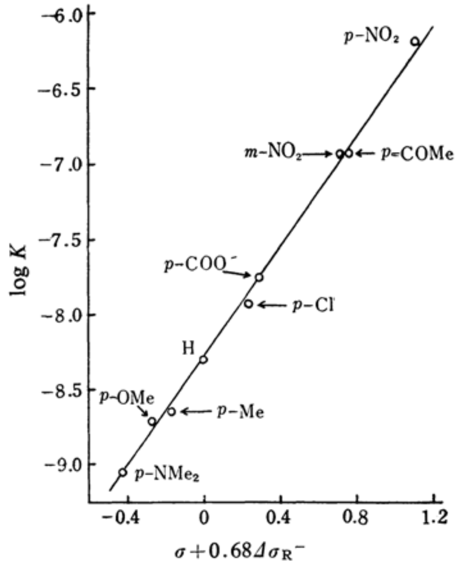

Fig. 7. Correlation of the dissociation of *N*-arylbenzenesulfonamide.

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[19] A. V. Willi, *Helv. Chim. Acta*, **39**, 46 (1959).

[20] A. V. Willi and T. F. Stocker, ibid., **38**, 1279 (1955). In this paper the σ^- value of p-COO⁻ has been given as 0.335; this is an average of the 0.367 obtained from dissociation of phenols and the 0.335 obtained from that of $ArNHSO_2C_6H_5$. Only the former value should be adopted.

Therefore, the dissociation of *N*-arylbenzenesulfonamides can be expressed well by Eq. 8, as is shown in Fig. 7:

$$\log K = 1.833(\sigma + 0.68\ \Delta\sigma_R^-) - 8.285 \qquad (8)$$

Since the number of the substituents is only eight and some of them are not reliable enough, the values of ρ and r' will be somewhat uncertain. Nevertheless, clearly the modified Hammett equation (Eq. 6) can be applied also to the dissociation of these sulfonamides.

The results obtained from the sulfanilamides ($ArNHSO_2C_6H_4NH_2$) and the benzenesulfonamides ($ArNHSO_2C_6H_5$) show that the modified Hammett relationship for nucleophilic reactions should be applied to the dissociation of $Ar-NH-SO_2-$ type anilides.

Summary

1. Acid dissociation constants of twenty-one N_1-arylsulfanilamides ($ArNHSO_2C_6H_4NH_2$) were exactly determined by the spectrophotometric method at 27±2°C and in an ionic strength of 0.2.

2. A modified Hammett relationship for nucleophilic reactions (Eq. 6) can be applied to acid dissociation of N_1-arylsulfanilamides and also of *N*-arylbenzenesulfonamides ($Ar\cdot NHSO_2C_6H_5$).

3. These results show that the modified Hammett relationship should be applied to the dissociation of $Ar-NH-SO_2-$ type anilides.

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