become necessary to prepare additional compounds of the same class. These were prepared and purified and the nitrogen determinations made in the same way as for the others.

Name	Formula	M. p., °C. (cor.)	Nitrogen, % Calcd.	Nitrogen, % Found
N Ethylpiperonylamide	$C_{10}H_{11}NO_3$	87-88	7.25	7.29
N-Propylpiperonylamide	$C_{11}H_{13}NO_3$	86-7	6.76	6.57
N-Amylpiperonylamide	$C_{13}H_{17}NO_3$	104-5	5.95	5.84
N-(*m*-Chlorophenyl)-piperonylamide	$C_{14}H_{10}ClNO_3$	110.5-112.5	5.08	4.94
N-(*o*-Bromophenyl)-piperonylamide	$C_{14}H_{10}BrNO_3$	109.5-110	4.37	4.35
N-(*m*-Bromophenyl)-piperonylamide	$C_{14}H_{10}BrNO_3$	116-117	4.37	4.30
N-(*p*-Bromophenyl)-piperonylamide	$C_{14}H_{10}BrNO_3$	222-222.5	4.37	4.34

BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE
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N^1-Acetyl-N^4-benzoyl-sulfanilamide

N^1-Acetyl-N^4-benzoyl-sulfanilamide, the simplest N^1-acyl-N^4-aracylsulfanilamide, has been prepared both by acetylation of N^4-benzoyl-sulfanilamide and by benzoylation of N^1-acetyl-sulfanilamide.

Acetylation of N^4-Benzoyl-sulfanilamide.—A solution of N^4-benzoyl-sulfanilamide (m. p. 285–286°[1]) (1.4 g.) in acetic anhydride (11 ml.) and anhydrous pyridine (6 ml.) was refluxed in a boiling water-bath for one hour, and then cooled. The solid was collected and dried; it weighed 1.14 g. (70%), m. p. 261–263°. The N^1-acetyl-N^4-benzoyl-sulfanilamide was recrystallized from ethanol; it formed needles melting at 262–263°. *Anal.* Calcd. for $C_{15}H_{14}O_4N_2S$: N, 8.80; neut. equiv., 318. Found: N, 9.01; neut. equiv., 317.

Benzoylation of N^1-Acetyl-sulfanilamide.—To a solution of 0.21 g. of N^1-acetyl-sulfanilamide[2] (m. p. 181–182°) in 2 ml. of pyridine, five drops of benzoyl chloride was added. The solution was refluxed in a boiling water-bath for one hour. It was then diluted with water and acidified, whereupon 0.29 g. of N^1-acetyl-N^4-benzoyl-sulfanilamide, m. p. 255–257°, precipitated. After crystallization from ethanol, it melted at 261–262° alone or when mixed with the product obtained by the first method.

The N^1,N^4-dibenzoyl-sulfanilamide has also been prepared by refluxing either sulfanilamide or N^4-benzoyl-sulfanilamide with excess of benzoyl chloride in the presence of pyridine for one hour. The mixture was then diluted with about ten times its volume of ethanol and allowed to stand in the icebox. The solid was recrystallized from ethanol in which it is only slightly soluble. The m. p. of the pure product was found to be 260° (with decomposition).[3] Yields in both cases were 70%. *Anal.* Calcd. for $C_{20}H_{16}O_4N_2S$: N, 7.37. Found: N, 7.57.

Thanks are due to Dr. T. S. Ma, University of Chicago, for the micro-analyses.

NATIONAL RESEARCH INSTITUTE OF CHEMISTRY
ACADEMIA SINICA, KUNMING, CHINA CHIEN-PEN LO[4]
LUCY JU-YUNG CHU

RECEIVED JANUARY 11, 1944

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[1] Miller, Rock and Moore, THIS JOURNAL, **61**, 1199 (1939), reported the m. p. as 280°.

[2] Crossley, Northey and Hultquist, *ibid.*, **61**, 2591 (1939); Huang, Lo and Chu, *J. Chinese Chem. Soc.*, **9**, 63 (1942).

[3] The m. p. of N^1,N^4-dibenzoyl-sulfanilamide has been reported as 268–270° by Dewing, Gray, Platt and Stephenson, *J. Chem. Soc.*, 239 (1942), and as 252° (dec.) by Siebenmann and Schnitzer, THIS JOURNAL, **65**, 2126 (1943).

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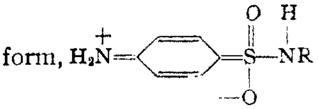
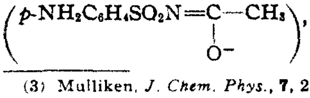
COMMUNICATIONS TO THE EDITOR

STRUCTURE AND ACTIVITY OF SULFANILAMIDES

Sir:

In a recent paper, Kumler and Daniels[1] have suggested that the activity of sulfonamides may be correlated with the contribution of the resonance form,  (1) to the structure of the molecule. To account for the fact that the sulfonamide anion seems to be the active form of the drug, they have postulated that the contribution of the resonance structure with the separation of charge is greater in the anion than in the undissociated molecule. *A priori*, one would be inclined to the contrary conclusion, and we believe the spectral evidence[2] confirms this interpretation.

High intensity ultraviolet absorption spectra are due to transitions from the neutral ground state of the molecule to an ionic excited state.[3] An increase in the number or contribution of ionic resonance structures stabilizes the excited state, *i. e.*, decreases its energy relative to that of the ground state, and hence shifts the maximum of the absorption toward larger wave lengths. Consequently, the fact that the maximum absorption of sulfanilamide in neutral solution is at 2600 Å., whereas that in basic solution is at 2500 Å., indicates that ionic resonance forms contribute *less* to the anion than they do to the undissociated molecule.

The Kumler and Daniels theory also does not explain the low activity of sulfanilylurea and 3-sulfanilamido-1,2,4-triazole. Resonance structures similar to those written for these molecules could be written for N^1-acetylsulfanilamide,  $\left(p\text{-}NH_2C_6H_4SO_2N{=}\underset{\displaystyle O^-}{\overset{}{C}}{-}CH_3\right)$, for sulfadiazine,

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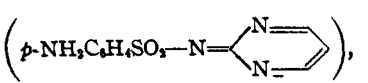
[1] Kumler and Daniels, THIS JOURNAL, **65**, 2190 (1943).

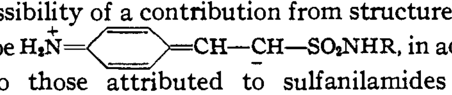
[2] Kumler and Strait, *ibid.*, **65**, 2349 (1943).

[3] Mulliken, *J. Chem. Phys.*, **7**, 20 (1939); **7**, 121 (1939); **7**, 339 (1939); O'Shaughnessy and Rodebush, THIS JOURNAL, **62**, 2906 (1940).



, and for many other active sulfanilamides. It should be observed that Bell and Roblin[4] originally suggested that the *individual anions* in more acidic sulfanilamides such as sulfadiazine, *sulfanilylurea,* and *3-sulfanilamido-1,2,4-triazole* are less active than sulfanilamide anions because of the decrease in negative character of the —SO$_2$ group, but that this effect is counteracted *by a greater number* of anions.[5]

Simple vinylogs of sulfanilamide such as p-NH$_2$C$_6$H$_4$CH=CH—SO$_2$NHR have occupied the attention of one of us for some time. These compounds are now of especial interest since the contribution of resonance structures with a coplanar amino group should be appreciable due to the possibility of a contribution from structures of the type



, in addition to those attributed to sulfanilamides by Kumler and Daniels. If, as Kumler and Daniels suggest, the sulfonamide group is significant for activity only insofar as it affects the amino group, these vinylogs should be active. Up to now only one compound of this type has been tested. 2-p-Aminophenylethene-1-sulfonamide (R = H) appears to be practically inactive *in vitro.*

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(4) Bell and Roblin, This Journal, **64**, 2905 (1942).

(5) Kumler and Daniels attribute the low activity of very acidic sulfanilamides to the impenetrability of the cell wall toward anions, as originally suggested by Cowles, *Yale J. Biol. Med.*, **14**, 599 (1942), rather than to the concentration effects postulated by Bell and Roblin.

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Received January 3, 1944

AN AZEOTROPE IN THE SYSTEM *n*-BUTANE-METHYL BROMIDE

Sir:

In analyzing the products of reactions of mixtures containing butanes, methyl bromide, and aluminum bromide,[1] a successful procedure has been to remove excess methyl bromide from the volatile fraction by reaction with ethanolamine and to determine the paraffin hydrocarbons remaining by low temperature micro-fractionation. In one such experiment, where there was poor contact between the halide and amine, the distillation showed no *n*-butane (b. p. −0.6°), but did give a methyl bromide flat (b. p. 3.5°[2]), and in addition a puzzling fraction boiling at approximately −5° (atm. pressure).

The only possibilities for this −5° fraction would be unsaturates (butadiene, b. p. −4.8°; isobutene, b. p. −6.6°; butene-1, b. p. −6.1°) and methylamine (b. p. −6.5°), although the former are very unlikely because they all are polymerized by and form stable complexes with aluminum bromide, and the latter could come only from decomposition of the ethanolamine, which is extremely improbable.

The distillate was shaken with 96% sulfuric acid at room temperature for two days and refractionated. It showed the same distillation characteristics as before, with the exception of a slight diminution of the methyl bromide fraction, which was to be expected.

Sulfuric acid will absorb unsaturates and amines readily, and these possibilities are therefore eliminated. The only hypothesis that will fit the facts is that *n*-butane and methyl bromide form a minimum boiling mixture. Indeed, when the product reacted with excess fresh ethanolamine and was refractionated, the flat at −5° disappeared and the expected *n*-butane fraction appeared, in accord with the hypothesis.

To determine the properties of the azeotrope, a synthetic mixture of 49.1 mole % of *n*-butane and 50.9 mole % of methyl bromide was prepared and fractionated in a Podbielniak micro-precision type R column[3] with 3.0 mm. unpacked inner bore, manually operated, the pressure being regulated at 760 mm. (cor.). The distillation curve is shown below. Each mm. of distillate corresponds to 1.85×10^{-4} mole at 26°, the temperature of the vapor receiving bulb in this case, and the thermocouple-galvanometer system gives a deflection of almost exactly 2 per deg. (R, $t < 0°$; L, $t > 0°$) in the range −15 to 15°.

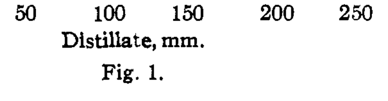

Fig. 1.

From the distillation plot, it is apparent that the azeotrope boils at −4.4°. A material balance suffices to fix its composition at 58.1 ± 0.5 mole % *n*-butane.

A detailed study of the vapor–liquid equilibrium in the above system is now in progress.

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Received March 6, 1944

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(1) These experiments are to be presented shortly for publication This Journal.

in (2) The value 4.6° in the "Handbook of Chemistry and Physics," 25th Edition, Chemical Rubber Publishing Co., Cleveland, Ohio, p. 880, is in error. See Egan and Kemp, This Journal, **60**, 2097 (1938).

(3) Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 177 (1931); **5**, 119 (1933).