4. The viscosities of dilute solutions of amino acids of long dipole moments increase with the length of the hydrocarbon chain, according to the equation $(\eta/\eta_0 - 1) = (0.052 + 0.10 \times n_{CH_2})\ C = 2.5\ K\varphi$, where $\varphi$ is the volume fraction occupied by the solute, $C$ its concentration per liter of solution, and $V$ its molal volume. $K$ is defined by this equation and represents deviation from the behavior of a large ideal spherical solute molecule.

5. The comparable equation for aqueous solutions of aliphatic acids and amides is $(\eta/\eta_0 - 1) = (0.035 + 0.076 \times n_{CH_2}) = 2.5\ K\varphi$.

6. Measurements upon aliphatic amides, amino acids and peptides even up to viscosities more than three times that of water are given by the equation $(\eta/\eta_0 - 1) = 2.5\ K\varphi + (2.5\ K\varphi)^{2.8}$.

7. The sodium salts of the amino acids are all more viscous than the free amino acids, behave much as do the sodium salts of aliphatic acids and have the same viscosity at the same volume fraction. The above equation holds for the salts of amino and aliphatic acids up to solutions as concentrated as 10% with $K$ equal to 2.3.

8. Those proteins which obey Poiseuille's law and are approximately spherical have roughly the same viscosity at the same volume fraction as amino acids and peptides. The higher viscosities of protein salts than of isoelectric proteins may be compared with the higher viscosity of the sodium salts of the amino acids and with the higher viscosity of the sodium salts of citric acid.

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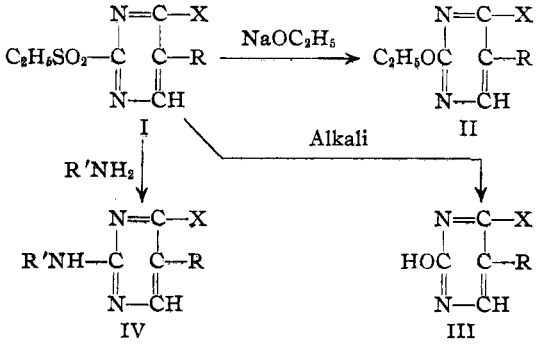
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

# Researches on Pyrimidines. CXLIX. Reactions of Some 2-Ethylsulfonylpyrimidines

BY JAMES M. SPRAGUE[1] AND TREAT B. JOHNSON

A study of the action of chlorine on some ethylmercaptopyrimidines has resulted recently in the preparation of a series of new ethylsulfonylpyrimidine compounds.[2] These are the first representatives of this type to be described in the pyrimidine literature. In an attempt to establish the structure of these interesting compounds, it was observed that an ethoxyl group was easily substituted for an ethylsulfonyl group by the action of alcoholic alkali upon 2-ethylsulfonyl-4-ethoxy-5-methylpyrimidine.[2] This has led to a more detailed study of the behavior of the ethylsulfonylpyrimidines toward such reagents as sodium ethoxide, alkali, ammonia and aniline.

It has been found that the ethylsulfonyl group when substituted in a pyrimidine molecule behaves in a manner analogous to the corresponding chloropyrimidines. Thus this group may be replaced easily by an ethoxyl group when the ethylsulfonylpyrimidine (I) is treated with a cold alcoholic solution of sodium ethoxide. Consequently, it was not possible to prepare an ethoxysulfone derivative (I, X = $OC_2H_5$) from a chlorosulfone (I, X = Cl) by reaction with sodium ethoxide; instead the ethylsulfonyl group and chlorine were simultaneously replaced by ethoxyl. 2,4-Diethoxy-5-methylpyrimidine (II, X = $OC_2H_5$, R = $CH_3$) was formed from both 2-ethylsulfonyl-4-ethoxy-5-methyl (I, X = $OC_2H_5$, R = $CH_3$) and 2-ethylsulfonyl-4-chloro-5-methylpyrimidine (I, X = Cl, R = $CH_3$). Likewise, 2,4-diethoxy-5-bromopyrimidine was obtained from 2-ethylsulfonyl-4-ethoxy-5-bromo- (I, X = $OC_2H_5$, R = Br) and from 2-ethylsulfonyl-4-chloro-5-bromopyrimidine (I, X = Cl, R = Br).

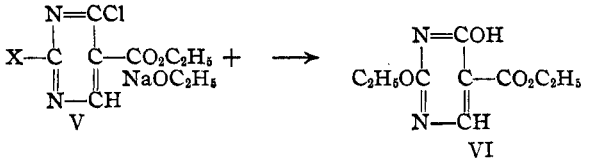



The aminosulfone, 2-ethylsulfonyl-4-amino-5-carbethoxypyrimidine (I, X = $NH_2$, R = $CO_2C_2H_5$) reacts with sodium ethoxide to give 2-ethoxy-4-amino-5-carbethoxypyrimidine (II, X = $NH_2$, R = $CO_2C_2H_5$). Also, when 2-ethylsulfonyl-4-chloro-5-carbethoxypyrimidine (V, X

(1) Sterling Professorship of Chemistry Research Assistant (1935–36).

(2) Sprague and Johnson, THIS JOURNAL, 57, 2252 (1935).

$= C_2H_5SO_2$) was allowed to react with an excess of sodium ethoxide in alcoholic solution, a 2-ethoxy-4-oxy-5-carbethoxypyrimidine (VI) was obtained. The same compound (VI) was also obtained from 2,4-dichloro-5-carbethoxypyrimidine (V, X = Cl) and an excess of sodium ethoxide. To establish the position of the ethoxy group in compound VI,



attempts were made to produce a pyrimidine of this structure (VI) by the removal of the amino group in 2-ethoxy-4-amino-5-carbethoxypyrimidine (II, X = $NH_2$, R = $CO_2C_2H_5$) by action of nitrous acid. However, these attempts were not successful. Likewise the reverse procedure, converting (VI) into 2-ethoxy-4-amino-5-carbethoxypyrimidine by proceeding through the corresponding 4-chloro compound, was not successful on the quantity of pyrimidine available for the work. A product of indefinite composition was obtained. Consequently at present the exact structure of VI is not established with certainty. However, the reaction of V (X = $C_2H_5SO_2$ or Cl) with excess sodium ethoxide is apparently similar to that reported by Hilbert and Jansen.[3] They observed the formation of 2-ethoxy-4-oxy-5-bromopyrimidine from 2,4-dichloro-5-bromopyrimidine and 2-oxy-4-ethoxypyrimidine from 2,4-dichloropyrimidine in presence of an excess of sodium ethoxide in alcohol. Thus the influence of a negative substituent in position 5 of the pyrimidine cycle is exhibited in this type of exchange. Since 2,4-dichlorocarbethoxypyrimidine (V) has the strongly negative carbethoxy group at position 5 of the pyrimidine ring the structure VI is tentatively assigned to the monoethoxy compound formed in the above reaction with sodium alcoholate.

On acid hydrolysis, the ethylsulfonyl group is replaced by hydroxyl and sulfur dioxide is evolved.[2] Under these conditions an ethoxyl (or a chlorine) group in position 4 (I, X = $OC_2H_5$) is simultaneously replaced by an hydroxyl group. However, if alkali instead of acid is used for this reaction an ethoxyl group is position 4 of the pyrimidine cycle may be left intact. Thus, by the action of alkali upon 2-ethylsulfonyl-4-ethoxypyrimidines, the corresponding 2-oxy-4-ethoxypyrimidines (III, X = $OC_2H_5$, R = H, $CH_3$ or Br) were obtained. Of these compounds Hilbert and Jansen had previously prepared 2-oxy-4-ethoxypyrimidine (III, X = $OC_2H_5$, R = H). However, by their procedure, they obtained 2-ethoxy-4-oxy-5-bromopyrimidine rather than the isomeric 2-oxy-4-ethoxy-5-bromopyrimidine (III, X = $OC_2H_5$, R = Br) which we have now obtained from the corresponding ethylsulfonylpyrimidine.

The 2-ethylsulfonyl group is also replaceable by an amino or phenylamino group through the reaction with alcoholic ammonia or aniline. As in the chloropyrimidines, this reaction with ammonia and aniline emphasizes the effect of structure upon the activity of the ethylsulfonyl group. 2 - Ethylsulfonyl - 4 - amino - 5 - carbethoxypyrimidine (I, X = $NH_2$, R = $CO_2C_2H_5$) with alcoholic ammonia gave 2,4-diamino-5-carbethoxypyrimidine. 2-Anilino-4-ethoxy-5-methylpyrimidine was obtained by the reaction of aniline on 2-ethylsulfonyl-4-ethoxy-5-methylpyrimidine. However, this ethylsulfonylpyrimidine was unreactive toward alcoholic ammonia at 110 or 130° and was recovered unchanged. This suggests that an amino ethylsulfonylpyrimidine would be obtained by the action of alcoholic ammonia on a chloroethylsulfonylpyrimidine (I, X = Cl). This was found to be true. 2-Ethylsulfonyl-4-amino-5-methylpyrimidine was obtained from the corresponding 4-chloropyrimidine (I, X = Cl, R = $CH_3$) and alcoholic ammonia at 100°.

Attempts to replace the ethylsulfonyl group by hydrogen through action of reducing agents have thus far been unsuccessful.

## Experimental Part

**2,4-Dimethoxy-5-methylpyrimidine.**—A solution of 2.2 g. of 2-ethylsulfonyl-4-chloro-5-methylpyrimidine in 30 cc. of absolute ethanol was added with cooling to a solution of 0.57 g. of sodium in 25 cc. of dry ethanol. The mixture was allowed to stand overnight at room temperature and the alcohol removed in a vacuum below 40° (bath temperature). Water was added and the reaction product extracted with petroleum ether. After drying over calcium chloride the ether extract was evaporated. The residue (1.2 g., m. p. 35.5–36.5°) was identical with an authentic sample[4] of 2,4-diethoxy-5-methylpyrimidine.

Likewise under similar conditions 2-ethylsulfonyl-4-ethoxy-5-methylpyrimidine (1.0 g.) with an alcoholic solution of sodium (0.15 g.) gave 2,4-diethoxy-5-methylpyrimidine (0.5 g.).

**2,4 - Diethoxy - 5 - bromopyrimidine.**—2 - Ethylsulfonyl-4-chloro-5-bromopyrimidine (1.2 g.) in dry ethanol

(3) Hilbert and Jansen, THIS JOURNAL, **56**, 134 (1934); **57**, 552 (1935).

(4) Johnson and Schmidt-Nickels, *ibid.*, **52**, 4514 (1930).

(20 cc.) was added to a solution of sodium (0.24 g.) in alcohol (20 cc.). On working up as described above 0.85 g. of 2,4-diethoxy-5-bromopyrimidine (m. p. 72.5–73.5°) was obtained. This gave no depression of melting point when mixed with 2,4-diethoxy-5-bromopyrimidine prepared as described by Hilbert and Jansen.[4]

Under the same conditions 0.5 g. of 2-ethylsulfonyl-4-ethoxy-5-bromopyrimidine with 0.07 g. of sodium gave 0.32 g. of the same diethoxypyrimidine.

**2-Ethoxy-4-amino-5-carbethoxypyrimidine.**—A solution of 3.9 g. of 2-ethylsulfonyl-4-amino-5-carbethoxypyrimidine in 130 cc. of dry ethanol was added to a cold solution of 0.53 g. of sodium in 30 cc. of dry ethanol. After standing overnight at room temperature the alcohol was removed in a vacuum below 40°. The solid residue was extracted thoroughly with hot benzene. On evaporation the benzene extract gave 2.1 g. of crystalline product, m. p. 104–105.5°. This may be recrystallized from an alcohol–water mixture or benzene, m. p. 105–105.5°.

*Anal.*[5] Calcd. for $C_9H_{13}O_3N_3$: C, 51.16; H, 6.21; N, 19.90. Found: C, 51.31; H, 6.47; N, 19.97.

Attempts to determine the ethoxyl content of this compound by the Vieback and Schwappach method as described by Clark[6] were unsuccessful. The values obtained ranged from 31 to 40% (calcd. 42.77) for one to five hours' duration. Likewise, 2,4-diamino-5-carbethoxypyrimidine gave low values, 16–20% (calcd. 24.74%) for duration of one to two and one-half hours.

On evaporating on a steam-bath with concentrated hydrochloric acid this pyrimidine was converted into 2-oxy-4-amino-5-carbethoxypyrimidine,[7] m. p. 276° (dec.).

*Anal.* Calcd. for $C_7H_9O_3N_3$: N, 22.95. Found: N, 22.88.

**The 2-Ethoxy-4-oxy-5-carbethoxypyrimidine.**—(1) One gram of 2-ethylsulfonyl-4-chloro-5-carbethoxypyrimidine in 22 cc. of dry ethanol was added to a solution of 0.24 g. of sodium in 15 cc. of dry ethanol with cooling. After standing at room temperature overnight, the precipitated sodium chloride was filtered off and the alcohol removed in a vacuum below 40°. The residue was dissolved in about 10 cc. of water, and, after washing with ether, acidified with acetic acid, whereupon a solid separated (m. p. 184–185°). This was recrystallized from water and separated in the form of needles; yield 0.4 g., m. p. 185–186°.

*Anal.* Calcd. for $C_9H_{12}O_4N_2$: N, 13.20; $OC_2H_5$, 42.45. Found: N, 13.14; $OC_2H_5$, 42.00.

(2) To a solution of 1.15 g. of sodium in 30 cc. of absolute ethanol, 3.6 g. of 2,4-dichloro-5-carbethoxypyrimidine[2] in 30 cc. of dry ethanol was slowly added with cooling in ice. After addition was complete, the reaction was allowed to stand overnight (sixteen hours). The alcohol was removed below 35° in a vacuum, and the residue dissolved in 25 cc. of water, filtered and extracted with ether. The ether extract, after washing with water, was dried with calcium chloride and evaporated. The residue (0.62 g., m. p. 33–35°) was recrystallized from an alcohol–water mixture, m. p. 33.5–34°. The results of a nitrogen analysis agreed with the calculated for 2,4-diethoxy-5-carbethoxypyrimidine.

*Anal.* Calcd. for $C_{11}H_{16}O_4N_2$: N, 11.66. Found: N, 11.68.

The aqueous solution on acidification with 2 cc. of acetic acid gave a precipitate which after drying weighed 2.20 g., m. p. 186°. This was recrystallized from water, m. p. 186–186.5°. It was shown by mixed melting point and analysis to be identical with the pyrimidine obtained from the chlorosulfone above.

*Anal.* Calcd. for $C_9H_{12}O_4N_2$: N, 13.20; $OC_2H_5$, 42.45. Found: N, 13.28; $OC_2H_5$, 42.34.

**2 - Oxy - 4 - ethoxypyrimidine.**—2 - Ethylsulfonyl - 4-ethoxypyrimidine (0.3 cc.) was boiled with 10% sodium hydroxide solution (1–2 cc.) until solution was complete. The solution was cooled in ice and acidified with acetic acid. The precipitate obtained here was recrystallized from water or an alcohol–ethyl acetate mixture and melted at 164–165°. A mixed melting point with a sample prepared by the method of Hilbert and Jansen (m. p. 164–165°) showed no depression. It gave the Wheeler and Johnson cytosine color test.[3]

**2-Oxy-4-ethoxy-5-bromopyrimidine.**—One-half gram of 2-ethylsulfonyl-4-ethoxy-5-bromopyrimidine was boiled with 10 cc. of 10% sodium hydroxide until solution was complete (about five minutes). The solution was then cooled and acidified with acetic acid. The dried precipitate (0.3 g.) was recrystallized from water, m. p. 234°. This gave the Wheeler and Johnson color test for cytosine.[3]

*Anal.* Calcd. for $C_6H_7O_2N_2Br$: N, 12.79; $OC_2H_5$, 20.57. Found: N, 12.78; $OC_2H_5$, 20.24.

**2-Oxy-4-ethoxy-5-methylpyrimidine.**—One gram of 2-ethylsulfonyl-4-ethoxy-5-methylpyrimidine with 30 cc. of sodium hydroxide on acidification gave 0.5 g. of product. This was recrystallized from water, m. p. 212–213°.

*Anal.* Calcd. for $C_7H_{10}O_2N_2$: N, 18.17; $OC_2H_5$, 29.23. Found: N, 18.18; $OC_2H_5$, 29.15.

**2,4 - Diamino - 5 - carbethoxypyrimidine.**[6]—2 - Ethylsulfonyl-4-amino-5-carbethoxypyrimidine (1.3 g.) was heated at 110° for one and one-half hours with 16 cc. of alcoholic ammonia, saturated at 0°. On cooling, large needle-formed crystals separated, yield 0.90 g. This was recrystallized from alcohol, m. p. 204–205°.

*Anal.* Calcd. for $C_7H_{10}O_2N_4$: N, 30.76. Found: N, 30.50.

**2-Aniline-4-ethoxy-5-methylpyrimidine.**—Freshly distilled aniline, 1.8 cc., and 1.15 g. of 2-ethylsulfonyl-4-ethoxy-5-methylpyrimidine were heated in an atmosphere of carbon dioxide for two to three hours at 130°. During the reaction a solid separated and the odor of sulfur dioxide was noticeable. At the end of the reaction, hot ethyl acetate was added and the solid filtered off. The filtrate was treated with norite and evaporated. The residue solidified and was triturated with cold 50% alcohol and filtered. This gave 0.45 g., m. p. 118–119°. However, a further quantity may be obtained from the alcoholic filtrate. This was recrystallized from alcohol–water mixture; m. p. 120.5–121°. It was found later that this reaction could be carried out at the temperature of the steam-bath.

(5) We are indebted to Dr. Frank Stodola of this Laboratory for the carbon and hydrogen analyses of this compound.

(6) Clark, *J. Assoc. Official Agr. Chem.*, **15**, 136 (1932).

(7) Wheeler and Johns, *Am. Chem. J.*, **38**, 594 (1907).

*Anal.* Calcd. for $C_{13}H_{15}ON_5$: N, 18.33; $OC_2H_5$, 19.66. Found: N, 18.14; $OC_2H_5$, 19.50.

On evaporating on a steam-bath with concentrated hydrochloric acid and making alkaline with ammonia, this compound gave 2-anilino-4-oxy-5-methoxypyrimidine, m. p. 254–255° from alcohol. This same compound was obtained for comparison by heating 2-ethylmercapto-4-oxy-5-methylpyrimidine with aniline on a steam-bath until all the ethylmercaptan was evolved. Benzene was added and the solid removed by filtering. This was recrystallized from alcohol, m. p. 254–255°.

*Anal.* Calcd. for $C_{11}H_{11}ON_3$: N, 20.88. Found: N, 20.70.

**2 - Ethylsulfonyl - 4 - amino - 5 - methylpyrimidine.**—Two grams of 2-ethylsulfonyl-4-chloro-5-methylpyrimidine was heated with 25 cc. of ethanol, saturated with dry ammonia at 0°, for two hours at 100°. The alcohol was then evaporated and the residue extracted with hot ethyl acetate. The ethyl acetate solution was concentrated to a small volume and cooled. There was obtained 0.9 g. of crystals, m. p. 128–130°. A further quantity was obtained from the filtrate (0.13 g.). This was recrystallized from ethyl acetate, m. p. 135.5–136.5°.

*Anal.* Calcd. for $C_7H_{11}O_2N_3S$: N, 20.88; S, 15.94. Found: N, 20.90; S, 16.18.

On hydrolysis[7] with hydrochloric acid this sulfone evolved sulfur dioxide. The aqueous solution on evaporation gave 5-methylcytosine hydrochloride.[8] This was recrystallized from an alcohol-concentrated hydrochloric acid solution by addition of ether, m. p. 288–290° (dec.).

*Anal.* Calcd. for $C_5H_7O_3N_3 \cdot HCl$: N, 26.00; Cl, 21.95. Found: N, 25.80; Cl, 22.21.

## Summary

In this paper is described the behavior of several 2-ethylsulfonylpyrimidines when allowed to interact with sodium alcoholate, alkali, ammonia and aniline. The ethylsulfonyl group of the pyrimidine reacts in all these changes in a similar manner as a halogen atom being easily replaced by alkoxyl, hydroxyl and amino groups.

(8) Wheeler and Johnson, *Am. Chem. J.*, **31**, 598 (1904).

NEW HAVEN, CONNECTICUT

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# Calculation of the Solubility of a Mixture of Hydrogen and Nitrogen in Water at 25° in the Pressure Range of 50 to 1000 Atmospheres

BY JACOB KIELLAND[1]

## Introduction

R. Wiebe and V. L. Gaddy[2] have recently published experimental data concerning the solubility of a 76.42:23.58 hydrogen–nitrogen mixture in water at 25°, and at high pressure. It was found that the solubility of the mixture could be calculated to within a few per cent. from the values of the pure constituents, by multiplying the mole fraction of each separate gas by its own solubility at a pressure equal to the total pressure of the mixture, and then adding these values together.

However, on examining the solubility of each one of the constituents it will be found that there is a certain amount of difference between the values observed and those calculated. As far as the nitrogen is concerned, there is a deviation of about 13% at 800 to 1000 atm., Wiebe and Gaddy's own analyses of the composition of the gas in the water phase being employed (see Table I).

## Discussion

The difference between the calculated and observed solubilities—assuming that there is no systematical error in measurement—may be explained by the existence of deviations from the fugacity rule[3] of Lewis and Randall, which is the basis of method of calculation, and states

$$\bar{f}_i = \frac{\partial f_i}{\partial n_i} = N_i f_i$$

or, in other words, that the activity coefficient of a gas is the same at constant pressure, irrespective of whether the gas occurs alone or in mixtures. According to A. R. Merz and C. W. Whittaker,[4] however, this rule does not apply to hydrogen–nitrogen mixtures at the pressures in question in the present case. From the work carried out by them, the values for $\gamma_i/\gamma_i^0$ or $\bar{f}_i/N_i f_i^0$, given in Table II, columns 2 and 3, have been taken.

In the water phase, where the action of the water molecules on the activity coefficients must be assumed to be of greater importance than the interaction of the separate gases, the latter process will not be taken into consideration. The results obtained prove this assumption to be perfectly justified.

It must be pointed out that the solubility correction for deviations from the Lewis and Randall

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(2) Wiebe and Gaddy, THIS JOURNAL, **57**, 1487 (1935).

(3) *Cf.* Newton and Dodge, *Ind. Eng. Chem.*, **27**, 578 (1935).

(4) Merz and Whittaker, THIS JOURNAL, **50**, 1522 (1928).