Chemistry of Sulfanilamidopyrimidine. Abnormal Condensation Products of 4-Amino-6-chloro-2-methoxypyrimidine with p-Nitrobenzenesulfonyl Chloride

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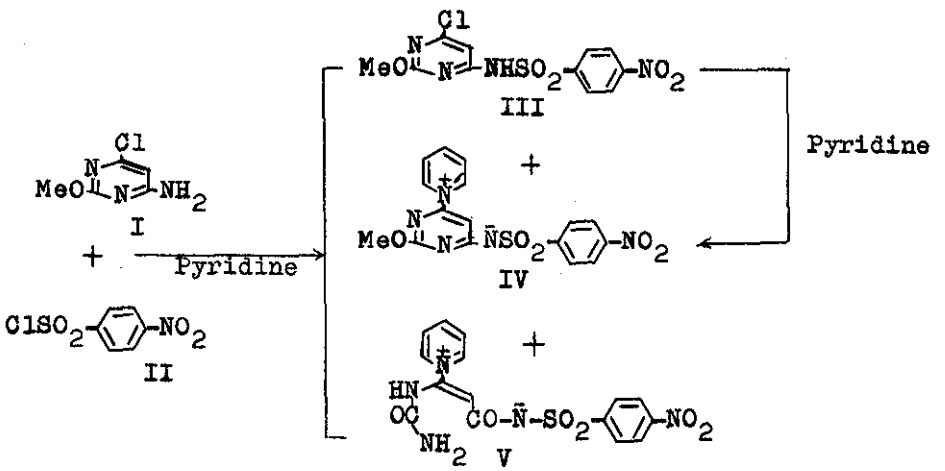
The development of Sulfadimethoxine as a therapeutically sulfa drug[1] stimulated my interest in changing the substituents on the pyrimidine ring. A number of sulfanilamides having dialkylamino- and alkoxy groups in the pyrimidine nucleus were synthesized by the different ways[2].

Among these ways, condensation of 4-amino-6-chloro-2-methoxypyrimidine(I) with p-nitrobenzenesulfonyl chloride(II) in the presence of pyridine afforded the expected 6-chloro-2-methoxy-4-(p-nitrobenzenesulfonamido)pyrimidine(III) besides two by-products, melted at 240° and at 243-245°. The structure of the above abnormal products were assigned as 1-[2-methoxy-4-(p-nitrobenzenesulfonamido)pyrimidine-6-yl]pyridinium N,N-betaine (IV) and N-(p-nitrobenzenesulfonyl)-β-ureido-β-pyridinium acrylamide N,N-betaine(V)[3].

The yields of the products III, IV, and V in this condensation based on reaction time are shown in Table from the point of the reaction time. Examination of Table shows that an increase in reaction time leads to the decrease of III and an



increase of IV, which indicates that product III was converted to IV. When III was heated in pyridine, IV was obtained in good yield.

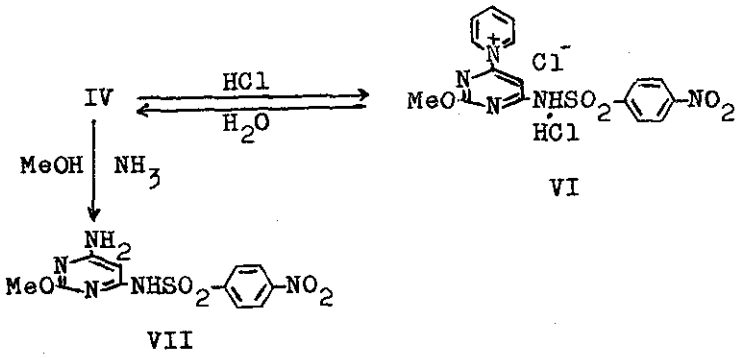
Table

The Relation Between Yield(%) of III, IV, and V and Reaction Times

Compounds / Reaction Time(hr)	III	IV	V	Total
5	21.6	7.8	25.3	54.7
15	28.4	21.7	24.4	74.5
40	15.2	35.4	19.5	70.1
80	11.4	45.0	14.6	71.0
160	3.8	58.9	8.2	70.9

To begin with, heating of the yellow compound IV, $C_{16}H_{13}N_5O_5S$ with 10% hydrochloric acid gave the hydrochloride VI, which however dissociated back to the free base IV upon addition of water. Treatment of IV with 10% aqueous sodium hydroxide gave a dark brown resinous product[4]. Heating of IV with dilute

hydrochloric acid in a sealed tube at 150° afforded p-nitrobenzenesulfonamide, pyridine and ammonium chloride, indicating the presence of pyridine and p-nitrobenzenesulfonyl moieties in the structure. The structure of the pyridinium betaine IV was further supported by the fact that the betaine of p-nitrobenzenesulfonyl-ω-pyridinium acetamide had been obtained by treatment of N-chloroacetyl-p-nitrobenzenesulfonamide with pyridine at 100-110°[5]. Reaction of IV with ammonia in methanol gave 6-amino-2-methoxy-4-(p-nitrobenzenesulfonamido)pyrimidine (VII), which was also obtained by treatment of III with ammonia.



This type of N,N-betaine has been reported in the past, along with the recent synthesis of 1-(2-substituted 6-arylsulfonamidopyrimidine-4-yl)pyridinium inner salts[6], which have the same skeleton as IV.

In order to examine the generality of the reaction, I was condensed with various sulfonyl halides in the presence of different bases at room temperature. The condensation of I with benzenesulfonyl chloride in pyridine gave the correspond-

ing normal sulfonamide without giving the betaine. The reaction of I with o-nitrobenzenesulfonyl chloride in pyridine gave the starting material. Replacement of pyridine with trimethylamine afforded the trimethylammonium N,N-betaine. The reaction of I in 4-picoline or 2,4-lutidine proceeded violently to give a resinous product. This fact is due to the removal of the acidic methyl proton of the pyridinium compound by the pyridine base, resulting in the formation of reactive cyclic enamines. The reaction of I with p-nitrobenzoyl chloride in pyridine only afforded 6-chloro-2-methoxy-4-(p-nitrobenzamido)pyrimidine. The condensation of 4-amino-6-chloro-2-ethoxyprimidine with p-nitrobenzenesulfonyl chloride in pyridine also gave the corresponding N,N-betaine. In the above reaction, the higher reaction temperature might cause the elimination of the methyl group of the methoxypyrimidine resulting in reaction products.

The pale yellow compound V, $C_{15}H_{13}N_5O_6S$, m.p. 243-245 dec., decomposed in 10% sodium hydroxide to give a brown resinous material. The ir spectrum of V shows the following absorptions: 3370(NH), 3175(amide NH), 1710(CO), 1630(amide CO), 1595(amide CO), 1122(SO_2), 1515 and 1352(NO_2), and 855 cm^{-1}(1,4-disubstituted benzene). The nmr spectrum (δ) of V in deuteriodimethylsulfoxide showed no signal in the higher field, indicating the absence of alkyl protons. In the lower field, there were observed five pyridyl protons(2:1:2) and four phenyl protons. The signal at 7.9(2H) and 11.5 ppm (1H, broad), which disappeared by addition of deuterium oxide, was assigned to the carboxamide protons of the $CONH_2$ and CONH groups of urea. Moreover, an ole-

finic proton was observed at 6.20, which was shifted to 7.15 in deuteriotrifluoroacetic acid as in the case of compound IV.

Hydrogenation of V in the presence of Adams' catalyst gave, after an uptake of 7 moles of hydrogen, an extremely soluble material in water, which was acetylated to give a resinous substance. Furthermore, treatment of V with nitrous acid gave p-nitrobenzenesulfonamide, during which an evolution of nitrogen and carbon dioxide was observed and the odor of pyridine was detected. These facts also support the structure of V.

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