No butane was obtained from either the 4-*n*-butyl or 4-isobutyl hydrocarbon, even when the mixture was heated at 75° for an additional three hours.

1,3-Dimethyl-4-ethylbenzene and Aluminum Chloride.—The hydrocarbon (30 g.) and aluminum chloride (9 g.) were heated at 130° for six hours. The following fractions were obtained at 7 mm.: (I) 2 g. 40–54°; (II) 4 g. 54–60°; (III) 12 g. 60–73°; 7 g. residue.

The trinitro derivative of III melted at 126° and did not depress the melting point of trinitro-1,3-dimethyl-4-ethylbenzene m. p. 126°, recorded value 129°.[6] Some 1,3,5 isomer may have been formed, however.

Summary

The 1,3-dimethyl-4-*s*- and 4-*t*-butylbenzenes undergo rearrangement to 1,3-dimethyl-5-*t*-butylbenzene when warmed with ferric chloride at 80°.

Some 1,3-dimethyl-5-*t*-butylbenzene is formed from the 4-isobutyl hydrocarbon, but a higher temperature is required. This is also true of the 4-*s*-butyl hydrocarbon.

Only unchanged 1,3,4-hydrocarbon was isolated from the two 1,3-dimethyl-4-propylbenzenes and 1,3-dimethyl-4-ethylbenzene, after warming them with ferric chloride at temperatures up to 150°.

(6) Smith and Kiess, THIS JOURNAL, **61**, 994 (1939).

COLUMBIA, MISSOURI RECEIVED OCTOBER 21, 1940

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Chlorination of Pyrimidine Thiocyanates[1]

BY TREAT B. JOHNSON[2] AND GYULA DE SÜTÖ-NAGY[3]

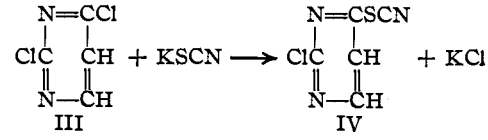
The remarkable chemotherapeutic success attained by sulfanilamide, sulfapyridine and sulfathiazole led the authors to attempt the synthesis of some sulfonamide derivatives in the pyrimidine series. That the synthesis of such constructions might open up a new route to a new type of useful therapeutical agents was postulated by one of the authors[4] (de S.-N.) already in 1938.

In a recent United States Patent issued under the title "Sulfonyl Halides"[5] is described a method for the commercial production of sulfonyl chlorides II by the action of aqueous chlorine on organic thiocyanates I.[6]

$$\underset{\text{I}}{\text{R—SCN}} + 3\text{Cl}_2 + 2\text{H}_2\text{O} \longrightarrow \text{CNCl} + 4\text{HCl} + \underset{\text{II}}{\text{R—SO}_2\text{Cl}}$$

This reaction has proved of wide application whether the organic nucleus R attached to the —SCN group in I, is substituted or unsubstituted, and whether it is alkyl, aryl, arylalkyl and alicyclic in nature. The mechanism of this reaction was discussed in a recent publication from this Laboratory.[7]

Attempts have now been made by the authors to apply this technique for the preparation of sulfonyl chlorides to a thiocyanate of the pyrimidine series. The pyrimidine chosen for preliminary investigation was 2-chloro-6-thiocyanopyrimidine IV, already described by Chi and Chen,[8] and which is prepared by interaction of 2,6-dichloropyrimidine[9] III with potassium thiocyanate. The thiocyanate IV was easily obtained in a 75% yield, and was purified for our work by crystallization from absolute alcohol and melted at 125–126°.



(1) Researches on Pyrimidines, CLXVI.

(2) This investigation was supported in part by a grant from the George Sheffield Research Fund of the Sheffield Scientific School of Yale University. This preliminary paper is presented at this time on account of the resignation of Dr. de Sütö-Nagy to accept the opportunity to undertake new work in the field of physiological chemistry. While the investigation is incomplete the authors desire to file a record at this time of their preliminary observations. The research will be continued by the senior author.

(3) Assistant Professor in the Institute of General Pathology, Royal Hungarian University of Budapest, Hungary, on sabbatical leave for 1939–1940.

(4) Experiments of C. Moncorps and O. Gunther (*Klin. Wochschr.*, 979 (1933), and those of G. de Sütö-Nagy (Kliebert: Congr. Hungarian Physiol. Soc. 1938, Ref.: *Orvosi Hetilap*, 1938, No. 38) suggest that certain pyrimidines of the cytosine type may actually stimulate the characteristic function of the reticuloendothelial system in the animal organism.

(5) "Sulfonyl Halides," by Treat B. Johnson (to Röhm and Haas Company), U. S. Patent No. 2,174,856 (September 26, 1939); *Chem. Abstr.*, **34**, 778 (1940). See also "Process of preparing sulfonyl halides and sulfonic acids from pseudothioureas," U. S. Patent No. 2,146,744 (February 14, 1939).

(6) T. B. Johnson and I. B. Douglass, THIS JOURNAL, **61**, 2548 (1939).

(7) T. B. Johnson, *Proc. Natl. Acad. Sci.*, **25**, 448 (1939).

(8) Yuoh-Fong Chi and Yun-Chwang Chen, *J. Chem. Eng.* (China), **5**, 35 (1938).

(9) S. Gabriel, *Ber.*, **38**, 1690 (1905); T. B. Johnson and G. Menge, *J. Biol. Chem.*, **2**, 114 (1906).

Technique of Chlorination of the Pyrimidine Thiocyanate.—In order to determine the reactivity of the thiocyanate IV toward chlorine, we first conducted a series of chlorination experiments of the pyrimidine suspended in (1) glacial acetic acid, (2) water, and (3) 60% methanol at room temperature. Chlorination in water was also applied at 70°. The time of chlorination was about one and one-half hours, and the stirring was continuous throughout each operation. In no one of these experiments did we observe, however, any interaction with the halogen, and the thiocyanopyrimidine IV was recovered unaltered, melting at 125–126°. The pyrimidine IV proved to be much more stable toward chlorine gas than we expected. Under similar experimental conditions a pyrimidine of the uracil type would have been converted quantitatively into an oxychloropyrimidine[10] derivative.

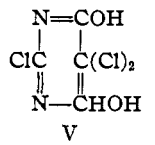
Interaction of the pyrimidine thiocyanate IV with chlorine gas was finally brought about by chlorination in dilute alcohol solution. Our procedure was as follows.

Ten grams of 2-chloro-5-thiocyanopyrimidine IV was suspended in dilute alcohol (50 cc. alcohol and 30 cc. water) and the chlorination conducted at an observed temperature of 15 to 25°. Chlorine was absorbed immediately during the first twenty minutes of treatment, and within thirty-five minutes the 2-chloro-6-thiocyanopyrimidine had completely dissolved with formation of a light green solution. The chlorination was continued for one hour and the excess of chlorine gas then expelled by passage of carbon dioxide gas for ten minutes. As nothing separated on cooling this solution in an ice-bath, it was repeatedly extracted with ether and the reaction products thereby divided into two fractions: (1) alcohol and water fraction, (2) ether extraction, and these finally analyzed as follows.

A. The Alcohol–Water Fraction.—This solution was strongly acid and gave an immediate precipitate with barium hydroxide solution, which was identified as barium sulfate. This is positive evidence of the oxidation of the —SCN grouping in the original thiocyanate IV. The solution did not respond to the Wheeler and Johnson color test for uracil.[11] After evaporating this solution to dryness in a vacuum at a bath temperature of 55°, we obtained a semi-crystalline residue weighing 5.5 g. which was strongly acidic due to the presence of sulfuric acid. This residue was soluble in dilute sodium hydroxide, and on acidifying the alkaline solution with hydrochloric acid an immediate precipitation of a crystalline substance resulted. After purification by crystallization from boiling water it melted at 228–229° to an oil with violent effervescence. This compound contained chlorine, but did not respond to a test for sulfur. It was dried for one hour in a vacuum at 100° before analysis.

Anal. Calcd. for $C_4H_3O_2N_2Cl_3$: N, 12.87; Cl, 48.90. Found: N, 13.00, 12.31, 12.82, 12.80; Cl, 48.70.

This same compound was also isolated in two other experiments when chlorination of the thiocyanate IV was applied in dilute methanol solution. This substance is decomposed by action of boiling water and undergoes transformation to an unknown substance which melts at about 295–300° with decomposition. The structural formula V is proposed provisionally to represent the constitution of this reaction product. It did not respond to the murexide test.



V

The aqueous filtrate remaining after filtering off this compound V was concentrated by heating on a steam-bath. During this treatment it deposited a fine colorless precipitate. This was soluble in hot glacial acetic acid and separated, on cooling, as a colorless, crystalline powder. This did not contain sulfur but gave a positive test for chlorine. Also, it failed to give a murexide test, and decomposed without melting when heated above 300°.[12]

Anal. Calcd. for $C_3H_3ON_2Cl$: C, 28.01; N, 23.63; H, 2.3. Found: C, 28.5, 28.4; N, 23.90, 23.88; H, 2.1.

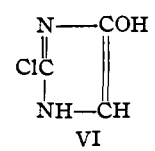
B. The Ether Fraction.—This was first dried over calcium chloride, and the ether removed in the usual way by distillation from a steam-bath. About 8 g. of a dark red oil was left behind having an unpleasant odor. It began to deposit a colorless powder immediately on standing which was identified as 5-chlorouracil. It did not melt below 300°, and responded to the Wheeler and Johnson color test for uracil.

On longer standing the oily fraction continued to deposit a solid product which was found to be identical with the material already isolated above from the alcohol–water fraction. It contained chlorine but no sulfur, and was easily purified by crystallization from boiling glacial acetic acid. It decomposed without melting above 300°. It did not give a murexide test.

Anal. Calcd. for $C_3H_3ON_2Cl$: N, 23.63. Found: N, 24.1.

The final residue of oil and solid was finely dissolved in strong hydrochloric acid and the solution evaporated to dryness on a steam-bath. We recovered 0.55 g. of crystalline material which did not melt below 300°. This proved to be a mixture of the above compound and 5-chlorouracil.

To represent the structure of this compound $C_3H_3ON_2Cl$ we propose provisionally the constitution expressed by formula VI.



VI

Acknowledgments.—The authors wish to thank Doctors Elizabeth Ballard and Joseph C. Ambelang for their assistance in making several semimicro Kjeldahl determinations.

(10) See T. B. Johnson, *Am. Chem. J.*, **40**, 19 (1908).

(11) H. L. Wheeler and T. B. Johnson, *J. Biol. Chem.*, **3**, 183 (1907).

(12) It is quite apparent from observations made during the various experiments that several factors influence the course of this chlorination operation. In one experiment we were able to identify *chlorouracil* as a product of reaction. Also unless the reaction of chlorine is continued for a given time the result is a multiplicity of secondary or intermediate products difficult to separate. Mixtures are formed melting from 180–295°.

Conclusions

It seems probable to the authors that the reaction products expressed by the provisional formulas V and VI are two representatives of a progressive series of chemical changes produced by interaction of chlorine with the thiocyanopyrimidine IV and resulting in complete destruction of the pyrimidine ring. Chlorination of 2-chloro-6-thiocyanopyrimidine is not productive of a pyrimidine sulfonchloride and apparently leads to a welter of related chemical substances difficult to separate and purify. It is not improbable that we are dealing here with a type of chemical change closely related to the reactions taking place in the well-known transformation of alloxan hydrate VII into alloxanic acid[13] VIII and hydantoin IX, respectively.

Further work will be undertaken as soon as possible to determine whether such a postulation is tenable.

(13) Biltz, Hahn and Bergius, *Ann.*, **413**, 69 (1917); Schliepper, *ibid.*, **56**, 1 (1845); Baeyer, *ibid.*, **119**, 126 (1861).

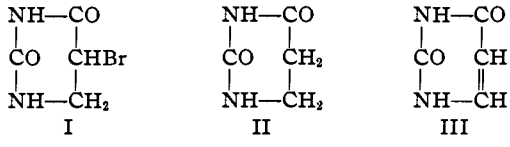
NEW HAVEN, CONNECTICUT RECEIVED AUGUST 26, 1940

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Dehydrogenation of Hydrouracil[1]

BY TREAT B. JOHNSON

During the progress of some new pyrimidine research receiving attention in this Laboratory, experimental conditions arose calling for a modification of the present procedure employed for the dehydrogenation of hydrouracil II to uracil III.



The reverse change can easily be accomplished by catalytic reduction of uracil in the presence of platinum.[2]

For successful results in biochemical experimentation dealing with seusitive oxidation changes, it was necessary to use a hydrogen acceptor which would be selective in its action and active in aqueous solution, thereby permitting of the direct oxidation of hydrouracil II in neutral solution. Two experimental techniques are available at present for the successful dehydrogenation of this pyrimidine, but both methods are indirect, involving first bromination of hydrouracil with formation of 5-bromohydrouracil I. Fischer and Roëder[3] accomplished this dehydrogenation change in their original procedure for the synthesis of uracil III by heating this brominated pyrimidine with alkali or pyridine. Gabriel[4] later succeeded in improving this technique by making the discovery that the brominated pyrimidine I dissociates quantitatively into uracil III and hydrobromic acid when heated above its melting point temperature (195°). From a biochemical point of view both of these operations are impractical, and could not be considered for the experimental program receiving our attention.

It is a well-known fact that alloxan can serve as a hydrogen acceptor under mild experimental conditions. In consequence of its easy reducibility to *alloxantine* it interacts, for example, with absolute alcohol, in the presence of sunlight, to form acetaldehyde[5]; converts hydrazobenzene to azobenzene and indigo-white to indigo blue.[6] Strecker also showed as early as 1862 that α-aminoacids are oxidized by alloxan to their corresponding aldehyde derivatives.[7] It seemed

$$CH_3CH(NH_2)COOH \longrightarrow CH_3CHO$$

probable to the author, in the light of these observations, that alloxan would meet the conditions required in our experiments and serve as a suitable oxidizing reagent for the dehydrogenation of hydrouracil II.

The author now finds that hydrouracil II is oxidized quantitatively to uracil III by digestion in aqueous solution with commercial alloxan hydrate. Partial destruction of the alloxan molecule takes place as is evidenced by the fact that both oxalic acid and urea are formed during the digestion. This pyrimidine reagent fully

(1) Researches on Pyrimidines, CLXVII.

(2) Johnson and Brown, *Proc. Natl. Acad. Sci.*, **7**, 75 (1921); Brown and Johnson, THIS JOURNAL, **45**, 2702 (1923).

(3) Fischer and Roëder, *Ber.*, **34**, 3751 (1901).

(4) Gabriel, *ibid.*, **38**, 637, 1690 (1905).

(5) Ciamician and Silber, *ibid.*, **36**, 1581 (1903).

(6) Pellizzari, *Gazz. chim. ital.*, **17**, 256 (1888).

(7) Strecker, *Ann.*, **123**, 364 (1862).