[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXXVIII. THE REDUCTION OF 2-MERCAPTO-6-CHLOROPYRIMIDINES.

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In a previous paper from this laboratory Johnson and Joyce¹ have shown that 2-mercapto-6-chloropyrimidines (IV) can be reduced easily by the action of zinc dust with formation of the corresponding 2-mercapto-pyrimidines. They prepared in this manner 2-ethylmercaptopyrimidine (I), 2-ethylmercapto-4-methylpyrimidine (II) and 2-ethylmercapto-5-ethoxypyrimidine (III). These are the only representatives known of this new class of mercaptopyrimidines. Such combinations can now be prepared easily in quantity by application of our method. In no case have we failed, thus far, to bring about a smooth reduction when we employed pyrimidine combinations containing methyl- and ethylmercapto groups in the 2-position of the pyrimidine ring. 2-Methylmercapto-6-chloropyrimidine (V) has been prepared² and we find that this undergoes reduction as smoothly as its corresponding 2-ethylmercapto compound. The yield of the reduced pyrimidine (VI), in this case, was 70% of the theoretical. A chlorine atom in position 2 also does not hinder the reduction of a halogen in the 6-position as 2,6-dichloro-5-ethoxypyrimidine is readily reduced by zinc dust to the corresponding 2-chloro-5-ethoxypyrimidine.³ We have now introduced a benzylmercapto group-
ing into position 2, and have prepared the hitherto unknown 2-benzylmercapto-6-chloropyrimidine (VIII). The latter was easily obtained by the action of phosphorus oxychloride on 2-benzylmercapto-6-oxy-pyrimidine⁴ (VII). All attempts to reduce this pyrimidine to the corresponding 2-benzylmercaptopyrimidine (IX) have so far been unsuccessful. Not only was it found to be extremely stable in the presence of zinc dust, but it was also not reduced by sodium-amalgam and zinc-amalgam. We also investigated its behavior towards hydriodic acid and found that here also the pyrimidine exhibited great stability. Owing to its weak basic properties it simply combined with hydriodic acid forming a characteristic, crystalline salt (X). This ability to form salts is a property of these mercaptochloropyrimidines which hitherto has not been emphasized by us. On warming with hydriodic acid such combinations are decomposed with evolution of mercaptans. The hydriodide of this base (X) is easily decomposed by water with dissociation into the free pyrimidine and hydriodic acid. There was no evidence of an exchange of halogens

¹ THIS JOURNAL, 37, 2151 (1915).² Wheeler and Bristol, *Am. Chem. J.*, 33, 437 (1905).³ Johnson and Joyce, *Loc. cit.*⁴ Wheeler and Liddle, *Am. Chem. J.*, 40, 554 (1908).

with production of 2-benzylmercapto-6-iodopyrimidine (XI) and hydrochloric acid.

While bases of the type of 2-methylmercaptopyrimidine (VI) resist further reduction by the action of zinc dust, on the other hand, when subjected to the action of metallic sodium in alcoholic solution they undergo characteristic changes. Not only is the ring completely saturated with hydrogen, but the pyrimidine cycle is finally ruptured and an aliphatic diamine is formed. 2-Methylmercaptopyrimidine, for example, is reduced under such conditions with production of trimethylenediamine (XII) and methylmercaptan. The yield of the diamine was equivalent to 60 per cent. of a theoretical yield showing that we have here a prac-

tical method of synthesizing aliphatic combinations of this type. Regarding the mechanism of this reaction it seems probable that the first phase of the transformation involves a complete reduction of the pyrimidine (VI), with formation of its hexahydro derivative represented by Formula XIII. This then might break down theoretically in two ways, namely, either undergo further reduction in the alkaline solution to mercaptan and the sulfur-free pyrimidine (XIV), which on hydrolysis would give formaldehyde and the diamine (XII), or the pyrimidine (XIII) undergo hydrolysis directly with production of the diamine (XII) and methylthiolformate (XV). The latter would then be saponified by the alkali present giving formic acid and methylmercaptan. Mercaptan was always recognized by its odor, but the formation of formaldehyde or formic acid was not established. The reaction may be expressed as follows:

An increase in the basicity of the pyrimidine molecule is brought about by the transformation of a 2-mercapto-6-oxypyrimidine into a 2-mercapto-6-chloropyrimidine and a 2-mercaptopyrimidine. The oxygen pyrimidines are extremely weak bases¹ and possess acid properties on account of the presence of a CO-NH grouping in their molecules. The mercaptochloropyrimidines and corresponding 2-mercaptopyrimidines, on the other hand, are insoluble in alkaline solutions. They do not contain any ionizable hydrogen and interact with acids with formation of salts. The latter are, however, unstable and easily undergo dissociation in aqueous solution. The 2-mercaptopyrimidines are also characterized by their property of forming addition products with alkyl halides. Two combinations of this type have been prepared and are represented by Formulas XVI and XVII. Both were obtained in a crystalline condition and could be crystallized from alcohol without decomposition. So far as we are aware, the corresponding 2-mercapto-6-oxypyrimidines have not been shown to form analogous

¹ Wheeler and Bristol, *Loc. cit.*

addition combinations with alkyl halides. The investigation of the behavior of pyrimidine compounds towards reducing agents will be continued.

Experimental Part.

Reduction of 2-Methylmercapto-6-chloropyrimidine with Zinc Dust. The Formation of 2-Methylmercaptopyrimidine (VI).—The 2-methylmercapto-6-chloropyrimidine, which was used in this work, was prepared according to the method of Wheeler and Bristol¹ by the action of phosphorus oxychloride on 2-methylmercapto-6-oxypyrimidine. In order to obtain the best yields of the reduced pyrimidine, it was found advisable, by experience, to work with small quantities of the chloropyrimidine at a time. Our procedure was as follows: Eighty grams of the chloropyrimidine were divided into four portions and 20 grams placed in separate flasks with 40 grams of zinc dust, 100 cc. of water and 100 cc. of alcohol. These mixtures were then boiled for one-half an hour, when the excess of zinc dust was filtered off and the alcoholic filtrates combined, and then concentrated under diminished pressure. A dark-colored oil was obtained, which was extracted with ether and dried over calcium chloride. A small amount of 2-methylmercapto-6-oxypyrimidine was identified here and was formed by partial hydrolysis of the 2-methylmercapto-6-chloropyrimidine during the reduction. After removing the ether, the oil was purified by distillation under diminished pressure and boiled at 99–100° at 14 mm. pressure. This was a colorless liquid having an odor similar to that of pyridine and quinoline. On exposure to the air the pyrimidine gradually turns light brown, but this change does not take place as readily as in the case of the corresponding 2-ethylmercaptopyrimidine previously described by Johnson and Joyce.¹ The yield is about 70% of the theoretical. This pyrimidine, as well as the 2-ethylmercaptopyrimidine, forms salts with strong acids, the hydrochloride dissolving in water without dissociation. One part of the base dissolves in about 20 parts of cold water. This aqueous solution does not give an alkaline reaction with litmus or turmeric paper. The pyrimidine is volatile with steam. Analysis:

Calc. for $\text{C}_5\text{H}_6\text{N}_2\text{S}$: N, 22.22. Found: N, 22.19, 22.02.

Index of refraction: N_D at 20° = 1.5856 (Abbe). Index of refraction of 2-ethylmercaptopyrimidine: N_D at 20° = 1.5673 (Abbe).

¹ *Loc. cit.*

Hydrochloride.—This salt was prepared by passing dry hydrochloric acid gas into an ethereal solution of the pyrimidine. It crystallized in needles which melted at 147° . Analysis:

Calc. for $C_6H_8N_2S.HCl$: N, 17.23. Found: N, 17.1, 17.00.

Hydrobromide.—This was prepared by mixing strong hydrobromic acid solution with the mercaptopyrimidine. They interacted immediately with formation of a crystalline salt. This was purified by crystallization from absolute alcohol and separated in the form of rectangular prisms melting at 187° . Analysis:

Calc. for $C_6H_8N_2S.HBr$: N, 13.52. Found: N, 13.2, 13.31.

The Addition of Methyl iodide to 2-Methylmercaptopyrimidine. 1,1-

of the pyrimidine were added 2 grams of methyl iodide and the mixture allowed to stand at room temperature overnight. When examined the next morning the mixture had solidified to a crystalline mass of needles. These were triturated with cold ether and crystallized from boiling absolute alcohol. The pyrimidine separated, on cooling, in the form of irregular, prismatic rods or needles. They melted at $146-147^{\circ}$ to a red oil. This addition product is very soluble in water. Concentrated sulfuric acid interacted with it with liberation of iodine and when the compound was treated with dilute alkali methylmercaptan was slowly evolved.

Calc. for $C_6H_8N_2SI$: N, 10.44. Found: N, 10.11, 10.36.

1,1-Methyliodo-2-ethylmercaptopyrimidine.—This pyrimidine was prepared in a manner similar to that employed for the preparation of the preceding addition product. It crystallized from absolute alcohol in needles which melted at 135° to a red oil. Analysis:

Calc. for $C_8H_{11}N_2SI$: N, 9.52. Found: N, 9.36.

The Formation of Trimethylenediamine by Reduction of 2-Ethylmercaptopyrimidine.—This mercaptopyrimidine is easily converted into trimethylenediamine by reduction with sodium and alcohol. The procedure was as follows: Ten grams of the 2-ethylmercaptopyrimidine were dissolved in 150 cc. of absolute alcohol and this solution then added slowly upon 20 grams of metallic sodium (2 molecular proportions). As the reduction proceeded the alcoholic solution assumed a dark red color and ethylmercaptan and ammonia were evolved. For complete solution of the sodium 100 cc. more of alcohol were finally added and the solution finally heated on the steam bath. After complete solution of the sodium,

air was blown through the mixture to expel as much ammonia as possible and the solution then subjected to steam distillation. The distillate containing alcohol and base were conducted into hydrochloric acid. After complete distillation the hydrochloric acid solution was evaporated to dryness, *in vacuo*, and the hydrochloride of trimethylenediamine purified by crystallization from 25% alcohol. In this manner it was easily separated from ammonium chloride. The salt crystallized in beautiful transparent prisms which melted at 242–243°. This same melting point is also to be assigned to the compound prepared by Fischer's¹ method. A mixture of the salt prepared by both methods melted at 242–243°. The yield of hydrochloride was 6.2 grams or 60% of the theoretical. Analysis:

Calc. for $C_3H_{10}N_2 \cdot 2HCl$: N, 19.04. Found: N, 19.00, 19.02.

Alkylation of 2-Thiouracil with Benzylchloride. The Formation of 2-Benzylmercapto-6-oxypyrimidine (IX) and 2-Benzylmercapto-3-benzyl-6-oxypyrimidine.—2-Benzylmercapto-6-oxypyrimidine has been described by Wheeler and Liddle,² and was prepared for our work according to their directions. We made the observation, however, that this is not the only product formed by allylation with benzyl chloride. We succeeded in isolating another derivative in small quantity, which crystallized from alcohol in colorless, flat prisms melting at 144–145° to a clear oil. The yield of this pyrimidine was about 5–10% of the theoretical and it was identified as 2-benzylmercapto-3-benzyl-6-oxypyrimidine. It was very soluble in alcohol and ether, and insoluble in water, aqueous alkali and acid solutions. Analysis:

Calc. for $C_{18}H_{16}ON_2S$: N, 9.09. Found: N, 8.8.

half grams of the above 2-benzylmercaptopyrimidine were dissolved in 100 cc. of concentrated hydrochloric acid, by warming on the steam bath, and the solution then evaporated to dryness. The residue was crystallized from boiling alcohol. On cooling, this thiopyrimidine separated in the form of plates, which melted at 231°. These gave a strong test for sulfur. Analysis:

Calc. for $C_{11}H_{10}ON_2S$: N, 12.84. Found: N, 13.00.

Desulfurization of 2-Thio-3-benzyl-6-oxypyrimidine with Formation of 2,6-Dioxy-3-benzylpyrimidine.³—One and two-tenths grams of the thiopyrimidine were digested for seven hours with 4 grams of chloro-

¹ Ber., 17, 1799 (1884).

² Am. Chem. J., 40, 554 (1908).

³ Johnson and Derby, Am. Chem. J., 40, 444 (1908).

acetic acid. The pyrimidine dissolved completely and, on cooling, the desulfurized pyrimidine separated in a crystalline condition. It crystallized from alcohol in prisms melting at $173-174^{\circ}$ as originally observed by Johnson and Derby. A mixture of our pyrimidine and the isomeric 1-benzyl-2,6-dioxypyrimidine melted at $140-155^{\circ}$.

2-Benzylmercapto-6-chloropyrimidine.—Forty-four grams of the 2-benzylmercapto-6-oxypyrimidine were mixed with 25 cc. of phosphorus oxychloride in a distilling flask and the mixture then heated in an oil bath for about 5.5 hours. The pyrimidine dissolved completely and hydrogen chloride was evolved. The excess of phosphorus oxychloride was then removed by distillation, under diminished pressure at 100° , and the thick, viscous oil remaining behind poured upon crushed ice to destroy the last traces of phosphorus halide. After extraction with ether and drying over calcium chloride the oil was then distilled under diminished pressure. It boiled at 210° at 18 mm. On cooling, this oil solidified in the form of long prisms which melted at $48-49^{\circ}$. The yield was 33 grams or 70% of the theoretical. Analysis:

Calc. for $C_{11}H_9N_2SCl$: N, 11.84. Found: N, 11.71, 11.86.

This pyrimidine is soluble in ether, alcohol and benzene. It is insoluble in water, dilute acid and alkaline solutions and is hydrolyzed by digestion with strong hydrochloric acid with formation of uracil.

Attempts to Reduce 2-Benzylmercapto-6-chloropyrimidine: Action of Zinc Dust.—Five grams of the chloropyrimidine were dissolved in a mixture of 100 cc. of alcohol and 50 cc. of water, and 15 grams of zinc dust added. After boiling for 5 hours the excess of zinc was separated by filtration and the alcohol removed by evaporation under diminished pressure. The oil remaining behind was then extracted with ether and dried over calcium chloride. On evaporating the ether, unaltered 2-benzylmercapto-6-chloropyrimidine separated in the form of needles and melted at $45-47^{\circ}$.

Action of Zinc Amalgam.—Five grams of the chloropyrimidine were dissolved in a mixture of equal volumes of water and alcohol (150 cc.) and 20 grams of amalgamated zinc suspended in the solution. This was then boiled for 4 hours and the zinc separated by filtration. On evaporating the alcohol and water under diminished pressure, we obtained an oil which finally solidified and was identified as the unaltered chloride. The same result was obtained when an attempt was made to reduce the chloropyrimidine with sodium amalgam.

The Action of Hydriodic Acid.—Nine grams of 2-benzylmercapto-6-chloropyrimidine were melted in a flask and 15 cc. of colorless hydriodic acid (b. p. 127°) added. There was an immediate reaction with evolution of heat and formation of a crystalline product. The entire mixture became solid. The odor of benzyliodide was also noticeable, indicating

a partial hydrolysis of the pyrimidine. The crystals, which were yellow, were filtered off, washed with ether and dried in a vacuum over sulfuric acid. They melted at 136° . A nitrogen determination showed that we were dealing with a hydriodic acid salt of the chloropyrimidine. The compound also gave tests for chlorine and iodine.

Calc. for $C_{11}H_9N_2SCl.HI$: N, 7.68. Found: N, 7.3, 7.26.

This salt could not be crystallized from the common solvents without dissociation. It is insoluble in ether, carbon tetrachloride and benzene, slightly soluble in acetone and very soluble in absolute alcohol. It was easily hydrolyzed by water, giving an oil which finally solidified and melted without further purification at 45° . This was identified as the original chloropyrimidine. When this was mixed with some of the chloro compound there was no lowering of the melting point. The yield of the salt was 12 grams of 84% of the theoretical.

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**STUDIES ON NITRATED PROTEINS. V. THE HYDROLYSIS OF
NITRO-FIBROIN WITH HYDROCHLORIC ACID.**

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The term "Nitro-Fibroin," as we shall apply it in this paper, is the name of a modified protein which is obtained by treatment of pure fibroin, under definite conditions, with nitric acid of specific gravity 1.12. This sulfur-free protein is very easily attacked by strong nitric acid, but the reaction is not productive of consistent results unless applied under carefully regulated conditions. We have found that, if the protein be exposed to the action of acid of the above strength for a long time and at ordinary temperature ($18-25^{\circ}$), a stage in the transformation is finally reached where practically no further action on the protein takes place. In other words, it has been our experience that a nitrated protein of quite definite constitution is formed, which is optically active and does not respond to Millon's test for tyrosine. This substance is obtained in the form of an orange-colored powder and the yield corresponds to about 70% of the weight of the original protein. The method of preparing this interesting product (nitro-fibroin) has already been described in a previous paper from this laboratory.¹

Inouye² prepared a nitrated fibroin by the action of cold nitric acid (sp. gr. 1.12) on silk fibroin and obtained after 48 hours' treatment a yield of nitroprotein corresponding to 85-90% of the weight of fibroin taken. This product was subjected to hydrolysis with dilute sulfuric

¹ Johnson, Hill and O'Hara, *THIS JOURNAL*, 37, 2170 (1915).

² *Z. physiol. Chem.*, 81, 80 (1912).