

*p*-Carboethoxy-, *p*-benzoxy-, *p*-acetoxy-carbinol chlorides do give the respective free radicals, but these were found to be too unstable to be isolated as such, and consequently could not be used for the preparation of the hydroxytriphenylmethyl.

4. From the experimental facts obtained, an explanation is derived to account for the impermanent character of these free radicals, which may also serve to explain similar results previously reported by others, namely, a tendency of the radicals towards spontaneous polymerization or isomerization, or both.

ANN ARBOR, MICHIGAN.

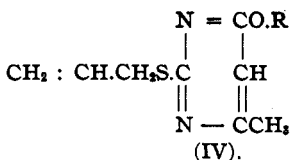
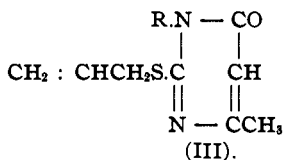
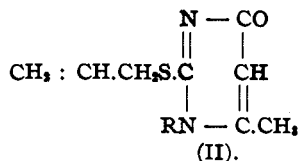
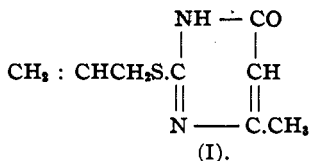
[CONTRIBUTION FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

## RESEARCHES ON PYRIMIDINES. LXXVII. THE ALKYLATION OF 2-MERCAPTOPYRIMIDINES.

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Johnson and Haggard<sup>1</sup> made the observation that, when 2-allylmercapto-4-methyl-6-oxypyrimidine (I) undergoes alkylation in alcoholic solution and in the presence of sodium ethylate, there is no tendency, apparently, for the alkyl group of the halide to substitute in position 3 of the pyrimidine ring to form a compound corresponding to Formula II. Either an imido ester combination (IV) is formed or a mixture of this with a 1-alkyl derivative as represented by Formula III. When allyl iodide was used the corresponding imido ester (IV) (R = CH<sub>2</sub>:CHCH<sub>2</sub>) was the only product formed. In other words, the sodium salt of this pyrimidine (I) exhibited an exceptional behavior towards alkyl halides, and the presence of the negative, unsaturated, allyl mercapto group in position 2 was favorable for the formation of oxygen derivatives.



In the light of these interesting results it was of especial interest to investigate the behavior on alkylation of a 2-mercaptopyrimidine containing a more negative radical than the vinyl group CH<sub>2</sub>:CH— in the com-

<sup>1</sup> THIS JOURNAL, 37, 177 (1915).

pound (I). Such a radical is the benzoyl group, which is present in the pyrimidine-2-benzoylmethylmercapto-4-methyl-6-oxypyrimidine. This compound (VIII) has already been described in a previous paper from this laboratory,<sup>1</sup> and is easily prepared by the action of bromoacetophenon on the sodium salt of 2-thio-4-methyl-6-oxypyrimidine.<sup>2</sup> The results obtained with the allylmercaptopyrimidine (I) suggested that, the more negative the group which we incorporate in place of a hydrogen in a 2-methylmercapto radical, the less tendency there will be for an alkyl halide to add to the 1-nitrogen atom of the ring and form a 1-nitrogen substituted pyrimidine. Oxygen compounds should then be the chief products of the reaction and if the specific group were sufficiently negative in character they would be the only products formed. The results which we have obtained by alkylation of this benzoylmercaptopyrimidine (VIII), and now described in this paper, are in accord with such an assumption.

Johnson and Moran<sup>3</sup> observed that the sodium salt of this pyrimidine (VIII) interacts with bromoacetophenone giving exclusively the pyrimidine (VI). It therefore reacted with this halide in a manner perfectly analogous to that of the corresponding 2-allylmercaptopyrimidine (I) when treated with allyl bromide. The allylpyrimidine (I) and methyl iodide interacted to form the 1-methylpyrimidine (III) ( $R = CH_3$ ).<sup>4</sup> Our benzoylpyrimidine (VIII) reacted in a similar manner with this halide forming 2-benzoylmethylmercapto-1,4-dimethyl-6-oxypyrimidine (VII). We obtained no evidence of the formation of the imido ester combination (XI).

Besides that of methyl iodide, we have investigated the action on the pyrimidine (VIII) of ethyl bromide and benzylchloride. The former halide interacted smoothly to form exclusively the ethoxypyrimidine represented by Formula X. This same pyrimidine was also formed when the reaction was applied in methylalcohol solution. There was no evidence of the exchange of alkyl groups with formation of the imidoester (XI). The structure of our alkylated product was established by the fact that it underwent hydrolysis with formation of 4-methyluracil (XII) and 2,5-diphenyl-1,4-dithiene.<sup>5</sup>

When we came to investigate the action of benzylchloride on the sodium salt of the pyrimidine (VIII), in ethyl alcohol solution, we were surprised to obtain very abnormal results. In all our previous work this halide has been observed to interact smoothly in such reactions. In this case, however, we obtained no evidence of the formation of a benzylpyrimidine

<sup>1</sup> Johnson and Moran, *Am. Chem. J.*, **48**, 307 (1912).

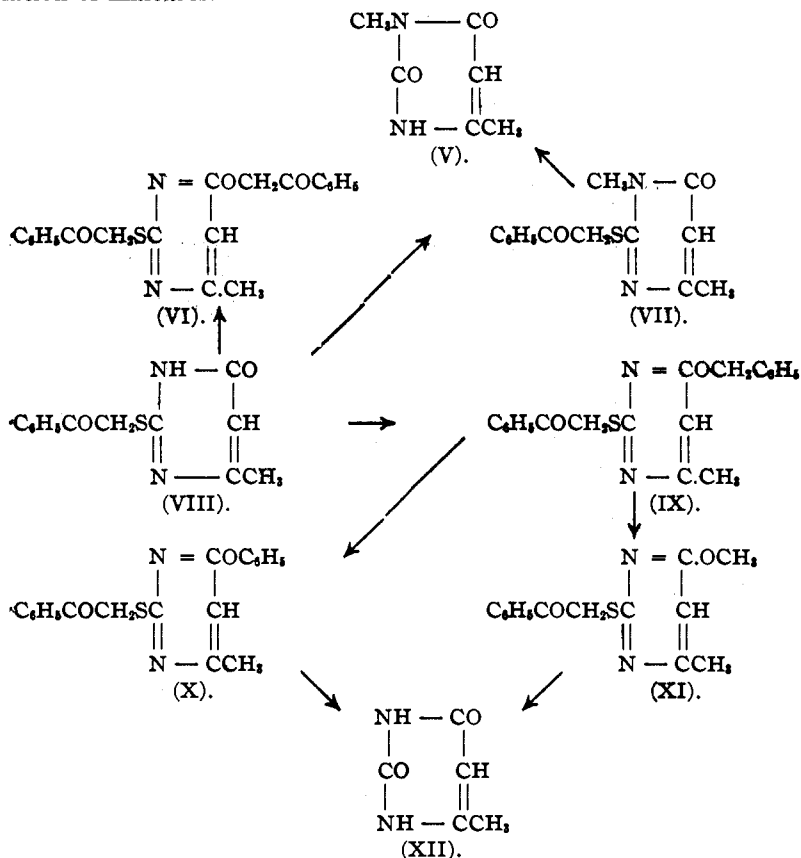
<sup>2</sup> List, *Ann.*, **236**, 3 (1886).

<sup>3</sup> *Loc. cit.*

<sup>4</sup> Johnson and Haggard, *Loc. cit.*

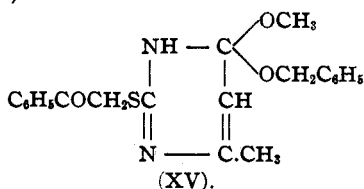
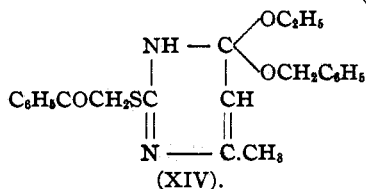
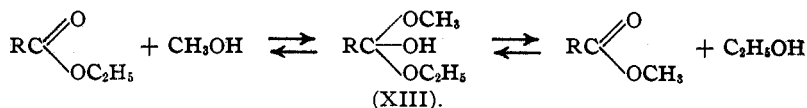
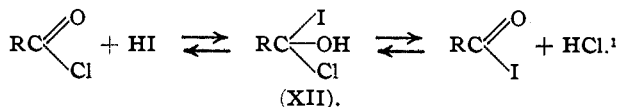
<sup>5</sup> Johnson, Moran and Kohmann, *THIS JOURNAL*, **35**, 447 (1913).

corresponding to Formula IX or a 1-benzyl derivative. On the other hand, the pyrimidine interacted with the benzylchloride, in ethyl alcohol, to form the ethoxypyrimidine (X), and the yield was excellent. Furthermore, when we applied the same reaction in a solution of methyl alcohol the same abnormality was observed, and we obtained the corresponding methoxypyrimidine (XI). This is the first time that we have observed such metathetical changes in our pyrimidine investigations, and the results suggest to us why, in some of our alkylation experiments, we have experienced great difficulty in isolating pure compounds. Undoubtedly changes such as the above have taken place leading to the formation of mixtures.



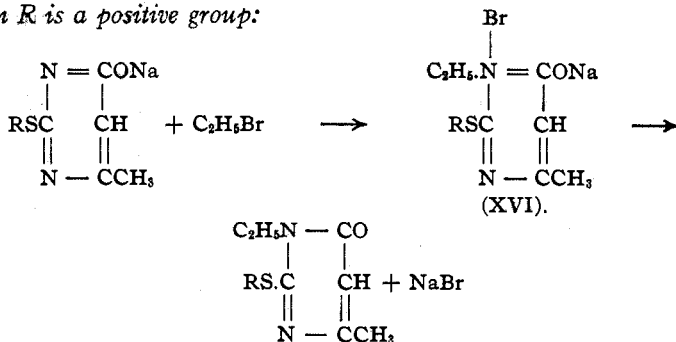
These interesting changes are analogous to those in which an alkyl group of an ester is displaced by another alcohol (XIII), and an acylchloride is converted into its corresponding iodide by the action of hydrogen iodide (XII). Intermediate addition products can be assumed to be formed in each case. In our experiment with benzylchloride the benzyl-

compound (IX) is very probably the first product of the reaction, which then adds the alcohol, serving as solvent, to form the corresponding addition compounds represented by Formulas XIV and XV. These then break down with formation of the corresponding ethoxy- (X) and methoxy-pyrimidines (XI) with generation of benzylalcohol.

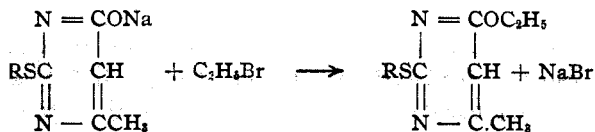


The results, which we have thus far obtained in our alkylation work, are all in accord with our previous assumption that the sodium salts of 2-mercapto-6-oxypyrimidines can interact with alkylhalides in two ways—either by addition to form nitrogen substituted pyrimidines, or by direct substitution to form oxygen derivatives. Methyl iodide generally reacts by addition to form 1- or 3-methylated pyrimidines. The two changes may be expressed by the following equations:

When *R* is a positive group:

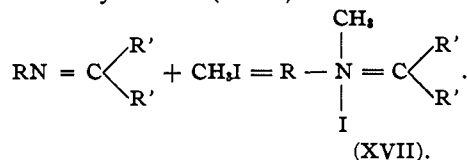


When *R* is a negative group:



<sup>1</sup> Standinger and Anthes, *Ber.*, 46, 1417 (1913); Aschan, *Ibid.*, 45, 954; Meyer, *Ibid.*, 45, 2869 (1912); Michael, *Ibid.*, 46, 136 (1913).

The addition-product (XVI) may be viewed as a quaternary salt of a cyclic azomethin  $\text{—C} = \text{N}$ , corresponding to that formed by treating a Schiff base with an alkylhalide<sup>1</sup> (XVII).



Our researches on the alkylation of pyrimidines will be continued.

### Experimental Part.

**1,4-Dimethyl-2-benzoylmethylmercapto-6-oxypyrimidine** (VII). — Five grams of 2-benzoylmethylmercapto-4-methyl-6-oxypyrimidine were dissolved in 50 cc. of absolute alcohol containing a molecular proportion of sodium (0.44 g.). Two and seventy-three hundredths grams of methyl iodide were then added and the solution warmed on the steam bath until neutral. The alcohol was then removed by evaporating under diminished pressure and the residue cooled, when this pyrimidine was obtained in the form of prismatic crystals. It was purified by recrystallization from ethyl alcohol and separated in stout well-developed prisms which melted at 155° to a clear oil. The yield of purified material was 2.8 g.

Calc. for  $\text{C}_{14}\text{H}_{14}\text{O}_2\text{N}_2\text{S}$ : N, 10.22. Found (Kjeldahl): 10.51.

**Hydrolysis with Hydrochloric Acid.**—One gram of the above mercapto-pyrimidine was suspended in 50 cc. of concentrated hydrochloric acid and the acid boiled for about one hour. A clear solution was obtained, and suspended in the liquid were globules of a yellow oil, which solidified on cooling. This was identified as 2,5-diphenyl-1,4-dithiene and melted after crystallization from alcohol at 116–118° to a yellow oil. The acid solution was evaporated to dryness and the crystalline residue purified by crystallization from hot water. On cooling 1,4-dimethyluracil separated and melted at 259–262° to an oil.<sup>2</sup> The yield was practically quantitative.

**2-Benzoylmethylmercapto-4-methyl-6-ethoxypyrimidine** (X). — This pyrimidine was formed by alkylation of 2-benzoylmethylmercapto-4-methyl-6-oxypyrimidine (5 g.) with ethylbromide (2.5 g.) in the presence of sodiummethylate (0.44 g. sodium in 50 cc. of alcohol). After cooling, and filtering off undissolved sodium bromide, the alcoholic solution was then concentrated under diminished pressure. This pyrimidine then separated as flat prisms. It was purified by crystallization from ethyl acetate and separated in flat prisms containing ethyl acetate of crystallization. They melted at 83.5° to a yellow oil. The pyrimidine

<sup>1</sup> Decker and Becker, *Ann.*, 395, 362 (1913).

<sup>2</sup> Behrend and Dietrich, *Ibid.*, 309, 268 (1899).

is sparingly soluble in benzene and ether, and extremely soluble in alcohol and water. Analysis (Kjeldahl):

Calc. for  $(C_{10}H_{16}O_2N_2S)_2 \cdot CH_3CO_2C_2H_5$ : N, 8.43. Found (Kjeldahl): 8.22, 8.31.

In a second experiment the same proportions of mercaptopyrimidine, ethylbromide and sodium were taken as above, but methyl alcohol was used as the solvent instead of ethyl alcohol. After the reaction was complete the excess of methyl alcohol and ethyl bromide were removed by evaporating under diminished pressure and the residue then triturated with ether when the pyrimidine was obtained mixed with sodium bromide. It was purified for analysis by crystallization from a large volume of petroleum ether and separated in colorless, prismatic crystals which melted at 86–88° to an amber-colored oil. The yield of crude pyrimidine was 4 g.

Calc. for  $C_{10}H_{16}O_2N_2S$ : N, 9.72. Found (Kjeldahl): 9.64.

**Hydrolysis with Hydrochloric Acid.**—One gram of this pyrimidine was dissolved in 25 cc. of concentrated hydrochloric acid and the solution boiled for several hours. 2,5-Diphenyl-1,4-dithiene was obtained as usual and melted at 116–118°. After removal of the dithiene the acid filtrate was then evaporated to dryness and the residue dissolved in hot water. On cooling a quantitative yield of 4-methyluracil was obtained. It was free from sulfur and did not melt below 280°. 1-Ethyl-4-methyluracil<sup>1</sup> melts at 195°.

**Action of Benzylchloride on the Sodium Salt of 2-Benzoylmethylmercapto-4-methyl-6-oxypyrimidine.**—The sodium salt of the mercaptopyrimidine was prepared as usual by dissolving 0.44 g. of sodium in 50 cc. of absolute alcohol and then dissolving 5 g. of the pyrimidine in this solution. Two and forty-four hundredths grams of pure distilled benzylchloride were then added and the solution heated on the steam bath for 3 hours, when the reaction was complete. The undissolved sodium chloride was then separated by filtration and the alcohol filtrate concentrated when a syrup was obtained, which partially solidified on cooling. This product was then triturated with ether and water and the water solution finally concentrated to a small volume and cooled. After standing for about 10–12 hours this solution finally deposited a crystalline substance, which was very soluble in water and alcohol. It was identified as 2-benzoylmethylmercapto-4-methyl-6-ethoxypyrimidine and it crystallized from ethylacetate in characteristic flat prisms melting at 83.5° to a yellow oil. A mixture of this substance and some of the pure ethoxypyrimidine from the preceding experiment melted at exactly the same temperature. We obtained no evidence of the formation of a benzyl derivative.

Calc. for  $(C_{16}H_{16}O_2N_2S)_2 \cdot CH_3COOC_2H_5$ : N, 8.43. Found (Kjeldahl): 8.15.

<sup>1</sup> Beilstein's Handbuch, I, 1351; also THIS JOURNAL, 42, 109.

**Alkylation with Benzylchloride in Methyl Alcohol Solution. 2-Benzoylmethylmercapto-4-methyl-6-methoxypyrimidine (XI).**—This methoxypyrimidine was obtained by alkylation of 2-benzoylmethylmercapto-4-methyl-6-oxypyrimidine with benzylchloride in methyl alcohol solution. The following proportions were used: 0.44 g. of sodium dissolved in 50 cc. of methylalcohol, 5.0 g. of the mercaptopyrimidine and 2.44 g. of benzylchloride. The manipulation was similar to that described in the previous experiment, and the reaction was complete after digesting on the steam bath for 12 hours. The undissolved sodium chloride was then separated by filtration and the alcohol filtrate concentrated, under diminished pressure, to a volume of 15 cc. and cooled. The methoxypyrimidine then separated and was purified by washing with ether and finally crystallizing from ethylacetate. It separated in slender needles, which melted at  $143-4^{\circ}$  to a yellow oil without decomposition. The yield was 3.5 g.

Calc. for  $C_{14}H_{14}O_2N_2S$ : N, 10.22. Found (Kjeldahl): 10.05.

**Hydrolysis with Hydrochloric Acid.**—One gram of the above methoxypyrimidine was dissolved in 25 cc. of concentrated hydrochloric acid and the solution boiled for 2 hours. 2,5-Diphenyl-1,4-dithiene was obtained as usual and melted after crystallizing from alcohol at  $116-117^{\circ}$  to an oil. The acid solution was concentrated to a volume of about 10 cc. and cooled when 4-methyluracil was obtained. We obtained no evidence of the formation of a benzoxypyrimidine or of 1- and 3-benzyl-4-methyl-6-oxypyrimidines.<sup>1</sup>

Calc. for  $C_8H_8O_2N_2$ : N, 22.22. Found (Kjeldahl): 22.1.

2-Benzoylmethylmercapto-4-methyl-6-methoxypyrimidine is not converted into its corresponding ethoxy derivative (above) by warming with ethyl alcohol. It was recovered unaltered, and melting at  $143^{\circ}$ , after digesting with an excess of ethyl alcohol for 5 hours.

An attempt to alkylate 2-benzoylmethylmercapto-4-methyl-6-oxypyrimidine in alcohol solution with ethyl chloroacetate was unsuccessful. The sodium salt of the pyrimidine was prepared by dissolving 0.44 g. of sodium and 5.0 g. of the mercaptopyrimidine, respectively, in 50 cc. of absolute alcohol and 2.36 g. of ethyl chloroacetate then added. After digesting at  $100^{\circ}$  for 5 hours the solution was neutral to turmeric and blue litmus and sodium chloride had deposited. After filtering off the salt the solution was concentrated and cooled when we obtained the original mercaptopyrimidine. It was purified by recrystallization from alcohol and separated in prismatic crystals melting at  $165^{\circ}$  to a clear oil. The experiment was repeated and the same result was obtained.

Calc. for  $C_{13}H_{12}O_2N_2S$ : N, 10.7. Found (Kjeldahl): 10.44.

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<sup>1</sup> Wheeler and McFarland, THIS JOURNAL, 42, 101.