[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY.]

# RESEARCHES ON PYRIMIDINES. LXXXIX. THE CONDENSATION OF BENZAMIDINE WITH ETHYL γ-DIETHOXY-ACETO-ACETATE.

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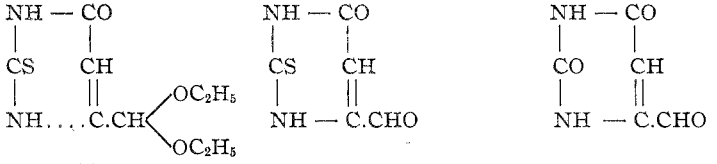
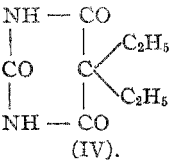
It has been shown in a previous paper from the Sheffield Laboratory[1] that ethyl γ-diethoxy-aceto-acetate condenses smoothly with thio-urea in the presence of sodium ethylate to give the thiopyrimidine (I), containing an acetal grouping in the 4-position of the pyrimidine ring. This acetal group is very susceptible to hydrolysis in acid solution, and, by digestion of the pyrimidine (I) with hydrochloric acid, is easily destroyed in this case with formation of the corresponding aldehyde group as is represented in Formula II. In fact, this is the only synthetical method that has yet been developed for the introduction of an aldehyde group into the pyrimidine ring, and is apparently a reaction of general application in the uracil series. Desulfurization of the thiopyrimidine (II) leads to the production of the corresponding oxygen derivative, uracil-aldehyde (III), a pyrimidine combination of biochemical interest, and one whose value for synthetical work in this series has not yet been realized.



(I). (II). (III).

It became of special interest to us in the development of different phases of our researches on amines to extend the application of our method of synthesizing cyclic aldehydes in the pyrimidine series. We have, therefore, turned our attention to an investigation of the behavior of ethyl γ-diethoxy-aceto-acetate towards amidine combinations. Theoretically this ester should interact with amidines in a manner similar to that of ethyl aceto-acetate to give representatives of a new class of pyrimidine acetals which, on hydrolysis, should undergo conversion into their corresponding aldehydes. The successful application of this synthesis with amidines would make possible the preparation of representatives of a new type of cyclic amine compounds which give promise of having considerable interest from a pharmacological standpoint. With the exception of the work that has been contributed dealing with the chemistry of diethyl-barbituric acid (IV) and related compounds, practically no attention has been paid to the pharmacology of pyrimidine compounds. The unsaturated or simplest forms of pyrimidine compounds contain the characteristic

[1] Johnson and Cretcher, THIS JOURNAL, 37, 2144 (1915).

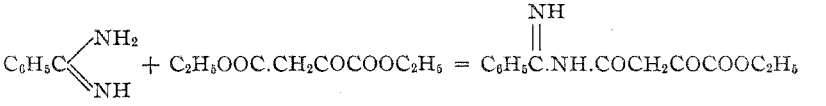


(IV).

nitrogen carbon linking ...N = CR — NH..., which is known to exhibit, in other cyclic series, marked physiological properties. It is not improbable, therefore, that a careful pharmacological and physiological study of pyrimidines containing this amidine grouping will reveal to us other combinations which may prove to be as important medicinally as the hypnotics discovered in the barbituric acid series. With a reactive aldehyde group present in such combinations we would have at our command means of introducing synthetically into the cycle a great variety of side groups through application of reactions characteristic of this unsaturated grouping.

The work which we now describe in this paper is of a preliminary nature and deals only with a study of the behavior of ethyl $\gamma$-diethoxy-aceto-acetate towards benzamidine. We find that these reagents have a very pronounced affinity for each other, and, by interaction, lead to a variety of condensation products depending upon the experimental conditions employed.

Benzamidine reacts with ethyl $\gamma$-diethoxy-aceto-acetate to form 3 different compounds, 2 of which are acyclic and one cyclic in nature. If the amidine is allowed to interact with the $\beta$-ketone ester in molecular proportions, and in the absence of free alkali, they combine smoothly with loss of alcohol giving an acyclic combination to which we have assigned the constitution expressed in Formula VIII. The reaction takes place at ordinary temperature, and this compound (VIII) is apparently the only product formed under such conditions. The evidence which has led us to assign to this condensation product this constitution and not that of an acrylic acid (IX), or a cyclic salt (X), are the facts that (1) it is not stable in the presence of alkali, and (2) it undergoes a smooth rearrangement by such treatment, or when heated above its melting point, to give the normal pyrimidine (VI). In other words, benzamidine reacts with this ketone ester in a manner similar to diethyl oxalyl-acetate which Pinner observed to condense with benzamidine as shown below.[1]

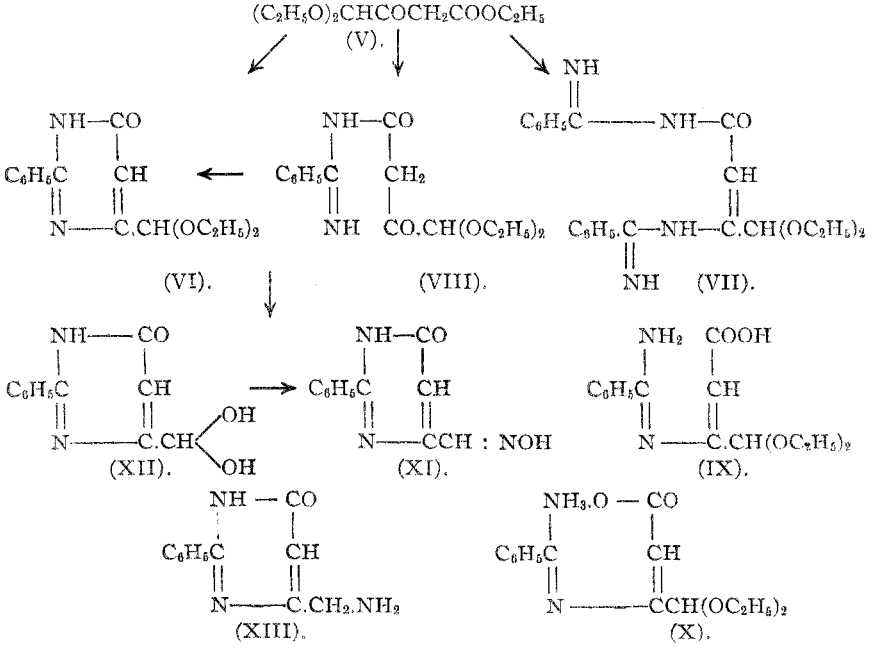


Condensation of benzamidine with the $\beta$-ketone ester in aqueous solution and in the presence of a molecular proportion of alkali leads to an

[1] "Imidoaether," pp. 255–6. Gustave Schmidt, Berlin (1892).

entirely different result. Here we obtained no evidence of the formation of the compound represented by Formula VIII. The chief product of reaction was the normal pyrimidine acetal (VI). Along with this, a secondary product was formed to which we assigned the constitution of a crotonic acid derivative represented by Formula VII. This substance very probably results from the action of benzamidine on the acylbenzamidine (VIII). We were not able to submit this substance to a careful investigation on account of the small amount of material available.

2-Phenyl-6-oxy-4-aldehydo-pyrimidine (XII) is formed almost quantitatively by acid hydrolysis of its corresponding acetal (VI). While this pyrimidine-aldehyde gives all the reactions characteristic of its class, we have not represented it structurally as containing a free aldehyde group. The compound contains a molecule of water which is so firmly bound that we have represented it structurally as water of constitution instead of water of crystallization. In other words, the pyrimidine (XII) bears the same relationship to its corresponding aldehyde as chloralhydrate does to chloral. The aldehyde hydrate interacts with hydroxylamine, as might be expected, to form the oxime of the aldehyde (XI). On reduction with stannous chloride the latter is transformed smoothly into the amine (XIII). This is the first amine, containing the amino group in an aliphatic side chain of the pyrimidine, to be synthesized in this series. These various transformations are expressed by the following formulas.



Further work dealing with a study of the reactions of pyrimidine aldehydes is in progress. The amine combinations, which we propose to synthesize and of which the pyrimidine (XIII) is our first representative, will be subject to a pharmacological research in order to determine whether they possess any specific therapeutic value. It is our intention to prepare also the higher homologues of pyrimidines corresponding to Formula XIII and related compounds in which the amino group is linked to carbons in the $\beta$ and $\gamma$ positions, respectively, with respect to the pyrimidine cycle.

## Experimental Part.

**Ethyl $\gamma$-Diethoxy-aceto-acetate,** $(C_2H_5O)_2CH.CO.CH_2COOC_2H_5$.—This ester was prepared by condensing ethyl diethoxy-acetate with ethyl acetate according to the procedure described in a previous paper from this laboratory.[1]

**The Condensation of Ethyl $\gamma$-Diethoxy-aceto-acetate with Benzamidine: $\gamma$-Diethoxy-$\beta$-benzamidino-crotonyl-benzamidine. Formula VII.**—Benzamidine and ethyl diethoxy-aceto-acetate (V) interact at ordinary temperature and if the operation is conducted according to the following procedure it is possible to isolate and identify 2 definite products of reaction. Ten g. of the ketone ester is dissolved in sufficient 10% sodium hydroxide solution to form the sodium salt of the ester. A molecular proportion (7.15 g.) of the hydrochloride of benzamidine is also dissolved in the same amount of 10% sodium hydroxide solution to liberate the free benzamidine base. Then these two akaline solutions are mixed, and the resulting solution allowed to stand at ordinary temperature. The slight evolution of heat which occurs when the 2 solutions are mixed indicates immediate reaction. After this mixture has stood for about 24 hours, a crystalline substance begins to deposit; when the reaction has proceeded for 2 days, this solid is separated by filtration and the aqueous filtrate saved (see below). The weight of this insoluble product is generally about 3.0 g. It was colorless and crystalline and was purified by crystallization from hot alcohol in which solvent it is quite soluble. It crystallized in prismatic crystals and exhibited the characteristic property of possessing a double melting point. The compound first melts at 106° to an oil, then solidifies in the capillary tube; on further heating, it melts at 136° to a clear oil with slight effervescence. The compound is insoluble in alkali and soluble in acids.

Calc. for $C_{22}H_{26}O_3N$: N, 14.2. Found: 13.96.

The alkaline filtrate saved above was exactly neutralized by addition of the required amount of hydrochloric acid, whereupon a crystalline product immediately separated in the form of a voluminous colorless precipitate. The compound is soluble in an excess of hydrochloric acid. It

[1] Johnson and Cretcher, *loc. cit*

was purified without difficulty by crystallization from boiling 95% alcohol from which is separated, as the solution cooled, in the form of slender needles. These melted at 175°. A complete analysis of this substance indicated that we were dealing with a true pyrimidine combination, namely, *2-phenyl-4-diethoxymethyl-6-oxypyrimidine*, Formula VI.

Calc. for $C_{15}H_{18}O_3N_2$: C, 65.6; H, 6.57; N, 10.2. Found: C, 65.4; H, 6.50; N, 10.1.

**2-Phenyl-6-oxy-4-aldehydo-pyrimidine. Formula XII.**—This new pyrimidine aldehyde is easily obtained by digesting its acetal, described above, with dil. hydrochloric acid. On evaporating the solution to dryness the pyrimidine is obtained in a crystalline condition and is easily purified by crystallization from water or 95% alcohol. The aldehyde is quite soluble in this solvent. It melts at 205°. The results obtained by analysis showed that we are dealing here with a compound containing a molecule of water. It is bound, however, very firmly in the pyrimidine molecule, and the fact that it cannot be expelled by heating at 135° indicates that it is not linked as water of crystallization but as water of constitution as in chloral hydrate.

Calc. for $C_{11}H_{10}O_3N_2$: N, 12.8. Found: 12.63.

**Condensation of Benzamidine with the β-Ketone Ester in Neutral Solution.**—The 2 compounds described above and represented in the introduction of this paper by Formulas VII and VI are products of the condensation reaction between the β-ketone ester and benzamidine when applied in the presence of 2 molecular proportions of sodium hydroxide. An entirely different result is obtained if the β-ketone ester (V) is added directly to an aqueous solution of the free amidine in the absence of alkali. A molecular proportion of the amidine hydrochloride (7.15 g.) was first dissolved in a 10% alkaline solution containing in solution 1.83 g. of sodium hydroxide. To this solution the β-ketone ester was added when there was an immediate reaction with evolution of heat. A yellow oil began to separate immediately and within a few minutes, if it was stirred, it solidified completely. After the reaction mixture had stood at ordinary temperature for about 48 hours, the reaction was considered complete and the crystalline product then separated by filtration. It was purified by crystallization from 95% alcohol and separated from the solution as it cooled, in the form of colorless crystals which melted constant at 145° with slight evolution of gas. This decomposition involves a profound change which is a very characteristic property of this substance. If the temperature of the sulfuric acid bath is held at the temperature of decomposition, namely, 145°, this solid melts completely; then the oil solidifies entirely and the new substance does not melt until it is heated to 174°. (This change will be discussed below.) The compound melting at 145° did not lose water at 100°, and was extremely soluble in sodium hydroxide

solution. The properties of the substance and the results obtained by complete analysis proved that we were not dealing here with a pyrimidine combination, but with one of 3 cyclic derivatives, namely, γ-diethoxy-β-benzamidino-crotonic acid (IX), a salt (X), or an acyl derivative of benzamidine, represented structurally by Formula VIII. The chemical properties of the compound and the conditions under which it is formed have led us to assign to it provisionally the constitution of *γ-diethoxy-acetoacetyl-benzamidine*, Formula VIII.

Calc. for $C_{15}H_{20}O_4N_2$: C, 61.64; H, 6.86; N, 9.59. Found: C, 61.74; H, 7.2; N, 9.8.

**Rearrangement of γ-Diethoxy-acetoacetyl-benzamidine (VIII) into 2-Phenyl-4-diethoxy-methyl-6-oxypyrimidine (VII).**—As stated above, the substance melting at 145° undergoes a rearrangement at this temperature, being transformed into a product melting at 174°. This latter compound proved to be identical with 2-phenyl-4-diethoxy-methyl-6-oxy-pyrimidine, VI. It crystallized from boiling 95% alcohol in the form of needles, and when mixed with the acetal the melting point was not altered. This acyclic compound (VIII) is also rearranged into the pyrimidine (VI) by the action of alkali. About 0.8 g. of the compound was dissolved in 7 cc. of a 10% aqueous solution of sodium hydroxide and the solution allowed to stand at ordinary temperature for 12 hours. On acidifying with hydrochloric acid the pyrimidine melting at 172–3° separated at once. The same transformation could also be brought about within a few minutes by simply heating the alkaline solution of the acyclic compound.

**The Oxime of 2-Phenyl-6-oxy-4-aldehydo-pyrimidine, $C_{11}H_9O_2N_3$. Formula XI.**—This compound can be prepared by dissolving the pyrimidine aldehyde (XII) (0.97 g.) in 10 cc. of water containing in solution 0.5 g. of sodium hydroxide or slightly more than 2 molecular proportions of alkali, and then adding to this solution a molecular proportion of hydroxylamine hydrochloride. The mixture is then allowed to stand at ordinary temperature for 6 to 8 hours and the alkaline condition finally neutralized with dil. acetic acid. The oxime separates at once upon neutralization and can be purified by crystallization from alcohol. It melts with decomposition at about 268°. This method of operating does not always lead, however, to a pure sample of the oxime. Oftentimes the oxime is accompanied by a powder which is insoluble in alcohol and contains sodium. In fact, it is extremely difficult to remove this element, when present, by treatment with acids. In order to obtain the oxime quantitatively and free from sodium the following procedure is recommended: dissolve the aldehyde in boiling water and add to the aqueous solution a concentrated aqueous solution containing a molecular proportion of hydroxylamine hydrochloride. The oxime will separate instantaneously and the yield is practically quantitative.

Calc. for $C_{11}H_9O_2N_3$: N, 19.5. Found: 19.33, 19.4.

**Reduction of the Oxime $C_{11}H_9O_2N_3$, Formula XI, to the Corresponding Amine 2-Phenyl-4-Aminomethyl-6-oxypyrimidine $C_{11}H_{11}ON_3$. Formula XIII.**—The reduction of the oxime is easily brought about by the action of tin chloride in hydrochloric acid solution. For 2 g. of the oxime we used 6 g. of the tin salt. The reaction is allowed to proceed at ordinary temperature for about 24 hours and finally at 45–50° for 2 hours. The tin is then removed in the usual manner by precipitation as sulfide, and the aqueous solution evaporated to dryness *in vacuo*. The pyrimidine base is obtained in the form of a stable, crystalline hydrochloride, which is easily purified by crystallization from 95% alcohol. This salt is colorless and melts with decomposition at 263–5°.

Subs., dried at 100°.

Calc. for $C_{11}H_{11}ON_3.HCl$: N, 17.72. Found: 17.6.

## Summary.

1. Benzamidine condenses with ethyl γ-diethoxy-aceto-acetate in the presence of alkali to give the pyrimidine, 2-phenyl-4-diethoxy-methyl-6-oxypyrimidine (VI).

2. Hydrolysis of this pyrimidine (VI) leads to the formation of the corresponding pyrimidine aldehyde which exists in the form of a stable hydrate (XII).

3. The pyrimidine aldehyde-2-phenyl-6-oxy-4-aldehydo-pyrimidine (XII) interacts normally with hydroxylamine to give an oxime, which is converted by reduction into 2-phenyl-4-aminomethyl-6-oxypyrimidine (XIII).

4. Benzamidine and ethyl γ-diethoxy-aceto-acetate interact in neutral solution with formation of diethoxy-acetoacetyl-benzamidine (VIII).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE, JOHNS HOPKINS HOSPITAL.]

# MERCURY DERIVATIVES OF PHTHALEINS.[1]

BY EDWIN C. WHITE.

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During the past 3 years the writer and collaborators have been engaged on studies of organic mercury compounds, particularly with reference to their use, both internally and locally, in the treatment of genito-urinary infections and of syphilis. The results obtained in the laboratory and the clinic with some of these compounds[2] have been of sufficient value to

[1] This work was carried out with the aid of funds granted by the United States Interdepartmental Social Hygiene Board for Research in the prevention and treatment of venereal diseases.

[2] E. G. Davis, E. C. White and R. Rosen, "Urinary Antisepsis," *J. Urology*, **2**, 277 (1918); J. E. Burns, E. C. White and J. G. Cheetham, "Experimental Nephropathy Produced by a Mercury Derivative of Phenolsulphonphthalein," *ibid.*, **3**, 1 (1919); H. H. Young, E. C. White and E. O. Swartz, "A New Germicide for Use in the Genito-Urinary Tract—Mercurochrome-220," *J. Am. Med. Assn.*, **73**, 1483 (1919).