hydrogen chloride against the logarithm of its concentration in the benzene. The black circles represent the cases in which the benzene was saturated with water. The straight line is drawn with a slope of unity which it must have if hydrogen chloride obeys Henry's law. The plot indicates that hydrogen chloride is a normal solute in benzene and that it is not affected if the benzene is simultaneously saturated with water.

Summary

The partial pressures of hydrogen chloride from benzene solutions have been determined directly and the results indicate that it is a normal solute in dry benzene and in benzene simultaneously saturated with water.

DURHAM, N. C. RECEIVED JULY 6, 1937

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FORDHAM UNIVERSITY]

Studies on Pyrimidines. I. The Preparation of 2-Methyl-6-oxypyrimidine-5-acetic Acid and Some of its Derivatives

BY LEOPOLD R. CERECEDO AND FRANK D. PICKEL

Once the structure of vitamin B_1 had been established by the research groups of Williams, of Windaus, of Todd, and of others, it became clear to us that the problem of the synthesis might be attacked by condensing 2-methyl-5-chloromethyl-6-aminopyrimidine with 4-methyl-5-β-hydroxyethylthiazole. If we keep in mind the similarity between the chemical properties of thiazole and pyridine, an abundance of prototypes of this synthesis may be found in the field of pyridine chemistry.

Our experiments on the thiazole moiety of the vitamin will be the subject of a separate communication. As regards the pyrimidine required for the synthesis, it was realized that 2-methyl-6-oxy-5-hydroxymethylpyrimidine would be a key substance in its preparation. Several methods for the synthesis of this compound suggested themselves. The most convenient one appeared to be the direct introduction of the hydroxymethyl or chloromethyl group into the corresponding pyrimidine. The investigation of this phase of the problem is still in progress. Another method which was considered was the preparation of 2-methyl-6-oxy-5-aminomethylpyrimidine by the degradation of 2-methyl-6-oxypyrimidine-5-acetic acid and the subsequent conversion of the amine into the alcohol. For the degradation of the acid, the two well-known methods of Hofmann and of Curtius suggested themselves. The degradation by the Hofmann reaction caused difficulties which so far have not been overcome. On the other hand, our experiments with the Curtius method were successful. From ethyl 2-methyl-6-oxypyrimidine-5-acetate we prepared the corresponding hydrazide. Degradation of this hydrazide according to Lindemann's modification of the Curtius method yielded the amine containing one less carbon atom. From the amine the corresponding alcohol was obtained. During the course of this work a number of interesting observations regarding the chemistry of pyrimidines have been made which we have not yet had time to study in all their ramifications. They will be reported as the work progresses.

It would have been surprising if others working in the same field would not have experimented along similar lines. Thus, after the main part of the work to be described in the present report had been completed, a paper by Todd and his associates[1] appeared in which they described the preparation of several compounds that had been synthesized independently in this Laboratory. It is a source of gratification to us that our data confirm and supplement those of the English workers. Likewise, Williams and his associates[2] state in a recent paper that the three modes of attack for the preparation of the pyrimidine mentioned above were, among others, also considered by them.

Experimental Part

Ethyl 2-Methyl-6-oxypyrimidine-5-acetate (I).—Acetamidine hydrochloride, freshly distilled ethyl formylsuccinate, and sodium hydroxide were mixed in equimolar amounts with enough cold water to just dissolve the sodium hydroxide. The mixture was kept in a cold place

(1) Todd, Bergel, Fraenkel-Conrat and Jacob, *J. Chem. Soc.*, 1601 (1936).

(2) Cline, Williams and Finkelstein, THIS JOURNAL, **59**, 1052 (1937).

for three to four days, whereupon a white precipitate settled out. It was filtered and recrystallized from a mixture of benzene and ethyl acetate (10 cc. of benzene and 3 cc. of ethyl acetate). The ester crystallizes in the form of fine colorless needles and melts at 179–180°. A second crop of crystals was obtained by neutralizing the filtrate with dilute hydrochloric acid, evaporating the mixture to dryness, and extracting the residue with the mixture of benzene and ethyl acetate (total yield 43%).

Anal. Calcd. for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.07, 55.15; H, 6.24, 6.44; N, 14.23, 14.39.

On treatment of the alcoholic solution of the ester with picric acid, a picrate separated on standing. Recrystallized from alcohol, it formed yellow needles, m. p. 157–158°.

Anal. Calcd. for $C_{15}H_{15}O_{10}N_5$: N, 16.49. Found: N, 16.20, 16.47.

2-Methyl-6-oxypyrimidine-5-acethydrazide (II).—To a boiling solution of 11.9 g. of the ester (I) in 90 cc. of absolute ethyl alcohol 18 g. of 50% hydrazine hydrate was added and the mixture refluxed for six hours. Shortly after the heating commenced, the hydrazide began to crystallize out on the walls of the flask. After cooling, the precipitate was filtered and recrystallized from ethyl alcohol. It separated in irregular colorless prisms melting at 246°, yield 85%.

Anal. Calcd. for $C_7H_{10}O_2N_4$: C, 46.15; H, 5.53; N, 30.76. Found: C, 46.12, 46.33; H, 5.40, 5.48; N, 30.77, 30.70.

2-Methyl-6-oxy-5-aminomethylpyrimidine Hydrochloride (III).[3]—To a solution of 0.612 g. of the hydrazide (II) in 8 cc. of normal hydrochloric acid, cooled to −2°, a concentrated solution of 0.24 g. of sodium nitrite was added gradually with stirring. After all the nitrite had been added, the solution was stirred for fifteen minutes, then transferred to a crystallizing dish and heated on the steam-bath. A lively evolution of nitrogen took place at this point. The solution was evaporated to dryness and the residue extracted several times with ethyl alcohol. From the alcoholic extract a substance was recovered which was recrystallized from absolute ethyl alcohol. A crystalline precipitate separated in the form of small slender colorless rods melting with decomposition at 277°; yield 60%.

Anal. Calcd. for $C_6H_{10}ON_3Cl$: C, 41.03; H, 5.70; N, 23.93. Found: C, 41.35, 41.04; H, 5.63, 5.71; N, 23.68, 23.76.

The aqueous solution of the amine hydrochloride (III) yielded on treatment with picric acid a picrate which, after recrystallization from water, separated in the form of square flat plates, m. p. 157–158°.

Anal. Calcd. for $C_{12}H_{13}O_8N_6Cl$: N, 20.77. Found: N, 20.69, 20.62.

2-Methyl-6-oxy-5-hydroxymethylpyrimidine (IV).—The amine hydrochloride (III) (5 g.) was dissolved in 60 cc. of 5% hydrochloric acid. To the mixture a concentrated solution of 15 g. of sodium nitrite was added drop by drop with stirring. After all the nitrite had been added, the reaction mixture was heated on the steam-bath for six hours and then evaporated to dryness. The residue was extracted with ethyl acetate in a Soxhlet apparatus. From the extract a substance was recovered which, after recrystallization from dioxane, separated in fine colorless needles, m. p. 215°, yield 40%.

Anal. Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.33, 51.51; H, 5.62, 5.78; N, 19.75, 19.66.

2-Methyl-6-oxypyrimidine-5-acetamide (V).—A solution of 0.4 g. of the ester (I) in 10 cc. of concentrated ammonia was allowed to stand for two days at room temperature. It was then heated on the steam-bath to remove the excess of ammonia and concentrated to dryness *in vacuo*. The resultant residue was recrystallized from ethyl alcohol. It separated in clusters of colorless needles, m. p. 242°, yield 93%.

Anal. Calcd. for $C_7H_9O_2N_3$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.41, 50.48; H, 5.48, 5.25; N, 25.12, 25.21.

With picric acid a picrate was obtained which crystallized from alcohol in long slender rods, m. p. 207°.

Anal. Calcd. for $C_{13}H_{12}O_9N_6$: N, 21.21. Found: N, 21.17, 21.21.

2-Methyl-6-oxypyrimidine-5-acetic Acid (VI).—One gram of the ester (I) was dissolved in 15 cc. of concentrated hydrochloric acid and the solution concentrated on the steam-bath. After about two-thirds of the hydrochloric acid had been removed, the acid separated out. The reaction mixture was cooled in ice, filtered, and the precipitate recrystallized from ethyl alcohol. The acid, combined with one mole of hydrochloric acid, separated in colorless slender rods, m. p. 254–256°.

Anal. Calcd. for $C_7H_9O_3N_2Cl$: C, 41.09; H, 4.43; N, 13.69; Cl, 17.33. Found: C, 41.03, 41.27; H, 4.43, 4.17; N, 13.61, 13.70; Cl, 17.74.

The free acid may be obtained from a saturated aqueous solution of this compound by treatment with one equivalent of sodium carbonate. The product separates immediately and recrystallizes from water as thin colorless plates, m. p. 245–246°.

Anal. Calcd. for $C_7H_8O_3N_2$: C, 50; H, 4.8; N, 16.66. Found: C, 49.98, 49.89; H, 4.83, 5.03; N, 16.77, 16.71.

Ethyl 2-Methyl-6-chloropyrimidine-5-acetate (VII).—One gram of ester (I) was heated with 4 cc. of phosphorous oxychloride at 115–120° for twenty minutes. The excess of the reagent was removed *in vacuo* at 60°. The viscous amber colored residue was dissolved in ice water and sodium carbonate added until the solution was faintly alkaline, whereupon the chloropyrimidine separated as an oil. The mixture was extracted with ether and the ether extract dried over sodium sulfate. The filtered extract yielded on evaporation of the ether an oily residue which solidified to a crystalline mass. It was purified by distillation *in vacuo*. The fraction distilling between 108 and 112° at 11 mm. was collected; yield 70%. On solidification, a colorless waxy solid was obtained, m. p. 35–36°.

Anal. Calcd. for $C_9H_{11}O_2N_2Cl$: C, 50.36; H, 5.17; N, 13.06. Found: C, 50.31, 50.34; H, 5.37, 5.15; N, 13.18, 12.97.

(3) Lindemann, *Helv. Chim. Acta*, **11**, 1027 (1928).

The phenylhydrazide of this ester was prepared as follows: 0.248 g. of the substance was dissolved in 3 cc. of methyl alcohol and the solution refluxed with 1.5 cc. of phenylhydrazine for four hours. On cooling in the ice-box, a few crystals separated. Ether was added to the mixture, when the compound separated as a colorless powder. The phenylhydrazide crystallized from alcohol in colorless glistening plates, m. p. 236°.

Anal. Calcd. for $C_{13}H_{13}ON_4Cl$: N, 20.25. Found: N, 20.41, 20.29.

Summary

Ethyl 2-methyl-6-oxypyrimidine-5-acetate has been synthesized, and from it the corresponding acid has been obtained. Treatment of the ester with hydrazine resulted in the hydrazide of the acid; treatment with concentrated ammonia gave the amide.

The hydrazide has been degraded to the amine containing one less carbon atom. From the amine the corresponding alcohol has been prepared.

The ester gave with phosphorus oxychloride the corresponding 6-chloro derivative, from which the phenylhydrazide was obtained.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Meta Arsenated Phenoxyethanols

BY STEPHEN B. BINKLEY[1] AND CLIFF S. HAMILTON

The fact that certain para arsenated phenoxyalkanols possess considerable therapeutic value suggested a study of the corresponding meta derivatives. Although the para derivatives[2] were prepared by condensing *p*-hydroxyphenylarsonic acid with chlorohydrins, attempts to prepare meta derivatives[3] by this method were unsuccessful. In the case of the ortho and para arsenated phenoxyalkanols the orientation is definitely known. However, in the case of the meta compounds the nitro group may enter any one of three positions, -2, -4, or -6, with reference to the arsono group if it is assumed that the alkoxy group exerts a stronger directive influence than the weakly meta-directing arsono group. This investigation deals with the preparation of, and the orientation of, the nitro group in β-3-arsonophenoxyethanol.

β-3-Arsonophenoxyethanol was prepared by condensing ethylene chlorohydrin with *m*-nitrophenol, reducing to the corresponding amine, and replacing the amino group by the arsono group by means of the Bart[4] reaction.

Nitration of the sodium salt of β-3-arsonophenoxyethanol at 0° for three hours with 3 molecular proportions of fuming nitric acid (sp. gr. 1.50) gave a mixture of isomeric compounds containing one nuclear nitro group with the alcoholic hydroxyl group esterified.

The mixture of nitro-3-arsonophenoxyethyl nitrates was hydrolyzed with 3 *N* hydrochloric acid to yield β-2-nitro-3-arsonophenoxyethanol and β-6-nitro-3-arsonophenoxyethanol which were separated by fractional crystallization, the former being less soluble than the latter.

Refluxing the isomeric nitro compounds with 6 *N* sodium hydroxide gave the corresponding nitro-3-hydroxyphenylarsonic acids.

3-β-Hydroxyethoxyphenylarsenious oxide, the 2- and 4-nitro derivatives, and 2-nitro-3-hydroxyphenylarsenious oxide were prepared from the corresponding arsonic acids by reduction with sulfurous acid employing hydriodic acid as a catalyst.

The 2- and 4-nitro-3-β-hydroxyethoxyphenylarsenious oxides were converted to the corresponding chloromercuri compounds by refluxing in glacial acetic acid with mercuric acetate and precipitating with sodium chloride or calcium chloride.

The β-2- and 6-nitro-3-chloromercuriphenoxyethanols were converted to β-2-nitrophenoxyethanol[5] by refluxing with dilute hydrochloric acid, which was in turn converted to *o*-nitrophenol showing that the nitro group in each of the isomeric nitro compounds was ortho to the ether linkage. Attempts to replace the chloromercuri group in these compounds with bromine or iodine gave polyhalogenated compounds.

2-Nitro-3-chloromercuriphenol gave *o*-nitrophenol when treated with dilute hydrochloric acid,

(1) Parke, Davis and Company Fellow.

(2) Sweet and Hamilton, THIS JOURNAL, **56**, 2409 (1934); Stevinson and Hamilton, *ibid.*, **57**, 1600 (1935).

(3) Unpublished work, Chemical Laboratory, University of Nebraska.

(4) Bart, *Ann.*, **429**, 55 (1922).

(5) Boyd and Marle, *J. Chem. Soc.*, **105**, 2117 (1914).