which on dehydration may be expected to yield olefins of the type $C_6H_5CC=C(CH_3)_2$ are converted into indanes by 85% sulfuric acid.

2. The isolated intermediate olefins are cyclized to indanes under the influence of 85% sulfuric acid.

3. A case of direct cyclodehydration appears to exist in the conversion of 4-phenyl-1-butanol into tetralin by the action of hot phosphoric acid.

NEW YORK, N. Y. RECEIVED SEPTEMBER 6, 1933

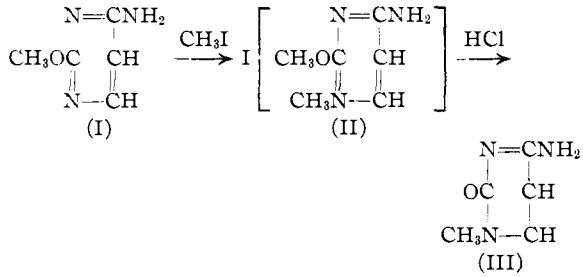
[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY, AND THE FIXED NITROGEN DIVISION OF THE BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

The Alkylation of Pyrimidines. An Attempt to Prepare 1-Glucosidocytosine

BY GUIDO E. HILBERT

With the object of seeking a method for the synthesis of a model of cytidine, the action of methyl iodide on 4-amino-2-methoxypyrimidine (I) was investigated. This method of attack was suggested by previous work[1] in which it was shown that the action of methyl iodide on 2,4-dimethoxypyrimidine yielded 1,2-dihydro-2-keto-1-methyl-4-methoxypyrimidine which was readily converted by hydrolysis to 1-methyluracil. Subsequently,[2] this method for the synthesis of 1-alkyl uracils was extended to the synthesis of nucleosides by the substitution of acetobromoglucose for the alkyl halides in the interaction with 2,4-dimethoxypyrimidine and resulted in the formation of 1,2-dihydro-2-keto-1-tetraacetylglucosido-4-methoxypyrimidine, which on simultaneous deacetylation and dealkylation with alcoholic hydrochloric acid yielded 1-glucosidouracil. One would thus expect by analogy that 4-amino-2-methoxypyrimidine would interact with methyl iodide to form 1-methylcytosine and with acetobromoglucose to form 1-tetraacetylglucosidocytosine, in which the glucose residue probably occupies the same position as ribose in cytidine.

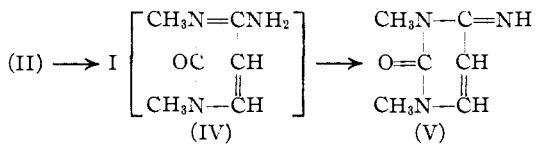
Methyl iodide interacted with 4-amino-2-methoxypyrimidine (I) to yield a crystalline methiodide, $C_6H_{10}N_3OI$. Since there are three potential basic groupings in (I), methyl iodide could form an ammonium salt by combining with either of the cyclic nitrogen atoms in the (1) and (3) positions or with the amino group in the (4) position. Theoretically, since the grouping (—N=C(NH_2)—) is the ammono analog of an amide, (O=C(NH_2)—), interaction of the amino radical with methyl iodide would not be expected under the conditions of this experiment. There is, however, no information that allows one to predict which of the nitrogens in positions (1) and (3) would be more subject to attack. Upon treatment with hydrochloric acid the methiodide lost the elements of methyl iodide to form 1-methylcytosine (III). The structure of this was confirmed by conversion on bromination in aqueous solution to 1-methyl-5-bromouracil, the properties of which were identical with those of a specimen prepared by the bromination of 1-methyluracil. Methyl iodide therefore attacked 4-amino-2-methoxypyrimidine in the (1) position, forming 4-amino-2-methoxypyrimidine-1-methiodide (II). This is the first case in which a stable methiodide has been obtained from this type of pyrimidine and is additional evidence in favor of the mechanism postulating the intermediate formation of a methiodide in the reaction between alkyl halides and 2,4-dialkoxypyrimidines to form 1,2-dihydro-2-keto-1-alkyl-4-alkoxypyrimidines.



On heating, the methiodide (II) melted at 128° with vigorous effervescence and then resolidified to melt again over a wide range from 190–235°. Since Knorr[3] showed that 4-methoxyquinoline-1-methiodide was decomposed on heating to form

(1) Hilbert and Johnson, THIS JOURNAL, **52**, 2001 (1930).
(2) Hilbert and Johnson, *ibid.*, **52**, 4489 (1930).
(3) Knorr, *Ber.*, **30**, 922 (1897).

1-methyl-4-quinolone and methyl iodide, it was expected that at 128° (II) would behave similarly to form 1-methylcytosine (III) and methyl iodide. This in part was found to be the case. As the yield of methyl iodide was only 30–40% of the theoretical, it was evident, however, that the main course of the reaction was in another direction. The pyrolyzed solid was found to consist of a trace of 1,3-dimethylcytosine (V), 1-methylcytosine and an iodo salt which was probably 1-methylcytosine-3-methiodide (IV). As it was impossible to separate (IV) from this mixture in the pure state by ordinary means it was converted in an aqueous solution with silver sulfate to 1,3-dimethylcytosine which in the acid medium hydrolyzed to 1,3-dimethyluracil. This was readily separated from 1-methylcytosine by sublimation. The identification of 1,3-dimethyluracil was completed by a comparison of the properties of it and the bromo derivative with those of authentic specimens. Without doubt, the presence of free 1,3-dimethylcytosine in the degradation product arose from the interaction between (IV) and a base, perhaps 1-methylcytosine. The thermal decomposition of (II) thus involves two reactions (1) degradation with liberation of methyl iodide to yield 1-methylcytosine and (2) the formation of 1-methylcytosine-3-methiodide (IV).



It does not seem possible, since the decomposition is practically instantaneous, that (IV) could have been formed by the interaction of molecular methyl iodide and molecular 1-methylcytosine. The alternative mechanism, in which formation takes place by way of intramolecular rearrangement, seems much more plausible. If this latter mechanism is correct, it is of interest as it may be a new type of rearrangement depending upon whether the rearrangement took place within the positive ion or resulted from the internal reaction of active methyl iodide and active 1-methylcytosine.

As Knorr[4] has shown that cyclic lactams containing the configuration (—N(CH3)—CO—) do not interact with methyl iodide and since the amino group is analogous to that in an amide, it was expected that the nitrogen atom in the (3) position of 1-methylcytosine would be most susceptible to attack by alkyl halides and this has been confirmed. The interaction between 1-methylcytosine and methyl iodide at room temperature required several weeks for completion. The methiodide formed was converted by alkali to 1,3-dimethylcytosine (V), and the introduced methyl group was definitely shown to be in the (3) position since bromination of (V) in water yielded 1,3-dimethyl-5-bromouracil. This particular type of alkylation is interesting since it affords a method for the synthesis of imides, a class of compounds which previously was unknown in the pyrimidine series.

Of theoretical interest is the rearrangement on heating of 4-amino-2-methoxypyrimidine to 1-methylcytosine. This occurred at about 180° and because of interference by the amino group was not nearly as smooth as the analogous rearrangement of 2,4-dimethoxypyrimidine to 1,3-dimethyluracil.[1]

Since the reaction between methyl iodide and 4-amino-2-methoxypyrimidine (I) produced a stable methiodide, the analogous reaction between acetobromoglucose and (I) to yield a stable bromide was anticipated. As one would expect the isolation of either 1-tetraacetylglucosidocytosine or 1-glucosidocytosine to be facilitated by the use of mild conditions in their preparation from 4-amino-2-methoxypyrimidine - 1 - tetraacetylglucosidobromide, it was logical to seek such conditions indirectly by the development of mild means for the preparation of 1-methylcytosine from 4-amino - 2 - methoxypyrimidine - 1 - methiodide (II). A number of methods have been elaborated and perhaps the most desirable, although somewhat laborious, was that involving treatment of an aqueous solution of (II) with silver sulfate. The sulfate presumably was formed and at room temperature was unstable and decomposed to form (III) exclusively.

Acetobromoglucose reacts smoothly with 2,4-dimethoxypyrimidine and as the latter is a liquid, an excess serves as the medium for carrying out the reaction. In the reaction between acetobromoglucose and 4-amino-2-methoxypyrimidine these favorable conditions, however, do not hold since in this case the pyrimidine is a high melting solid that has only slight solubility in organic solvents. The lack of success in finding a proper medium for the reactants has resulted in the uni-

(4) Knorr, *Ber.*, **30**, 929 (1897).

form failure to effect their combination. Since Richardson and Soper[5] have shown that the rate of formation of ammonium salts from alkyl halides and amines is enormously increased by the use of a medium having high "cohesion," most attention was centered on such solvents as acetonitrile and nitromethane. Only in the case of nitromethane were crystalline products isolated. These were the impure hydrobromides of 4-amino-2-methoxypyrimidine and 1-methylcytosine, from which it may be inferred that one of the side reactions involved removal of hydrogen bromide from acetobromoglucose.

An improved procedure for preparing cytosine and isocytosine from 4-amino-2-chloropyrimidine and 2-amino-4-chloropyrimidine, respectively, is recorded in the experimental part.

I wish to express my appreciation for advice and coöperation from Professor Treat B. Johnson. The microanalyses recorded were kindly carried out by Dr. Reid T. Milner and Mrs. M. S. Sherman.

Experimental Part

Preparation of 4-Amino-2-methoxypyrimidine and its Rearrangement to 1-Methylcytosine

Preparation of 4-Amino-2-methoxypyrimidine.—It has been shown previously[6] that the action of a saturated solution of ammonia in alcohol in 2,4-dichloropyrimidine results in the formation of the isomeric 2,4-aminochloropyrimidines and since they are difficult to separate in good yield, the mixture was converted into the isomeric 2,4-aminomethoxypyrimidines by interacting with sodium methylate in alcohol. 4-Amino-2-methoxypyrimidine, the product desired for this investigation, was readily obtained pure by taking advantage of its greater insolubility in water. A mixture of 97 g. of crude, finely divided 2,4-dichloropyrimidine (from 100 g. of uracil) and 500 cc. of concentrated ammonia was warmed on a steam-bath for six hours. The reaction mixture was cooled in an ice-bath and filtered; yield, 68 g. of the crude yellow mixed 2,4-aminochloropyrimidines. The product was converted into the 2,4-aminomethoxypyrimidines as previously described; the yield of pure 4-amino-2-methoxypyrimidine was 20 g.; sintered 168°, m. p. 170°.[7] In the latter reaction it is desirable to use a generous excess of sodium methylate since in one experiment in which there apparently was an insufficient amount, the product more insoluble in water was not homogeneous. On crystallization, various fractions were obtained which individually melted rather sharply somewhere in the range of 176–210°; the different fractions gave tests for halogen and were solid solutions of 4-amino-2-chloropyrimidine with 4-amino-2-methoxypyrimidine, as on further treatment with sodium methylate pure 4-amino-2-methoxypyrimidine was obtained.

Rearrangement of 4-Amino-2-methoxypyrimidine to 1-Methylcytosine.—One-half gram of 4-amino-2-methoxypyrimidine was heated in a test-tube at 180° for five hours. During the course of the heating the melt gradually solidified and turned brown; it had a strong amine-like odor. A small amount of the original pyrimidine that had sublimed on the side of the tube was removed mechanically. The residue was dissolved in a small amount of hot methyl alcohol and the solution treated with an equal volume of benzene. This was placed in the ice box and a brown amorphous powder slowly separated. The solid was collected on a filter, dissolved in 4 cc. of boiling water and decolorized with bone black. The aqueous filtrate was evaporated to dryness and the residue recrystallized several times from alcohol. It separated as colorless prisms; yield 0.025 g.; m. p. 303° (decomp.). It was shown to be 1-methylcytosine by a comparison of its properties with those of an authentic specimen (see below).

Anal. Calcd. for $C_5H_7ON_3$: C, 47.97; H, 5.64; N, 33.60. Found: C, 48.02; H, 5.79; N, 33.55.

Johnson and Clapp[8] prepared 1-methylcytosine by the methylation of cytosine in alkaline solution, and since this method is well known to lead to mixtures which are difficult to separate, it is not surprising that the decomposition point (278–279°) recorded by them is lower than that obtained in this work. However, their statement that the base is volatilized with aqueous vapors has not been confirmed.

4-Amino-2-methoxypyrimidine-1-methiodide and Methods for its Conversion to 1-Methylcytosine

Preparation of 4-Amino-2-methoxypyrimidine-1-methiodide.—A solution of 3 g. of 4-amino-2-methoxypyrimidine in 40 cc. of methyl alcohol was treated with 10 cc. of methyl iodide. The reaction mixture rapidly turned yellow and was allowed to stand at room temperature for twenty-four hours. Upon the rapid addition of 100 cc. of anhydrous ether to the clear solution, the methiodide crystallized in dendritic aggregates of colorless plates. The mixture was cooled overnight and filtered; yield 4.8 g. (75% of the theoretical). The methiodide melted with vigorous effervescence at 128°; the melt quickly solidified and on continued heating sintered at 190° and was completely melted at 230–235° (brown liquid). It is stable for months at room temperature and is extremely soluble in cold water and cold alcohol and insoluble in ether.

Anal. Calcd. for $C_6H_{10}N_3OI$: C, 26.95; H, 3.77; N, 15.74; I, 47.53. Found: C, 26.98; H, 3.88; N, 15.71; I, 47.15.

Preparation of 1-Methylcytosine by the Action of Silver Sulfate on 4-Amino-2-methoxypyrimidine-1-methiodide.—To a solution of 1.92 g. of the methiodide in 10 cc. of water was added a boiling solution of 1.3 g. of silver sulfate in 150 cc. of water. Silver iodide precipitated immediately and after several minutes was filtered off. The excess silver was removed with hydrogen sulfide and the latter expelled by heating the solution for a short time. The excess sulfuric acid was removed quantitatively with

(5) Richardson and Soper, *J. Chem. Soc.*, 1873 (1929).
(6) Hilbert and Johnson, THIS JOURNAL, **52**, 1152 (1930).
(7) All temperatures corrected.
(8) Johnson and Clapp, *J. Biol. Chem.*, **5**, 62 (1908–1909).

barium hydroxide, and the filtrate evaporated to dryness under diminished pressure. The colorless residue was recrystallized from alcohol; yield 0.65 g., m. p. 303° (dec.); a mixed m. p. with 1-methylcytosine was unchanged.

Anal. Calcd. for $C_5H_7ON_3$: C, 47.97; H, 5.64. Found: C, 47.90; H, 5.85.

Decomposition of 4-Amino-2-methoxypyrimidine-1-methiodide in Alcohol.—A solution of 1 g. of the methiodide in 20 cc. of 95% alcohol was heated under reflux on a steam-bath for three hours. Within thirty minutes large crystals separated. The reaction mixture was cooled in an ice-bath and filtered; yield 0.35 g. (75% of the theoretical) of 1-methylcytosine. It was recrystallized from 40 cc. of alcohol and separated as large colorless prisms; it turned brown at 295° and melted with decomposition at 303°.

Anal. Calcd for $C_5H_7ON_3$: C, 47.97; H, 5.64; N, 33.60. Found: C, 47.95; H, 5.77; N, 33.15.

The filtrates from the 1-methylcytosine contained an ammonium salt which gave a test for iodine. That it was not the original methiodide was shown by the fact that on further heating of the alcoholic solution it was recovered unchanged. Later work indicated that it was probably 1-methylcytosine-3-methiodide.

Interaction of the Methiodide with Hydrochloric Acid.—To 1.5 g. of the methiodide was added a few cc. of concentrated hydrochloric acid. On slight warming the solution immediately became cloudy and a heavy oil separated. The reaction mixture was concentrated to dryness on a steam-bath and the crystalline residue dissolved in water and made slightly ammoniacal. The yield of 1-methylcytosine was practically quantitative; m. p. 303° (dec.).

Anal. Calcd. for $C_5H_7ON_3$: N, 33.60. Found: N, 33.43.

Bromination of 1-Methylcytosine.—An excess of bromine was added to a suspension of 0.8 g. of 1-methylcytosine in 5 cc. of water. The resulting clear yellow solution was concentrated to dryness on a steam-bath. The yellowish white crystalline residue was decolorized with bone black and recrystallized from 200 cc. of hot water. 1-Methyl-5-bromouracil separated as a mass of colorless needles; yield 2.0 g.; m. p. 272–274° to a red liquid.

Anal. Calcd. for $C_5H_5O_2N_2Br$: C, 29.27; H, 2.46; N, 13.67. Found: C, 29.40; H, 2.60; N, 13.40.

For purposes of identification it was compared with and found to be the same as a specimen prepared by brominating 1-methyluracil in the same manner as described above. Johnson and Clapp[8] reported the decomposition point of this compound to be at 255–260°.

Thermal Decomposition of 4-Amino-2-methoxypyrimidine-1-methiodide

The methiodide (1.494 g.) was heated in a short, wide test-tube at 130-135°. It liquefied with vigorous effervescence and in a few minutes had resolidified to a pale yellow solid. The volatile matter evolved in the pyrolysis was passed with the aid of a stream of dry air into a tube, which was cooled in a bath of acetone and solid carbon dioxide, and the colorless liquid which condensed was identified as methyl iodide. The pyrolysis of the methiodide was accompanied by a loss in weight of 0.254 g., corresponding to a yield of methyl iodide which was only 32% of the theoretical.

In another experiment 10.8 g. of the methiodide was pyrolyzed by heating at 140° for fifteen minutes. The solid product had an amine-like odor and weighed 8.4 g.; the loss in weight calculated as methyl iodide in this case was 42% of the theoretical.

1,3-Dimethylcytosine.—This was obtained when the reaction product after grinding to a fine powder in a mortar was heated at 140–145° at 1 mm. pressure in a round-bottomed, wide-necked flask. A crystalline product sublimed on the cooler portions of the neck; yield 0.14 g. It melted at 70–115° and was obviously a mixture. 1,3-Dimethylcytosine was separated and obtained quite pure by recrystallizing twice from 2 cc. of benzene; yield 0.04 g.; m. p. 144°. A mixed melting point with that prepared from 1-methylcytosine-3-methiodide (see below) was unchanged.

Anal. Calcd. for $C_6H_9ON_3$: C, 51.76; H, 6.52; N, 30.21. Found: C, 52.21; H, 6.49; N, 30.06.

1,3-Dimethyluracil.—The residue after removal of the above mixture by sublimation was dissolved in 50 cc. of hot water, treated with a suspension of 65 g. of silver sulfate in 300 cc. of water, allowed to stand overnight and filtered. The excess of silver ion was removed by hydrogen sulfide and the sulfate ion quantitatively by barium hydroxide. At this stage considerable ammonia was liberated and expelled by concentrating the filtrate to dryness under diminished pressure. A separation of the more volatile material in the finely ground residue was effected by sublimation by heating at 100° at 1 mm. pressure in a manner similar to that described above. Sublimation was facilitated by occasionally interrupting the experiment and breaking up the residue, which had a tendency to cake. The sublimed material consisted of yellow crystals and weighed 2.34 g.; m. p. 100–120°. It was dissolved in 30 cc. of water, decolorized with bone black, filtered, concentrated to dryness under diminished pressure, recrystallized several times from benzene and finally from a little alcohol; yield 1.8 g., m. p. 122° (corr.). It was very soluble in cold water and hot alcohol and moderately soluble in hot benzene. A striking property was the behavior of the crystals in alcohol, from which they first separated as long needles that on standing for a short time were transformed into large, long rods. A melting point of the product when mixed with 1,3-dimethyluracil[9] was unchanged.

Anal. Calcd. for $C_6H_8O_2N_2$: C, 51.40; H, 5.76; N, 20.00. Found: C, 51.51; H, 5.84; N, 19.76.

1,3-Dimethyl-5-bromouracil.—This has been previously[8] prepared by refluxing 5,5-dibromo-6-hydroxy-5,6-dihydrouracil in absolute alcohol. It was more simply prepared by brominating 1,3-dimethyluracil (0.20 g.) according to the method described for the preparation of 1-methyl-5-bromouracil. 1,3-Dimethyl-5-bromouracil was recrystallized from 25 cc. of hot water and separated as large jagged plates; yield 0.24 g., m. p. 182–183°. A mixed melting point with an authentic specimen was unchanged.

Anal. Calcd. for $C_6H_7O_2N_2Br$: N, 12.79. Found: N, 12.72.

(9) Davidson and Baudisch, THIS JOURNAL, **48**, 2379 (1926)

1-Methylcytosine.—The product remaining after removal of 1,3-dimethyluracil was a yellowish brown solid; weight 2.18 g. It was dissolved in 100 cc. of boiling alcohol and filtered from a small amount of flocculent matter; the alcoholic solution was evaporated to dryness and the residue purified as described above; m. p. 301°; yield 1.2 g.

Anal. Calcd. for $C_5H_9ON_3$: C, 47.97; H, 5.64; N, 33.60. Found: C, 47.99; H, 5.50; N, 33.78.

In one experiment the procedure following the treatment of the pyrolyzed product with silver sulfate was altered in order to avoid hydrolysis of 1,3-dimethylcytosine by neutralizing the acid as rapidly as possible. This allowed the isolation of a considerable amount of 1,3-dimethylcytosine, which was, however, difficult to separate from 1,3-dimethyluracil by simple crystallization.

1,3-Dimethylcytosine

Preparation of 1-Methylcytosine-3-methiodide.—A suspension of 0.46 g. of 1-methylcytosine in a solution of 1.5 cc. of methyl iodide and 7 cc. of absolute methyl alcohol was allowed to stand in the dark at room temperature for several months. The solution became dark red in color and a mass of enormous colorless blocky prisms was present. The solution was decanted from the crystals, which were then thoroughly washed with dry methyl alcohol; yield 0.59 g., m. p. 265–266° (dec. to a red liquid). From the decanted liquid, after adding 40 cc. of ether, cooling and filtering, an additional 0.28 g. of the methiodide was obtained; total yield 88% of the theoretical. It contains iodine and a Zeisel determination showed the absence of methoxy groups. It is soluble in cold water and hot alcohol, from which it may be recrystallized.

Anal. Calcd. for $C_6H_{10}N_3OI$: C, 26.96; H, 3.77; N, 15.74. Found: C, 27.02; H, 3.84; N, 15.48.

Preparation of 1,3-Dimethylcytosine.—A solution of 0.125 g. of 1-methylcytosine-3-methiodide in 2 cc. of water was treated with 4 cc. of concentrated sodium hydroxide. A colorless oil immediately separated and was removed by extraction with chloroform. The chloroform extract was concentrated to dryness, redissolved in dry chloroform and filtered from a small amount of flocculent matter. On evaporation prisms separated; m. p. 144–145°, yield 0.053 g. It was purified by sublimation and separated as bundles of rods of m. p. 147.5°. 1,3-Dimethylcytosine is very soluble in water and alcohol and moderately soluble in benzene.

Anal. Calcd. for $C_6H_8O_2N_2$: C, 51.76; H, 6.52; N, 30.21. Found: C, 51.96; H, 6.53; N, 30.34.

The ammonia liberated by hydrolysis with hydrochloric acid was determined quantitatively. Digestion of 1.920 mg. of substance with 0.01007 *N* hydrochloric acid was carried out on the steam-bath for one hour. The amount of acid neutralized was 1.36 cc., whereas that required by theory for one molecule of ammonia was 1.37 cc.

Bromination of 1,3-Dimethylcytosine.—This was carried out in the same manner as that described for the bromination of 1,3-dimethyluracil. The reaction mixture after evaporation to dryness was digested with cold water and filtered; m. p. 182°. A mixed melting point with 1,3-dimethyl-5-bromouracil was unchanged.

Anal. Calcd. for $C_6H_7O_2N_2Br$: C, 32.88; H, 3.22. Found: C, 32.95; H, 3.61.

Attempts to Prepare 3-Glucosidocytosine

A mixture of 4-amino-2-methoxypyrimidine and acetobromoglucose, when heated above the melting point of the latter, liquefied and then immediately solidified. Further heating was without visible effect. All attempts to isolate a homogeneous product were unsuccessful. No reaction took place when a solution of 4-amino-2-methoxypyrimidine and acetobromoglucose in ether were allowed to stand for several weeks. When quinoline was used as a solvent and the reaction mixture heated at 80° for several hours a brown intractable sirup resulted.

One gram of 4-amino-2-methoxypyrimidine was treated with 50 cc. of nitromethane; the major portion of the pyrimidine dissolved. Upon the addition of 3.33 g. of acetobromoglucose the solution became brown. After standing at room temperature for twenty-four hours large colorless prisms separated; yield 1.0 g.; m. p. 147° (effervescence). The crystals, in the air, very rapidly assumed a chalky appearance, which was apparently due to the loss of solvent of crystallization. The product was very soluble in water and alcohol and attempts to purify by reprecipitating several times from alcohol with ether only depressed the melting point (145°).

Anal. Calcd. for $C_5H_8ON_3Br$: C, 29.13; H, 3.91; N, 20.40. Found: C, 31.20; H, 4.33; N, 22.84.

The analysis would suggest that it was 4-amino-2-methoxypyrimidine hydrobromide contaminated with some of the free base.

Treatment of the salt with an aqueous solution of sodium bicarbonate resulted in vigorous effervescence and the immediate separation of needles of m. p. 170°; a mixed melting point with a specimen of 4-amino-2-methoxypyrimidine was unchanged.

The nitromethane filtrate on standing deposited more crystalline material; yield 0.35 g., m. p. 95–105° (effervescence).

Anal. Found: C, 27.06; H, 4.37; N, 21.33. The calculated values for 1-methylcytosine hydrobromide are C, 25.00; H, 4.19; N, 21.95.

The filtrate from the crystalline material was concentrated and yielded a sirup that did not crystallize.

Preparation of Cytosine.—This has been prepared[6] by hydrolyzing 4-amino-2-chloropyrimidine with water in a bomb tube at 140°. It was more easily prepared by hydrolyzing with concentrated hydrochloric acid.

One-half gram of 4-amino-2-chloropyrimidine was treated with 10 cc. of hydrochloric acid and evaporated to dryness on a steam-bath. The hydrochloride was converted to the free base with ammonia and recrystallized from 15 cc. of water (decolorized with bone black) containing a trace of ammonia. It separated in the large flat plates characteristic of cytosine and contained one molecule of water of crystallization; yield 0.37 g.

Preparation of Isocytosine.—This was also more easily prepared by the same method as that described for cytosine. Isocytosine separated from a hot water solution on rapid chilling in the form of needles and when cooled slowly crystallized as large diamond shaped prisms of m. p. 274–276° (dec.).

Summary

1. A method for the preparation of cytosine derivatives alkylated in the (1) position has been described. Methyl iodide interacts with 4-amino-2-methoxypyrimidine to form 4-amino-2-methoxypyrimidine-1-methiodide which can be converted by a number of procedures to 1-methylcytosine.

2. The thermal decomposition of the methiodide proceeds in two directions (1) degradation to 1-methylcytosine with liberation of methyl iodide and (2) the formation of 1-methylcytosine-3-methiodide probably by intramolecular rearrangement.

3. Interaction of 1-methylcytosine and methyl iodide yielded 1 - methylcytosine - 3 - methiodide, from which 1,3-dimethylcytosine was prepared by treatment with alkali.

4. 4 - Amino - 2 - methoxypyrimidine on heating at 180° rearranged to form 1-methylcytosine.

5. Attempts to introduce glucose in the (1) position of cytosine by the interaction of acetobromoglucose and 4 - amino - 2 - methoxypyrimidine were unsuccessful.

WASHINGTON, D. C. RECEIVED SEPTEMBER 6, 1933

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BROWN UNIVERSITY]

The Chemistry of the Triethylsilicyl Group

BY CHARLES A. KRAUS AND WALTER K. NELSON

I. Introduction

The groups of the type R_3A, where R is an organic group or, occasionally, hydrogen, and A an element of the fourth group of the periodic system, exhibit marked amphoteric properties. Thus, on the one hand, they form compounds with the halogens of the type R_3AX, which exhibit electropolar properties[1] to some extent, and compounds with the alkali metals of the type R_3AM, which exhibit marked electropolar properties.[2] With increasing atomic number, the compounds R_3AX become more electropolar although never strongly so. On the other hand, the compounds R_3AM are in all cases strongly electropolar and there is no marked change in properties with increasing atomic number.

Save in exceptional cases, the free groups R_3A do not normally exist in a monomeric condition; they ordinarily combine to form dimers. Certain of the triarylmethyls seem to be markedly dissociated into the free groups in solution, but the corresponding derivatives of silicon, germanium and tin do not seem to be markedly dissociated in solution under ordinary conditions. Evidence, however, exists that goes to show that as the atomic number of the central element increases, the bond joining the groups in the dimer becomes increasingly weak. In boiling benzene, trimethyltin seems to be partially dissociated.[3] In freezing benzene, however, the compound exists as a dimer.[4] The Ge–Ge bond is much more stable than the corresponding Sn–Sn bond. However, even in the case of germanium the bond is readily broken by either strong oxidizing or reducing agents.[5] The Si–Si bond seems to be uncommonly stable and is not broken either by a strong oxidizing agent such as chlorine[6] or reducing agent such as sodium in liquid ammonia or lithium in ethylamine.[7]

With three stable organic groups attached to an element such as silicon, it becomes possible to investigate the properties of the remaining, fourth, valence of that element. While the properties of this residual valence are doubtless more or less influenced by the nature of the substituents R, nevertheless, in the main, they seem to be controlled by the central atom–silicon, germanium or tin. Some work has previously been carried out in this Laboratory on the triphenylsilicyl group[8] and it seemed worth while to extend the study to aliphatic silicon derivatives. One difficulty with the phenylsilicon derivatives is that the compounds seem to break down completely under the action of strong reducing agents.[9]

The corresponding alkyl derivatives, on the other hand, are entirely stable. Accordingly, the

(1) Kraus and Callis, THIS JOURNAL, **45**, 2624 (1923); Kraus and Greer, *ibid.*, **45**, 2946 (1923).

(2) Kraus and Johnson, *ibid.*, **55**, 2776 (1933); Kraus and Kahler, *ibid.*, **55**, 3537 (1933).

(3) Kraus and Sessions, *ibid.*, **47**, 2361 (1925).

(4) Kraus and Bullard, *ibid.*, **48**, 2131 (1926).

(5) Kraus and Foster, *ibid.*, **49**, 457 (1927).

(6) Meyer and Jacobson, "Lehrbuch der organischen Chemie," Veit and Co., Leipzig, 1907, ed. 2, Vol I, part 1, p. 444.

(7) See Section VIII, below.

(8) Reynolds, Bigelow and Kraus, THIS JOURNAL, **51**, 3067 (1929); Kraus and Eatough, *ibid.*, **55**, 5008 (1933).

(9) Kraus and Rosen, *ibid.*, **47**, 2739 (1925).