TABLE I

PROPERTIES OF BRIDGED COMPOUNDS

No.	Substance	M. p., °C.	Empirical formula	Analyses, % Calcd. C	H	Cl	Mol. wt.	Found C	H	Cl	Mol. wt.	Act. H
IV R, R' = CH_3	Methylated carbinol	286–288[a]	$C_{37}H_{32}O_2$	87.4	6.3			87.5	6.5			2
IV R = CH_3, R' = C_6H_5	Phenylated carbinol	229[b]	$C_{42}H_{34}O_2$	88.5	6.0							2
IV R = CH_3, R' = 4-$CH_3OC_6H_4$	Anisylated carbinol	258[c]	$C_{43}H_{36}O_3$	86.0	6.0		600	86.1	6.3		540[e]	2
IV R = n-C_6H_{11}, R' = C_6H_5	Phenylated carbinol	180–181[d]	$C_{50}H_{50}O_2$	88.0	7.3			87.6	7.2			2
VI R, R' = CH_3	Methylated chloride	235	$C_{37}H_{31}ClO$			6.8	527			6.6	569[c]	1
VI R = CH_3, R' = C_6H_5	Phenylated chloride	198–199[d]	$C_{42}H_{33}ClO$			6.0	588			6.0	508[e]	0[h]
VII R, R' = CH_3	Methylated acetate	199[a]	$C_{39}H_{34}O_3$	85.0	6.2		550	85.1	6.2		543[e]	
VII R = CH_3, R' = C_6H_5	Phenylated acetate	281[f]	$C_{44}H_{36}O_3$	86.3	5.9			86.7	5.8			
VII R = CH_3, R' = 4-$CH_3OC_6H_4$	Anisylated acetate	270[g]	$C_{45}H_{38}O_4$	84.3	5.9			84.3	6.2			
XII R = CH_3	Methylated carbinol	206	$C_{39}H_{36}O_2$	87.3	6.7		536	87.0	6.5		543[e]	1[i]
XII R = C_6H_5	Phenylated carbinol	223	$C_{44}H_{38}O_2$	88.3	6.4			88.2	6.4			
XVII	Anhydride	210–212[a]	$C_{30}H_{26}O_6$	77.2	5.6			77.1	5.6			

[a] From xylene. [b] From n-octane. [c] From butanol. [d] From chloroform–methanol. [e] In benzene. [f] From cymene. [g] From toluene. [h] One addition. [i] Insoluble in reagent.

eighteen hours. The products were handled by suitable operations. The properties of the two bridged products are given in Table I.

1-*p*-Methoxyphenyl-2,5-dimethyl-3,4-diphenylcyclopentadienol, XI, resulted when *p*-methoxyphenylmagnesium bromide reacted with the dimer, IX, by the procedure just described; it crystallized well from benzene, toluene and butanol; and has the melting point of 193–194°. It gives a bluish-violet solution, tinged with red, when dissolved in concentrated sulfuric acid.

Anal. Calcd. for $C_{26}H_{24}O_2$: C, 84.7; H, 6.5; act. H, 1. Found: C, 84.9; H, 6.5; act. H, 1.

The **anhydride,** XVII, of 3,6-dimethyl-4,6-diphenyl-7-*p*-methoxyphenyl-7-hydroxy-3,6-methano-1,2,3,6-tetrahydrobenzene-1,2-dicarboxylic acid was formed by the addition of maleic anhydride to the carbinol, XI, equal weights of the components being heated for two hours at 200°. It was also obtained by two hours' refluxing a benzene solution of the components; any acidic material was extracted by shaking with aqueous sodium carbonate. The properties are given in Table I.

The product from the action of phenylmagnesium bromide upon the dimer, IX, was distilled *in vacuo*, b. p. 197–201° (2 mm.). After recrystallization from *i*-propyl alcohol or heptane, the white 2,5-dimethyl-3,3,4-triphenylcyclopentadienol-1, X, has a melting point of 137–138°; nothing else could be obtained from the yellow solution. The enol gives a yellow solution, with a slight greenish fluorescence, in concentrated sulfuric acid.

Anal. Calcd. for $C_{25}H_{22}O$: C, 88.7; H, 6.6; mol. wt., 338; act. H, 1; addn., 0. Found: C, 88.7; H, 6.5; act. H, 1; addn., 0.25; mol. wt., 304 (in C_6H_6).

It was oxidized by chromic acid and the benzophenone formed was identified in the usual way.[4]

When the phenylated carbinol, (XII, R = C_6H_5), was distilled, there was some decomposition. The solid distillate was triturated with methanol, followed by extraction with hot ligroin (b. p. 90–100°). The latter removed the enol, X, which was identified by a mixed melting point. The insoluble portion was crystallized from benzene–ligroin, and identified by comparison with an authentic specimen of the bimolecular product, IX, and also with its 2,4-dinitrophenylhydrazone. The dimer, IX, was also identified after the other carbinols in the series (XII) had been heated, but the remainder of the material failed to crystallize.

Summary

All three types of bimolecular products formed by the dehydration of anhydroacetonebenzils under acidic conditions have been compared with respect to their behavior with Grignard reagents. They fall into three groups, each having characteristic properties.

The structures which are postulated for the organomagnesium complex of each group appear to account satisfactorily for the behavior.

ROCHESTER 4, NEW YORK RECEIVED MAY 17, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Analogs of Pyridoxine. I. Some Hydroxymethylpyrimidine Derivatives[1]

BY G. E. McCASLAND,[2] D. STANLEY TARBELL, R. B. CARLIN[3] AND NANCY SHAKESPEARE[4]

The synthesis of analogs of pyridoxine (I) for testing as antimalarials was suggested by the work of Seeler,[5] who found that large doses of pyridoxine counteracted the effects of atebrine or quinine on *P. lophurae* in ducks. This might mean that pyridoxine was necessary for growth of the parasites, and hence that its action might be antagonized by a compound differing slightly from it in structure. Accordingly, we attempted the preparation of compounds in which the characteristic groups of pyridoxine are attached to a different heterocyclic ring[6] than the pyridine ring.

There are seven different ways in which the four characteristic groups of pyridoxine might be attached to the four carbon atoms in the pyrimidine ring. The most promising route for any of

(1) The early work on this problem was conducted under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester.

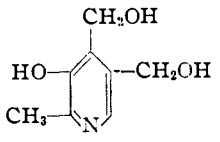
(2) Present address: Department of Chemistry, University of Illinois.

(3) Present address: Department of Chemistry, Carnegie Institute of Technology.

(4) Present address: American Cyanamid Company, Stamford, Connecticut.

(5) Seeler, *Proc. Soc. Exp. Biol. Med.*, **57**, 113 (1944).

(6) Work on thiazole analogs is now in progress in this Laboratory.



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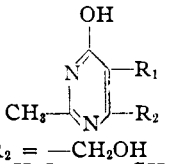
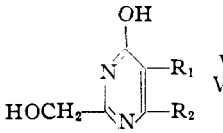


II, $R_1 = R_2 = -CH_2OH$
V, $R_1 = -H$, $R_2 = -CH_2OH$ (hydrochloride)
VI, $R_1 = -H$, $R_2 = -CH_2OC_2H_5$
VII, $R_1 = -Br$, $R_2 = -CH_2OC_2H_5$
VIII, $R_1 = -CN$, $R_2 = -CH_2OC_6H_5$
XI, Diethyl ether of V (picrate)



III, $R_1 = -CH_3$, $R_2 = -CH_2OH$
IV, $R_1 = -CH_2OH$, $R_2 = -CH_3$

these seven analogs seemed to be the condensation of the appropriate amidine or (thio)urea with a suitable β-dicarbonyl component (β-keto-ester or β-diketone). Because pyrimidine has two hetero-atoms and pyridine one, no strictly analogous placement of the four groups on the pyrimidine ring is possible. Since no prediction could be made as to the structure most likely to show activity, attention has arbitrarily been limited to those pyrimidine analogs (II, III, and IV) derivable from β-keto-esters.

Of these three analogs, II would involve the use of acetamidine, and III or IV, hydroxyacetamidine. A β-ketoester of the type R_2COCHR_1COOEt would be required in each case. Theoretically, there were three possibilities as to the R-groups which might be used: (1) either R_1 or R_2, or both, could be the group $-CH_2OH$ itself; or (2) R_1 and R_2 could be groups readily convertible into $-CH_2OH$, such as $-CH_2OR$, $-CH_2NH_2$, $-CN$, $-CH(OEt)_2$, $-CONH_2$, or $-COOEt$; or (3) R_1 or R_2, or both, might be hydrogen, and the $-CH_2OH$ group or a suitable precursor might be introduced after formation of the pyrimidine ring. No very feasible method of preparing a keto-ester such as $HOCH_2COCH(CH_2OH)COOEt$ seemed to be available.

The first synthesis tried for the analog II was suggested by a report of Kircher[7] that 6-methyluracil on treatment with alkaline or acid formaldehyde solution readily gave the 5-hydroxymethyl derivative in high yield. Unfortunately, the reaction failed completely[8] when tried with 2-methyl-4-hydroxy-6-hydroxymethylpyrimidine (V).

The 6-hydroxymethyl compound V was obtained by cleavage of its ether VI with hydrobromic acid. The ether VI was prepared by condensing ethyl γ-ethoxyacetoacetate with acetamidine. It is interesting to note that the hydrobromic acid cleavage gave, instead of the expected bromomethyl hydrobromide, a mixture containing about 75% hydroxymethyl hydrobromide. The pure hydroxymethyl hydrochloride was obtained by hydrolysis with water and debromination with silver chloride.

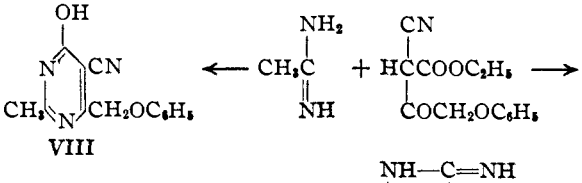
When direct hydroxymethylation of V or VI was found to be impossible, the introduction of one of the precursor groups $-CH_2OCOCH_3$, $-CH_2OCH_3$, $-CH_2Cl$, $-CHO$, and $-NO_2$ into VI was attempted, using a variety of methods and conditions, but without success.

The 5-bromo derivative VII was easily prepared[9] from VI, but it in turn proved to be extremely unreactive, and could not be converted to the 5-nitrile.

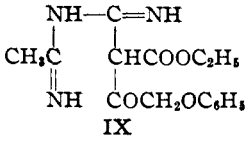
The diethyl ether of V was prepared in the hope that it would be more suitable than VI for some of the reactions previously mentioned. Because the 4-ethoxy group was found unstable to acids (imino-ether properties), the substance was not used for this purpose.

The second attempted synthesis of analog II involved the condensation of the previously reported keto-ester $(C_2H_5O)_2CHCOCH(CH_2OCH_3)COOC_2H_5$[10] with acetamidine. Unfortunately this condensation failed to take place, possibly due to steric hindrance around the keto group.

The third approach to the synthesis of II was by the condensation of ethyl phenoxyacetylcyanoacetate with acetamidine. It was recognized in advance that competitive reactions might result in the formation of any of three pyrimidines, or of three "half-cyclized" intermediates. Nevertheless, there was reason to believe[10a] that the reaction might yield the desired pyridimine (VIII). Actually, the only product isolated gave an analysis agreeing only with the half-cyclized intermediate IX (or isomer).



VIII



IX

In view of the synthetic difficulties encountered with analog II, attention was shifted to the

(7) Kircher, *Ann.*, **335**, 293 (1911).

(8) Work to be described in a subsequent paper indicates that this reaction fails also with 2-hydroxymethyl-4-hydroxy-6-methylpyrimidine, a compound even more closely analogous to 6-methyluracil. It seems that the electron-donating effects of ring-hydroxyls in both ortho and para positions are essential to give the ring-carbon β to nitrogen sufficient nucleophilic properties to condense with formaldehyde. It has also been reported by Johnson and Litzinger [THIS JOURNAL, **58**, 1940 (1936)] that uracil itself fails to condense with formaldehyde. Apparently the electron-donating inductive effect of an ortho methyl group is also important; the hydroxymethyl or alkoxymethyl group would presumably have a smaller effect.

(9) Under acid conditions salt formation at one nitrogen atom would deactivate the pyrimidine ring; but under the alkaline conditions used in bromination the ring would be activated at the β-position, to electrophilic reagents.

(10) Prepared by the method of Rugeley and Johnson, THIS JOURNAL, **47**, 3000 (1925). The ethyl diethoxyacetate needed as starting material for ethyl γ,γ-diethoxyacetoacetate ("Organic Reactions" Vol. I, p. 282) is most conveniently prepared from commercial ethyl dichloroacetate by the one-step method of Cope. THIS JOURNAL, **58**, 570 (1936).

(10a) Todd and Bergel, *J. Chem. Soc.*, 364 (1937); Foldi and Salamon, *Ber.*, **74**, 1126 (1941); *C. A.*, **36**, 4825 (1942).

more promising compounds III and IV, and the experimental work on II is now described.

Experimental[11]

Ethyl γ-Ethoxyacetoacetate[12] (X).—This compound was prepared in 11% yield from ethyl ethoxyacetate. The method was similar to that described for the alpha methyl derivative in Paper II. In view of the low yield, numerous other methods of preparing X were investigated, but all were less satisfactory than the above method.[13]

2-Methyl-4-hydroxy-6-ethoxymethylpyrimidine[14] (VI).—A 51.0-g. portion of X and a 27.6-g. portion of acetamidine hydrochloride (Merck) were dissolved in 118 cc. of 5 *N* sodium hydroxide. The resulting solution was kept at 25° for ninety hours, filtered, and glacial acetic acid (about 16 cc.) added until precipitation was complete. The dried product (VI) weighed 38.5 g., m. p. 130–140°. It was dissolved in boiling benzene (4 cc. per g.) and filtered (heated funnel). On cooling, the filtrate yielded colorless flat needles; weight 24 g. (49%), m. p. 150–154°. A sample recrystallized again from benzene, for analysis, showed a m. p. of 155–157°.

Anal.[15] Calcd. for $C_8H_{12}O_2N_2$: C, 57.12; H, 7.19. Found: C, 57.62; H, 7.27.

The ultraviolet absorption spectrum (absolute ethanol) showed an extinction maximum of 9300 at $\lambda = 275$ mμ, a minimum of 4300 at 240 mμ, and strong end-absorption below 230 mμ. A comparison with spectra reported by Heyroth and Loofbourow[16] for various pyrimidines agreed with the assigned structure.

Slow evaporation of a solution of VI in 6 *N* hydrochloric acid yielded a hydrochloride, stout colorless needles, m. p. 199–201°, with dec. A similar procedure gave the hydrobromide, plates, m. p. 190–191°, with dec. Treatment of VI with ethanolic picric acid gave a picrate, photosensitive yellow needles, m. p. 155–157°.

2-Methyl-4-hydroxy-6-hydroxymethylpyrimidine Hydrochloride (V).[17] A.—A 17.0-g. portion of VI was dissolved in 100 ml. of 8.8 *M* hydrobromic acid and the solution refluxed for nine hours. The solvent was removed under reduced pressure, the residue was dissolved in 100 ml. of water, and again distilled to dryness. The residue was filtered, washed (ethanol, 20 ml.), and dried *in vacuo*. The yield was 20.4 g. colorless powder, m. p. 231–232°, with decomposition. A sample was recrystallized for analysis from 80% acetic acid, yielding colorless prisms, m. p. 251–253°, with decomposition. The analysis indicated that the sample was not the expected 6-bromomethyl hydrobromide, but a mixture containing about 92% of the 6-hydroxymethyl hydrobromide.

Anal. Calcd. for 92% mixture: C, 32.0; H, 4.0; Br, 37.7. Found: C, 31.69; H, 4.21; Br, 37.43.

B.—Another portion (14.4 g.) of VI was cleaved with hydrobromic acid in the same manner, except that no water (other than that in the concentrated acid) was added. The distillation residue was washed with ethanol, and dried *in vacuo*. The colorless powder thus obtained weighed 18.0 g. and melted at 236–237°, with decomposition. A sample of this product was recrystallized for analysis from 8.8 *M* hydrobromic acid; the melting point was unchanged. Analysis indicated that the product so prepared contained about 75% of the hydroxymethyl hydrobromide.

Anal. Calcd. for 75% mixture: C, 30.79; H, 3.79; Found: C, 30.72, 30.91; H, 4.01, 3.95.

C.—In order to obtain V, 38.0 g. of the crude cleavage product from B was added to 58 g. of freshly precipitated silver chloride. The mixture was suspended in one liter of water and boiled about thirty minutes with stirring, cooled, and filtered with suction. The filtrate was evaporated to dryness *in vacuo* over sodium hydroxide, and the residue recrystallized by dissolving it in 27 ml. of boiling water and adding 100 ml. of acetone. The colorless crystalline powder which separated weighed, after drying, 16.0 g. (55%, based on VI). The powder melted at 244–246°, with decomposition. A sample was recrystallized for analysis from acetone–water (4:1), yielding colorless needles, m. p. 248–250°, with decomposition.

Anal. Calcd. for $C_6H_8O_2N_2 \cdot HCl$: C, 40.80; H, 5.14; Cl, 20.08. Found: C, 40.51; H, 5.32; Cl, 19.93.

The attempted hydroxymethylation (or chloromethylation) of V with formaldehyde or paraformaldehyde in aqueous solutions of alkali hydroxide or hydrochloric acid yielded unchanged starting material (or the corresponding free base).

2-Methyl-4-hydroxy-5-bromo-6-ethoxymethylpyrimidine (VII).—A 6.8-g. portion of VI was suspended in a solution of 2.1 g. of sodium carbonate in 15 ml. of water, and 6.5 g. of bromine was added dropwise with stirring. The mixture was decolorized with sodium bisulfite, heated just to boiling, and allowed to cool. The colorless prisms which separated weighed, after drying, 8.6 g., m. p. 135–138°. The crystals (7.3 g.) were recrystallized from 8 ml. of water, yielding 6.7 g. of colorless prisms; m. p. 136–138°. A sample recrystallized again from water, for analysis, showed a m. p. of 136–138°.

The compound gave a positive sodium-fusion test for halogen, but was completely inert to hot alcoholic silver nitrate. Likewise all attempts to prepare the analogous nitrile by treatment with potassium cyanide in aqueous ethanol or aqueous diethylene glycol, or with cuprous cyanide in pyridine, were unsuccessful.

Anal. Cald. for $C_6H_{11}N_2Br$: C, 38.88; H, 4.49; Br, 32.34. Found: C, 38.79; H, 4.54; Br, 32.52.

2-Methyl-4-ethoxy-6-ethoxymethylpyrimidine Picrate (XI).—A 3.4-g. portion of VI was converted to the crude 4-chloro compound (red liquid) according to the directions of Stein, *et al.*[18]

A solution of 4.3 g. of the crude chloro compound in 15 ml. of absolute ethanol was added dropwise to a boiling solution of 0.7 g. of sodium in 30 ml. of absolute ethanol during thirty minutes. The mixture was cooled, brought to *p*H 6–7 with acetic acid, and filtered. To the hot filtrate was added 3.5 g. of picric acid. On cooling, the solution deposited 4.4 g. of thick orange needles, m. p. 90–92°. A second crop of 0.5 g., m. p. 90–92° was obtained: total yield, 4.9 g. (57%). The compound gave a negative sodium-fusion test for halogen. A sample recrystallized twice more from ethanol, for analysis, gave thick yellow needles, m. p. 91–93°.

Anal.[19] Calcd. for $C_{16}H_{20}O_9N_5$: C, 45.07; H, 4.74; N, 16.43. Found: C, 45.20; H, 4.57; N, 16.26.

(11) Analyses by Dr. Carl Tiedcke, except as noted. All melting and boiling points are corrected.

(12) Sommelet, *Bull. soc. chim.*, [4] **29**, 553 (1931); Johnson and Chernoff, This Journal, **36**, 1742 (1914).

(13) Only one of these will be mentioned. It was hoped that ethyl ethoxyacetylacetoacetate could be split preferentially, following the method of Bouveault and Bongert, *Bull. soc. chim.*, [3] **27**, 1090 (1902), to yield acetamide and X; the cleavage, however, took the other course exclusively, to give ethyl acetoacetate and ethoxyacetamide.

(14) This compound is apparently not listed in *C. A.* It is mentioned in *Chem. Zentr.*, **109**, I, 937 (1938), referring to some patents (British 471,416; French 816,432). Ethyl γ-ethoxyacetoacetate and acetamidine were condensed with sodium ethoxide to give a compound melting at 158°. In 1941 Stein, *et al.* (This Journal, **63**, 2059 (1941)) mentioned preparation of the compound and gave the above patents as reference, but gave no analysis or further details.

(15) Analysis by Lois E. May, Columbia University.

(16) Heyroth and Loofbourow, This Journal, **56**, 1728 (1934).

(17) This compound is not listed in the indices to either *C. A.* or the *Chem. Zentr.* However, its preparation is mentioned in the *Zentralblatt* patent abstract above.[14] Heating of the ether (VI) with hydrochloric acid reportedly gave a mixture of the 6-hydroxymethyl hydrochloride (m. p. 264°) and the 6-chloromethyl hydrochloride (m. p. 232°) (we found the former m. p. to be 246°). The abstract gives no further details.

(18) Stein, *et al.*, This Journal, **63**, 2059 (1941). The compound name was misprinted "...5-chloro..."

(19) Analysis by Micro-Technical Laboratories.

By treatment of the picrate with lithium hydroxide[20] and ether, the free base was obtained as a yellow oil, which was unstable in the presence of mineral acids.

Ethyl α-Phenoxyacetyl-β-imino-β-acetamidinopropionate (IX).—To a solution of 0.23 g. of sodium in absolute alcohol was added 0.95 g. of acetamidine hydrochloride, the mixture chilled, and the sodium chloride filtered off; the residue was washed with 1 ml. of absolute alcohol, and the combined filtrates added to a solution of 2.5 g. of ethyl phenoxyacetylcyanoacetate (XVI)[21] in 5 ml. of alcohol. After standing for two days at room temperature, the colorless hexagonal prisms which separated weighed 0.9 g., m. p. about 125°. The product (0.7 g.) was recrystallized from 5 ml. of water, giving 0.7 g., m. p. 130–132°. If allowed to resolidify, the compound melted again at the same temperature. The analytical sample (from water) melted at 131–132°. The analysis agrees only with IX.

Anal. Calcd. for $C_{15}H_{18}N_3O_4$: C, 59.02; H, 6.27; N, 13.77. Found: C, 59.16; H, 6.50; N, 13.43.

The reaction of one mole each of acetamidine hydrochloride, XVI, and sodium hydroxide in dilute aqueous ethanol also gave the product IX.

When two or three moles of sodium hydroxide were used, IX was not obtained but colorless needles separated from the alkaline solution. The analyses showed a high ash content (17–21%), and indicated that the product in this case was probably sodium phenoxyacetylcyanoacetate.

(20) Burger, THIS JOURNAL, **67**, 1615 (1945).

(21) Prepared in 46% yield by the action of phenoxyacetyl chloride on ethyl sodiocyanoacetate (Weizmann, Stephen and Agashe, *J. Chem. Soc.*, **103**, 1865 (1913).

Summary

Investigations concerning the synthesis of pyrimidine analogs of pyridoxine, and leading to the preparation of 2-methyl-4-hydroxy-6-hydroxymethylpyrimidine hydrochloride and a number of related compounds, are described.

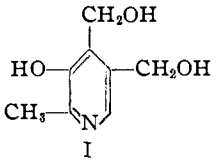
ROCHESTER, NEW YORK RECEIVED JUNE 12, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

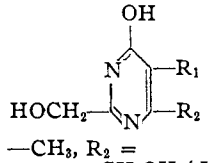
Analogs of Pyridoxine. II. Synthesis of a Pyrimidine Analog

BY G. E. MCCASLAND[1] AND D. STANLEY TARBELL

In continuation of our studies[2] on the synthesis of analogs of pyridoxine (I), we wish to report the synthesis of 2-hydroxymethyl-4-hydroxy-5-methyl-6-hydroxymethylpyrimidine hydrochloride (II). This analog has the four characteristic groups of pyridoxine attached to a pyrimidine, instead of a pyridine, ring.

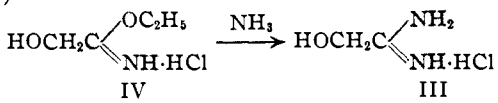


I



II, R_1 = $-CH_3$, R_2 = $-CH_2OH$ (·HCl)
V, R_1 = $-H$, R_2 = $-CH_3$
VI, R_1 = $-CH_2OH$, R_2 = $-CH_3$

The needed intermediate, hydroxyacetamidine hydrochloride (III), was prepared by ammonolysis of the corresponding imino-ether hydrochloride (IV)



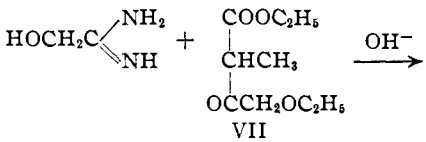
IV III

The imino-ether hydrochloride was obtained on treatment of an ethereal solution of formaldehyde cyanohydrin with absolute ethanol and anhydrous hydrogen chloride; the cyanohydrin itself was not isolated.

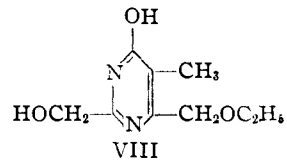
Since hydroxyacetamidine had not previously been used for the preparation of pyrimidines,[3] a reaction with ethyl acetoacetate was first tried. The desired pyrimidine (V), which is apparently the first known pyrimidine with a 2-hydroxymethyl group, was readily obtained. The insolubility of V in water is rather surprising when compared with the high solubility of similar pyrimidines.

It was hoped that V would react with formaldehyde, in the same manner[4] as 6-methyluracil, to give the pyridoxine analog, VI. This reaction failed to occur, and other methods of preparing VI are being investigated.

For the synthesis of the analog II, ethyl α-methyl-γ-ethoxyacetoacetate (VII) was needed. This keto-ester was prepared by a Reformatsky reaction from ethyl α-bromopropionate and ethyl ethoxyacetate. Condensation with hydroxyacetamidine yielded the pyrimidine-ether (VIII)



VII



VIII

This ether was cleaved with hydrobromic acid, presumably first forming the di-(bromomethyl) hydrobromide. Hydrolysis of the latter with boiling water, followed by debromination with silver chloride, gave the di-(hydroxymethyl) hydrochloride (II), an analog of pyridoxine. This is

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(2) For preceding paper see McCasland, Tarbell, Carlin and Shakespeare, THIS JOURNAL, **68**, 2390 (1946).

(3) The use of hydroxyacetamidine for the preparation of 2-hydroxymethylimidazolines was recently reported by Klarer and Urech (*Helv. chim. acta*, **27**, 1762 (1944); *C. A.*, **40**, 1493 (1946)).

(4) For discussion, see preceding paper.[2]