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.

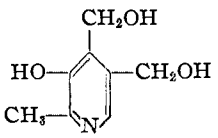
ROCHESTER, NEW YORK RECEIVED JUNE 12, 1946

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

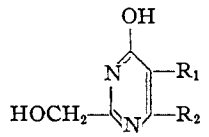
Analogs of Pyridoxine. II. Synthesis of a Pyrimidine Analog

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.

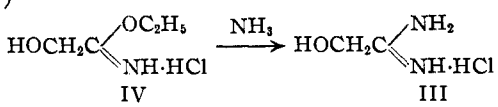


I



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)



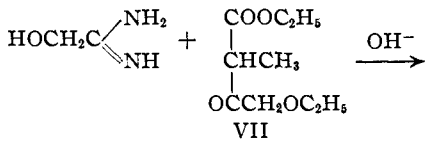
IV III

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.

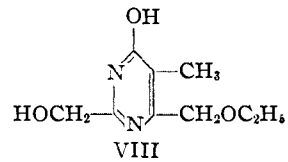
Since hydroxyacetamidine had not previously been used for the preparation of pyrimidines,[3] a reaction with ethyl acetoacetate was first tried. The desired pyrimidine (V), which is apparently the first known pyrimidine with a 2-hydroxymethyl group, was readily obtained. The insolubility of V in water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

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

(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]

apparently the first known pyrimidine with two hydroxymethyl groups.

A preliminary attempt to synthesize II from the intermediate ethyl α-methyl-γ,γ-diethoxyacetoacetate and hydroxyacetamidine was unsuccessful, when the pyrimidine condensation failed to occur.

Tests of the analog II for antimalarial activity are planned. Tests of II for pyridoxine, and for anti-pyridoxine, activity by Dr. H. W. Cromwell and Mrs. Eleanor Willerton of the Abbott Laboratories, using cultures of *Saccharomyces cerevisiae*, showed negative results.

Experimental[5]

Hydroxyacetimino-ether Hydrochloride (IV).—The method of Slater and Stephen[6] for the preparation of hydroxyacetonitrile was found much more satisfactory than that of Houben and Pfankuch[7]; it was modified as follows. To a solution of 65 g. of potassium cyanide in 200 ml. of water at 0–5° was added 30 g. of finely ground paraformaldehyde in portions, during twenty to forty minutes, keeping the temperature below 10°. After stirring one hour more, a small residue of solid remained (not filtered). Then 7.5 *N* sulfuric acid (about 140 ml.) was added until the *p*H fell to 2. Sodium carbonate was added until the *p*H rose to 3–5, and the solution and precipitate were washed with 800 ml. of ether in three portions. (Use of a continuous extractor at this point would undoubtedly raise the yield.) The ethereal solution of nitrile was dried successively over anhydrous sodium sulfate and Drierite, concentrated *in vacuo* to about 175 ml., and used directly for preparation of IV.

To the ethereal nitrile solution was added 46.5 ml. of absolute ethanol, and thoroughly dried hydrogen chloride was passed in at 0° until crystallization of IV was complete (about four hours). The crystals were collected on a sintered glass filter, washed with dry ether, and dried *in vacuo*, giving 39 g. (28%) of IV, colorless flat needles, m. p. 119–121°, with decomposition.[8]

Hydroxyacetamidine Hydrochloride[9] (III).—Absolute ethanol was saturated with dry ammonia gas at 0°, the concentration checked by titration, and adjusted to 6 *M*. Then 75 ml. of the resulting solution was added to a suspension of 39 g. of IV in 100 ml. of absolute ethanol (the solid was first ground to a paste with part of the ethanol). The mixture was stirred for three hours at 25° with exclusion of moisture. Then 100 ml. more ethanol was added, and the mixture refluxed for twenty to thirty minutes, and filtered with a hot funnel. The filtrate, on cooling, deposited 21 g. of colorless needles, m. p. 143–145°. Recrystallization from 200 ml. of absolute ethanol gave 11.9 g. (38%) of III, m. p. 147–149° (reported m. p. 150°).

2-Hydroxymethyl-4-hydroxy-6-methylpyrimidine (V).—An 8.3-g. portion of hydroxyacetamidine hydrochloride was dissolved in 38 ml. of 2 *N* sodium hydroxide, and 9.4 ml. of ethyl acetoacetate was added immediately. The mixture was shaken well, and allowed to stand at 25°. After a few hours, crystals of V began to separate, and the *p*H had fallen from 12–13 to 8. After twenty-four hours, the *p*H was adjusted to 4–6 with acetic acid, and the mixture refrigerated for a day. The crystals were collected, washed with water (10 ml.) and ether (10 ml.) and dried, giving 5.0 g. (48%) of V, stout colorless needles, melting range 180–205°. The resolidified compound melted again over the same range. The melting range was unchanged on repeated recrystallization from 85% ethanol.

Anal. Calcd. for $C_6H_8O_2N_2$: C, 51.47; H, 5.76; N, 20.01. Found: C, 51.53; H, 5.56; N, 19.67.

Attempted hydroxymethylation of V with alkaline formaldehyde gave only starting material. Attempted acetoxymethylation (or chloromethylation) with chloromethyl ether in acetic acid gave unpurifiable mixtures.

Ethyl α-Methyl-γ,γ-diethoxyacetoacetate[10] (IX).—To 36 ml. of absolute ethanol was added 2.3 g. of sodium in small pieces under reflux. When all the sodium had dissolved, 21.8 g. of ethyl γ,γ-diethoxyacetoacetate[2] was added all at once, and the red solution refluxed thirty minutes. After distilling off most of the ethanol *in vacuo*, and cooling, 30 ml. of ether and 20 ml. of water were added. The aqueous phase was extracted with ether, and the combined ethereal phases dried and fractionated. The product, a colorless liquid, b. p. 110–112° (4–6 mm.), $n^{20}D$ 1.4262, weighed 17.1 g. (74%) [reported b. p., 110–112° (4–6 mm.)].

When IX was treated with hydroxyacetamidine in aqueous alkali, no pyrimidine was formed.

Ethyl α-Methyl-γ-ethoxyacetoacetate (VII).—The method of Johnson and Chernoff[11] was modified as follows. C. P. cleaned and dried[12] zinc turnings (65.4 g.) were placed in a 2-liter, 3-necked flask provided with a reflux condenser, dropping funnel, and sealed Hershberg stirrer. Under anhydrous conditions, a mixture of 10 ml. each of ethyl ethoxyacetate,[2] ethyl α-bromopropionate, and dry benzene was added all at once. A crystal of iodine was added, and the mixture heated with a flame, with stirring, until a vigorous exothermic reaction started. Then a mixture of 125 ml. of ethoxyacetate, 15 ml. of bromopropionate, and 100 ml. of dry benzene was added dropwise, with sufficient external heating to maintain boiling. Finally, the mixture was heated on the steam-bath while a mixture of 113 ml. of bromopropionate and 100 ml. of benzene was added dropwise. Heating was continued for one hour after the last addition (nearly all zinc dissolved), and the mixture allowed to cool for several hours.

The mixture was finally cooled to 0°, and decomposed by adding gradually 100 g. of ice in small pieces, followed by an ice-cold solution of 520 ml. of 2.8 *N* sulfuric acid. The mixture was transferred to a separatory funnel, shaken well and separated. The separated aqueous phase was washed with benzene. The combined benzene phases were washed with a 300-ml. portion of 3 *M* ammonium hydroxide, and twice more with 100-ml. portions. The benzene phase was then washed repeatedly with water, and dried.

Most of the benzene was removed by distillation on the steam-bath down to 40 mm. On fractionation of the residue there was obtained 39–40 g. of forerun (mainly ethyl ethoxyacetate). The product boiled at 91–96° (6 mm.), $n^{20}D$ 1.4270, $M^{20}D$ 47.6 (calcd. 47.0), and weighed 27 g. (14%, based on ethoxyacetate and not allowing for recoverable starting material). The distilling flask residue, $n^{20}D$ 1.4420, weighed 26 g.

2-Hydroxymethyl-4-hydroxy-5-methyl-6-ethoxymethylpyrimidine (VIII).—A 2.2-g. portion of hydroxyacetamidine hydrochloride was dissolved in 10 ml. of 2 *M* sodium hydroxide, and 3.68 ml. of the keto-ester VII was immediately added. The mixture was shaken vigorously at intervals for a few hours. After one day, 10 ml. more of 2 *M* sodium hydroxide was added, and the mixture allowed to stand for three days more. The mixture was then filtered, and the clear yellow filtrate adjusted to *p*H 4–6 with hydrochloric acid, and distilled to dryness *in vacuo*. The solid residue was extracted twice with 15-ml. portions of boiling ethanol, sodium chloride removed by filtration, and the ethanolic filtrate distilled to dryness *in vacuo*. The slightly sticky solid residue was recrystallized from

(5) Analyses by Micro-Technical Laboratories. All melting and boiling points are corrected.

(6) Slater and Stephen, *J. Chem. Soc.*, 312 (1920).

(7) Houben and Pfankuch, *Ber.*, **59**, 2398 (1926).

(8) Houben and Pfankuch[7] reported the preparation of the imino-ether hydrochloride, but did not give its melting point.

(9) Rule (*J. Chem. Soc.*, **113**, 5 (1918)) mentioned the preparation of this compound, but few details were given.

(10) Dakin and Dudley, *J. Chem. Soc.*, 2456 (1914); Johnson and Cretcher, *J. Biol. Chem.*, **26** 106 (1916).

(11) Johnson and Chernoff, THIS JOURNAL, **35**, 593 (1913); Johnson, *ibid.*, **35**, 582 (1913).

(12) "Organic Reactions," Vol. I, p. 16.

10 ml. of nitromethane, yielding 1.6 g. of colorless needles, m. p. 91–114°. Two more recrystallizations from nitromethane gave 0.7 g. (18%) of VIII, colorless needles, m. p. 124–126° (m. p. unchanged after fusion). The compound is very soluble in water, less soluble in alcohol or acetone, and insoluble in benzene.

Anal. Calcd. for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.14. Found: C, 54.50; H, 7.00; N, 14.04.

2,6-Di-(hydroxymethyl)-4-hydroxy-5-methylpyrimidine Hydrochloride (II).—The pyrimidine-ether VIII (400 mg.) was boiled under reflux for two hours with 2.0 ml. of 8.8 *M* hydrobromic acid. After cooling, the mixture was diluted with 20 ml. of water, filtered, and the filtrate distilled to dryness *in vacuo*. Addition of water and distillation were repeated twice more, to remove excess acid. The residue, a viscous, brown, non-crystallizable oil, was dissolved in 20 ml. of water and the solution boiled one hour. The hot solution was debrominated by stirring a few minutes with 1.3 g. of freshly precipitated and washed silver chloride. The filtrate from the yellow silver halide precipitate was distilled to dryness *in vacuo*, leaving 200 mg. of solid residue, m. p. 152–162°. After two recrystallizations from acetic acid, there was obtained 154 mg. of II, colorless irregular platelets, m. p. 167–169°.

Anal. Calcd. for $C_7H_{11}O_3N_2Cl$: C, 40.68; H, 5.37; N, 13.56. Found: C, 40.31; H, 5.43; N, 13.18.

Summary

The synthesis of 2,6-di-(hydroxymethyl)-4-hydroxy-5-methylpyrimidine hydrochloride, a pyrimidine analog of pyridoxine, has been described. The synthesis of two other 2-hydroxymethylpyrimidines is reported.

ROCHESTER, NEW YORK RECEIVED JUNE 12, 1946

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some 4-Aminoquinoline and 9-Aminoacridine Derivatives

BY CHARLES E. KWARTLER AND PHILIP LUCAS[1]

The preparations of some 4-aminoquinoline derivatives[2] in these Laboratories have been described recently. Further work has been carried out on the preparation of 4-amino-7-chloroquinoline and 4-amino-7-chloro-3-methylquinoline derivatives. The necessary 4,7-dichloroquinoline and 4,7-dichloro-3-methylquinoline were prepared as described previously.[2b,2f]

For this study a series of 4-dialkylamino-2-phenylbutylamines (Table II) with substituents on the benzene ring was prepared by catalytic reduction, in the presence of Raney nickel and excess ammonia, of the correspondingly substituted γ-dialkylamino-α-phenylbutyronitriles (Table I). The preparation of γ-diethylamino-α-phenylbutyronitrile by the condensation of β-chloroethyl-

TABLE I

NITRILES

Compd., nitrile	B. p. °C.	Mm.	Formula	Analyses, % Basicity as amino nitrogen Calcd.	Found	Nitrogen Calcd.	Found
γ-Dimethylamino-α-phenylbutyro-[a]	130	4	$C_{12}H_{16}N_2$	..	..	...	...
γ-Diethylamino-α-phenylbutyro-[b]	110	0.5	$C_{14}H_{20}N_2$	6.48	6.49	...	...
α-(*p*-Chlorophenyl)-γ-diethylaminobutyro-	124–126	1	$C_{14}H_{19}ClN_2$	5.59	5.51	11.18	10.94
α-(3,4-Dichlorophenyl)-γ-diethylaminobutyro-	130	0.5	$C_{14}H_{18}Cl_2N_2$	4.92	4.90	9.83	9.55
γ-Diethylamino-α-(*p*-methoxyphenyl)-butyro-	120	0.5	$C_{15}H_{22}N_2O$	5.69	5.74	11.38	11.07
α-(*p*-Chlorophenyl)-δ-diethylaminovalero-	138–139	0.5	$C_{15}H_{21}ClN_2$	5.29	5.32	...	...

[a] Hydrochloric acid salt, m. p. 163–165°; *anal.* Calcd. for $C_{12}H_{16}N_2 \cdot HCl$: N, 12.46. Found: N, 12.40, 12.20. [b] Eisleb, *Ber.*, **74B**, 1433–1450 (1941). Hydrochloric acid salt, m. p. 115–117°; *anal.* Calcd. for $C_{14}H_{20}N_2 \cdot HCl$: N, 11.09. Found: N, 11.02, 11.33.

TABLE II

AMINES

Compd., amine	B. p. °C.	Mm.	Formula	Analyses, % Basicity as amino nitrogen Calcd.	Found	Nitrogen Calcd.	Found
4-Dimethylamino-2-phenylbutyl-	145	13	$C_{12}H_{20}N_2$	14.59	14.10	...	...
4-Diethylamino-2-phenylbutyl-	174–176	27	$C_{14}H_{24}N_2$	12.72	12.42	...	...
2-(*p*-Chlorophenyl)-4-diethylaminobutyl-	113	1	$C_{14}H_{23}ClN_2$	11.00	10.83	11.00	10.72
2-(3,4-Dichlorophenyl)-4-diethylaminobutyl-	125	1	$C_{14}H_{22}Cl_2N_2$	9.77	9.77	9.77	9.90
4-Diethylamino-2-(*p*-methoxyphenyl)-butyl-	133–136	1	$C_{15}H_{26}N_2O$	11.20	11.02	11.20	10.88
2-(*p*-Chlorophenyl)-5-diethylaminopentyl-	123–124	0.5	$C_{15}H_{25}ClN_2$	10.42	9.89	...	...

(1) Present address: Massengill Chemical Co., Bristol, Tennessee.

(2) (a) Huber, Bair and Laskowski, THIS JOURNAL, **67**, 1619 (1945); (b) Surrey and Hammer, *ibid.*, **68**, 113 (1946); (c) Steck, Hallock and Holland, *ibid.*, **68**, 129 (1946); (d) Steck, Hallock and Holland, *ibid.*, **68**, 132 (1946); (e) Huber, Laskowski, Jackman and Clinton, *ibid.*, **68**, 322 (1946); (f) Steck, Hallock and Holland, *ibid.*, **68**, 380 (1946).