RMgX and RLi compounds if an organic halide is also present.[4] Actually, rhenium trichloride also catalyzed a reaction between methylmagnesium iodide and methyl iodide.

Experimental

A sample of rhenium trichloride[5] was freshly resublimed *in vacuo* at 500–550° to give a dark red crystalline solid.[6]

Anal.[7] Calcd. for $ReCl_3$: Re, 63.65; Cl, 36.35. Found: Re, 63.82, 64.35; Cl, 36.05, 36.24.

The powdered rhenium trichloride, 2.50 g. (0.0085 mole), dissolved partially in 20 cc. of ether to give a red-violet solution. This mixture was stirred while 27 cc. of 1.09 molar (0.0294 mole) of methylmagnesium iodide was added during ten minutes. An immediate darkening occurred, but there was no noticeable heat evolution. The mixture was stirred at room temperature for thirty minutes, during which time a steady evolution of gas took place. This gas was collected over water, and analysis showed a 27.2% yield of methane and an 8.2% yield of ethane based on the methylmagnesium iodide. After thirty minutes, the mixture (still evolving gas) was cooled in an ice-bath and cautiously hydrolyzed with 50 cc. of 2 *N* hydrochloric acid, to yield an additional 56% of methane, and a trace (0.00073 mole) of hydrogen.

In another experiment, carried out under corresponding conditions, there was isolated 0.00095 mole of hydrogen, in addition to methane, from the hydrolysis. It is probable that the hydrogen resulted from the action of hydrochloric acid on metallic rhenium, which may have been formed by reduction of some of the rhenium trichloride by methylmagnesium iodide.

A mixture of 0.03 mole of methyl iodide, 0.03 mole of methylmagnesium iodide and 0.0005 mole of rhenium trichloride in 50 cc. of ether was allowed to stand for seventy-two hours. During this time 0.0104 mole of methane was evolved. A blank experiment run in the same apparatus but using only methylmagnesium iodide and pure ether, gave 0.0029 mole of methane due to hydrolysis of the methylmagnesium iodide.

(4) A striking illustration is the effect of the quality of magnesium on the yields of cyclohexylmagnesium chloride and bromide: Gilman, Zoellner, Selby and Boatner, *Rec. trav. chim.*, **54**, 584 (1935); see, particularly, pp. 590–593.

(5) The authors are grateful to Dr. George Calingaert for supplying the rhenium trichloride.

(6) Geilmann, Wrigge and Biltz, *Nachr. Ges. Wiss. Göttingen, Math.-physik. Klasse* No. 5, 579 (1932); [*C. A.*, **28**, 60 (1934)].

(7) The rhenium was precipitated as nitron perrhenate which was dried and weighed: Geilmann and Voigt, *Z. anorg. allgem. Chem.*, **193**, 311 (1930).

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

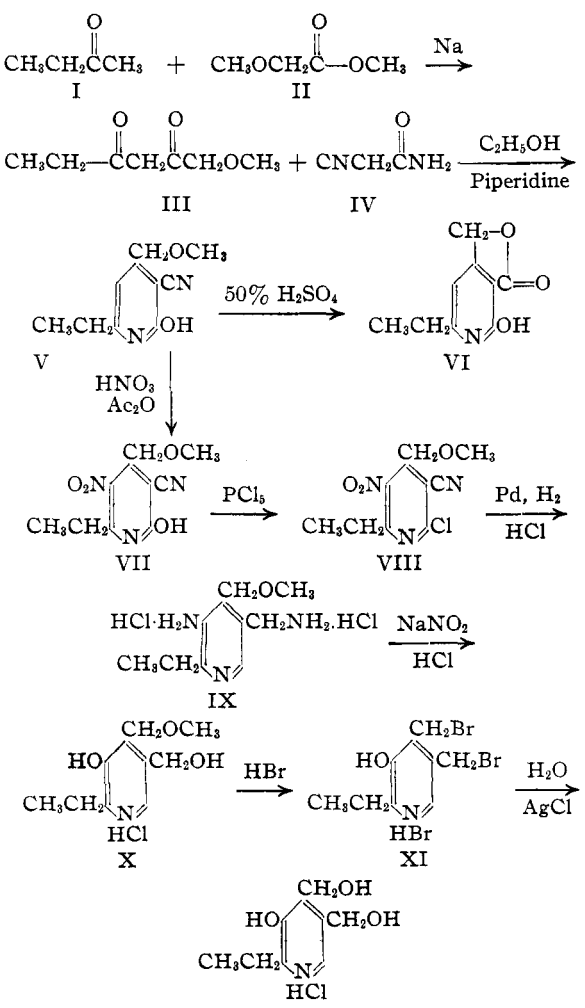
RECEIVED JULY 14, 1941

Chemistry of Vitamin B_6. III. 2-Ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine—A Homolog of Vitamin B_6

BY STANTON A. HARRIS AND ANDREW N. WILSON

The effect of substitution of various groups of the vitamin B_6 molecule on its biological activity has been reported previously from this Laboratory.[1,2,3] It was found[1] that esters of vitamin B_6 were fully active on vitamin B_6 deficient rats, and that ether derivatives showed less than 10% activity while replacement of an hydroxyl group by hydrogen or the amino group completely inactivated the molecule. It was reported later[2] that substitution of the nitrogen atom by a methyl group also showed inactivation at dose levels fifty times greater than that of vitamin B_6.

In continuing this study it was of interest to determine the effect of replacing the methyl group of vitamin B_6 with an ethyl group. This compound has been prepared by the set of reactions I → XII which are exactly analogous to those used for the preparation of vitamin B_6.[4]



(1) Unna, *Proc. Soc. Exptl. Biol. Med.*, **43**, 122 (1940).

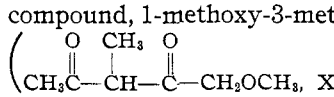
(2) Harris, Webb and Folkers, THIS JOURNAL, **62**, 3198 (1940).

(3) Harris, *ibid.*, **62**, 3203 (1940).

(4) Harris and Folkers, *ibid.*, **61**, 1245 (1939).

The structure of V was proved by treatment with 50% sulfuric acid as described previously[5] for the 2-methyl derivative. The formation of this lactone VI definitely allocated the methoxymethyl group to the 4-position in the pyridine ring.

Tracy and Elderfield[6] reported that ethyl formate condensed with the methylene group of ethyl methyl ketone, while ethyl oxalate condensed with the methyl group. It is evident from the above reactions (III + IV → V → VII) that methyl methoxyacetate reacted with the methyl group of ethyl methyl ketone to give 1-methoxy-3-methyl-2,4-hexadione (III). If the reaction had taken place on the methylene group, the resulting compound, 1-methoxy-3-methyl-2,4-pentadione



(XIII) would have reacted with cyanacetamide to give 2,3-dimethyl-4-methoxymethyl-5-cyano-6-hydroxypyridine. This compound would have been incapable of undergoing the reactions V → VII → XII.

The biological activity of 2-ethyl-3-hydroxy-4,5-bis-(hydroxy-methyl)-pyridine hydrochloride (XII) was determined in the Merck Institute for Therapeutic Research by Dr. Klaus Unna using a single dose curative assay[7] on vitamin B_6 depleted rats. Some vitamin B_6 activity was found for this sample in dosages of 1000 and 2500 micrograms, but even the larger dose was not sufficient to produce cures which are effected by 50 micrograms of vitamin B_6. Thus, the ethyl homolog possesses less than 2% of the activity of vitamin B_6 hydrochloride.

Experimental

Since the reactions are so similar to the published synthesis of vitamin B_6,[4] only the physical constants and analyses of the products are given here.

1-Methoxy-2,4-hexadione (III).—B. p. 69.5–70° at 7.5 mm. *Anal.* Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.37, 58.28; H, 8.34, 8.33.

2-Ethyl-4-methoxymethyl-5-cyano-6-hydroxypyridine (V).—M. p. 190–191°. *Anal.* Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.30; N, 14.57. Found: C, 62.69, 62.52; H, 6.20, 6.26; N, 14.73.

The Lactone of 2-Ethyl-3-hydroxymethyl-4-carboxy-6-hydroxypyridine (VI).—M. p. 285°. *Anal.* Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.56; H, 4.98; N, 7.76.

2-Ethyl-3-nitro-4-methoxymethyl-5-cyano-6-hydroxypyridine (VII).—M. p. 171–172°. *Anal.* Calcd. for $C_{10}H_{11}O_4N_3$: C, 50.64; H, 4.64; N, 17.72. Found: C, 50.63, 50.81; H, 4.65, 4.54; N, 18.05.

2-Ethyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (VIII).—M. p. 56–57°. *Anal.* Calcd. for $C_{10}H_{10}O_3N_3Cl$: C, 46.96; H, 3.91; N, 16.46. Found: C, 47.12, 46.86; H, 3.89, 3.68; N, 16.34.

The Dihydrochloride of 2-Ethyl-3-amino-4-methoxymethyl-5-aminomethylpyridine (IX).—M. p. 214°. *Anal.* Calcd. for $C_{10}H_{19}ON_3Cl_2$: C, 44.78; H, 7.09; N, 15.67. Found: C, 44.81; H, 7.37; N, 15.89, 15.89.

2-Ethyl-3-hydroxy-4-methoxymethyl-5-hydroxymethylpyridine Hydrochloride (X).—This compound was not obtained crystalline, but was converted to the dibromide by treatment with constant boiling hydrobromic acid.

2-Ethyl-3-hydroxy-4,5-bis-(bromomethyl)-pyridine Hydrobromide (XI).—M. p. 196°. *Anal.* Calcd. for $C_9H_{12}ONBr_3$: C, 27.72; H, 3.10; N, 3.59. Found: C, 27.95; H, 3.19; N, 3.50.

2-Ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine Hydrochloride (XII).—M. p. 192°. *Anal.* Calcd. for $C_9H_{14}NO_3Cl$: C, 49.12; H, 6.42; N, 6.37. Found: C, 49.11, 49.39; H, 6.44, 6.39; N, 6.36.

The authors wish to express their appreciation to Messrs. D. F. Hayman, W. R. Reiss, R. B. Boos and H. S. Clark for the microanalyses reported in this paper.

RESEARCH LABORATORY
MERCK & CO., INC.
RAHWAY, NEW JERSEY

RECEIVED JULY 15, 1941

(5) Harris, Stiller and Folkers, THIS JOURNAL, **61**, 1242 (1939).

(6) Tracy and Elderfield, *J. Org. Chem.*, **6**, 63, 70 (1941).

(7) Reedman, Sampson and Unna, *Proc. Soc. Exptl. Biol. Med.*, **43**, 112 (1940). By this method it has been shown that a single dose of 100 micrograms of vitamin B_6 hydrochloride cures 100% of the deficient animals within 14 days, and that a dose of 50 micrograms produces complete cures in 75% of the animals. Lower doses fail to produce complete cures, but signs of partial healing were obtained regularly with 25 micrograms.

Investigations in the 1-Methylphenanthrene Series. II. Some Substitution Products of 1-Methylphenanthrene

BY TORSTEN HASSELSTROM

The direct nitration of retene yields no crystalline derivatives.[1] On the other hand, it was found in this investigation that 1-methylphenanthrene like phenanthrene gives a crystalline mononitro derivative on nitration in glacial acetic acid. The corresponding amine was produced on reduction with sodium hyposulfite and acetylated. Through the diazo reaction 1-methylphenanthrol was obtained together with minute quantities of a dyestuff of unknown composition. The 1-methylphenanthrol was identified by its acetoxy derivative, which had the same melting point as a 1-

(1) (a) Fehling, *Ann.*, **106**, 390 (1858); (b) Fritzche, *ibid.*, **109**, 251 (1859); (c) Ekstrand, *ibid.*, **185**, 79 (1877); (d) Bamberger and Hooker, *ibid.*, **229**, 116, 144 (1885); (e) Arnot, German Patent 315,623 (1919); *Chem. Zentr.*, **91**, II, 188 (1920); (f) Arnot, British Patent 149,354 (1920); *Chem. Zentr.*, **92**, II, 37 (1921); (g) Wahlforss, Thesis, Helsingfors, 1924, p. 24; (h) Komppa and Wahlforss, THIS JOURNAL, **52**, 5009 (1930).