[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, TEACHERS COLLEGE, COLUMBIA UNIVERSITY]

Studies of Crystalline Vitamin B_1. IX. Action of Concentrated Hydrochloric Acid[1]

BY EDWIN R. BUCHMAN AND ROBERT R. WILLIAMS

Evidence presented in the preceding paper[2] of this series, indicates that vitamin B_1 is a derivative of 6-aminopyrimidine. The pyrimidine half of the molecule, on treatment with concentrated hydrochloric acid, is quantitatively converted to the corresponding oxy compound. In view of this fact, it was of interest to study the action of concentrated hydrochloric acid on the vitamin itself. In 1932[3] it had been shown by Windaus that, by the action of 2 *N* hydrochloric acid at 160°, approximately one mole of ammonia is split out, while the sulfur stays in the molecule. Also in the same year van Veen[4] reported that concentrated hydrochloric acid inactivates the vitamin and that under certain not specified conditions he was able to isolate a substance melting at about 210°. No further information is available from the literature.

We have found that, using 10–100 mg. portions of vitamin, treating with concentrated hydrochloric acid under conditions favorable for the conversion of 6-aminopyrimidines to the corresponding oxy derivatives and recrystallizing the product from methanol–ether, it is possible to isolate a 60% yield of a compound $[C_{12}H_{16}N_3SOCl]^{++}Cl_2^{=}\cdot CH_3OH$[5] (IV). The description of a typical experiment follows.

50.7 mg. of vitamin was placed in a sealed tube with 1.9 cc. of concentrated hydrochloric acid (d. 1.19) and heated for three hours at 150°. The contents of the tube were evaporated to dryness *in vacuo*, taken up in absolute methanol, centrifuged from a small amount of insoluble matter and dry ether added until a faint cloudiness appeared. On standing, radiating clusters of crystals formed, were centrifuged off and recrystallized a second time from methanol–ether, yield 31.2 mg. The mother liquors contained further amounts of material in addition to ammonium chloride. The above method gave quite consistent yields: a total of 301.2 mg. of vitamin gave 204.8 mg. of crystals. This product is almost pure white and when heated in a capillary decomposes at about 150° with vigorous gas evolution (loss of methanol). For analysis it was dried at 55° *in vacuo:* there was no perceptible loss in weight. The analyses indicate the formula $[C_{12}H_{16}N_3SOCl]^{++}Cl_2^{=}\cdot CH_3OH$.

	C	H	N	S	Cl	Cl^-	OCH_3
Calcd.	40.14	5.19	10.81	8.25	27.37	18.25	7.98
Found	40.07	5.23	10.77[a]	8.31	27.43	18.44	6.25[b]

[a] Dumas. [b] Pregl. Blank determinations using pure methanol gave correspondingly low results.

After the compound had been in contact with the atmosphere for two months, analyses showed that the major part of the methanol of crystallization had been lost. Heating at 105° *in vacuo* brings about a speedy loss of methanol but due to partial loss of hydrogen chloride the product is not homogeneous. Evaporation of its aqueous solution also frees the substance from methanol but no convenient method could be devised to purify the semi-crystalline product; addition of acetone or dioxane to the aqueous solution precipitates oils.

In our characterization of (IV) we used material freshly recrystallized from methanol–ether. In its solubility relations (IV) closely resembles the vitamin but is appreciably more soluble in methyl and ethyl alcohols. Like the vitamin it gives a white amorphous precipitate with phosphotungstic acid, with aqueous gold chloride an immediate yellow crystalline precipitate, and on standing with picrolonic acid an alcohol-soluble picrolonate. It gives a positive color test with diazotized sulfanilic acid. After heating with 20% sodium hydroxide for half an hour nitroprusside gives a distinct though very evanescent red color.

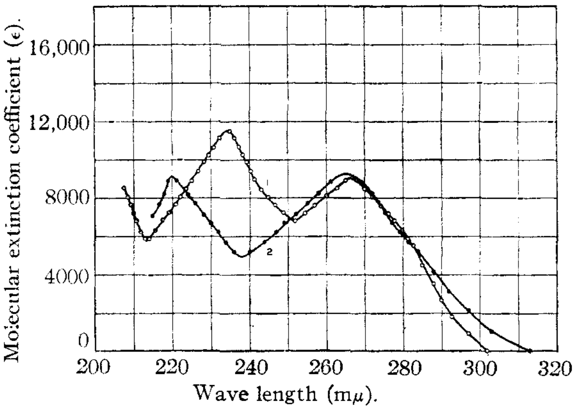

Fig. 1.—Ultraviolet absorption: 1, vitamin; 2, chlorooxy-vitamin IV.

The twelve carbon atoms of the vitamin are still present in (IV) and since the properties of the

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[1] Presented before the Organic Division of the American Chemical Society at the New York Meeting, April, 1935.

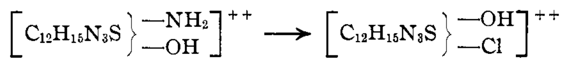
[2] R. R. Williams, E. R. Buchman and A. E. Ruehle, THIS JOURNAL, **57**, 1093 (1935).

[3] A. Windaus, R. Tschesche and H. Ruhkopf, *Nachr. ges. Wiss. Göttingen Math.-Phys. Klasse*, 111, 346 (1932).

[4] A. G. van Veen, *Rec. trav. chim.*, **51**, 281 (1932).

[5] Preliminary report: see Carnegie Institution of Washington Year Book, No. **33**, 299 (1934).

two substances are so similar it must be inferred that no rearrangement has taken place in the transformation. From a comparison of the two empirical formulas, it is evident that in addition to the hydrolysis of the amino group present in the original vitamin, we have replaced an —OH by non-ionic Cl.



$$\left[C_{12}H_{15}N_3S\left\{\begin{matrix}-NH_2\\-OH\end{matrix}\right.\right]^{++} \longrightarrow \left[C_{12}H_{15}N_3S\left\{\begin{matrix}-OH\\-Cl\end{matrix}\right.\right]^{++}$$

Vitamin "Chlorooxyvitamin" (IV)

The ultraviolet absorption spectrum of (IV) contrasted with that of the vitamin is shown in the accompanying chart. The peak at 267 mμ in the vitamin curve persists in the curve for our compound, while the absorption maximum at 235 mμ is shifted to 220 mμ. In a recent paper[6] from the University of Göttingen dealing with ultraviolet absorption spectra of compounds related to vitamin B_1, there is mention of a "hydrolysis product of the vitamin probably $C_{12}H_{15}N_3O_2S$." Its curve exhibits maxima at 265 and 219 mμ so that we may assume that structurally it resembles (IV). Judging from the tentative empirical formula, Windaus and collaborators have hydrolyzed the aminopyrimidine grouping, leaving the aliphatic hydroxyl intact. The chief value of our own work lies in the fact that it is the first evidence of the presence of a free hydroxyl group in the vitamin.

(IV) has no vitamin B_1 activity when injected into polyneuritic rats.

We wish to thank Miss Marion Ammerman for the bio-essays, Mr. A. E. Ruehle for the spectrograms, Drs. H. T. Clarke and O. Wintersteiner for securing the microanalyses, and the Carnegie Corporation for financial aid rendered through the Carnegie Institution of Washington.

Summary

1. Vitamin B_1 is converted by the action of concentrated hydrochloric acid into a compound $[C_{12}H_{16}N_3SOCl]^{++}Cl_2^{=}$ (IV).

2. This is interpreted as evidence for the presence of an aliphatic hydroxyl group in the vitamin.

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[6] A. Smakula, *Z. physiol. Chem.*, **230**, 232 (1934).

NOTES

2-Methyl- and 2-Ethyl-4-(*p*-fluorophenyl) Thiazoles and Some of their Derivatives

BY J. P. WETHERILL AND RAYMOND M. HANN

In a recent communication[1] the synthesis of 2-methyl and 2-ethyl thiazoles containing a *p*-chlorinated, brominated or iodinated phenyl group in the 4-position was reported. Subsequent preparation of *p*-fluorophenacyl chloride[2] (ω-chloro-*p*-fluoroacetophenone) now allows completion of the series of halogenated derivatives.

Experimental

The thiazoles were obtained by the interaction of ω-chloro-*p*-fluoroacetophenone with thioacetamide and thiopropionamide under conditions similar to those previously employed. The properties of the new compounds and of some simple derivatives are summarized in Table I.

TABLE I

2-METHYL- AND 2-ETHYL-4-*p*-(FLUOROPHENYL) THIAZOLES AND DERIVATIVES

	4-*p*-Fluorophenyl thiazole	Appearance	M. p., °C. (corr.)	Formula	N analyses, % Calcd.	N analyses, % Found
1	2-Methyl	Colorless glistening plates	81	$C_{10}H_8NSF$	7.25	7.24
2	2-Methyl, hydrochloride	Colorless glistening needles	131	$C_{10}H_8NSF \cdot HCl$	6.10	5.96
3	2-Methyl, picrate	Light yellow platelets	161	$C_{16}H_{11}O_7N_4SF$	13.27	13.19
4	2-Methyl, mercuri-chloride	Long colorless needles	160	$C_{10}H_8NSF \cdot HgCl_2$	3.01	3.09
5	2-Ethyl	Colorless plates	15–16	$C_{11}H_{10}NSF$	6.76	6.61
6	2-Ethyl, picrate	Thin yellow platelets	154	$C_{17}H_{13}O_7N_4SF$	12.84	12.71
7	2-Ethyl, mercuri-chloride	Long colorless needles	160[a]	$C_{11}H_{10}NSF \cdot HgCl_2$	2.93	2.55

[a] Decomposition with melting point lowering on recrystallization.

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[1] Wetherill and Hann, THIS JOURNAL, **56**, 970 (1934).

[2] Hann and Wetherill, *J. Wash. Acad. Sci.*, **24**, 526 (1934).