and the analysis of our Isolate 1 conforms to the formula for gliotoxin proposed by Dutcher,[2] *et al.*

Anal. Calcd. for $C_{13}H_{14}N_2O_4S_2$: C, 47.85; H, 4.32; N, 8.59; S, 19.65. Found: C, 47.89; H 4.44; N, 8.76; S, 19.76.

Isolate 2 was obtained from the mother liquor, available after the removal of gliotoxin, by chromatography on a column of alumina and elution with benzene containing 4% methanol. Large, pale yellow, rhombic crystals separated from the eluate. In general, Isolate 2 was found to be more soluble than gliotoxin. The material melted at 159–160° and showed a specific rotation of $[\alpha]^{19}D$ −197° (*c*, 0.600 in chloroform). The analysis and molecular weight indicated a formula corresponding to one-half of that proposed by Weindling[3] for gliotoxin, which probably will have to be doubled because of the degradation products obtained. A methoxyl determination failed to demonstrate the presence of any such group in the molecule.

Anal. Calcd. for $C_7H_8NO_2S$: C, 49.41; H, 4.71; N, 8.24; S, 18.82; mol. wt., 170. Found: C, 49.43; H, 4.68; N, 8.14; S, 18.84; mol. wt., 184, 194 (Rast).

The ultraviolet absorption spectra of gliotoxin and Isolate 2 showed almost identical maxima and minima.

Both reduction with hydriodic acid and alkaline hydrolysis with barium hydroxide of Isolate 2 gave products which on the basis of analysis, melting points and mixed melting point, were identical with those obtained from gliotoxin.[4,5]

An attempt to form crystalline acylation products of both gliotoxin and the second isolate resulted in the formation of the dibenzoate (m. p. 198–199°)[4] of gliotoxin, but thus far no crystalline benzoate of Isolate 2 has been secured. The quantitative acetylation procedure of Freed and Wynne,[6] however, indicated the consumption of identical amounts of acetic acid for both compounds.

The comparative antibacterial values of gliotoxin and Isolate 2, as determined by a broth dilution method, indicated the former to possess approximately ten times the bacteriostatic properties of the latter. The assay values were based on tests against a limited number of pathogenic bacteria, representing both gram-positive and gram-negative types.

The toxicity to mice of Isolate 2, however, was found to be almost identical with that reported for gliotoxin.[2]

Thanks are due to Dr. K. B. Raper, U. S. Department of Agriculture, Peoria, Ill., for the identification of the culture as *Penicillium obscurum* Biourge.

(2) Johnson, Bruce and Dutcher, THIS JOURNAL, **65**, 2005 (1943).
(3) Weindling and Emerson, *Phytopathology*, **26**, 1068 (1936).
(4) Bruce, Dutcher, Johnson and Miller, *ibid.*, **66**, 614 (1944).
(5) Dutcher, Johnson and Bruce, *ibid.*, **66**, 617 (1944).
(6) Freed and Wynne, *Ind. Eng. Chem., Anal. Ed.*, **8**, 278 (1936).

The isolation of the mold and broth filtrate preparation, as well as bacteriological and toxicological studies, were conducted by Dr. R. L. Mayer and Mr. W. S. Marsh of Ciba's Bacteriological Department.

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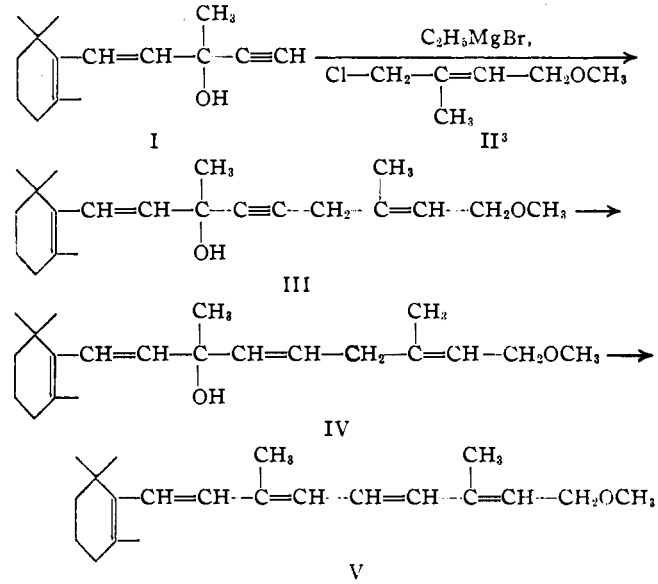
RECEIVED JULY 31, 1945

A SYNTHESIS OF VITAMIN A METHYL ETHER—PRELIMINARY REPORT

Sir:

During the past decade there have been two reports in the literature describing the synthesis of Vitamin A or its derivatives. The first, by Kuhn and Morris,[1] yielded an impure mixture of unknown constitution which showed some biological activity. However, all attempted repetitions reported have been unsuccessful. The second, by Kipping and Wild in 1939,[2] concerned the methyl ether of Vitamin A but was devoid of any supporting physical, chemical or biological evidence.

The synthesis of the methyl ether of Vitamin A has been attempted in this Laboratory by the following scheme



(1) Kuhn and Morris, *Ber.*, **70**, 853 (1937).

(2) Kipping and Wild, *Chemistry and Industry*, **58**, 802 (1939).

(3) Compound II and the analogous acetate were prepared by the reaction of isoprene with *t*-butyl hypochlorite in methanol and in glacial acetic acid, respectively. In both cases 1:2 and 1:4 addition products were isolated and their structures proven. Compound II, 1:2 product, b. p. 68–69° (55 mm.), $n^{25}D$ 1.4420. *Anal.* Calcd. for $C_6H_{11}OCl$: C, 53.53; H, 8.24; Cl, 26.34. Found: C, 53.46; H, 8.45; Cl, 26.27. Compound II, 1:4 product, b. p. 89–91° (55 mm.), $n^{25}D$ 1.4590. *Anal.* Found: C, 53.40; H, 8.20; Cl, 26.44

The acetate, 1:2 product, b. p. 61–63° (10 mm.), $n^{25}D$ 1.4445. *Anal.* Calcd. for $C_7H_{11}O_2Cl$: C, 51.70; H, 6.82; Cl, 21.81. Found: C, 51.90; H, 7.01; Cl, 21.96. The 1:4 product, b. p. 92–94° (10 mm.), $n^{25}D$ 1.4640. *Anal.* Found: C, 51.98; H, 6.83; Cl, 21.72.

The final product was obtained in two fractions: (a) The first distils at 100–103° (10^{-3} mm.), $n^{26}D$ 1.5640, showing an absorption maximum at 312 mμ and a molecular coefficient of extinction of 27,450. *Anal.* Calcd. for $C_{21}H_{32}O$: C, 83.94; H, 10.74. Found: C, 83.74; H, 10.59. (b) The second distils at 110–115° (10^{-3} mm.), $n^{26}D$ 1.5771, showing an absorption maximum at 315 mμ and a molecular coefficient of extinction of 33,750. *Anal.* Calcd. for $C_{21}H_{32}O$: C, 83.94; H, 10.74. Found: C, 83.79; H, 10.69.

Figure 1 shows the similarity in shape of the absorption curves of products V to that of Vitamin A alcohol. The slight displacement of the maxima and the lower maximum intensities of absorption may indicate stereoisomeric variations from the natural product. Biological assays are at present in progress.

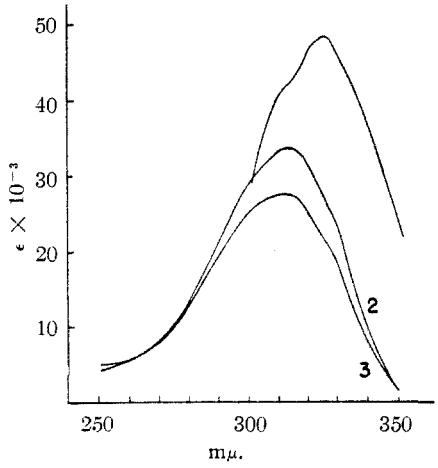


Fig. 1.—Curve 1, vitamin A, alcohol; curve 2, product V (b); curve 3, product V (a); solvent, isopropanol.

When the crude acetylenic compound III[4] was hydrogenated in the presence of a poisoned palladium catalyst only the theoretical quantity of hydrogen for the semihydrogenation of one acetylenic bond was absorbed. The resulting divinyl carbinol, IV, distilled at 113–115° (10^{-3} mm.), $n^{26}D$ 1.5099 and, as would be expected theoretically, showed no significant absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.37; H, 10.63. The yield of IV from I was 84%.

The rearrangement and simultaneous dehydration of the divinyl carbinol IV to products V (a) and V (b) was accomplished in glacial acetic acid with a trace of *p*-toluenesulfonic acid at room temperature. The total yield of (a) and (b) from IV was 77%.

Work is at present in progress toward the synthesis of the corresponding acetate of V by similar methods in which the acetoxy analog of II[3] is condensed with I. In addition to the magnesium derivative of I, the zinc derivative is being investigated in view of its inertness toward esters.

(4) The crude acetylenic compound III split out water spontaneously on distillation at 10^{-3} mm., and the redistilled product boiled at 112–114° (10^{-4} mm.), $n^{26}D$ 1.5715. *Anal.* Calcd. for $C_{21}H_{36}O$: C, 84.51; H, 10.13. Found: C, 84.10; H, 10.28.

ORTHO RESEARCH FOUNDATION
ORGANIC CHEMISTRY DIVISION
LINDEN, NEW JERSEY WILLIAM OROSHNIK

RECEIVED AUGUST 17, 1945

REACTIONS OF VANILLIN

Sir:

In a search for a simple process for converting vanillin directly into vanillic acid, it was found that silver oxide and excess alkali in aqueous solution effected this transformation. Unlike other alkaline silver oxide oxidations of aldehydes which require one mole of oxide to one mole of aldehyde, this oxidation took place with only one-half mole of silver oxide according to the equation

$$2\ RCHO + Ag_2O + 2\ NaOH \xrightarrow{NaOH} 2\ RCOONa + 2\ Ag + H_2O + H_2$$

This unexpected discovery led to the assumption of a Cannizzaro mechanism for the reaction and this hypothesis was confirmed by experiments employing less than one-half mole of silver oxide in which vanillyl alcohol (in the form of its dimer) was recovered in the calculated amount, depending upon the amount of silver oxide used. Thus, a mixture of 1.0 mole of vanillin, 0.25 mole of freshly prepared silver oxide, 4.0 moles of sodium hydroxide and 1000 g. of water was heated to boiling for one hour and filtered. Acidification of the filtrate with carbon dioxide yielded 34.2 g. (corresponding to 0.24 mole of vanillyl alcohol) 4,4′-dihydroxy-3,3′-dimethoxydiphenylmethane, m. p. 108–109° (from water or ligroin) (*Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.20; H, 6.20; CH_3O, 23.85. Found: C, 68.99; H, 6.23; CH_3O, 23.69). The carbonated filtrate yielded 119.6 g. (0.71 mole) of vanillic acid, m. p. 209–210°. It was further found that the active silver metal produced in the above reaction would catalyze a Cannizzaro reaction of vanillin to give equivalent amounts of vanillic acid and polymerized vanillyl alcohol. In the presence of alkali alone vanillin does not undergo a Cannizzaro reaction.[1-4]

In addition to vanillin, other ortho- and para-hydroxy- and amino-substituted benzaldehydes, ordinarily inert in the presence of strong alkali, easily underwent the Cannizzaro reaction in the presence of active silver to yield the derived acid and unpolymerized alcohol. Active silver also catalyzed the crossed Cannizzaro reaction of these aldehydes with formaldehyde to give substantially quantitative yields of unpolymerized alcohols, even in the case of vanillin.

(1) Lock, *Ber.*, **62**, 1181 (1929).
(2) Raikow and Raschtanow, *Oesterr. Chem. Ztg.*, **5**, 169 (1902).
(3) Tomlinson and Hibbert, THIS JOURNAL, **58**, 349 (1936).
(4) Geissman, Chapter 2 in Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 104–107