The authors are grateful to E. B. Towne and L. D. Apperson for assistance.

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RECEIVED MARCH 27, 1939

The Reduction of α-Bromocyclohexanone with Aluminum Isopropoxide

BY S. WINSTEIN

The reduction of some α-bromo ketones by aluminum isopropoxide was the subject of a recent communication to the Editor by Stevens,[1] who obtained from α-bromopropiophenone a 35% yield of bromohydrin and about an equal yield of product not containing bromine. Presumably hydrogen bromide was split out. Tertiary α-bromo ketones and cyclic secondary α-bromo ketones were reported to yield not bromohydrins but products almost entirely free of bromine. What type of product he obtained was not indicated. In the course of other work the author has had occasion to reduce with aluminum isopropoxide the cyclic secondary α-bromo ketone, α-bromocyclohexanone. Since Stevens is continuing his investigation of the reaction of α-bromo ketones with aluminum isopropoxide, the results obtained with this cyclic ketone should be reported.

The reaction product from the reduction of α-bromocyclohexanone was found to be a mixture of bromohydrin and cyclohexanol, in yields of 30 and 33%, respectively, with no unsaturated compound being isolated. It is possible that the cyclohexanol arises from dismutation of bromocyclohexanone to cyclohexanone and dibromocyclohexanone with subsequent reduction of the cyclohexanone to cyclohexanol.

(1) Stevens, THIS JOURNAL, **60**, 3089 (1938).

Experimental

75.8 g. (0.428 mole) of α-bromocyclohexanone, b. p. 69–71° (1.5 mm.), prepared by the method of Kötz,[2] dissolved in 200 ml. of anhydrous isopropanol (Shell) was added to aluminum isopropoxide solution prepared from 7.5 g. of aluminum and 75 ml. of anhydrous isopropanol, according to the directions of Young, Hartung and Crossley.[3] The mixture was refluxed for three and one-half hours. Then it was concentrated to a thick residue by distillation first of acetone, then of solvent through a 20-cm. column of glass helices for two hours at atmospheric pressure and finally with the aid of an aspirator. One hundred ml. of water and 130 ml. of 6 *N* sulfuric acid were added to the residue and all lumps were broken up. A little ether was added and the oil phase was separated, washed with bicarbonate solution and dried over sodium sulfate. Distillation and then refractionation at reduced pressure through a 40-cm. Weston[4] column yielded 22.6 g. (30%) of 2-bromocyclohexanol, b. p. (10 mm.) 85.5–86.5°, $n^{25}D$ 1.5164, and 14.3 g. (33%) of cyclohexanol, b. p. (10 mm.) 61.0–61.2°, $n^{25}D$ 1.4649, m. p. of 3,5-dinitrobenzoate and mixed m. p. with authentic specimen, 112°.

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RECEIVED MARCH 21, 1939

(2) Kötz, *Ann.*, **358**, 195 (1907).
(3) Young, Hartung and Crossley, THIS JOURNAL, **58**, 100 (1936).
(4) Weston, *Ind. Eng. Chem., Anal. Ed.*, **5**, 179 (1933).

COMMUNICATIONS TO THE EDITOR

COLOR REACTIONS IN VITAMIN K CONCENTRATES

Sir:

During studies of the inactivation of vitamin K by its reaction with bases, we have detected and separated an alcohol-soluble reddish pigment. Recently, Dam, *et al.* [*Helv. Chim. Acta*, **22**, 310 (1939)] described a color reaction of vitamin K concentrates with sodium ethylate in which a transient purple color changing to a reddish-brown color developed. We have determined that our pigment is the end stage of this color reaction and that the quantity of pigment formed is closely correlated with antihemorrhagic activity. The transient, deep purple color is considerably masked when carotenoid pigments are present; however, it is possible to employ the final, less intense but relatively stable, reddish-brown color as a quantitative measure of the vitamin.

The color reaction is carried out easily by dissolving a few milligrams of concentrate in 1 or 2 cc. of methanol and then adding 1 cc. of sodium methylate (2 to 3 g. of sodium dissolved in 50 cc. of methanol). When warmed for a few minutes, the mixture slowly develops a distinct purple

color, if sufficient vitamin K is present and interfering pigments are practically absent. Soon the color changes to a reddish-purple and finally to a reddish-brown. At this point, carotenoid pigments may be removed by partition with a hydrocarbon solvent. The color due to reaction of the vitamin with sodium methylate remains in the methanol phase. To test the agreement of color reaction with activity, we have applied this reaction to a variety of sources of the vitamin assayed by a procedure already described [*Biochem. J.*, **32,** 1897 (1938)]. Results are given in Table I.

Fractions obtained by chromatographic adsorption showed a consistent relation of color test to activity. This was also true of fractions obtained by incomplete molecular distillation and of a preparation (concentrate 1270) obtained by repeated precipitation from methanol by chilling with solid carbon dioxide [*J. Biol. Chem.*, **120,** 635 (1937)] but not purified from sterols. A preparation of the molecular compound of the vitamin with deoxycholic acid [THIS JOURNAL, **61,** 745 (1939)] showed a color reaction consistent with its activity, which was also true of the residue of this preparation remaining after partial extraction of the vitamin with xylene. A strong color reaction was also produced on testing an active concentrate prepared by repeated molecular distillation of soybean oil, followed by removal of sterols, free fatty acids and waxes. In addition to the data in the table, we may report that the color reaction has been obtained in extracts of several kinds of bacteria known to be good sources of the vitamin [*Proc. Soc. Exp. Biol. Med.*, **38,** 336 (1938)].

TABLE I

ANTIHEMORRHAGIC ACTIVITY AND COLOR REACTION INTENSITY OF VITAMIN K CONCENTRATES

	Concentrate	Level fed per kilo of diet, mg.	Av. blood clotting time, min.	Rel. intensity of color test
	Chromatographic adsorption fractions			
1	Orange zone	10	2.8	4
2	Light yellow zone	10	1.8	8
3	Yellow zone	10	6.3	2
4	Colorless zone	10	>30	0
	Incomplete distillation fractions			
1	Low temp. distillate, P11	80	>30	0
2	Vitamin distillate, P11	20	4.2	2
3	Residue, P11	20	7.3	1
4	Vitamin distillate, P8	10	3.5	4
5	Residue, P8	10	3.7	4
6	Vitamin distillate, P12	20	3.7	2
	Other preparations			
1	Concentrate 1270	10	4.7	4
2	K-choleic acid, 8P	30	2.7	4
3	K-choleic acid, 8P xylene extracted	30	14.1	1
4	Soybean oil concentrate	400	3.0	strong

The results strongly indicate that the color reaction is due to the vitamin itself. The character of the pigment is being studied further.

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RECEIVED MAY 19, 1939

THE ANTI-HEMORRHAGIC ACTIVITY OF PURE SYNTHETIC PHTHIOCOL

Sir:

We wish to announce the discovery of the anti-hemorrhagic activity of pure synthetic phthiocol, 2-methyl-3-hydroxy-1,4-naphthoquinone. The physical and chemical properties of this compound are in general similar to those known for vitamin K. When fed to chicks at a level of 20 mg. per kg. of vitamin K-free diet, phthiocol maintained the average blood-clotting time at 2.1 minutes in one test and 1.6 minutes in a second test. At a level of 10 mg. the blood-clotting time was maintained at 1.8 minutes. Chicks fed only the basal ration had prolonged blood-clotting times. The minimum required level is being determined. It is probable that phthiocol is the simplest member of an homologous series of anti-hemorrhagic substances.

We are indebted to Professor R. J. Anderson for the phthiocol used in these experiments.

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RECEIVED MAY 31, 1939

CHROMATOGRAPHIC ADSORPTION AND DIPOLES

Sir:

The use of the method of chromatographic adsorption has become extremely important for the separation of complex mixtures of organic molecules.

A careful survey of numerous experimental investigations has revealed the importance of dipoles in determining the order of adsorption of a mixture on a polar medium (*i. e.*, aluminum oxide). Thus Karrer [Karrer and Nielsen, *Ber.*