A detailed report of our work will be presented in the future.

We acknowledge gratefully valuable suggestions of Dr. H. Gilman and Dr. F. B. LaForge. We are also indebted to Merck & Co., Inc., for generously furnishing us with a supply of the pyrimidine derivative used in this work. The analytical work was carried out by Dr. Carl Tiedcke of New York City.

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RECEIVED JULY 3, 1939

VITAMIN K POTENCIES OF SYNTHETIC COMPOUNDS

Sir:

In view of the failure of the absorption of many patients in which vitamin K therapy is highly desirable, we have been examining various compounds which could be administered intravenously in aqueous solution. The most active compound found is 1,4-dihydroxy-2-methylnaphthalene which has a potency of approximately 1000 Thayer–Doisy units per milligram. It can be prepared readily by the reduction of the highly potent 2-methyl-1,4-naphthoquinone. Since this preparation is soluble in dilute alkali and has a high degree of potency (approximately equal to the potency of 2-methyl-1,4-naphthoquinone), it seems that this compound may prove very important for intravenous vitamin K therapy.

Supplementing our previous preliminary report [THIS JOURNAL, **61**, 1932 (1939)], we have reassayed several quinones to determine their optimum potency values. Except for 2-methyl-1,4-naphthoquinone, these more recent data agree with our previous findings. The assay of this compound was carried out by the Thayer–Doisy method, making a concurrent test, at six, eighteen and seventy-two hours. The standard was also run at varying levels at the same time for each series. The data are given in Table I. The details as to the method of feeding, care of the chicks, length of test period, manner of bleeding, etc., were essentially the same as described previously.

TABLE I

Assay period	Thayer–Doisy units per mg.
6 hours	1110
18 hours	970
72 hours	1070
Average	**1050**

The potency of 2-methyl-1,4-naphthoquinone (Thayer–Doisy units) agrees with the value previously assigned to the natural K_1, namely, 1000 units per milligram [*Proc. Soc. Exp. Biol. Med.*, **41**, 194 (1939)]. These results also confirm the findings of Ansbacher and Fernholz [THIS JOURNAL, **61**, 1932 (1939)].

Incidentally, in view of these observations and the lack at this time of a suitable standard, it is suggested that 2-methyl-1,4-naphthoquinone should be adopted as a basic standard for the assay of vitamin K. This compound has the desirable qualities of a standard in that it can be obtained readily in a satisfactory state of purity, has a definite melting point for characterization, and when protected from excessive exposure to light is relatively stable. The unit could then be defined in the terms used by the League of Nations committee as the specific vitamin K activity of one microgram of pure 2-methyl-1,4-naphthoquinone.

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RECEIVED AUGUST 21, 1939

ANTIHEMORRHAGIC ACTIVITY OF SIMPLE COMPOUNDS

Sir:

In connection with our investigation of vitamin K, we have tested recently a large number of derivatives of α-naphthoquinone, many of which have been prepared and reported by Professor Fieser and his collaborators[1] and some of which were synthesized in this Laboratory. At this time we wish to report our findings of the antihemorrhagic activity of 2-methyl-1,4-naphthoquinone and of some other related substances of significance.

One of the first quinones we assayed was 2-methylnaphthoquinone and, because it did not appear at that time to be as active as 2,3-dimethyl-1,4-naphthoquinone,[1] we did not determine its minimum dose.

Following the appearance of the extremely interesting report of Ansbacher and Fernholz,[2] we reinvestigated the activity of 2-methyl-1,4-naphthoquinone, and we are now in complete agreement with them.

(1) Fieser, *et al.*, THIS JOURNAL, **61**, 1925, 1926, 2206 (1939).
(2) Ansbacher and Fernholz, *ibid.*, **61**, 1924 (1939).

The assay method we employed was as follows: Day old chicks were placed on a vitamin K free diet and kept on this diet for fourteen to seventeen days. When a preliminary determination of clotting time showed that at least 90% of the chicks had clotting times above thirty minutes, the samples, dissolved in 0.1 cc. of peanut oil, were administered orally. Eighteen hours later, the clotting times on the dosed birds were determined. Usually ten chicks were used at each dose level.

In the course of six weeks, nine assays were run on 2-methylnaphthoquinone. Following is a typical protocol of our results:

Substance	Dose	No. birds	Clotting time in min. 0–5	6–10	11–30	>30	Per cent. under 10 min.
2-Methyl-naphthoquinone	1 γ	10	5	4	1	0	90
2-Methyl-naphthoquinone	0.75 γ	9	4	3	1	1	77
2-Methyl-naphthoquinone	0.5 γ	9	3	1	3	2	44
Alfalfa extract	≈75 mg.	9	3	3	2	1	67
Negative controls	0	10	0	0	0	10	0

In all over 120 chicks were used in testing 2-methyl-1,4-naphthoquinone at levels of 0.5 to 1.0 γ and the results in every case were essentially the same as above.

From the results of Ansbacher and Fernholz and from ours, it would appear that, in the chick at least, 2-methylnaphthoquinone possesses antihemorrhagic activity of the same order of magnitude as the vitamin K_1 reported by Thayer, *et al.*[3] These results are particularly striking inasmuch as hitherto no simple compounds corresponding in chemical structure to the chemically identified vitamins exhibit the same order of activity as the vitamins themselves. It is also noteworthy that 2-ethylnaphthoquinone (activity above 200 γ) and 2-*n*-propylnaphthoquinone[4] (inactive at 400 γ) are decidedly less effective than the methyl homolog. While 2,3-dimethylnaphthoquinone has some antihemorrhagic activity (effective at 50 γ), 2,6- and 2,7-dimethyl-1,4-naphthoquinone[1] exhibit little, if any (inactive at 400 γ), notwithstanding the fact that the substituents about the quinone systems of the latter two compounds are similar to 2-methylnaphthoquinone.

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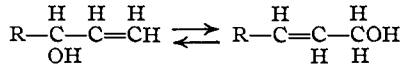
RECEIVED AUGUST 18, 1939

(3) Thayer, *et al.*, *Proc. Soc. Exp. Biol. Med.*, **41**, 194 (1939).
(4) Prepared by Professor Fieser and his collaborators.

THE INTERCONVERSION OF CROTYL ALCOHOL AND METHYLVINYLCARBINOL IN AQUEOUS SULFURIC ACID

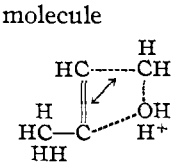
Sir:

According to the generally accepted ideas [Burton and Ingold, *J. Chem. Soc.*, 1907 (1928); J. W. Baker, "Tautomerism," pages 241–7, Routledge, London, 1934], carbinol systems of the type



are the least mobile of the allylic systems, exhibiting little or no tendency to isomerize. Although the system has been reported to be mobile when R = phenyl [Valeur and Luce, *Bull. soc. chim.*, **27**, 611 (1920)], Burton and Ingold [*loc. cit.*] were unable to verify the observation. Another example of isomerization was reported by Prévost [*Ann. chim.*, [10] **10**, 147 (1928)], who found that crotyl alcohol was formed during the dehydration of methylvinylcarbinol over alumina at high temperatures.

However, work on the mechanism of the reaction of the butenols with solutions of hydrogen bromide [Young and Lane, THIS JOURNAL, **60**, 847 (1938)] convinced us that crotyl alcohol and methylvinylcarbinol should be interconvertible in the presence of acids to form equilibrium mixtures even at room temperatures. This predicted interconversion was based on a postulate that activation of the oxonium ion of either crotyl alcohol or methylvinylcarbinol might lead to the same resonating molecule



in which the oxygen is bonded weakly to both carbons 1 and 3 [Young and Nozaki, paper in process of publication]. Consequently 50-ml. portions of crotyl alcohol and methylvinylcarbinol are being treated with mixtures of water and sulfuric acid adjusted so that the normality of acid in 228 ml. of reaction mixture is 7.4, 3.7, and 1.9. With methylvinylcarbinol after one week at room temperature the 7.4 *N* acid had caused the production of 4.5 g. of crotyl alcohol and 5 g. of a fraction which appears to be a mixture of crotyl and methylvinylcarbinyl ethers. With crotyl alcohol after two weeks the 7.4 *N* acid had produced 22 g. of the ether fraction and equal quantities, 4 g., of methylvinylcarbinol and