considerable amount. This was phenolic in nature and in an impure condition melted at 153–156°. It has now been determined that the same substance results from heating *p*-fluorophenol with benzene and aluminum chloride. When purified it melted at 163.5–164° and upon oxidation gave a high yield of benzoic acid. No depression of the melting point occurred when a sample of the unknown was mixed with *p*-hydroxybiphenyl. Hence

$$C_6H_6 + FC_6H_4OH \xrightarrow{AlCl_3} C_6H_5C_6H_4OH\ [+ HF]$$

*p*-fluorophenol must react as shown and the *p*-hydroxybiphenyl obtained in the deëthylation of *p*-fluorophenetole also results from this reaction.

Attempts to extend the reaction in various directions have been without success. Because aromatic fluorine may be under some conditions replaced by chlorine,[3] it seemed possible that *p*-chlorophenol was an intermediate in the reaction. However, *p*-chlorophenol showed no activity toward benzene in the presence of aluminum chloride. None of the corresponding hydroxybiphenyl was isolated when *p*-fluorophenol and aluminum chloride were heated with toluene or chlorobenzene.

By heating a mixture of 3 g. of *p*-fluorophenol, 7 ml. of benzene and 7 g. of aluminum chloride under reflux for two and one-half hours there was obtained about 1 g. of *p*-hydroxybiphenyl, m. p. 164°. The 51 g. obtained in the deëthylation of *p*-fluorophenetole[2] corresponds to 13% of the *p*-fluorophenol reacting with the benzene.

(3) Bacon and Gardiner, *J. Org. Chem.*, **3**, 281 (1938).

CHEMICAL LABORATORY
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RECEIVED APRIL 24, 1939

# COMMUNICATIONS TO THE EDITOR

## SYNTHETIC AND NATURAL ANTIHEMORRHAGIC COMPOUNDS

*Sir:*

In our last communication [THIS JOURNAL, **61**, 1923 (1939)] the reported antihemorrhagic activity of 2-methyl-1,4-naphthoquinone was a minimum assay result. The total comparative activity of this compound is given in Table I. It is by no means as active as vitamin K [Ansbacher and Fernholz, *ibid.*, **61**, 1924 (1939)] or as low in activity as reported by Thayer, *et al.*, [*ibid.*, **61**, 1932 (1939)] and would seem to provide an effective, cheap, synthetic substitute for vitamin K. This compound, like phthiocol and others, is capable of maintaining the prothrombin level of chick blood at a normal value when sufficient is given.

We have purified or synthesized and tested a number of naphthoquinones and related compounds (Table I). Assays were conducted and results expressed as noted previously [*ibid.*, **61**, 1923 (1939)]. Entirely negative results were obtained with 1,4-benzoquinone, naphthalene, 1,4-naphthoquinone, anthraquinone, 1,2-dihydroxyanthraquinone, and hydrolapachol at levels of 100 mg. or more per kg. of diet. Thayer, *et al.*, [*ibid.*, **61**, 1932 (1939)] have reported some activity in 1,4-naphthoquinone. Fieser, *et al.*, [*ibid.*, **61**, 1925 (1939)] have indicated activity in lomatiol, lapachol and hydrolapachol. We have previously found lomatiol and lapachol to be inactive [*ibid.*, **61**, 1923 (1939)]. These other workers employ assay methods which require only twenty-four hours or less but which are, in our experience, likely to give misleading results.

TABLE I

ANTIHEMORRHAGIC ACTIVITY OF NAPTHOQUINONES

| Substance | Level fed per kg. of diet, mg. | Activity in terms of cc. of ref. standard per g.[a] |
|---|---|---|
| 2-Methyl-1,4-naphthoquinone | 10 | > 2400 |
| 2-Methyl-1,4-naphthoquinone | 2.5 | 5150 |
| 2-Hydroxy-1,4-naphthoquinone | 75 | 139 |
| Phthiocol | 20 | 287 |
| Phthiocol ethyl ether | 15 | 100 |
| Phthiocol octadecyl ether | 20 | 95 |
| Phthiocol phytyl ether | 20 | < 50 |
| Phthiocol monoacetate | 15 | 420 |
| Phthiocol triacetate | 15 | 192 |
| Alfalfa concentrate | 0.5 | >53600 |
| Alfalfa concentrates[b] | 0.2 to 0.3 | 63000 |

[a] Standard hexane extract of dried alfalfa representing 1 g. per cc. [b] From preliminary assays of alfalfa preparations (E. A. Doisy, P. Karrer).

We have made the observation that solutions of the vitamin, the purified pigment derived from the vitamin by alkaline hydrolysis, the low temperature distillate from the molecular still (contains no vitamin K), and pure phytol all exhibit a characteristic white fluorescence when exposed to the light from an argon lamp. The same fluorescence was noted in samples of vitamin K obtained from Professor E. A. Doisy and Professor P. Karrer. The active nucleus, 2-methyl-1,4-naphthoquinone, does not show this fluorescence.

We prepared 2-methyl-3(?)-phytyl-1,4-naphthoquinone by condensation of 2-methyl-1,4-naphthoquinone with phytol. Purification was effected by repeated molecular distillation. *Anal.* Calcd. for $C_{31}H_{46}O_2$: C, 82.6; H, 10.3. Found: C, 82.5; H, 10.6. The product has the color, oily form and solubilities similar to those of vitamin K from alfalfa and sublimes in the molecular still under the same temperature and pressure. It shows the characteristic white fluorescence previously mentioned and gives the color changes of the natural vitamin in sodium methylate [*ibid.*, **61,** 1610 (1939)], although the transient purple is rather weak. When administered orally to vitamin K deficient chicks three weeks old at a level of 0.2 mg. per chick the compound restored blood clotting power to normal within a few hours. Quantitative assays have not been completed [see *Biochem. J.*, **33,** 1055 (1939)].

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H. J. ALMQUIST
A. A. KLOSE

RECEIVED JULY 21, 1939

## THE CONSTITUTION AND SYNTHESIS OF VITAMIN $K_1$

*Sir:*

In a previous communication [THIS JOURNAL, **61,** 1928 (1939)] we reported some experiments on the oxidation of vitamin $K_1$, in which we obtained phthalic acid, a quinone acid, and a ketone $C_{18}H_{36}O$. The ketone was identified as 2,6,10-trimethylpentadecanone-14 by means of the semicarbazone, melting point 66–67°. An authentic specimen of this semicarbazone was not available at the time but we have subsequently prepared it from the ketone which we obtained by the oxidation of phytol [F. G. Fischer and K. Löwenberg, *Ann.*, **464,** 69 (1929)]. The melting point was 64–66° and the mixed melting point 64–66°.

The amount of quinone acid obtained was so small (3.5 mg.) that only one analysis was possible, and the results indicated the formula $C_{14}H_{12}O_4$. On the basis of this, it was tentatively suggested that the acid was 2-ethyl-1,4-naphthoquinone-3-acetic acid. When this acid was synthesized and found to be different, we prepared an additional amount of the quinone acid from the vitamin and converted it to the methyl ester (melting point 121–122°). This was found to be identical with a synthetic specimen of the methyl ester of 2-methyl-1,4-naphthoquinone-3-acetic acid. *Anal.* Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.55; H, 5.22. The synthetic ester melted at 121.5–122.5° and the mixture showed no depression.

These results have been confirmed by further experiments with the diacetate of dihydro vitamin $K_1$ [THIS JOURNAL, **61,** 1612 (1939)]. Oxidation of this with chromic acid gave a good yield of a colorless diacetate acid melting without decomposition at 205°. *Anal.* Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.40, 64.56; H, 5.09, 5.16. Treatment with diazomethane gave the methyl ester which melted at 127.5–128.5°. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.12; H, 5.36. This was found to be identical with a synthetic specimen of the methyl ester of 1,4-diacetoxy-2-methylnaphthalene-3-acetic acid (melting point 125–126°). The mixed melting point was 126–127°. Chromic acid oxidation of the diacetate acid from the vitamin converted it to the quinone acid which gave a methyl ester identical with the methyl ester of 2-methyl-1,4-naphthoquinone-3-acetic acid. These experiments demonstrate conclusively that the structure of vitamin $K_1$ is correctly represented by the formula 2-methyl-3-phytyl-1,4-naphthoquinone.

Confirmation of this structural formula for vitamin $K_1$ has been obtained through synthesis which was easily accomplished through direct alkylation by the method of Claisen [*Ann.*, **442,** 210 (1925)] for direct carbon alkylation of phenols. The reaction of phytyl bromide with a benzene suspension of the monosodium salt of 2-methyl-1,4-naphthohydroquinone produced the hydroquinone of the vitamin which was oxidized by the air to the quinone. This was purified by chromatographic adsorption and by high-vacuum distillation and was then subjected to reductive acetylation. The diacetate obtained in this man-

ner was crystallized from methyl alcohol. *Anal.* Calcd. for $C_{35}H_{52}O_4$: C, 78.33; H, 9.77. Found: C, 78.06; H, 9.81. The mixed melting point with an authentic specimen of diacetate from the natural vitamin showed no depression.

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E. A. DOISY

RECEIVED AUGUST 21, 1939

## SYNTHETIC APPROACH TO VITAMIN K1

*Sir:*

In seeking a method for the introduction of the phytyl group into the 3-position of 2-alkyl-1,4-naphthoquinones we have investigated various procedures for condensing 2-methyl-1,4-naphthohydroquinone with phytol, geraniol and simpler $\beta$-unsaturated alcohols, and with dienes. In the work on vitamin E such condensations have been brought about in the presence of mineral acids (either added or liberated in the reaction) or zinc chloride and have been attended with cyclization to compounds of the tocopherol type. Since cyclization introduces a complication in the case at hand, trial was made of less powerful agents and it was found that, with anhydrous oxalic acid in dioxane solution, methylnaphthohydroquinone can be condensed with simple $\beta$-unsaturated alcohols and dienes to give considerable amounts of the uncyclized substituted hydroquinones. With 2,3-dimethylbutadiene, after refluxing for twenty-four hours, there was obtained 29% of the substituted hydroquinone, characterized as the diacetate (m. p. 119–120°, found: C, 74.04; H, 7.23), and 13% of a stable substance, m. p. 73–73.5°, which appears to be of the tocopherol type (found: C, 79.95; H, 7.63). The crude hydroquinone was converted quantitatively on oxidation to 2-methyl-3-($\beta,\gamma,\gamma$-trimethylallyl)-1,4-naphthoquinone, m. p. 95–95.5° (found: C, 80.33; H, 7.25); this gives the above diacetate on treatment with pyridine, acetic anhydride, and zinc dust. Condensation with cinnamyl alcohol gave a hydroquinone (extracted with 10% sodium hydroxide) which formed a diacetate, m. p. 167.5–168° (found: C, 77.17; H, 6.09) and a quinone, m. p. 127–127.5° (found: C, 83.63; H, 5.71).

The reaction is being extended to other examples, including the isoprenoid alcohols, and the use of esters and ethers of the hydroquinone is being investigated. We have ascertained that phytol enters into the condensation under the above conditions or at 140°, and viscous oils have been obtained of the composition of the substituted hydroquinone or tocopherol. One preparation, purified by rather drastic treatment with alkali and by high vacuum distillation, gave C, 82.62; H, 10.52 ($C_{31}H_{48}O_2$ requires C, 82.24; H, 10.69); another after distillation gave C, 82.36; H, 10.71. The general character of the distilled material suggests that it is the tocopherol. In the geranyl series a similar product was oxidized with lead tetraacetate to a substance having the composition of the acetoxyquinone (found: C, 74.92; H, 8.15; $C_{23}H_{28}O_4$ requires C, 74.93; H, 7.69), and this route is under investigation.

Synthesis by the addition of a Grignard reagent to a 2-alkyl-1,4-naphthoquinone oxide does not appear promising. Such oxides (2-methyl, 2,6- and 2,7-dimethyl) are conveniently prepared by adding aqueous sodium carbonate to an alcoholic solution of the quinone and excess hydrogen peroxide. The 2,6-dimethyl compound, m. p. 97–98° (found: C, 71.23; H, 5.07), with either allylmagnesium bromide or magnesium bromide in ether gave a considerable amount of the bromohydrin, m. p. 146–148° (found: C, 51.05; H, 4.18; Br, 28.33), characterized by conversion to the bromodimethylnaphthoquinone, m. p. 114–114.7° (found: C, 54.64; H, 3.61).

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LOUIS F. FIESER
WILLIAM P. CAMPBELL
EDWARD M. FRY
MARSHALL D. GATES, JR.

RECEIVED JULY 25, 1939

## SYNTHESIS OF 2-METHYL-3-PHYTYL-1,4-NAPHTHOQUINONE

*Sir:*

When equivalent amounts of phytol and 2-methyl-1,4-naphthohydroquinone are heated in dioxane solution in the presence of anhydrous oxalic acid at the reflux temperature, condensation occurs readily but the methylphytylnaphthohydroquinone produced is cyclized about as rapidly as formed and the chief reaction product appears to be the naphthotocopherol. By using a large excess of methylnaphthohydroquinone to accelerate the bimolecular condensation reaction and by operating at a temperature (75°) where cyclization is slow, it is possible to produce a considerable amount of the substituted hydroquinone.

The unchanged hydroquinone is removed by extraction from ether with dilute alkaline hydrosulfite and the phytyl-substituted hydroquinone is separated from the ether residue as a waxy, white solid by digestion with petroleum ether and centrifugation. The white sludge is oxidized in dry ether with silver oxide, and evaporation gives 2-methyl-3-phytyl-1,4-naphthoquinone as a pure yellow, rather mobile oil (Calcd. for $C_{31}H_{46}O_2$: C, 82.61; H, 10.29. Found: C, 82.76; H, 10.53). The preparation has been completed successfully ten times under slight variation of the conditions and the pure quinone obtained in yields up to half the weight of the phytol employed. Trichloroacetic acid has been used satisfactorily in place of oxalic acid and the procedure has been applied to the preparation of 2,6-dimethyl-3-phytyl-1,4-naphthoquinone (M. D. Gates, Jr.) and 2-methyl-3-geranyl-1,4-naphthoquinone (yellow oils).

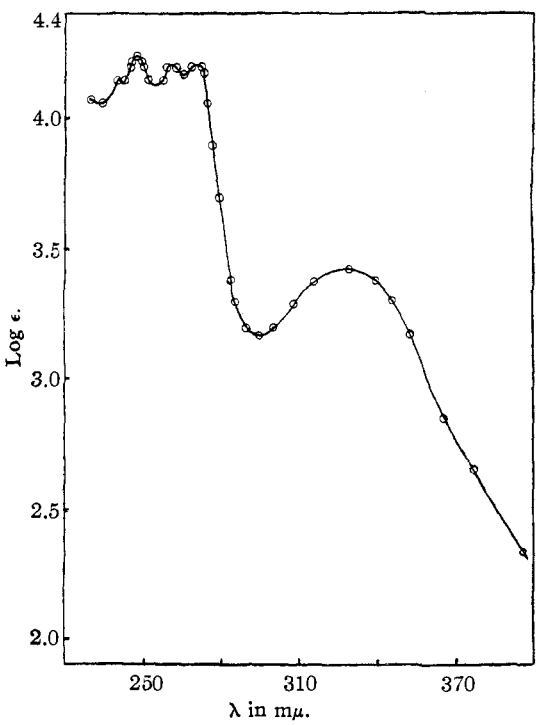


Fig. 1.—2-Methyl-3-phytyl-1,4-naphthoquinone in absolute alcohol. Maxima in mμ (with log ε values in parentheses): 241 (4.15), 248 (4.24), 260.5 (4.20), 270.5 (4.20), 328 (2.42).

In the Dam–Karrer test with alcoholic alkali, 2-methyl-3-phytyl-1,4-naphthoquinone gives striking purple or deep blue colors, depending upon the concentrations. The absorption spectrum, kindly determined by D. M. Bowen, closely resembles that reported for vitamin $K_1$, the curve being practically identical in form with that given by Dam, Karrer, *et al.* [*Helv. Chim. Acta*, **21**, 310 (1939)]. The positions of the maxima correspond closely with the values given for the vitamin by Dam, Karrer, *et al.*, and by Doisy, *et al.*, THIS JOURNAL, **61**, 1295, 1612 (1939), although the high extinction coefficient reported by Doisy has not been observed.

Dr. W. L. Sampson has found synthetic 2-methyl-3-phytyl-1,4-naphthoquinone to have marked antihemorrhagic activity. The substance was administered in 0.1 cc. of peanut oil to chicks which had been on a vitamin K deficient diet for two weeks and the blood clotting time determined eighteen hours after administration. The control birds all showed a clotting time of more than two hours and the following assays were made on the same day with the same group of chicks. With the Walker–Gordon standard alfalfa 75 mg. reduced the clotting time of 90% of the birds below ten minutes (av. 6.1 min.). With 2-methyl-3-phytyl-1,4-naphthoquinone a dose of 4 γ reduced the c. t. below ten minutes in 90% of the birds (av. 5 min.), while 2 γ was effective in 50%; thus 2–4 γ of the quinone is equivalent to approximately 75 mg. of alfalfa. Doses of 1 γ and 0.5 γ of 2-methyl-1,4-naphthoquinone were effective in 90% (av. c. t. 5 min.) and 30%, respectively, indicating an activity definitely greater than that of the phytyl derivative.

That the phytyl group very probably is linked through the terminal carbon atom is inferred from (1) analogy to the synthetic compounds of the vitamin E group, (2) analogy to similar condensations observed with cinnamyl alcohol and benzyl alcohol, and (3) the color reaction, which is interpreted as requiring an enolizable hydrogen on the α-carbon of the unsaturated side chain. Reductive acetylation gave the hydroquinone diacetate as a nearly colorless oil (Calcd. for $C_{35}H_{52}O_4$: C, 78.31; H, 9.77. Found: C, 78.43; H, 10.01), which resisted first attempts to effect crystallization but which eventually separated in part from methanol as colorless nodules after exposure of the solution in a Pyrex flask to sunlight, although it is not yet established that this treatment is essential. Recrystallized from methanol, the diacetate melted at 57–59° (Found: C, 78.34; H, 9.87). The hydroquinone dibenzoate, obtained as a solid after exposure to sunlight, melted at 85–86° (Calcd. for $C_{45}H_{56}O_4$: C, 81.77; H, 8.54.

Found: C, 81.63; H, 8.59). For the corresponding diacetyl derivative of natural vitamin $K_1$ Doisy (*loc. cit.*) found the m. p. 59°.

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RECEIVED AUGUST 12, 1939

## IDENTITY OF SYNTHETIC 2-METHYL-3-PHYTYL-1,4-NAPHTHOQUINONE AND VITAMIN $K_1$

*Sir:*

A comparison of the synthetic product described earlier with the natural vitamin was made possible by Dr. Byron Riegel, who generously supplied me with a highly purified 3–5% alfalfa concentrate [Riegel, Schweitzer and Smith, *J. Biol. Chem.*, **129**, 495 (1939)]. An alcoholic suspension of 5.3 g. of this oil was shaken with aqueous hydrosulfite and the vitamin hydroquinone taken into petroleum ether, extracted with Claisen's alkali containing hydrosulfite, and recovered from the yellow liquor by dilution with water and extraction with ether. Digestion with petroleum ether and centrifugation, following the procedure of the synthesis, gave a white solid yielding on oxidation 60 mg. of vitamin $K_1$ as a yellow oil (Found: C, 82.64; H, 10.20). The substance gives the characteristic Dam–Karrer color test, the spectrum agrees very closely with that of the synthetic quinone (T. J. Webb), and in antihemorrhagic activity the two substances appear identical within the limit of error (W. L. Sampson). Reductive acetylation gave a diacetate, m. p. 58.5–60° (Found: C, 78.13; H, 10.11) showing no depression when mixed with synthetic 2-methyl-3-phytyl-1,4-naphthohydroquinone diacetate (purified sample, m. p. 60–61.5°, remelting at 60–60.5°). Subsequent to my comparison, this finding has been confirmed by Dr. E. A. Doisy, who kindly examined my synthetic diacetate and found that it did not depress the m. p. of a purified sample of his diacetate from natural vitamin $K_1$. The sample was sent, at Dr. Doisy's stipulation, at the conclusion of his own work (sample received August 21, examined August 22). In contrast to the behavior noted with the synthetic compound of the methyl series and with the natural vitamin, synthetic 2-ethyl-3-phytyl-1,4-naphthohydroquinone did not separate from petroleum ether even after considerable purification had been effected by extraction with Claisen's alkali, and a sample of the quinone showing a strong color test was found inactive in fairly high dosage. The conclusion from this work is indicated by the title. A further observation, made with a sample of the synthetic material, is that the Dam–Karrer reaction results in the formation of phthiocol, m. p. 171–172°, mixed m. p. 171.5–172.5°.

In a clinical trial Drs. H. A. Frank and A. M. Seligman of the Beth Israel Hospital, Boston, found that 10 mg. of the synthetic vitamin given by mouth with 3 g. of ox bile to a patient with a complete malignant biliary obstruction reduced the prothrombin clotting time (method of Quick) from 37.5 to 17 seconds on one occasion and from 55 to 28 seconds on another. Intravenous injection of the quinone (10 mg.) in dispersion in 10% glucose solution (1 liter) was also successful and the patient was carried through operation without abnormal bleeding.

CONVERSE MEMORIAL LABORATORY LOUIS F. FIESER
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RECEIVED AUGUST 25, 1939

## NEW THERMODYNAMIC DATA FOR THE CYCLOHEXANE–METHYLCYCLOPENTANE ISOMERIZATION

*Sir:*

The equilibria at several temperatures in the isomerization reaction Cyclohexane (liq.) $\rightleftarrows$ Methylcyclopentane (liq.) have been studied carefully by Glasebrook and Lovell [THIS JOURNAL, **61**, 1717 (1939)]. From their measurements on this reaction they have calculated the thermodynamic data at 25° which appear in the second column of Table I and then have compared these results with similar ones (Column 3) derived from the free energy studies of Parks and Huffman ["The Free Energies of Some Organic Compounds," The Chemical Catalog Co., New York, 1932, p. 90]. Here the Parks–Huffman value for $\Delta S$, which should be quite reliable, is in fairly good agreement with the value derived indirectly by Glasebrook and Lovell but the $\Delta H$ and $\Delta F°$ values differ even in sign. These discrepancies are undoubtedly due to the fact that the Parks–Huffman $\Delta H$ value (and therefore also their $\Delta F°$) is based on early and somewhat uncertain combustion data for these two hydrocarbons. Indeed an error of only 0.25% in the two heats of combustion might conceivably account for this difference.

TABLE I

THERMODYNAMIC DATA FOR THE REACTION: CYCLOHEXANE (liq., 25°) ⟶ METHYLCYCLOPENTANE (liq., 25°)

| | Calcd. from equil. meas. | Calcd. from Parks and Huffman | Calcd. by Moore and Parks |
|---|---|---|---|
| $\Delta H$, cal. | 3510 | −1100 | 3930 |
| $\Delta S$, e. u. | 7.9 | 10.0 | 10.0 |
| $\Delta F°$, cal. | 1150 | −4100 | 950 |

In view of this situation we recently included these two substances in an extensive and very precise investigation of the heats of combustion of organic compounds which is in progress in this Laboratory. We have now obtained the following values, in terms of the "defined" calorie, for the heats of combustion of the liquid hydrocarbons per gram (*in vacuo*) at 25° and 1 atm. constant pressure: cyclohexane, 11,126.7 (±2.1) cal.; methylcyclopentane, 11,173.4 (±3.6) cal. From these data we find for the cyclohexane–methylcyclopentane isomerization $\Delta H_{298.16} = 46.7$ (±4.2) cal. per gram or 3930 (±350) cal. per mole. Taking $\Delta S = 10.0$ (±0.8) e. u. and using the relation $\Delta F = \Delta H - T\Delta S$, we next obtain $\Delta F°_{298.16} =$ 950 (±420) cal. per mole. This new third law value for the free energy of isomerization is thus in good agreement with that derived from the equilibrium study of Glasebrook and Lovell.

The new thermodynamic data are now recorded in Column 4 of the table. They serve to emphasize the necessity of very precise combustion data in any accurate free energy calculations based on the third law.

Before concluding, we wish to thank the Shell Development Company for the preparation of extremely pure samples of these hydrocarbons and for the financial support which made this study possible.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD UNIVERSITY, CALIF.
GEORGE E. MOORE
GEORGE S. PARKS

RECEIVED JULY 31, 1939

## SYNTHESIS OF 2-METHYL-3-β-HYDROXY-ETHYL-N-[(2-METHYL-6-AMINOPYRIMIDYL-(5))-METHYL]-PYRIDINIUM BROMIDE HYDROBROMIDE

*Sir:*

In view of the marked specificity of thiamin with respect to the loading of the heterocyclic rings, it seemed of interest to synthesize the isosteric 2-methyl-3-β-hydroxy-ethyl-N-[(2-methyl-6-aminopyrimidyl-(5))-methyl]-pyridinium bromide hydrobromide. This has been accomplished in ten steps, starting with 6-amino-3-nitro-2-picoline [Seide, *J. Russ. Phys.-Chem. Soc.*, **50,** 542 (1920)]. This was converted into the 6-hydroxy-3-nitro-2-picoline according to the method of Seide (*ibid.*, p. 540). From the hydroxy compound the 6-chloro-3-nitro-2-picoline was obtained by treatment with phosphorus pentachloride. Chlorine was eliminated and the nitro group simultaneously reduced to the amino group with hydrogen and a palladium catalyst [Binz and von Schickh, *Ber.*, **68,** 320 (1935)]. The 3-amino-2-picoline (m. p. 113°) was converted into the corresponding nitrile (m. p. 58°) by a Sandmeyer reaction at *p*H 4.5. The nitrile was converted into the 2-picolyl methyl ketone (b. p. 75–78°, 2 mm.) by a modified LaForge procedure [THIS JOURNAL, **50,** 2480 (1928)]. The ketone was brominated, the reaction product without isolation being converted into the acetyl derivative by treatment with potassium acetate in alcohol. The acetylated ketol was reduced without isolating it to 2-methyl-3-β-hydroxyethylpyridine (b. p. 125°, 3 mm.), picrate (m. p. 125°). (*Anal.* Calcd. for $C_{14}H_{14}O_8N_4$: C, 45.95; H, 3.81; N, 15.3. Found: C, 46.04; H, 3.66; N, 15.37). This compound was acetylated using the method described by Kuhn [*Z. physiol. Chem.*, **259,** 50–51 (1939)] (b. p. 90–92°, 3 mm.). (*Anal.* Calcd. for $C_{10}H_{13}O_2N$: N, 7.82; $CH_3CO$, 24.02. Found: N, 7.9; $CH_3CO$, 24.4, 24.2.) The β-hydroxyethyl derivative was condensed with 2-methyl-5-bromomethyl-6-aminopyrimidine hydrobromide [THIS JOURNAL, **59,** 1052 (1937)] and the 2-methyl-3-β-hydroxyethyl-N-[(2-methyl-6-aminopyrimidyl-(5))-methyl]-pyridinium bromide hydrobromide (m. p. 247°) was obtained. (*Anal.* Calcd. for $C_{14}H_{20}ON_4Br$: C, 40.00; H, 4.76; N, 13.33; Br, 38.09. Found: C, 39.72; H, 4.97; N, 13.83; Br, 37.75.)

Owing to the difference between the pyridine and thiazole rings, the new derivative permits synthesis of isomers not possible for a thiazole and, therefore, the corresponding 2-methyl-5-β-hydroxyethyl-N-[(2-methyl-6-aminopyrimidyl-(5))-methyl]-pyridinium bromide hydrobromide (m. p. 245°?) was synthesized in a similar manner starting from the corresponding ketone [*Ber.*, **57,** 832 (1924)]. The 2-methyl-5-β-hydroxyethylpyridine is a low melting solid (b. p. 103°, 2 mm.). (*Anal.* Calcd. for $C_8H_{11}ON$: C, 70.00; H, 8.03; N, 10.21. Found: C, 69.60; H, 7.77; N, 10.08.)

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.

RESEARCH LABORATORY FRANZ C. SCHMELKES
WALLACE & TIERNAN PRODUCTS, INC. ROBERT R. JOINER
BELLEVILLE, NEW JERSEY

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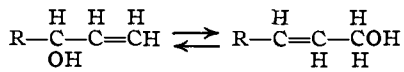
(3) Thayer, *et al.*, *Proc. Soc. Exp. Biol. Med.*, **41**, 194 (1939).
(4) Prepared by Professor Fieser and his collaborators.

## THE INTERCONVERSION OF CROTYL ALCOHOL AND METHYLVINYLCARBINOL IN AQUEOUS SULFURIC ACID

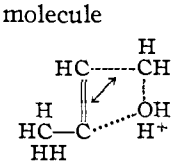
*Sir:*

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

crotyl alcohol, while the 3.7 *N* acid had produced less ether and more alcohol, 7 g. of each. Since the problem requires a careful study of the effect of the acid concentration on the proportion of hydration, ether formation and alcohol rearrangement, we wish to record the fact that mobility may be induced in this supposedly stable allylic system even at low temperatures. The possibility that butenyl sulfates are involved in the rearrangement is being investigated.

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RECEIVED JULY 31, 1939

# NEW BOOKS

**Lehrbuch der organischen Chemie.** (Textbook of Organic Chemistry.) By PAUL KARRER, Professor in the University of Zurich. Sixth, revised and enlarged edition. Georg Thieme Verlag, Rossplatz 12, Leipzig C 1, Germany, 1939. xxiii + 689 pp. 6 figs. 17.5 × 24 cm. Price, RM. 34; bound, RM. 36.

The sixth German edition is practically identical with the English edition recently reviewed in these pages [THIS JOURNAL, 61, 756 (1939)]. The new subject matter in the sixth edition (which is also incorporated in the English translation) includes only the section on organic deuterium compounds (five pages), a page on ergot alkaloids and half a page on phthalocyanins. Other topics have been brought up to date, especially in the active fields of natural products. In the preface the author calls attention to a greater inquiry into reaction mechanisms than in previous editions. The change in this regard seems slight, the text retaining its almost purely descriptive character.

PAUL D. BARTLETT

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**The Oxidation States of the Elements and their Potentials in Aqueous Solutions.** By WENDELL M. LATIMER, Ph.D., Professor of Chemistry, University of California. Prentice-Hall, Inc., 70 Fifth Avenue, New York, N. Y., 1938. xiv + 352 pp. 16 × 24 cm. Price, $3.00.

The usefullness of thermodynamic data is determined by the carefullness with which they have been obtained, the clearness with which they are presented and the convenience with which they may be used. Judged by these criteria Latimer has achieved a remarkably successful volume. The author has endeavored to include references to all works published up to 1938. The results of these investigations are presented concisely in a series of tables in the appendix. The first two give $E^0$ values for several hundred half cell reactions, one for acid solutions and one for alkaline solutions. Then follows a table of free energies of formation and one giving equilibrium constants, arranged alphabetically by the elements. The next table gives values for the activity coefficients of strong electrolytes and the last gives values for the entropy of elements, compounds and ions. If the volume contained only these thirty pages of tables it would be invaluable.

For the convenience of students who are not working in the field of physical chemistry, the first two chapters give an introduction to the use of the tables. These chapters discuss the subject of units, conventions, general methods employed in the determination of oxidation–reduction potentials, ionization potentials, electron affinities, lattice energies, and their relation to standard oxidation–reduction potentials. A section of the appendix serves as a guide in the use of activity coefficients and the concept of the ionic strength. Although these chapters of a general nature are designed to make the remainder of the volume useful they will also serve as a convenient review of the most often used portions of thermodynamics for students of organic and inorganic chemistry.

Nineteen chapters follow these first two general sections, taking up in detail the chemistry of the elements arranged by families. Here an investigator interested in any particular element will find gathered together the available thermodynamic data and references to the literature. These data are interpreted and applied to the chemical behavior of the element. Where no data are available the author frequently has given estimates, which will be useful guides to those without a background of long experience in this field.

This volume will not only constitute an essential part of every chemist's reference library but will also introduce students who wish to use physico-chemical data to the elements of thermodynamics.

HENRY E. BENT

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**Inorganic Quantitative Analysis.** By HAROLD A. FALES, Ph.D., Columbia University, and FREDERIC KENNY, Ph.D., St. Francis College. Second edition. D. Appleton-Century Company, Inc., 35 West 32nd Street New York, N. Y., 1939. xiii + 713 pp. 132 figs. 15 × 22.5 cm. Price, $4.00.

The educational philosophy of this excellent book is contained in the following sentences from the preface: "It has been the aim of the authors, in preparing this work, to apply the principles of Physical Chemistry to the theory of Quantitative Analysis in a detailed and thorough manner. In stressing this point of view, it has not been forgotten, however, that the two other