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°.

CONVERSE MEMORIAL LABORATORY LOUIS F. FIESER
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS
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
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS
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 ΔS, which should be quite reliable, is in fairly good agreement with the value derived indirectly by Glasebrook and Lovell but the ΔH and $\Delta F°$ values differ even in sign. These discrepancies are undoubtedly due to the fact that the Parks–Huffman ΔH 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
ΔH, cal.	3510	−1100	3930
ΔS, 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 $\Delta F^{\circ}_{298.16} =$ 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.)