solution containing 10 mg. per ml. of II suspended in water with emulphor and DMA as dispersants.

Both monkeys had an unequivocally favorable clinical response to the 6-chromanol of hexahydrocoenzyme Q_4. In addition, there was a pronounced reticulocyte response in the anemic monkey that was followed by an increase in hemoglobin (Fig. 1). The excretion of creatine was sharply reduced in both animals, as in Fig. 2 for No. 218. This response is similar to that obtained when α-tocopherol is given.[1] A dose of 20 mg. of II given intravenously daily for 8 days produced a remission in the monkey supplied with the low-fat diet, but 40 mg., given intravenously daily for an extended period, was required to keep the creatine to creatinine ratio below 1 in the monkey receiving fat in the diet.

Although these studies were done in only two animals, they had received extensive over-all study, and the response appears clearly due to the administration of the 6-chromanol of hexahydrocoenzyme Q_4. Remissions, such as those reported here, have not occurred previously without specific therapy. The interpretation of this finding may be based upon answers to the following questions: (a) Are both vitamin E and the chromanol of coenzyme Q_4 exhibiting a basic biological activity in the deficient monkey in the sense that each is functioning in a native biochemical sequence? (b) Is only vitamin E or the chromanol of coenzyme Q_4 exhibiting a basic biological activity with the other substituting solely on the basis of similarity of structure? (c) Is one compound merely protecting the other, because of its antioxidant properties?

After about twenty-five years of research on vitamin E, a direct relationship between it and a given disease state in man is not generally recognized in medicine. Horwitt[9] has investigated man's need for tocopherol as a function of peroxidizable lipids in the diet. Coenzyme Q_{10} is present in man.[10] That it, or other enzymic forms, may show effects in man not seen with vitamin E requires new medical research which may be further justified by these new data on the response of the anemic and dystrophic monkey to therapy with II.

(9) M. K. Horwitt, *Am. J. Clin. Nutr.*, **8**, 451 (1960).

(10) P. H. Gale, F. R. Koniuszy, A. C. Page, Jr., and K. Folkers, *Arch. Biochem. Biophys.*, **93**, 211 (1961).

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF ARKANSAS — JAMES S. DINNING
LITTLE ROCK, ARKANSAS — COY D. FITCH
MERCK SHARP & DOHME RESEARCH LABORATORIES*
DIVISION OF MERCK & CO., INC. — CLIFFORD H. SHUNK
RAHWAY, NEW JERSEY — KARL FOLKERS

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* Coenzyme Q. XXXIII.

SYNTHESIS OF SOME STABILIZED 2,3-NAPHTHOQUINONOID SYSTEMS

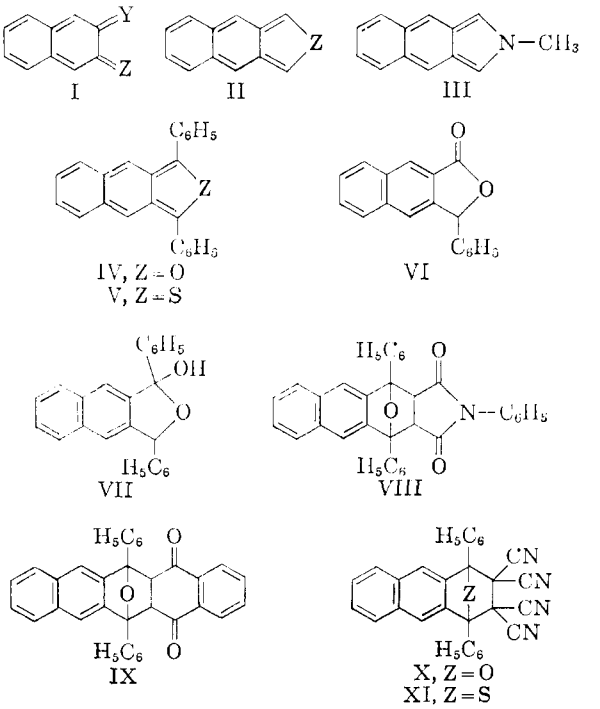
Sir:

With the exception of anthracene and higher fused linear polynuclear aromatic hydrocarbons, no compounds of the type I or II have been reported. Substances of this sort may be considered to be formally related to the unknown 2,3-naphthoquinone (I, Y = Z = O), a high energy system containing no true benzenoid ring. A recent attempt to synthesize 2-methyl-5,6-benzisoindole (III), a system of type II, was not successful; the product, if formed, was too unstable to permit isolation or even trapping by maleic anhydride.[1] We wish now to report the synthesis of furan IV and thiophene V, both of which represent isolable 2,3-naphthoquinonoid systems.

Reduction of 3-benzoyl-2-naphthoic acid[2] with sodium borohydride, then acidification, gave the lactone VI, m.p. 153–155°, in 80% yield.[3] Reaction of VI with excess phenylmagnesium bromide gave, in 65% yield, alcohol VII, m.p. 153–156°. Brief heating of VII with acetic acid gave, in 88% yield, 1,3-diphenylnaphtho[2,3-c]furan (IV), m.p. 148–154°, as small dark red plates: $\lambda_{max}^{benzene}$ 367 mμ (ϵ = 5700), 383 (5700), 524 (7900), 546 (7900).

In the absence of light, compound IV was unchanged after standing at room temperature for several months. In solution it is much less stable, and all attempts at recrystallization have failed. Substance IV is extraordinarily reactive as a diene in the Diels–Alder reaction. It reacts instantaneously in solution with N-phenylmaleimide, 1,4-naphthoquinone and tetracyanoethylene to give excellent yields of the corresponding adducts VIII (m.p. 287–290°), IX (m.p. 198–203°) and X (m.p. 235–258°). Adducts IX and X, however, can reverse to their precursors with surprising ease: solutions of these colorless compounds in benzene become red on heating and lose their color once more when cooled.

Reaction of IV with phosphorus pentasulfide in disulfide for one day gave, in 38–61% yield, 1,3-diphenylnaphtho[2,3-c]thiophene (V), isolated as its deep purple 2,4,7-trinitrofluorenone complex, m.p. 169–171°. The free thiophene (V), obtained



(1) G. Wittig and H. Ludwig, *Ann.*, **589**, 55 (1954).

(2) H. Waldmann and H. Mathiowitz, *Ber.*, **64**, 1713 (1931).

(3) Melting points are uncorrected. Satisfactory analyses were obtained for all compounds whose melting points are recorded.

by alumina chromatography of the complex, formed red needles, m.p. 198–202°; $\lambda_{max}^{benzene}$ 513 mμ (ϵ = 8700). Compound V is more stable in solution and less reactive as a diene than its oxygen analog IV. Although its reacts rapidly with tetracyanoethylene to give an adduct (XI), m.p. 268–280°, it did not react with N-phenylmaleimide on standing for sixteen hours in benzene solution at room temperature.

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(4) Fellow of the Alfred P. Sloan Foundation.

EVANS CHEMICAL LABORATORY
THE OHIO STATE UNIVERSITY M. P. CAVA[4]
COLUMBUS 10, OHIO J. P. VAN METER

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PROTON SPIN–SPIN COUPLING CONSTANTS IN VINYLACETYLENES

Sir:

Kreevoy, Charman and Vinard[1] recently have presented coupling constants for the spin–spin splittings observed in the acetylenic region of the n.m.r. spectra for several monosubstituted acetylenes. In ten of these compounds the magnitude of the coupling between the acetylenic hydrogen and the α-hydrogen was found to fall in the range 2.1 cps. to 2.8 cps. Failure to observe a measurable splitting in the acetylenic peak of vinylacetylene and propynal, however, led these workers to conclude that the coupling was anomalous in these

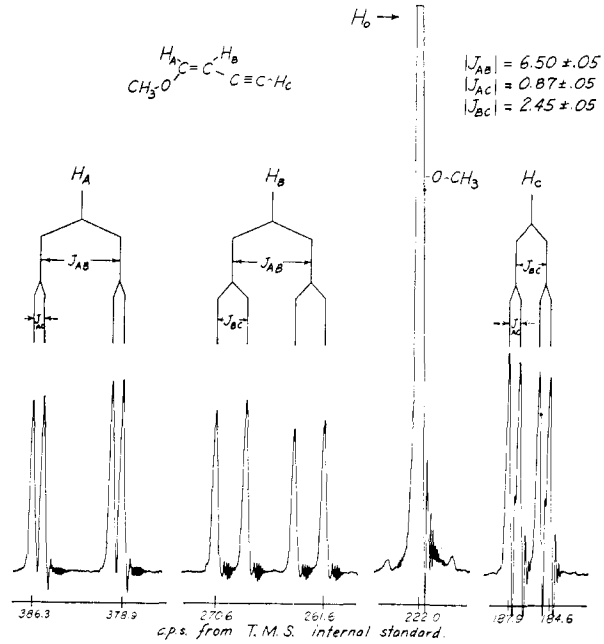

Fig. 1.—N.m.r. spectrum of 1-methoxy-1-buten-3-yne.

two molecules. As an explanation, it was proposed that π electrons centered on the α-carbon participate in such a manner as to yield a small coupling constant of non-measurable magnitude.

Work in this laboratory on vinylacetylenes indicates that the coupling constant in question has

(1) M. M. Kreevoy, H. B. Charman and D. R. Vinard, *J. Am. Chem. Soc.*, **83**, 1978 (1961).

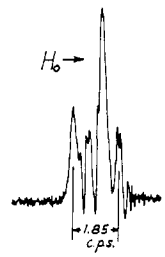

Fig. 2.—Acetylenic region of the n.m.r. spectrum of monovinylacetylene.

a magnitude in the prescribed range, 2.1 to 2.8 cps., and is not abnormally small as previously suggested. In the n.m.r. spectrum of *cis*-1-methoxy-1-butene-3-yne,[2] this splitting was measured to be 2.47 ± 0.05 cps. The essential features of the spectrum and the remaining spectral parameters are given in Fig. 1. As the multiplets are separated by relatively large chemical shifts, the coupling constants and chemical shifts can be taken directly from the experimental data. In addition to the chemical shift values which form a sufficient basis for the assignment, supporting evidence is found in the agreement of the 6.5 cps. vinyl coupling with the 6.4 and 6.8 cps. *cis*-couplings noted by Banwell and Sheppard,[3] respectively, for divinyl and methyl vinyl ethers. Furthermore, the 0.87 cps. long range acetylenic coupling is comparable with the values found in this laboratory for 2-methyl-1-butene-3-yne and vinylacetylene.

The high resolution n.m.r. spectrum of the acetylenic proton of 30% by volume vinylacetylene[4] dissolved in chloroform is presented in Fig. 2 as evidence that the splittings in this compound are not less than 0.5 cps. (the proposed limit of resolution for data presented in ref. 1). By first obtaining the vinyl couplings from the deuterated compound, $CH_2{=}CH{-}C{\equiv}C{-}D$, the spectrum of $CH_2{=}CH{-}C{\equiv}C{-}H$ was fitted[5] numerically with an high speed digital computer. Using a system of labeling where X and A, B, C are, respectively, the acetylenic and three vinyl protons with A *cis* to B and *trans* to C, the spectral parameters and their relative signs were found as follows: $\nu_0\delta_{AB}$ = 13.7 cps., $\nu_0\delta_{AC}$ = 2.9 cps., $\nu_0\delta_{AX}$ = 168.3 cps., J_{AB} = 11.5 cps., J_{AC} = 17.3$_5$ cps., J_{BC} = 2.0$_5$ cps., J_{AX} = −2.1 cps., J_{BX} = 0.8 cps. and J_{CX} = 0.7 cps. The acetylenic multiplet was 88.6 cps. downfield from cyclohexane. A standard deviation of 0.047 cps. was obtained from the difference in the positions of the experimental and the theoretical lines.

(2) This sample was obtained from L. Light and Company.

(3) C. N. Banwell and N. Sheppard, *Mol. Phys.*, **3**, 351 (1960).

(4) Dr. H. E. Schroeder of E. I. du Pont de Nemours and Co. provided this sample.

(5) This calculation was finished during the interim between submitting the original and revised forms of this communication. As such, the calculations of Snyder, Altman, and Roberts in the accompanying manuscript predate ours. The difference in the two sets of parameters exceeds slightly the limits of error of both calculations. We have noted, however, that the parameters are very sensitive to the determined positions of the experimental lines, and minor errors in these values might account for the variation. Our spectrum was obtained on a Varian A-60 console used in conjunction with the standard 12 inch magnet.