Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.17; H, 6.93; OC_2H_5, 22.25. Found: C, 76.98; H, 6.94; OC_2H_5, 21.64.

The monoethyl ether shows complete vitamin K activity at a dosage of 1γ.

2,3 - Dimethyl - 2 - phytyl - 2,3 - dihydro - 1,4 - naphthoquinone (X).—A solution of 7.5 g. of phytol, 15 g. of 2,3-dimethyl-1,4-naphthohydroquinone and 5 g. of oxalic acid in 75 cc. of dioxane was heated in a closed vessel at 75° for thirty-four hours. The mixture was diluted with water containing hydrosulfite, extracted with ether and unchanged hydroquinone was removed by extraction with 2% potassium hydroxide containing 2% sodium hydrosulfite. After a further washing with 10% alkali the product obtained from the dried ether was distilled at 10^{-4} mm. A fore-run of phytadiene and phytol distilled at an inside temperature of 90° and about 4 g. of X distilled at 140–150°, leaving about 0.5 g. of tarry residue. On redistillation the substance was obtained as a pale yellow oil. It reacted readily with bromine in carbon tetrachloride with the liberation of hydrogen bromide. No reaction was observed with 2,4-dinitrophenylhydrazine under the conditions employed with the K_1 by-product.

Anal. Calcd. for $C_{32}H_{50}O_2$: C, 82.36; H, 10.78. Found: C, 82.27; H, 10.67.

In the Zerewitinoff determination (R. D. C.) the substance liberated 0.28 equiv. of methane and added 2.07 equiv. of reagent.

Summary

The by-product isomeric with 2-methyl-3-phytyl-1,4-naphthohydroquinone in the vitamin K_1 synthesis is shown to be 2-methyl-2-phytyl-2,3-dihydro-1,4-naphthoquinone. The substance, which has been characterized by degradation, aluminum isopropoxide reduction, and other reactions affording crystalline derivatives, has marked antihemorrhagic activity and can be converted in small part into vitamin K_1 by pyrolysis.

The isomeric naphthotocopherol has been prepared by the action of stannous chloride and acid on vitamin K_1 and converted to γ-hydroxy-β,γ-dihydrovitamin K_1. This substance yields a hydroquinone diacetate on reductive acetylation.

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The Methoxymercurials from *cis* and *trans* Styryl Cyanide[1]

BY WILLIAM H. BROWN AND GEORGE F. WRIGHT

Introduction

It has been shown[2] that the *cis* isomer of certain stereoisomeric pairs reacts more rapidly with a solution of mercuric acetate in methanol than does the *trans* isomer. Since the reaction is easy to follow analytically, this would seem to afford a method of ascertaining the geoisomeric configuration of such a pair. Furthermore, there is a possibility that the difference in rate of addition might be utilized as a method of evaluating the *cis–trans* content of mixtures. Accordingly several pairs of geoisomers whose configurations have been determined by other means have been tested by this procedure. One of these pairs was β-styryl cyanide.

Ghosez,[3] who separated *cis* and *trans* β-styryl cyanide by fractionation, considered the low-melting isomer to be the *cis* form. Kistiakowsky and Smith,[4] after a study of the thermal isomerization, agreed with this designation. It might then be expected that this isomer would react more rapidly with a methanol solution of mercuric acetate than the higher melting form. Actually a trial showed that neither reacted appreciably at room temperature. Since a small amount of nitric acid has been found to accelerate the addition,[2b] this modification was then used with success; both isomers added the elements of methoxymercuric acetate at a rate convenient to study. The analytical procedure, though modified to suit the present study was essentially that previously outlined[2b] involving chloroform extraction to separate organomercurial from mercuric acetate prior to titration with thiocyanate. This separation is necessary owing to the fact that the product, II, reacts with thiocyanate.

The low melting styryl cyanide reacted with an equivalent of mercuric acetate in excess of methanol at such a rate that the reaction half-life was one hundred eighty-five minutes at 25° and one hundred minutes at 35°. The corresponding half-life reaction periods for the high melting isomer

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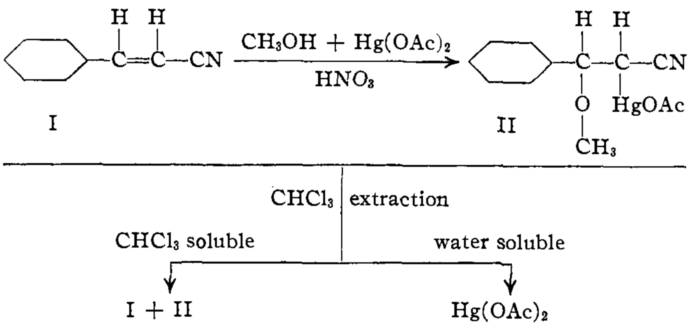
(1) Presented before the Division of Organic Chemistry, American Chemical Society at Boston, September, 1939.

(2) (a) Biilmann, *Ber.*, **35**, 2571 (1902). (b) Wright, THIS JOURNAL, **57**, 1993 (1935).

(3) Ghosez, *Bull. soc. chim. Belg.*, **41**, 477 (1932).

(4) Kistiakowsky and Smith, THIS JOURNAL, **58**, 2438 (1936).

were nine hundred minutes at 25° and six hundred minutes at 35°. The much more rapid reaction with the low-melting isomer would designate it as the *cis* isomer, in conformity therefore with the assignment of configuration by Ghosez and by Kistiakowsky and Smith. Admixture of the β-phenyl-β-methoxy-α-acetoxymercuripropionitriles from either *cis* or *trans* styryl cyanide with an equivalent of acetic acid in methanol containing nitric acid as catalyst demonstrated that the equilibrium was at least 99% in the direction of mercurial formation.



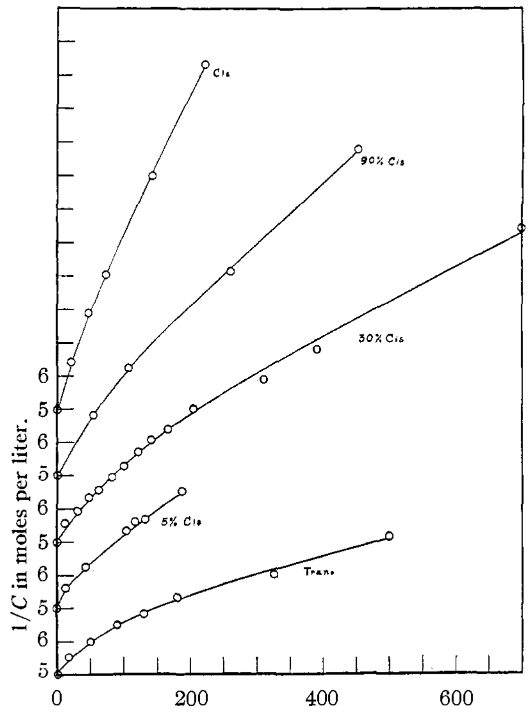


Fig. 1.—Second order rates, *cis–trans* mixtures of styryl cyanide.

It might be expected that a reaction so predominantly in one direction would show a reasonably good velocity constant in this direction, but such was not the case. This is probably owing to disappearance of the catalyst by a side reaction. When 0.0003 mole of nitric acid per 0.01 mole of both mercuric acetate and styryl cyanide in methanol was used, the reaction stopped after five hours; a test for nitrate was then negative. Upon addition of 0.0015 mole of nitric acid, the reaction then continued to completion. Consequently, in subsequent experiments 0.0015 mole of nitric acid per 0.01 mole of reactants was used consistently. Obviously the rate constants dropped off markedly as the catalyst was destroyed. Inspection of Fig. 1 shows that this dropping off is more pronounced in the case of the slower reaction (*trans*) than in the more rapid addition to the *cis* styryl cyanide. It is evident that a satisfactory analytical method for estimation of the *cis–trans* content of mixtures cannot be devised for the catalyzed addition of the elements of methoxymercuric acetate to ethylenes unless that catalyst either is not destroyed during the reaction, or the addition reaction is much more rapid than the destruction of catalyst. The latter alternative is illustrated in Fig. 2, where the rate constant drops off badly when a 1:1 molar concentration of mercuric acetate and styryl cyanide reacts in methanol at 25° (C and F). The faster reaction at 35° shows an equally bad drift, probably because

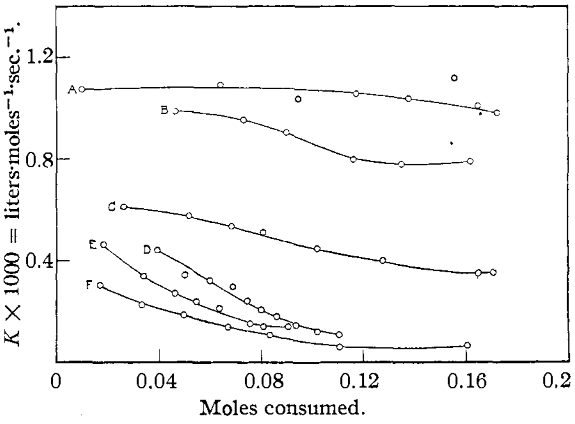


Fig. 2.—Second order rate constants, preparation of β-methoxy-β-phenyl-α-acetoxymercuripropionitrile:

	Moles	$Hg(OAc)_2$, mole	Temp., °C.	Half-life, min.
A	0.2 *cis*	0.1	35	30
B	.1 *cis*	.1	35	80
C	.1 *cis*	.1	25	190
D	.2 *trans*	.1	35	280
E	.1 *trans*	.1	35	600
F	.1 *trans*	.1	25	1000

decomposition of catalyst is likewise accelerated (B and E), while the rapid reaction at 2:1 concentration at 35° (A) gives in the case of the *cis*-ethylene a second order constant which drops off only 5% over four-fifths of the reaction period. It would, therefore, appear that when the rate study was undisturbed by disappearance of catalyst the addition reaction was purely bimolecular (Formulation A, ref. 2b) and no evidence for a more intricate mechanism[5] has been apparent in our studies of the addition reaction. It may be possible that the reaction with cyclohexene and mercuric nitrate in water, which was examined by Lucas and co-workers, is different in type from the addition of methoxy and acetoxy mercuri-groups to a double bond. In the instance[2b] when α-methoxycyclohexylmercuric chloride was isolated from such addition to cyclohexene the reaction was much too rapid to measure by the analytical procedure described above.

The smoother progress of reaction shown by the *cis*-styryl cyanide was reflected in the easier isolation and greater yield of β-phenyl-β-methoxy-α-acetoxymercuripropionitrile obtained from the *cis* geoisomer than from the *trans* compound. Both compounds were thermally unstable and were necessarily purified by crystallization at room temperature. This difficulty might have been alleviated by conversion of the acetoxymercurials to chloromercurials or bromomercurials which, in general, have been found to be more stable.[2b] It was, however, of interest to ascertain whether conditions could be imposed so as to isolate such unstable derivatives, and in this we were successful. The higher yield of mercurial from the *cis* nitrile than from the *trans* nitrile was likewise expected on the basis of the infusible white precipitate which appeared in both reaction mixtures but was in larger quantity in the slower reaction of the *trans* ethylene. This precipitate was not mercurous salt, the usual contaminant in these addition reactions, but contained mercury and nitrogen and was undoubtedly involved in the side reactions leading to destruction of the nitric acid catalyst.

The positions assumed by the entering groups were located by conversion *via* bromination and hydrolysis of both diastereomers to a mixture of the known α-bromo-β-methoxy-β-phenylpropionic acids.[6] The report that racemization occurs during bromination[6c] of such methoxymercurials is thus confirmed.

All attempts to relate the α-acetoxymercuri-β-methoxy-β-phenylpropionitriles configurationally to the corresponding known diastereomers of α-acetoxymercuri-β-methoxy-β-phenylpropionic acid or their esters failed. No method of nitrile hydrolysis could be found that would leave the HgX linkage intact.

Experimental Part

Determination of Reaction Rates.—In an orienting run employing 1.29 g. (0.01 mole) of low melting styryl cyanide, 3.19 g. (0.01 mole) of mercuric acetate and 0.02 cc. (0.0003 mole) of concentrated nitric acid in 50 ml. of absolute methanol the reaction stopped after four hours when about one-third of the reactants was used up. A 0.3-ml. test portion diluted to 1 ml. with water and added to 1 ml. of a 0.2% solution of brucine in concentrated sulfuric acid gave no red color at the interface. Since nitrate was thus proved to be absent, 0.1 ml. of concentrated nitric acid (0.0015 mole) was added to the reaction mixture. This addition re-induced the reaction, which then went to completion. Thereafter 1 ml. of a solution of 1 ml. of nitric acid per 10 ml. of methanol was used per 0.01 mole of styryl cyanide in 50 ml. of methanol.

A solution of mercuric acetate in methanol was allowed to come to temperature in the thermostat; the styryl cyanide and catalyst solution were added and the reaction diluted to the appropriate volume with methanol. Aliquot samples of 5 ml. were withdrawn at appropriate time intervals and run into 50 ml. of distilled water containing 2 ml. of saturated potassium nitrate solution. The resulting mixture was extracted rapidly with five 5-ml. portions of chloroform. The remaining aqueous solution was titrated with 0.1 *N* thiocyanate, an end-point permanent for two minutes being recorded.

***cis* and *trans* Styryl Cyanides.**—The preparation and properties of these styryl cyanide isomers have been described[7]: The low melting isomer (m. p. −10.0°) n^{20}_D 1.5845 showed less than 0.1° drift in a ten minute cooling curve, but the high melting isomer, m. p. 23.5–24°, n^{20}_D 1.6031, showed a 0.4–0.5° drift over the same time of heating or cooling. Attempted purification by means of fractional crystallization or preferential adsorption on aluminum oxide in a Tswett column failed to level out this latter cooling curve.

Preparation of β-Phenyl-β-methoxy-α-acetoxymercuripropionitrile

1. **From Low Melting (*cis*) Styryl Cyanide.**—A solution of 3.8 g. (0.03 mole) of *cis*-styryl cyanide and 9.54 g. (0.03 mole) of mercuric acetate (Merck) in 75 cc. of absolute methanol was treated with 0.30 cc. (0.0047 mole) of concentrated nitric acid. After eleven days a white precipitate (wt. 1.3 g.) was filtered off and the methanol distilled from the filtrate at 40° (10 mm.). The residue crystallized to a white sticky mass, 11.1 g. When the product was dissolved in chloroform and the solution di-

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[5] Lucas, Hepner and Winstein, THIS JOURNAL, **61**, 3102 (1939).

[6] (a) Schrauth and Geller, *Ber.*, **55**, 2783 (1922); (b) Conant and Jackson, THIS JOURNAL, **46**, 1727 (1924); (c) Van Loon and Carter, *ibid.*, **59**, 2555 (1937).

[7] Kistiakowsky and Smith, *ibid.*, **58**, 2428 (1936).

luted with ether, 3.26 g. (26% of theoretical) of material of m. p. 118–120° crystallized out. Further dilution precipitated 1.59 g. m. p. 110–114° and 0.91 g. m. p. 84–89°. Repeated crystallization in this manner gave an analytical sample, m. p. 121°, containing nitrogen and mercury.

Anal. Calcd. for $C_{12}H_{13}O_3NHg$: C, 34.32; H, 3.12; OCH_3, 7.39. Found: C, 34.32; H, 3.14; OCH_3, 7.51

2. **From *trans*-Styryl Cyanide.**—This preparation under identical conditions gave a white precipitate, wt. 2.7 g., which was filtered off. The filtrate upon evaporation at 15 mm. left 10 g. of an oil, from which 2.0 g. (16% of theoretic) of crystalline compound m. p. 84–94° was obtained by solution in chloroform and precipitation with ether. A subsequent crop m. p. 78–82°, wt. 0.31 g. was obtained. This product was recrystallized to constant melting point, 96°, which point was depressed 6° on admixture with the 120° compound obtained from the *cis* nitrile.

Anal. Calcd. for $C_{12}H_{13}O_3NHg$: C, 34.32; H, 3.12; OCH_3, 7.39. Found: C, 34.41; H, 3.07; OCH_3, 7.34.

The fine white precipitates which were thrown down in the reaction mixtures appear to be identical. The material does not melt before decomposition at 300–400°, is insoluble in acid, alkali and organic solvents and is not mercurous salt since it does not turn black with ammonium hydroxide.

3. **Reaction without Catalyst.**—When nitric acid was not used, the apparent half-life of the reaction with *trans*-styryl cyanide was about twelve days as compared to about eight days for the *cis*-isomer. Yields were very small

Conversion to α-Bromo-β-methoxy-β-phenylpropionic Acids.—A solution of 0.42 g. (0.001 mole) of either diastereomer of α-acetoxymercuri-β-methoxy-β-phenylpropionitrile in 5 cc. of chloroform was treated at +5° with 0.32 g. (0.002 mole) of bromine in 5 cc. of chloroform. After twenty-four hours the solvent was removed under 15 mm. and the residue redissolved in chloroform and washed with water until the aqueous layer gave no more test for mercuric ion. After a subsequent wash with 1% sodium hydroxide, the solution dried with calcium chloride was evaporated at 15 mm. to yield 0.20 g. of oil. The latter was shaken with 4 cc. of concentrated hydrochloric acid for twenty-nine hours, then diluted with water and taken up in ether. This ether solution was extracted with 5% sodium hydroxide solution to leave a compound, m. p. 209–213° (cryst. benzene, m. p. 219–223°) presumably the amide, which constituted the bulk of the product but was not investigated further since neither of the diastereomeric α-bromo-β-methoxy-β-phenylpropionamides are known. The alkaline solution, decolorized with charcoal, was acidified with hydrochloric acid to yield 3 mg. of acid, m. p. 179–180°, mixed m. p. with authentic α-bromo-β-methoxy-β-phenylpropionic acid m. p. 179° (prepared from the ethyl ester) not lowered. Evaporation of the filtered acidified solution yielded 10 mg. of the other diastereomer m. p. 125°, cryst. water to melt at 126–127°, and likewise identified by mixed m. p. with the authentic diastereomer. We have been unable to isolate the 139–140° acid reported by Van Loon and Carter.

Equilibrium of the Addition Reaction.—When 0.84 g. (0.0002 mole) of either mercurial was mixed with 0.012 g. (0.0002 mole) of acetic acid and 0.02 ml. of nitric acid and diluted with methanol to a total volume of 10 ml., immediate titration showed that 0.8% of the mercury was present as inorganic salt and the value did not change over a three-day period. The equilibrium is therefore over 99% in the direction of the mercurial formation.

The authors wish to thank Miss Joan Romeyn for the microanalytical determinations.

Summary

1. The diastereomeric α-acetoxymercuri-β-methoxy-β-phenylpropionitriles have been prepared from the *cis* and *trans* styryl cyanides.

2. The addition to the low-melting styryl cyanide was about six times more rapid than addition to the high-melting isomer, thus designating the low-melting nitrile as *cis*.

3. The reaction does not proceed at a measurable rate with these nitriles unless nitric acid catalyst is employed. The resulting rate constants are unsatisfactory unless the reaction proceeds so fast that the catalyst is not appreciably destroyed by side reactions.

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