TABLE I

SOLUBILITY OF HALOGENATED METHANES IN NITRILES

Theoretical solubility	Formula	B. p., °C.	CH_2Cl_2 G./g.	CH_2Cl_2 M. F., 0.311	$CHCl_2F$ G./g.	$CHCl_2F$ M. F., 0.381
Caprylonitrile	$CH_3(CH_2)_6CN$	198–200	0.462	0.405	0.875	0.420
Benzonitrile	C_6H_5CN	190.7	.463	.359	See Ref. 1	
Succinonitrile	$CN(CH_2)_2CN$	265–267	.199	.158	.231	.152
Glutaronitrile	$CN(CH_2)_3CN$	285–287	.319	.261	.457	.294
Adiponitrile	$CN(CH_2)_4CN$	295	.364	.316	.560	.428
Sebaconitrile	$CN(CH_2)_8CN$	199–200 (15 mm.)	.425	.435	.730	.522

It is obvious that succinonitrile and glutaronitrile are associated to a considerable extent; this undoubtedly is due to bonding between hydrogens of the methylene groups and the nitrogen atom of the nitrile groups. In succinonitrile the —CH_2— group is alpha to one nitrile residue and beta to another and the cumulative effect is sufficient to give labile hydrogen atoms. In glutaronitrile the further separation of the nitrile groups makes their cumulative effect less on each —CH_2— group. In adiponitrile this effect is fairly well overcome by the distance between the nitrile groups. In sebaconitrile the solubility goes above the calculated value but not as much as might have been expected from the solubility of the mononitriles. This evidence for hydrogen bond association in the dinitriles is of interest in view of the recent estimation that hydrogen cyanide is similarly associated to the extent of 3% at the boiling point.[2]

The solubility determinations were made at 32.2° as described earlier[3] and are reported in the table.

(2) Giauque and Ruehrwein, THIS JOURNAL, **61**, 2626 (1939).
(3) Zellhoefer, *Ind. Eng. Chem.*, **29**, 584 (1937).

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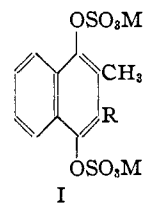
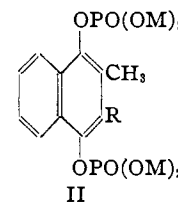
Water-Soluble Antihemorrhagic Esters

BY LOUIS F. FIESER AND EDWARD M. FRY

As a possible means of providing antihemorrhagic compounds which can be administered parenterally in a small volume of aqueous solution, we have prepared a series of water-soluble sulfuric and phosphoric acid ester derivatives of vitamin K_1 and of other quinones of established vitamin K activity. In chick assays conducted by Dr. W. L. Sampson potassium vitamin K_1 hydroquinone disulfate (I, R = phytyl, M = K) was found inactive at a dosage of 500 γ, an observation which perhaps finds a counterpart in the great loss of biological activity attending the conversion of oestrone into oestrone sulfate.[1] Similarly sodium 2,3-dimethyl-1,4-naphthohydroquinone disulfate was inactive at the same high dosage, in contrast to the corresponding quinone which is active at 50 γ. On the other hand, vitamin K_1 hydro-



I



II

quinone diphosphoric acid II (R = phytyl, M = H) shows activity at dosages down to 25 γ, but not at 10 γ, and thus does not fall greatly short of vitamin K_1, which gives a response at 1.5–2 γ by the same procedure. Still more potent is the sodium salt of 2-methyl-1,4-naphthohydroquinone disulfuric acid (I, R = H, M = Na), which shows antihemorrhagic activity at a level of 2 γ (assays at lower dosages are still to be made). The substance crystallizes as a dihydrate, and if the administered material undergoes hydrolysis it could give rise to only 52% of its weight of 2-methyl-1,4-naphthoquinone.

Of the water-soluble substances previously suggested for use in vitamin K therapy, phthiocol[2] suffers from being only weakly active, and free naphthohydroquinone and aminonaphthol derivatives[3] are highly sensitive to oxidation. The above active ester derivatives are colorless solids which are stable in aqueous solution and not sensitive to air or light. Furthermore, 2-methyl-3-phytyl-1,4-naphthohydroquinone diphosphoric acid can be described as a water-soluble form of vitamin K_1.

In a clinical trial conducted by Drs. H. A. Frank, A. Hurwitz and A. M. Seligman at the

(1) Butenandt and Hofstetter, *Z. physiol. Chem.*, **259**, 222 (1939).
(2) Almquist and Klose, THIS JOURNAL, **61**, 1923 (1939).
(3) Doisy, *et al.*, *ibid.*, **61**, 1932, 2563 (1939).

Beth Israel Hospital, Boston, sodium 2-methyl-1,4-naphthohydroquinone disulfate was given to a patient having a complete biliary fistula. A solution of 10 mg. of the salt in 10 cc. of 0.9% salt solution remained clear after autoclaving at 250°F. and when given intravenously reduced the prothrombin clotting time from 54 seconds to 28.5 seconds in four hours; the lowest level reached was 25 seconds in about twelve hours (normal, 15 seconds).

Experimental Part[4]

Potassium Vitamin K_1 Hydroquinone Disulfate.—A cooled suspension prepared by slowly adding 0.6 cc. of chlorosulfonic acid to 2 cc. of pyridine and 5 cc. of carbon tetrachloride was treated with 0.48 g. of vitamin K_1 hydroquinone. On manipulating the mixture with a stirring rod and boiling for ten minutes, the pyridine salt separated as a viscous mass which went to a sticky solid on cooling and diluting with ether. The liquor and washings afforded 0.17 g. of oil giving no color test with alcoholic alkali. The solid was treated while cooling with sufficient 10 *N* sodium hydroxide to produce a red color, ether was added to dissolve the liberated pyridine, and the sodium disulfate ester was separated by centrifugation as a dark red oil. This was stirred with excess 25% absolute alcoholic potassium hydroxide to effect conversion to the potassium salt, which separated as a light brown crystalline solid after dilution with absolute alcohol. Crystallization from 95% alcohol (Norite) gave colorless plates. The salt gives a clear solution in water. The sample was dried at 80° and 18 mm.

Anal. Calcd. for $C_{31}H_{46}O_8S_2K_2$: C, 54.04; H, 6.73; K, 11.35. Found: C, 54.54; H, 6.71; K, 10.67.

Sodium 2-Methyl-1,4-naphthohydroquinone Disulfate.—A mixture of 0.5 g. of 2-methyl-1,4-naphthohydroquinone with a cooled suspension from 1 cc. of pyridine, 10 cc. of carbon tetrachloride and 0.5 cc. of chlorosulfonic acid was heated for ten minutes on the steam-bath, cooled, and the solvent decanted from the oily yellow pyridine salt. This was treated with a slight excess of 10 *N* alkali, the mixture was extracted with ether, and the residual red oil taken up in a little hot water. Alcohol added in portions precipitated first inorganic material, which was removed, and then the ester salt as tan crystals (0.58 g., 0.27 g. more from the mother liquor). Crystallization from water gave 0.4 g. of colorless product free from inorganic salts, and this was further purified by dissolving it in water and adding alcohol. The air dried material proved to be a dihydrate.

Anal. Calcd. for $C_{11}H_8O_8S_2Na_2 \cdot 2H_2O$: C, 31.89; H, 2.92; Na, 11.10; H_2O, 8.70. Found: C, 31.82; H, 3.20; Na, 11.21; H_2O, 8.29.

Sodium 2,3-dimethyl-1,4-naphthohydroquinone disulfate was prepared as above from 0.5 g. of the hydroquinone. The pyridine salt was obtained on cooling as a highly hygroscopic solid. The sodium salt was crystallized once from water (0.8 g.) and then from water diluted with alcohol, giving colorless plates (air dried).

Anal. Calcd. for $C_{12}H_{10}O_8S_2Na_2 \cdot 2H_2O$: C, 33.64; H, 3.29; Na, 10.74; H_2O, 8.41. Found: C, 33.47; H, 3.49; Na, 10.97; H_2O, 9.00.

Sodium 2-Methyl-1,4-naphthohydroquinone Diphosphate (Normal Salt; II, M = Na).—A solution of 0.3 g. of the hydroquinone in 0.8 cc. of pyridine was added by drops with ice cooling to a suspension prepared by adding 0.5 cc. of phosphorus oxychloride with cooling to 1 cc. of pyridine. At the end the mixture was allowed to warm up until the exothermic reaction was over. The white suspension was then treated with 6 cc. of water, added cautiously at first with ice cooling and later heating to dissolve the product. Solid sodium carbonate was added until alkaline to litmus and the pyridine layer which separated was removed. The solution of sodium salts was stirred with absolute alcohol and the solvent decanted, leaving an aqueous solution of greatly diminished volume. The remainder of the water can be removed by stirring either with fresh portions of alcohol or with smaller portions of pyridine, leaving the sodium salt as a gum. Inorganic salts can be largely eliminated by dissolving in the least amount of hot water, cooling in ice, centrifuging and decanting from the crystallizate. Alternately, the gum is treated in the cold with methanol and enough water to bring the oily salt into solution; by adjusting the proportions inorganic salts are left undissolved and are removed by filtration. For crystallization of the product such a methanol–water filtrate was concentrated and cooled, oily salt was brought into solution with a little water, pyridine was added by drops until the solution became cloudy, and on warming on the steam-bath the sodium diphosphate separated as an oil which then crystallized (it is less soluble hot than cold). The colorless crystals were washed with methanol and dried; yield 0.68 g. The substance is very hygroscopic and liquefies on exposure to moist air. The sample for analysis was dried at 150° and 2 mm.

Anal. Calcd. for $C_{11}H_8O_8P_2Na_4 \cdot 2H_2O$: C, 28.83; H, 2.64. Found: C, 28.36; H, 2.21.

Vitamin K_1 Hydroquinone Diphosphoric Acid.—A solution of 0.48 g. of vitamin K_1 hydroquinone in 10 cc. of pyridine was cooled and added to an iced mixture of 1 cc. of phosphorus oxychloride and 5 cc. of pyridine (temperature rise to 15°). The solvent was largely removed in vacuum at 45° and the residue treated with 10 cc. of water and extracted with ether. The ethereal extract was shaken with a slight excess of 1 *N* sodium hydroxide and the alkaline layer separated and acidified with hydrochloric acid, when the diphosphoric acid precipitated. Collected by extraction with ether, the substance was obtained as a light tan amorphous solid (0.4 g.). Repetition of the process of purification by extraction from ether with alkali and precipitation with acid gave a somewhat waxy, nearly colorless solid. It gives a gel with a small amount of water and a clear solution with an adequate quantity. The sample was dried at 100° and 1 mm. (oil).

Anal. Calcd. for $C_{31}H_{50}O_8P_2$: C, 60.76; H, 8.28. Found: C, 60.92; H, 8.20.

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(4) Microanalyses by Lyon Southworth.