or 1.48, that is, substance N-123 is about 50% more active than methyl naphthoquinone on a molecular basis.

Summary. 1. The CD50 (Thayer-Doisy unit) by subcutaneous administration of tetra sodium-2-methyl-1,4-naphthohydroquinone diphosphoric acid ester ($C_{11}H_8O_8P_2Na_4 \cdot 6H_2O$)[4] is 1.34 γ. 2. The subcutaneous CD50 of 2-methyl-1,4-naphthoquinone ($C_{11}H_8O_2$) is 0.64 γ.

3. The ratio of these potencies is 0.48 but on a molecular basis allowing for 6 molecules of water of crystallization the phosphoric ester is 50% more potent than methyl naphthoquinone.

4. Five naphthoquinone derivatives not hitherto reported are shown to be inactive in doses from 200 to 1000 γ.

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Pharmacological Observations on Tetra-Sodium-2-Methyl-1, 4-Naphthohydroquinone Diphosphoric Acid Ester.

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The antihemorrhagic activity of tetra-sodium-2-methyl-1,4-naphthohydroquinone diphosphoric acid ester ($C_{11}H_8O_8P_2Na_4 \cdot 6H_2O$)* referred to as N-123 hereafter) has been reported elsewhere.[1, 2] Molecule for molecule it was found to be about 50% more potent than methyl naphthoquinone. In this report we wish to give the general pharmacological properties.

Fatal Dose. Molitor and Robinson[3] reported the LD50 of 2-methyl-1,4-naphthoquinone as 500 mg/kg orally in mice and 75 mg/kg intraperitoneally. In 19-day chicks they found the intraperitoneal dose to be < 100 mg/kg. If their figures of 70% mortality for 100 mg and 90% mortality for 150 mg are plotted on logarithmic probability paper the LD 50 is calculated to be 76 mg/kg.

Although our routes of administration were such that a direct

* See footnote ‡ of previous paper.

1 Foster, R. H. K., Lee, J., and Solmssen, U. V., *J. Am. Chem. Soc.*, 1940, **62**, 453.

2 Lee, J., Solmssen, U. V., Steyermark, Al, and Foster, R. H. K., PROC. SOC. EXP. BIOL. AND MED., 1940, **45**, 407.

3 Molitor, H., and Robinson, H. J., *ibid.*, 1940, **43**, 125.

TABLE I.
Toxicity Studies on Tetra Sodium 2-methyl-1,4-naphthohydroquinone Diphosphoric Acid Ester.

Animal	Route of administration	N	LD50 mg/kg
Mouse	I.V.	50	450
,,	S.C.	40	450
Chick (normal diet)	,,	20	675
Rabbit	I.V.	2	>100 and <200
Cat*	,,	1	690 (divided doses)

*Circulatory experiment under Alurate anesthesia.

comparison between methyl naphthoquinone and substance N-123 is not possible, the following data illustrate the obviously lesser toxicity of the latter substance. In mice we found the intravenous LD50 to be 450 mg/kg and the subcutaneous LD50 was likewise 450 mg/kg.

Accurate toxicities noted above for substance N-123 were determined only in mice. Using 20 normal chicks the subcutaneous LD50 was estimated at 675 mg/kg. One rabbit died with an intravenous dose of 200 mg/kg, whereas one receiving 100 mg/kg recovered with no severe symptoms. All toxicities are listed in Table I. The fatal doses are far beyond the antihemorrhagic doses. In chicks the ratio of the antihemorrhagic CD50 to the LD50 is about 1:30,000.

Toxic Signs. One rabbit was given 50 mg/kg intravenously and this caused an acceleration of respiration, marked constriction of the pupils, increased alertness and a rise in temperature of the ears. The pupils were normal in 15 minutes though the respiration continued rapid for some time. After 100 mg/kg intravenously in another rabbit there was a more marked increase in alertness, the animal moving about the cage with some agitation and showing signs of anxiety or apprehension. In 3 or 4 minutes it became quiet and crouched in one corner of the cage. The pupils were pin point in size and remained so for an hour, becoming normal at the end of 2 hours. A third rabbit received 200 mg/kg intravenously and showed greater agitation than the previous rabbit (but still much less than, for example, the violent morphine excitement in cats). Seven minutes after injection the animal screamed. The screaming lasted about 15 seconds and was repeated a few minutes later. At 30 minutes after injection a convulsion occurred and at 35 minutes after injection the animal died. Respiration was not accelerated as with the smaller doses but remained slow and labored throughout with the animal in prostration after the first few minutes. Considerable salivation occurred. There were no particular findings at

autopsy except a generalized moderate congestion and a darkening of arterial blood indicating death by respiratory paralysis.

In chicks the outstanding signs were the panting type of respiration with the beaks open, pupillary constriction, preliminary mild excitement or anxiety, later prostration and death. Convulsions did not occur. In mice the syndrome was essentially the same as in chicks and rabbits, though the preliminary excitement and stimulation was usually somewhat greater. Occasional convulsions occurred.

Circulation and Respiration. In cats anesthetized with Alurate* there was a rise in both systolic and diastolic blood pressure amounting to as much as 50-60 mm mercury following the administration of 5 or 10 mg/kg. Subsequent doses caused a somewhat diminishing response. The rise in blood pressure was invariably well sustained with return to normal occurring only after 10 or 15 minutes or more. The pulse rate was generally stimulated from a slight to moderate extent, in one case corresponding from 170 to 220 per minute, this being about the extreme.

The effect on respiration was marked, 10 mg/kg often causing violent respiratory activity both in rate and depth. This usually diminished after two to five minutes to somewhat less than normal and later recovered. Following two or three preliminary small doses one cat was given 50 mg/kg every 5 minutes until death. The total amount administered was 690 mg/kg.

In cats under ether the effect on blood pressure was less than when under Alurate anesthesia. The pulse was stimulated slightly and the respiration showed as high a degree of stimulation as under Alurate.

Another type of respiratory experiment was tried in which rabbits received 10 mg/kg morphine sulfate. A head mask connected with a spirometer was employed so that minute volume of respired air could be measured. Ten and 20 mg/kg had substantially no effect and 50 mg/kg caused but a slight increase in minute volume and in rate. There was later a decrease in both minute volume and rate.

Irritation. In no case was any sign of irritation noticed after subcutaneous injection of a 5% solution in guinea pigs in doses of 50 to 150 mg/kg or in chicks or mice surviving doses in the lethal range.

Discussion and Summary. Although from the standpoint of treating prothrombin deficiencies lethal and sublethal doses of tetrasodium-2-methyl-1,4-naphthohydroquinone diphosphoric acid ester

* Allyl-isopropylbarbituric acid.

are without practical significance, it is interesting to note their effects on the central nervous system. It seems likely that most of the peripheral effects observed are the result of central action but complete analysis of the manner of action has not yet been made. The anesthetic employed appears to possess a quantitative influence on the circulatory but not so much on the respiratory action. With ether anesthesia in cats there is less hypertension after substance N-123 than with Alurate anesthesia. The substance had very little influence on respiration in morphinized rabbits, but in cats under Alurate or ether anesthesia there was marked respiratory stimulation. As is true with most substances acting as biological catalysts (enzymes, vitamins, hormones) the safety margin of its antihemorrhagic effect is enormous. All doses are for the crystalline product containing a moisture equivalent of 6 molecules of water.

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Effects of Spinal Anesthesia upon Venous Pressure in Man.

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The fall in arterial pressure accompanying high spinal anesthesia in man has been widely investigated. Although paresis of sympathetic fibres with dilation of the arterioles has been regarded as the mechanism for the fall, a recent report by Smith and co-workers[1] indicates an autonomous control of the arterioles of the viscera. They postulate that circulatory failure is primarily venous failure. A fall in venous pressure would be expected. Venous pressures during spinal anesthesia have been reported by Schuberth[2] and Seevers,[3] Goldfarb, *et al*,[4] but the observations have been either on animals or isolated readings in the course of anesthesia for man and there is no agreement among these authors. No studies have been found that correlated arterial tension, with venous pressure and the extent or

1 Smith, H. W., Rovenstine, E. A., Goldring, W., Chasis, H., and Ranges, H. A., *J. Clin. Invest.*, 1939, **18**, 319.

2 Schuberth, O. O., *Acta Chir. Scandinav.*, 1936, 78 supp., **48**, 1.

3 Seevers, M. H., and Waters, R. M., *J. A. M. A.*, 1932, **99**, 961.

4 Goldfarb, W., Provisor, B., Koster, H., *Arch. Surg.*, 1939, **39**, 429.