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Synthetic Antimalarials. The Preparation and Properties of 7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (SN-7618)[1,2]

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When it became apparent that SN-7618, 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline, held considerable promise as a suppressive, we were called upon to produce considerable quantities of the drug for clinical use. The present paper describes a satisfactory method of preparation of the base and its solvent-free diphosphate, with particular reference to the conditions necessary for a high yield of substantially solvent-free salt. The drug has been described previously in the patent literature[3] and more recently by Surrey and Hammer.[4]

A good quality of 4,7-dichloroquinoline (hereinafter called DCQ) is important in a satisfactory synthesis of SN-7618.[5] The DCQ used was purified by distillation *in vacuo* followed by crystallization from methanol (1.5 ml. of methanol/g. of distillate); it melted at 86.4–87.4°.[6] The side chain was commercial "Noval diamine" (4-diethylamino-1-aminopentane) which was purified before use by the method of Jones.[7] The material was assayed as better than 99.5% pure. It is, of course, possible to prepare SN-7618 using less pure starting materials, but in order to eliminate as many variables as possible, we chose to operate with pure DCQ and pure side chain.

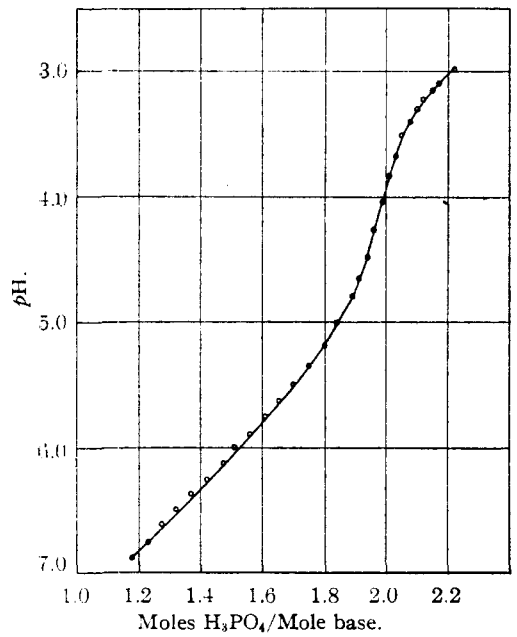


Fig. 1.—Titration curve of SN-7618.

The reaction between DCQ and "Noval diamine" (1 mole to 2.2 moles) takes place at 160–170° (temperature of reactants) with the evolution of considerable heat and is substantially complete when the mixture has been heated for four to five hours. Steam distillation of the mixture following the addition of excess concentrated sodium hydroxide serves to remove unreacted DCQ and most of the excess side chain. The layers can then be separated and the product dissolved in 95% ethanol. Addition of 85% phosphoric acid dropwise to the refluxing ethanol solution precipitates the diphosphate of SN-7618. The crude product melts at 213.8–215.7° with preliminary softening at 212° and is obtained in about 82% yield. A recrystallization followed by reconversion of the salt to the base, extraction of the base with ether, removal of the solvent, and reprecipitation of the phosphate yields a product that melts at 215.8–217°. 7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline distils cleanly under a pressure of a few millimeters as a light yellow oil. It can be crystallized satisfactorily from benzene–petroleum ether. The pure product melts at 88.7–89.5°.

In early experiments low-melting phosphates were frequently obtained. A series of experiments was therefore carried out to elucidate the causes of the formation of these low-melting products from apparently pure base.

In Fig. 1 is shown the variation of *p*H of a solution of the base in water containing about one mole of phosphoric acid (4 g. of water/g. of base) as 85% phosphoric acid is added slowly up to an amount slightly in excess of that required for a diphosphate. It is apparent that at *p*H's below 4.0 the formation of diphosphate is complete.

Table I shows the effect of precipitating the diphosphate of SN-7618 with four different solvent combinations at different *p*H's. As would be expected after a consideration of Fig. 1, the yield of product increases as the *p*H of the original aqueous solution is lowered to 4.0 and below. It should be noted that the yields are given as per cent. of the

(1) This work was carried out under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Maryland.

(2) The Survey Number, designated SN- identifies a drug in the files of the Survey of Antimalarial Drugs. The activities of these will be tabulated in a forthcoming monograph.

(3) Andersag, Breitner and Jung, U. S. Patent 2,233,970, March 4, 1941.

(4) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(5) The DCQ used was obtained principally from the Illinois and Columbia groups; some was also obtained from Northwestern University. We should like to express our thanks to Dr. C. C. Price, Dr. R. C. Elderfield, Dr. B. Riegel and their associates for their coöperation.

(6) All melting points are corrected.

(7) R. G. Jones, *Ind. Eng. Chem., Anal. Ed.*, **7**, 431 (1944).

TABLE I

	Precipitating agents in ml./g. of base														
				Yield,[b]	M. p.,	Analyses,[c] %									
*p*H[a]	CH_3OH	C_2H_5OH	$(CH_3)_2CHOH$	%	°C.	P		C		H		Methoxyl			Moisture
5.0	2.75		11	68	214-218	11.95	12.01								
5.0	13.75			60	192-194	11.25	11.34								
5.0		13.75		66	214-217	11.96	12.08								
5.0			13.75	72	211-213	12.00	12.05								
4.5	2.75		11	83	194-213	11.25	11.09								
4.5	13.75			90	192-194	11.30	11.40								
4.5		13.75		79	212-215	11.80	11.85								
4.5			13.75	87	193-195	11.09	10.95								
4.0	2.75		11	96	192-193	11.28									
4.0	13.75			82	192-193	11.15									
4.0		13.75		80	190-194	11.45	11.37								
4.0			13.75	95	194-197	11.15	11.23								
3.5	2.75		11	97	192-193	11.11	11.05							2.17	3.87
3.5	13.75			98	191-192	11.21	11.10	41.4	41.9	6.44	6.61	5.19	5.35	5.14	
3.5		13.75		89	194-196	11.35	11.42	39.7	40.4	6.1	6.2		0.19		3.54
3.5			13.75	97	194-196	11.67	11.76						0.20		3.87
<3.5	2		8	76-83	>216	12.01									

[a] The *p*H values are for aqueous solutions containing 4 g. H_2O/g. of base before addition of precipitating agents. [b] Calculated on the basis of solvent-free diphosphate. [c] Calculated values for mono-methanol solvate: C, 41.6; H, 6.63; P, 11.31%; methoxyl, 5.66; for dihydrate, P, 11.22; for solvent-free diphosphate, C, 41.9; H, 6.25; P, 12.01.

calculated yield of *solvent-free* diphosphate. It is apparent from the phosphorus contents of these products that they are more or less solvated; they contain both water and alcohol of solvation.

Our initial production of diphosphate was carried out under the conditions described in the bottom line in Table I, using 2.08 moles of 85% phosphoric acid per mole of base. It seems that the causes of formation of the low-melting products which were frequently obtained for no obvious reason were inadvertent changes of composition of the solutions which brought them into the region where partially solvated products separated.

It is interesting to note that the product which separates from methanol–water is a solvate of the composition $C_{18}H_{26}N_3Cl\cdot 2H_3PO_4\cdot CH_3OH$. This compound separates in heavy, well-formed, compact crystals and differs markedly in crystalline form from the diphosphates obtained from the other solvents studied. The latter are extremely finely divided, micro-crystalline precipitates

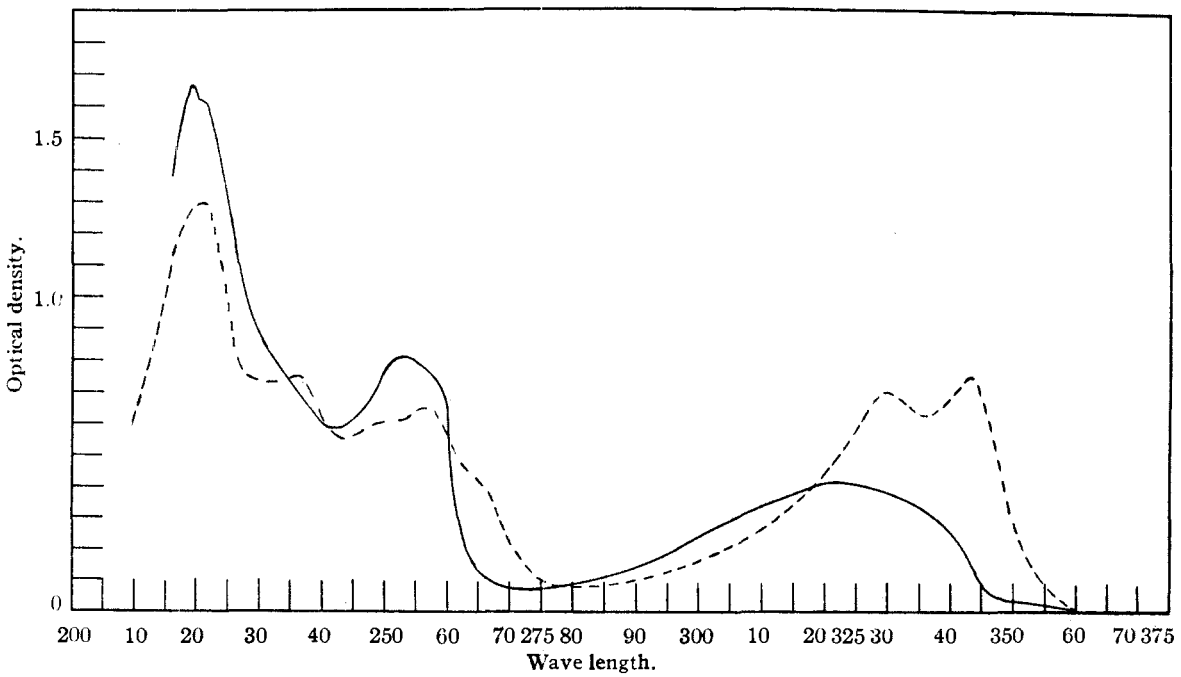
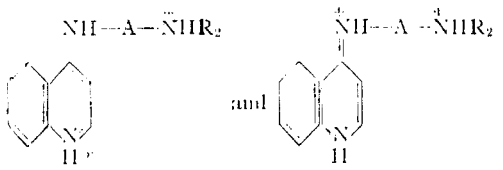


Fig. 2.—Absorption spectra of SN-7618 and its diphosphate: molality = 3.88×10^{-5}; salt in 0.01 *N* hydrochloric acid; base in dioxane; ---- SN-7618 (diphosphate), ——— free base of SN-7618.

which are filtered very slowly and sucked dry with difficulty; they have a relatively broad melting range. The solvate from methanol–water has a much sharper melting range and possesses the composition required by the above formula when thrown out of solutions having any of the *p*H's studied.

The ultraviolet absorption spectra of SN-7618 as free base and as diphosphate are shown in Fig. 2. The peak at 343 mμ can be used to determine the per cent. of base in a specimen of drug. The absorption of the base was measured in purified dioxane, that of the diphosphate in 0.01 *N* hydrochloric acid. A Beckmann spectrophotometer was used.

Two absorption maxima in the region between 325 and 350 mμ are characteristic of the absorption spectra of the salts of all of the 4-aminoquinolines which we have examined. It seems likely that this absorption is caused by the introduction of a new resonator through salt formation, and it should be noted that di-acid salts of the 4-aminoquinolines in question may be considered as resonance hybrids, involving the ions



Our investigations led us to a method of preparation of the diphosphate which is simple and always leads to a substantially solvent-free product. This method is described in detail below.

Experimental

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline and its Diphosphate.—A mixture of 100 g. of DCQ and 175 g. of Noval diamine was heated and stirred for four to five hours. The reaction was considered complete when a small sample of the reaction mixture, dissolved in dilute nitric acid, gave no precipitate when saturated sodium acetate in excess was added. Sodium hydroxide (21 g. in 75 ml. of water) was added and the mixture was steam distilled to remove the bulk of the excess side chain and any unreacted DCQ. The DCQ is removed very slowly; about 10 liters of steam distillate was collected.[8]

The organic layer was separated from the water and dissolved in 1.5 liters of ethanol. This solution was heated under reflux and 110.5 g. of 85% phosphoric acid was added dropwise while the refluxing solution was well stirred. The mixture was allowed to stand overnight, and was then filtered. The filter-cake was twice heated with ethanol for about three hours and filtered hot. The product weighed 215 g. (82.5%) and melted at 213.8–215.7° with preliminary softening at 212°.

A portion (197 g.) of this material was dissolved in 400 ml. of hot water, and heated with Darco. An additional 100 ml. of water was added and the diphosphate precipitated by adding 250 ml. of methanol and 1 liter of 2-propanol. After the mixture had been cooled overnight, the product was filtered; it weighed 177 g. (74% over-all yield) and melted at 190–191°. Analysis showed that the substance contained some moisture and methanol. *Anal.* Calcd. for $C_{18}H_{26}N_3Cl\cdot 2H_3PO_4$: C, 41.9; H, 6.24; P, 12.02. Found: C, 40.63; H, 6.04; P, 11.52; moisture, 2.03[9]; alkoxyl shown to be present.

Forty grams of this product was reconverted to base, taken up in ether and the ether removed *in vacuo*. The colorless residue weighed about 25 g. It was dissolved in ethanol and heated with stirring under reflux while 17.9 g. of 85% phosphoric acid was added dropwise. Heating under reflux was continued for one hour after the addition of the acid was complete and the mixture was then allowed to stand overnight. After filtration and drying the product weighed 37.6 g.; its melting range was 215.8–217°. The yield was 94% for this step and 69.6% over-all from DCQ.

Anal. Found: C, 41.99, 41.87; H, 6.41, 6.62; P, 12.14, 12.09; moisture, 0.1; alkoxyl, 0.3 (as methoxyl).

The base crystallizes nicely from benzene–petroleum ether. For recrystallization it is dissolved in benzene (0.6 ml./g. of base) and diluted with 30–60° petroleum ether (7 ml./g. of base). The base melts at 88.7–89.5° after several recrystallizations; it distils without appreciable decomposition at 189–193° (0.2–0.3 mm.) (bath temperature 215–225°). The boiling range is highly dependent on bath temperature and construction of the distilling apparatus. The above data were obtained with a modified von Braun flask with large-bore tubes.

Summary

1. The preparation of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (SN-7618) as its substantially solvent-free diphosphate, starting with DCQ and "Noval diamine" is described.

2. Precipitation of the diphosphate from aqueous solution with several alcohols shows that a *p*H of 4.0 or below is necessary for complete formation of the diphosphate.

3. The titration curve of the base with phosphoric acid has been studied.

4. A solvate of the diphosphate of SN-7618 with methanol, $C_{18}H_{26}N_3Cl\cdot 2H_3PO_4\cdot CH_3OH$ is described.

5. The absorption in the ultraviolet of SN-7618 and its diphosphate is described and discussed briefly.

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[8] Practically no DCQ came distilled after 5 liters of distillate had been collected. The steam distillation may be omitted and the side chain can be separated by washing the mass with water; the amount of DCQ separated amounts to only a few grams.

[9] Determined at 100° without vacuum. If vacuum is applied during drying at 100°, the phosphate loses water apparently from the phosphoric acid molecules. This property is shared by phosphates of other 4-aminoquinolines studied.