Anal. Calcd. for $C_5H_4N_2O_4 \cdot H_2O$: C, 34.5; H, 3.47; N, 16.1. Found: C, 34.7; H, 3.54; N, 16.2.

5-Bromoörotic acid. Orotic acid monohydrate (52 g., 0.30 mole) was suspended in 30% aqueous hydrogen peroxide ("Superoxol") (63 ml., 0.80 mole) at about 0°, and 90 ml. (0.80 mole) 48% aqueous hydrobromic acid was added dropwise with mechanical stirring. The violent reaction was moderated by ice cooling to maintain the temperature below 35°. After addition of the hydrobromic acid was complete, the mixture was allowed to stand overnight. The precipitated solid was isolated by filtration, washed with cold water, and dried to give a 73% yield of crude product.

Recrystallization from water gave pale yellow needles of 5-bromoörotic acid dihydrate, m.p. 288° (dec.) (immersed at 280°).

Anal. Calcd. for $C_5H_3BrN_2O_4 \cdot 2H_2O$: C, 22.2; H, 2.60; N, 10.3. Found: C, 22.8; H, 2.57; N, 10.3.

The anhydrous acid was obtained by drying at 80° over phosphorus pentoxide.

Anal. Calcd. for $C_5H_3BrN_2O_4$: C, 25.6; H, 1.29; N, 11.9. Found: C, 25.6; H, 1.27; N, 12.1.

A sample of 5-bromoörotic acid was boiled for 1 hr. with 10% aqueous sodium hydroxide solution, and was recovered unchanged after acidification, isolation, and drying. Samples of the acid were titrated in approximately 0.01*M* aqueous solution with 0.100*M* sodium hydroxide solution. A Photovolt *p*H meter, equipped with standard glass and calomel electrodes, was employed for these measurements, and the usual precautions were observed. The *p*H of the solutions at 50% of the stoichiometric volume of alkali was taken as pK_a' for each ionizing group. The pK_a' calculated from eight other points on the titration curves was in reasonable agreement with these values. 5-Bromoörotic acid was found to have pK_{a1}' of 2.2_1 and a pK_{a2}' of 7.5_9.

The ultraviolet absorption spectrum of a $10^{-4}M$ solution of 5-bromoörotic acid in deionized water was measured with a Beckman Model DU spectrophotometer. At *p*H 5.6, λ_{max} 279.5 mμ ($\epsilon = 8.75 \times 10^3$), λ_{min} 243 mμ ($\epsilon = 1.02 \times 10^3$) were observed.

5-Bromouracil. A 2.0-g. sample of pure 5-bromoörotic acid was carefully heated to about 300° in a Wood's metal bath until gas evolution ceased. The cooled residue was recrystallized from water to give an almost quantitative yield of 5-bromouracil, m.p. 296° (dec.) (lit. 293°).[7]

Anal. Calcd. for $C_4H_3BrN_2O_2$: C, 25.2; H, 1.58. Found: C, 25.3; H, 1.64.

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Improved Syntheses of Certain Derivatives of 5,6-Dimethoxy-8-aminoquinoline[1]

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5,6-Dimethoxy-8-(4′-isopropylamino-1′-methylbutylamino)quinoline (SN-9972)[2] [5,6-dimethoxy-8-butylamino(1′-methyl-4′-diethylamino)quinoline and 5,6-dimethoxy-8-(4′-diethylamino-1′-methylbutylamino)quinoline (SN-8233)[2] have recently provided encouraging data when examined against experimental tumors in animals.[3] It therefore became of interest to develop more efficient syntheses than those heretofore available for these substances.

In the preparation of SN-8233 previously reported[4] the key step involves alkylation of 5,6-dimethoxy-8-aminoquinoline with 1-diethylamino-4-bromopentane (as the hydrobromide) at *p*H 4.8.[5] However, even under the optimum conditions the yield of SN-8233, isolated as the oxalate, was only 21% largely because of cyclization of the bromoamine to 1,1-diethyl-2-methylpyrrolidinium bromide.

Shiho[6] has described the condensation of 1-diethylamino-4-ethoxy-3-pentene with 6-methoxy-8-aminoquinoline followed by reduction of the resulting anil to yield pamaquin. Barber and co-workers[7] have successfully condensed the aminoquinoline with 1-diethylamino-4,4-diethoxypentane to yield the same anil which was similarly reduced to pamaquin in high yield. This general method has been adapted, with some modifications, to the preparation of SN-8233 after attempts to effect the direct reductive alkylation of 5,6-dimethoxy-8-aminoquinoline or 5,6-dimethoxy-8-nitroquinoline with 1-diethylamino-4-pentanone as reported by Bergmann[8] failed. It should also be noted that Barber and co-workers[7] were also unable to obtain pamaquin by Bergmann's method.

In the preparation of the requisite intermediates, unexpected complications were encountered in the bromination of 6-methoxy-8-nitroquinoline. When the method described in detail by Elderfield and co-workers,[9] based on a Japanese report,[10] was followed, the expected 5-bromo-6-methoxy-8-nitroquinoline was not obtained. Rather, what appeared to be a perbromide of the desired compound was isolated. This could be readily converted to the 5-bromo compound by treatment with cyclohexene

(1) This work was supported by a Research Grant (CY-2961) from the National Cancer Institute to the University of Michigan.

(2) The prefix SN identifies a compound in F. Y. Wiselogle, *Survey of Antimalarial Drugs*, Edwards Brothers, Ann Arbor, Mich., 1946.

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which underwent bromination as in the analogous reaction with pyridine perbromide.[11] Further, the iron and large excesses of bromine and calcium carbonate used in the earlier preparation[9] were found to be unnecessary, and a simpler procedure which gives the desired bromo compound directly has been worked out.

In the displacement of the bromine in 5-bromo-6-methoxy-8-nitroquinoline by methoxyl, the reaction time has been reduced from 4 days to 20 hr. by employing an excess of sodium methoxide instead of the equivalent amount previously used. Of the two methods for reducing the nitro group in 5,6-dimethoxy-8-nitroquinoline[9,12] catalytic reduction over palladium was manipulatively easier than the stannous chloride reduction, but the product from the latter reaction was easier to purify.

When the preparation of larger amounts of SN-9972 by the method used previously[4] was attempted, cyclization of the amino bromide, 1-isopropylamino-4-bromopentane, prior to alkylation of 5,6-dimethoxy-8-aminoquinoline, likewise was the cause of prohibitively low yields. Accordingly, SN-9972 has been prepared in acceptable yields by reductive alkylation of 5,6-dimethoxy-8-(4-amino-1-methylbutylamino)quinoline (CN-1104)[9] with acetone substantially according to Cope and co-workers.[13]

EXPERIMENTAL[14,15]

5-Bromo-6-methoxy-8-nitroquinoline and its perbromide. A. According to Elderfield et al.[9] To a suspension of 491 g. (2.4 moles) of 6-methoxy-8-nitroquinoline, 183 g. (1.83 moles) of calcium carbonate, and 9.6 g. of iron filings in a refluxing mixture of 2.4 l. of chloroform and 490 ml. of water, 480 ml. (9.4 moles) of bromine was added with stirring. After refluxing for 6 hr. and stirring for 15 hr. at room temperature, the precipitate was collected, washed successively with water and chloroform, and dried to yield 1075 g. of crude perbromide. Crystallization of a sample from benzene-nitrobenzene gave pale orange prisms of the perbromide, m.p. 155–157° (dec.).

Anal. Calcd. for $C_{10}H_7Br_3N_2O_3$: Br, 54.2. Found: Br, 54.2.

A mild exothermic reaction ensued when the crude perbromide was stirred for 15 hr. with 280 ml. of cyclohexene and 2.5 l. of benzene. After heating the mixture to the boiling point and cooling, the precipitate of crude bromo compound (734 g.) was collected. The main contaminant, calcium carbonate, was removed by hot filtration, and crystallization from pyridine gave pure 5-bromo-6-methoxy-8-nitroquinoline (362 g., 53%), m.p. 203.0–205.5°. Reported 204–205°.[9]

B. To a stirred suspension of 40.8 g. (0.2 mole) of 6-methoxy-8-nitroquinoline and 9 g. (0.09 mole) of calcium carbonate in 180 ml. of chloroform and 50 ml. of water, 12.2 ml. (0.24 mole) of bromine was added at such a rate as to maintain a gentle reflux. After refluxing for 1.75 hr., 40 ml. of cyclohexene was added followed, after 5 min., by 12 ml. of 28% ammonium hydroxide. After heating for a further 10 min., the mixture was diluted with 180 ml. of petroleum ether (40–60°) and 140 ml. of water. The product was collected, washed successively with 1:1 chloroform–petroleum ether and water, and dried to yield 49 g. (85%) of crude 5-bromo-6-methoxy-8-nitroquinoline, m.p. 170–195° (dec.). Crystallization from benzene-nitrobenzene gave pale yellow needles of the pure compound, m.p. 205–206°.

1-Diethylamino-4,4-diethoxypentane. A mixture of 222 ml. (1.21 moles) of 1-diethylamino-4-pentanone, 555 ml. of redistilled ethyl orthoformate, 240 g. (1.25 moles) of *p*-toluenesulfonic acid monohydrate, and 870 ml. of absolute ethanol was refluxed for 3 days. The alcohol (about one liter) was distilled off under reduced pressure. After addition of a solution of 61 g. of sodium hydroxide in 500 ml. of water, the mixture was extracted with ether. Removal of the ether from the dried extract and distillation under reduced pressure gave 197 g. (70%) of the ketal, b.p. 127–132° (27 mm.), n_D^{21} 1.433, d_4^{25} 0.86. Reported b.p. 121–122° (22 mm.).[16]

5,6-Dimethoxy-8-(4′-diethylamino-1′-methylbutylamino)-quinoline. (SN-8233). A mixture of 46 ml. (0.17 mole) of 1-diethylamino-4,4-diethoxypentane, 25 g. (0.12 mole) of 5,6-dimethoxy-8-aminoquinoline, and 0.17 g. of ammonium chloride was heated in an oil bath with stirring at 155° for 2 hr. during which the temperature was raised to 182°. Ethanol (16 ml., 81%) distilled. The residue was taken up in 300 ml. of absolute ethanol and shaken with 0.55 g. of prereduced Adams' platinum oxide catalyst at room temperature and 50 lb. hydrogen pressure. After 20 hr. 0.13 mole (77%) of hydrogen had been absorbed. The filtrate from the catalyst was added to a solution of 30 ml. of glacial acetic acid in 750 ml. of water and the resulting mixture was extracted three times with benzene. Removal of the solvent from the dried benzene extracts and distillation of the residue gave 2.0 g. (8%) of unreacted 5,6-dimethoxy-8-aminoquinoline.

The aqueous suspension was made alkaline with sodium carbonate and extracted with four portions of benzene. Removal of the solvent from the dried benzene extracts and distillation of the residue *in vacuo* gave an oily fraction (2 g., 5%), b.p. up to 170° (0.1 mm.) followed by the drug base (28.9 g., 70%) as a yellow oil, b.p. 170–171° (0.1 mm.). Reported b.p. 179–185° (0.3 mm.).[4] The base was converted to the oxalate (96% yield) as previously described.[4] The salt formed yellow prisms, m.p. 132–136°, after recrystallization from absolute ethanol. Reported m.p. 126–128°.[4] When assayed by the Craig countercurrent procedure, the drug base showed an inhomogeneity of 4.6%[17] (*cf.* Fig. 1).

Anal. Calcd. for $C_{22}H_{33}N_3O_5$: C, 60.66; H, 7.64; N, 9.65; $(COOH)_2$, 20.69; drug base, 79.31. Found: C, 61.03; H, 7.34; N, 9.50; $(COOH)_2$, 21.18; drug base, 79.67.

5,6-Dimethoxy-8-(4′-isopropylamino-1-methylbutylamino)-quinoline. SN-9972. When 15 g. (0.045 mole) of 5,6-dimethoxy-8-(4′-amino-1-methylbutylamino)-quinoline[9] was reductively alkylated with acetone according to Cope and co-workers,[13] 13.9 g. (72%) of viscous yellow oil, b.p. 168–173° (0.2 mm.) was obtained. The reported b.p. is 190–195° (0.3 mm.).[4] From this the oxalate, m.p. 143–145° with sintering at 139°, was prepared in 73% yield. The reported m.p. is 138–141°. The drug base showed the presence of 5% inhomogeneity when assayed by the Craig method[17] (*cf.* Fig. 1).

Anal. Calcd. for $C_{21}H_{31}N_3O_5$: C, 59.84; H, 7.42; N, 9.97; $(COOH)_2$, 21.38; drug base, 78.62. Found: C, 59.97, 59.88;

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(15) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

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(17) Craig analyses, free base and oxalate determinations were done at Applied Science Laboratories, Inc., State College, Pa.

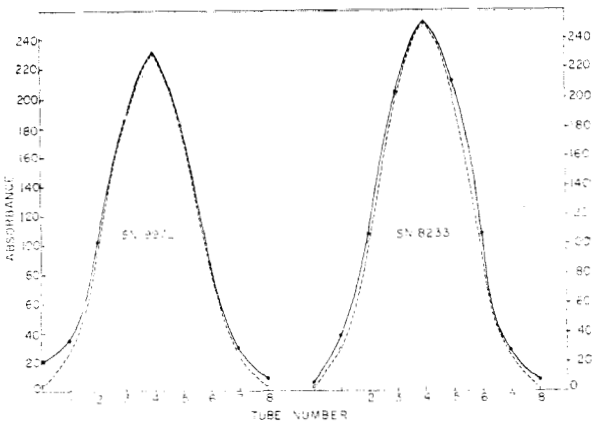

Fig. 1. SN-9972: system of isopropyl ether–*n*-butyl alcohol *vs.* 2*M* (total) citrate buffer at *p*H 3.86; concentration of base, 1.0 mg. per ml. of each phase. SN-8233: system of isopropyl ether–*n*-butyl alcohol *vs.* 2M (total) citrate buffer at *p*H 3.52; concentration of base 0.8 mg. per ml. of each phase. Concentrations determined by absorption at 390 mμ; dashed lines, theoretical; solid lines, experimental

H, 7.14, 7.19; N, 9.99, 10.04; $(COOH)_2$, 21.00; drug base, 79.88.

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Cyclic Sulfides. II. Ring Size and the Ultraviolet Absorption Spectra[1]

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The measurement of the ultraviolet absorption of ethylene sulfide[1] has now allowed a discussion of the effect of ring size upon the spectra of cyclic sulfides. The data are presented[2] in Fig. 1. Perusal shows that the four membered ring sulfide has the weak absorption band at the longest wave length. It is difficult to offer a complete explanation designating the energy levels and the transitions involved. However, an empirical relationship can be discerned between the electron density and basicity

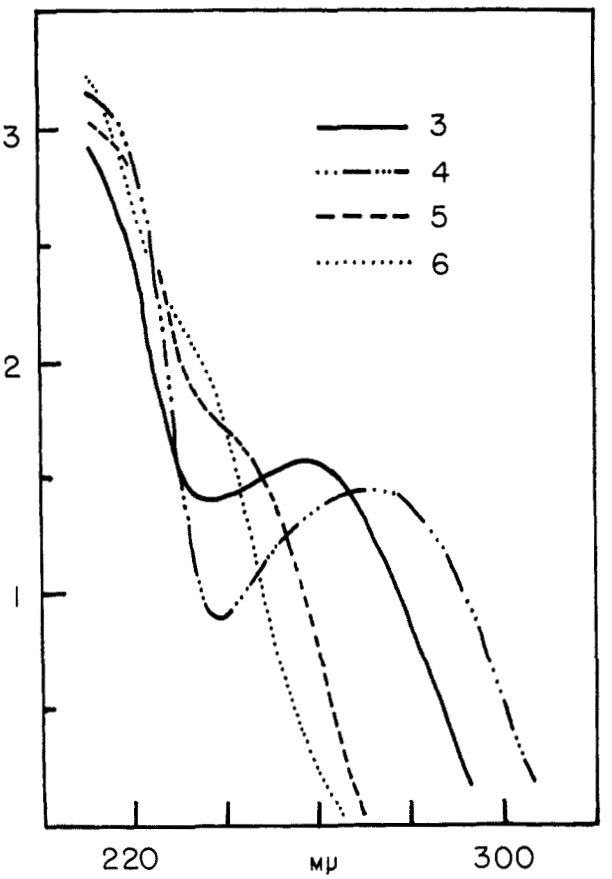

Fig. 1. Spectra of cyclic sulfides in absolute ethanol. Log ε *vs.* λ in mμ. 3 ethylene sulfide, 4 trimethylene sulfide, 5 tetramethylene sulfide, 6 pentamethylene sulfide

of the sulfur atom and the position of the transition in divalent sulfur compounds. The more the electron density on the sulfur, the further the absorption towards longer wave lengths. This can be seen in the following series.

The sulfur atom spectrum[6] serves as the basis for discussion. Hydrogen sulfide[7,8] (λ_{max} hexane 190 mμ log ε 3.2) can be compared with sodium sulfide[9] (λ_{max} 230 mμ log ε 3.8 in aqueous sodium hydroxide). Ethanethiol[7,8] has a band at 195 mμ (log ε 3.15) and an inflection at 225 mμ (log ε 2.2) in ethanol. The sodium salt of 1-*n*-butanethiol[9] in aqueous sodium hydroxide has a band at 240 mμ (log ε 3.7). The spectra of dialkyl sulfides[5] show strong bands in the region 210–215 mμ with inflections near 230 mμ (log about 2). Alkyl groups donate electrons to the sulfur. Unbonded pairs of electrons are needed in divalent sulfur compounds on the sulfur atom to have absorption above 200 mμ.

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