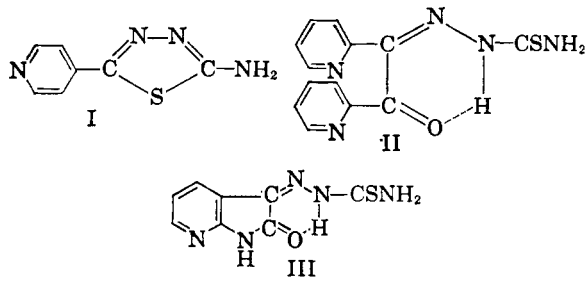

I II III

Infrared spectra of α-pyridilmonothiosemicarbazone II and 7-pyrisatin-β-thiosemicarbazone III showed lowering and broadening of the 2′-imino N—H and carbonyl stretching frequencies characteristic of hydrogen bonding, and dilution studies indicated that this was mainly intramolecular, but neither II nor III possess antivaccinial activity. This finding is perhaps not surprising in the case of II as benzilmonothiosemicarbazone is also inactive, but the lack of activity of III suggests that isatin and pyridine derivatives exert their antivaccinial effects by completely different routes.

EXPERIMENTAL

Spectra. Compounds were examined as potassium bromide discs and in solution in chloroform, a Perkin-Elmer 21 double-beam recording spectrometer fitted with a rock salt prism being used.

Test of antiviral activity. Groups of mice infected intracerebrally with about 1,000 LD 50 of the IHD strain of neurovaccinia virus were treated with doses of 125 mg./kg. and the survival times were compared with those of a control group of mice which were similarly infected but left untreated.[4] Compounds which gave no significant reduction of the mean reciprocal survival time at this dose were considered to be inactive.

Thiosemicarbazones of 2-, 3- and 4-formylpyridine and 2-, 3- and 4-acetylpyridine were prepared by standard methods and had melting points in agreement with those reported.[5, 6]

4-Formylpyridine-2′-phenylthiosemicarbazone. Equimolar quantities of 2-phenylthiosemicarbazide[7] and 4-formylpyridine were refluxed for 1 hr. in ethanol. The product which separated on cooling was recrystallized from ethanol, m.p. 207°.

Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 61.4; H, 4.7; N, 22.1; S, 12.6. Found: C, 61.2; H, 4.8; N, 21.6; S, 12.4.

4-Formylpyridiniumthiosemicarbazonemethiodide. To a hot solution of 12.5 g. of 4-formylpyridinium methiodide[8] in 100 cc. of water was added 4.6 g. of thiosemicarbazide in an equal volume of hot water. A yellow product 12.3 g., m.p. 251°, was obtained on cooling, which after recrystallization from water had a melting point of 252°.

Anal. Calcd for $C_8H_{11}N_4SI$: C, 33.3; H, 3.5; N, 17.3. Found: C, 33.1; H, 3.5; N, 17.7.

4-Formyltrimethylaniliniumiodide thiosemicarbazone was obtained as pale yellow plates, m.p. 209°, by a similar method.

Anal. Calcd. for $C_{11}H_{17}N_4SI$: C, 36.2; H, 4.7; S, 8.8. Found: C, 36.2; H, 4.6; S, 9.0.

α-Pyridilmonothiosemicarbazone. α-Pyridil 21.2 g. and thiosemicarbazide 9.1 g. were heated under reflux in 200 cc. ethanol for 24 hr. The product was removed from the hot reaction mixture, washed well with hot water and crystallized from butyl alcohol, m.p. 212°.

Anal. Calcd. for $C_{12}H_{11}N_5SO$: C, 54.6; H, 3.9; S, 11.5. Found: C, 54.6; H, 3.8; S, 11.7.

7-Pyrisatin-β-thiosemicarbazone was prepared from 7-pyrisatin[9] in the usual manner,[3] recrystallization from aqueous ethanol gave yellow needles which decomposed at 285°.

Anal. Calcd. for $C_8H_7N_5SO$: C, 43.4; H, 3.2; S, 14.5. Found: C, 43.2; H, 3.2; S, 14.3.

2-Amino-4-pyridylthiodiazole. Ferric chloride 30 g. was added to 15.9 g. of finely ground 4-formylpyridinethiosemicarbazone in 300 cc. water at 85° and stirred vigorously for 0.5 hr.[10] The reaction mixture was filtered and the filtrate concentrated to 100 cc. and chilled, giving the hydrochloride of the base as white plates, m.p. 260°. Treatment with 2*N* ammonium hydroxide solution gave a yellow amorphous precipitate, m.p. 225°, which was raised to 226° on crystallization from ethanol.

Anal. Calcd. for $C_7H_6N_4S$: C, 47.1; H, 3.4; N, 31.5; S, 18.4. Found; C, 47.2; H, 3.4; N, 31.6; S, 18.2.

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Naphthoquinone Chemistry. 6H,11H-Benzo-[*f*]pyrido[*a*]benzimidazole-6,11-dione

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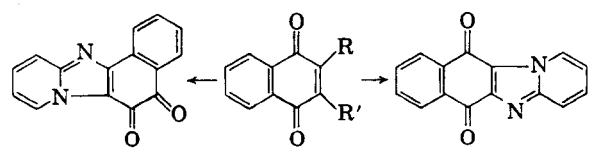
In Part I of these studies,[1] it was shown that 2,3-dichloro-1,4-naphthoquinone (I. R = R′ = Cl) reacted with 2-aminopyridine to yield the angular quinone II. This same product was produced[1] by the reaction of 2-aminopyridine with either



II I III

2-acetamido-3-chloro-1,4-naphthoquinone (I. R = Cl, R′ = NHAc) or 3,4-dichloro-1,2-naphthoquinone.

However, the reaction of 2-aminopyridine with 2-hydroxy(or ethoxy or acetoxy)-3-chloro-1,4-naphthoquinone (I. R = OH, or OC_2H_5 or OAc, R′ = Cl) took a different course, and the *linear* quinone III was produced. Although the formation of III

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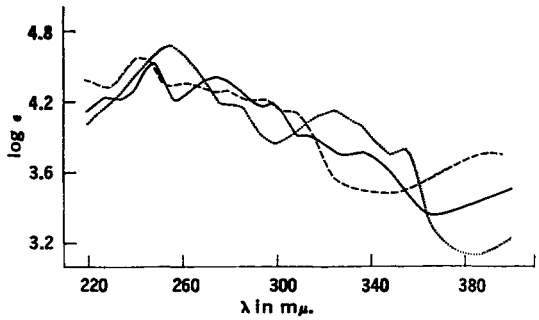


Fig. 1. The ultraviolet spectra in ethanol of Compound II (----), Compound III (———), and of 2,3-Phthaloylpyrrocoline (.....)

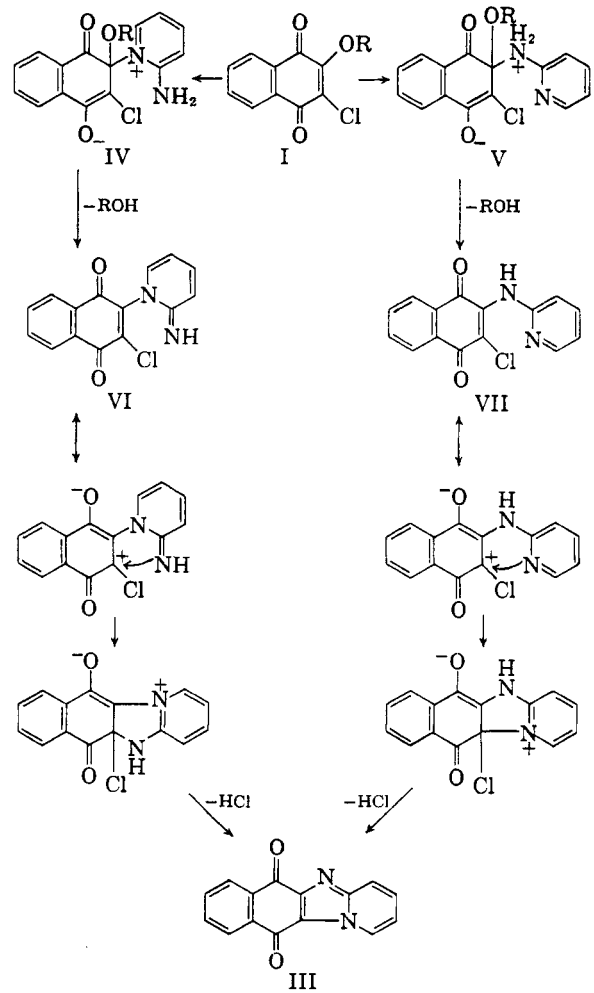
was less efficient (the yield of pure product is ~34%) than that of II, and required more vigorous reaction conditions, the quinone was easily isolated, and it did not appear to be accompanied by any of the angular isomer (II). The linear quinone formed golden-tan needles having distinctly different melting point, infrared and ultraviolet spectra from those of the angular isomer. A mixture melting point of II with III showed an appreciable depression. That the new quinone was indeed the linear isomer, and not the second possible angular isomer (see Part I),[1] was demonstrated by the reduction of III to the known[2] 1,2,3,4-tetrahydro derivative, and by the failure of III to form a phenazine when treated with *o*-phenylenediamine. The linear quinone had erroneously been reported[3] to be the product of the reaction of I (R = R′ = Cl) with 2-aminopyridine.

Fig. 1 shows the ultraviolet absorption spectra of the quinones II and III compared with that of the known[4] 2,3-phthaloylpyrrocoline.

As mentioned, rather vigorous conditions (refluxing ethyleneglycol dimethyl ether) were required for the production of III. Refluxing the reactants in ethyl acetate for many hours failed to produce III, and the naphthoquinone (I. R = Cl, R′ = OC_2H_5) was recovered. Under these same conditions 2-acetoxy-3-chloro-1,4-naphthoquinone also failed to form III, but, unlike the ethoxy homolog, it suffered hydrolysis to the red 2-aminopyridine salt of 2-chloro-3-hydroxy-1,4-naphthoquinone. As 2-hydroxy- and 2-hydroxy-3-chloro-1,4-naphthoquinones are known to be reasonably strong acids, it is not surprising that the products of their reaction with 2-aminopyridine (in ethyl acetate or toluene) are merely the 2-aminopyridine salts. These red salts are stable to recrystallization, but treatment with acetic anhydride readily yields the corresponding acetoxy-1,4-naphthoquinones. However, when the initially formed red salt of 2-hydroxy-3-chloro-1,4-naphthoquinone and 2-aminopyridine is heated in ethyleneglycol dimethyl ether the red color quickly changes to brown, and III is produced.

The formation of III appears to be a curiously circumscribed reaction. Attempts to replace 2-aminopyridine with 2-aminopyrimidine or 2-aminopyrazine gave only carbonaceous matter and not the aza homologs of III. Also, 2-aminopyridine failed to react with 2,3-bismethylthio-1,4-naphthoquinone (I. R = R′ = SCH_3) or with 2-acetamido-3-methoxy-1,4-naphthoquinone (I. R = $NHCOCH_3$, R′ = OCH_3) to produce III, and the quinones were recovered. Efforts to prepare III by treating 2-aminopyridine with 2-bromo-1,4-naphthoquinone yielded mixtures of dark intractable products, and under these conditions, 1,4-naphthoquinone itself is rapidly and efficiently converted into triphthaloylbenzene.[5]

From the information available, one may draw certain inferences concerning the mechanism of the reaction producing III. In the earlier study[1] of the reactions of 2,3-dichloro-1,4-naphthoquinone



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leading to II, both 1,2- and 1,4-addition mechanisms were considered. It seems evident, however, that III could not be formed by 1,2-addition of aminopyridine to the quinone carbonyl groups. One can envision four possible structures for the initial reaction intermediate produced by 1,4-addition and attachment of either the ring nitrogen or the amino group to the carbon atom of II bearing either the chlorine or the oxygen function. Insomuch as Fieser has shown[6] that 2-ethoxy-3-chloro-1,4-naphthoquinone yields the 2-anilino-3-chloro compound when treated with aniline, structures IV and V appear more attractive for the initial intermediate than do the two alternative possibilities. The formation of III could then occur from either IV or V by the paths shown. Now VI and VII could, *a priori*, also be produced by the 1,4-addition of 2-aminopyridine to 2,3-dichloronaphthoquinone, and in Part I[1] it was remarked that if such were the case, it is curious that III was not produced instead of II. As III is produced in the present reactions, it seems probable that VI (or VII) is not an intermediate in the formation of II, and this lends weight to the probability that the reaction of 2-aminopyridine and 2,3-dichloronaphthoquinone occurs by a 1,2- and not a 1,4-addition mechanism.

While the foregoing may provide a useful working hypothesis, it is in no way a complete explanation of the problem. Left unexplained, for example, are the curious differences in the behavior of I (R = Cl, R′ = OH, OCH_3, or $OCOCH_3$) and 2-acetamino-3-chloro-1,4-naphthoquinone,[1] and the nonreactivity of I (R = OCH_3, R′ = $NHCOCH_3$, or R = R′ = SCH_3) with 2-aminopyridine.

EXPERIMENTAL[7]

6H,11H-Benzo[f]pyrido[a]benzimidazole-6,11-dione (III). A mixture of 2.36 g. of 2-ethoxy-3-chloro-1,4-naphthoquinone,[8] 2.00 g. of 2-aminopyridine, and 5 ml. of dry ethyleneglycol dimethyl ether ("Diglyme") was stirred and boiled under reflux for 20 hr., then was diluted with water and filtered. The dark solid (2.28 g.) was dissolved in acetic acid, diluted with water, refiltered, and washed well with water and methanol. Vacuum sublimation of this material, (weight 1.60 g.) gave 1.08 g. of yellow-brown needles. Crystallization from chlorobenzene gave 0.85 g. (34.3% yield) of golden-tan needles, m.p. 297–298°, λ_{max} 227, 242.5*, 248, 275, 298, 312, and 336 mμ (ϵ 17,450, 26,570, 34,140, 25,900, 15,450, 8,320, 3,735).

This same product was obtained by this procedure when the ethoxychloronaphthoquinone was replaced by either hydroxychloro- or acetoxychloronaphthoquinone.

Anal. Calcd. for $C_{15}H_8N_2O_2$: C, 72.57; H, 3.25; N, 11.29; O, 12.80. Found: C, 72.45; H, 3.41; N, 10.93; O, 12.80.

1,2,3,4-Tetrahydro-6H,11H-benzo[f]pyrido[a]benzimidazole-6,11-dione. Hydrogenation of I in ethanol over Adams catalyst, and air-oxidation of the resulting hydroquinone produced the tetrahydro compound, which crystallized from acetonitrile in yellow needles, m.p. 251–252°, having an infrared spectrum identical with that of the material prepared[2] by another route.

2-Aminopyridine salt of 2-chloro-3-hydroxy-1,4-naphthoquinone. A solution of 2.09 g. of 2-chloro-3-hydroxynaphthoquinone and 1.00 g. of 2-aminopyridine in 45 ml. of ethyl acetate was stirred and boiled for 0.25 hr., then cooled and filtered. The bright red solid weighed 2.84 g. (100% yield) and melted at 174–176°. A sample crystallized twice from acetonitrile formed brick red microcrystals, m.p. 178.4–179.4°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_3$: C, 59.50; H, 3.63; Cl, 11.72; N, 9.25; O, 15.85. Found: C, 59.48; H, 3.55; Cl, 11.71; N, 9.13; O, 16.00.

Acknowledgment. The author is indebted to Dr. J. L. Gove for the infrared spectra, Mr. A. M. Ferri for the ultraviolet spectra, and Mr. O. E. Sundberg and his associates for the microanalyses.

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A Convenient Preparation of the 1-Methyl Betaines of Pyridine Carboxylic Acids

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The 1-methyl betaines of the various pyridine carboxylic acids have been prepared in many ways. For example, pyrolysis of methyl *iso*-nicotinate has afforded the 1-methyl betaine of isonicotinic acid[2] in fair yield. The various betaines have also been prepared by methylation of the acid with methyl iodide followed by treatment with silver oxide,[3] and by methylation with methyl sulfate followed by treatment with barium hydroxide.[4] Ion exchange columns have also been used. The methiodides of the three pyridine carboxylic acids were converted to the corresponding betaines by passing the solutions through a quaternary ammonium resin in the hydroxide form.[5]

These preparations suffer from several disadvantages. Those that use silver oxide invariably afford dark solutions and betaines that are difficult to purify. The use of strong base hydroxide exchange columns on the acid salts necessitates the use of very dilute solutions, for the heat of neutralization of the strong base with the acid salt liberates a considerable amount of heat. This latter

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