60°) to a fine crystalline solid, m.p. 55–57° which weighed 26.6 g.

3-Methyl-5,5-dicarbohydrazinopyrrolidinone-2 (V). A mixture of 24.3 g. of I, 15 g. of 64% aqueous hydrazine hydrate and 100 ml. of ethanol was refluxed for 2 hr. The reaction mixture was cooled to precipitate 20.0 g. of 3-methyl-5,5-dicarbohydrazinopyrrolidinone-2 (V). The product was recrystallized from a mixture of water-ethanol, m.p. 183–184°.

3-Methyl-5-carbohydrazinopyrrolidinone-2 (VI). The same procedure as described above was employed using 8.5 g. of the monocarboxylic ester (IV), 8.0 g. of 64% aqueous hydrazine hydrate in 50 ml. of ethanol to give 5.5 g. of 3-methyl-5-carbohydrazinopyrrolidinone-2 (VI). Recrystallization from an ethanol-ether mixture gave a product melting at 149–150°.

3-Methyl-5,5-diallylcarbamylpyrrolidinone-2 (VII). A mixture of 23.4 g. of I and 25 g. of allylamine were refluxed for 8 hr. at which time the unchanged amine was recovered by distillation. The residue was distilled under high vacuum and the fraction boiling at 195–210° at 0.05 mm. was collected. Redistillation of the oil gave an analytically pure sample of VII, b.p. 205–210° at 0.05 mm.

3-Methyl-5,5-di-β-diethylaminoethylcarbamylpyrrolidinone-2 (VIII). A mixture of 24.3 g. of I and 30 g. of *N,N*-diethylethylenediamine was heated on an oil bath at 150° for 2 hr. The unchanged amine was removed under reduced pressure and the residue distilled to collect 25.0 g. of VIII, b.p. 215–217° at 0.03 mm.

3-Methyl-5,5-di-γ-methoxypropylcarbamylpyrrolidinone-2 (IX). This compound was prepared in the manner described in the preceding experiment. A viscous amber oil, b.p. 202–205° at 0.03 mm., having a tendency to solidify on standing was obtained.

3-Methyl-5-β-morpholinoethylcarbamylpyrrolidinone-2 (X). Ten grams of IV and 30 g. of 4-β-aminoethylmorpholine were heated on an oil bath at 150° for 3 hr. The unchanged 4-β-aminoethylmorpholine was removed *in vacuo* and the residue taken up in ethanol and cooled to precipitate 12.0 g. of the product (X), m.p. 151–154°. One recrystallization from ethanol gave an analytically pure sample, m.p. 152–154°.

3-Methyl-5-β-dimethylaminoethylcarbamylpyrrolidinone-2 (XI). The same procedure was employed as described directly above. Ten grams of IV and 25 g. of *N,N*-dimethylethylenediamine yielded 7.4 g. of the product XI, m.p. 152–154° after recrystallization from alcohol.

3-Methyl-5-γ-diethylaminopropylcarbamylpyrrolidinone-2 (XII). The same procedure was employed as is described above. Ten grams of IV and 30 g. of *N,N*-dimethyl-1,3-diaminopropane yielded 6.0 g. of XII, m.p. 135–138°.

3-Methyl-5-N,N-dimethylcarbamylcarbomethoxypyrrolidinone-2 (XIII). A mixture of 10 g. of 3-methyl-5-carboxypyrrolidinone-2 (III), 20 g. of α-chloro-*N,N*-dimethylacetamide,[5] and 7.0 g. of triethylamine in 50 ml. of toluene was refluxed for 6 hr. The reaction was then stripped of its solvent under reduced pressure and the unchanged chloroacetamide distilled *in vacuo*. The residue was then dissolved in 25 ml. of ethanol and chilled to precipitate 11.5 g. of the crystalline product XIII, m.p. 148–151°. Recrystallization from ethanol gave an analytically pure sample, m.p. 150–152°.

3-Methyl-5-N,N-diallylcarbamylcarbomethoxypyrrolidinone-2 (XIV). The same procedure was employed as described above. Seven grams of III and 20 g. of α-chloro-*N,N*-diallylacetamide in the presence of 6.5 g. of triethylamine in 50 ml. of toluene yielded 8.5 g. of the crystalline product XIV, m.p. 78–81°. Recrystallization from a mixture of ethanol-ether gave a pure product, m.p. 80–82°.

Spirobarbituric acid-5,5-(3-methylpyrrolidinone-2) (XV). Three grams of magnesium turnings were dissolved in 75 ml. of methanol by refluxing for 1 hr. A mixture of 20 g. of I and 10 g. of urea dissolved in 100 ml. of methanol was added to the methanolic magnesium solution. The reaction was refluxed for 15 min. at which time the spirobarbituric acid derivative began to precipitate. Refluxing was continued for 15 min. more before cooling the mixture and collecting the product on a Buchner funnel. The precipitate was washed with ethanol and water to give 11.7 g. of XV, m.p. 269–272° with browning at 250°.

THE NATIONAL DRUG CO.
HAINES AND MCCALLUM STS.
PHILADELPHIA 44, PA.

(5) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 145 (1915).

Synthesis of Potential Antiviral Agents. Part II. Pyridine Derivatives

P. W. SADLER

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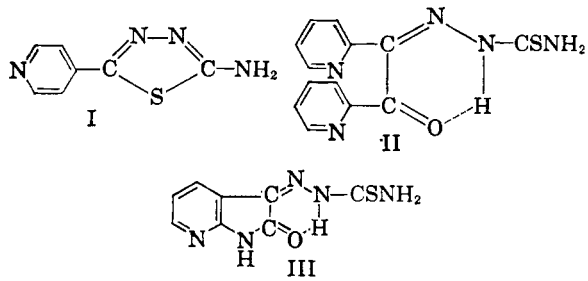
In Part I compounds directly related to isatin-β-thiosemicarbazone were examined,[1] in this, formylpyridine derivatives have been investigated, some of which have detectable antiviral activity (4-formylpyridine thiosemicarbazone has approximately 10% the antivaccinial activity of isatin-β-thiosemicarbazone). The order of antivaccinial action of the formylpyridine thiosemicarbazones is 4>3>2; this is not the same as the order of chemical reactivity, *i.e.*, 2>4>3. Replacement of the formyl hydrogen atom by a methyl group abolishes activity, as acetylpyridine thiosemicarbazones are inactive. In both groups of compounds the 2-derivatives are the most toxic. Quaternization of 4-formylpyridine thiosemicarbazone results in loss of activity, as also does quaternization of *p*-dimethylaminobenzaldehyde thiosemicarbazone; but ferric chloride oxidation, which forms the corresponding 2-amino-4-pyridyl thiodiazole I, does not affect the antivaccinial activity. Therefore, this cyclization may be reversible *in vivo*. Modification of the side chain produces the usual effects, as substitution in the 2'-position or replacement of sulfur by oxygen, *i.e.*, 2-, 3-, and 4-formylpyridine semicarbazones, results in inactive compounds.

The most notable structural difference between *N*-alkylisatin-β-thiosemicarbazones, which show pronounced antivaccinial and antivariola activity,[2] and the less active formylpyridine thiosemicarbazones, is the absence of an α-carbonyl group in the latter. The α-carbonyl group of isatin-β-thiosemicarbazone has been shown to be essential for the retention of antivaccinial activity,[3] and is also involved in the formation of an intramolecular hydrogen bond with the 2'-imino hydrogen atom. Therefore, two pyridine derivatives were prepared which could possess related intramolecularly bonded structures.

(1) P. W. Sadler, *J. Chem. Soc.*, 243 (1961).
(2) D. J. Bauer and P. W. Sadler, *Lancet*, 1110 (1960).
(3) D. J. Bauer and P. W. Sadler, *Brit. J. Pharmacol.*, **15**, 101 (1960).



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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THE MIDDLESEX HOSPITAL, LONDON, W.1., ENGLAND

(4) D. J. Bauer, *Brit. J. Exp. Path.*, 39, 480 (1958).
(5) J. Supniewski, T. Bany, and J. Krupińska, *Bull. acad. polon. sci., Classe II*, 3, 55 (1955).
(6) J. V. Scudi, U. S. Patent 2,723,270 (1955), *Chem. Abstr.*, 50, 3504f (1956).
(7) H. G. Mautner and W. D. Kumler, *J. Am. Chem. Soc.*, 78, 97 (1956).
(8) S. Ginsberg and I. B. Wilson, *J. Am. Chem. Soc.*, 79, 481 (1957).
(9) H. Kägi, *Helv. Chim. Acta*, 141 E (1941).
(10) G. Young and W. Eyre, *J. Chem. Soc.*, 54 (1901).

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

WILLIAM L. MOSBY

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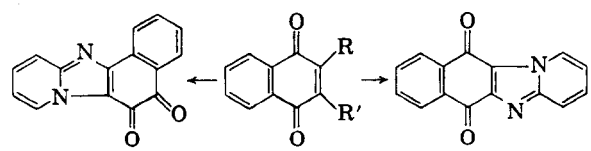
In Part I of these studies,[1] it was shown that 2,3-dichloro-1,4-naphthoquinone (I. R = R′ = Cl) reacted with 2-aminopyridine to yield the angular quinone II. This same product was produced[1] by the reaction of 2-aminopyridine with either



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

(1) W. L. Mosby and R. J. Boyle, *J. Org. Chem.*, 24, 374 (1959).