TABLE I

8-QUINOLINOL DERIVATIVES OF C_6H_5—$\overset{R}{\underset{|}{B}}$—OH

R	M.P.[a]	Formula	Carbon[b] Calcd.	Carbon[b] Found	Hydrogen[b] Calcd.	Hydrogen[b] Found	Boron[c] Calcd.	Boron[c] Found	Neut. Equiv.[d] Calcd.	Neut. Equiv.[d] Found
C_2H_5	152–153	$C_{17}H_{16}BNO$	78.21	78.09	6.17	6.14	4.14	4.10	261	262
i-C_3H_7	87	$C_{18}H_{18}BNO$	78.56	79.23	6.60	6.58	3.93	3.88	275	275
t-C_4H_9	108–109	$C_{19}H_{20}BNO$	78.91	78.65	6.97	7.29	3.74	3.70	289	291
$C_6H_5CH_2$[e]	133–133.5	$C_{22}H_{18}BNO$	81.75	81.27	5.62	5.66	3.35	3.34	323	325
C_6H_5	204–205[f]	$C_{21}H_{16}BNO$	81.47	81.84	5.22	5.30	3.50	3.48	309	308

[a] Melting points are corrected. [b] Analyses by Drs. Weiler and Straus, Oxford, England. [c] Boron analyses by the method described by J. M. Thoburn, Dissertation, Northwestern University, 1954. [d] By titration with perchloric acid in glacial acetic acid; sample dissolved in acetic acid–acetic anhydride (4 to 1). [e] This compound does form a crystalline aminoethyl ester, m.p. 211–213°; reported[5] m.p. 208–212.5°. [f] Reported[3] m.p. 203°.

The 8-quinolinol derivatives are stable in air (no indication of decomposition over a period of several months) and resist hydrolysis in neutral aqueous ethanol (as judged by the persistence of strong fluorescence for several weeks).

Each of these compounds has an absorption maximum in chloroform in the region 397–405 mμ (ε 2700–3100). These data, joined with those of Moeller and Cohen, who found that the 8-quinolinol chelates aluminum, gallium, indium, and thallium have λ_{max} in the same region (390–401 mμ),[3] indicate that absorption near 400 mμ is characteristic of the 8-quinolinol chelates of all the Group III-A elements.

EXPERIMENTAL

Boronic acids. The previously reported ethylphenylborinic acid[4] and benzylphenylborinic acid[5] were prepared as described by Torssell[4]; the previously unreported isopropylphenylborinic acid was prepared similarly. Diphenylborinic acid was prepared by the method of Povlock and Lippincott.[6]

t-Butylphenylborinic acid. As conventional methods for the preparation of unsymmetrically substituted borinic acids[7] failed to give detectable amounts of this acid, its synthesis will be described in some detail.

A solution of *t*-butylmagnesium chloride (0.1 mole) in 45 ml. of dry tetrahydrofuran was added dropwise to a well stirred solution of 10.4 g. (0.10 mole) of benzeneboronic anhydride (triphenylboroxin)[8] in 150 ml. of dry tetrahydrofuran cooled to 0° and under an atmosphere of dry nitrogen. After the addition was complete (about 30 min.), stirring at 0° was continued for 1 hr. The mixture was then hydrolyzed with 100 ml. of 3*M* hydrochloric acid, the two layers were separated, and the solvent was evaporated under reduced pressure from the organic layer to give 2.6 g. (16%) of crude product.[9]

8-Quinolinol derivatives. An equivalent amount of 8-quinolinol (in a 20% solution of 95% alcohol) was added to a solution of the crude borinic acid (about 0.5 g. of acid per 10 ml. of 95% alcohol); in most cases the product crystallized immediately and in high yield. The crude derivatives were recrystallized from 95% alcohol, with the exception of the diphenyl derivative which was more conveniently recrystallized from methanol-tetrahydrofuran (3 to 1).

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5-Substituted Derivatives of 3-Methylpyrrolidinone-2

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In the light of a recent investigation[4] in which is described a concomitant addition and cyclization between acrylic esters and diethyl acetamidomalonate to form 2-pyrrolidinone derivatives, it became of interest to prepare various carboxylic acid derivatives utilizing one or both of the carboxyl groups of the pyrrolidinone prepared from diethyl acetamidomalonate and ethyl methacrylate as indicated in Fig. 1.

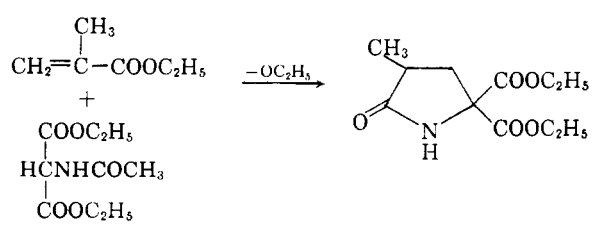

Figure 1

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TABLE I

5-SUBSTITUTED DERIVATIVES

3-Methylpyrrolidinone-2	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	M.P.[a]	Yield, %
Intermediates					
5,5-Dicarbethoxy-	$C_{11}H_{17}NO_5$	5.76	5.75, 5.71	111–113	91
5-Carboxy-	$C_6H_9NO_3$	9.79	9.80, 9.82	153–156 (lit. 175°)[c]	55
5-Carbethoxy-	$C_8H_{13}NO_3$	8.18	8.02, 8.03	55–57	64
Diamides					
5,5-Dicarbohydrazino-	$C_7H_{13}N_5O_3$	32.54	31.90, 31.99	183–184	92
5,5-Diallylcarbamyl-	$C_{13}H_{19}N_3O_3$	15.84	16.05, 16.01	205–210/0.05 mm.[b]	65
5,5-Di-β-diethylaminoethylcarbamyl-	$C_{19}H_{46}N_3O_3$	18.26	18.21, 18.20	215–217/0.03 mm.[b]	79
5,5-Di-γ-methoxypropylcarbamyl-	$C_{15}H_{27}N_3O_5$	12.76	12.38, 12.35	202–205/0.05 mm.[b]	65
Monoamides					
5-Carbohydrazino-	$C_6H_{10}N_3O_2$	26.74	26.36, 26.78	149–150	71
5-β-Dimethylaminoethylcarbamyl-	$C_{10}H_{19}N_3O_2$	19.70	19.07, 19.28	152–154	82
5-γ-Dimethylaminopropylcarbamyl	$C_{11}H_{21}N_3O_2$	18.49	18.14, 17.95	135–138	45
5-β-Morpholinoethylcarbamyl-	$C_{12}H_{21}N_3O_3$	16.46	16.19, 16.20	152–154	82
Esters					
5-*N*,*N*-Dimethylcarbamylcarbomethoxy-	$C_{10}H_{16}N_2O_4$	12.27	12.01, 11.95	150–152	72
5-*N*,*N*-Diallylcarbamylcarbomethoxy-	$C_{14}H_{20}N_2O_4$	9.99	9.92, 9.93	80–82	62
Misc.					
Spirobarbituric acid-5,5'-	$C_8H_8N_2O_4$	19.90	19.85, 19.87	269–272	64

[a] All readings are uncorrected. [b] Boiling points. [c] J. Fillman and N. Albertson, *J. Am. Chem. Soc.*, **74**, 4969 (1952).

The 5-mono- and 5,5-dicarboxylic esters (IV, I) were conveniently converted to the mono- and diamides by heating with the corresponding amine. It was expedient in the synthesis of monoamides to prepare the intermediate ester (IV) from the monocarboxylic acid (III) which could be easily separated from the reaction mixture.

The monoesters (XIII, XIV) were prepared from the corresponding 3-methyl-5-carboxypyrrolidinone-2 (III) using the appropriate chloroacetamide and triethylamine.

Listed in Table I are the compounds prepared.

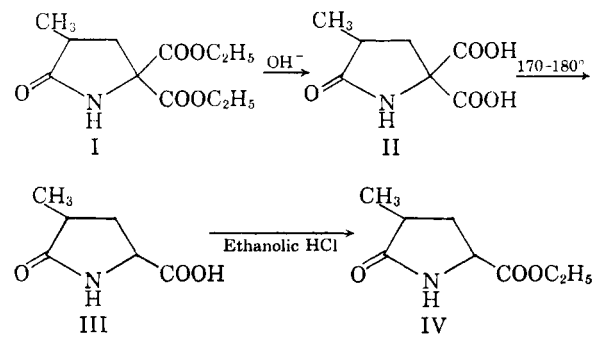

Figure 2

EXPERIMENTAL

3-Methyl-5,5-dicarbethoxypyrrolidone-2 (I). Two hundred and seventy-five grams of ethyl methacrylate were added to a mixture of 655 g. of diethyl acetamidomalonate in 1500 ml. of ethanol containing 6.9 g. of dissolved sodium metal and the mixture refluxed for 5–6 hr. The condenser was then set for downward distillation and the ethanol removed with the aid of a steam bath. The last traces of solvent were removed by application of a water aspirator to leave a solid residue. The residue was taken up in 1 l. of boiling benzene and filtered free from insoluble sodium ethoxide and methacrylate polymer. On cooling the filtrate 576 g. of 3-methyl-5,5-dicarbethoxypyrrolidinone-2 (I) precipitated, m.p. 108–110°. Concentration of the mother liquor yielded 83 g. more of I. A sample recrystallized for analysis melted at 113–115°.

3-Methyl-5-carboxypyrrolidinone-2 (III). A solution of 240 g. of potassium hydroxide in 750 ml. of water was added dropwise to a warm solution of 315 g. of 3-methyl-5,5-dicarbethoxypyrrolidinone-2 (I) in 750 ml. of ethanol. The mixture was refluxed for 20 hr. and then concentrated to 300 ml. under reduced pressure. The residue was cooled to 0° and then treated with 360 ml. of concd. hydrochloric acid and 200 ml. of acetone. The potassium chloride which precipitated was filtered and the filtrate was concentrated to 200 ml. *in vacuo* at room temperature. The 3-methyl-5,5-dicarboxypyrrolidinone-2 (II) which precipitated from the solution was collected (185 g., crude) and the filtrate cooled to precipitate 35 g. more of II, m.p. 158–159°. The melting point was accompanied by effervescence. The crude dicarboxylic acid was fused at 170–180° for 2 hr. and the residue taken up in 150 ml. of ethanol. A small amount of potassium chloride which remained insoluble was removed by filtration and the filtrate was concentrated to one half its original volume and cooled. Petroleum ether (b.p. 30–60°) was added to aid in precipitating 90 g. of 3-methyl-5-carboxypyrrolidinone-2 (III). Two recrystallizations from ethanol gave an analytical sample, m.p. 153–156°.

3-Methyl-5-carbethoxypyrrolidinone-2 (IV). A solution of 35 g. of 3-methyl-5-carboxypyrrolidinone-2 (III) in 200 ml. of ethanol saturated with anhydrous hydrogen chloride was allowed to stand at room temperature for 2 days. The solvent was then removed *in vacuo* with the aid of a steam bath and the residue was taken up in benzene and washed with an aqueous solution of potassium carbonate. The organic layer was dried over anhydrous potassium carbonate and distilled to collect 3-methyl-5-carbethoxypyrrolidinone-2 (IV), b.p. 120–126° at 0.1 mm. The distillate solidified on standing and was rubbed with petroleum ether (b.p. 30–

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°.

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Synthesis of Potential Antiviral Agents. Part II. Pyridine Derivatives

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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.

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