from the perfused pancreas as well as from isolated islets are required to clarify this point.

The significant increase in the evolution of respiratory $^{14}CO_2$ by the animals treated with cadmium indicates that multiple dosages of cadmium alter carbohydrate metabolism. The affected mechanisms may involve glycolysis, the tricarboxylic acid cycle, respiration, or a combination of these. It was reported (15–17) that cadmium ions uncouple oxidative phosphorylation. This uncoupling may be due to the effect of cadmium on the transport of ions across the mitochondrial membrane (16) or to the blocking of some free active site (15). Uncoupling oxidative phosphorylation increases the adenosine diphosphate concentration relative to that of adenosine triphosphate. This causes an increase in the rate of glycolysis and the tricarboxylic acid cycle since it activates certain enzymes such as phosphorylase *a*, adenosine triphosphate:D-fructose 6-phosphate 1-phosphotransferase, adenosine triphosphate:pyruvate phosphokinase, and isocitrate dehydrogenase.

With the increase in the rates of glycolysis and the tricarboxylic acid cycle after cadmium treatment, there may be a concomitant increase in labeled glucose utilization. With the information available, it is not possible to explain further the effect of cadmium on the evolution of carbon dioxide *in vivo* and further work is indicated.

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Synthesis and Hypotensive Properties of 4-Amino-6,7-dimethoxyisoquinoline

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Abstract □ The compound 4-amino-6,7-dimethoxyisoquinoline hydrochloride, a structural isomer of amiquinsin hydrochloride (4-amino-6,7-dimethoxyquinoline hydrochloride), was synthesized. It was shown to be hypotensive in anesthetized normotensive dogs and produced an antihypertensive effect in unanesthetized renal hypertensive dogs.

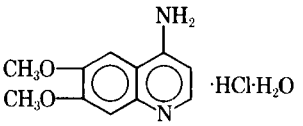
Keyphrases □ 4-Amino-6,7-dimethoxyisoquinoline—synthesis and hypotensive properties, structural isomer of amiquinsin hydrochloride □ Amiquinsin hydrochloride—synthesis and hypotensive properties of the structural isomer 4-amino-6,7-dimethoxyisoquinoline □ Antihypertensive agents, potential—synthesis and screening of 4-amino-6,7-dimethoxyisoquinoline, a structural isomer of amiquinsin hydrochloride

Since the hypotensive properties of amiquinsin hydrochloride [1] (4-amino-6,7-dimethoxyquinoline hydrochloride hydrate) (I) were well known (1), there was a desire to prepare the isomeric 4-amino-6,7-dimethoxyisoquinoline hydrochloride (II) for hypotensive screening. This paper discusses the synthesis of II and several related intermediates, as well as the hypotensive properties of II.

The key intermediate, 2,3-dihydro-6,7-dimethoxy-4(1*H*)-isoquinolone (IV), in the synthesis of II was prepared *via* a two-step process (Scheme I). Reductive condensation of veratraldehyde and glycine gave *N*-veratrylglycine (III) which, upon subsequent cyclization in polyphosphoric acid, gave IV [2]. Although the intermediate Schiff-base product of veratraldehyde and glycine was not isolated, it was necessary to heat briefly the reaction solution prior to reduction to avoid formation of *N,N*-diveratrylglycine (VII). The reductive alkylation at room temperature

[1] Norwich Pharmacal Co.

[2] The present synthesis of IV is more direct than the four-step synthesis used in the similar preparation of 2,3-dihydro-6,7-dimethoxy-1-methyl-4(1*H*)-isoquinolone (3).



I

gave VII in 32% yield. Direct synthesis of VII from III and 3,4-dimethoxybenzyl chloride (VIII) established the *N,N*-diveratrylglycine structure.

Intermediate IV was previously prepared by an alternative four-step synthesis (2), without an improvement in yield over that of the presently described method.

The intermediate 6,7-dimethoxy-4-isoquinolinol (V) (2) was obtained through aromatization of IV with palladium-on-charcoal in refluxing toluene. Initially unsuccessful attempts were made to convert V to 4-amino-6,7-dimethoxyisoquinoline hydrochloride (II) through usual methods. Alternatively, the hydrazone (VI) of IV was prepared and subjected to aromatization (palladium-on-charcoal in refluxing alcohol), with the cleavage of the hydrazine moiety of VI to give the desired II.

Compound II was hypotensive in anesthetized normotensive dogs and produced an antihypertensive effect when administered to unanesthetized renal hypertensive dogs. In comparison with the activity of I, II was equipotent in regard to pressure lowering in the anesthetized dog; however, the duration of hypotensive effect was shorter. In the renal hypertensive dog, II was less active than I in regard to both potency and duration.

EXPERIMENTAL [3]

***N*-Veratrylglycine (III)**—To a solution of glycine (10.8 g, 0.14 mole) in water (110 ml) was added a solution of veratraldehyde (24.9 g, 0.15 mole) in ethanol (60 ml). The resultant solution was heated to boiling and cooled in an ice bath to room temperature. With the addition of 5% palladium-on-charcoal (2.0 g), the mixture was hydrogenated in a Parr apparatus at room temperature for 1 hr; a quantitative drop in pressure was observed. The reaction solution was filtered of catalyst, and the filtrate was evaporated under reduced pressure. The solid residue was triturated with hot 95% ethanol (70 ml) and cooled in an ice bath. The white crystalline product, III, was collected and washed with ethanol and ether, mp 200–202°, yielding 21.4 g (68%).

***N*-Veratrylglycine Hydrochloride (III-HCl)**—A mixture of III (70 g, 0.31 mole) and ethanol (700 ml) was treated with hydrogen chloride (2-propanol) solution (250 ml). The mixture was heated on the steam bath, and water (50 ml) was added to obtain solution. The solution was cooled, and the product was collected and washed with 95% ethanol and ether, mp 207–210°, yielding 55 g (68%).

Anal.—Calc. for $C_{11}H_{15}NO_4 \cdot HCl$: C, 50.48; H, 6.16; N, 5.35. Found: C, 50.27; H, 6.26; N, 5.30.

***N,N*-Diveratrylglycine (VII)**—*Method A*—To a solution of glycine (7.5 g, 0.10 mole) in water (120 ml) was added a solution of veratraldehyde (16.6 g, 0.10 mole) in ethanol (45 ml) and platinic oxide (0.3 g). The mixture was hydrogenated in a Parr apparatus at room temperature for 3.5 hr. The reaction mixture was cooled, and the product was collected and washed with water. Recrystallization from ethanol gave 6.0 g (32%) of a white crystalline solid, mp 196–199°.

The hydrochloride of VII was prepared by the same procedure as described for III-HCl, mp 187–189°.

Anal.—Calc. for $C_{20}H_{25}NO_6 \cdot HCl$: C, 58.32; H, 6.36; Cl, 8.61; N, 3.40. Found: C, 58.45; H, 6.47; Cl, 8.68; N, 3.48.

Method B—A mixture of III (6.6 g, 0.029 mole), VIII (5.8 g, 0.031 mole), anhydrous sodium carbonate (3.0 g, 0.028 mole), and dimethylformamide (150 ml) was heated at 85–90° overnight with mechanical stirring. The reaction mixture was filtered hot, and the filtrate was evaporated to dryness under reduced pressure. The amorphous residue, washed twice with ether, was treated with 2-propanol and diluted with ether. A cream-colored solid was isolated, mp 185–188°, yielding 2.6 g (23%). The IR absorption spectrum [4] was identical to that of authentic VII. Recrystallization from methanol gave a white crystalline solid, mp 197–200°; the mixed melting point with authentic VII was 199–202°.

2,3-Dihydro-6,7-dimethoxy-4(1*H*)-isoquinolone Hydrochloride (IV-HCl)—To polyphosphoric acid (730 g) was added, portionwise, III (60 g, 0.27 mole) with mechanical stirring. The mixture was heated (85–90°) on the steam bath for 2 hr and allowed to stand overnight. The reaction syrup was gradually triturated with ice (3 liters) and water (1 liter) and then treated with benzene (1.5 liters) and solid sodium carbonate (880 g) to pH 6–7. The organic layer was separated, and the aqueous layer was further extracted with four 1-liter portions of benzene. After drying over magnesium sulfate and charcoal, the filtered extracts were treated with hydrogen chloride while being cooled in an ice bath. Recrystallization of the product from 97% ethanol gave white crystals, yielding 11.9 g (18%), mp 235–237° dec. [lit. (2) mp 237–238°, from methanol].

Anal.—Calc. for $C_{11}H_{13}NO_3 \cdot HCl$: C, 54.21; H, 5.79; N, 5.75. Found: C, 54.09; H, 5.81; N, 5.64.

6,7-Dimethoxy-4-isoquinolinol Hydrochloride (V-HCl)—A mixture of IV (30 g, 0.15 mole), toluene (1500 ml), and 5% palladium-on-charcoal (15 g) was heated on the steam bath for 22 hr. The insoluble product was extracted from the catalyst with hot dimethylformamide (340 ml). The extract was evaporated to dryness under reduced pressure, and the residue was washed with ether. The product in 95% ethanol (1200 ml) was heated with charcoal for 7 min and filtered. The cooled filtrate was treated with hydrogen chloride; then one volume of ether was added, and a cream-colored solid was deposited. The isolated solid melted at 239–244° and yielded 17.7 g (49%). Recrystallization from 95% ethanol gave the hydrochloride, mp 242–244° dec. [lit. (2) mp 264–265°, from methanol].

Anal.—Calc. for $C_{11}H_{11}NO_3 \cdot HCl$: C, 54.67; H, 5.01; N, 5.80. Found: C, 54.69; H, 5.01; N, 5.64.

2,3-Dihydro-6,7-dimethoxy-4(1*H*)-isoquinolone Hydrazone (VI)—To a mixture of IV (64.0 g, 0.31 mole) and ethanol (525 ml) was added hydrazine hydrate (29.0 ml, 0.58 mole). The reaction solution was refluxed for 1.5 hr, and the solution was cooled in an ice bath for 2 hr. The resultant brown, crystalline solid was collected and washed with ethanol and ether, yielding 48.1 g (70%), mp 156–159°. Recrystallization from ethanol gave pale-yellow crystals, mp 155–158°.

Anal.—Calc. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.51; H, 6.81; N, 18.48.

4-Amino-6,7-dimethoxyisoquinoline Hydrochloride (II-HCl)—A mixture of VI (38 g, 0.17 mole), ethanol (600 ml), and 5% palladium-on-charcoal (19 g) was refluxed for 16 hr. The hot solution was filtered, cooled, and treated with dry hydrogen chloride. The resultant tan, crystalline solid was collected and washed with cold 2-propanol. The product was recrystallized from a mixture of ethanol and methanol (with charcoal), yielding 13 g (32%), mp 249–251° dec. A second crop of crystals was isolated, yielding 12 g (29%), mp 251–254° dec.

Anal.—Calc. for $C_{11}H_{12}N_2O_2 \cdot HCl$: C, 54.89; H, 5.44; Cl, 14.73; N, 11.64. Found: C, 54.63; H, 5.36; Cl, 14.59; N, 11.40.

The NMR spectrum [5] in D_2O showed δ 3.76, singlet (two CH_3O); 6.41 and 6.71, singlets (two aromatic); and 7.25 and 7.88, singlets (two heteromatic).

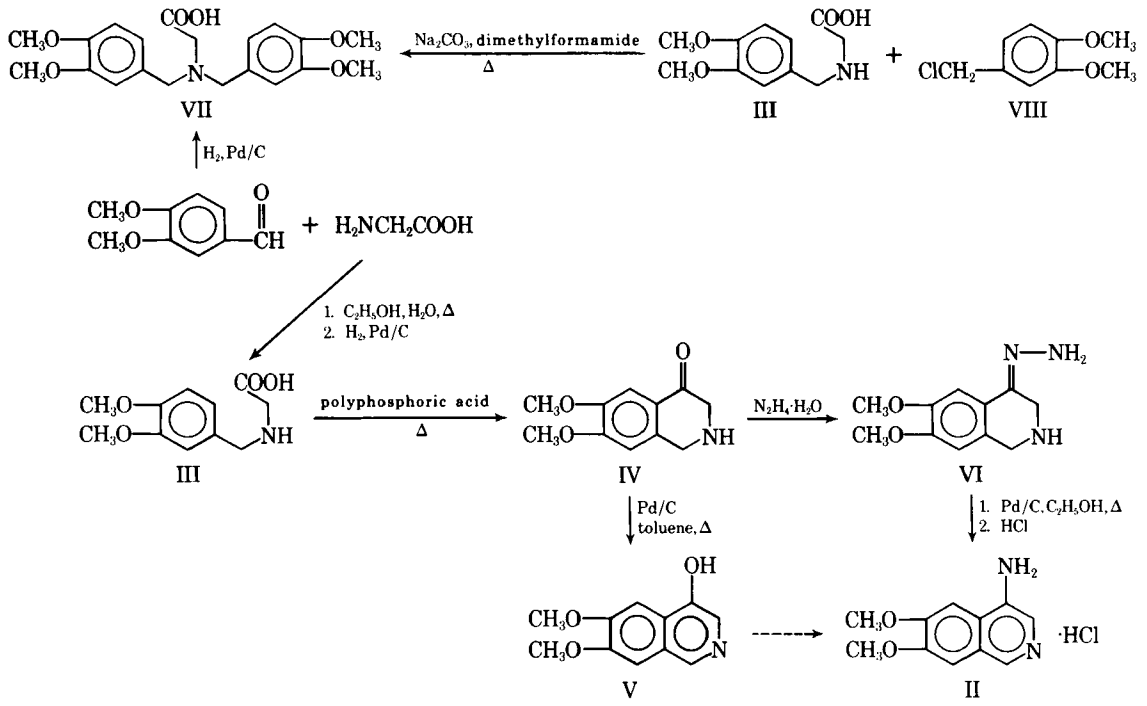
RESULTS AND DISCUSSION

Compounds I and II were evaluated for hypotensive activity in

[3] Melting points were determined on a Fisher-Johns hot-stage apparatus and are uncorrected.

[4] The IR spectrum (Nujol) was determined on a Perkin-Elmer model 137B spectrophotometer.

[5] Determined on a Varian A-60A spectrophotometer with tetramethylsilane as the internal standard.



Scheme I

barbiturate-anesthetized mongrel dogs. Blood pressure was recorded from a cannulated femoral artery. The compounds were administered intravenously in water. At a dose of 5 mg/kg, II showed a maximum blood pressure fall of 47% for 90 min; at 10 mg/kg, it showed a maximum fall of 85% for >210 min. Compound I, at 1 mg/kg, showed a maximum blood pressure fall of 17% for >270 min; at 10 mg/kg, it showed a maximum fall of 51% for >270 min.

The compounds were further evaluated for antihypertensive activity in renal hypertensive dogs (4). Systolic blood pressure was measured by the indirect tail-cuff method (5).

When I and II were administered to unanesthetized, renal hypertensive dogs at a dose of 20 mg/kg perorally, a reduction in systemic arterial pressure was observed. Compound I produced an average decrease in systolic blood pressure of 36% which persisted longer than 6 hr, and II produced an average decrease in systolic pressure of 14% with an average duration of 3 hr.

These findings indicate that II may be equipotent to I with regard to blood pressure lowering in the anesthetized dog when given intravenously but is of shorter duration. When compared in renal hypertensive dogs, II is less active than I with regard to both potency and duration.

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