Isoquinolines. 4.[1] The Synthesis of C(α)-Hydroxylated Tetrahydrobenzylisoquinolines and Related Compounds Using the 4-Oxazolin-2-one System as a Protecting Group[2a]

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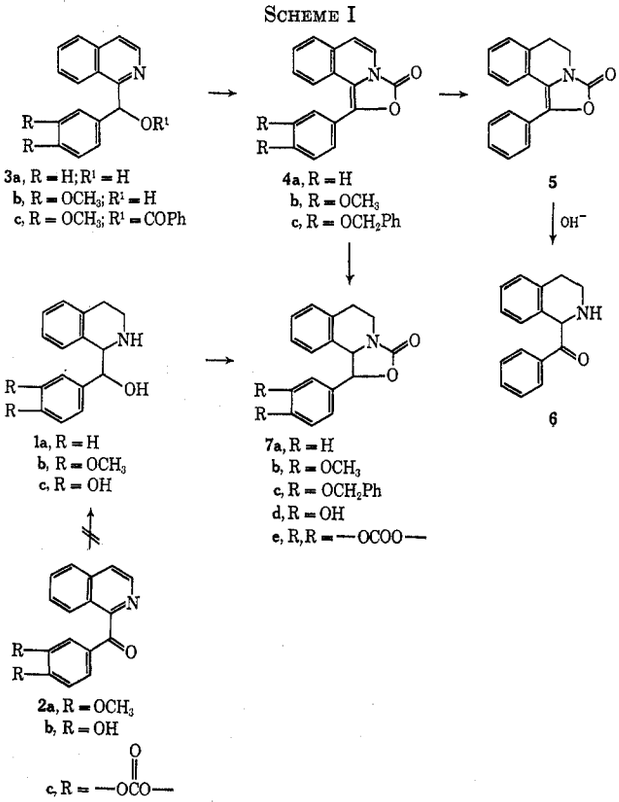
A convenient synthesis of the unstable 3,4-dihydroxybenzylmethanolamine (1) was devised by way of the 4-oxazolin-2-one system (4) as a protecting group. These compounds were prepared from the corresponding 1-(α-hydroxybenzyl)isoquinolines **3** by treatment with phosgene. These oxazolines were stable, recrystallizable intermediates which could be selectively reduced to the 5,6-dihydro (5) or 1,5,6,10b-tetrahydro (7) derivatives. Hydrolysis (acidic or basic) yielded the corresponding 1-(α-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinolines (1) or the 1-benzoyl-1,2,3,4-tetrahydroisoquinolines (6), respectively.

The benzylisoquinoline alkaloids are abundantly found in nature and have been the subject of extensive chemical and pharmacological investigations.[3] The related α-hydroxy-1-benzyltetrahydroisoquinoline alkaloid types have not been found in nature nor have they been thoroughly examined either in their methods of synthesis or for their biological activity. This investigation was initiated to develop methods for the synthesis of the 1,2-diaryl-2-aminoethanol system as shown in structure **1**, by incorporating the reactive carbinolamine into a more stable 4-oxazolin-2-one ring system. It was further considered that, if successful, this method would also serve as a means for the stereoselective synthesis of the C-7 hydroxy aporphine alkaloids. We have found the 4-oxazolin-2-one ring system[4] to be a versatile protecting group for such secondary amino nitrogens containing a β hydroxyl group that may be removed by mild hydrolysis conditions at the terminal stage of the synthesis. This method has been utilized in our laboratory for the synthesis of 7-hydroxyaporphine and 7-hydroxynoraporphine[5] and for the attempted synthesis of phenanthrene amino alcohols *via* photochemical cyclization of 4,5-diphenyloxazolin-2-one.[6] In the present report we wish to describe the details of our studies in the isoquinoline series.

Our initial effort in the synthesis of the α-hydroxytetrahydroisoquinoline **1c** (Scheme I) was directed at the reduction of 3,4-dihydroxyphenyl-1-isoquinolyl ketone (**2b**) and the cyclic carbonate **2c** to the desired

SCHEME I



1c under a variety of reduction conditions. In all instances the desired product proved to be extremely sensitive to air and could not be isolated. Similarly, the reduction of 3,4-dimethoxyphenyl-1-isoquinolylcarbinyl benzoate (**3c**)[7] with platinum in acetic acid yielded a mixture of compounds from which no crystalline compound could be isolated. However, saponification of the crude reaction mixture gave the alcohol **1b** in 46% yield. Attempts to demethylate **3c** with hydriodic acid in acetic acid[8] yielded only tarry, acid-insoluble material plus mixtures which eluded isolation.

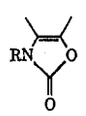
Unable to effect these reductions satisfactorily, we abandoned this route and developed an alternative synthesis which involved the oxazolone **4** in which the methanolamine functions were protected during the reduction and subsequent ether cleavage. Compound **4a** was prepared from the known alcohol **3a**[9] with

(1) K. K. Weinhardt and J. L. Neumeyer, *J. Med. Chem.*, **16**, in press.

(2) (a) Presented in part at the Seventh International Symposium on the Chemistry of Natural Products, Riga, June 1970, Abstract E 82. (b) To whom inquiries should be addressed at the Department of Medicinal Chemistry and Pharmacology, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Mass. 02115.

(3) For reviews on the benzylisoquinoline alkaloids see V. Devlofev, J. Comin, and M. J. Vernego in "The Alkaloids," Vol. 10, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, p 401; M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, N. Y., 1972, p 45.

(4) Reviewed by R. Filler in *Advan. Heterocycl. Chem.*, **4**, 103 (1965). The skeletal structure for the oxazolone, the *Chemical Abstracts* nomenclature (listed first), and the names with more common usage are shown below.



4-oxazolin-2-one
2(3*H*)-oxazolone

(5) J. L. Neumeyer and F. E. Granchelli, *Tetrahedron Lett.*, 5261 (1970).

(6) A. S. Dey and J. L. Neumeyer, 2nd Northeastern Regional Meeting of the American Chemical Society, Providence, R. I., Oct 1970, Abstract 122.

(7) F. D. Popp and W. E. Williams, *J. Amer. Chem. Soc.*, **79**, 3773 (1957).

(8) J. L. Neumeyer, B. R. Neustadt, and K. K. Weinhardt, *J. Pharm. Sci.*, **59**, 1850 (1970).

(9) L. Walters, N. Iyer, and W. E. McEwen, *J. Amer. Chem. Soc.*, **80**, 1177 (1958).

phosgene in triethylamine to give the oxazolone[10] in 91% yield. Catalytic hydrogenation of **4a** with platinum oxide in glacial acetic acid–tetrahydrofuran can be terminated after 1 mol of hydrogen has been absorbed, resulting in reduction of only the endocyclic isoquinoline double bond in **4** to give **5**. However, when the reduction was allowed to go to completion, **7a** was obtained which was converted without isolation to **1a** when treated with trifluoroacetic acid (TFA). However, when the oxazolone **5** was treated with potassium hydroxide in absolute ethanol, the ketone **6** was isolated in 86% yield. The oxazolone **4b** was prepared by reduction of the ketone **2a** without isolation of the intermediate alcohol. The catalytic reduction of **4b** over platinum oxide followed by hydrolysis with TFA gave 70% of **1b** hydrochloride. The successful synthesis of **1a** and **1b** encouraged us to prepare **4c** and its reduction product **7c**. We briefly examined the hydrogenolysis of **7c** to the phenol **7d** over palladium on charcoal in tetrahydrofuran. The hydrogenolysis product **7d** could not be purified sufficiently to permit a satisfactory identification, but the nmr spectrum clearly showed that the benzyl ether groups had been cleaved. Thus, in order to protect the sensitive pyrocatechol system, the carbonate ester **7e** was prepared *in situ* with phosgene and pyridine. 1-(3,4-Dihydroxyphenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one cyclic carbonate (**7e**) was isolated and characterized as a crystalline solid which could be readily converted to the catecholamine **1c** by mild hydrolysis with TFA.

We contemplate that this method will provide the basis for stereoselective syntheses of both such phthalideisoquinoline alkaloids as narcotine and hydrastine and such C-7 hydroxylated aporphines as ushinsunine and norushinsunine.

Experimental Section[11]

1-Phenyl-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4a).—To a solution of 1.64 g of phenyl-1-isoquinolylcarbinol[9] in 100 ml of methylene chloride was added 2 ml of triethylamine and 100 ml of 8% aqueous sodium bicarbonate. The two phases were vigorously stirred as phosgene was bubbled into the mixture. When a vigorous evolution of CO_2 began, the addition was stopped. After stirring for 10 min, the layers were separated and the organic layer was washed with aqueous bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated until crystallization ensued. The resulting yellow product was recrystallized from methylene chloride–methanol to give 1.66 g (91%) of **4a**, mp 165–166° (lit.[10] mp 166–168°).

1-(3,4-Dimethoxyphenyl)-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4b).—To a rapidly stirred suspension of 1 g of 3,4-dimethoxyphenyl-1-isoquinolyl ketone in 30 ml of ethanol was added 0.5 g of sodium borohydride in small portions. The mixture was stirred for 2 hr, then 2 ml of water was added and stirring was continued for an additional 30 min. The inorganic solids were filtered off and the filtrate was evaporated under vacuum to give a gummy oil, which was extracted with ether. The ether extracts were combined, washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered, and evaporated to dryness to give an oil, **3b**, that could not be induced to crystallize. The oil was dissolved in anhydrous ether, 20 ml of triethylamine was added, and then a solution of about 7 g of phosgene in 75 ml of anhydrous ether was added dropwise. A vigorous reaction ensued, a heavy precipitate formed, and the solution turned bright yellow. After standing overnight the mixture was poured into water to give a dense yellow precipitate. The precipitate was filtered off, and the ether and water filtrates were separated. The ether layer was washed with water, aqueous hydrochloric acid, and finally aqueous sodium bicarbonate. It was then dried over magnesium sulfate, filtered, and evaporated to dryness. The residue and the precipitate already collected were combined and dissolved in methylene chloride, and 10 ml of ethanol was added to the solution. Methylene chloride was distilled from the mixture until crystallization occurred. There was obtained 0.87 g (79%) of **4b**: mp 178–181°; ν^{KBr} 1748 cm^{-1} (s); λ_{max}^{EtOH} 325 mμ (ϵ 22,300), 227 (12,800), 352 (12,000); nmr ($CDCl_3$) δ 3.84 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 6.2 (1 H, d, J = 8 Hz), 7.1 (7 H, m, PhH), 7.8 (1 H).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.84; H, 4.70; N, 4.23.

1-[3,4-Bis(benzyloxy)phenyl]-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4c).—To a solution of 11.9 g of 2-benzoyl-1,2-dihydroisoquinaldonitrile[12] and 14.5 g of 3,4-dibenzyloxybenzaldehyde[13] in 150 ml of dimethylformamide cooled to −40° was added 3.5 g of 54% sodium hydride dispersion in oil. This mixture was stirred under nitrogen and allowed to warm to −20°, where it was maintained for 1 hr. Then the temperature was raised and held at 0° for another hour. The mixture was allowed to warm to room temperature overnight with good stirring. The solution was diluted with 300 ml of water and extracted with ether. The ether extract was washed with water, then with saturated sodium chloride solution. It was evaporated to dryness and the residual oil was dissolved in ethanol. The alcohol solution was treated with 2 g of sodium borohydride and stirred for 1 hr. To this mixture was added 10 ml of 50% aqueous potassium hydroxide and the mixture was refluxed for 2 hr. The solvent was evaporated and the residue was taken up in ether and water. The aqueous layer was separated and the ether layer was treated with a little dilute sulfuric acid, which immediately gave a gummy precipitate. The ether was removed by decantation and the gum was washed with water and then with ether. The coagulated semisolid was redissolved by shaking with aqueous sodium hydroxide and ether. The ether layer was separated, washed twice with water and once with saturated salt solution, and then dried over magnesium sulfate. After filtration and evaporation of the ether solution, the residue was dissolved in a mixture of 75 ml of dry methylene chloride and 20 ml of triethylamine. This solution was treated dropwise with 9 g of phosgene dissolved in methylene chloride. A vigorous exothermic reaction took place and the resulting mixture was allowed to stand overnight. The mixture was extracted twice with water, twice with dilute hydrochloric acid, once with sodium bicarbonate, and once with saturated salt solution. After the methylene chloride solution had been dried over magnesium sulfate and been evaporated to dryness, the residue was crystallized from methylene chloride–methanol to give 8.96 g (41%) of product **4c** as yellow needles: mp 135–137°; ν^{KBr} 1762 cm^{-1}, no absorption for OH; λ_{max}^{EtOH} 243 mμ (ϵ 22,800), 258 (s, 15,000), 277 (13,400), 353 (12,600); nmr δ 5.12 (s, 2 H, $PhCH_2O$), 5.17 (s, 2 H, CH_2O), 6.15 (d, J = 7.5 Hz, 1 H, CH=CHN), 7.3 (m, 6 H, PhH), 7.8 (d, J = 7.5 Hz, 1 H, CH=CHN).

Anal. Calcd for $C_{31}H_{23}NO_4$: C, 78.63; H, 4.90; N, 2.96. Found: C, 78.63; H, 4.87; N, 2.93.

5,6-Dihydro-1-phenyl-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5).—A solution of 0.52 g (2 mmol) of **4a** in 10 ml of tetrahydrofuran and 10 ml of glacial acetic acid was hydrogenated over 50 mg of platinum oxide until about 2 mmol of hydrogen had been absorbed. The catalyst was filtered off and the solvents were evaporated under vacuum. The residue was crystallized first from methanol and then from ethyl acetate, yielding 0.32 g (62%) of **5**, mp 155–157°.

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 79.63; H, 7.94; H, 5.80. Found: C, 79.56; H, 8.09; N, 5.95.

(10) F. D. Popp, L. E. Katz, C. W. Klinowski, and J. M. Wefer, *J. Org. Chem.*, **33**, 4447 (1968). These authors prepared this compound in 13% yield from the Reissert compound derived from ethyl chloroformate and benzaldehyde.

(11) Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded with a Beckman grating spectrophotometer, Model 521, ultraviolet spectra were recorded with a Beckman Model DK-1A1, and the nmr spectra were determined on a Varian A-60 spectrophotometer with TMS as the internal standard.

(12) J. Weinstock and V. Boekelheide, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 641.

(13) H. S. Mahal, H. S. Roi, and K. Venkataraman, *J. Chem. Soc.*, 866 (1935).

1-Benzoyl-1,2,3,4-tetrahydroisoquinoline (6).—A solution of 0.238 g (1.0 mmol) of **5** and 0.250 g (4.5 mmol) of potassium hydroxide in 10 ml of absolute ethanol was allowed to reflux under nitrogen until thin layer chromatography no longer indicated the presence of **5** (about 2 hr). The volume was reduced to 2 ml and 5 ml of 10% aqueous hydrochloric acid was added. The volume was again reduced to about 5 ml and the hot solution was set aside. The resulting salt was recrystallized from water, yielding 0.205 g (86%) of **6**, mp 184–186° dec.

Anal. Calcd for $C_{16}H_{16}NOCl$: C, 70.19; H, 5.89; N, 5.12. Found: C, 69.85; H, 5.92; N, 4.91.

Phenyl-1-(1,2,3,4-tetrahydroisoquinolyl)methanol (1a).—A solution of 0.52 g (2 mmol) of **4a** in 5 ml of tetrahydrofuran and 10 ml of glacial acetic acid was hydrogenated over 50 mg of platinum oxide until hydrogen uptake ceased. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in 5 ml of trifluoroacetic acid and 2 ml of water. The solution was refluxed until no hydrogenation product was visible on thin layer chromatography. The solvent was removed and the residue was warmed with 10% sodium carbonate and extracted into ether. The ether was evaporated and the residue was crystallized twice from hexane to give 0.32 g (69%) of product, mp 90–93°.

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.53; H, 7.27; N, 6.08. Found: C, 80.30; H, 7.16; N, 5.85.

3,4-Dimethoxyphenyl-1-(1,2,3,4-tetrahydroisoquinolyl)methanol Hydrochloride (1b HCl).—A solution of 0.64 g (2 mmol) of **4b** in 10 ml of tetrahydrofuran and 10 ml of glacial acetic acid was hydrogenated over 60 mg of platinum oxide until about 4 mmol of hydrogen had been absorbed. The catalyst was filtered and the solvent was evaporated to dryness. The residue was dissolved in 5 ml of trifluoroacetic acid and 1 ml of water and allowed to reflux until thin layer chromatography indicated complete hydrolysis. The solvent was evaporated to about 2 ml and the residue was taken up in 5 ml of 10% aqueous hydrochloric acid. The product was recrystallized from water, yielding 4.7 g (70%) of **1b** HCl, mp 219–221° dec.

Anal. Calcd for $C_{18}H_{22}NO_3Cl$: C, 64.37; H, 6.60; N, 4.17. Found: C, 64.46; H, 6.80; N, 4.08.

1-[3,4-Bis(benzyloxy)phenyl]-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (7c).—A solution of 5.0 g of 1-(3,4-dibenzyloxyphenyl)-3*H*-oxazolo[4.3-*a*]isoquinolin-3-one (**4c**) in 25 ml of tetrahydrofuran and 25 ml of acetic acid was hydrogenated over 0.5 g of platinum oxide at 60 psi for 32 hr. The catalyst was filtered off and the filtrate was evaporated to dryness under vacuum. The residue was dissolved in ether and the solution was thoroughly washed with aqueous bicarbonate and saturated salt solution. The ether solution was dried over magnesium sulfate, evaporated to about 10 ml, and allowed to deposit 4.3 g of solid, which was recrystallized from ethyl acetate to give 3.75 g (74%) of **7c**: mp 139–149°; ν^{KBr} 1740 cm^{-1}; nmr ($CDCl_3$) δ 2.5–3.2 (m, 3, H, $PhCH_2CH_2$ and $CH_2CH_1H_aN$), 4.1 (m, 1 H, $CH_2CH_1H_aN$), 4.84 (s, 2 H, PhCHO), 4.98 (s, 2 H), PhCHO), 5.25 [d, J = 9 Hz, 1 H, PhCH[CH)N], 5.74 [d, J = 9 Hz, 1 H, PhCH(CH)O], 6.52–6.91 (m, 6 H, PhH), 7.34 (s 10 H, PhH), 6.64 (s, 1 H).

Anal. Calcd for $C_{31}H_{27}NO_4$: C, 77.97; H, 5.70; N, 2.93. Found: C, 77.96; H, 5.71; N, 2.84.

1-3,4-(Dihydroxyphenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo-[4,3-*a*]-isoquinolin-3-one Cyclic Carbonate (7e).—A solution of 9.42 g (19.7 mmol) of **7c** in 75 ml of tetrahydrofuran was hydrogenated over 5 g of 10% Pd on carbon. The hydrogenation was stopped after the uptake of about 40 mmol of hydrogen (about 2 hr). The catalyst was filtered and the filtrate was treated with 40 ml of pyridine. The solution was cooled to 5° and phosgene was added until a distinct yellow color developed. The solution was poured into ice and dilute hydrochloric acid and extracted with methylene chloride. The organic filtrates were washed, dried, and evaporated until crystallization occurred. Ethyl acetate was added to complete the crystallization, yielding 3.28 g (51%) of **7e**, mp 189–192°.

Anal. Calcd for $C_{18}H_{13}NO_5$: C, 66.64; H, 4.10; N, 4.23. Found: C, 66.87; H, 4.05; N, 4.33.

3,4-Dihydroxyphenyl-1-(1,2,3,4-tetrahydroisoquinolyl)carbinol Hydriodide (1c HI).—To a solution of 0.86 g (2.7 mmol) of **7e** in 5 ml of trifluoroacetic acid was added 5 ml of water. The solution was allowed to reflux gently until the volume was reduced to 5 ml. Dilution with 5 ml of water and refluxing was repeated and to the warm solution was added 1 ml of 50% hydriodic acid and charcoal. The solution was filtered and set aside to cool, yielding 0.56 g (60%) of **1c**, mp 139–141° dec.

Anal. Calcd for $C_{16}H_{18}NO_3I \cdot H_2O$: C, 46.05; H, 4.83; N, 3.36. Found: C, 46.23; H, 4.80; N, 3.40.

3,4-Dimethoxyphenyl-1-isoquinolyl Ketone (2a).—To a hot solution of 5 g (12.5 mmol) of **3c**[7] in 50 ml of alcohol was added a solution of 1.75 g (43.8 mmol) of sodium hydroxide in 100 ml of water. The solution was heated on a steam bath for 6 hr, partially evaporated to remove the ethanol, and allowed to cool to room temperature. The oil which separated was extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated. The oily residue was dissolved in 60 ml of glacial acetic acid and a solution of 2.0 g (6.6 mmol) of sodium dichromate dihydrate in 20 ml of glacial acetic acid was slowly added. The solution was allowed to stand for 5 min at room temperature, then it was heated on a steam bath for 5 min. When the solution had been cooled to room temperature, 10 ml of methanol was added. The solvent was removed under reduced pressure and to the resulting gum was added 5 ml of concentrated hydrochloric acid and 20 ml of water. The acid solution was treated with aqueous ammonium hydroxide until the pH was about 5. The brownish gummy solid which precipitated from the solution was filtered and washed with water. The solid was redissolved in 5 ml of concentrated hydrochloric acid with 10 ml of water, treated with charcoal, and filtered. The aqueous filtrate was treated with aqueous ammonium hydroxide until crystallization ensued at about pH 2. After the product was collected and washed with water and methanol, 2.65 g (72%) of **2a** was obtained, mp 145–147°. An analytical sample was prepared by recrystallization from ethanol, mp 145–146°.

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.76; H, 5.26; N, 4.66.

1-Isoquinolyl-3,4-dihydroxyphenyl Ketone (2b).—One gram of 3,4-dimethoxyphenyl-1-isoquinolyl ketone (**2a**) was dissolved in 25 ml of dry methylene chloride. The solution was placed under a nitrogen atmosphere and 0.9 ml of boron tribromide was added dropwise. A vigorous reaction ensued and the solution turned a dark purple color. The mixture was stirred for 6 hr at room temperature. The excess boron tribromide was destroyed by the cautious addition of 20 ml of water, whereupon the purple color was discharged to give an orange-yellow solution.

The methylene chloride was removed by evaporation on a steam bath. The solids which had precipitated were brought into isolation by the addition of 10 ml of methanol. The hot solution was treated with charcoal and filtered, and the methanol was removed by distillation. The hot aqueous solution was treated with a saturated solution of ammonium acetate to reduce the pH to about 3. The resulting pale yellow crystals were collected and washed with water and finally with methanol to give 0.71 g (78%) of **2b**, mp 257–262° dec.

Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.31; H, 4.25; N, 4.83.

1-Isoquinolyl-3,4-dihydroxyphenyl Ketone Cyclic Carbonate (2c).—Diphenyl carbonate (6 g, 28 mmol) and 3,4-dihydroxyphenyl-1-isoquinolyl ketone (**2b**) (3.8 g, 14 mmol) were fused at 200° under a stream of nitrogen for 45 min. The melt was allowed to cool and the resulting glass was crushed with ether. The solid was filtered, washed with ether, and dissolved in chloroform. The hot chloroform solution was treated with charcoal, filtered, and reduced to a volume of about 10 ml. The resulting crystals were collected and washed with a little chloroform to give 2.96 g (71%) of **2c**, mp 165–167°.

Anal. Calcd for $C_{17}H_9NO_4$: C, 70.10; H, 3.12; N, 4.81. Found: C, 70.31; H, 3.25; N, 4.83.

Registry No.—**1a**, 39949-72-9; **1b** HCl, 39949-73-0; **1c** HI, 39949-74-1; **2a**, 39971-69-2; **2b**, 39949-75-2; **2c**, 39949-76-3; **3c**, 39971-70-5; **4a**, 17954-30-2; **4b**, 39949-78-5; **4c**, 39949-79-6; **5**, 39949-80-9; **6** HCl, 39949-81-0; **7c**, 39949-82-1; **7e**, 39949-83-2; phenyl-1-isoquinolylcarbinol, 10175-00-5; 2-benzoyl-1,2-dihydroisoquinaldonitrile, 844-25-7; 3,4-dibenzyloxybenzaldehyde, 5447-02-9; diphenyl carbonate, 102-09-0.