ported for the photolytic decomposition of dimethyl diazidomalonate and for the pyrolytic decompositions of 2,2-diazido- and 2-azido-2-aryl-1,3-indandiones. See respectively R. M. Moriarty and P. Serridge, *J. Amer. Chem. Soc.*, **93**, 1534 (1971), and H. W. Moore and D. S. Pearce, *Tetrahedron Lett.*, 1621 (1971).
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(12) L. R. Caswell, D. C. Yung, H. G. Reid, C. J. Linn, C. E. Ryan, and C. A. Davidson, *J. Heterocycl. Chem.*, **7**, 1205 (1970).
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(15) H. W. Moore, H. R. Shelden, and W. Weyler, Jr., *Tetrahedron Lett.*, 1243 (1969).
(16) D. S. Pearce and H. W. Moore, unpublished data.
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(18) R. Gaertner, *J. Amer. Chem. Soc.*, **76**, 6150 (1954).
(19) No C≡N absorption was detected for this compound. This is not unexpected, particularly for acetoxy cyanohydrins. See L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1959, p 266.

A Synthetic Approach to Aporphine Alkaloids. A New Tetracyclic Benzodiazepine Derivative from the Benzyne Cyclization of a Bromophenolic 1-Benzyltetrahydroisoquinoline

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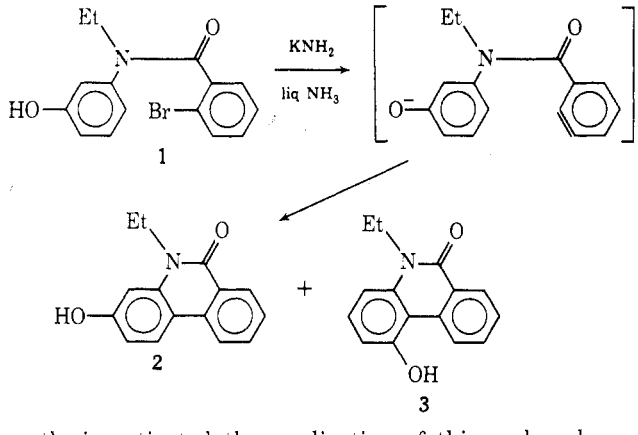
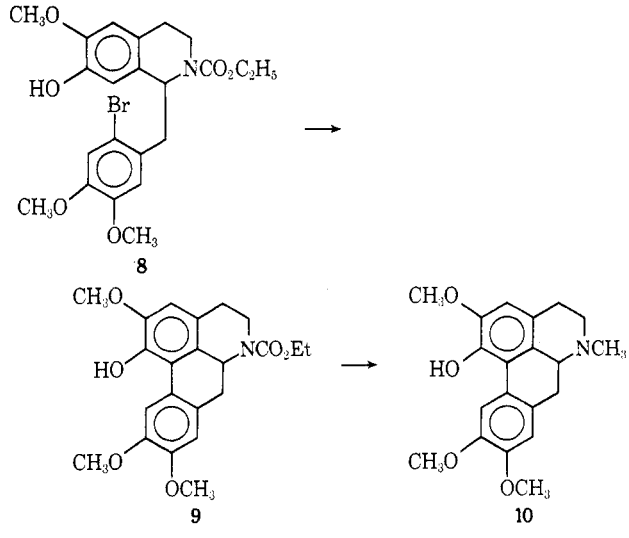
The synthesis of aporphine alkaloids by the benzyne reaction of bromophenolic 1-benzyltetrahydroisoquinolines containing a carbethoxy protecting group on the isoquinoline nitrogen was examined. The benzyne reaction of 1-(2′-bromo-4′,5′-dimethoxybenzyl)-2-carbethoxy-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (8) gave a new tetracyclic benzylisoquinoline derivative, 17, in good yield. Aryl-aryl coupling *via* intramolecular attack of phenoxide on the intermediate aryne to give the *N*-carbethoxynoraporphine 9 was not observed. This process provides a useful new synthesis of certain benzodiazepines.

It is well established that a variety of nucleophiles readily add to benzyne. When the nucleophile is part of a side chain attached to the benzyne, the intramolecular nucleophilic addition results in ring closure; numerous demonstrations of this process have been described.[1] For example, Hey, Leonard, and Rees have shown that, when the nucleophile is the ambident phenoxide ion, its intramolecular nucleophilic addition results in an aryl-aryl coupling reaction (1 → 2 + 3).[2] Several groups[3-8] have recently investigated the application of this aryl-aryl coupling process to the synthesis of aporphine alkaloids[9] (*e.g.*, 5) from 1-benzyltetrahydroisoquinoline precursors (*e.g.*, 4) as shown in Scheme I, path a. In every case except one in which the yield of aporphine 5 is reported as "about 30% as estimated by tlc,"[6] only minor amounts of aporphine are obtained.[10] Competing with aporphine formation is the formation of morphinandienones (*e.g.*, 6) *via* para attack of the phenoxide on the aryne (Scheme I, path b), the formation of indolizine derivatives (*e.g.*, 7) by the attack of the nucleophilic isoquinoline nitrogen on the aryne (Scheme I, path c), and the formation of primary aromatic amines by the addition of ammonia to the aryne. In most cases the major cyclized products are the indolizine derivatives 7; in fact this general method provides a useful synthesis of indolizine derivatives.[11,12] Thus, if this process is to be a useful synthesis of aporphine alkaloids, the isoquinoline nitrogen must be protected during the cyclization reaction. In this paper we wish to describe the results of the reaction of urethane 8 with potassium amide–liquid ammonia; in 8 the isoquinoline nitrogen is no longer nucleophilic, indolizine formation is thus prevented, and we anticipated that synthetically useful yields of aporphine alkaloid precursors such as 9 might be obtained. After cyclization the *N*-carbethoxy noraporphines (*e.g.*, 9) can be readily converted to the desired aporphine alkaloids (*e.g.*, 10); this last step has also been used in other recent aporphine syntheses.[9b,f]

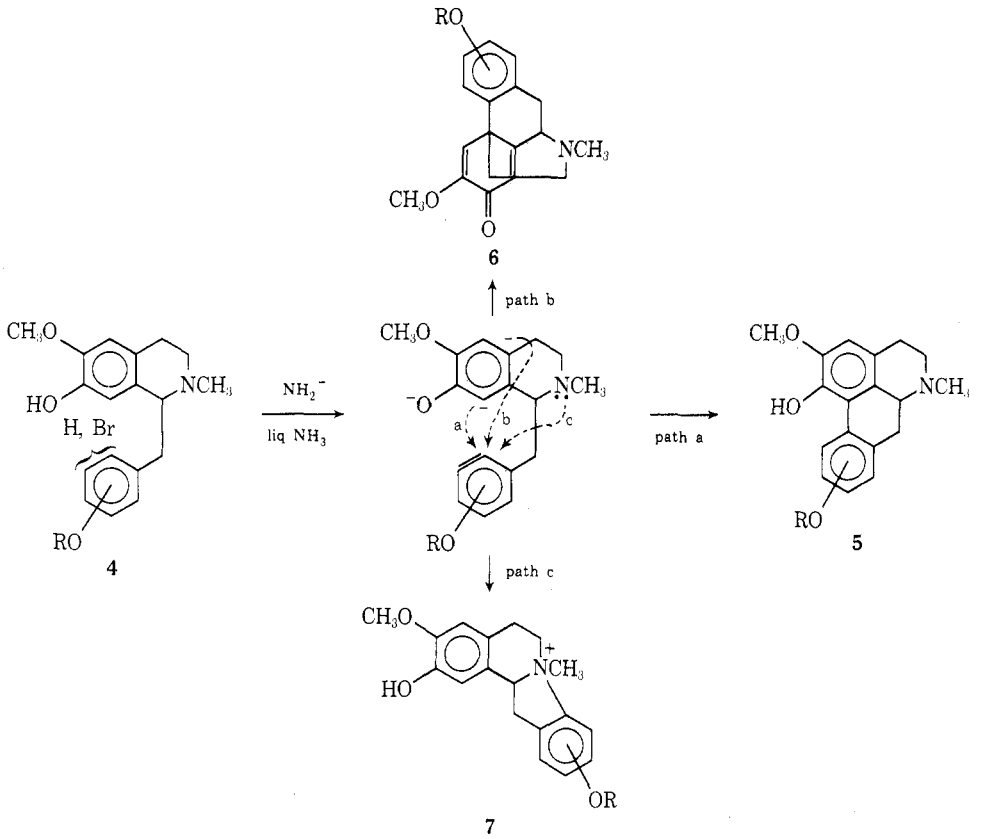




Results and Discussion

The required precursor 8 was synthesized as outlined in Scheme II. Thus heating the β-phenethylamine 11[13] with the phenylacetic ester 12[14] at 140–150° gave the amide 13 (70% yield), which was then readily converted to the hy-

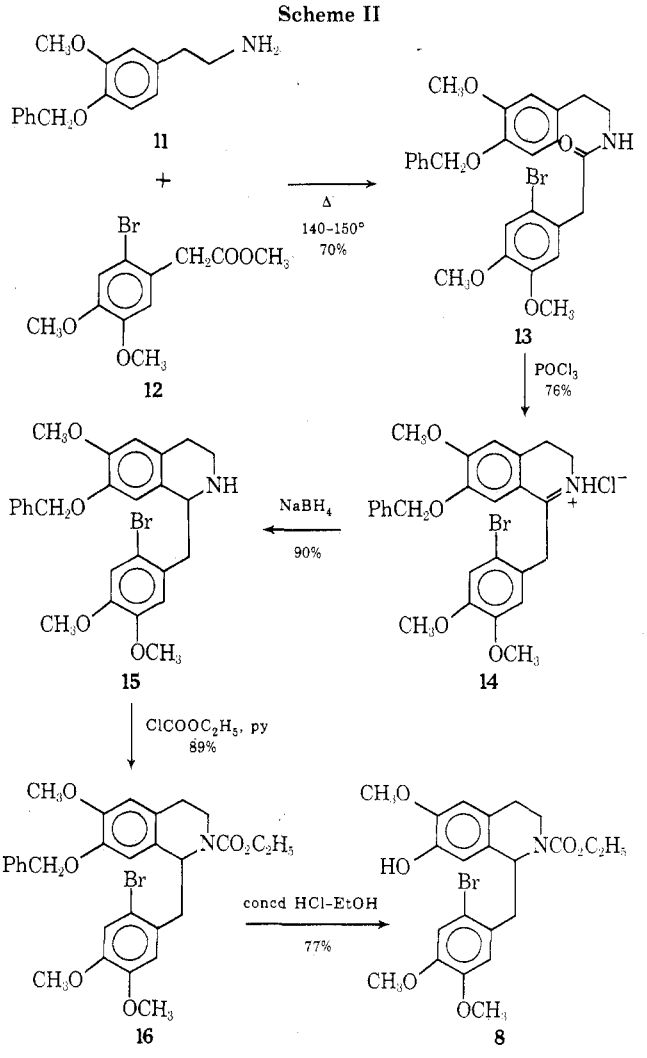
Scheme I

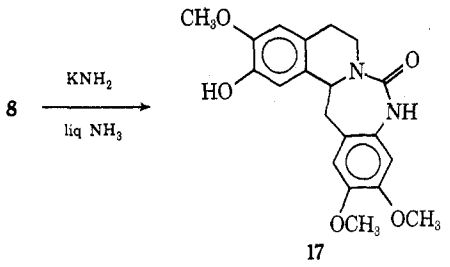


drochloride salt 14 in 76% yield upon treatment with phosphoryl chloride. Conversion of 14 to the tetrahydroisoquinoline 15 with sodium borohydride proceeded in 90% yield; treatment of 15 with ethyl chloroformate and pyridine gave the urethane 16 (90% yield), which was in turn debenzylated with concentrated hydrochloric acid to give the desired bromophenol 8 in 77% yield. The good yields obtained in this sequence further enhance the attractiveness of 8 as an aporphine precursor. All the compounds in Scheme II were fully characterized spectrally. Especially noteworthy are the nmr spectra of compounds 16 and 8. The benzyl ether 16 shows a complex multiplet instead of the expected triplet for the urethane methyl group and a broadened singlet for the methylene protons of the benzyl ether group. Urethane 8 shows a quintet centered at δ 1.10 rather than the expected triplet for the urethane methyl group. We attribute these effects to the existence of 16 and 8 in more than one conformation. The quintet at δ 1.10 in the spectrum of 8 can be attributed to the existence of two conformations, resulting in two overlapping triplets which appear as a quintet. The peak areas of the quintet show that the two conformers of 8 are present in a ratio of about 1:3. Dalton and coworkers have described in detail the conformational analysis of similar tetrahydroisoquinolines.[15,16]

The reaction of 8 with potassium amide in liquid ammonia did not give the expected aporphine derivative 9 but instead gave a 74% yield of the white, crystalline urea 17, which was obtained nearly pure directly from the reaction mixture. After removal of urea 17 from the reaction mixture the residue was examined for the presence of the aporphine derivative 9. None of the aporphine derivative 9 could be detected by comparing the tlc behavior and nmr spectrum of the residue with those of an authentic sample of 9. Authentic 9 was prepared by the ultraviolet irradiation of 8 and sodium hydroxide in aqueous methanol. We have described the preparation of a number of aporphine alkaloids by this method.[9c,17]

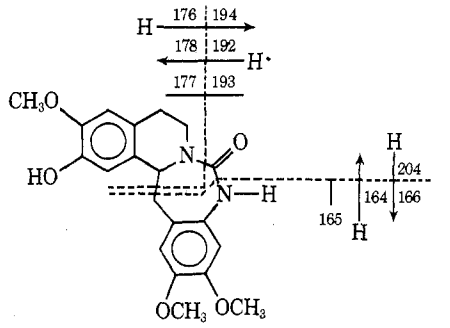
Scheme II





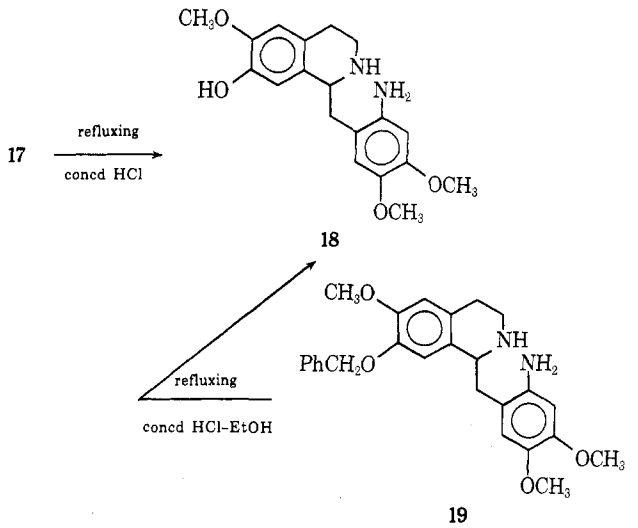
17

The structure assignment of **17** follows from its spectral properties and its acid hydrolysis product. The complete high-resolution mass spectrum of **17** was especially helpful. Thus the elemental composition of **17** was established as $C_{20}H_{22}N_2O_5$, also in accord with the elemental analysis. The most useful fragmentations were those resulting in cleavage of the doubly benzylic carbon-carbon bond and one of the carbonyl to nitrogen linkages of the urea group. These fragments, which are shown below, are clearly indicative of the cyclic urea structure of **17**. Fragmentations leading to $M\cdot^+ - CH_3$, $M\cdot^+ - CO$, $M\cdot^+ - CHO$, $M\cdot^+ - CONH_2$, and secondary fragmentations account for the majority of the remaining peaks. The nmr spectrum of **17** shows the six methylene protons as a mul-



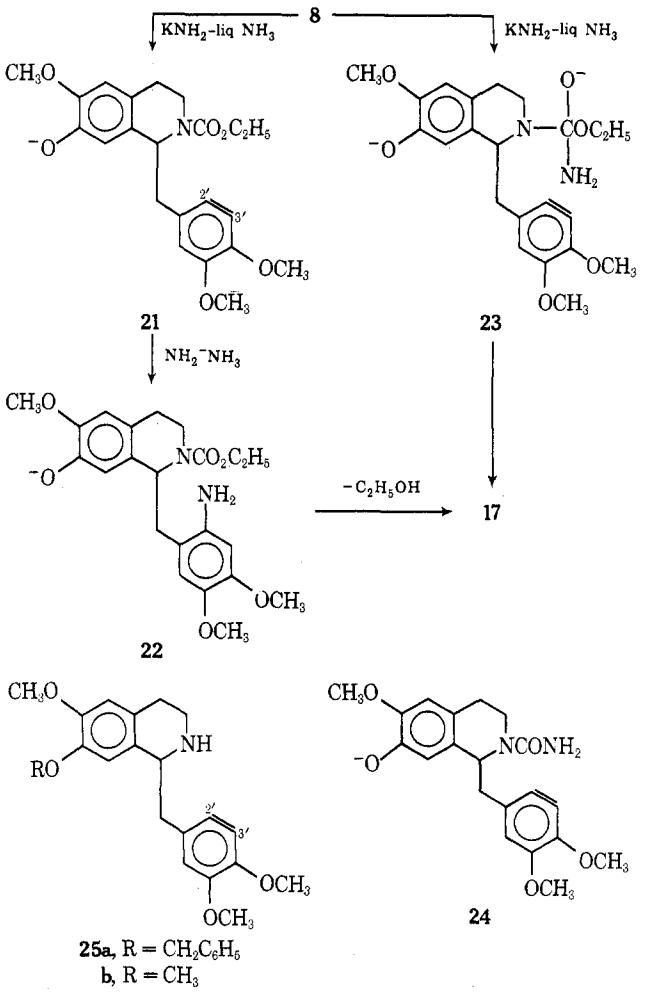
17

tiplet at δ 2.49–3.81, the benzylic methine proton as a multiplet at δ 5.00, the three methoxy groups at δ 3.83, 3.85, and 3.91, the NH proton as a very broad peak at δ 5.56, the phenolic proton slightly broadened at δ 6.44, and the four aromatic protons as singlets at δ 6.33, 6.57, 6.67, and 6.79. The nmr spectrum also shows that the ethyl group present in the urethane **8** is not present in **17**. The infrared spectrum is likewise consistent with structure **17**, showing multiple OH and NH absorptions in the 3100–3500-cm^{-1} region and a carbonyl stretching band at 1660 cm^{-1} which is consistent with the presence of a urea group.[18] Acid hydrolysis of **17** gave the benzylisoquinoline **18**, which was identical with a sample of **18** prepared by



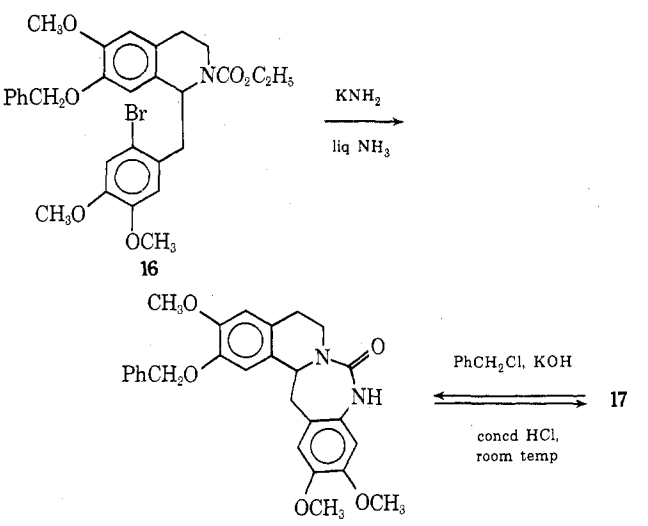
19

Scheme III



the debenzylation of the known **19**.[12] The benzyl ether **19** was prepared by the action of sodium amide–liquid ammonia on **15**, as described by Kametani and Ogasawara;[12] the ir and nmr spectra of **19** were identical with the reference spectra provided to us by these workers.

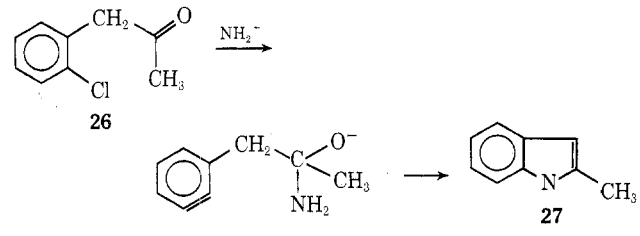
Thus even in the presence of the *N*-carbethoxy blocking group aryl–aryl coupling *via* intramolecular attack of the phenoxide ion on the intermediate aryne is not a facile process and the desired aporphine derivative **9** is not obtained; the phenoxide ion apparently plays no active role in the formation of urea **17**. To test this latter hypothesis we also allowed the benzyl ether **16** to react with potassi-



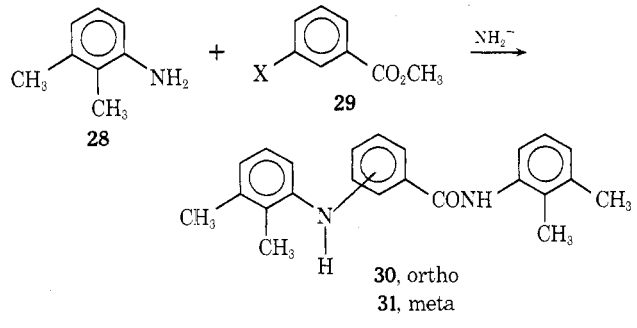
20

um amide in liquid ammonia. The reaction proceeded smoothly and gave a 75% yield of the benzyl ether **20**. Debenzylation of **20** with hydrochloric acid gave **17** and benzylation of **17** gave **20**. These interconversions and its spectral properties (see Experimental Section) secure our structure assignment of **20**. The cyclic ureas **17** and **20** constitute a new class of tetracyclic benzodiazepine derivatives. This cyclization reaction provides a useful new synthesis of certain benzodiazepines.

Two routes to the unexpected ring closure product **17** can be envisioned (Scheme III).[19] One involves the addition of amide ion to the aryne intermediate **21**, producing **22**, which then closes to **17** with loss of ethanol. The addition of amide ion to the 2′ position rather than the 3′ position of the benzyl group of **21** is in accord with Hoffmann's discussion of substituent effects[20] and the observation that the related aryne **25a** undergoes addition of amide ion at the 2′ position.[12] The other route involves the formation of **23**, which then closes to **17**. Urea **24** is a less likely intermediate in that Bunnett, *et al.*, has shown that carboxamides (or carboxamide anions) are usually poor nucleophiles toward arynes.[21] Analogy for the type of ring closure described here is found in the potassium amide initiated closure of *o*-chlorophenylacetone (**26**) to 2-methylindole (**27**)[19] and in the benzyne reaction of 2,3-



xylidine (**28**) with methyl *m*-halobenzoates (**29**) to give the benzamides **30** and **31**.[22]



The failure of this reaction to produce the desired aporphine derivative **9** cannot be due to the low nucleophilicity of phenoxide ion *vs.* external amide ion toward arynes in that Hey, Leonard, and Rees have provided several examples of the efficient intramolecular attack of phenoxide on an aryne.[2] Failure is most likely due to the fact that the primary amino group in intermediate **23** is a much better nucleophile than the phenoxide anion and therefore adds much more rapidly to the aryne.[23] Analogously external oxygen nucleophiles (including phenoxide) cannot compete with potassium amide–liquid ammonia for benzyne.[24] The conformation of **21** and/or **23** may play a smaller role in determining the mode of cyclization. Conformation has been discussed with regard to similar aryne cyclizations[24] and could also be in part responsible for the 68% yield of indolizine derivative obtained from the aryne **25b**.[12] Conformation is known to be important in the synthesis of aporphine alkaloids by the Pschorr cyclization reaction.[25]

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed at the University of Idaho with a Perkin-Elmer 240 elemental analyzer. Infrared (ir) spectra were determined with a Perkin-Elmer 621 or 237B spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained in $CDCl_3$ with TMS as internal standard using a Varian Model A-60 or HA-100 spectrometer. Ultraviolet (uv) spectra were taken with a Perkin-Elmer Model 202 spectrometer. Low-resolution mass spectra were obtained at 70 eV using a Hitachi Perkin-Elmer RMU-6E mass spectrometer. The high-resolution mass spectra were obtained at Stanford University using a MAT 711 mass spectrometer, and at Cornell University. Column chromatography employed either neutral aluminum oxide, activity grade I (M. Woelm, Eschwege, Germany) or silica gel (30–70 mesh ASTM; E. Merck, Darmstadt, Germany). Analytical thin layer chromatography (tlc) employed precoated sheets of aluminum oxide (F-254, neutral, Type T, 0.20 mm thick) or silica gel (F-254, 0.25 mm thick) on aluminum (E. Merck, Darmstadt, Germany).

***N*-(4-Benzyloxy-3-methoxy-β-phenethyl)-2-(2′-bromo-4′,5′-dimethoxyphenyl)acetamide (13).** A stirred mixture of 4-benzyloxy-3-methoxy-β-phenethylamine (**11**,[13] 24.5 g, 88.5 mmol) and methyl 2-bromo-4,5-dimethoxyphenylacetate (**12**,[14] 30.4 g, 118.5 mmol) was heated at 140–150° in an oil bath for 12 hr. The dark brown solid which formed upon cooling the mixture was recrystallized from benzene–*n*-hexane to give light tan crystals of acetamide **13** (31.7 g, 69.7%): mp 158–160° (lit.[12] mp 160–162°); ir (film) 3280, 3040, 2900, 1640, 1585, 1568, 1535, 1500, 1450, 1430, 1410, 1375, 1330, 1250, 1215, 1160, 1140, 1030, 1010, 965, 915, 850, 825, 800, 765, 740, and 695 cm^{-1}; nmr δ 2.71 (t, 2 H, J = 7 Hz, CH_2CH_2NHCO–), 3.23–3.73 (m, 2 H, CH_2CH_2NH), 3.58 (s, 2 H, $NHCOCH_2$), 3.85 (s, 9 H, OCH_3), 5.14 (s, 2 H, $OCH_2C_6H_5$), 5.60 (broad s, 1 H, NH), 6.47–6.95 (m, 4 H, ArH), 7.02 (s, 1 H, ArH), and 7.39 (s, 5 H, $OCH_2C_6H_5$); mass spectrum *m/e* (rel intensity) 515 (2), 513 (2), 434 (3), 424 (<1), 422 (<1), 240 (40), 231 (10), 229 (10), 194 (2), 151 (6), 150 (7), 149 (21), 137 (23), 134 (6), and 91 (100).

7-Benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline Hydrochloride Monohydrate (14·H_2O). Acetamide **13** (39.6 g, 77.1 mmol) was dissolved with heating in 500 ml of dry benzene, and phosphoryl chloride (50.0 ml, 0.574 mol) was slowly added. After the mixture was refluxed for 4 hr, the benzene was evaporated, giving a dark oil which crystallized upon stirring and cooling externally in an NaCl–ice bath. The yellow crystals of crude isoquinoline hydrochloride were washed with hot *n*-hexane (3 × 100 ml) and recrystallized from 95% ethanol, giving **14**·H_2O (32.2 g, 76.0%) as pale yellow needles: mp 207–210° dec (lit.[12] mp 217–218° dec); ir (film) 2900 (broad), 1640, 1600, 1550, 1450, 1430, 1410, 1370, 1330, 1295, 1290, 1270, 1210, 1150, 1100, 1070, 1030, 975, 860, 805, 750, and 695 cm^{-1}; nmr δ 3.12 (t, 2 H, J = 7 Hz, 4-H_2), 3.80–4.50 (m, 3 H, 3-H_2 and $^+C{=}NH$), 3.85 (s, 6 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.74 (broad s, 2 H, methylene protons of 1-benzyl group), 5.10 (s, 2H, $OCH_2C_6H_5$), 6.89 (s, 1 H, ArH), 7.02 (s, 1 H, ArH), 7.09 (s, 1 H, ArH), and 7.37 (s, 6 H, $OCH_2C_6H_5$ and one ArH); mass spectrum *m/e* (rel intensity) 497 (<1), 495 (<1), 416 (44), 326 (15), 325 (58), 324 (21), 310 (16), 296 (23), 295 (11), 294 (26), 282 (7), 281 (5), 280 (8), 267 (6), 266 (9), 265 (6), 231 (<1), 229 (4), and 91 (100).

7-Benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (15).[12] Sodium borohydride (2.50 g, 65.8 mmol) was added portionwise at room temperature to a stirred solution of 7-benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride monohydrate (**14**·H_2O, 3.38 g, 6.14 mmol) in methanol (40 ml) and water (5 ml). Stirring was maintained for 0.5 hr followed by refluxing for an additional 1 hr. Evaporation of the methanol gave a white, solid residue which was suspended in water (30 ml) and then extracted with chloroform (5 × 20 ml). The chloroform extracts were washed with water (15 ml), dried (K_2CO_3), and evaporated, giving a clear pale yellow gum (3.2 g), which was then dissolved in a minimal amount of hot 95% ethanol. The solution was cooled and crystallization was induced by scratching the vessel wall, giving 2.77 g (90.6%) of colorless bromotetrahydroisoquinoline **15**: mp 120–120.5°; ir (KBr) 3410 (broad), 2920, 2830, 1600, 1510, 1463, 1455, 1438, 1425, 1381, 1373, 1324, 1301, 1257, 1216, 1165, 1120, 1022, 985, 951, 855, 800, 780, 730, 692, and 600 cm^{-1}; nmr δ 1.63 (broad s, 1 H, NH), 2.50–3.50 (m, 6 H, 3-H_2, 4-H_2, methylene protons of 1-benzyl group), 3.80 (s, 3 H, OCH_3), 3.82

(s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.00–4.34 (m, 1 H, 1-H), 5.09 (s, 2 H, $OCH_2C_6H_5$), 6.61 (s, 1 H, ArH), 6.73 (s, 1 H, ArH), 6.77 (s, 1 H, ArH), 7.03 (s, 1 H, ArH), and 7.20–7.56 (m, 5 H, $OCH_2C_6H_5$); mass spectrum *m/e* (rel intensity) 499 (<1), 498 (<1), 497 (<1), 496 (<1), 417 (2), 416 (5), 326 (1), 268 (100), 231 (2), 229 (2), 177 (23), 176 (9), 148 (14), and 91 (15).

7-Benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-2-carbethoxy-1,2,3,4-tetrahydro-6-methoxyisoquinoline (16). A solution of the isoquinoline **15** (2.5 g, 5.02 mmol) and pyridine (5.0 ml) in chloroform (60 ml) was chilled in ice water and stirred while ethyl chloroformate (5.0 ml, 63 mmol) was added dropwise. Upon completion of the addition, the solution was stirred for 10 min more at room temperature, heated for 5 min on a steam bath, and evaporated, giving an opaque, pale yellow residue. The residue was suspended in water (300 ml), extracted with ether (4 × 50 ml), and washed successively with 1.2 *N* hydrochloric acid (50 ml), 5% sodium bicarbonate (50 ml), and water (50 ml). Drying (Na_2SO_4) and evaporation of the ether gave a pale yellow gum (3.16 g) which was crystallized from 95% ethanol, giving white crystals of the carbethoxyisoquinoline **16** (2.55 g, 89.3%): mp 113–114°; ir (KBr) 2940, 2910, 2840, 1692, 1605, 1505, 1465, 1440, 1425, 1382, 1330, 1310, 1260, 1240, 1228, 1218, 1200, 1165, 1116, 1100, 1095, 1027, 990, 970, 950, 855, 800, 759, 740, and 698 cm^{-1}; nmr δ 0.78–1.39 (m, 3 H, $COOCH_2CH_3$), 2.45–4.40 (m, 8 H, 3-H_2, 4-H_2, methylene of 1-benzyl group, $COOCH_2CH_3$), 3.76 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.07 (broad s, 2 H, $OCH_2C_6H_5$), 5.32 (m, 1 H, 1-H), 6.33–6.83 (m, 2 H, ArH), 6.64 (s, 1 H, ArH), 7.02 (s, 1 H, ArH), and 7.38 (s, 5 H, $OCH_2C_6H_5$); mass spectrum *m/e* (rel intensity) 571 (<1), 569 (<1), 340 (100), 312 (10), 249 (6), 231 (3), 229 (3), 221 (8), 220 (4), 205 (3), 204 (3), 177 (7), 176 (10), 148 (7), and 91 (30).

Anal. Calcd for $C_{29}H_{32}BrNO_6$: C, 61.05; H, 5.66; N, 2.46. Found: C, 60.86; H, 5.51; N, 2.39.

1-(2′-Bromo-4′,5′-dimethoxybenzyl)-2-carbethoxy-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (8). A mixture of the benzyloxyisoquinoline **16** (1.0 g, 1.8 mmol) and concentrated hydrochloric acid–95% ethanol (10 ml, 1:1 v/v) was refluxed for 2 hr and the ethanol was then removed by rotary evaporation. The remaining aqueous layer was extracted with chloroform (3 × 50 ml). The extracts were washed with water (100 ml), dried (Na_2SO_4), and evaporated, leaving a pale yellow gum which yielded a white solid upon addition of ether. Recrystallization from ethanol–ether gave colorless needles of isoquinoline **8** (0.65 g, 77%) which were dried overnight at 60° (0.02 mm): mp 123–126°; ir (KBr) 3580, 3350 (broad), 2970, 2935, 2840, 1670, 1645, 1600, 1510, 1483, 1465, 1445, 1382, 1336, 1311, 1262, 1238, 1220, 1167, 1105, 1030, 1000, 983, 970, 951, 872, 860, 808, and 765 cm^{-1}; uv λ_{max} (MeOH) 290 nm (ϵ 7000), 233 (14,400) and 211 (43,700); nmr δ 1.10 (apparent quintet, 3 H, distance between peaks = 7 Hz, $COOCH_2CH_3$), 2.42–4.48 (m, 8 H, 3-H_2, 4-H_2, $COOCH_2CH_3$, methylene protons of 1-benzyl group), 3.75 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.76–6.07 (broad m, 2 H, 1-H, ArOH), 6.17, 6.53, 6.79, and 6.96 (all s, 4 H, ArH); mass spectrum *m/e* (rel intensity) 481 (<1), 479 (<1), 434 (<1), 406 (<1), 399 (<1), 398 (<1), 250 (100), 235 (3), 231 (4), 229 (4), 222 (36), 206 (5), 191 (9), 178 (23), 177 (6), 176 (8), 163 (17), and 162 (8).

Anal. Calcd for $C_{22}H_{26}BrNO_6$: C, 55.01; H, 5.46; N, 2.92. Found: C, 55.03; H, 5.48; N, 2.97.

***N*-Carbethoxy-1-hydroxy-2,9,10-trimethoxynoraporphine (9).** A stirred solution of the bromophenolic isoquinoline **8** (203 mg, 0.423 mmol), sodium hydroxide (200 mg, 5.0 mmol), methanol (9 ml), and water (1 ml) in a quartz vessel was purged with nitrogen for 15 min and irradiated under nitrogen for 24 hr with an Ultraviolet Products Model PCQ-X1 low-pressure mercury lamp. The methanol was removed on a rotary evaporator and the brown aqueous solution was diluted with 5% aqueous sodium hydroxide solution (40 ml). After the basic solution was made ammoniacal with an excess of ammonium chloride, the resulting suspension was extracted with ether (10 × 25 ml). The extracts were washed with water (2 × 10 ml), dried (Na_2SO_4), and evaporated, yielding an orange-yellow film (141 mg) containing the noraporphine **9**. The crude noraporphine was purified by column chromatography on neutral alumina (50 g), using ether [fractions 1–130 (each 2.5 ml)] and chloroform [fractions 131–134 (each 50 ml)]. Fractions 90–134 were combined and evaporated, giving a solid yellow film (35 mg) which was recrystallized twice from methanol, yielding the noraporphine **9** as pale yellow granules (13 mg, 7.7%): mp 108–109°; analytical tlc on neutral alumina using ether–chloroform–methanol (70:20:1 v/v/v) gave a single spot, R_f 0.73; ir ($CHCl_3$) 3520, 3035, 3000, 2965, 2940, 2915, 2850, 1675, 1605, 1580, 1510, 1440, 1390, 1340, 1300, 1280, 1255, 1180, 1155, 1120, 1110, 1090, 1025, 1010, 1000, 960, 945, 870, 855, 825, and 725 cm^{-1}; uv λ_{max} (MeOH) 306 nm (ϵ 23,300), 281 (20,000), and 224 (47,800); nmr δ 1.30 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.50–3.27 (m, 4 H, 4-H_2, 5-H_2), 3.50 (m, 2 H, 7-H_2), 4.07 (s, 9 H, OCH_3), 4.24 (quartet, 2 H, J = 7 Hz, $COOCH_2CH_3$), 4.50–5.00 (m, 1 H, 6a-H), 6.18 (s, 1 H, ArOH), 6.61 (s, 1 H, 8-H), 6.79 (s, 1 H, 3-H), and 8.15 (s, 1 H, 11-H); mass spectrum *m/e* (rel intensity) 399 (70), 371 (3), 370 (8), 354 (4), 311 (3), 310 (9), 298 (30), 297 (100), 283 (11), 268 (6), and 267 (13); high-resolution mass spectrum, *m/e* 399.1677 (calcd for $C_{22}H_{25}NO_6$, *m/e* 399.1682).

Cyclization of Bromophenolic Isoquinoline 8 with Potassium Amide in Liquid Ammonia. A three-necked, 100-ml, round-bottomed flask equipped with a magnetic stirrer and surrounded by a pan was fitted with a Dry Ice condenser, a three-way stopcock gas inlet, and a glass stopper. The outlet of the Dry Ice condenser was protected by a potassium hydroxide drying tower. After the apparatus had been flamed dry under a stream of dry nitrogen gas and had cooled to room temperature, the condenser and pan were filled with Dry Ice and acetone. The nitrogen flow was discontinued and anhydrous ammonia gas (through KOH) was condensed into the flask until about 50 ml of liquid ammonia was collected. A gentle nitrogen flow and stirring was maintained while small pieces of potassium metal (391 mg, 10.0 mmol) were added to the liquid ammonia until a deep blue color persisted. *Ca.* 1 mg of ferric nitrate hydrate was then added to the liquid ammonia followed by the addition of the remaining potassium metal in small portions. About 15 min was required for the addition. After all the blue color had turned to a gray (*ca.* 3 hr later) the bromophenolic isoquinoline **8** (480 mg, 1.00 mmol) was added as a powder to the stirred potassium amide suspension; anhydrous ether was used to wash the last traces of powder into the flask. The Dry Ice pan was removed and the reaction mixture was refluxed for 3 hr. The excess potassium amide was destroyed by cautiously adding crystalline ammonium chloride (10 g). Replacement of the Dry Ice condenser with a water-cooled condenser permitted the liquid ammonia to evaporate, leaving a white residue to which water (30 ml) was added. Extraction of the mixture with chloroform (5 × 50 ml) gave a yellow solution which was washed with water (30 ml). Because crystals began forming on the sides of the flask after standing for a few minutes, the chloroform extracts were not dried but the solution was evaporated directly, giving a peach-colored, chalky solid (430 mg). The crude product was recrystallized twice by suspending the solid in refluxing chloroform (15 ml) and slowly adding 95% ethanol until all the solid dissolved. The solution was filtered hot and the filtrate was slowly evaporated on a steam bath until leaflets began to appear. After cooling, the colorless leaflets were collected by filtration to give 274 mg (74.0%) of **17**, mp 261–262° dec. A second recrystallization afforded 198 mg (53.5%) of **17**: mp 262–264° dec; ir ($CHCl_3$) 3540, 3410, 3320, 3220, 3100, 2930, 2840, 1660, 1605, 1525, 1518, 1440, 1420, 1272, 1237, 1120, 1088, 1015, and 841 cm^{-1}; uv λ_{max} (MeOH) 291 nm (ϵ 11.700), 247 (sh, 13,200), and 217 (42,400); nmr (TMS external standard) δ 2.49–3.81 (m, 6 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.00 (m, 1 H, methine proton), 5.56 (broad s, 1 H, NH), 6.33 (s, 1 H, ArH), 6.44 (s, 1 H, ArOH), 6.57 (s, 1 H, ArH), 6.67 (s, 1 H, ArH), and 6.79 (s, 1 H, ArH); mass spectrum *m/e* (rel intensity, formula) 370.15381 (74.2, $C_{20}H_{22}N_2O_5$), 369.14526 (4.2, $C_{20}H_{21}N_2O_5$), 355.12915 (2.6, $C_{19}H_{19}N_2O_5$), 354.13184 (1.2, $C_{20}H_{20}NO_5$), 342.15820 (6.6, $C_{19}H_{22}N_2O_4$), 341.15063 (1.2, $C_{19}H_{21}N_2O_4$), 326.13892 (2.9, $C_{19}H_{20}NO_4$), 204.06676 (1.7, $C_{11}H_{10}NO_3$), 194.07817 (12.3, $C_{10}H_{12}NO_3$), 193.07384 (86.7, $C_{10}H_{11}NO_3$), 192.06538 (9.5, $C_{10}H_{10}NO_3$), 178.08698 (100.0, $C_{10}H_{12}NO_2$), 178.05066 (14.1, $C_9H_8NO_3$), 177.07816 (21.4, $C_{10}H_{11}NO_2$), 176.07149 (35.5, $C_{10}H_{10}NO_2$), 166.08705 (14.6, $C_9H_{12}NO_2$), 165.07938 (1.0, $C_9H_{11}NO_2$), 164.06973 (5.5, $C_9H_{10}NO_2$), 163.06322 (23.7, $C_9H_9NO_2$), 162.05560 (7.8, $C_9H_8NO_2$), and 150.05641 (5.0, $C_8H_8NO_2$).

Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 6.00; N, 7.56. Found: C, 64.73; H, 6.06; N, 7.44.

Evaporation of the filtrates from compound **17** gave a black residue. A comparison of the nmr spectrum and tlc [neutral alumina; ether–chloroform–methanol (70:20:1 v/v/v)] of the black residue with those of the authentic noraporphine **9** showed that no noraporphine **9** was present in the residue.

Cyclization of Bromobenzyloxyisoquinoline 16 with Potassium Amide in Liquid Ammonia. Dropwise addition of a solution of bromoisoquinoline **16** (570 mg, 1.00 mmol) in dry tetrahydrofuran (5 ml) to a stirred suspension of potassium amide [prepared as above from potassium metal (391 mg, 10.0 mmol)] in liquid

ammonia (50 ml) produced a milky gray mixture which was refluxed for 3 hr under nitrogen. Cautious addition of solid ammonium chloride followed by evaporation of the liquid ammonia and tetrahydrofuran gave a white residue. Water (30 ml) was then added and the mixture was extracted with chloroform (5 × 50 ml). The extracts were washed with water (30 ml) and concentrated to 50 ml on a rotary evaporator. Addition of ether (100 ml) gave white crystals, which were filtered and dried at 110°, giving cyclic urea **20** (344 mg, 74.8%), mp 268–270° dec. Two recrystallizations from chloroform–petroleum ether (bp 30–60°) yielded 300 mg (65.2%) of colorless **20**: mp 271–272° dec; ir ($CHCl_3$) 3400, 3200, 2995, 2930, 2910, 2835, 1665, 1605, 1510, 1440, 1423, 1375, 1335, 1259, 1242, 1227, 1120, 1080, 1010, and 860 cm^{-1}; uv λ_{max} (MeOH) 288 nm (ε 5100), 248 (sh, 6800), and 208 (41,000); nmr δ 2.20–3.81 (m, 6 H, $CH_2CHNCH_2CH_2$), 3.84 (s, 6 H, OCH_3), 3.92 (s, 3 H, OCH_3), 5.00 (m, 1 H, methine proton), 5.14 (s, 2 H, $OCH_2C_6H_5$), 6.38 (s, 1 H, ArH), 6.53 (s, 1 H, ArH), 6.73 (s, 2 H, ArH), and 7.40 (s, 5 H, $OCH_2C_6H_5$) (the expected broad NH signal could not be detected because of limited sample solubility); mass spectrum *m/e* (rel intensity) 460 (80), 459 (5), 458 (5), 445 (5), 442 (2), 432 (10), 369 (20), 341 (2), 326 (7), 268 (48), 267 (32), 266 (23), 194 (10), 193 (76), 192 (19), 178 (27), 177 (37), 176 (56), 166 (25), 150 (9), 148 (28), and 91 (100).

Anal. Calcd for $C_{27}H_{28}N_2O_5$: C, 70.41; H, 6.13; N, 6.08. Found: C, 70.16; H, 5.93; N, 6.03.

Interconversion of Cyclic Ureas 17 and 20. A mixture of compound **17** (37 mg, 0.10 mmol), potassium hydroxide (17 mg, 0.30 mmol), benzyl chloride (28 mg, 0.22 mmol), water (1 drop), and 95% ethanol (2 ml) was refluxed for 15 hr. The white solid which formed was filtered, washed successively with 95% EtOH, water, and absolute ether, dried in air, and recrystallized from chloroform–petroleum ether to give **20** (26 mg, 57%), mp 270–271.5° dec, identical (ir, mass spectrum, tlc, mixture melting point) with that obtained above.

Stirring a mixture of compound **20** (30 mg, 0.065 mmol) in concentrated hydrochloric acid (10 ml) for 20 hr at room temperature under nitrogen produced a white precipitate, which was filtered, washed with water, and dried at 120° to give **17** (16 mg, 67%), mp 260–261°. The properties of this compound (tlc, mass spectrum, mixture melting point) were identical with that of compound **17** obtained from the reaction of **8** with potassium amide in liquid ammonia.

Acid Hydrolysis of Cyclic Urea 17. A mixture of compound **17** (100 mg, 0.271 mmol), water (2 ml), and concentrated hydrochloric acid (6 ml) were refluxed under nitrogen for 10 hr until all of the solid went into solution and no starting material remained, as shown by analytical tlc. After filtration, the cooled solution was diluted with water (20 ml) and washed with ether (3 × 50 ml). The acidic aqueous layer was made basic (pH ~10) with cold 6 *N* ammonium hydroxide and the resulting dark purple-black solution was extracted with ether (3 × 50 ml). The clear extracts were dried (Na_2SO_4) and evaporated, giving a pale yellow solid (31 mg) which was shown by tlc on alumina using chloroform–methanol (10:1 v/v) to be a complex mixture of products which were not identified.

The aqueous layer was then extracted with chloroform (8 × 30 ml). The black extracts were washed with water (20 ml), dried (Na_2SO_4), and evaporated, giving the aminoisoquinoline **18** as a black-green solid (50 mg, 54%): ir ($CHCl_3$) 3555, 3450 (broad sh), 3360 (broad), 3005, 2960 (sh), 2940, 2910 (sh), 2840, 1725 (broad), 1620, 1600, 1510, 1480, 1465, 1450, 1415, 1370, 1330, 1265, 1175, 1170, 1160, 1135, 1105, 1025, 1000, 865, 825, and 730 cm^{-1} (broad); nmr δ 2.40–3.46 (m, 6 H, 3-H_2, 4-H_2, and methylene protons of 1-benzyl group), 3.74 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.00–4.70 (m, 5 H, 1-H, NH, NH_2, ArOH), 6.30 (s, 1 H, ArH), 6.54 (s, 2 H, ArH), and 6.77 (s, 1 H, ArH); mass spectrum *m/e* (rel intensity) 382 (<1), 356 (<1), 355 (<1), 354 (<1), 344 (<1), 343 (<1), 342 (<1), 326 (<1), 325 (<1), 324 (<1), 313 (<1), 296 (<1), 295 (<1), 178 (100), 177 (9), 176 (3), 167 (10), 166 (7), 163 (11), and 162 (7).

The spectral data and tlc [R_f 0.12, neutral alumina, chloroform–methanol (10:1 v/v)] of compound **18** obtained here by hydrolysis of cyclic urea **17** were identical with that of aminoisoquinoline **18** prepared by debenzylation of the known **19** as described below.

1-(2′-Amino-4′,5′-dimethoxybenzyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxyisoquinoline (19). This compound was prepared as described in the literature[12] by the dropwise addition of a solution of 7-benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**15**, 1.00 g, 2.01 mmol) in dry tetrahydrofuran (6 ml) to a stirred suspension of sodium amide [prepared from sodium metal (2.00 g, 87.0 mmol)] in liquid ammonia (50 ml) under nitrogen. After 4 hr of refluxing with stirring, the reaction mixture was cautiously treated with solid ammonium chloride (10.0 g). The dark brown residue which remained after the liquid ammonia evaporated was mixed with ice water (30 ml) and extracted with chloroform (6 × 40 ml). The extracts were washed with water (2 × 10 ml), dried (K_2CO_3), and evaporated, giving a dark brown solid (733 mg), which was chromatographed on a column of neutral alumina (60 g) using chloroform [fractions 1–40 (10 ml each)] and chloroform–methanol (100:1 v/v) [fractions 41–66 (10 ml each)].

Evaporation of fractions 41–66 gave a brown yellow film (160 mg) which was shown by nmr to be mostly the desired aminoisoquinoline **19**. Elution of the column with methanol (320 ml) gave a deep orange solid (186 mg) which was also shown to be mostly **19**. The combined residues of **19** were crystallized four times from 95% ethanol to give a constant-melting, tan-white solid (92 mg, 11%): mp 114–115° (lit.[12] mp 163–164°);[26] ir ($CHCl_3$) 3390 (broad), 3030, 3005, 2960, 2940, 2915, 2875, 2840, 1610, 1515, 1470, 1450, 1415, 1375, 1350, 1325, 1290, 1260, 1255, 1175, 1170, 1165, 1110, 1005, 855, 750, 695, and 655 cm^{-1}; nmr[26] δ 2.45–3.60 (m, 9 H, 3-H_2, 4-H_2, methylene protons of 1-benzyl group, NH, NH_2), 3.75 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.05 (t, 1 H, J = 7 Hz, 1-H), 5.05 (s, 2 H, $OCH_2C_6H_5$), 6.27 (s, 1 H, ArH), 6.55 (s, 1 H, ArH), 6.58 (s, 1 H, ArH), 6.66 (s, 1 H, ArH), and 7.10–7.58 (m, 5 H, $OCH_2C_6H_5$): mass spectrum *m/e* (rel intensity) 446 (1, impurity), 434 (1), 433 (1), 432 (1), 268 (100), 267 (5), 178 (6), 177 (17) 176 (9), 167 (8), 166 (8), 148 (10), and 91 (8).

Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.12; H, 6.89; N, 6.35.

1-(2′-Amino-4′,5′-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (18). A solution of the aminobenzyloxyisoquinoline **19** (43 mg, 0.10 mmol) in 2 ml of concentrated hydrochloric acid–ethanol (1:1 v/v) was refluxed under nitrogen for 1 hr and cooled, and the ethanol was removed with a rotary evaporator. The residual yellow liquid was diluted with 6 *N* hydrochloric acid (3 ml) and washed with ether (3 × 5 ml) to remove benzyl impurities. The aqueous layer was made basic with 10% ammonium hydroxide and extracted with chloroform (6 × 10 ml). The combined $CHCl_3$ extracts were washed with water (5 ml), dried (Na_2SO_4), and evaporated, giving a pale yellow solid film of the hydroxyisoquinoline **18** (32 mg, 94%), whose properties (tlc, nmr, ir, mass spectrum) were identical with those of the sample of **18** obtained by the hydrolysis of cyclic urea **17**.

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Registry No.—**8**, 51015-09-9; **9**, 51015-10-2; **11**, 22231-61-4; **12**, 4697-57-8; **13**, 18883-64-2; **14**, 17138-37-3; **15**, 47706-25-2; **16**, 51015-11-3; **17**, 51015-12-4; **18**, 51015-13-5; **19**, 51015-14-6; **20**, 51015-15-7.

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C-Glycosyl Nucleosides. V. A Novel One-Step Asymmetric Synthesis of C-Nucleoside Analogs[1]

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Reaction of lithiated heterocycles such as pyridine, benzothiazole, imidazole, benzimidazole, and sydnone with sugar lactones, 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone (3) or 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (7), afforded a variety of 1-(2-substituted heterocyclic)-2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranose (4) or 1-(2-substituted heterocyclic)-2,3-*O*-isopropylidene-β-D-ribofuranose (8). Attempted dehydroxygenation of the anomeric hydroxyl group failed. These C-nucleoside analogs were reduced with sodium borohydride to gulitols and ribitols. The configuration of gulitols, which had a π-electron ring system, was determined with CD and ORD spectra to confirm their absolute configuration. It was concluded that a similar Cotton effect is observed in furanose-type and gulitol-type nucleosides.

Synthetic studies on the nucleoside antibiotic, pyrazomycin, have been reported by Tronchet and Perret.[2] On the other hand, Townsend and his collaborators synthesized its analogous N-nucleoside[3] and pyrazolopyrimidine nucleosides.[4] Several synthetic routes directed to C-nucleosides have also been reported by Fox and Ohrui.[5] In the previous paper,[6] we reported the reaction of ethynyl compounds with lactones, and the resulting compound had been expected as an intermediate for the preparation of the carbon-linked nucleoside. In another paper,[7] we reported the ethynylation of glucosyl bromide with ethynylmagnesium bromide, although we could not obtain the desired carbon-linked nucleoside. The attempted 1,3-dipolar cycloaddition reaction of 1-ethynylphenyl-2,3-*O*-isopropylidene-α-D-ribofuranose (1) and *N*-benzylsydnone failed.

The present paper concerns itself with a direct reaction of some lithiated heterocycles with sugar lactones to yield a carbon-linked nucleoside. The reaction of 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone (3) or 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (7) with various lithiated heterocycles gave gulofuranosyl derivatives (**4a–g**) or ribofuranosyl derivatives (**8b,c**).

By application of the reported method[6] of ethynylation with lactones to the reaction of heterocycles with sugar lactones, it has been possible to obtain heterocyclic sugar lactols. Treatment of 3 with *n*-butyllithium and α-bromopyridine, benzothiazole, or 1-benzylbenzimidazole gave 1-substituted 2,3:5,6-di-*O*-isopropylidenegulonolactols (**4a–c**) in a good yield (74, 56, and 40%, respectively, Chart I). The ir spectra of these compounds showed hydroxyl bands in the 3200–3380-cm^{-1} region, and no lactonic band at around 1780 cm^{-1}. Gulonolactols (**4a–c**) were acetylated with acetic anhydride in pyridine to yield their acetyl derivatives (**5a–c**). This result was similar to those of ethynyl derivatives.[6] In the case of 1-benzylbenzimidazole, the lithiation does occur at the 2 position similar to that of benzothiazole,[8] and this fact was confirmed from the nmr spectra of **4b**. Micetich[9] reported that lith-

Chart I