Syntheses of an Antipsychotic Pyrrolo[2,3-*g*]isoquinoline from Areca Alkaloids

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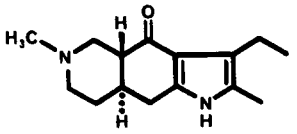
2,6-Dimethyl-3-ethyl-4,4a,5,6,7,8,8a,9-octahydro-4a,8a-*trans*-1*H*-pyrrolo[2,3-*q*]isoquinolin-4-one, a conformationally defined antipsychotic agent of current clinical interest, can be synthesized in a two-step, single-pot process from arecoline, a commercially available member of the areca alkaloid group. The yield is diminished by the competing, base-induced rearrangement of arecoline to 1,3-dimethyl-2-pyridone. This problem can be circumvented by using arecolone as the starting material. A convenient synthesis of arecolone from 3-acetylpyridine is described. A modified form of the Neber rearrangement was used to prepare 2-amino-3-pentanone hydrochloride for use in the Knorr pyrrole synthesis step of the process. Two isomeric pyrroloisoquinolines produced as minor byproducts were isolated and characterized as the cis-[2,3-*g*] and trans-[2,3-*h*] isomers. Characterization of the latter included an X-ray crystal structure determination.

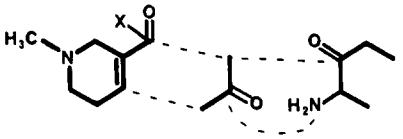
The conformationally rigid pyrrolo[2,3-*g*]isoquinoline 1 (Ro 22-1319, piquindone, USAN) was designed to exhibit a high degree of complementarity to a hypothetical molecular model of the dopamine receptor.[1] Pharmacological studies[2] showed that 1 has potent dopamine antagonist properties and is highly selective for a D-2 dopamine receptor subtype. The promising side-effect profile and inability to elicit receptor supersensitivity led to the selection of 1 for development. Clinical trials in progress indicate that 1 is an efficacious antipsychotic drug.



1

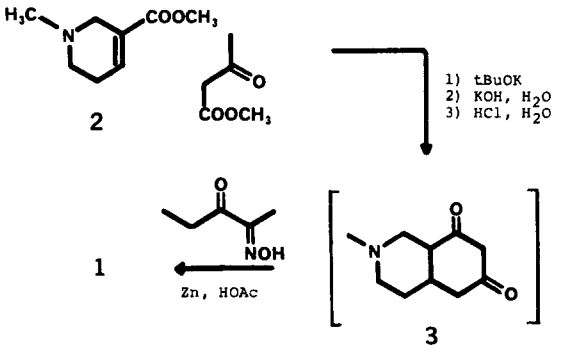
While the original, multistep synthesis[1] of 1 provided adequate supplies for early investigations, a more direct and efficient route was desired to meet the requirements of broader pharmacology, toxicology, and clinical studies.

Structure 1 may be dissected retrosynthetically in a number of ways, one of which suggested that the compound may be assembled from acetone, a tetrahydronicotinic acid derivative, and 2-amino-3-pentanone.



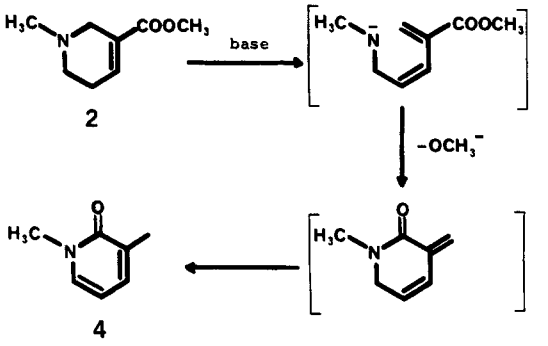
Synthesis from Arecoline. The most direct, although not the most efficient, expression of the concept outlined above starts with arecoline 2 as the tetrahydronicotinic acid derivative. Arecoline is a naturally occurring member of the areca alkaloid group of compounds that are found in seeds of the betel nut palm; the compound is also manufactured and available in bulk as the hydrobromide salt. Methyl acetoacetate was taken as a more highly disciplined equivalent of acetone for condensation reactions. The aminopentane was generated in situ by zinc reduction of 2-oximido-3-pentanone as with the standard Knorr pyrrole synthesis.

The product is obtained directly as a solid and purified by recrystallization. The process was, therefore, ideal in every respect but one: the overall yield was very poor.



2 1 3

Only 12–18% of 1 was obtained. An examination of byproducts revealed that much of the arecoline was diverted to a liquid substance, identified spectroscopically as 1,3-dimethyl-2-pyridone (4).[3]



2 4

This genesis of 4 was confirmed by treatment of 2 with potassium *tert*-butoxide in *n*-butyl alcohol at reflux to give 4. This reaction resembles the "α-methylene lactam rearrangement" studied by Rapoport et al.,[4] even though the conditions are quite different.

Synthesis from Arecolone. Since the irreversible step on the path from 2 to 4 is the *N*-acylation (loss of methoxide), it is clearly possible to block this rearrangement by using arecolone (5) instead of arecoline. In order to

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(1) Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Blount, J. F. Todaro, L.; Berger, L. *J. Med. Chem.* **1981**, *24*, 1026. Olson, G. L.; Cheung, H.-C.; Chiang, E.; Berger, L. "Dopamine Receptors"; Kaiser, C., Kebabian, J. W.; Eds.; American Chemical Society: Washington, D.C., 1983: *ACS Symp. Ser. No. 224*, p 251.

(2) Davidson, A. B.; Boff, E.; MacNeil, D. A.; Wenger, J.; Cook, L. *Psychopharmacology (Berlin)* **1983**, *79*, 32.

(3) Comins, D. L.; Lyle, R. E. *J. Org. Chem.* **1976**, *41*, 2065.

(4) Lee, D. L.; Morrow, C. J.; Rapoport, H. *J. Org. Chem.* **1974**, *39*, 893.

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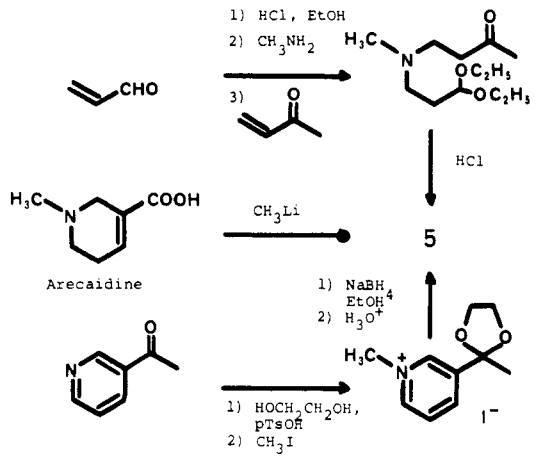
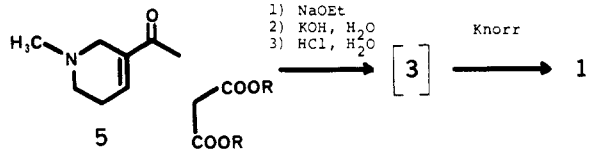
Scheme I



make this change compatible with the synthetic scheme, methyl acetoacetate is replaced by dimethyl or diethyl malonate.



Arecolone is neither naturally occurring nor an item of commerce. However, it is a well-known compound, often grouped with the areca alkaloids, and is readily prepared by a variety of methods, including those outlined in Scheme I.

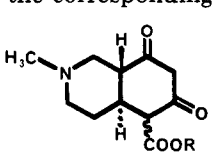
The synthesis from arecaidine, another one of the areca alkaloids, is the most direct but frequently gives arecolone contaminated with the corresponding tertiary alcohol.

Initially, our requirements were met by developing the low-yield route from acrolein reported many years ago by Wohl and Prill.[5] Subsequently, a more reliable and efficient process based on 3-acetylpyridine was worked out.

Irrespective of how the arecolone was prepared, it was most conveniently purified and stored in the form of its highly crystalline hydrobromide salt.

Preempting the "α-methylene lactam rearrangement" did indeed produce the desired effect. A threefold improvement in the yield of 1 was realized when arecolone was used as the starting material. This being therefore the more useful process, a more detailed study of the intermediates and byproducts was conducted.

The Michael adduct of arecolone and malonate has only a fleeting existence under the condensation conditions. However, the cyclized compound **6** was isolated and characterized. The material appears to exist in an enolic form. The assignment of trans-ring fusion is inferred by analogy with the corresponding carbocyclic system.[6]

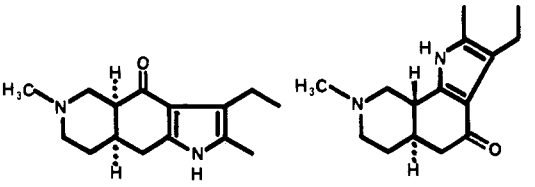


6 R = CH_3
7 R = H

The acid **7** obtained by alkaline hydrolysis of **6** is fairly stable to decarboxylation at low pH; it decarboxylated smoothly above 50 °C in the pH range of 3–5. This behavior also parallels that reported for the carbocyclic analogue.

The diketone **3** produced by this decarboxylation was isolated by ion-exchange chromatography. Both the hydrochloride and the free base are crystalline and both were characterized. The UV spectrum of the free base [λ_{max} in H_2O 280 nm (ϵ 22 000)] suggests an enolic structure.

Crude compound **3** prepared without isolation of intermediates **6** and **7** was subjected to the Knorr reaction (2-oximido-3-pentanone, Zn, HOAc) to afford, typically, a 45% overall yield of crude **1**. Analysis of this material by analytical LC and quantitative TLC showed that it contained about 90% of the desired linear, trans-fused product **1**. Byproducts present in the amounts of 6–11% and 1–3% were subsequently isolated and characterized as, respectively, the [2,3-*g*] cis-fused isomer **8** and the [2,3-*h*] trans-fused isomer **9**. A very minor byproduct detected by TLC is believed to be the [2,3-*h*] cis-fused isomer.



8 **9**

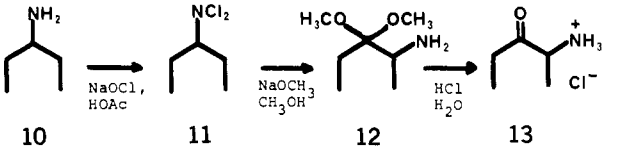
The spectral properties of the major byproduct support structure **8**. More convincing, however, is the fact that is can be isomerized to **1** (HCl in hot ethylene glycol or ethanolic KOH) and that it is identical with a sample prepared from **1** by similar treatment.

A single-crystal X-ray analysis was used to confirm structure **9**. A computer-generated drawing of the structure, and pertinent crystal data are available as supplementary materials.

It appeared that any additional improvement in the yield of **1** must come from improvements in the Knorr pyrrole synthesis step. To this end, the use of preformed 2-amino-3-pentanone was evaluated and found to be salutary, the overall yield of **1** being increased to 62%.

For the preparation of 2-amino-3-pentanone (made, kept, and used as the hydrochloride salt to suppress pyrazine formation[7]), the catalytic reduction of 2-oximido-3-pentanone in ethanolic HCl was used initially. However, a more convenient method was found that involved a modified form of the Neber rearrangement.[8]

The steps shown for the preparation of **13** from **10** are based on the procedure of Baumgarten and Peterson.[8]



10 **11** **12** **13**

These authors formulated the intermediate products produced in the reaction of *N,N*-dichloroamines with methoxide as azirine or methoxyaziridine derivatives. The intermediate obtained in our case was isolated and characterized spectroscopically as the amino ketal **12** (cf. ref 9).

The dichloroamine is an oily substance, stable at 25 °C but found to decompose explosively above 100 °C, after an induction period.

The new overall process (five steps, ~35% overall yield from acetylpyridine) for the preparation of **1** via arecolone

(5) Wohl, A.; Prill, A. *Justus Liebigs Ann. Chem.* **1924**, *440*, 139.
(6) Muhle, H.; Tamm, C. H. *Helv. Chim. Acta* **1962**, *45*, 1475.
(7) Vinod, N.; Pinson, J. *Bull. Soc. Chim. Fr.* **1968**, 970.
(8) Baumgarten, H. E.; Petersen, J. M. *J. Am. Chem. Soc.* **1960**, *82*, 459. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 909.
(9) LaMattina, J. L.; Suleske, R. T. *Synthesis* **1980**, 329.

proceeds well on a multikilogram scale.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on Varian XL-100 instruments and are reported in parts per million from internal Me_4Si. Elemental analyses were carried out in our Microanalytical Laboratory under the direction of Dr. F. Scheidl.

Condensation of Arecoline with Methyl Acetoacetate. Clean potassium (83 g, 2.12 mol) was added to a 3-L one-neck flask containing 1800 mL of *tert*-butyl alcohol. The potassium dissolved during about 8 h of heating and stirring at reflux under argon. Distilled methyl acetoacetate (140 g, 1.21 mol) was added to the cooled potassium *tert*-butoxide solution, and then 160 g (1.03 mol) of arecoline was added. The resulting red solution was stirred under argon at room temperature for 24 h and then at reflux for 48 h. A solution of potassium hydroxide (300 g) in water (75 mL) was added carefully in portions, with the condenser set down for distillation. Heating and stirring were continued for approximately 2 h during which 1750 mL of distillate (wet *tert*-butyl alcohol) was collected between 80 and 94 °C. Concentrated hydrochloric acid (800 mL) was added in very small portions. Boiling was continued for 1 h, during which a further 100 mL of distillate was collected. The solution was cooled and concentrated as much as possible on the rotary evaporator using aspirator vacuum. (Alternatively, the cooled solution may be freed of 1,3-dimethyl-2-pyridone by extraction with ether.)

Knorr Reaction. 2,6-Dimethyl-3-ethyl-4,4a,5,6,7,8,8a,9-octahydro-4a,8a-*trans*-1*H*-pyrrolo[2,3-*g*]isoquinolin-4-one (1). The salt mixture from the previous step was taken up into 1800 mL of glacial acetic acid and cooled in an ice bath. 2-Oximido-3-pentanone (40 g, 0.35 mol) and zinc dust (45 g, 0.69 mol) were added, and the cooled mixture was stirred mechanically for 15 min. The mixture was then stirred at reflux for 15 min and cooled again in an ice bath. Additional ketooxime (40 g, 0.35 mol) and zinc dust (45 g, 0.69 mol) were added, and the mixture was stirred for 15 min while being kept cold. It was then heated to reflux for 15 min and again cooled in ice, and a third portion of ketooxime (40 g, 0.35 mol) and zinc dust (45 g, 0.69 mol) were added. After another 15 min of stirring while cold, the mixture was heated to reflux and kept at reflux for 75 min. Most of the acetic acid was removed by using a rotary evaporator and aspirator vacuum. Then 3 N hydrochloric acid (1250 mL) and water (1050 mL) were added to dissolve the residue. The solution was transferred to a 4-L separatory funnel and washed three times with ether (1000-mL each). The ether layer from each wash was discarded. Then concentrated aqueous ammonia (1500 mL) was added to the aqueous layer to make it strongly basic while the zinc salts were kept in solution. The crude product separated as a solid precipitate. It was collected, washed with water, and air-dried overnight to give 38.3 g of light yellow powder. Extractive (CH_2Cl_2) workup of the aqueous filtrate afforded an additional 1.6 g of crude product. The total yield of crude 1 was 39.9 g (15.7% of theory from 2). Two recrystallizations using methylene chloride and ethanol (charcoal) gave 20.0 g of pink crystals with a melting point of 260–265 265 °C (some decomposition). This material was 99.5% pure by analytical HPLC [methanol (4.75%) and aqueous ammonia (0.25%) in methylene chloride (95%) as the mobile phase; stationary phase, silica]. The spectroscopic properties of 1 agreed with those previously described.[1]

1,3-Dimethyl-2-pyridone (4) from Arecoline. A suspension of arecoline hydrochloride (5.0 g, 0.026 mol) in *n*-butyl alcohol (50 mL) was treated with potassium *tert*-butoxide (6.0 g, 0.053 mol) and stirred at reflux under argon for 48 h. The cooled mixture was treated with concentrated hydrochloric acid (2 mL) and stirred overnight. The resulting suspension was diluted with ether (150 mL) and filtered. The filter cake was washed with ether (50 mL). The combined filtrate and wash was stripped of solvent on a rotary evaporator using a 70 °C bath and water aspirator vacuum. The residue of light brown oil was crude compound 4, 2.74 g (86% yield). Kugelrohr distillation at 0.05 mm afforded 1.60 g (50% yield) of pale yellow liquid which was 98.5% pure by GC analysis: mass spectrum, m/e 123 (M^+); ^1H NMR ($CDCl_3$) δ 2.15 (s, 3 H), 3.53 (s, 3 H), 6.1 (t, J = 7 Hz, 1 H), 7.2 (d, 2 H). Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.47; N, 11.37. Found: C, 67.79; H, 7.92; N, 10.70.

3-(2-Methyl-1,3-dioxolan-2-yl)pyridine. Ketalization of 3-acetylpyridine was effected in the usual manner with ethylene glycol (50% excess) and *p*-toluenesulfonic acid (20% excess) in toluene at reflux with azeotropic removal of water. The product was distilled in vacuo, affording a 94.6% yield of colorless mobile oil, bp 73–75 °C (0.9 mm). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.21; H, 6.65; N, 8.62.

1-Methyl-3-(2-methyl-1,3-dioxolan-2-yl)pyridinium Iodide. Quaternization of 3-(2-methyl-1,3-dioxolan-2-yl)pyridine using methyl iodide in toluene (53 °C/32 h) afforded a 99.3% yield of product as light yellow crystals, mp 185.5–187 °C (sinters at 167 °C). Anal. Calcd for $C_{10}H_{14}INO_2$: C, 39.11; H, 4.59; N, 4.56. Found: C, 39.23; H, 4.57; N, 4.47.

Crude Arecolone (5). A 5-L three-necked flask, equipped with mechanical stirrer, thermometer, and reflux condenser with nitrogen inlet was charged under nitrogen with 1-methyl-3-(2-methyl-1,3-dioxolan-2-yl)pyridinium iodide (285.8 g, 0.930 mol) and absolute ethanol (2.0 L). The suspension was stirred while sodium borohydride (38.0 g, 1.0 mol) was added in small portions over 30 min and the internal temperature was kept at 25 °C with an ice bath. At this point, all starting material had gone into solution. Additional sodium borohydride (60 g, 1.6 mol) was added in portions over 30 min while the internal temperature was kept at 35 °C with a cold water bath. The mixture was then stirred at reflux for 30 min. The heating mantle was removed, 6 N aqueous hydrochloric acid (1.0 L, 6.0 mol) was slowly added from a dropping funnel, and the white suspension was stirred at reflux for 1 h. Then 1.8 L of solvent was distilled off (180 mm, bp 54–60 °C). The reaction mixture was cooled to 20 °C and stirred while water (1.0 L) was added, followed by portionwise addition of anhydrous potassium carbonate (900 g, 6.5 mol; CO_2 evolution). The product, which separated as a brown organic layer, was taken up in ether (2.0 L), and the aqueous layer, which contained some crystalline inorganic salt, was extracted three times with ether (500-mL each). The combined ether extracts were dried over anhydrous potassium carbonate and concentrated in vacuo. The residual red brown oil (132 g) was distilled in vacuo to give 114.5 g (88%) of arecolone as a light yellow oil, bp 58–75 °C (0.9 mm). This material was 83.9% pure by GC analysis. It was stored at 0 °C until used.

Arecolone Hydrobromide. Crude arecolone base (114.5 g, 0.82 mol) dissolved in absolute ethanol (500 mL) was treated slowly with 48% aqueous hydrobromic acid (150.0 g, 0.89 mol) to give a slurry of the hydrobromide. The precipitate was collected by filtration and washed with ice cold absolute ethanol to give 157 g (71.8%) of white solid in two crops. An analytical sample recrystallized from 95% ethanol had a melting point of 227–228 °C. Anal Calcd for $C_8H_{13}NO{\cdot}HBr$: C, 43.65; H, 6.41; N, 6.36; Br, 36.30. Found: C, 43.45; H, 6.48; N, 6.46; Br, 36.37.

Preparation of 1 from Arecolone, Diethyl Malonate, and 2-Oximido-3-pentanone. The procedure used was essentially the same as that described for the preparation of 1 from arecoline and methyl acetoacetate. The condensation step was conducted by adding diethyl malonate (119.5 g, 0.746 mol) and arecolone base (from 144 g of the hydrobromide, 0.655 mol) to a solution of sodium (21.2 g, 0.92 mol) in ethanol (750 mL) and refluxing for 5 h.

Hydrolysis with potassium hydroxide (95 g), decarboxylation (400 mL of concentrated HCl), and the Knorr reaction were carried out as described above. Crude compound 1, 73.0 g (45.3% overall yield), was obtained as an off-white powder, mp 256–259 °C. Recrystallization from methylene chloride/ethanol gave 63.0 g of slightly pink crystals with a melting point of 262–264 °C. By HPLC analysis, this material contained 98.8% compound 1, 0.4% isomer 8, and 0.8% isomer 9.

Methyl (±)-Hexahydro-2-methyl-6,8(2*H*,7*H*)-isoquinolinedione-5-carboxylate (6). Sodium methoxide in methanol (142 g, 25% $NaOCH_3$ by weight, 0.66 mol) was added over 15 min to a stirred suspension of arecolone hydrobromide (66.0 g, 0.30 mol) in absolute methanol (75 mL) and dimethyl malonate (59.4 g, 0.45 mol). The resulting suspension was stirred at reflux for 2 h and then, over the course of 2 h, distilled to dry solids, first atmospherically and later at 100 mm. The solids were dissolved in water (150 mL), the pH was adjusted to 6.5 with hydrochloric acid (12 N, 22.5 mL), and the solution was cooled to +5 °C. After 1.5 h at +5 °C, the slurry of crystalline solids

was filtered. The solids were rinsed once with methanol/water (40 mL, 50% by volume, +5 °C) and then dried at 50 °C (200 mm). The yield of nearly pure **6** (containing traces of sodium chloride), mp 246–248 °C (decomposition), was 38.3 g (53% of theory). The analytical sample was obtained by recrystallization from cold water: mp 246–247.5 °C (decomposition); ^{1}H NMR (D_2O) δ 3.0 (s, 3 H), 3.9 (s, 3 H), 1.6–4.1 (envelope 9–10 H); IR (KBr) ν_{max} 3400, 1710, 1605, 1530 cm^{-1}; UV λ_{max} (H_2O) 282 mm (log ε 4.42). Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.00; H, 6.90; N, 5.84.

(±)-Hexahydro-2-methyl-6,8(2*H*,7*H*)-isoquinolinedione (3) (Free Base). The dry solids obtained from the condensation of arecolone hydrobromide and dimethyl malonate (see preparation of **6**, same scale) were dissolved in water (500 mL) and sodium hydroxide (400 mL, 25% by weight) and heated at 40 °C under nitrogen for 5 h. Concentrated hydrochloric acid (375 mL, 12 N) was added, and the solution was heated at 95 °C for 40 min. After the pH was adjusted to 6.5 with sodium hydroxide solution (47 mL, 25% by weight NaOH), the solution was applied to a column of Dowex 50W-X8 20–50 mesh (2.0-L bed volume, H^+ form). The column was eluted first with water (1500 mL) and then with 2 M aqueous pyridine (3000 mL). Vacuum concentration of the pyridine eluates afforded an off-white mushy solid of crude **3** (free base), 20.8 g. Recrystallization of crude diketone **3** (9.3 g) from cold water (0 °C, 18 mL) gave 3.6 g of pure diketone **3**: mp 149–150 °C dec; UV λ_{max} (H_2O) 280 nm (log ε 4.34), λ_{max} (0.1 N HCl) 255 nm (log ε 4.14); titration (H_2O, 0.1 NaOH), equiv wt 182, pK_{a_1} = 4.3, pK_{a_2} = 9.4; ^{1}H NMR (Me_2SO-d_6) δ 1.2–3.4 (envelope, ~12 H), 2.4 (s, 3 H).

For further characterization, a sample was converted to the hydrochloride salt **3**. The free base (300 mg) in ethanol (6 mL) solution was treated with concentrated HCl (0.2 mL) followed by addition of anhydrous ether (8 mL). The mixture was chilled in an ice bath for 1 h. The precipitate was collected by filtration and washed with ether. On drying the solids in vacuum (3 days, 0.2 mm), there was obtained 133.1 mg of white crystals with a melting point of 214–217 °C. Anal. Calcd for $C_{10}H_{15}NO_2HCl$: C, 55.17; H, 7.41; N, 6.43; Cl, 16.28. Found: C, 55.10; H, 7.42; N, 6.41; Cl, 16.44.

3,3-Dimethoxypentan-2-amine (12). A solution of 3-aminopentane (35.0 g, 0.40 mol) in acetic acid (50 mL, 0.98 mol) and water (20 mL) was added dropwise over 1 h to a stirred solution of sodium hypochlorite (672 g, 13.2% by weight, 1.19 mol) at 0 to +5 °C. The yellow oil layer was separated and dried over anhydrous calcium chloride to yield 60.2 g of crude *N,N*-dichloropentan-3-amine (**11**): IR (neat) ν_{max} 1465, 700 cm^{-1}. Anal. Calcd for $C_5H_{11}NCl_2$: Cl, 45.50. Found: Cl, 41.91 (iodimetry).

This compound possesses a strongly irritating chlorine-like odor. Samples have been stored at 25 °C for days without decomposition. *Caution: This compound was found to decompose violently above 100 °C after an induction period.*

Crude *N,N*-dichloropentanamine (57.3 g) was added dropwise to a refluxing solution of sodium methoxide in methanol (173 g, 25% $NaOCH_3$ by weight, 0.4 mol) over 0.5 h. The mixture was refluxed for 1.5 h. Then some solvent was removed by atmospheric distillation to a paste. This residue was dissolved in water (1560 mL) and the solution extracted twice with methylene chloride (250-mL each). The combined organic phases were dried (potassium carbonate) and stripped at 100 mm to an oil. Distillation of the oil in vacuo yielded 31.3 g of 3,3-dimethoxypentan-2-amine (56% yield) as a nearly colorless liquid: bp 60 °C (4 mm); ^{1}H NMR ($CDCl_3$) δ 1.0 (3 H, t, *J* = 8 Hz), 1.1 (3 H, d, *J* = 8 Hz), 1.75 (2 H, q, *J* = 8 Hz), 3.20, 3.25 (6 H, s), 3.0–3.5 (1 H, m); IR (neat) λ_{max} 3400, 3220, 1460, 1140, 1050 cm^{-1}. Anal. Calcd for $C_7H_{17}NO_2$: C, 57.11; H, 11.64; N, 9.51. Found: C, 57.51; H, 11.63; N, 9.91.

2-Aminopentan-3-one Hydrochloride (13). A solution of 3-aminopentane (87.5 g, 1.0 mol) in acetic acid (140 mL, 2.11 mol) and water (50 mL) was added over 1 h to a stirred suspension of toluene (175 mL) in sodium hypochlorite (1720 g, 2.81 mol) at 0 to +5 °C. The organic phase was removed, dried over anhydrous calcium chloride, and then added over 30 min to a stirred, refluxing solution of sodium methoxide in methanol (433 g 25% $NaOCH_3$, 1.98 mol). Reflux was continued for 2 h. Methanol (390 mL) was removed by atmospheric distillation through a 15-cm column of porcelain saddles. Water (375 mL) was added to the residue, and this solution was extracted twice with toluene (250-mL each) and twice more with toluene (125-mL each). The combined toluene extracts were extracted with 37% hydrochloric acid (90 mL) and water (25 mL). The combined acid and water extracts were distilled in vacuo (50 °C (5 mm)) to dry solids. The solids were slurried in acetone (250 mL), filtered, rinsed with acetone (2 × 100 mL), and dried in vacuo (35 °C (100 mm)) to yield 104 g (76% yield) of pure 2-aminopentan-3-one hydrochloride as off-white crystals: mp 127–129 °C. ^{1}H NMR (Me_2SO-d_6) δ 0.95 (3 H, t, *J* = 8 Hz), 1.4 (3 H, d, *J* = 8 Hz), 3.7 (2 H, q, *J* = 8 Hz), 4.1 (1 H, q, *J* = 11 Hz), 8.5 (br s, 3 H); IR (KBr) ν_{max} 3000, 1720, 1490 cm^{-1}; titration (H_2O, 0.1 N NaOH), equiv wt 137.5, pK_a = 8.4. Anal. Calcd for $C_5H_{12}ClNO$: C, 43.64; H, 8.79; N, 10.17, Cl, 25.81. Found: C, 43.48; H, 8.75; N, 10.05.

(±)-2,6-Dimethyl-3-ethyl-4,4a,5,6,7,8,8a,9-octahydro-4a,8a-*trans*-1*H*-pyrrolo[2,3-*g*]isoquinolin-4-one (1). The dry solids obtained from the condensation of arecolone hydrobromide and dimethyl malonate (see preparation of **6**, same scale) were dissolved in water (275 mL), potassium hydroxide (42 g, 88% by weight KOH, 0.66 mol) was added, and the solution was heated at 100 °C for 3 h. The solution was cooled to 60 °C, its pH was adjusted to 4 with concentrated hydrochloric acid (85 mL), and 2-aminopentan-3-one hydrochloride (72 g, 0.52 mol) was added. The pH of the resulting solution was readjusted to 4 with concentrated hydrochloric acid (6 mL), and the solution was heated at 95 °C. The pH of this solution dropped and was readjusted at 2-h intervals by addition of small amounts of sodium hydroxide solution (25% by weight NaOH). After 8 h at 95–100 °C, the solution was cooled to +60 °C. To the crystal slurry was added ammonium hydroxide (160 mL, 28%) over 1 h. The suspension was digested at 60 °C for 0.5 h, cooled to 25 °C, and filtered. The off-white solids were rinsed five times with 1% aqueous ammonium hydroxide (100-mL each) and dried to constant weight at 60 C (1 mm) vacuum. Crude **1** (52.3 g) was obtained. HPLC assay (Zorbax TMS, 25 × 0.5 cm, CH_3OH–H_2O 50% by volume water, 0.005 M in heptanesulfonic acid, 25 °C, UV 254 nm) showed a mixture of *trans*-**1** and -**9** (88%) and cis (7%). Quantitative TLC (SiO_2, eluting with the lower phase of a mixture $CHCl_3$/MeOH/HOAc/H_2O, 45/15/3/5 by volume): *trans*-**1** (88%), R_f 0.23; cis isomer **8**, R_f 0.11; [2,3-*h*] isomer **9**. The yield of **1** is therefore 62%.

The crude free base was recrystallized from ethanol (charcoal) to furnish pure **1**: mp 261.5–263.5 °C dec; 100% pure by both HPLC and TLC analysis.

Isolation and Characterization of Byproducts: 2,6-Dimethyl-3-ethyl-4,4a,5,6,7,8,8a,9-octahydro-4a,8a-*cis*-1*H*-pyrrolo[2,3-*g*]isoquinolin-4-one (8) and 2,8-Dimethyl-3-ethyl-1,5,5a,6,7,8,9,9a-octahydro-5a,9a-*trans*-4*H*-pyrrolo-[2,3-*h*]isoquinolin-4-one (9). The residue obtained from combined mother liquors of large-scale recrystallizations of compound **1** was dissolved in dilute aqueous HCl. The solution was heated to 60 °C, and the pH was adjusted to 7.5 by addition of 28% aqueous ammonium hydroxide. The slurry of precipitated crude **1** was digested at 60 °C for 15 min, cooled to 25 °C, and filtered. The filtrate was thus enriched in byproducts **8** and **9**. This material was recovered as solids from the filtrate by precipitation at higher pH with ammonium hydroxide.

A sample of the mixture (9 g) enriched in byproducts was chromatographed on 250 g of 70–230 mesh silica gel using the dry-column technique. Eluting with the organic phase of a mixture prepared by shaking 90 parts of $CHCl_3$, 30 parts of CH_3OH, 10 parts of H_2O, and 6 parts of HOAc gave fractions containing pure compounds **9**, **1**, and **8** (in their order of elution). The fractions containing **8** and **9** were separately washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated.

Compound 9 was obtained by recrystallization from ethanol/ethyl acetate as colorless crystals (241 mg) with a melting point of >260 °C: IR (KBr) ν_{max} 3250, 1620, 1600 cm^{-1}; mass spectrum, *m/e* 246 (M^+), UV λ_{max} 251 (ε 10 500), 293 nm (4700); ^{1}H NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.02 (t, 3 H), 2.08 (s, 3 H), 2.32 (s, 3 H), 10.58 (s, 1H), 1.5–3.6 (m, 12 H). See also the X-ray crystal structure. Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13, H, 9.00; N, 11.37. Found: C, 73.20; H, 8.83; N, 11.35.

Compound 8 was obtained by recrystallization from acetone as colorless crystals (1.00 g): mp 217–8 °C; IR (KBr) ν_{max} 3245, 1620, 1600 cm^{-1}; mass spectrum, *m/e* 246 (M^+); UV λ_{max} 252 (ε 13 200), 290 nm (4400); ^{1}H NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.03 (t,

3 H), 1.60 (q, 2 H), 2.07 (s, 3 H), 2.18 (s, 3 H), 2.2–3.0 (m, 10 H), 10.42 (s, 1 H). Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.04; H, 8.98; N, 11.40.

The isomerization of 8 to 1 was previously described.[1]

Registry No. (±)-1, 78541-97-6; 2, 63-75-2; 2·HCl, 61-94-9; 2·HBr, 300-08-3; 3, 75690-06-1; 3·HCl, 75690-07-2; 4, 6456-92-4; 5, 55806-53-6; (±)-6, 93222-91-4; (±)-8, 93222-95-8; (±)-9, 93222-94-7; 11, 78685-86-6; (±)-12, 93222-92-5; (±)-13, 93222-93-6; 2-oximido-3-pentanone, 32818-79-4; 3-(2-methyl-1,3-dioxolan-2-yl)pyridine, 55676-25-0; 1-methyl-3-(2-methyl-1,3-dioxolan-2-yl)pyridinium iodide, 88599-19-3; diethyl malonate, 105-53-3; methyl acetylacetate, 105-45-3; 3-acetylpyridine, 350-03-8; 3-aminopentane, 616-24-0.

Supplementary Material Available: A computer-generated drawing of 9 and tables of crystal data, final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for 9 (5 pages). Ordering information is given on any current masthead page.

Bicyclic Imides with Bridgehead Nitrogen. Synthesis and X-ray Crystal Structure of a Bicyclic 2,4-Oxazolidinedione[1]

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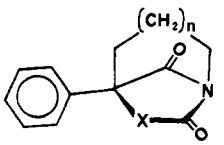
The first successful synthesis of bicyclic 2,4-oxazolidinediones with bridgehead nitrogen, examples of anti-Bredt imides, was accomplished. The synthetic approaches involved three homologous bridging sizes, and the smallest product capable of preparation was 1-aza-8,9-dioxo-7-oxa-6-phenylbicyclo[4.2.1]nonane, for which the structure was verified by X-ray diffraction. Also prepared was 1-aza-9,10-dioxo-8-oxa-7-phenylbicyclo[5.2.1]decane. These results were accurately predicted by using anti-Bredt olefins as models, suggesting that resonance effects may be essential for the stability of anti-Bredt imides.

Bicyclic imides with bridghead nitrogen, of the type shown in structures 1–3, were first proposed[2] by Edward E. Smissman as potential stereoselective anticonvulsants.



	X
1	-O-
2	-NH-
3	-CONH-

Despite numerous attempts by him to prepare examples of these compounds with $n = 1$, the only reported[3] success was for a methoxy-substituted bicyclic barbiturate related to 3. However, we recently demonstrated via ^1H and ^{13}C NMR studies[4] that the structure assignment for this bicyclic barbiturate was incorrect.

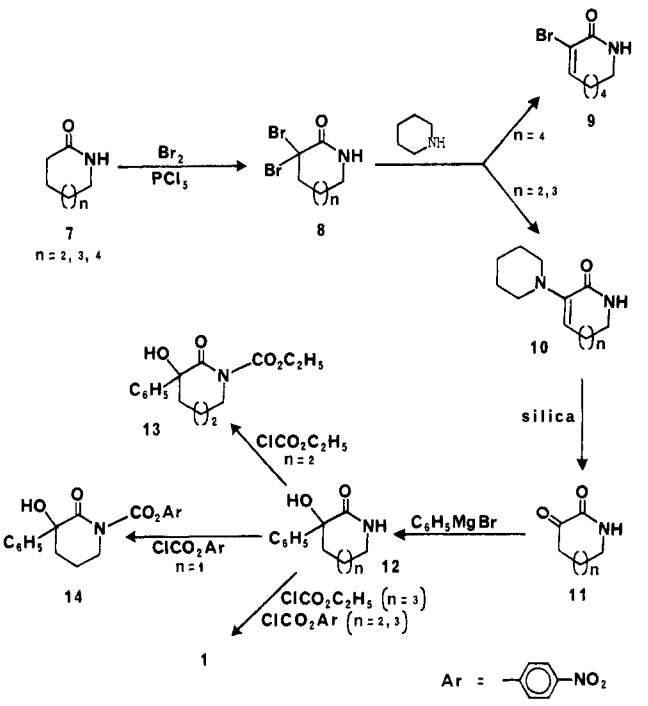
The difficulty encountered in preparing imides 1–3 with $n = 1$ is not surprising since these compounds are examples of anti-Bredt bridgehead nitrogen amides.[5] Such compounds are destabilized when n is small, possibly because delocalization of the lone pair of electrons on nitrogen into the π orbitals of the carbonyls is minimal. As shown by Hall,[5–7] such destabilization in related compounds is characterized by a tendency to undergo ring-opening polymerization, which may preclude isolation of monomer.

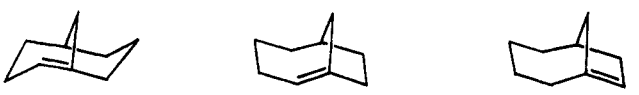
Here we report the preparation ($n = 2$ and 3) and X-ray crystal structure ($n = 2$) of bicyclic 2,4-oxazolidinedione 1, which represents the first successful synthesis of anti-Bredt bicyclic imides of the type proposed by Smissman.

Results and Discussion

If resonance is required for the stability of bicyclic imides 1–3, anti-Bredt olefins might serve as models for predicting their lower size limits. One finds that the smallest anti-Bredt olefins capable of isolation at present are compounds 4–6.[8–10] If similar restraints apply, model

Scheme I





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(1) Dedicated to the memory of Professor Edward E. Smissman. In recognition of his accomplishments in this area, we routinely refer to anti-Bredt bicyclic imides related to 1–3 as "smissmanones".

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