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Oxazolines. 2.[1] 2-Substituted 2-Oxazolines as Synthons for *N*-(β-Hydroxyethyl)arylalkylamines, Intermediates in a Synthesis of 1,2,3,4-Tetrahydroisoquinolines and 2,3,4,5-Tetrahydro-1*H*-3-Benzazepines

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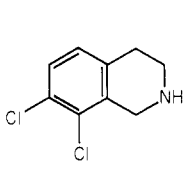
2-(Arylalkyl)-2-oxazolines **4** (n = 1) and 2-aryl-2-oxazolines **4** (n = 0), the latter prepared in a novel reaction by cross-coupling aryl Grignard reagents with 2-(methylthio)-5-phenyl-2-oxazoline (**10**) and using [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) chloride (**14**) as a catalyst, were reduced in a previously unreported reaction by diborane in refluxing THF to yield *N*-(β-hydroxyethyl)arylalkylamines **5** (n = 1, 2). Amino alcohols **5** were cyclized to their respective heterocyclic derivatives **6** (n = 1, 2) by treatment with H_2SO_4/TFA in refluxing methylene chloride. This paper discusses how 2-substituted 2-oxazolines may be used to prepare 1,2,3,4-tetrahydroisoquinolines **6** (n = 1) and 2,3,4,5-tetrahydro-1*H*-3-benzazepines **6** (n = 2) via amino alcohols **5**.

Recently this laboratory reported the synthesis of 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline (**1**; SK&F no. 64139), which was found capable of inhibiting the enzyme



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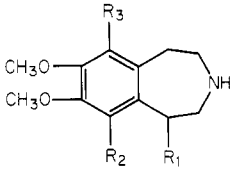

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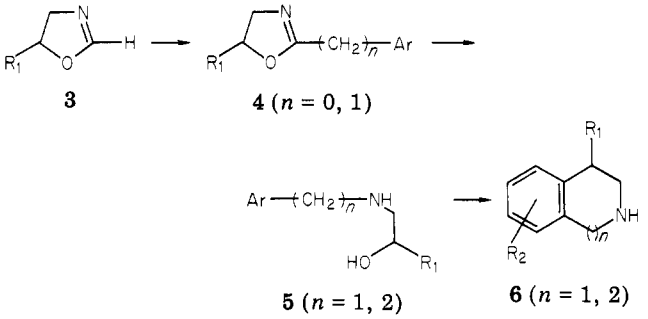
phenylethanolamine *N*-methyltransferase (PNMT),[2] and several 2,3,4,5-tetrahydro-1*H*-3-benzazepines **2** which are dopamine receptor antagonists and agonists as well as neuroleptics.[3] Common to both these syntheses is the formation of the tetrahydro heterocyclic ring by acid-catalyzed cyclization of a (β-hydroxyethyl)amino substituent into an arene ring. To develop a general synthesis of several different heterocycles **6**, we decided to explore the utility of 2-substituted 2-oxazolines **4** as synthons for the synthesis of amino alcohols **5** as shown in Scheme I.

Scheme I



3 **4** (n = 0, 1) **5** (n = 1, 2) **6** (n = 1, 2)

The 2-oxazolinyl moiety was chosen as the precursor of **5** for the following reasons: (1) the 2-oxazolinyl functionality inherently has the required O–C–C–N grouping; (2) synthesis of 2-oxazolines **3** is facile[4,5] and may be done without using a β-hydroxyethylamine as starting material; (3) alkylation or arylation of **3** to form **4** could provide an efficient means of introducing the eventual nitrogen sub-

(1) (a) For part I of this series see: Pridgen, L. N.; Killmer, L. *J. Org. Chem.* **1981**, *46*, 5402. Pridgen, L. N. "Abstracts of Papers", 182nd National Meeting of the American Chemical Society, New York, NY, Aug 23–28, 1981; American Chemical Society: Washington, DC; INORG 60. (b) This work was presented in part at the 183rd National Meeting of the American Chemical Society, Las Vegas, NV, Mar 1982; American Chemical Society: Washington, DC; ORGN 168.

(2) Mendelson, W. L.; Spainhour, C. B., Jr.; Jones, S. S.; Lam, B. L.; Wert, K. L. *Tetrahedron Lett.* **1980**, 1393.

(3) (a) Weinstock, J. *J. Med. Chem.* **1980**, *23*, 973 and references therein. (b) Ross, S. T.; Weinstock, J.; Yim, N. C.-F. Great Britain Patent 1574208, 1980. (c) Weinstock, J. U.S. Patent 4197297, 1980.

(4) For reviews on oxazoline synthesis and synthetic applications see: (a) Wiley, R. H.; Bennett, L. L. *Chem. Rev.* **1949**, *44*, 447. (b) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483. (c) Seeliger, W.; Aufderhaar, E.; Diepers, W.; Feinauer, R.; Nehring, N.; Thier, W.; Hellmann, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 875. (d) Meyers, A. I.; Mihelich, E. D. *Ibid.* **1976**, *15*, 270. (e) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787. (f) Meyers, A. I.; Avila, W. B. *Ibid.* **1981**, *46*, 3881 and references therein.

(5) (a) Schöllkopf, U.; Gerhart, F.; Hoppe, I.; Harms, R.; Hantke, K.; Scheunemann, K.-H.; Eiters, E.; Blume, R. *Justus Liebigs Ann. Chem.* **1976**, 183. (b) Gerhart, F.; Schöllkopf, U. *Tetrahedron Lett.* **1968**, 6231.

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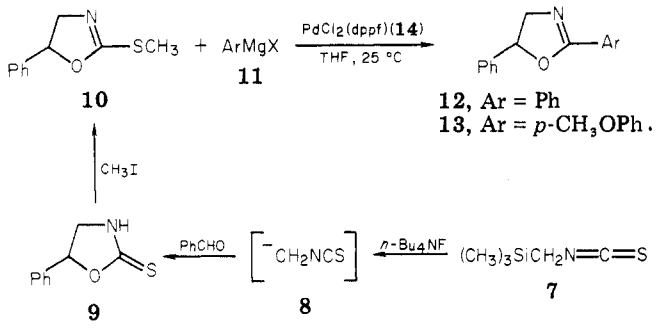
Scheme II



stituent; (4) the 2-oxazolinyl system is structurally related to imidates which are easily reduced.[6] In order for our proposed route (Scheme I) to be successful, it was imperative to find conditions that would reductively cleave only the 2-oxazolinyl C_2–O bond. Reductive cleavage of the C_5–O bond, as reported to be the case for oxazoles,[7] would lead to the amide.

We now report our results in preparing and reducing 2-oxazolines **4** to β-hydroxyethylamines **5**, pentultimate intermediates to 1,2,3,4-tetrahydroisoquinolines **6** (n = 1)[8] and 2,3,4,5-tetrahydro-1-aryl-1*H*-3-benzazepines **6** (n = 2).

Results and Discussions

Preparation of 2-Substituted 2-Oxazolines 4. Generally, 2-substituted 2-oxazolines are prepared by condensing β-hydroxyethylamines (ethanolamines) with appropriate alkyl imidates,[4,6,9] nitriles,[4,10] or amides.[4] Since syntheses of ethanolamines are sometimes cumbersome,[11] we sought syntheses which did not require them as starting materials. The lithiomethyl isocyanide approach employed by Schöllkopf,[5] which avoids the use of ethanolamines, therefore appeared attractive.

However, as he and others[8] have observed, the 2-lithio-2-oxazolinyl moiety is in equilibrium with its open-chain isomer and preferentially alkylates or acylates as the isocyanide. Our observations using benzyl halide as the electrophile gave similar results. We then explored alkylation at C-2 of 2-(methylthio)-5-phenyl-2-oxazoline (**10**) using a transition-metal-catalyzed Grignard cross-coupling reaction just recently reported on 2-(methylthio)benzothiazole,[12a] benzenethiols,[12c] and enol sulfides.[12c] In our cross-coupling reaction, aryl Grignard reagents **11** react with 2-(methylthio)-5-phenyl-2-oxazoline (**10**) in the presence of a catalytic amount of [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) chloride (**14**)[12b,13] to yield 2-aryl-5-phenyl-2-oxazolines **12** and **13**. Only cross-coupling products resulting from cleavage of the sp^2 C–S bond were observed (Scheme II). Thus, we have shown how 2-aryl-2-oxazolines **4** (n = 0) may be perpared *without benzoic acid derivatives as precursors*.[13] The C_2 carbon of the oxazolinyl moiety of **10** is in effect equivalent to the imino, nitrilo, and carbonyl carbon used in the above-mentioned imidate, nitrile, and amide precursors, respectively. Also, the 2-oxazolinyl moiety of 2-aryl-2-oxazoline is known to activate the ortho position toward deprotonation and nucleophilic displacement.[4] Thus, one may use ortho metalation or the ortho methoxide displacement reaction to suitably substitute on the 2-aryl group in **4** (n = 0), the precursor to the amino alcohol **5** (n = 1). Our 2-oxazoline approach (Scheme I), therefore, complements existing syntheses of *N*-(β-hydroxyethyl)-arylalkylamine **5** (n = 1).

Agawa[14] has recently reported the synthesis of 5-phenyl-2-oxazolidinethione (**9**) from trimethylsilyl isothiocyanate (**7**) and benzaldehyde (Scheme II). Although we synthesized **10** by methylation of **9**, prepared from the commercially available 1-phenylethanolamine, we have nevertheless demonstrated in a formal sense that 2-aryl-2-oxazolines such as **12** and **13** may be prepared *without using ethanolamines or benzoic acid derivatives.*

Since benzyl Grignards did not appreciably undergo the cross-coupling to yield 2-oxazolines **4** (n = 1), we used the traditional imidate[4,6,9] approach (see below) to prepare 2-(arylalkyl)-5-aryl-2-oxazolines **16**, **24**, and **26**.

Reduction of 2-Substituted 2-Oxazolines 4. At the onset of this work, to our knowledge, the only reported reduction of a 2-substituted 2-oxazoline having a basic nitrogen was carried out by using sodium in alcohol. Thus, 2,5-diphenyl-2-oxazoline (**12**) may be reduced to *N*-(β-hydroxy-2-phenylethyl)benzylamine (**15**).[15] Generally, 2-oxazolines have been reported to be inert to commonly used reducing agents, (e.g., $LiAlH_4$, $NaBH_4$) and are used as protecting groups for esters.[4e] This inertness to reduction appears to be a unique property of 2-oxazolines since, as we have previously mentioned, acyclic and other cyclic imidates are easily reduced.[6]

To study the reduction of the 2-oxazolinyl group, we prepared 5-phenyl-2-[(3,4-dimethoxyphenyl)methyl]-2-oxazoline (**16**) from ethyl (3,4-dimethoxyphenyl)acetimidate hydrochloride and 1-phenylethanolamine in 87% yield. Under a variety of reducing conditions, we were unable to produce the desired *N*-[(β-hydroxy-2-phenyl)-ethyl]-2-(3,4-dimethoxyphenyl)ethylamine (**17**). $LiAlH_4$ and $NaBH_4$ were unreactive while $NaCNBH_4$ gave a com-

(6) (a) Roger, R.; Neilson, D. G. *Chem. Rev.* **1960**, *60*, 179. (b) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36.

(7) Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1980**, *45*, 2548.

(8) For other reports of 2-oxazolines being used as templates for tetrahydroisoquinolines see: (a) Falck, J. R.; Manna, S. *J. Org. Chem.* **1981**, *46*, 3742. (b) Barnett, A. G. M.; Barton, D. H. R.; Falck, J. R.; Papaionnou, D.; Widdowson, D. W. *J. Chem. Soc., Perkin Trans. 1* **1979**, 652 and references therein.

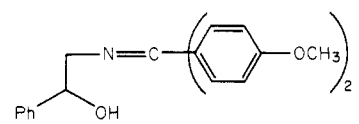
(9) (a) Pinner, A. "Die Iminoather und Ihre Derivate"; Oppenheim: West Berlin, 1892. (b) Meyers, A. I.; Hanagan, M. A.; Mazzu, A. L. *Heterocycles* **1981**, *15*, 361.

(10) (a) Siegl, W. O. *J. Org. Chem.* **1977**, *42*, 1872. (b) Witte, H.; Seeliger, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 287. (c) Witte, H.; Seeliger, W. *Justus Liebigs Ann. Chem.* **1974**, 996.

(11) For examples see: (a) Babowski, G.; Gottlieb, J. M.; West, B.; Shavel, J., Jr. *J. Heterocycl. Chem.* **1979**, *16*, 1525. (b) Babowski, G.; Gottlieb, J. M.; West, B. J. *Ibid.* **1980**, *17*, 1563.

(12) (a) Takei, H.; Morikazu, M.; Sugimura, H. *Chem. Lett.* **1979**, 1447. (b) Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, *1971*. (c) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 637.

(13) The scope of this cross-coupling reaction is the subject of a preliminary communication,[1] including other examples, and will not be elaborated on here. However, a side product of this cross-coupling reaction has been isolated and characterized (experimental) as *N*-(β-hydroxy-2-phenylethyl)bis(4-methoxyphenyl)methylimine (**35**). By analogy, as previously demonstrated, this material was formed by addition of *p*-anisyl Grignard to 2-(4-methoxyphenyl)-5-phenyl-2-oxazoline (**13**).



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(14) Hirao, T.; Yamada, A.; Ohshiro, Y.; Agawa, T. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 126.

(15) Gabriel, S.; Stelzner, R., *Chem. Ber.* **1896**, *29*, 2381.

(16) Schwan, T. J.; Lougheed, G. S.; Burrows, S. E. *J. Heterocycl. Chem.* **1974**, *11*, 807.

(17) Ose, S.; Yoshimura, Y. Japanese Patent 10859, **1960**; *Chem. Abst.*, **1961**, *55*, 462*d*.

Scheme III

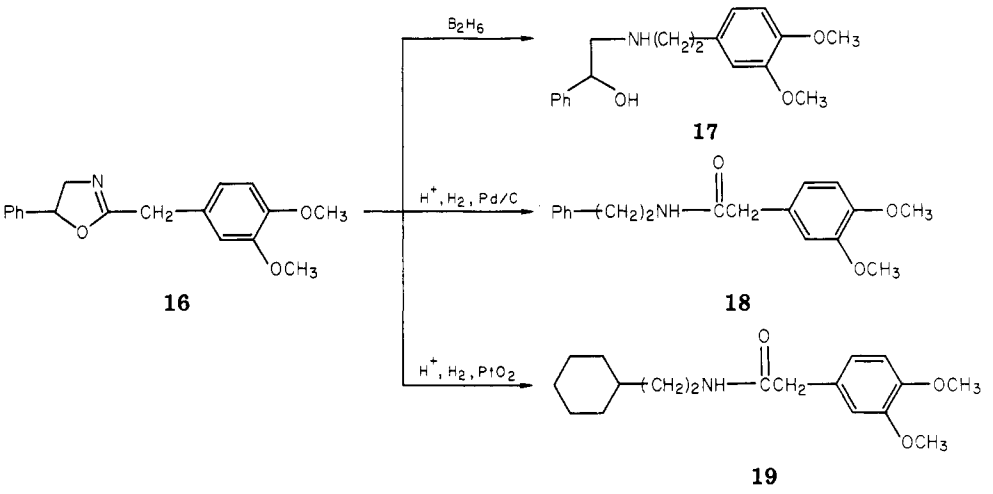
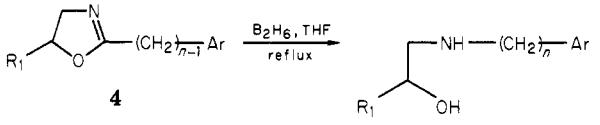


Table I. Reduction of 2-Oxazolines 4



starting matl	product	R_1	n	Ar	time, h	% yield	mp[b] °C (HCl)
20	21	H	1	Ph	5	96	106-108, 94-95[d]
22	23	H	1	2,3-Cl_2Ph	6	70	131-132, 133.5-134.5[e]
16	17	Ph	2	3,4-$(CH_3O)_2$Ph	8	94	94-95 (base), 94.5-96[c]
24	25	Ph	2	2-Cl-3,4-$(CH_3O)_2$Ph	16	80	100-102 (base)
26	27	4-(CH_3O)Ph	2	2-Cl-3,4-$(CH_3O)_2$Ph	3	56	115-116 (base), 116-118[c]
12	15	Ph	1	Ph	4	95[a]	227-229, 229-232[f]
13	28	Ph	1	4-(CH_3O)Ph	3	63	223-224[c]

[a] $LiAlH_4$ used as the reducing agent. [b] Satisfactory analytical values (±0.3 for C, H, and N) were reported for all compounds. [c] Contained 0.25 mol of H_2O by combustion analysis. [d] See ref. 17. [e] Obtained from a sample provided by Dr. W. Mendelson. [f] See ref. 16.

plex mixture. Catalytic hydrogenation of **16** at 50 psi of H_2 with 10% palladium on carbon or Adam's catalyst gave the hydrogenolysis products *N*-(2-phenylethyl)(3,4-dimethoxyphenyl)acetamide (**18**) and *N*-(2-cyclohexylethyl)(3,4-dimethoxyphenyl)acetamide (**19**), respectively (Scheme III). After several unsuccessful attempts to form **17** via reduction of **16**, we found diborane in *refluxing* THF to be effective, giving the desired product **17** cleanly in excellent yield. Only in the case of **12** did borane give overreduced products. To avoid this problem, $LiAlH_4$ was tried and proved to be effective, affording **15** in excellent yield. Table I lists our results in reducing 2-oxazolines **4** using diborane.

Acid-Catalyzed Cyclization of *N*-(β-Hydroxyethyl)arylalkylamines 5. Cyclizations of *N*-(β-hydroxyethyl)arylalkylamines **5** to 1,2,3,4-tetrahydroisoquinolines **6** (n = 1)[18,19] and 2,3,4,5-tetrahydro-1*H*-3-benzazepines **6** (n = 2)[20] under acidic conditions have been reported but are usually harsh. In the case of **23** where R = H and the aromatic ring (Ar) is deactivated by two chlorine atoms, it has previously been shown that this cyclization can be effected satisfactorily by using $AlCl_3$/NH_4Cl to form **1**.[2] When R_1 is aromatic, cyclization to the bicyclic heterocyclic ring system occurs very easily and, for example, is an approach used to synthesize the *Amaryllidaceae* alkaloid cherylline (**34**) (N-CH_3).[21] We have been able to routinely cyclize amino alcohols **15** and **28** to **29** and **30**, respectively, in a trifluoroacetic acid/sulfuric acid/methylene chloride suspension (Table II). Similar conditions have been reported by this laboratory to be effective in forming 2,3,4,5-tetrahydro-1-aryl-1*H*-3-benzazepines **31** and **32** from amino alcohols **17** and **27**, respectively.[3]

In summary, we have shown how β-hydroxyethylamines **5** may be prepared in one step by diborane reduction of 2-substituted 2-oxazolines **4**. These prerequisite 2-oxazolines **4** were prepared either by conventional methods or, as in the case of 2-aryl-2-oxazoline **4** (n = 0), by a novel cross-coupling reaction of aryl Grignard with 2-(methylthio)-2-oxazoline **10** under palladium–phosphine complex catalysis (Scheme II). Preparation of 2-oxazoline **4** (n =

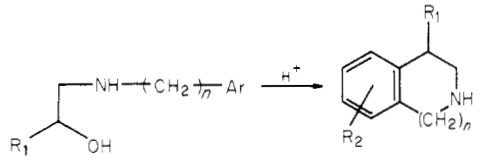
(18) Kametani, T.; Fukumoto, K. In "Isoquinolines"; Grethe, G., Ed.; Wiley: New York, 1981; Part 1, Chapter 2. This is Vol. 38 of *Chem. Heterocycl. Comp.*

(19) (a) Jacob, J. N.; Nichols, D. E. *J. Med. Chem.* **1981**, *24*, 1013. (b) Hoffman, I.; Ehrhart, G.; Schmitt, K. *J. Pharm. Pharmacol.* **1978**, *30*, 514.

(20) For a review on benzazepine alkaloid syntheses see: Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 931.

(21) Schwartz, M. A.; Scott, S. W. *J. Org. Chem.* **1971**, *36*, 1827.

Table II. Acid-Catalyzed Cyclization of *N*-(β-Hydroxyethyl)arylalkylamines 5



5 6

starting matl	R_1	Ar	n	product	% yield	R_1	R_2
15	Ph	Ph	1	**29**	78	Ph	H
28	Ph	4-(CH_3O)Ph	1	**30**	82	Ph	6-CH_3O
17	Ph	3,4-(CH_3O)$_2$Ph	2	**31**	*a*	Ph	7,8-(CH_3O)$_2$
27	4-(CH_3O)Ph	2-Cl-3,4-(CH_3O)$_2$Ph	2	**32**	85[b]	4-(CH_3O)Ph	6-Cl-7,8-(CH_3O)$_2$
33	4-HOPh	4-(CH_3O)-3-HOPh	1	**34**	79[c]	4-(HO)Ph	6-(CH_3O)-7-HO

[a] See ref 3b for experimental procedure. [b] See ref **3a,c** for experimental procedure. [c] Basic, rather than acidic, conditions were used (see ref 21).

0) as shown in Scheme II avoids using benzoic acid derivatives and ethanolamines as starting materials, thereby complementing existing syntheses. The resulting reduction products of **4**, i.e., amino alcohols **5**, were cyclized under acidic conditions to the heterocyclic 1,2,3,4-tetrahydroisoquinolines **6** (n = 1) and 2,3,4,5-tetrahydro-1*H*-3-benzazepines **6** (n = 2), two important biologically active classes of heterocycles.

Experimental Section

^{1}H NMR spectra were taken on a Perkin-Elmer R-24 or a Varian CFT-20 using with Me_4Si as an internal standard. Infrared spectra were obtained on Perkin-Elmer 580 and 283 spectrometers. Low-resolution mass spectra by electron impact (EI) were obtained at 70 eV on a Hitachi Perkin-Elmer RMU-6E by direct insertion. High-resolution and field-desorption (FD) mass spectra were obtained on a Varian MAT-CH_5 double-focusing spectrometer. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

2-(2,3-Dichlorophenyl)-2-oxazoline (22). A melt of 2,3-dichlorobenzonitrile (17.4 g, 100 mmol), ethanolamine (9.15 g, 150 mmol), and calcium chloride (1.11 g, 10 mmol) was kept at 110–120 °C for 8 h according to the procedure of Siegl.[10a] At that time, the reaction mixture was distilled to yield a considerable amount of polymeric material, starting materials, and the desired product: bp 160 °C (0.25 mm); 2.0 g (9.2 mmol, 10% yield); IR (film) 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.8–4.6 (4 H, m), 7.0–7.6 (3 H, m); high-resolution mass spectrum, m/e 214.990 ($C_9H_7Cl_2NO$ requires 214.990).

2-[(3,4-Dimethoxyphenyl)methyl]-5-phenyl-2-oxazoline (16). Ethyl (3,4-dimethoxyphenyl)acetimidate hydrochloride (6.4 g, 29 mmol), which was prepared in quantitative yield (mp 115–117 °C) by using Pinner conditions,[22] and 1-phenylethanolamine (4.0 g, 29 mmol) were suspended in CH_2Cl_2 with stirring for 18 h at ambient temperature. At the end of this time, the suspension was filtered and the filtrate concentrated to yield an oily product which was dissolved in acetone–ether, and petroleum ether was added. The desired product crystallized from the suspension: 7.5 g (25.6 mmol, 85%); mp 59–62 °C; mass spectrum, m/e 297 (M$^+$, free base); IR (KBr) 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.4–4.5 (10 H, m), 5.4 (1 H, t), 6.6–7.0 (3 H, m), 7.0–7.4 (5 H, m).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.49; H, 6.46; N, 4.67.

2-[(2-Chloro-3,4-dimethoxyphenyl)methyl]-5-phenyl-2-oxazoline (24). In a stirred methylene chloride solution of 1-phenylethanolamine (3.03 g, 22 mmol) was suspended ethyl (2-chloro-3,4-dimethoxyphenyl)acetimidate hydrochloride (6.5 g, 22 mmol, which was prepared in 94% yield (mp 111–114 °C) by using Pinner conditions.[22] After being stirred at room temperature 18 h, the suspension was filtered and the filtrate concentrated to dryness to yield 5.3 g (16 mmol, 74%) of crude product as an oil: mass spectrum, m/e 331 (M$^+$, free base); IR (film) 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.5–4.6 (10 H, m), 5.5 (1 H, t), 6.9 (2 H, q), 7.2 (5 H, br s); high-resolution mass spectrum, m/e 331.097 ($C_{18}H_{18}ClNO$ required 331.098).

2-[(2-Chloro-3,4-dimethoxyphenyl)methyl]-5-(4-methoxyphenyl)-2-oxazoline (26). In a stirred methylene chloride solution of 1-(4-methoxyphenyl)ethanolamine (0.57 g, 3.4 mmol) was suspended (1.0 g, 3.4 mmol) of ethyl (2-chloro-3,4-dimethoxyphenyl)acetimidate hydrochloride, prepared as described above. After being stirred at ambient temperature 18 h, the suspension was filtered and the filtrate concentrated to yield 1.3 g of crude impure product: IR (film) 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.4–4.4 (13 H, m), 5.5 (1 H, t), 6.65–7.25 (6 H, m); high-resolution mass spectrum, m/e 361.107 ($C_{19}H_{20}ClNO_4$ requires 361.108).

2-(Methylthio)-5-phenyl-2-oxazoline (10). 5-Phenyl-2-oxazolidine-2-thione (**9**;[23] 2.0 g, 11 mmol) was dissolved in methanol along with sodium methylate (0.59 g, 11 mmol) and treated dropwise at 0 °C with methanolic methyl iodide (1.57 g, 11 mmol). The resulting suspension was stirred at room temperature for 16 h, filtered, and concentrated to yield product: 2.0 g (10.4 mmol, 95% yield); bp 97 °C (0.1 mm); IR (film) 1750 (w), 1600 (s), 1275, 1120 (s), 950 (s), 750, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.5 (3 H, s), 4.1 (2 H, octet), 5.7 (1 H, t), 7.35 (5 H, s).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.75; N, 7.25. Found: C, 61.81; H, 5.59; N, 7.64.

2,5-Diphenyl-2-oxazoline (12). 2-(Methylthio)-5-phenyl-2-oxazoline (**10**; 2.0 g, 10 mmol) was dissolved in ether and 25 mg of bis[(1,1′-diphenylphosphino)ferrocene]palladium(II) chloride (**14**)[12b] was added under nitrogen with stirring. To this stirred suspension was added phenylmagnesium bromide (12 mmol). The resulting suspension was stirred at room temperature 16 h, poured onto NH_4Cl(aq), and extracted with ether several times. The combined and dried ether layer was concentrated to yield 1.8 g (8.07 mmol, 81%) of the desired product: bp 120 °C (0.1 mm); mass spectrum, m/e 223 (M$^+$); IR (film) 1775 (w), 1650 (s), 1350 (s), 1060, 775, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.75–4.7 (2 H, octet), 5.65 (1 H, dd), 7.1–8.15 (10 H, m).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.39; H, 5.80; N, 6.40.

2-(4-Methoxyphenyl)-5-phenyl-2-oxazoline (13). The same conditions as above for preparation off **12** were used to prepare 3.3 g of impure **13** from 3.5 g (18 mmol) of 2-(methylthio)-5-phenyl-2-oxazoline (**10**) and (4-methoxyphenyl)magnesium bromide: IR (film) 1775 (w), 1650 (s), 1500 (s), 1250 (s), 840, 750, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.8 (3 H, s), 3.7–4.7 (2 H, m), 5.6 (1 H, t), 7.5 (4 H, q), 7.4 (5 H, s); high-resolution mass spectrum, m/e 253.110 ($C_{16}H_{15}NO_2$ requires 253.110).

A second component, *N*-(β-hydroxy-2-phenylethyl)bis(4-methoxyphenyl)methylimine (**35**) was isolated from the reaction: mp 126–128 °C (acetone–hexanes); mass spectrum, m/e 361 (M$^+$); IR (KBr) 3420, 3200, 1610, 1520, 1250 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$)

(22) Dox, A. W. "Organic Synthesis", Wiley: New York, 1941; Collect. Vol. I, p 5.

(23) Kjaer, A.; Gmelin, R. *Acta Chem. Scand.* **1957**, *11*, 906.

3.45 (2 H, d), 3.88 (6 H, m), 5.2 (1 H, m), 6.8–8.0 (13 H, m).

Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.21; H, 6.43; N, 3.83.

General Procedure for Diborane Reduction of 2-Oxazolines (4). The 2-oxazolines 4 listed in Table I were treated with 2–3 equiv of B_2H_6 in THF at reflux for the specified time. At the end of that time, the solvent was removed and the residue dissolved in 10% HCl. The acidic aqueous solution was washed with ether, basified with K_2CO_3(aq), and extracted several times with chloroform. The combined and dried ($MgSO_4$) organic solution was concentrated to yield alcohols 5.

***N*-(2-Phenylethyl)(3,4-dimethoxyphenyl)acetamide (18).** 5-Phenyl-2-(3,4-dimethoxyphenyl)-2-oxazoline (16; 0.5 g, 1.7 mmol) was dissolved in 100 mL of ethanol and the solution acidified with 4 mL of concentrated hydrochloric acid. To this solution was added 200 mg of 10% palladium on carbon, and the solution was kept under 50-psi hydrogen pressure in a Parr apparatus for 13 h. At the end of this time, the suspension was filtered and concentrated to yield 0.5 g (1.67 mmol, 98%) of amide 18: mp 108 °C; mass spectrum, *m/e* 299 (M^+); IR (KBr) 1640 (s), 1250 (s) cm^{-1}; ^1H NMR ($CDCl_3$) 2.70 (2 H, t), 3.43 (4 H, m), 3.78 (3 H, s), 3.84 (3 H, s), 6.5–7.3 (8 H, m).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.67. Found: C, 71.81; H, 7.13; N, 4.62.

***N*-(2-Cyclohexylethyl)(3,4-dimethoxyphenyl)acetamide (19).** 5-Phenyl-2-(3,4-dimethoxyphenyl)-2-oxazoline (16; 0.5 g, 1.7 mmol) was dissolved in 100 mL of ethanol and the solution acidified with 4 mL of concentrated hydrochloric acid. Platinum oxide (50 mg) was added, and the suspension was kept under hydrogen pressure (50 psi) for 13 h and then filtered. The filtrate was concentrated to yield an oil which was basified with 10% NaOH and extracted with methylene chloride. The combined and dried organic layer was concentrated to yield a white solid: 0.4 g (1.31 mmol, 77%); mp 100–102 °C; mass spectrum, *m/e* 305 (M^+); IR (KBr) 3200 (s), 1230 (s), 1260 (s), 1030 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.5–2.0 (13 H, m), 2.5–3.5 (4 H, m), 3.75 (6 H, s), 6.9 (3 H, m), 7.8 (1 H, t, NH).

Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.71; H, 8.34; N, 4.23.

4-Phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (30). *N*-[(β-Hydroxy-2-phenyl)ethyl]-(4-methoxyphenyl)methylamine (28; 0.4 g, 1.55 mmol) was suspended in a mixture of trifluoroacetic acid (1 mL), sulfuric acid (1 mL), and methylene chloride (10 mL). The suspension was heated under reflux 0.5 h and then concentrated to yield an oil that was basified with K_2CO_3(aq) and extracted with chloroform several times. The combined and dried ($MgSO_4$) organic solution was concentrated to yield 0.45 g of crude product. This material was dissolved in ethanolic hydrogen chloride and recrystallized from ethanol–ether to yield product: 0.35 g (1.27 mmol, 82%); mp (hydrochloride) 238–239 °C; mass spectrum, *m/e* 239 (M^+); IR (KBr) 1600 (s), 1500 (s), 1280, 1250, 700; ^1H NMR (Me_2SO-d_6) δ 3.40 (2 H, m), 3.55 (3 H, s), 4.35 (2 H, s), 4.45 (1 H, dd), 6.20 (1 H, d), 6.75 (1 H, dd), 7.2 (6 H, m).

Anal. Calcd for $C_{16}H_{18}ClNO$: C, 69.69; H, 6.58; N, 5.08. Found: C, 69.31; H, 6.63; N, 4.98.

4-Phenyl-1,2,3,4-tetrahydroisoquinoline (29). *N*-(β-Hydroxy-2-phenylethyl)benzylamine (15; 0.35 g, 154 mmol) was treated as above to yield the desired product 29: 78% yield (0.25 g, 1.2 mmol); mp (hydrochloride 224–225 °C; IR (KBr) 1575, 750 (d), 705; ^1H NMR (Me_2SO-d_6) δ 3.5 (2 H, m), 4.3 (3 H, m), 6.7 (1 H, m), 7.25 (8 H, m).

Anal. Calcd for $C_{15}H_{16}ClN$: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.31; H, 6.60; N, 5.67.

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Registry No. 9, 3433-15-6; 10, 81316-48-5; 12, 22020-69-5; 13, 81316-49-6; 15, 27159-30-4; 16, 81316-50-9; 17, 20011-97-6; 18, 3972-81-4; 19, 81316-51-0; 20, 7127-19-7; 21, 104-63-2; 22, 81316-52-1; 23, 81316-53-2; 24, 81316-54-3; 25, 67287-37-0; 26, 81316-55-4; 27, 71636-38-9; 28, 81316-56-5; 29, 75626-12-9; 29 HCl, 6109-35-9; 30, 81316-57-6; 30·HCl, 81316-58-7; 32, 67287-53-0; 33, 81316-59-8; 34, 81316-60-1; 35, 81316-61-2; 2,3-dichlorobenzonitrile, 6574-97-6; ethanolamine, 141-43-5; ethyl(3,4-dimethoxyphenyl)acetimidate hydrochloride, 81316-62-3; 1-phenylethanolamine, 7568-93-6; ethyl(2-chloro-3,4-dimethoxyphenyl)acetimidate hydrochloride, 81316-63-4; 1-(4-methoxyphenyl)ethanolamine, 55275-61-1.

Supplementary Material Available: Continuation of Table I with IR, NMR, and mass spectral data (1 page). Ordering information is given on any current masthead page.

Reexamination of Stereochemical Issues Concerning 2-Phenyl-1,2-dihydropyridine–Maleimide Cycloadditions

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The reaction of *N*-acetyl- and *N*-(carbomethoxy)-2-phenyl-1,2-dihydropyridines **1d–e** with maleimides **5a–c** has been shown by chemical correlation and X-ray analysis to proceed with only *endo*-maleimide, *anti*-phenyl stereoselectivity, rather than via stereoselectivity favoring a *syn*-phenyl configuration as previously described.[6] The X-ray crystal structure indicates a planar s-cis conformation for the *N*-carbomethoxy function of 2-(carbomethoxy)-3-*endo*-phenyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic acid *N*-phenylimide (**7d**), not tetrahedral configuration about nitrogen as earlier proposed.[6]

Diels–Alder cycloaddition reactions utilizing *N*-acyl-1,2-dihydropyridines **1** offer a convenient pathway to isoquinuclidines **3**, substituted at the 7- and/or 3,7-positions. A number of 7-substituted[1a–f] and 3-substituted[1g] iso-

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