Synthesis of Hexahydro-5*H*-benz[*g*]imidazo[2,1-*a*]-isoindole **2** *via* an Intramolecular Diels-Alder Reaction and a Novel Lawesson's Reagent Mediated Cyclization

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The 2-(5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthyl)imidazoline **1** is a recently reported potent *alpha*-adrenergic agent [1]. In continuation of our work on the synthesis of potential adrenergic agents we required imidazoisoindole **2** in order to investigate the biological effects of incorporation of additional rigidity into the parent system. This paper describes the synthesis of **2** *via* an intramolecular Diels-Alder reaction and a novel Lawesson's reagent mediated cyclization.

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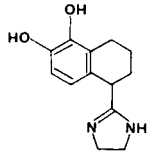
We envisioned a short synthesis of compound **2** as illustrated in Scheme I. The known benzocyclobutane carboximidate **4** [1] was prepared by reaction of the corresponding nitrile **3** with gaseous hydrogen chloride in a



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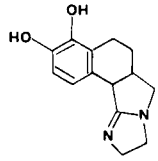
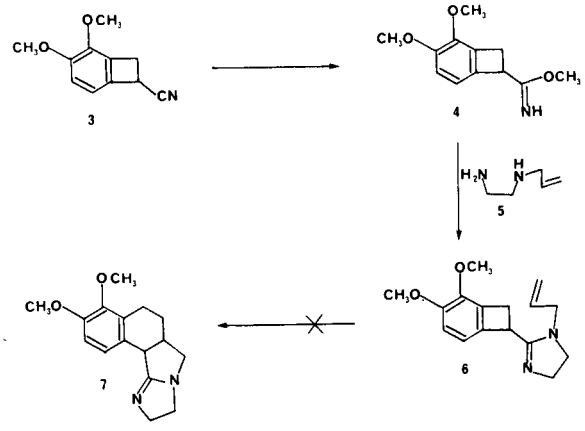


2

solution of methylene chloride/diethyl ether/methanol at 0°. The imino-ether **4** was dissolved in ethanol and treated with *N*-allylethylenediamine (**5**) [2] at room temperature for 3 hours to afford the *n*-allylimidazoline derivative **6** in 50% yield.

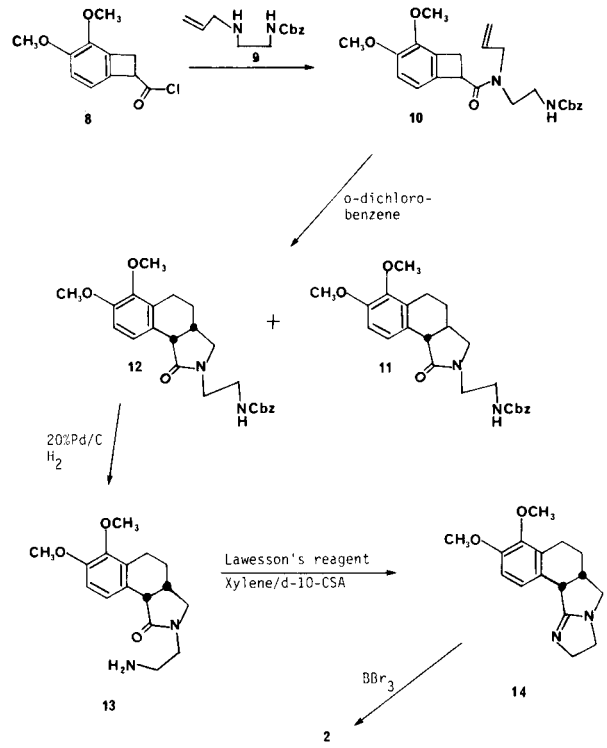
Scheme I



The thermolysis of the *N*-allylbenzocyclobutane **6** in *o*-dichlorobenzene or bromobenzene at various temperatures was expected to give **7** *via* a well precedented electrocyclic ring opening and intramolecular cycloaddition sequence, however, this was unsuccessful [3]. We attributed the failure of this ring closure to the rigidity in the quinodimethane intermediate. This rigidity restricts access of the allyl double bond to the ends of the quinodimethane in the transition state required for cyclization.

Examination of Dreiding models suggested that without the rigidity imparted by the imidazoline ring the required cyclization should proceed smoothly. Accordingly, an alternative synthesis was designed as shown in Scheme II. In this approach, since the imidazoline ring is formed at the last step in the synthesis, we felt this would circumvent the problem.

Scheme II



The open chain benzocyclobutane **10**, the key intermediate in Scheme II, was synthesized in a convergent fashion starting with the benzocyclobutane acid chloride **8** [4] and the selectively differentiated ethylenediamine derivative **9**. This afforded an 88% yield of the desired amide **10**. Thermolysis of **10** afforded the desired tricyclic amides **11** and **12** in a 1:1 *cis*/*trans* mixture which could be easily separated by flash column chromatography. This was in accord with our speculation about the importance of flexibility in the intramolecular Diels-Alder reaction. The *trans* lactam **11** could be converted to the corresponding *cis* lactam **12** either by refluxing in xylene with a catalytic amount of *p*-toluenesulfonic acid or by stirring in DBU/tetrahydrofuran at room temperature. The *N*-carbobenzoxy group in **12** was removed by hydrogenolysis [5] with 20% palladium on carbon in either methanol or methyl cellosolve affording the corresponding *cis* aminolactam **13**.

We were unable to achieve cyclization of **13** either in refluxing toluene or xylene in the presence of d-10 camphorsulfonic acid. In view of this, we felt the thioamide might be more susceptible to nucleophilic addition and therefore sought that species. Treatment of **13** with Lawesson's reagent [6] in the presence of a catalytic amount of d-10 camphorsulfonic acid in refluxing xylene afforded the desired imidazoisoindole **14** in 35-40% yield. The methyl ethers could easily be cleaved to the corresponding catechol **2** using boron tribromide [7] in excess, followed by a methanol quench, and removal of the boron as the trimethyl borate/methanol azeotrope.

In summary, we have found that an intramolecular Diels-Alder reaction can be promoted by the preparation of a molecule which has sufficient flexibility to allow appropriate juxtaposition of the reactive groups in the transition state. We have also shown that intramolecular cyclization of an amide can be achieved by treatment with Lawesson's reagent possibly involving the thioamide as an intermediate or perhaps trapping of another species which is in the pathway between the amide and thioamide.

EXPERIMENTAL

The nmr spectra were recorded on either a GE QE-300 or a Nicolet HT-360 wide bore instrument. The infrared spectra were recorded on a Perkin-Elmer 521 spectrophotometer. Mass spectra were obtained with either a Kratos MS50 high resolution (10,000 resolution) with a DS/55 Rev. 4.0 software and Nova/312 computer or a Varian CH7 spectrometer. Melting points were determined on a Thomas-Hoover "Uni-Melt" melting point apparatus and are uncorrected. Elemental analyses were done in house and determined values are within 0.4% of theoretical values.

3,4-Dimethoxy-2'-(1-benzocyclobutane)-*N*-allylimidazoline (**6**).

An ethanol (20 ml) suspension of methyl-3,4-dimethoxybenzocyclobutane-1-carboximidate (**4**) (1.0 g, 3.9 mmoles) was treated with *N*-allylethylenediamine (**5**) (0.5 g, 5 mmoles). The resulting clear solution was stirred at room temperature under nitrogen for 3 hours. The solvent was removed and the oily residue was partitioned between 2*N* hydrochloric acid and methylene chloride. The acidic layer was basified with 2*N* sodium hydroxide and extracted with methylene chloride. The organic layer was separated, dried (magnesium sulfate), filtered, and evaporated affording 530 mg (50%) of the desired compound **6** as an oil; nmr (deuteriochloroform): δ 3.0-3.5 (m, 4H), 3.6-3.85 (m, 4H), 3.8 (s, 3H), 3.9 (s, 3H), 4.2 (t, 1H, J = 5 Hz), 5.0-5.3 (m, 2H), 5.4-6.1 (m, 1H), 6.6 (d, 1H, J = 8.5 Hz), 6.7 (d, 1H, J = 8.5 Hz); ms: 272 (M^+), 257 (M^+-15).

Anal. Calcd. for $C_{16}H_{21}ClN_2O_2 \cdot ½\ H_2O$ [8]: C, 60.47; H, 6.97; N, 8.82. Found: C, 60.07; H, 6.74; N, 8.81.

N-Allyl-*N'*-carbobenzoxyethylenediamine (**9**).

A solution of *N*-carbobenzoxyethyl bromide (24.0 g, 0.093 mole) in ethanol (100 ml) was added to a solution of allylamine (30 ml, 0.4 mole). The resulting solution was allowed to reflux for 3 hours and the solvent evaporated to a gummy residue. This was chromatographed on basic alumina and eluted with ethanol-methylene chloride (2/98) and afforded 17.4 g (80%) of a white solid. An analytical sample was prepared by recrystallization from ether-hexane mp 105-107°; nmr (deuteriochloroform): δ 3.0-3.25 (m, 2H), 3.6 (m, 4H), 5.1 (s, 2H), 5.5-6.4 (m, 3H), 7.3 (s, 5H), 8.7 (bs, 1H); ms: 234 (M^+).

Anal. Calcd. for $C_{13}H_{19}ClN_2O_2 \cdot ½\ H_2O$ [9]: C, 55.82; H, 7.21; N, 10.01. Found: C, 56.08; H, 6.99; N, 10.01.

3,4-Dimethoxy-*N*-allyl-*N'*-carbobenzoxybenzocyclobutane-1-carboxamide (**10**).

A solution of the benzocyclobutane acid chloride **8** (3.0 g, 13.3 mmoles) in methylene chloride (25 ml) was added to a solution of *N*-allyl-*N'*-carbobenzoxyethylenediamine (**9**) (3.5 g, 15 mmoles), and triethylamine (4 ml) in methylene chloride (25 ml) at 0° under nitrogen. The reaction mixture was allowed to warm to room temperature, stirred for 2 hours and diluted with methylene chloride (100 ml) and water. The organic layer was separated and successively washed with 1*N* hydrochloric acid, brine, aqueous sodium bicarbonate, and then dried (magnesium sulfate). The solvent was evaporated and the residue crystallized from ether-hexane to afford 4.83 (88%) of a white crystalline solid, mp 160-161°; nmr (deuteriochloroform): δ 3.3-3.7 (m, 6H), 3.75-3.85 (m, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 4.4 (dd, 1H, J = 4.0, 6.0 Hz), 5.05 (s, 2H), 5.2-5.3 (m, 2H), 5.8-5.9 (m, 1H), 6.65 (d, 1H, J = 8.0 Hz), 6.75 (d, 1H, J = 8.0 Hz), 7.35 (s, 5H); ms: 424 (M^+).

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67.92; H, 6.60; N, 6.60. Found: C, 67.72; H, 6.51; N, 6.44.

Thermolysis of **10**.

A solution of the benzocyclobutane **10** (4.5 g, 0.01 mole) in *o*-dichlorobenzene (150 ml) was degassed with nitrogen for 20 minutes and allowed to reflux for 8 hours. The reaction mixture was concentrated to ~1/4 volume *in vacuo*. Chromatography of the residue on silica gel eluting with ethyl acetate-hexane (1/1) furnished 300 mg (6.6%) unchanged **10**, 1.98 g (44%) of *trans* lactam **11**, and 1.9 g (44%) of *cis* lactam **12**.

2-[2-[(Carbobenzoxy)amino]ethyl]-*trans*-3a,4,5,9b-tetrahydro-6,7-dimethoxy-1*H*-benz[*e*]isoindole-1(2*H*)-one (**11**).

Compound **11** had a mp of 147-148°; nmr (deuteriochloroform): δ 2.05-2.2 (m, 2H), 2.8-3.1 (m, 5H), 3.2 (t, 1H, J = 8.0 Hz), 2.35-3.5 (m, 4H), 3.8 (s, 3H), 3.87 (s, 3H), 5.1 (dd, 2H, J = 12.0, 15.0 Hz), 6.8 (d, 1H, J = 8.0 Hz), 7.3 (s, 5H), 7.95 (d, 1H, J = 8.0 Hz); ms: 424 (M^+); ir (chloroform): 3500, 2900, 1720 and 1640 cm^{-1}.

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67.92; H, 6.60; N, 6.60. Found: C, 67.75; H, 6.56; N, 6.48.

2-[2-[(Carbobenzoxy)amino]ethyl]-*cis*-3a,4,5,9b-tetrahydro-6,7-dimethoxy-1*H*-benz[*e*]isoindole-1(2*H*)-one (**12**).

Compound **12** had a mp of 155-156°; nmr (deuteriochloroform): δ 1.5-1.6 (m, 1H), 1.85-1.95 (m, 1H), 2.5-2.7 (m, 2H), 2.8-2.9 (m, 1H), 3.15 (d, 1H, J = 9.0 Hz), 3.35-3.45 (m, 4H), 3.5 (d, 1H, J = 9.0 Hz), 3.65 (dd, 1H, J = 6.0, 9.0 Hz), 3.75 (s, 3H), 3.85 (s, 3H), 5.05 (dd, 2H, 11.0, 16.0 Hz), 6.85 (d, 1H, J = 9.0 Hz), 7.3 (d, 1H, J = 9.0 Hz); ms: 424 (M^+); ir (chloroform):

3490, 2950, 1720 and 1680 cm^{-1}.

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67.92; H, 6.60; N, 6.60. Found: C, 67.73; H, 6.68; N, 6.56.

2-(2-Aminoethyl)-*cis*-3a,4,5,9b-tetrahydro-6,7-dimethoxy-1*H*-benz[*e*]-isoindole-1(2*H*)-one (**13**).

A solution of the *cis* lactam **12** (1.2 g, 2.8 mmoles) in methyl cellosolve (100 ml) was hydrogenated with 20% Pd/C (150 mg) for 4 hours at room temperature and 3 atmospheres. The solvent was evaporated and the crystalline residue was triturated with ether to afford 600 mg (74%) of a white solid **13**; mp 214-216° dec; nmr (DMSO-d_6/deuteriochloroform): δ 1.35-1.5 (m, 1H), 1.8-1.9 (m, 1H), 2.4-2.8 (m, 4H), 3.2-3.6 (m, 6H), 3.67 (s, 3H), 3.8 (s, 3H), 6.7 (d, 1H, J = 8.0 Hz), 7.15 (d, 1H, J = 8.0 Hz); ms: 290 (M^+), 273 (M^+-17); ir (potassium bromide): 3300, 1710 and 1620 cm^{-1}.

Anal. Calcd. for $C_{16}H_{23}ClN_2O_3 \cdot ½\ H_2O$: C, 57.23; H, 7.15; N, 8.34. Found: C, 56.90; H, 7.03; N, 8.21.

2,3,5a,6,7,11b-Hexahydro-8,9-dimethoxy-5*H*-benz[*g*]imidazo[2,1-*a*]isoindole (**14**).

A mixture of the *cis* lactam **13** (4.0 g, 13.8 mmoles), d-10 camphorsulfonic acid (400 mg, ~10% by weight) and Lawesson's reagent (3.35 g, 8.3 mmoles) in xylene (600 ml) was allowed to reflux for 72 hours under a nitrogen atmosphere. After cooling, the reaction mixture was concentrated to 1/3 volume and treated with hexane to precipitate the crude product. The dark precipitates were dissolved in methylene chloride and extracted into 2*N* hydrochloric acid. The acidic layer was separated, basified with 2*N* sodium hydroxide, and extracted with ether-methylene chloride (1/1). The organic layer was washed with brine, dried (magnesium sulfate), filtered and evaporated to afford 1.68 g of a yellow solid which was converted to the hydrochloride salt. Trituration with acetonitrile afforded 1.41 g (38%) **14**; nmr (DMSO-d_6/deuteriochloroform): δ 1.5-1.6 (m, 1H), 1.8-1.9 (m, 1H), 2.45-2.55 (m, 1H), 2.65-2.75 (m, 1H), 2.8-2.9 (m, 1H), 3.1 (dd, 1H, J = 2.5, 10.0 Hz), 3.4-3.75 (m, 6H), 3.74 (s, 3H), 3.82 (s, 3H), 6.85 (d, 1H, J = 8.0 Hz), 7.2 (d, 1H, J = 8.0 Hz); ms: 272 (M^+).

Anal. Calcd. for $C_{16}H_{21}ClN_2O_2 \cdot ¼\ H_2O$: C, 61.34; H, 6.92; N, 8.94. Found: C, 61.41; H, 6.82; N, 8.94.

2,3-5a,6,7,11b-Hexahydro-5*H*-benz[*g*]imidazo[2,1-*a*]isoindole-8,9-diol Hydrobromide **2**.

A suspension of the tetracyclic-dimethyl ether **14**, in methylene chloride (20 ml) was cooled to −78° in an atmosphere of nitrogen and was treated with a solution of boron tribromide (0.76 ml, 8 mmoles) in 10 ml of methylene chloride. The reaction mixture was allowed to warm to −20° and stirred at this temperature for 3 hours, cooled to −78°, and quenched carefully with methanol. The solvent was evaporated and the residue was again dissolved in methanol and stripped. The residue was triturated with methanol-acetonitrile to afford a tan solid 340 mg (52%) of **2**, mp 301-303° dec; nmr (DMSO-d_6): δ 1.6-1.8 (m, 2H), 2.55-2.65 (t, 2H, J = 9.0 Hz), 3.2-3.4 (m, 2H), 3.6-3.85 (m, 3H), 4.05-4.15 (m, 2H), 4.3 (d, 1H, J = 9.0 Hz), 6.78 (d, 1H, J = 9.0 Hz), 6.7 (d, 1H, J = 9.0 Hz), 8.4 (bs, 1H), 9.3 (bs, 1H), 9.8 (bs, 1H); ms: 244 (M^+); ir (potassium bromide): 3250-3100 and 1630 cm^{-1}.

Anal. Calcd. for $C_{14}H_{17}BrN_2O_2 \cdot H_2O$: C, 48.98; H, 5.25; N, 8.16. Found: C, 48.99; H, 4.95; N, 7.99.

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[8] Analysis was obtained on hydrochloride salt of **6**.

[9] We were unable to obtain a satisfactory analysis on the free base of **9**. However, conversion of **9** to the corresponding hydrochloride salt provided an appropriate combustion analysis.