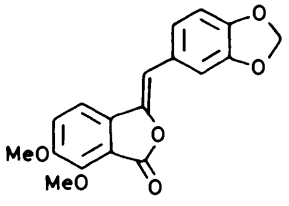
A Simple Total Synthesis of the Isoindolobenzazepine Alkaloids Lennoxamine and Chilenamine

Elio Napolitano,* Guido Spinelli, Rita Fiaschi, and Antonio Marsili
Istituto di Chimica Organica della Facoltà di Farmacia, Via Bonnano, 6, 56100, Pisa, Italy

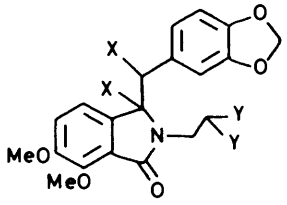
Lennoxamine (**8**) and chilenamine (**9**) have been synthesized from 3-(3,4-methylenedioxybenzylidene)-6,7-dimethoxyphthalide (**1**) in four and five high-yielding steps, respectively. The key step of the process is the cyclization, by intramolecular alkylation, of 3-(3,4-methylenedioxybenzyl)-6,7-dimethoxyphthalimidin-2-ylacetaldehyde dimethyl acetal (**3**) to 13,13a-dihydro-3,4-dimethoxy-10,11-methylenedioxyisoindolo[1,2-*b*][3]benzazepin-5-one (**7**). Attempts to prepare (**3**) by base-catalysed cyclization of 3,4-dimethoxy-3',4'-methylenedioxystilbene-2-(2,2-dimethoxyethyl)carboxamide (**15**) were unsuccessful.

Isoindolobenzazepine alkaloids are a new class of alkaloids, belonging to the aporhoeadane series, recently isolated from Chilean Berberidaceae.[1] Although biogenetically related to protoberberines and usually ranked as isoquinoline alkaloids, the distinctive structural feature of their molecules is the presence of an isoindolo[1,2-*b*][3]benzazepine system, bearing oxygenated substituents in the benzene rings at positions 3, 4, 10, and 11 (usually two methoxy and one methylenedioxy group). Differences among these alkaloids lie mainly in the oxidation of the heterocyclic portion. Concerning their obtention by synthetic routes, lennoxamine (**8**) and chilenamine (**9**) were already known as products derived from other isoquinoline alkaloids, and for (**9**) (also named Schoepf-Schweickert base VI) a total synthesis has also been reported.[2]

Previous work from this laboratory has shown that 3-benzylphthalimidin-2-ylacetic acid derivatives may be converted into isoindolo[1,2-*b*][3]benzazepines by intramolecular acylation.[3] Although our attempts to apply such a process to methylenedioxy substituted substrates until now have failed,[4] we have devised a simple and high-yielding total synthesis of lennoxamine and chilenamine, which is a variant of the previously described approach. This synthesis uses, as the precursor of the isoindolobenzazepine system, a suitably substituted 3-benzylphthalimidin-2-ylacetaldehyde dimethyl acetal in the place of the corresponding acetic acid derivative.



(**1**)

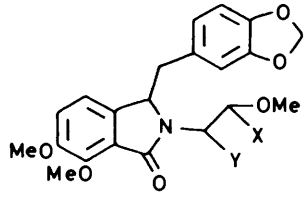


(**2**) X,X = bond, Y = OMe
(**3**) X = H, Y = OMe
(**4**) X = H, Y,Y = O

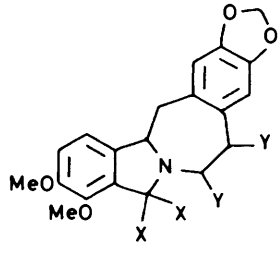
Results and Discussion

3-(3,4-Methylenedioxybenzylidene)-6,7-dimethoxyphthalide (**1**) was condensed with aminoacetaldehyde dimethyl acetal to give a high yield of the phthalimidine (**2**). The likely intermediate adduct (a 3-benzyl-3-hydroxyphthalimidine derivative)[5] was directly dehydrated to compound (**2**), without isolation, by the action of acid in the presence of methyl orthoformate as a water scavenger (to minimize the possible hydrolysis of the acetal group). The ^{1}H n.m.r. spectrum of the crude compound (**2**) exhibits a single vinyl signal: although no additional data are available to establish its configuration, this may tentatively be assumed to be *E* on the basis of previous results.[3,6] Compound (**2**) was quantitatively converted into (**3**) by catalytic hydrogenation.

The cyclization of (**3**) appeared to be rather troublesome, and a number of conditions were tested in order to optimize the reaction. Reaction of this compound with formic acid, or with sulphuric acid in acetone, which are reported to induce cyclization of appropriate amidoacetals to tetrahydroisoquinolines[7] led only to hydrolysis of the acetal group to form compound (**4**). No cyclization was observed even when the temperature was raised, compound (**4**) being formed again, but in lower yield, owing to extensive decomposition leading to complex mixtures of uncharacterizable products. Neither compound (**3**) nor (**4**) underwent cyclization in other protic solvents (*e.g.* acetic acid, ethanol) in the presence of a variety of acid catalysts. Boron trifluoride–diethyl ether complex in dichloromethane also caused decomposition to tarry products, and toluene-*p*-sulphonic acid caused conversion of compound (**3**) into the tetracycle (**7**), but in very low yield.



(**5**) X = Cl, Y = H
(**6**) X,Y = bond

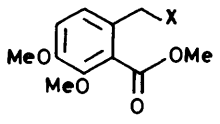


(**7**) X = O, Y,Y = bond
(**8**) X,X = O, Y = H
(**9**) X = Y = H

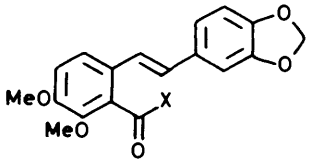
Finally, when compound (**3**) was treated with acetyl chloride in dichloromethane, and the reaction product heated with zinc chloride in tetrahydrofuran, compound (**7**) was formed in good yield. Although no attempt was made to fully characterize the intermediate product, n.m.r. analysis indicated that it may be a mixture of the diastereoisomeric chloro and vinyl ethers (**5**) and (**6**). Direct treatment of compound (**3**) with hydrogen chloride and zinc chloride in boiling tetrahydrofuran also gave compound (**7**); however, this procedure appeared less practical. Catalytic hydrogenation of this cyclic product gave lennoxamine

(**8**) from which, by reduction with borane–tetrahydrofuran complex in tetrahydrofuran, chilenamine (**9**) was obtained.

In the hope of finding a shorter route to intermediate (**3**), an alternative approach was also attempted, involving the base-catalysed cyclization of stilbene-2-carboxamides.[8] The required precursor (**15**) was obtained as follows. Treatment of methyl



(**10**) X = OMe
(**11**) X = Cl
(**12**) X = $PO(OMe)_2$



(**13**) X = OMe
(**14**) X = OH
(**15**) X = $NHCH_2CH(OMe)_2$

2,3-dimethoxy-5-methoxymethylbenzoate (**10**) (easily obtainable from 3,4-dimethoxybenzyl methyl ether) with acetyl chloride–zinc chloride afforded methyl 5-chloromethyl-2,3-dimethoxybenzoate (**11**) which, on heating with trimethyl phosphite, was transformed into the phosphonate (**12**). Reaction of this compound with 3,4-methylenedioxybenzaldehyde in the presence of potassium t-butoxide gave methyl 3,4-dimethoxy-3′,4′-methylenedioxystilbene-2-carboxylate (**13**) in good yield. Since the condensation of (**13**) with aminoacetaldehyde dimethyl acetal appeared to be exceedingly slow, the ester was hydrolysed to the acid (**14**) which, on treatment with oxalyl chloride in benzene, afforded the corresponding acid chloride which was readily converted into the amide (**15**). However, this amide failed to undergo the expected cyclization to compound (**3**). This behaviour could be due to steric hindrance, generated by the methoxy group at C-3, which prevents the amide anion from achieving a suitable orientation for attack on the double bond.

Experimental

M.p.s were determined with a Kofler apparatus; i.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 197 spectrophotometer, and the most intense and/or representative absorption bands are given; n.m.r. spectra were recorded with a Varian EM 360A instrument, except for that of compound (**7**) which was recorded on a Varian CFT-20 spectrometer, and the most significant signals are quoted in p.p.m. from $SiMe_4$ as the internal standard; evaporation of solvents was carried out on a rotary evaporator under reduced pressure.

3-(3,4-*Methylenedioxybenzylidene*)-6,7-*dimethoxyphthalimidin*-2-*ylacetaldehyde Dimethyl Acetal* (**2**).—A mixture of 3-(3,4-methylenedioxybenzylidene)-6,7-dimethoxyphthalide (**1**) (5.0 g, 15.4 mmol, a mixture of *E*- and *Z*-isomers),[9] aminoacetaldehyde dimethyl acetal (1.8 ml, 16.8 mmol), and dry dioxane (50 ml) was refluxed under nitrogen until t.l.c. (SiO_2–Et_2O) showed almost complete conversion of the phthalide (**1**) (R_F 0.7) into a new compound (R_F 0.25) (12 h). Trimethyl orthoformate (2.5 ml) and oxalic acid monohydrate (1.5 g) were then added and the mixture was refluxed for a further 2 h, after which time it was cooled, made basic by the addition of concentrated ammonia (3 ml), and evaporated. The residue was partitioned between water and dichloromethane and the organic layer was washed with water, dried, and evaporated to afford the *phthalimidine* (**2**) (6.8 g, 96%), which crystallized from methanol as prisms, m.p. 152—154 °C (Found: C, 63.8; H, 5.6; N, 3.2. $C_{22}H_{23}NO_7$ requires C, 63.9; H, 5.6; N, 3.4%); $\nu_{max.}$ 1 630 and 1 680 cm^{-1}; $\delta_H(CDCl_3)$ 3.46 (6 H, s, $CH(OMe)_2$, 3.86 and 4.08 (3 H and 3 H, s, ArOMe), 3.96 (2 H, d, *J* 5.3 Hz, NCH_2CH), 4.70 (1 H, t, *J* 5.3 Hz, NCH_2CH), 6.03 (2 H, s, OCH_2O), 6.50 (1 H, s, vinylic H), 6.83, 6.97, 7.09, and 7.23 (2 H, 4-H and 5-H), and 6.90 (3 H, s, other ArH).

3-(3,4-*Methylenedioxybenzyl*)-6,7-*dimethoxyphthalimidin*-2-*ylacetaldehyde Dimethyl Acetal* (**3**).—Compound (**2**) (5.9 g) was hydrogenated (18 h) in methanol (25 ml) in the presence of 3% Pt–C (0.1 g) to give the *acetal* (**3**) (5.8 g, 98%), which crystallized from dichloromethane–ether as prisms, m.p. 126—127 °C (Found: C, 63.3; H, 6.0; N, 3.2. $C_{22}H_{25}NO_7$ requires C, 63.6; H, 6.1; N, 3.4%); $\nu_{max.}$ 1 665 cm^{-1}; $\delta_H(CDCl_3)$ 3.42 and 3.47 (3 H and 3 H, s, $CH(OMe)_2$, 3.86 and 4.03 (3 H and 3 H, s, ArOMe), 2.50—4.91 (6 H, m, CH_2CH), 5.93 (2 H, s, OCH_2O), and 6.43—7.36 (5 H, m, ArH).

3-(3,4-*Methylenedioxybenzyl*)-6,7-*dimethoxyphthalimidin*-2-*ylacetaldehyde* (**4**).—A mixture of compound (**3**) (0.2 g), acetone (15 ml), water (2 ml), and concentrated sulphuric acid (1 ml) was left overnight at room temperature and then poured into ice-cold water and extracted with dichloromethane. The organic phase was washed with aqueous sodium hydrogen carbonate, dried, and evaporated to afford *compound* (**4**) in quantitative yield, which crystallized from dichloromethane–light petroleum as blades, m.p. 159—161 °C (Found: C, 65.2; H, 5.1; N, 3.6. $C_{20}H_{19}NO_6$ requires C, 65.0; H, 5.2; N, 3.8%); $\nu_{max.}$ 1 660 and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 2.90—3.05 (2 H, m, $ArCH_2$), 3.80, 4.12, 4.45, and 4.77 (2 H, ABq, NCH_2), 3.93 and 4.10 (3 H and 3 H, s, OMe), 4.83 (1 H, m, 3-H), 6.00 (2 H, s, OCH_2O), 6.50—7.36 (5 H, m, ArH), and 9.68 (1 H, s, CHO).

13,13a-*Dihydro*-3,4-*dimethoxy*-10,11-*methylenedioxy*-5H-*isoindolo*[1,2-b][3]*benzazepin*-5-*one* (**7**).—A solution of compound (**3**) (2.0 g) and acetyl chloride (2 ml) in dichloromethane (20 ml) was left overnight at room temperature, and then evaporated. The residue showed on t.l.c. that the starting material had almost completely disappeared, and its ^1H n.m.r. spectrum, in addition to singlets at δ 3.90 (3 H, ArOMe), 4.03 and 4.05 (total intensity 3 H, ArOMe) and 5.93 and 5.95 (total intensity 2 H, OCH_2O), showed a signal whose total intensity corresponded to 3 H, formed by four closely spaced singlets of comparable height (at δ 3.41, 3.46, 3.53, and 3.58), that may be attributed to an OMe group bound to aliphatic carbon. This mixture was dissolved in dry tetrahydrofuran, anhydrous zinc chloride (1.0 g) was added, and the solution was refluxed for 6 h and then evaporated. The residue was taken up in dichloromethane and the solution was washed with water and dried. Evaporation gave *compound* (**7**) (1.4 g, 74%) as a yellow solid, which crystallized from dichloromethane–ether as prisms, m.p. 226—228 °C (Found: C, 68.2; H, 4.8; N, 4.1. $C_{20}H_{17}NO_5$ requires C, 68.4; H, 4.9; N, 4.0%); $\nu_{max.}$ 1 030, 1 260, 1 440, 1 640, and 1 680 cm^{-1}; $\delta_H(CDCl_3)$ 2.81, 2.92, 3.00, 3.11, 3.24, 3.26, 3.44, and 3.46 (2 H, *ABX* pattern 13-H), 3.91 and 4.09 (3 H and 3 H, s, OMe), 4.60, 4.62, 4.72, and 4.73 (1 H, AB*X* pattern 13a-H), 5.64 (1 H, d, *J* 10.3 Hz, 8-H), 5.95 (2 H, s, OCH_2O), 6.69 and 7.17 (2 H and 2 H, s, ArH), and 7.09 (1 H, d, *J* 10.3 Hz, 7-H).

Lennoxamine (**8**) *and Chilenamine* (**9**).—Hydrogenation of compound (**7**) (1.0 g), at room temperature and pressure for 18h in acetic acid (20 ml) in the presence of 3% Pt–C (0.2 g), afforded, after work-up, compound (**8**) in quantitative yield, which crystallized from methanol as prisms, m.p. 228—229 °C (lit.,[10,11] 228—229 °C and 225 °C). The spectroscopic properties of this compound were identical with those reported.[10,11] The amine (**9**) was obtained from compound (**8**) by reduction with borane in tetrahydrofuran using exactly the same procedure described in the literature.[11]

Methyl 2,3-*Dimethoxy*-5-*methoxymethylbenzoate* (**10**) *and Methyl* 5-*Chloromethyl*-2,3-*dimethoxybenzoate* (**11**).—These two products were obtained in 85% overall yield from 3,4-dimethoxybenzyl methyl ether, following exactly the same procedure used to prepare the corresponding ethyl esters.[12] *Compound* (**10**) had b.p. 126 °C/0.1 mmHg; m.p. 44 °C (Found: C, 59.8; H, 6.6. $C_{12}H_{16}O_5$ requires C, 60.0; H, 6.7%); $\nu_{max.}$ 1 060, 1 260, and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 3.32, 3.85, 3.87, and 3.90 (3 H, 3 H, 3 H, and 3 H, s, OMe), 4.40 (2 H, s, CH_2), 6.83, 6.97, 7.03, and 7.17 (2 H, ArH). *Compound* (**11**) had b.p. 142 °C/0.05 mmHg (Found: C, 53.8; H, 5.4. $C_{11}H_{13}ClO_4$ requires C, 54.0; H, 5.3%); $\nu_{max.}$ 1 060, 1 260, and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 3.87 (6 H, s, ArOMe), 3.94 (3 H, s, CO_2Me), 4.58 (2 H, s, CH_2), and 6.83, 6.97, 7.06, and 7.20 (2 H, ABq, ArH).

Dimethyl (2-*Methoxycarbonyl*-3,4-*dimethoxybenzyl*)*phosphonate* (**12**).—A solution of the chloro ester (**11**) (10.0 g) in trimethyl phosphite (30 ml) was refluxed for 18 h under nitrogen. Upon cooling and dilution with ether, the phosphonate (**12**) precipitated as a solid (10.0 g, 77%) which crystallized from dichloromethane–ether as prisms, m.p. 91—93 °C (Found: C, 48.9; H, 5.9. $C_{13}H_{19}O_7P$ requires C, 49.1; H, 6.0%); $\nu_{max.}$ 1 030, 1 050, 1 260, and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 3.25 (2 H, d, *J* 22 Hz, CH_2), 3.70 (6 H, d, *J* 11 Hz, POMe), 3.88 (6 H, s, ArOMe), 3.95 (3 H, s, CO_2Me), and 6.90—7.37 (2 H, m, ArH).

Methyl 3,4-*Dimethoxy*-3′,4′-*methylenedioxystilbene*-2-*carboxylate* (**13**).—To a solution of the phosphonate (**12**) (0.9 g, 2.8 mmol) and 3.4-methylenedioxybenzaldehyde (0.48 g, 3.2 mmol) in dry tetrahydrofuran, stirred under nitrogen, potassium t-butoxide (0.37 g, 3.2 mmol) was added in one portion at 0 °C. After the addition the mixture was stirred for 1 h at room temperature and then acidified with acetic acid, washed with brine, dried, and evaporated. The residue, on crystallization from dichloromethane–methanol, gave the *carboxylate* (**13**) (0.7 g, 73%) as prisms, m.p. 110—112 °C (Found: C, 66.5; H, 5.1. $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3%); $\nu_{max.}$ 1 260, 1 590, and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 3.87 (6 H, s, ArOMe), 3.93 (3 H, s, CO_2Me), 5.93 (2 H, s, OCH_2O), and 6.83—7.04 (7 H, m, vinylic H and ArH).

3,4-*Dimethoxy*-3′,4′-*methylenedioxystilbene*-2-*carboxylic Acid* (**14**).—A stirred mixture of the ester (**13**) (2.0 g, 5.8 mmol), potassium hydroxide (0.5 g, 8.9 mmol), and methanol (20 ml) was refluxed for 18 h under nitrogen, and then evaporated. The residue was taken up in water and the solution, after acidification with 2M-hydrochloric acid, was extracted with chloroform. Evaporation of the dried organic phase and crystallization of the residue from dichloromethane–ether afforded (**14**) (1.5 g, 79%) as prisms, m.p. 149—151 °C (Found: C, 65.7; H, 4.9. $C_{18}H_{16}O_6$ requires C, 65.85; H, 4.9%); $\nu_{max.}$ 1 680 cm^{-1}; $\delta_H(CDCl_3)$ 3.89 and 3.94 (3 H and 3 H, s, OMe), 5.93 (2 H, s, OCH_2O), and 6.67—7.48 (7 H, m, vinylic H and ArH).

3,4-*Dimethoxy*-3′,4′-*methylenedioxystilbene*-2-(2,2-*dimethoxyethyl*)*carboxamide* (**15**).—Acid (**14**) (2.0 g, 6.1 mmol) was converted into the corresponding chloride by reaction with oxalyl chloride as described.[13] The crude acid chloride was dissolved in dichloromethane (30 ml) and treated at 0 °C, with stirring, with aminoacetaldehyde dimethyl acetal (0.95 g, 9 mmol) and with 1M-sodium hydroxide (15 ml). After 15 min the organic phase was washed with water, dried, and evaporated. The residue, on crystallization from dichloromethane–ether, afforded the *carboxamide* (**15**) as prisms, m.p. 98—99 °C (Found: C, 63.3; H, 6.1; N, 3.3. $C_{22}H_{25}NO_7$ requires C, 63.6; H, 6.0; N, 3.4%); $\nu_{max.}$ 1 250 and 1 630 cm^{-1}; $\delta_H(CDCl_3)$ 3.40 [6 H, s, $CH(OMe)_2$], 3.65 (2 H, t, *J* 5 Hz; after prolonged treatment with D_2O, d, *J* 5 Hz, NCH_2), 3.88 (6 H, s, ArOMe), 4.53 [1 H, t, *J* 5 Hz, $CH(OMe)_2$], 5.97 (2 H, s, OCH_2O), 6.20 (1 H, t, *J* 5 Hz, NH), and 6.70—7.47 (7 H, m, vinylic H and ArH). This compound was recovered unchanged after prolonged treatment with base in the conditions described in ref. 8.

Acknowledgements

We thank the Ministero della Publica Istruzione for financial support.

References

1 E. Valencia, I. Weiss, S. Firdous, A. J. Freyer, M. Shamma, A. Urzua, and V. Fajardo, *Tetrahedron*, 1984, **40**, 3957.
2 For a recent account on synthetic work in the field of aporhoeadanes, see: S. Ruchirawat, W. Lertwanawatana, S. Thianpatanagul, J. L. Cashaw, and V. E. Davis, *Tetrahedron Lett.*, 1984, 3485.
3 P. L. Barili, R. Fiaschi, E. Napolitano, V. Scartoni, and A. Marsili, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1654, and references cited therein.
4 Preceding paper.
5 A. Marsili and V. Scartoni, *Gazz. Chim. Ital.*, 1972, **102**, 507.
6 A. Marsili and V. Scartoni, *Gazz. Chim. Ital.*, 1972, **102**, 806.
7 R. Elliot, F. Hewgill, E. McDonald, and P. McKenna, *Tetrahedron Lett.*, 1980, 4633.
8 E. Napolitano, R. Fiaschi, and A. Marsili, *Tetrahedron Lett.*, 1983, 1319.
9 E. Napolitano, G. Spinelli, R. Fiaschi, and A. Marsili, *Synthesis*, 1985, 38.
10 S. Teitel, W. Klötzer, J. Borgese, and A. Brossi, *Can. J. Chem.*, 1972, **50**, 2022.
11 E. Valencia, A. J. Freyer, M. Shamma, and V. Fajardo, *Tetrahedron Lett.*, 1984, 599.
12 E. Napolitano, E. Giannone, R. Fiaschi, and A. Marsili, *J. Org. Chem.*, 1983, **48**, 3653.
13 R. Adams and L. H. Ulich, *J. Am. Chem. Soc.*, 1920, **42**, 599.

Received 24*th June* 1985; *Paper* 5/1066