Verapamil Analogues with Restricted Molecular Flexibility

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Three analogues with restricted flexibility were designed to study the active conformation of verapamil during interaction with the slow calcium channel. Thus *cis*- and *trans*-1-(3,4-dimethoxyphenyl)-4-[*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methylamino]-*r*-1-cyclohexanecarbonitrile (**5a** and **5b**), and 4-(3,4-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-4-cyanopiperidine (**6**), in which the verapamil structure is inserted into a cyclohexane or piperidine ring, were synthesized. Conformational analysis was performed with NMR and theoretical methods, and slow calcium channel antagonism was tested on guinea pig aorta strips. The compounds are some 100 times less potent than the parent compound even if they are able to reach conformations that are quite close to the lowest energy conformation proposed for verapamil and similar compounds. It appears that the flexibility to rotate around the bond between the quaternary atom and the adjacent methylene, a property which is lost in compounds **5a**, **5b**, and **6**, is a major requisite for the calcium antagonism of verapamil.

Verapamil (**1**) is a well-established slow calcium channel antagonist whose structure–activity relationships have been thoroughly studied.[1,2] However, the molecules of verapamil and related compounds have many rotational degrees of freedom, thus their conformation at the receptor site is difficult to predict and might be quite different from that shown by X-ray diffraction analysis[3] or calculated by theoretical methods.[4,5]

As a matter of fact, it is widely accepted that a flexible fit occurs at the receptor site with the conformation that allows the highest number of stabilizing interactions; such a conformation may or may not be the lowest energy one of the isolated molecule.

Rigid molecules, strictly related to the active compound, might be very useful in collecting information about the active conformation. Unfortunately, very few molecules of this kind are known in the verapamil series,[6-9] and most of them involve the quaternary carbon atom.[6-8]

As a continuation of our research in this field[6] we have synthesized and evaluated for slow calcium channel antagonist activity the compounds shown in Chart I (**5a**, **5b**, and **6**). In these examples the rotational freedom of the verapamil molecule has been reduced while a close resemblance to verapamil has been maintained.

Compound **5** is among the many claimed in a patent of Knoll.[10] No chemical and physical characterization of the mixture or of the single isomers is however reported.

Chemistry

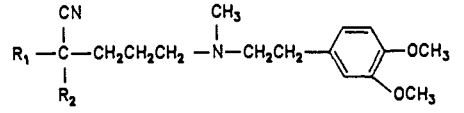
The synthetic pathways used to obtain compounds **5a**, **5b**, and **6** are shown in Schemes I–III.

Cyclohexanone **9**, obtained through standard methods, when reduced with $NaBH_4$ gives two isomeric alcohols (**10a** and **10b**) in a 85:15 ratio (isolated weight). Their stereochemistry was attributed on the basis of the NMR characteristics of the proton in position 4, which in the most abundant isomer (**10a**) shows prevalent axial characteristics ($\delta = 3.71$, $w/2 = 30$ Hz) as compared to that of the minor isomer (**10b**), which shows equatorial characteristics ($\delta = 4.20$, $w/2 = 8$).[11-13]

This fact indicates that the major conformer of **10a** is the one having the phenyl and the hydroxy group in an equatorial position, which implies that the cyano and hydroxy groups are cis to each other.[14]

As a consequence, **10b** will have the cyano and hydroxy groups trans; the fact that its proton in position 4 shows equatorial characteristics suggests that also in this case the phenyl group prefers an equatorial position.

Chart I

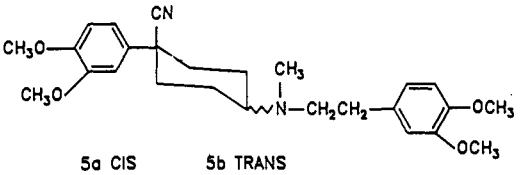


1 R_1 = 3,4-$(CH_3O)_2C_6H_3$ R_2 = $CH(CH_3)_2$ VERAPAMIL

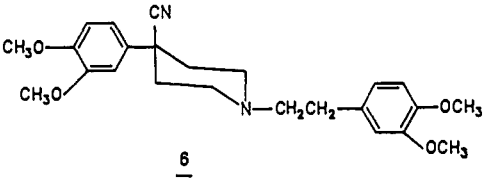
2 R_1 = 3,4-$Cl_2C_6H_3$ R_2 = $CH(CH_3)_2$ DICHLOROVERAPAMIL

3 R_1 = 3,4,5-$(CH_3O)_3C_6H_2$ R_2 = $CH(CH_3)_2$ GALLOPAMIL

4 R_1R_2=



5a CIS 5b TRANS



6

(1) Mannhold, R. In *Recent Advances in Receptor Chemistry*; Melchiorre, C., Giannella, M., Eds.; Elsevier Science Publishers: Amsterdam, 1988, p 147, and references cited therein.
(2) Mannhold, R.; Bayer, R.; Ransdorf, M.; Martens, L. *Arzneim. Forschung* **1987**, *37*, 419.
(3) Carpy, A.; Leger, J. M.; Melchiorre, C. *Acta Crystallogr. Sect. C* **1985**, *41*, 624.
(4) Brasseur, R.; Deleers, M.; Malaisse, W. J. *Biochem. Pharmacol.* **1983**, *32* (*111*), 437.
(5) Höltje, H. D.; Maurhofer, E. *Quant. Struct.-Act. Relat.* **1989**, *8*, 259.
(6) Gualtieri, F.; Teodori, E.; Bellucci, C.; Pesce, E.; Piacenza, G. *J. Med. Chem.* **1985**, *28*, 1621.
(7) Trautwein, W.; Pelzer, D.; McDonald, T. F.; Osterrieder, W. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1981**, *317*, 220.
(8) Daennungen, J.; Lamping, K.; Gross, G. J. *J. Cardiovasc. Pharmacol.* **1985**, *7*, 71.
(9) Clark, R. D.; Berger, J.; Lee, C. H.; Muchowski, J. M. *Heterocycles* **1987**, *26* (*5*), 1291.

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‡ Università di Bologna.

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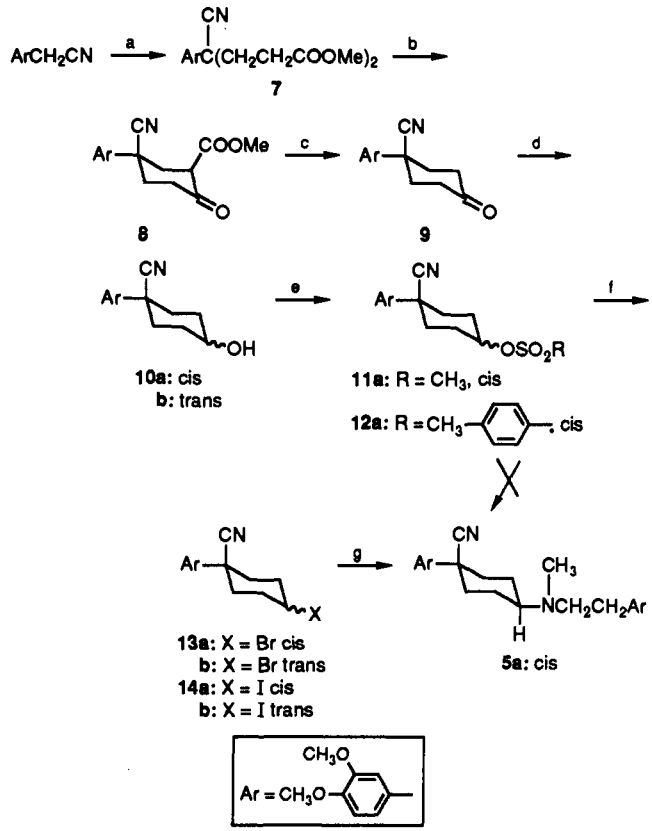
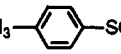
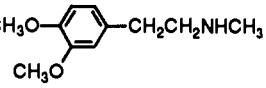
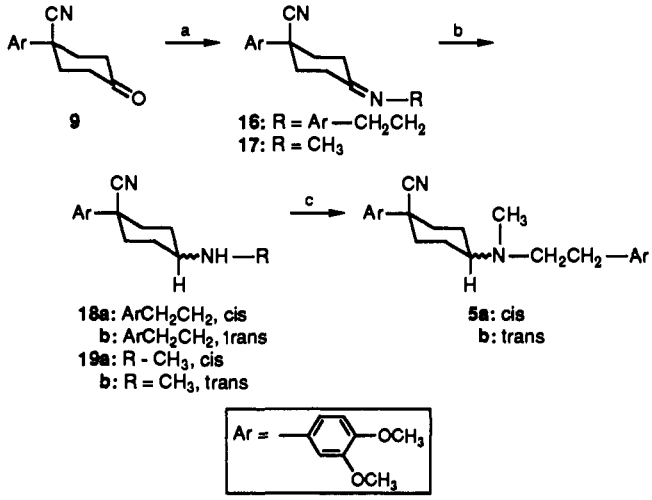
Scheme I[a]



[a](a) Triton B, $CH_2=CHCOOMe$; (b) NaH, xylene; (c) H_2SO_4 10%; (d) $NaBH_4$, MeOH; (e) CH_3SO_2Cl or CH_3—  —SO_2Cl; (f) LiBr or NaI/acetone; (g) 

Scheme II[a]



[a](a) $ArCH_2CH_2NH_2$ or CH_3NH_2; (b) $NaBH_4$, MeOH; (c) CH_2O, HCOOH or $ArCH_2CH_2Br$.

Unfortunately, direct substitution of the hydroxy group with bromine, by means of PBr_3, proceeds with very poor yields and with isomerization, as from both **10a** and **10b** a nearly 1:1 mixture of **13a** and **13b** was obtained. When the corresponding mesyl (**11a**) and tosyl (**12a**) derivatives, which can be easily obtained from the isomeric mixture of **10a** and **10b**, were reacted with halides, the yields are much better, but again isomerization occurs.

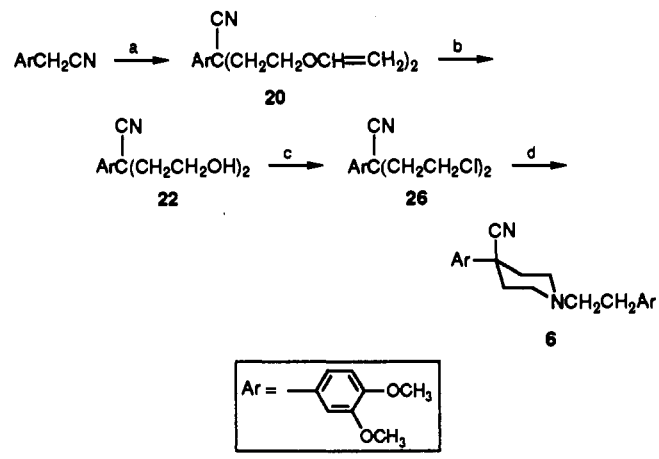
On the other hand, there was no reaction when **11a** and **12a** were directly reacted with homoveratrylamine. Therefore we separated the two isomeric bromides (**13a** and **13b**) and also in this case attributed their stereochemistry on the basis of the NMR characteristics of the C4 proton (see the Experimental Section).

However, both isomers **13a** and **13b** when reacted with *N*-methylhomoveratrylamine gave only the most stable isomer of **5** (**5a**).

To overcome this problem (Scheme II) we decided to proceed through Schiff base **16**, which in fact can easily be reduced to isomeric amines **18a** and **18b**; these were separated through column chromatography and methylated to give **5a** and **5b**, respectively. The problem with this approach is that the trans isomer **18b** is only 10% of the total mixture (isolated yield). Substitution of homoveratrylamine with methylamine resulted in a 13% yield of the corresponding methylamino derivative **19b**.

This fact seems to indicate that the size of the substituent on the nitrogen atom does not influence the trans:cis ratio, while it is relevant to the kind of conformers present. As a matter of fact, while **19a** and **19b** showed the expected clearcut difference between the protons in position 4 (see Figure 1) (in compliance with the criteria we have used for attributing stereochemistry), confirming that the major isomer (**19a**) has a cis stereochemistry (δ = 2.47; $w/2$ = 25 Hz) and the minor isomer (**19b**) a trans stereochemistry (δ = 2.86; $w/2$ = 10 Hz), the situation is not so clear when the substituent is larger. In fact the chemical shifts of the C4 protons of **18a** and **18b** are very close (δ = 2.7–3.0 and δ = 3.0, respectively) even if the half-height width of **18b** has the expected value ($w/2$ =

Scheme III[a]



[a](a) $NaNH_2$, $ClCH_2CH_2OCH=CH_2$; (b) dilute HCl; (c) $SOCl_2$, CH_2Cl_2; (d) $ArCH_2CH_2NHCH_3$.

(10) S. African patent 6906,431 18 May 1970 (*Chem. Abstr.* **1970**, *73*, 109530*f*).
(11) Casy, A. F.; Wu, E. S. C.; Whelfan, B. D. *Can. J. Chem.* **1972**, *50*, 3948.
(12) Hassner, A.; Heathcook, C. *J. Org. Chem.* **1964**, *29*, 1350.
(13) The use of $w/2$ (half-height width) to estimate the equatorial or axial properties of cyclohexane protons is a simple way to evaluate the size of coupling constants. Of course it is unsuitable for rigorous conformational analysis, where the exact value of coupling constants is necessary.
(14) Stereochemistry of the substituent in position 4 refers to the nitrile in position 1 according to the IUPAC rules. See: *Nomenclature of Organic Chemistry*; Rigaudy, J., Klesney, S. P., Eds.; Pergamon Press: Oxford, 1979.

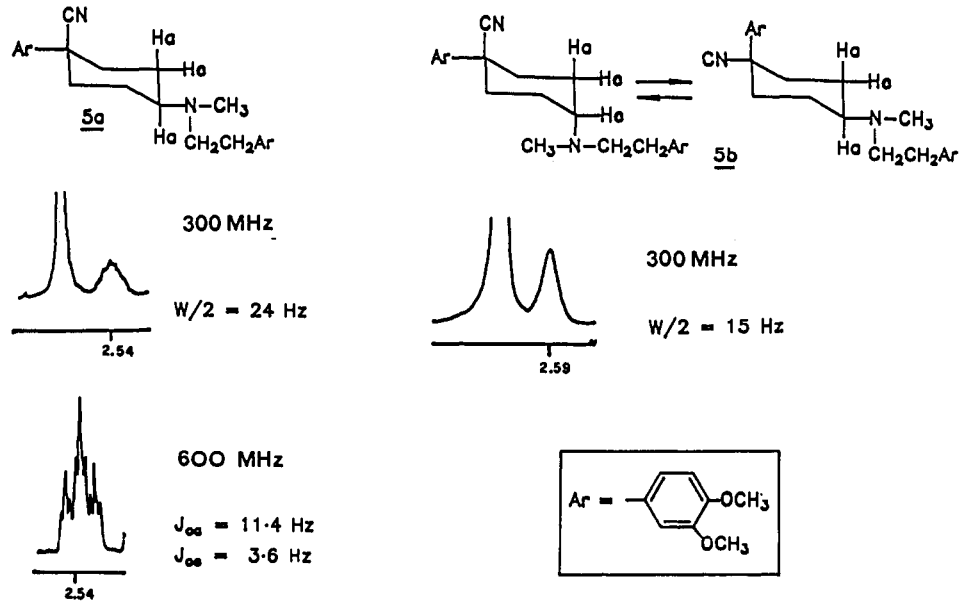
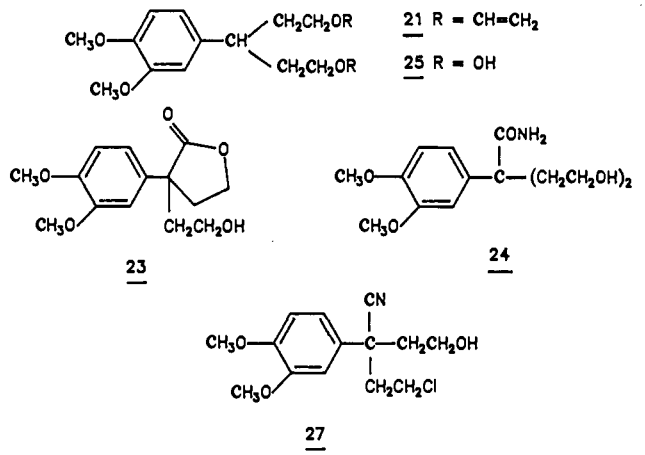


Figure 1. ^{1}H NMR signals due to C4 proton of compounds **5a** and **5b**.

Chart II



10 Hz; that of **18b** could not be measured). Compounds **5a** and **5b**, whose cis and trans stereochemistry was proved by the fact that they were obtained from **18a** (or **19a**) and **18b** (or **19b**), show little differentiation among the protons of C4, both in terms of half-height width and chemical shift (**5a**, δ = 2.63, $w/2$ = 24 Hz; **5b**, δ = 2.59, $w/2$ = 15 Hz). The implication in terms of conformers present in solution will be discussed later.

Compound **6** was obtained according to Scheme III. The crucial step in the reactions is the synthesis of **20**, which is always accompanied by a substantial amount of the decyanation product **21** that must be eliminated to avoid problems in the following reactions. Hydrolysis of **20** is sensitive to reaction conditions: lactone **23**, amide **24**, and alcohol **25** are byproducts of the reaction. Finally, the two hydroxy groups of compound **22** do not seem to be chemically equivalent since even by forcing the reaction only a small amount of monochloride **27** is always obtained (Chart II).

Conformational Analysis

Conformational analysis of compounds **5a**, **5b**, and **6** was attempted on the basis of the ^{1}H NMR spectra. A 600-MHz spectrum was required to obtain suitable signals of the C4 proton in order to determine the coupling constants of **5a**. They show that the cyclohexane portion of the molecule is pratically frozen into an axial–equatorial conformation of the CN group in position 1 and the substituent in position 4 (see Figure 1). It is reasonable to suppose that this is also the situation of compound **6**.

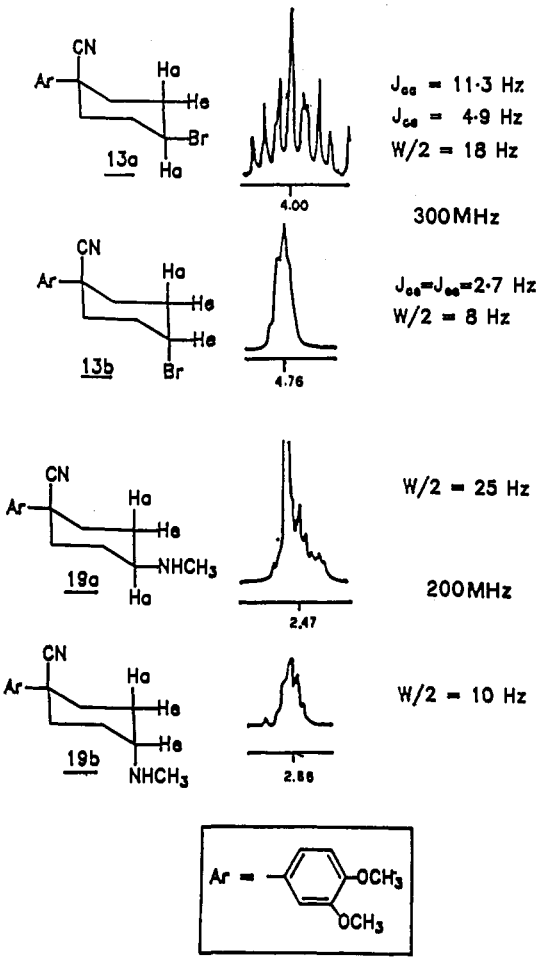


Figure 2. ^{1}H NMR signals due to C4 proton of compounds **13a**, **13b**, **19a**, and **19b**.

It was not possible to extract coupling constants for the C4 proton of **5b**, which even at 600 MHz gives a broad signal. However, the fact that the chemical shift of this proton is nearly identical with that of the corresponding hydrogen of **5a** and that its half-height width is somewhat intermediate between that of equatorial and axial protons (see also Figure 2) suggests that the large group in position

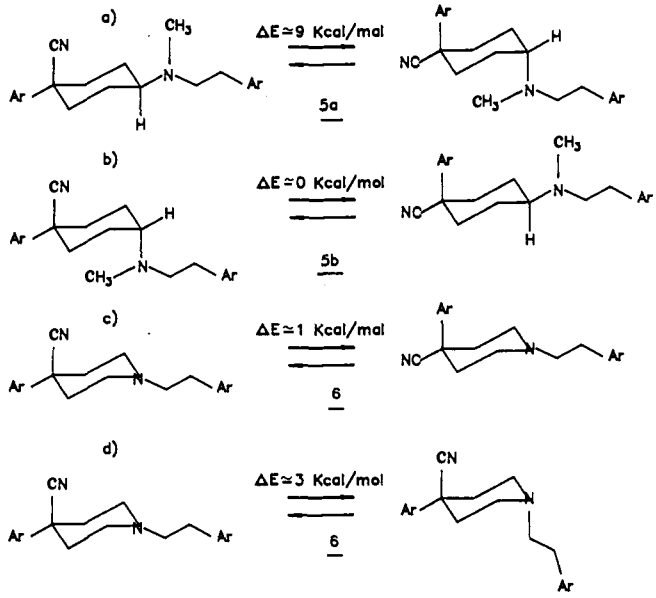


Figure 3. Energy difference between configurational isomers of **5** and **6**.

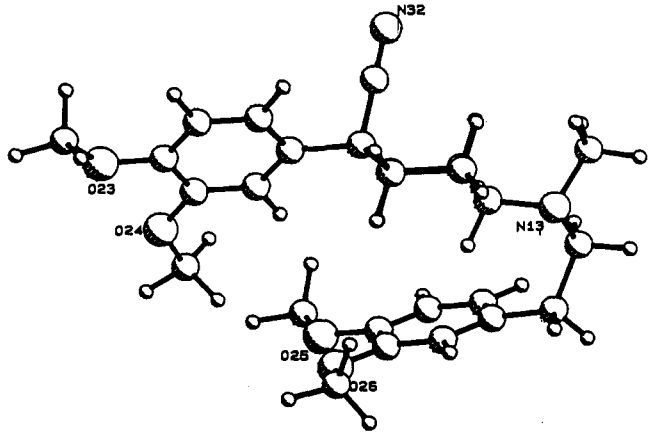


Figure 4. PLUTO plot of the calculated most stable conformation of **5a**.

4 competes with the phenyl ring in position 1 for the equatorial position and that at room temperature an equilibrium exists between the corresponding conformers.

To confirm the evidence shown by the ^{1}H NMR spectra and to extend conformational analysis to the flexible part of the molecule (the homoveratryl moiety), computer-assisted calculation of the more stable conformations was started.

Conformational analysis was performed by means of molecular mechanics (MMPMI[15]).

The energies of all the possible isomers, arising from the rotation of the basic part of the molecule, were calculated for each configurational isomer.

For the cis isomer **5a**, the axial(CN)–equatorial(amine) configuration is preferred to the equatorial–axial one by a factor of ~9 kcal/mol (Figure 3a), thus confirming the attribution made by means of NMR.

For the trans isomer **5b**, the most stable conformation in the axial–axial configuration is equienergetic with the most stable conformation in the equatorial–equatorial configuration (Figure 3b); this fact also confirms the data obtained by means of NMR. The most stable conformer of **5a**, which has an energy of at least 3 kcal/mol lower than the others, shows a folded arrangement of the chain, in accordance with the results found by Malaisse[4] (Figure 4). As far as compound **6** is concerned, there is only a small difference between the conformers that have equatorial or axial aryl groups (Figure 3c), suggesting that an equilibrium between the two conformers is present in solution. The preference for the equatorial orientation of the phenyl ethyl group (Figure 3d) is in agreement with the literature.[16]

Table I. Pharmacological Activities

compd	negative inotropic activity[a]	negative chronotropic activity[b]	calcium antagonistic activity[c]
5a	56 ± 5.8	67 ± 3.4	66 ± 2.3
5b	52 ± 2.9	65 ± 5.5	59 ± 3.6
6	17 ± 2.9	39 ± 1.0	25 ± 1.5
18a	66 ± 5.0	47 ± 2.3	39 ± 4.3
verapamil	60 ± 2.3[d]	94 ± 3.4[e]	79 ± 4.6[f]

[a] Decrease in the developed tension at 10^{-4} M expressed as percent changes from the control ± SEM (n = 4–5). The left atria were driven at 1 Hz. [b] Decrease in atrial rate at 10^{-4} M expressed as percent changes from control ± SEM (n = 4–5). The right atria were spontaneously beating. Pretreatment ranged from 165–190 beats/min. [c] Percent inhibition of Ca^{2+}-induced contraction on K^+-depolarized guinea pig aortic strips at $5\cdot10^{-4}$ M. Values are means ± SEM (n = 5–6). [d] At 10^{-6} M. [e] At 10^{-6} M; at this concentration verapamil produced a standstill of spontaneously beating right atria (two out of six experiments). [f] At 10^{-5} M.

Results and Discussion

The inotropic, chronotropic, and slow calcium channel antagonistic activity of compounds **5** and **6** and verapamil are reported in Table I.

These compounds are definitely less potent than verapamil in the assays; the two isomers **5a** and **5b** show more or less the same potency, which is a 100 times lower than that of verapamil. In order to explain such low activity for **5** and **6** we have compared the conformations of our compounds with those of gallopamil (**3**)[4] and of the dichloro analogue of verapamil (**2**).[5] It has been proposed that in order to show any calcium antagonistic activity the phenyl ring and the cyano group of verapamil-like compounds must lie on the same plane.[17,18] This fact has been used to explain the lack of Ca^{2+} antagonism of **4**. In our compounds calculations show that this is not the case, since there is a small deviation from coplanarity (30–40°) between the two groups, but this coplanarity can be easily achieved with a small energy expenditure (less than 1 kcal/mol), so it seems unlikely that this is the only reason for the poor activity of our compounds. The major difference between our compounds and those considered by Malaisse[4] and Höltje[5] is the lack of rotational freedom between the carbon bearing the cyano group and the three-methylene chain: the rigidity brought into the molecules through the six-membered rings forces the nitrile, the phenyl ring (if coplanar), and the basic nitrogen into the only possible arrangement that cannot be overcome by conformational changes of the molecules.

Since gallopamil and the dichloro analogue of verapamil are potent calcium antagonists, our results would indicate

(15) MMPMI (version 1.0; MM2 '77 and MMP1 Pi; obtained from *QCPE*) is an extended program of Allinger's MM2 to calculate molecules with the force-field method. The host computer is an IBM XT 286.

(16) Castiglione-Morelli, M. A.; Lelj, F.; Pastore, A.; Salvadori, S.; Tancredi, T.; Tomatis, R.; Trivellone, E.; Temussi, P. A. *J. Med. Chem.* **1987**, *30*, 2067 and references therein.
(17) Höltje, H. D.; Mannhold, R.; Rodenkirchen, R.; Bayer, R. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1981**, *316*, 217.
(18) Höltje, H. D.; Hense, M. *Pharm. Acta Helv.* **1985**, *60*, 9–10.

that the most stable conformation of verapamil-like compounds is not that responsible for calcium antagonistic activity, or (as seems more likely) free rotation of the lipophilic head of the molecule is crucial for calcium antagonistic activity.

Isomer **5a** and **5b** differ principally in the distance between the basic nitrogen and the phenyl or nitrile group; nevertheless their potency is more or less identical; this fact seems to stress again that free rotation of the lipophilic head of the molecule is a crucial requisite for activity.

Experimental Section

Chemistry. All melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 681 spectrophotometer in a Nujol mull for solids and neat for liquids. Mass spectra were measured with a Perkin-Elmer 8420 capillary gas chromatography connected to a Perkin-Elmer ion trap detector. Unless otherwise stated NMR spectra were measured on a Varian EM 360L spectrometer using Me_4Si as internal standard; 200-, and 300-, and 600-MHz instruments were also used when necessary. Chromatographic separations were performed on a silica gel column by gravity chromatography (Kieselgel 40, 0.063–0.200 mm, Merck) or by flash chromatography (Kieselgel 40, 0.040–0.063 mm, Merck). Yields are given after purification, unless otherwise stated. Where analyses are indicated by symbols, the analytical results are within ±0.4% of the theoretical values.

Dimethyl 4-Cyano-4-(3,4-dimethoxyphenyl)heptanedioate (7). A solution of 40% methanolic Triton B (15.8 mL) in *tert*-butyl alcohol (33 mL) was rapidly added to a stirred boiling solution of the commercially available 3,4-dimethoxybenzyl cyanide (30 g, 170 mmol) and methyl acrilate (48.40 mL, 535 mmol) in *tert*-butyl alcohol (50 mL). The mixture was heated to reflux for 18 h then the solvent was distilled off and the residue dissolved in chloroform. The solution was washed with dilute HCl and with water, dried, and evaporated under vacuum to give a solid that was recrystallized from methanol. Yield: 44.3 g (75%). Mp: 60–62 °C. IR (Nujol): ν 2240 (CN), 1745 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.00–2.70 (m, 8, CH_2), 3.65 (s, 6, 2 $COOCH_3$), 3.90 (s, 6, 2 OCH_3), 6.90–7.00 (m, 3, aromatics) ppm. Anal. ($C_{18}H_{23}NO_6$): C, H, N.

Methyl 5-Cyano-5-(3,4-dimethoxyphenyl)-2-oxocyclohexanecarboxylate (8). A mixture of 7 (44 g, 126 mmol) and NaH (46 g of 50% oil dispersion, 126 mmol) was heated to reflux for 5 h in dry xylene. After cooling, the solution was treated with dilute acetic acid, and the organic layer was separated and washed with 10% $NaHCO_3$ solution and then water. Anhydrification and evaporation of the solvent gave a solid that was recrystallized from ethanol. Yield: 27.1 g (68%). Mp: 115–117 °C. IR (Nujol): ν 2240 (CN) and 1650, 1740 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.00–3.20 (m, 6, CH_2), 3.70–3.90 (m, 1, CHCO), 3.80 (s, 3, $COOCH_3$), 3.90 and 3.92 (s, 6, 2 OCH_3), 6.80–7.10 (m, 3, aromatics). Anal. ($C_{17}H_{19}NO_5$): C, H, N.

1-(3,4-Dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (9). A suspension of 8 (25 g, 78.86 mmol) in acetic acid (538 mL) and 10% sulfuric acid (270 mL) was heated to reflux for 5 h. The mixture was then extracted with benzene; the extracts were washed with Na_2CO_3 solution and water and dried. Evaporation of the solvent gave a solid that was recrystallized from ethanol. Yield: 66% (13.53 g). Mp: 109–112 °C. IR (Nujol): ν 2235 (CN), 1725 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.00–3.10 (m, 8, cyclohexanone protons), 3.88 and 3.90 (s, 6, 2 OCH_3), 6.90–7.20 (m, 3, aromatics) ppm. Anal. ($C_{15}H_{17}NO_3$): C, H, N.

1-(3,4-Dimethoxyphenyl)-*c*-4-hydroxy-*r*-1-cyclohexanecarbonitrile (10a) and 1-(3,4-Dimethoxyphenyl)-*t*-4-hydroxy-*r*-1-cyclohexanecarbonitrile (10b). A portion of 9 (4.0 g, 15.4 mmol) in anhydrous THF (20 mL) was added dropwise to a suspension of 0.6 g (15.9 mmol) of $NaBH_4$ in anhydrous THF at −80 °C. The mixture was allowed to warm to room temperature overnight. The mixture was then cooled to −20 °C and 20 mL of 30% solution of NH_4OH added. The organic layer was separated, dried, and evaporated to give a solid that was crystallized from water. Yield: 3.2 g (79%). Mp: 115–117 °C. TLC showed the presence of two isomers that could be separated by column chromatography using ethyl acetate–cyclohexane (50:50) as eluent. The first eluted compound was trans isomer **10b**, which was ca. 15% of the chromatographed mixture. IR (Nujol): ν 3500 (OH), 2235 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.50–2.50 (m, 9, OH and cyclohexane protons), 3.90 (s, 6, 2 OCH_3), 4.18 (bs, 1, CHO; $w/2$ = 8 Hz), 6.90–7.10 (m, 3, aromatics). MS: m/e 261 (M^+). Anal. ($C_{15}H_{19}NO_3$): C, H, N. Cis isomer **10a** was eluted as the second fraction and was ca. 85% of the chromatographed mixture. Mp: 106–108 °C. IR (Nujol): ν 3320 (OH), 2235 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.57 (s, 1, OH), 1.60–2.40 (m, 8, cyclohexane protons), 3.72 (bs, 1, CHO; $w/2$ = 30 Hz), 3.88 and 3.90 (s, 6, 2 OCH_3), 6.80–7.20 (m, 3, aromatics) ppm. MS: m/e 261 (M^+). Anal. ($C_{15}H_{19}NO_3$): C, H, N.

1-(3,4-Dimethoxyphenyl)-*c*-4-[(methylsulfonyl)oxy]-*r*-1-cyclohexanecarbonitrile (11a). A solution of 10 (as the mixture of cis and trans isomers) (2.6 g, 9.9 mmol) and triethylamine (1.6 mL, 11.5 mmol) in CH_2Cl_2 (20 mL) was treated with 0.9 mL (11.7 mmol) of methanesulfonyl chloride dissolved in CH_2Cl_2 (20 mL) at −20 °C and kept at this temperature for 2 h. The solution was then washed with water, dried, and evaporated under vacuum to give a solid that was purified by crystallization from ethanol. Yield: 2.86 g (85%). TLC indicated a small amount of the trans isomer that remained in the mother liquors. Mp: 95–97 °C. IR (Nujol): ν 2242 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.80–2.60 (m, 8, cyclohexane protons), 3.10 (s, 3, SO_2CH_3), 3.85 and 3.90 (s, 6, 2 OCH_3), 4.77 (m, 1, $CHOSO_2$; $w/2$ = 22 Hz), 6.90–7.10 (m, 3, aromatics) ppm. Anal. ($C_{16}H_{21}NO_5S$): C, H, N.

1-(3,4-Dimethoxyphenyl)-*c*-4-[(*p*-tolylsulfonyl)oxy]-*r*-1-cyclohexanecarbonitrile (12a). With the same procedure as described for **11a** compound **12a** was obtained as a white solid which crystallizes from ethyl acetate (yield: 85%. Mp: 134–136 °C.). As found for **11a** TLC indicated a small amount of the trans isomer that remained in the mother liquors. IR (Nujol): ν 2240 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75–2.30 (m, 8, cyclohexane protons), 2.50 (s, 3, CH_3Ar), 3.88 and 3.90 (s, 6, 2 OCH_3), 4.56 (m, 1, $CHOSO_2$; $w/2$ = 20 Hz), 6.70–6.90 (m, 3, aromatics), 7.30–7.90 (m, 4, aromatics) ppm. Anal. ($C_{22}H_{25}NO_5S$): C, H, N.

1-(3,4-Dimethoxyphenyl)-*c*-4-bromo-*r*-1-cyclohexanecarbonitrile (13a) and 1-(3,4-Dimethoxyphenyl)-*t*-4-bromo-*r*-1-cyclohexanecarbonitrile (13b). Procedure A. **11a** (or **12a**) (1.45 g, 4.3 mmol) was dissolved in dry acetone (30 mL), and a solution of LiBr (2.1 g, 24.2 mmol) in dry acetone (30 mL) was added. The mixture was heated to reflux for 48 h, then the solvent was removed and the residue dissolved in $CHCl_3$, washed with water, and dried. Evaporation of the solvent gave 1.07 g of a thick oil (77% yield) which was a mixture of two isomers (TLC) that were separated by column chromatography using ethyl acetate–cyclohexane (40:60) as eluting system. Trans isomer **13b** was eluted first and was ca. 40% of the chromatographed mixture. Mp: 130–132 °C. IR (Nujol): ν 2240 cm^{-1} (CN). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.00–2.10 (m, 2) and 2.20–2.50 (m, 6) (cyclohexane protons), 3.89 and 3.92 (s, 6, 2 OCH_3), 4.76 (quint, 1, CHBr, $w/2$ = 8 Hz), 6.90–7.10 (m, 3, aromatics) ppm. ^{13}C NMR ($CDCl_3$): δ 149.17, 148.83, 132.10, 121.96, 117.38, 111.21, 109.01, 56.00, 55.97, 47.61, 42.36, 37.99, 34.84 ppm. MS: m/e 323,325 (1:1, M^+). Anal. ($C_{15}H_{18}BrNO_2$): C, H, N.

The second fraction was cis isomer **13a** and constituted ca. 60% of the chromatographed mixture. Mp: 66–68 °C. IR (Nujol): ν 2240 cm^{-1} (CN). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.80–1.95 (m, 2) and 2.20–2.50 (m, 6) (cyclohexane protons), 3.87 and 3.90 (s, 6, 2 OCH_3), 4.00 (m, 1, CHBr; $w/2$ = 18 Hz), 6.80–7.00 (m, 3, aromatics) ppm. ^{13}C NMR ($CDCl_3$): δ 149.13, 148.75, 132.79, 122.30, 117.55, 111.21, 109.00, 55.96, 55.91, 51.40, 43.24, 32.15, 31.89 ppm. MS: m/e 323,325 (1:1, M^+). Anal. ($C_{15}H_{18}BrNO_2$): C, H, N.

Changing the reaction solvent (CH_3CN) and the reagents (KBr and 18-crown-6) gave the same ratio of cis and trans isomers.

Procedure B. PBr_3 (2 mL) was added at 0 °C to 250 mg (0.96 mmol) of **10**. After 24 h at room temperature the mixture was heated at 80 °C for 4 h. Cold water was then added and the mixture was extracted with $CHCl_3$. The organic layer was dried and the solvent distilled off. Gas chromatography analysis showed that only 20% of **10** had reacted, giving the two isomers **13a** and **13b** in the same ratio as procedure A.

1-(3,4-Dimethoxyphenyl)-*c*-4-iodo-*r*-1-cyclohexanecarbonitrile (14a) and 1-(3,4-Dimethoxyphenyl)-*t*-4-iodo-*r*-1-cyclohexanecarbonitrile (14b). Following procedure A as

described for 13 and using NaI, a mixture of the two isomers 14a and 14b was obtained. Conversion of the starting material was incomplete; after 48 h TLC showed that a great amount of the starting material was still present. The isomers were separated by column chromatography eluting with ethyl acetate–cyclohexane (40:60). Trans isomer 14b was eluted first and represented 42% of the converted products. IR (Nujol): ν 2240 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.80–2.60 (m, 8, cyclohexane protons), 3.90 and 3.95 (s, 6, 2 OCH_3), 4.98 (s, 1, CHI; $w/2$ = 7 Hz), 6.80–7.30 (m, 3, aromatics) ppm. Anal. ($C_{15}H_{19}INO_2$): C, H, N. The second fraction, which was 58% of the converted products, was cis isomer 14a. IR (Nujol): ν 2240 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.80–2.80 (m, 8, cyclohexane protons), 3.90 and 3.93 (s, 6, 2 OCH_3), 3.90–4.10 (m, 1, CHI; $w/2$ = signal obscured); 6.90–7.10 (m, 3, aromatics) ppm. Anal. ($C_{15}H_{18}INO_2$): C, H, N.

1-(3,4-Dimethoxyphenyl)-*c*-4-[*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methylamino]-*r*-1-cyclohexanecarbonitrile (5a). Procedure A. 13b (0.22 g, 0.67 mmol) was added to 0.27 g of *N*-methylhomoveratrylamine[19] (1.36 mmol) in xylene (10 mL) and the mixture was heated to reflux for 6 h. The solvent was evaporated and the residue treated with few drops of NaOH 10%, then dissolved in $CHCl_3$ and dried. Evaporation of the solvent gave 5a, which could be purified by column chromatography from elimination product **4-(3,4-dimethoxyphenyl)-4-cyano-1-cyclohexene (15)** (MS: *m/e* 243 (M^+). ^1H NMR: as expected) using chloroform–methanol (90:10) as eluting solvent. Yield: 52%. Mp: 88–90 °C. IR (Nujol): ν 2235 cm^{-1} (CN). ^1H NMR (CD_2Cl_2, 300 MHz): δ 1.80–2.05 (m, 6) and 2.20–2.35 (m, 2) cyclohexane CH_2), 2.23 (s, 3, NCH_3), 2.63 (m, 1, NCH; $w/2$ = 24 Hz), 2.78 (s, 4, NCH_2CH_2), 3.82, 3.84, 3.85, 3.88 (s, 12, 4 OCH_3), 6.75–7.10 (m, 6, aromatics).

The oxalate crystallized from absolute ethanol and melted at 169–172 °C. Anal. ($C_{26}H_{34}N_2O_4 \cdot C_2H_2O_4$): C, H, N. The hydrochloride crystallized from absolute ethanol and melted at 202–204 °C. Anal. ($C_{26}H_{34}N_2O_4 \cdot HCl$): C, H, N. When isomer 13a was used as starting material, the same compound 5a was obtained and it was not possible to detect any traces of isomer 5b. On the other hand, the reaction appeared slower than that with the trans compound, and after 24 h of reflux there was still some unreacted starting material. The same results were obtained with iodo derivatives 14a and 14b. No reaction was obtained when sulfonates 11a and 12a were reacted with *N*-methylhomoveratrylamine under a variety of conditions.

Procedure B. A solution of 18a (0.13 g, 0.31 mmol) and HCOOH (4 mL of 85% solution) in absolute ethanol (4 mL) was heated to reflux for 1 h. Then formaline (4 mL) was added and the mixture heated to reflux for 5 h. After removal of the solvent, the residue was dissolved in chloroform, washed with 10% NaOH, and dried. Evaporation of the solvent gave an oil that was purified by column chromatography eluting with chloroform–methanol (90:10) as eluting system. Yield: 60%.

Procedure C. A solution of 0.14 g of 2-(3,4-dimethoxyphenyl)ethyl bromide[20] (0.57 mmol) in anhydrous CH_3CN (10 mL) was added to a suspension of anhydrous K_2CO_3 (0.2 g) and 19a (0.14 g, 0.51 mmol) in anhydrous CH_3CN (10 mL). The mixture, vigorously stirred, was heated to reflux for 44 h. After cooling the solid was filtered off and the solvent removed to give an oil that was dissolved in $CHCl_3$, washed with a solution of Na_2CO_3 and with water, and then dried. Evaporation of the solvent gave an oil that was purified from minor side products as described above. Yield: 80%.

1-(3,4-Dimethoxyphenyl)-4-[*N*-[2-(3,4-dimethoxyphenyl)ethyl]imino]cyclohexanecarbonitrile (16). A toluene (50 mL) solution of 9 (5.0 g, 19.3 mmol), homoveratrylamine (3.5 g, 19.3 mmol), and *p*-toluenesulfonic acid monohydrate (0.6 g) was heated to reflux for 45 h and water was removed from the reaction with the aid of a Dean–Stark trap. The solvent was distilled off and the residue dissolved in ethyl acetate, washed with water, and dried. Evaporation of the solvent gave 9.3 g of an oil that is quite unstable and was used as such in the next reaction. IR (neat): ν 2240 (CN), 1660 (C=N) cm^{-1}.

1-(3,4-Dimethoxyphenyl)-*c*-4-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-*r*-1-cyclohexanecarbonitrile (18a) and 1-(3,4-Dimethoxyphenyl)-*t*-4-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-*r*-1-cyclohexanecarbonitrile (18b). To a solution of crude 16 (3.45 g) in hot methanol (30 mL) was cautiously added $NaBH_4$ (0.33 g) over 0.5 h. The mixture was then heated to reflux for 2 h. After cooling, the mixture was treated with a few drops of water and the excess solvent removed. The residue was dissolved in chloroform, washed with water, and dried. Evaporation of the solvent gave 3.50 g of an oil that was converted into the oxalate to eliminate nonbasic side products. The mixture of amines obtained from the oxalate (aqueous NaOH and $CHCl_3$ extraction) (1.6 g) was separated by column chromatography with chloroform–methanol (90:10). The first fraction was the trans isomer 18b and constituted about 10% of the chromatographed mixture. Mp: 175–177 °C dec. IR (Nujol): ν 3600, 3300 (NH), 2260, 2240 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.70–2.40 (m, 9, NH and cyclohexane protons), 2.70–2.90 (m, 4, NCH_2CH_2), 3.00 (bs, 1, CHN; $w/2$ = 10 Hz), 3.88 (s, 3, OCH_3), 3.90 (s, 6, 2 OCH_3), 3.92 (s, 3, OCH_3), 6.70–7.10 (m, 6, aromatics) ppm. The oxalate recrystallized from absolute ethanol and melted at 191–194 °C. ^1H NMR (DMSO, 200 MHz): δ 1.70–2.20 (m, 6, cyclohexane protons), 2.50 (bs, 2, cyclohexane protons), 2.85 (bs, 2, $NHCH_2CH_2$), 3.13 (bs, 2, NCH_2), 3.40 (bs, 1, CHN; $w/2$ = 12 Hz), 3.71, 3.74, 3.77, 3.80 (s, 12, 4 OCH_3), 6.70–7.20 (m, 6, aromatics) ppm. Anal. ($C_{25}H_{32}N_2O_4 \cdot H_2C_2O_4$): C, H, N.

The second fraction was cis isomer 18a and constituted about 90% of the chromatographed mixture. Mp: 58–60 °C. IR (Nujol): ν 3600, 3300 (NH), 2245, 2235 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.60–2.40 (m, 9, CHN and cyclohexane protons), 1.75 (bs, 1, NH), 2.60–3.10 (m, 4, NCH_2CH_2), 3.90 (s, 12, 4 OCH_3), 6.70–7.10 (m, 6, aromatics) ppm. The oxalate was recrystallized from absolute ethanol and melted at 219–222 °C. ^1H NMR (DMSO, 200 MHz): δ 1.60–2.10 (m, 4, cyclohexane protons), 2.10–2.35 (m, 4, cyclohexane protons), 2.85 (bs, 3, $NHCH_2$ and $CHNH$), 3.73, 3.75, 3.76, and 3.79 (s, 12, 4 OCH_3), 6.75–7.10 (m, 6, aromatics) ppm. Anal. ($C_{25}H_{32}N_2O_4 \cdot C_2H_2O_4$): C, H, N. The hydrochloride was recrystallized from absolute ethanol and melted at 270–275 °C dec. Anal. ($C_{25}H_{32}N_2O_4 \cdot HCl$): C, H, N.

1-(3,4-Dimethoxyphenyl)-4-(methylimino)cyclohexanecarbonitrile (17). A 20% toluene solution of methylamine (18 mL), 9 (4.2 g, 16.2 mmol), and *p*-toluenesulfonic acid monohydrate (0.5 g) was kept at 110 °C for 48 h in a small steel bomb. Evaporation of the solvent gave an oil that was dissolved in chloroform, washed with water, and dried. Removal of the solvent gave 4.8 g of an oil that was used as such in the following reaction. IR (neat): ν 2230 (CN), 1675 (C=N) cm^{-1}.

1-(3,4-Dimethoxyphenyl)-*c*-4-(methylamino)-*r*-1-cyclohexanecarbonitrile (19a) and 1-(3,4-Dimethoxyphenyl)-*t*-4-(methylamino)-*r*-1-cyclohexanecarbonitrile (19b). With the same procedure as that described for 18 and starting from 4.8 g of 17, 2.9 of a mixture of 19 isomers was obtained. The isomers were separated by column chromatography using a chloroform–absolute ethanol–petroleum ether–NH_4OH (4:1.5:0.6:0.2) mixture as eluent. The first fraction was trans isomer 19b, which constituted 13% of the mixture of isomers. Mp: 210–212 °C. IR (Nujol): ν 2235 (CN) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.75–2.50 (m, 9, NH and cyclohexane protons), 2.42 (s, 3, NCH_3), 2.86 (m, 1, CHN; $w/2$ = 10 Hz), 3.87 and 3.91 (s, 6, 2 OCH_3), 6.80–7.10 (m, 3, aromatics) ppm. The oxalate was recrystallized from absolute ethanol. Anal. ($C_{18}H_{22}N_2O_2 \cdot C_2H_2O_4$): C, H, N.

The second fraction was cis isomer 19a, which constituted 87% of the mixture of isomers. Mp: 85–87 °C. IR (Nujol): ν 2235 (CN) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.42 (bs, 1, NH), 1.60–2.00 (m, 4, cyclohexane protons), 2.10–2.30 (m, 4, cyclohexane protons), 2.47 (m, 1, CHN; $w/2$ = 25 Hz), 2.50 (s, 3, NCH_3), 3.90 and 3.93 (s, 6, 2 OCH_3), 6.80–7.10 (m, 3, aromatics) ppm. The oxalate recrystallized from absolute ethanol. Anal. ($C_{16}H_{22}N_2O_2 \cdot C_2H_2O_4$): C, H, N.

1-(3,4-Dimethoxyphenyl)-*t*-4-[*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methylamino]-*r*-1-cyclohexanecarbonitrile (5b). Procedure A. With procedure B as described for 5a and starting from 18b, compound 5b was obtained in 58% yield as a thick oil. IR (Nujol): ν 2230 (CN) cm^{-1}. ^1H NMR (CD_2Cl_2, 300 MHz): δ 1.80–2.05 (m, 6) and 2.15–2.30 (m, 2) (cyclohexane CH_2),

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2.35 (s, 3, NCH_3), 2.59 (m, 1, CHN; $w/2$ = 15 Hz), 2.72 (s, 4, NCH_2CH_2), 3.82, 3.84, 3.86, 3.88 (s, 12, 4 OCH_3), 6.70–7.05 (m, 6, aromatics). The oxalate recrystallized from absolute ethanol and melted at 175–177 °C. Anal. ($C_{26}H_{34}N_2O_4 \cdot C_2H_2O_4$): C, H, N. The hydrochloride crystallized from absolute ethanol and melted at 192–195 °C. Anal. ($C_{26}H_{34}N_2O_4 \cdot HCl$): C, H, N.

Procedure B. With procedure C as described for **5a** and starting from **19b**, compound **5b** was obtained in 75% yield.

α,α-Bis[2-(vinyloxy)ethyl]-3,4-dimethoxybenzeneacetonitrile (20). Homoveratronitrile (26.0 g, 0.15 mol) was added to a suspension in toluene (200 mL) of chloroethyl vinyl ether (49.8 mL, 0.48 mol) and $NaNH_2$ (39 g of a 50% toluene suspension, 0.5 mol) kept at 50 °C. The mixture was heated to reflux for 1 h and then, after cooling, 20 mL water was added. The organic layer, washed with water and dried, gave after evaporation of the solvent 18.7 g of an oily residue that was purified by flash chromatography using a mixture of ethyl acetate–cyclohexane (70:30) as eluting system. The first fraction, which was about 30% of the chromatographed mixture, was as oily compound identified as divinyl ether **21**. IR (neat): ν 1630 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.70–2.20 (m, 4, 2- and 4-CH_2), 2.82 (m, 1, 3-CH), 3.30–3.65 (m, 4, 1- and 5-CH_2), 3.82 (s, 6, 2 OCH_3), 3.70–4.20 (m, 4, CH_2=), 6.37 (q, 2, CH=), 6.60–7.00 (m, 3, aromatics) ppm. MS: m/e 292 (M^+). The second fraction was **20**, which was 70% of the chromatographed mixture. IR (neat): ν 2240 (CN), 1630 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.10–2.45 (m, 4, 2- and 4-CH_2), 3.40–3.80 (m, 4, CH_2=), 3.80 and 3.82 (s, 6, 2 OCH_3), 3.80–4.10 (m, 4, CH_2), 6.28 (q, 2, =CHO), 6.70–6.95 (m, 3, aromatics) ppm. MS: m/e 317 (M^+). Anal. ($C_{18}H_{23}NO_4$): C, H, N.

α,α-Bis(2-hydroxyethyl)-3,4-dimethoxybenzeneacetonitrile (22). A suspension of **20** (8.7 g, 27.4 mmol) in water (70 mL) was heated at 80 °C and, with vigorous stirring, concentrated HCl (2.5 mL) was added. After 10 min the mixture was cooled and extracted with $CHCl_3$ to give an oil that solidifies if sufficiently pure (see below) and can be recrystallized from ethyl acetate–petroleum ether. Yield: 70%. Mp: 78–80 °C. IR (neat): ν 3330 (OH), 2235 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.10–2.50 (m, 6, 2- and 4-CH_2 and OH), 3.50–3.90 (m, 4, 1- and 5-CH_2), 3.90 and 3.92 (s, 3, OCH_3), 6.80–7.30 (m, 3, aromatics) ppm. MS: m/e 265 (M^+). Anal. ($C_{14}H_{19}NO_4$): C, H, N.

When the hydrolysis time and temperature are not sufficiently controlled, the reaction is accompanied by increasing amounts of lactone **23** (up to 20%) and amide **24** (up to 10%). Some **25** found also as a 5% side product might derive from **21** which contaminates the starting material.

3-(3,4-Dimethoxyphenyl)-3-(2-hydroxyethyl)tetrahydrofuran-2-one (23). Morphology: oil. IR (neat): ν 3500,3400 (OH), 1770 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.15 (t, 2, 1′-CH_2), 2.15–3.00 (m, 3, 4-CH_2 and OH), 3.57 (t, 2, 2-CH_2), 3.90 (s, 6, 2 OCH_3), 3.90–4.50 (m, 2, 5-CH_2), 6.80–7.20 (m, 3, aromatics) ppm. MS: m/e 266 (M^+). Anal. ($C_{14}H_{18}O_5$): C, H.

α,α-Bis(2-hydroxyethyl)-3,4-dimethoxybenzeneacetamide (24). Morphology: thick oil. IR (neat): ν 3350 (OH), 1690 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.80–2.80 (m, 4, C-CH_2), 3.00–3.80 (m, 6, CH_2OH), 3.88 (s, 6, 2 OCH_3), 3.80–4.20 (bs, 2, NH_2), 6.80–7.10 (m, 3, aromatics) ppm. Anal. ($C_{14}H_{21}NO_5$): C, H.

3-(3,4-Dimethoxyphenyl)-1,5-pentanediol (25). Morphology: oil. IR (neat): ν 3520–3380 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.50–2.10 (m, 4, 2- and 4-CH_2), 2.95 (s, 2, OH), 3.50 (t, 4, 1- and 5-CH_2), 3.82 (s, 6, 2 OCH_3), 6.60–7.10 (m, 3, aromatics) ppm. MS: m/e 240 (M^+). Anal. ($C_{13}H_{20}O_4$): C, H.

α,α-Bis(2-chloroethyl)-3,4-dimethoxybenzeneacetonitrile (26). Thionyl chloride (5 mL) was cautiously added to 2.5 g of **22** (9.6 mmol). The mixture was heated to reflux for 18 h. Then the excess $SOCl_2$ was distilled off and the residue dissolved in ether, washed with aqueous Na_2CO_3 and water, and dried. Removal of the solvent gave an oil that was purified by column chromatography (ethyl acetate) to remove some 25% of the monochloride compound **27** (MS: m/e 283, 285 (3:1, M^+). ^1H NMR: as required). Yield: 80%. IR (neat): ν 2235 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.30–2.70 (m, 4, CCH_2), 3.10–3.70 (m, 4, CH_2Cl), 3.95 and 3.97 (s, 6, 2 OCH_3), 6.80–7.10 (m, 3, aromatics) ppm. MS: m/e 301, 303, 305 (M^+ 3:2:0.5). Anal. ($C_{14}H_{17}Cl_2NO_2$): C, H, N.

4-(3,4-Dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-4-cyanopiperidine (6). Homoveratrylamine (0.65 mL, 3.81 mmol), **26** (1.15 g, 3.81 mmol), and triethylamine (1.06 mL) were heated to reflux in xylene for 4 h. After cooling, the xylene was washed with water, dried, and evaporated to give an oil that was transformed to the hydrochloride and crystallized from absolute ethanol–ether. Yield: 35%. Mp: 261–263 °C. IR (Nujol): ν 2250 (CN) cm^{-1}. ^1H NMR: δ 2.00–3.30 (m, 12, piperidine and CH_2CH_2 protons), 3.93 (s, 12, 4 OCH_3), 6.7–7.3 (m, 6, aromatics) ppm. Anal. ($C_{24}H_{30}N_2O_4 \cdot HCl$): C, H, N.

Pharmacology. Inotropic and chronotropic activity were tested on guinea pig isolated atria preparations, and calcium antagonistic activity was tested on guinea pig aorta strips preparation following standard procedures of which details have been already reported.[21]

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Registry No. 1, 52-53-9; *cis*-**5a**, 133648-48-3; *cis*-**5a**·oxalate, 133648-49-4; *cis*-**5a**·HCl, 133648-50-7; *trans*-**5b**, 133648-51-8; **6**, 133648-52-9; **7**, 61330-09-4; **8**, 133648-53-0; **9**, 51533-65-4; **10a**, 51533-63-2; **10b**, 51533-66-5; **11a**, 133648-54-1; **12a**, 133648-55-2; **13a**, 133648-56-3; **13b**, 133648-57-4; **14a**, 133648-58-5; **14b**, 133648-59-6; **15**, 133648-60-9; **16**, 133648-61-0; **17**, 133648-62-1; **18a**, 133648-63-2; **18a**·oxalate, 133648-64-3; **18a**·HCl, 133648-65-4; **18b**, 133648-66-5; **18b**·oxalate, 133648-67-6; **19a**, 133648-68-7; **19a**·oxalate, 133648-69-8; **19b**, 133648-70-1; **19b**·oxalate, 133648-71-2; **20**, 133648-72-3; **21**, 133648-73-4; **22**, 133648-74-5; **23**, 133648-75-6; **24**, 133648-76-7; **25**, 133648-77-8; **26**, 133648-78-9; 3,4-dimethoxybenzyl cyanide, 93-17-4; methyl acrilate, 96-33-3; 2-(3,4-dimethoxyphenyl)ethyl bromide, 40173-90-8; *N*-methyl-*N*-homoveratrylamine, 3490-06-0; *N*-homoveratrylamine, 120-20-7.

(21) Bellucci, C.; Gualtieri, F.; Scapecchi, S.; Teodori, E.; Budriesi, R.; Chiarini, A. *Il Farmaco* **1989**, *44*, 1167.