prolyl peptide bond. The product was recrystallized from chloroform to obtain white crystals, mp 155–156 °C. The ^{1}H NMR spectrum in CD_3OD had resonances at δ 1.5 (doublet, 6 H), 1.8 (broad multiplet, 4 H), 3.6 (singlet, 3 H), 5.1 (singlet, 2 H), and 7.3 [multiplet, 10 H, including a singlet in the center (~5 H)]; other peaks were obscured by residual protons in the solvent.

Carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan was prepared from the above carbobenzyloxy tripeptide methyl ester in the same manner as was done at the dipeptide stage of the synthesis. The product was obtained in 82% yield and was recrystallized from methanol to afford white crystals, mp 158–159 °C. The mass spectrum exhibited a parent ion at *m/e* 520 and the ^{1}H NMR spectrum, in acetone-d_6, showed signals at δ 1.5 (broad singlet, 6 H), 1.8 (multiplet partially obscured by residual solvent peaks), 3.3 (singlet, 3 H), 3.5–4.7 (broad complex region, 6 H), 5.0 (singlet, 2 H), and 7.2 [complex multiplet, 10 H, including a singlet in the center (~5 H)]. The singlet at 3.3 ppm (3 H) represents a solvating molecule of methanol found in the crystalline material.

Anal. Calcd for $C_{28}H_{32}N_4O_6 \cdot CH_3OH$: C, 63.03; H, 6.57. Found: C, 62.94; H, 6.29.

Carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan and carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan were prepared by exactly the same methods as the unfluorinated carbobenzyloxy tripeptide described above. As in the unfluorinated case, the *cis*- and *trans*-4-fluoroprolyl peptide derivatives afforded carbobenzyloxy dipeptide methyl esters (85 and 78%, respectively) and carbobenzyloxy dipeptides (70 and 73%, respectively) which were oils, whereas the carbobenzyloxy tripeptide methyl esters (79% mp 109.5–111 °C, and 76%, mp 158–159 °C, respectively) and carbobenzyloxy tripeptides (80%, mp 190–191 °C, and 85%, mp 126–127 °C, respectively) were crystalline. Each step in these syntheses went smoothly, and ^{1}H NMR spectra were consistent with the expected products at each step. The ^{1}H NMR spectrum of the protected tripeptide containing *cis*-fluoroproline showed signals at δ 1.4 (unsymmetrical doublet, 6 H), 2.1–2.6 (broad band, 2 H), 5.6 (broad peak, 0.5 H), and 7.2 (broad, complex multiplet, 10 H). A number of peaks, some partially obscured by signals from residual protons of the solvent and spinning side bands, were observed between δ 3.0 and 5.0. The ^{1}H NMR spectrum (CD_3OD) of the corresponding trans isomer had δ 1.4 (doublet, 6 H), 1.8–2.5 (broad multiplet, 2 H), 2.7–4.9 (a number of resonances, many partially obscured by residual solvent signals and spinning side bands), 5.0 (singlet, 2 H), 6.0 (broad peak, 0.5 H), and 7.2 (broad complex multiplet, 10 H).

Carbobenzyloxyglycyl-L-prolyl-L-tryptophan was synthesized from carbobenzyloxyglycyl-L-proline (Sigma) by the same reactions described above, affording the carbobenzyloxy tripeptide methyl ester in 75% yield and carbobenzyloxy tripeptide in 79% yield. Both products were solids upon exhaustive evaporation of solvent, but could not be recrystallized, possibly because of traces of dicyclohexylurea present. The impure carbobenzyloxy tripeptide product had a ^{1}H NMR spectrum ($CDCl_3$) containing signals at δ 5.0 (singlet, 2 H), 6.0 (broad peak, 1 H), and 7.1 (complex multiplet, 10 H).

Carbobenzyloxy-L-alanyl-L-prolyl-L-tryptophan was synthesized from carbobenzyloxy-L-alanyl-L-proline (Sigma) by reactions similar to those used above. The saponification of the methyl ester resulted in a solid rather than an oily precipitate on addition of concentrated HCl. This solid was not readily extracted into ethyl acetate and was collected by vacuum filtration, washed with cold water, and dried (mp 171–173 °C). ^{1}H NMR (CD_3OD) of this unpurified solid had δ 1.2 (doublet, 3 H), 1.9 (broad band, 4 H), 5.0 (singlet, 2 H), and 7.3 (complex multiplet, 10 H). The solvent signals made accurate integration of other parts of the spectrum unreliable.

Hydrogenolyses of the carbobenzyloxy tripeptides were carried out by bubbling H_2 through a magnetically stirred solution of 0.4 mmol of the material in 14 ml of methanol; ~100 mg of 10% Pd/C was used as the catalyst.

The peptide syntheses and hydrogenolyses were monitored by TLC using Eastman Chromogram silica gel plates developed with a mixture of 1-butanol (63 ml), glacial acetic acid (23 ml), and water (14 ml). Plates were visualized with ninhydrin spray and iodine vapor.

^{1}H NMR spectra were recorded on a Varian Associates T-60 or HA-100 spectrometer using, as appropriate, deuterium oxide, acetone-d_6, deuteriochloroform, or deuterated methanol as solvents; chemical shifts are given relative to tetramethylsilane. Mass spectra were determined with an AEI MS-902 mass spectrometer. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

Acknowledgments. We are indebted to the National Science Foundation (Grant 43984X) for support of this work. J. T. G. is a Research Career Development Awardee of the National Institutes of Health (Grant GM-70373).

Registry No.—I, 58281-74-6; Carbobenzyloxy-2-methylalanyl-L-proline methyl ester, 15030-91-8; proline methyl ester HCl, 2133-40-6; carbobenzyloxy-2-methylalanyl-L-proline, 58281-75-7; carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan methyl ester, 58281-76-8; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan, 58281-77-9; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan, 58281-78-0; *cis*-4-fluoroproline methyl ester HCl, 58281-79-1; *trans*-4-fluoroproline methyl ester HCl, 58281-80-4; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoroproline methyl ester, 58281-81-5; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoroproline methyl ester, 58281-82-6; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoroproline, 58281-83-7; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoroproline, 58281-84-8; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan methyl ester, 58281-85-9; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan methyl ester, 58281-86-0; carbobenzyloxyglycyl-L-proline, 1160-54-9; carbobenzyloxyglycyl-L-prolyl-L-tryptophan methyl ester, 58281-87-1; carbobenzyloxyglycyl-L-prolyl-L-tryptophan, 58281-88-2; carbobenzyloxy-L-alanyl-L-proline, 21027-01-0; carbobenzyloxy-L-alanyl-L-prolyl-L-tryptophan methyl ester, 58281-89-3; carbobenzyloxy-L-alanyl-L-prolyl-L-tryptophan, 58281-90-6.

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Diels–Alder Reactions of *trans,trans*-1,4-Diacetoxybutadiene. Observations Concerning Some Literature Reports

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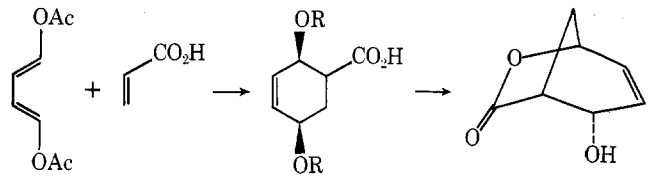
Diels–Alder cycloadditions of *trans,trans*-1,4-diacetoxybutadiene (1) with electrophilic olefins provide one valuable source of highly oxygenated six-membered carbocycles[1] which we have had occasion to explore. In this note we disclose further details regarding the reactivity of 1 as a diene component. We also describe the outcome of experiments which bring important new results to bear on some previously described cycloadditions.

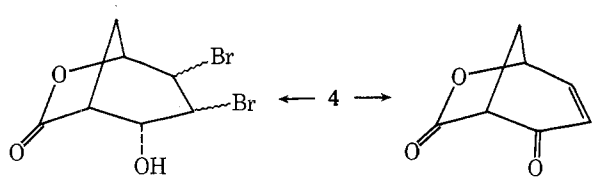
The condensation of 1 with acrylic acid and its esters has been the subject of some debate, focusing on the stereochemistry of the adduct 2.[2-4] Comprehensive NMR spectroscopic data have been gathered by Raphael,[5] Hill,[6] and Smissman[7] in support of the all-cis stereochemistry (shown in 2) predicted from an endo transition state. We have pre-



1 2, R = $COCH_3$ 3, R = H 4

pared this adduct (mp 141–143 °C) and now present *chemical* evidence consistent with the all-cis assignment.

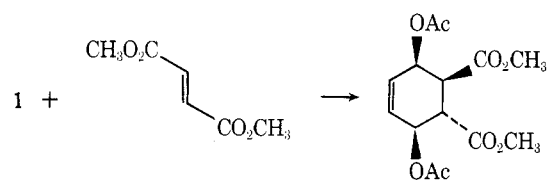
Saponification of **2** (10% NaOH, 0 °C, 2 h) proceeds without elimination to afford the dihydroxy acid **3**. When subjected to *p*-toluenesulfonic acid in chlorobenzene at reflux **3** is transformed into the bicyclic γ-lactone **4** in 85% yield after distillation. Consistent with its structure, **4** forms a customary dibromo derivative **5** and can as well be oxidized (Jones reagent) cleanly to the bicyclic enone **6**.



5 6

This lactonization thus provides chemical affirmation of the stereochemical assignment in **2**.

We have also investigated for the first time addition of **1** with more highly functionalized acrylate derivatives. Although **1** with fumaric acid affords only phthalic anhydride under a variety of conditions, the ene-tetraester **7** can be



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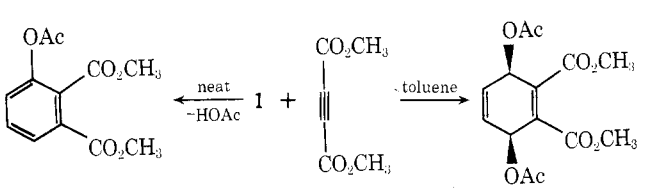
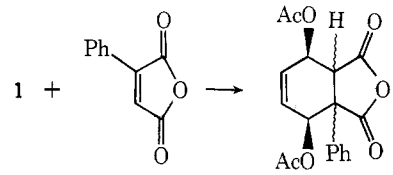
obtained in 76% yield (recrystallized) after boiling an equimolar mixture of **1** and dimethyl fumarate in xylene for 24 h. Surprisingly the crude reaction mixture gives no evidence of any aromatic by-products. Hill has reported the utility of **1** in constructing substituted aromatic rings by direct cycloaddition with acetylenic dienophiles and subsequent elimination of acetic acid.[8] In that work, a mixture of **1** and dimethyl acetylenedicarboxylate when heated at 110 °C (no solvent) furnished **8**. We have repeated this experiment in toluene at reflux (50 h) and found, in contrast, that a 70% (distilled) yield of the cyclohexadiene **9** may be obtained consistently. Efforts to extend this useful 1,4-cyclohexadiene synthesis to propiolic acid and ethyl propiolate were far less successful. In both cases numerous products in addition to diene were formed. None of these was acetylsalicylic acid (ethyl ester) or *m*-acetoxybenzoic acid (ethyl ester), the expected aromatic derivatives.



8 9

As part of another project we required the previously unprepared adduct of **1** with phenylmaleic anhydride.[9] This bicyclic anhydride **10** (mp 160–162 °C) could be isolated in 52% yield (xylene, reflux) as a mixture (ca. 10:1) of unassigned stereoisomers which were separable by high-pressure liquid chromatography. In other cycloadditions we have surveyed for purposes of natural product synthesis, no reaction could be engendered between **1** and ethyl cinnamate, ethyl *p*-nitrocinnamate, or cinnamoyl chloride.



10

Experimental Section

Melting points were determined in capillaries and are uncorrected. NMR spectra were recorded on a Varian A-60A spectrometer with tetramethylsilane as an internal standard. Infrared spectra were determined on a Perkin-Elmer 137 spectrophotometer. Mass spectra were carried out using a computerized AEI MS-902 instrument. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

***all-cis*-2,5-Dihydroxycyclohex-3-enecarboxylic acid (3).** *all-cis*-2,5-Diacetoxycyclohex-3-enecarboxylic acid (**2**,[3] 1.00 g, 4.13 mmol) was stirred with 10% aqueous NaOH solution (10 ml) at 0 °C for 2 h. While cold, the solution was acidified to pH 3 (10% H_2SO_4) and washed with three 25-ml portions of ether. The aqueous layer was evaporated to dryness under vacuum (0.5 mmHg) and the residue stirred overnight with 50 ml of distilled THF. The supernatant was dried ($MgSO_4$), filtered through Celite, and concentrated to yield 0.524 g (80%) of **3**, mp 155–157 °C after trituration with cold ether: NMR δ (D_2O) 5.90 (d, 2 H, J = 2 Hz), 4.1–4.5 (m, 2 H), 2.78 (d of t, 1 H, J = 12, 4, 3 Hz), 1.28–2.33 (complex m, 2 H); ir (nujol) 3.15. 5.76, 5.99 μ.

Anal. Calcd for $C_7H_{10}O_4$: C, 53.2; H, 6.4. Found: C, 53.2; H, 6.4.

Preparation of 6-Oxo-7-oxabicyclo[3.2.1]oct-2-en-4-ol (4). A 50-ml round-bottom flask containing **3** (0.097 g, 0.615 mmol) and a trace (<1 mg) of *p*-toluenesulfonic acid was fitted with a Soxhlet extractor containing a thimble half-filled with CaH_2. The apparatus was flushed with N_2, then chlorobenzene (30 ml, deaerated for 15 min in a stream of N_2) added. The mixture was heated at reflux for 6 h. After removal of solvent at reduced pressure the residue was stirred with solid $NaHCO_3$ in $CHCl_3$ for 30 min and filtered, and the filtrate was concentrated. Kugelrohr distillation (140 °C, 0.2 mm) afforded 0.073 g (85%) of lactone **4** as a colorless solid: mp 79–84 °C; NMR δ ($CDCl_3$) 6.33 (d of d, 1 H, J = 9, 5 Hz), 5.91 (broad d, 1 H, J = 9 Hz), 4.83 (broad d, 1 H, J = 5 Hz), 4.68 (m, 1 H), 3.78 (s, 1 H, hydroxyl), 3.10 (t, 1 H, J = 5 Hz), 2.55 (d of t, 1 H, J = 12, 5 Hz), 2.11 (d, 1 H, J = 12 Hz); ir ($CHCl_3$) 5.63 μ; mass spectrum (CI, methane) m/e 141 (M + 1), 123 (base).

Anal. Calcd for $C_7H_8O_3$: C, 60.0; H, 5.8. Found: C, 60.0; H, 5.7.

Preparation of 4,6-Dioxo-7-oxabicyclo[3.2.1]oct-2-ene (6). Oxidation of 4. A solution of the lactone **4** (0.047 g, 0.336 mmol) in acetone (5 ml) was chilled to 0 °C. Standard Jones reagent was added dropwise until the red color of the reagent persisted. Excess oxidant was destroyed with isopropyl alcohol, then sufficient water added to dissolve the chromium salts. Three ether extractions afforded 0.023 g (50%) of the enone as a yellow oil: NMR δ ($CDCl_3$) 7.42 (d of d, 1 H, J = 10, 5 Hz), 6.01 (d, 1 H, J = 10 Hz), 5.17 (broad t, 1 H), 3.64 (m, 1 H), 2.89 (m, 2 H); ir (film) 5.60, 5.88 μ.

Cycloaddition of 1 with dimethyl fumarate. A solution of dimethyl fumarate (1.695 g, 11.76 mmol) and **1**[10] (2.000 g, 11.76 mmol) in deaerated xylene (50 ml) was heated at reflux for 24 h under N_2. Removal of the solvent at reduced pressure, then crystallization of the residue from 1:2 benzene–hexane afforded 2.812 g (76%) of **7** as fine, colorless needles: mp 129–131 °C; NMR δ ($CDCl_3$) 5.98 (m, 2 H), 5.62 (m, 2 H), 3.72 and 3.71 (overlapping singlets, 6 H), 3.18 (d of d, 2 H, J = 6, 1.5, 1.5 Hz), 2.10 (s, 3 H), 2.00 (s, 3 H); ir ($CHCl_3$) 5.75 μ.

Anal. Calcd for $C_{14}H_{18}O_8$: C, 53.5; H, 5.8. Found: C, 53.6; H, 5.7.

Cycloaddition of 1 with Dimethyl Acetylenedicarboxylate. Dimethyl acetylenedicarboxylate (0.302 g, 2.14 mmol) and **1** (0.200 g, 1.18 mmol) were dissolved in deaerated toluene (15 ml) and the solution heated at reflux under N_2 for 48 h. Removal of the solvent at reduced pressure followed by Kugelrohr distillation (100–150 °C

at 0.1 mm) from a base-washed flask yielded 0.355 g (70%) of colorless oil which solidified on standing in the freezer (mp 56–61 °C): NMR δ ($CDCl_3$) 6.08 (s, 4 H), 3.85 (s, 6 H), 2.12 (s, 6 H); ir ($CHCl_3$) 5.75, 6.05 μ; mass spectrum (CI, methane) *m/e* 313 (M + 1), 222 (base). After one recrystallization from 2:1 cyclohexane–hexane the adduct **9** had mp 64–67° (recovery 56%).

Anal. Calcd for $C_{14}H_{16}O_8$: C, 53.8; H, 5.2. Found: C, 54.1; H, 5.2.

Cycloaddition of 1 with Phenylmaleic Anhydride. Phenylmaleic anhydride (0.870 g, 5.0 mmol) and **1** (0.750 g, 5.0 mmol) in xylene (25 ml, deaerated) were heated at reflux under N_2 for 40 h. Removal of the solvent at reduced pressure followed by crystallization (1:2 benzene–hexane) gave 0.900 g (50%) of **10** as fine, pale yellow needles: mp 160–162 °C; NMR δ ($CDCl_3$) 7.46 (s, 5 H), 6.20 (d, 2 H, *J* = 2 Hz), 5.72 (d of d, 1 H, *J* = 8, 2 Hz), 5.64 (d, 1 H, *J* = 2 Hz), 4.19 (d, 1 H, *J* = 8 Hz), 2.20 (s, 3 H), 2.05 (s, 3 H); ir ($CHCl_3$ 5.36, 5.58, 5.71 μ; mass spectrum *m/e* 284 (M − 60), 43 (base).

Anal. Calcd for $C_{18}H_{16}O_7$: C, 62.8; H, 4.7. Found: C, 63.0; H, 4.6.

Analysis of this product by high-pressure liquid chromatography[11] (Porasil, eluting with CH_2Cl_2) indicated two isomers with the major (ca. 10:1) having a longer retention time.

Acknowledgment. We acknowledge the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this research.

Registry No.—**1**, 15910-11-9; **2**, 58298-62-7; **3**, 58324-77-9; **4**, 58298-63-8; **6**, 58298-64-9; **7**, 58298-65-0; **9**, 58298-66-1; **10**, 58298-67-2; dimethyl fumarate, 624-49-7; dimethyl acetylenedicarboxylate, 762-42-5; phenylmaleic anhydride, 36122-35-7.

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(11) We are grateful to Mr. David P. Warren for carrying out this analysis.

Selective Removal of an Aromatic Methylenedioxy Group

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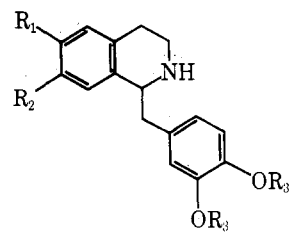
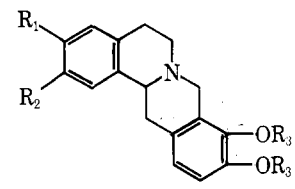
The preparation of tetrahydroisoquinolines devoid of substituents in one of the aromatic rings, such as **1e** and **2e**, by standard methods was recently described.[1] We now report the novel synthesis of related compounds based on the preferential O-demethylenation of dimethoxymethylenedioxy-substituted isoquinolines with boron trichloride[2] followed by elimination of the resulting catechol function via hydrogenolysis of the bistetrazoyl ether intermediate.[3]

To demonstrate the feasibility of removing a catechol function from a tetrahydroisoquinoline, the dimethoxycatechol **1b**[4] was treated with 2 equiv of 5-chloro-1-phenyl-1*H*-tetrazole in refluxing acetone containing anhydrous K_2CO_3 to furnish 70% of the bistetrazoyl ether **1c**. Hydrogenation of **1c** in acetic acid over Pd/C then provided 80% of the known[5] dimethoxy-substituted tetrahydroisoquinoline **1d**.

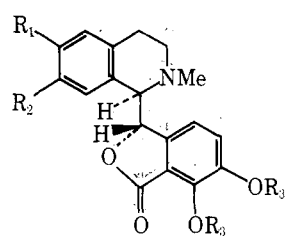
In applying this procedure to the selective removal of a methylenedioxy group from an isoquinoline, the dimethoxymethylenedioxy tetrahydroprotoberberine **2a**, obtained by borohydride reduction of the commercially available alkaloid berberine,[6] was O-demethylenated with 2 mol of boron trichloride in methylene chloride to provide 95% of the known[7] dimethoxycatechol **2b**. Etherification of **2b** with 5-chloro-1-phenyl-1*H*-tetrazole gave 95% of the bistetrazoyl ether **2c** which was then hydrogenolyzed to form 64% of the dimethoxy tetrahydroprotoberberine **2d** (58% overall from **2a**).



1b–e

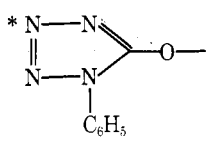


2a–e



3a–d

	R_1	R_2	R_3
a	$-OCH_2O-$		Me
b	OH	OH	Me
c	*	*	Me
d	H	H	Me
e	H	H	H



Finally, to test whether hydrogenolysis of an optically active substrate would cause racemization, the (+)-dimethoxydiphenolic phthalide **3b**, obtained in 81% yield by treating the alkaloid (−)-β-hydrastine (**3a**) with boron trichloride,[2] was converted into the (+)-bistetrazoyl ether **3c** (85% yield). Catalytic hydrogenation of **3c** in the presence of Pd/C then afforded 90% of the (−)-dimethoxyphthalide **3d** whose 1*R*,9*S* configuration was indicated by its NMR, ORD, and CD spectra.

Based on the above transformations, the novel elimination of a methylenedioxy group from a dimethoxymethylenedioxy isoquinoline has provided a facile route to a dimethoxy-substituted benzylisoquinoline, a tetrahydroprotoberberine, and a phthalideisoquinoline. The method appears to be applicable to secondary as well as tertiary amines and in the instant example did not affect the chiral centers of the substrate. Extension of this approach to other optically active isoquinolines is presently under investigation.

Experimental Section[8]

6,7-Bis(1-phenyl-1*H*-tetrazol-5-yloxy)-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1c HCl). A mixture of 5.3 g (15 mmol) of 6,7-dihydroxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride[5] (**1b** HCl), 6 g (30 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole, and 6.8 g (50 mmol) of anhydrous potassium carbonate in 300 ml of acetone was stirred and refluxed for 48 h, cooled, and filtered. The filtrate was evaporated, and the residue dissolved in ethanolic hydrogen chloride, evaporated, and crystallized from acetonitrile to give 6.6 g (70%) of **1c** HCl: mp 192–193 °C; NMR δ 2.8–3.8 (m, 6, 3 CH_2), 3.73 (s, 6, 2 OCH_3), 4.48 (m, 1, CH), 6.81 (m, 3, aromatic), 7.48, 7.51 (2 s, 10, aromatic), 7.80; 7.90 (2 s, 2, aromatic).

Anal. Calcd for $C_{32}H_{29}N_9O_4$·HCl: C, 59.68; H, 4.68; N, 19.70. Found: C, 59.24; H, 4.80; N, 19.28.