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.

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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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Selective Removal of an Aromatic Methylenedioxy Group

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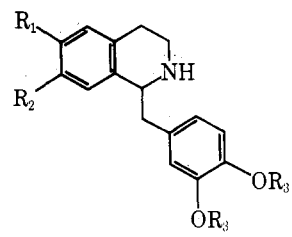
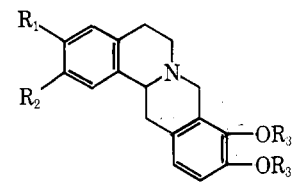
The preparation of tetrahydroisoquinolines devoid of substituents in one of the aromatic rings, such as **1e** and **2e**, by standard methods was recently described.[1] We now report the novel synthesis of related compounds based on the preferential O-demethylenation of dimethoxymethylenedioxy-substituted 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**.

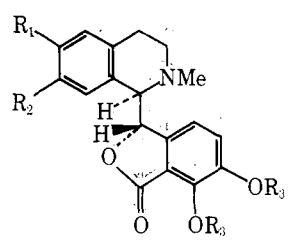
In applying this procedure to the selective removal of a methylenedioxy group from an isoquinoline, the dimethoxymethylenedioxy tetrahydroprotoberberine **2a**, obtained by borohydride reduction of the commercially available alkaloid berberine,[6] was O-demethylenated with 2 mol of boron trichloride 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

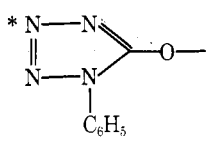


2a–e



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.

1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1d HCl). A solution of 4 g (6.6 mmol) of **1c** in 200 ml of acetic acid was hydrogenated at 50 psi in the presence of 2 g of 10% Pd/C at 40 °C in a Parr apparatus for 17 h and filtered. The filtrate was evaporated, the residue distributed between a mixture of 100 ml of 2 N hydrochloric acid and ethyl acetate, and the organic layer washed with 100 ml of water. The aqueous layers were combined, rendered alkaline with 10% sodium hydroxide, and extracted with ethyl acetate, and the organic phase was acidified with ethanolic hydrogen chloride, and evaporated. The residue was crystallized from a mixture of ethanol and ether to give 1.7 g (80%) of **1d** HCl, mp 228–230 °C, identical in mixture melting point, TLC, and NMR with authentic **1d** HCl.[4]

2,3-Bis(1-phenyl-1*H*-tetrazol-5-yloxy)-9,10-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizine Hydrobromide (2c HBr). To a solution of 6.8 g (20 mmol) of (±)-canadine[6] (**2a**) in 200 ml of methylene chloride at room temperature was added 48 ml of a methylene chloride solution containing 4.8 g (40 mmol) of boron trichloride. After storage overnight, 50 ml of methanol was added over 15 min, the mixture evaporated, and the residue crystallized from methanol to give 5.8 g (80%) of 2,3-dihydroxy-9,10-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizine hydrochloride (**2b** HCl): mp 259–261 °C; NMR δ 2.6–3.7 (m, 8, 4 CH_2), 3.77, 3.79 (2 s, 6, 2 OCH_3), 4.2–4.8 (m, 1, CH), 6.08 (s, 1, aromatic), 6.15 (s, 1, aromatic), 7.01 (s, 2, aromatic), 8.91, 9.15 (b, 2, 2 OH).

Neutralization of the above hydrochloride followed by acidification with hydriodic acid and crystallization from methanol afforded **2b** HI, mp 200–202 °C (lit.[7] mp 201–203 °C).

In a manner similar to the procedure for **1c** HCl, 3.3 g (10 mmol) of **2b** HCl, 4 g (20 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole and 4.5 g (33 mmol) of anhydrous potassium carbonate in 200 ml of acetone afforded 6.5 g (95%) of **2c** HBr: mp 205–207 °C (from acetonitrile); NMR δ 2.9–4.2 (m, 6, 3 CH_2), 3.80 (s, 6, 2 OCH_3), 4.2–5.2 (m, 3, CH_2 + CH), 7.04 (s, 2, aromatic), 7.50, 7.53 (2 s, 10, aromatic), 7.84, 8.02 (2 s, 2, aromatic).

Anal. Calcd for $C_{33}H_{29}N_9O_4$·HBr: C, 56.90; H, 4.34; N, 18.10. Found: C, 56.89; H, 4.33; N, 18.35.

9,10-Dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizine Hydrochloride (2d HCl). By the procedure given for the preparation of **1d** HCl, 10 g (16 mmol) of **2c** in 200 ml of acetic acid was hydrogenated in the presence of 3 g of 10% Pd/C to give 3 g (64%) of **2d** HCl: mp 234–235 °C (from ethanol); NMR δ 2.7–3.9 (m, 6, 3 CH_2), 3.76, 3.78 (2 s, 6, 2 OCH_3), 4.45 (b, 3, $^+NCH_2C_6H_5$ + CH), 6.99 (s, 2, aromatic), 7.24 (s, 2, aromatic), 7.38 (b, 2, aromatic), 12.0 (b, 1, NH^+).

Anal. Calcd for $C_{19}H_{21}NO_2$·HCl: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.54; H, 6.69; N, 4.35.

(+)-1(*R*)-1-[3(*S*)-6,7-Dimethoxyphthalidyl]-2-methyl-6,7-bis(1-phenyl-1*H*-tetrazol-5-yloxy)-1,2,3,4-tetrahydroisoquinoline (3c). In a manner similar to the procedure for **1c** HCl, 11 g (30 mmol) of (+)-1-(*R*)-[6,7-dimethoxy-3-(*S*)-phthalidyl]-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride[2] (**3b** HCl), 12 g (66 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole, and 9 g (66 mmol) of anhydrous potassium carbonate in 600 ml of acetone provided, after crystallization from ethyl acetate, 16.7 g (85%) of **3c**: mp 162–163 °C; $[\alpha]_D$ +9.0° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$) δ 2.20–3.36 (m, 4, CH_2CH_2), 2.60 (s, 3, NCH_3), 3.9, 4.03 (2 s, 3 each, 2 OCH_3), 4.08, 5.58 (AB, 2, J_{vic} = 4 Hz, CHCH), 6.86, 7.18 (AB, 2, J_{ortho} = 8.5 Hz, aromatic), 7.18 (s, 1, aromatic), 7.39, 7.43 (2 s, 10, aromatic), 7.56 (s, 1, aromatic); uv max 220 nm (ε 53 000), 235 (11 900) (infl), 278 (2700) (infl), 310 (4400); ORD (*c* 0.659, 50% MeOH in 0.1 N HCl) $[\phi]_{650}$ +920°, $[\phi]_{589}$ +320°, $[\phi]_{250}$ +75 000° (pk), $[\phi]_{218}$ −300 000° (tr); CD (*c* 0.659, 50% MeOH in 0.1 N HCl) $[\theta]_{348}$ 0, $[\theta]_{318}$ −3200, $[\theta]_{290}$ 0, $[\theta]_{276}$ +11 500, $[\theta]_{232}$ +232 500, $[\theta]_{219}$ 0, $[\theta]_{205}$ −290 000, $[\theta]_{200}$ −185 000.

Anal. Calcd for $C_{34}H_{29}N_9O_6$: C, 61.91; H, 4.43; N, 19.11. Found: C, 62.03; H, 4.36; N, 19.23.

(−)-1-(*R*)-[3(*S*)-6,7-Dimethoxyphthalidyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline (3d). By the procedure given for the preparation of **1d** HCl, 7 g (10 mmol) of **3c** in 200 ml of acetic acid was hydrogenated in the presence of 3 g of 10% Pd/C to give, after crystallization from a mixture of ether and petroleum ether (bp 30–60 °C), 3.1 g (90%) of **3d**: mp 89–90 °C; $[\alpha]_D$ −27.4° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$) δ 2.10–3.00 (m, 4, CH_2CH_2), 2.56 (s, 3, NCH_3), 4.00 (2 s, 3 each, 2 OCH_3), 4.10, 5.52 (AB, 2, J_{vic} = 4 Hz, CHCH), 6.28, 7.00 (AB, J_{ortho} = 8.5 Hz, aromatic), 6.90 (m, 1, aromatic), 7.12 (m, 3, aromatic); uv max 209 nm (ε 36 500), 263 (1130) (sh), 272 (1150), 310 (4150); ORD (*c* 0.679, MeOH) $[\phi]_{650}$ +220°, $[\phi]_{589}$ +275°, $[\phi]_{420}$ +510°, $[\phi]_{400}$ +520°, $[\phi]_{380}$ +470°, $[\phi]_{305}$ +5300°, $[\phi]_{294}$ +7400° (pk), $[\phi]_{283}$ +7100° (tr), $[\phi]_{231}$ +45 000° (pk), $[\phi]_{209}$ −137 500° (tr); CD (*c* 0.679, MeOH) $[\theta]_{365}$ 0, $[\theta]_{315}$ −6500, $[\theta]_{285}$ −1000, $[\theta]_{258}$ −4100, $[\theta]_{250}$ 0, $[\theta]_{236}$ +35 000, $[\theta]_{220}$ +118 750, $[\theta]_{207}$ 0, $[\theta]_{200}$ −81 250.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.55; H, 6.27; N, 4.03.

Acknowledgments. We wish to thank the following members of our Physical Chemistry Department (Director, Dr. R. P. W. Scott): Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the NMR spectra, and Dr. V. Toome for the uv, ORD, and CD spectra.

Registry No.—**1b** HCl, 19384-75-9; **1c**, 58298-39-8; **1c** HCl, 58298-40-1; **1d** HCl, 3972-77-8; **2a**, 29074-38-2; **2b** HCl, 58298-41-2; **2b** HI, 58298-42-3; **2c**, 58298-43-4; **2c** HBr, 58298-44-5; **2d** HCl, 58298-45-6; **3b** HCl, 58298-46-7; **3c**, 58298-47-8; **3d**, 58298-48-9; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4.

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Proton Transfer from the Monoanion of 1,1-Cyclopropanedicarboxylic Acid

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Hydrogen bonding in the monoanions of dicarboxylic acids has received much study since Brown and McDaniel suggested that extraordinarily high K_1/K_2 ratios arise from it.[1] Eberson and Wadsö[2] concluded that it is responsible for ratios greater than about 10 000, and Dygert, Muzii, and Saroff[3] proposed that it might be important in compounds with ratios larger than 1200.

Proton transfer rates confirm this interpretation. Eyring and co-workers have studied two families of dicarboxylic acids, and found that the rate of proton removal by hydroxide ion from the monoanion is inversely related to the strength of the hydrogen bond.[4] With dialkyl substituted malonic acids, the hydrogen bond strength is seemingly closely related to the bulk of the substituent groups. The diisopropyl compound has the greatest K_1/K_2 ratio and the smallest k_f for proton removal. It was suggested that spreading the angle between the alkyl groups results in decreasing the angle between the carboxyl groups, and that "closing the jaws" produces a stronger hydrogen bond.[4b]

In this connection, a study of 1,1-cyclopropanedicarboxylic acid seemed of interest. X-ray crystallography has re-