Time	δ, Methyl groups			
0 min	0.72	1.25	1.35	1.41
20 min	0.71[a]	1.22	1.32[a]	1.40
3.7 hr		1.21		1.41
24 hr		1.22		1.40

[a] Peak height is *ca.* 20% that of sample before addition of $HClO_4$.

The above sample was poured into water and extracted with chloroform. The extracts were dried (anhydrous Na_2SO_4), concentrated, and recrystallized from ether to give **6**: mp 149–152°; nmr (acetone-d_6) δ 3.70–4.50 (m, 6), 4.76 (s, 1), 7.88 (s, 4); mass spectrum *m/e* 395.

1-Phthalimido-1-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (7) by Hydrolysis of 6.—A solution of **6** (46 mg, 0.12 mmol), glacial acetic acid (1.0 ml), and water (0.5 ml) was stirred at room temperature for 86 hr. Pyridine was then added and the solution was concentrated to dryness and extracted with ether. The extract was dried (anhydrous Na_2SO_4), filtered, and concentrated to dryness to give **7** as an oil which was crystallized from benzene to give 23 mg (55%) of **7**, mp and mmp with later sample 175–178°, ir and nmr spectra identical within experimental error to data below.

By Hydrolysis of 1.—Phthalimide **1** (500 mg, 1.29 mmol), hydrolyzed and worked up in the same way as **6**, afforded from benzene crystals of **7**: mp 178–181°; $[\alpha]^{25}D$ −4.5° (*c* 1.05, C_2H_5OH); ir ($CHCl_3$) 3455, 1777, 1720, 1714, 1425, 1398 cm^{-1}; uv max (C_2H_5OH) 220.5 mμ (ε 46,000), 234 (14,100 infl), 242 (10,000), 293.5 (2200); nmr (DMSO-d_6) δ 1.10, 1.36 (s, 6, 2 CH_3), 3.40–4.20 (m, 5, CH + CH_2), 4.46 (s, 1, CH), 4.44 (t, 1, *J* = 6 Hz, exchanged by D_2O addition, CH_2OH), 5.01 (d, 1, *J* = 4.5 Hz, exchanged by D_2O addition, CHOH), 7.85 (s, 4, aromatic).

Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.62; H, 5.47; N, 4.03.

Registry No.—**1**, 35170-82-2; **2**, 35170-83-3; **3**, 35170-84-4; **4**, 35192-04-2; **5**, 35170-85-5; **6**, 35170-86-6; **7**, 35170-87-7.

Acknowledgment.—We thank Dr. E. P. Oliveto and Dr. P. Rosen for encouragement and helpful discussions, and Mr. S. Kwoh and Mr. A. Sheffron for assistance in preparing some of the compounds. We also thank Mr. S. Traiman, Dr. V. Toome, and Dr. W. Benz for the ir, uv, and mass spectra, respectively, and Dr. F. Scheidl for optical rotation data and microanalyses.

Preferential Cleavage of an Aromatic Methylenedioxy Group in the Presence of Methoxyls with Boron Trichloride

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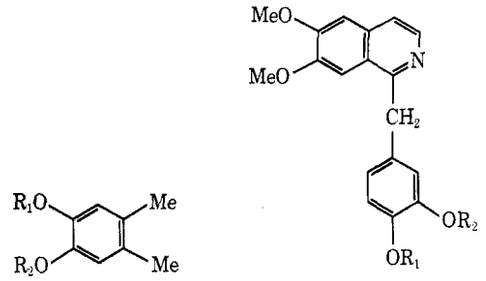
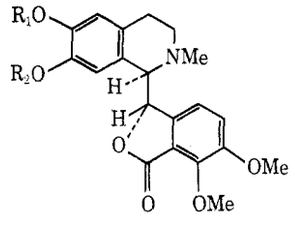
Received April 27, 1972

In connection with our studies on the transformation of phthalideisoquinolines into rheadans,[1] the methylenedioxy dimethoxy-substituted alkaloid (−)-β-hydrastine (**3a**) was deetherified with boron tribromide to the tetraphenol and methylated to the tetramethoxy phthalide (−)-cordrastine II[2] (**3c**). We now report a novel and more facile synthesis of **3c** based on the preferential O-demethylenation of **3a** with boron trichloride[3] followed by methylation of the resulting diphenol **3b**.



1a–c **2a–c**



3a–c

a, $R_1 + R_2 = -CH_2-$
b, $R_1 = R_2 = H$
c, $R_1 = R_2 = Me$

The type and extent of deetherification of model compounds treated with boron trichloride in methylene chloride was influenced by the ratio of substrate to reagent as well as the reaction temperature and time. By proper selection of conditions, cleavage of a methylenedioxy group in preference to aromatic methoxyls could be achieved. For example, treatment of 4,5-methylenedioxy-*o*-xylene (**1a**)[4] at room temperature with either 1 or 2 equiv of boron trichloride for 64 and 3 hr, respectively, gave 4,5-dimethylcatechol (**1b**)[5] in 80% yield while cleavage of 4,5-dimethoxy-*o*-xylene (**1c**)[5] required either higher temperatures or longer reaction times to effect ether cleavage. Similarly, while both the methylenedioxy-substituted isoquinoline **2a**[6] and its methoxy analog papaverine (**2c**) were converted by treatment with 2 molar equiv of the reagent for 5 hr at room temperature into a mixture of phenolic materials, only **2a** was cleanly cleaved at 4° to yield 78% 3′,4′-O-demethylpapaverine (**2b**)[7] while **2c** was recovered unchanged.

To further illustrate the synthetic applicability of preferential *O*-demethylenation, commercially available (−)-β-hydrastine (**3a**) was treated with 2 mol of boron trichloride in methylene chloride at room temperature for 6 hr to afford 81% the diphenol **3b**. Reaction of **3b** with diazomethane provided the tetra-

(1) W. Klötzer, S. Teitel, J. F. Blount, and A. Brossi, *J. Amer. Chem. Soc.*, **93**, 4321 (1971); W. Klötzer, S. Teitel, and A. Brossi, *Helv. Chim. Acta*, **54**, 2057 (1971).

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(3) Boron trichloride has been used in the selective scission of cyclic acetals [T. G. Bonner and N. M. Saville, *J. Chem. Soc.*, 2851 (1960)] and in the preferential O-demethylenation of certain podophyllotoxins [E. Schreier, *Helv. Chim. Acta*, **47**, 1529 (1964); H. MacLean and B. F. MacDonald, *Can. J. Chem.*, **47**, 457 (1969)]. Its selective action parallels that of aluminum bromide in nitrobenzene [E. Mosettig and A. Burger, *J. Amer. Chem. Soc.*, **52**, 2988 (1930)].

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methoxy phthalide isoquinoline (−)-cordrastine II[2] (**3c**). In contrast, boron tribromide under similar reaction conditions was not selective and cleaved **3a** to give mainly the corresponding tetraphenol.[2] This may be related to the stronger nucleophilic character of the bromide ion.

The above transformations demonstrate that boron trichloride can be used to selectively cleave a methylenedioxy group in methoxy-substituted aromatic compounds.

Experimental Section[8]

4,5-Dimethylcatechol (1b).—To 378 mg (2.5 mmol) of 4,5-methylenedioxy-*o*-xylene[4] (**1a**) dissolved in 70 ml of methylene chloride was added at room temperature 5 ml of a methylene chloride solution containing 585 mg (5 mmol) of boron trichloride. The solution was stored at ambient temperature for 3 hr; 5 ml of methanol was added and evaporated. The residue was crystallized from a mixture of benzene and petroleum ether to give 300 mg (80%) of **1b**, mp 89–91°, identical in mixture melting point and tlc with authentic 4,5-dimethylcatechol.[5] Under these reaction conditions 4,5-dimethoxy-*o*-xylene[5] (**1c**) was recovered unchanged.

6,7-Dimethoxy-1-(3,4-dihydroxybenzyl)isoquinoline Hydrochloride (2b HCl).—To a solution of 323 mg (1 mmol) of 6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline[6] (**2a**) in 15 ml of methylene chloride at 4° was added 7.1 ml of a methylene chloride solution containing 234 mg (2 mmol) of boron trichloride. The solution was stored at 4° for 5 hr; 5 ml of methanol was added and evaporated. The residue was dissolved in 30 ml of water and rendered neutral with saturated sodium bicarbonate; the resulting precipitate was collected and dissolved in ethanolic hydrogen chloride. The solution was evaporated and the residue crystallized from ethanol to give 275 mg (78%) of **2b** HCl, mp 232–233°, identical in mixture melting point, tlc, and nmr with authentic **2b** HCl.[7] Under these reaction conditions, papaverine (**2c**) was recovered unchanged.

(+)-1(*R*)-[6,7-Dimethoxy-3(*S*)-phthalidyl]-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3b).—To a solution of 6 g (14.3 mmol) of (−)-β-hydrastine hydrochloride (**3a** HCl) in 350 ml of methylene chloride at room temperature was added a solution of 3.34 g (28.6 mmol) of boron trichloride in 50 ml of methylene chloride. The resulting turbid mixture was stirred at room temperature for 6 hr; 50 ml of methanol was added over 10 min and then evaporated. The residue was dissolved in 150 ml of 1 *N* hydrochloric acid, washed with chloroform, heated for 20 min at 95°, cooled, and then neutralized with saturated sodium bicarbonate. The resulting precipitate was collected, washed with water, dried, and crystallized from chloroform to give 4.3 g (81%) of **3b**: mp 199–200°; nmr δ 2.45 (s, 3, NCH_3), 1.90–3.20 (m, 4, CH_2CH_2), 3.83, 3.86 (2 s, 6, 2 OCH_3), 3.94 (d, 1, J = 4 Hz, CHN), 5.54 (d, 1, J = 4 Hz, CHO), 6.35, 7.23 (2 d, 2, J_{ortho} = 8 Hz, aromatic), 6.35, 6.45 (2 s, 2, aromatic); uv max 218 nm (ε 29,000) (infl), 235 (12,500) (infl), 293 (6400), 313 (4500); $[\alpha]^{25}D$ +218° (*c* 1, 1 *N* HCl); ORD (*c* 0.371, MeOH) $[\phi]_{600}$ +10°, $[\phi]_{589}$ +12°, $[\phi]_{331}$ −4250° (tr), $[\phi]_{315}$ 0, $[\phi]_{295}$ +6000° (tr), $[\phi]_{232}$ +40,000° (pk), $[\phi]_{227}$ 0, $[\phi]_{209}$ −232,000° (tr); CD (*c* 0.01 *M*, MeOH) $[\theta]_{360}$ 0, $[\theta]_{315}$ −8400, $[\theta]_{294}$ −5100, $[\theta]_{278}$ −6000, $[\theta]_{255}$ 0, $[\theta]_{220}$ +106,000, $[\theta]_{210}$ 0, $[\theta]_{204}$ −145,000.

Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.43; H, 5.64; N, 3.77.

(−)-1(*R*)-[6,7-Dimethoxy-3(*S*)-phthalidyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide [(−)-Cordrastine II HBr] (3c HBr).—A mixture of 1 g (2.67 mmol) of **3b** in 20 ml of methanol was treated with an excess of diazomethane in ether; volatiles were removed at 40° in a stream of nitrogen; the residue was suspended in water, extracted with ethyl acetate and evaporated. The residue was dissolved in ethanolic hydrogen bromide, evaporated, and crystallized from ethanol to give 1.1 g (86%) of **3c** HBr, mp 212–213°, $[\alpha]^{25}D$ + 188° (*c* 1, MeOH), identical in mixture melting point, nmr, and optical rotation with (−)-cordrastine II hydrobromide previously described.[2]

Registry No.—**3b**, 35337-18-9; **3c** HBr, 34417-89-5; boron trichloride, 10294-34-5.

Acknowledgement.—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. We are grateful to Mr. J. Van Burik for his skillful technical assistance.

(8) Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Nmr spectra were obtained in DMSO-d_6 on a Varian Ha-100 instrument. Uv spectra were measured in ethanol with a Cary recording spectrophotometer Model 14M and optical rotations with a Perkin–Elmer instrument. Rotatory dispersion curves were determined at 23° with a Durrum–Jasco spectrophotometer Model 5 using 1-cm, 0.1-cm, or 0.1-mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. Reported yields are of isolated products homogeneous to tlc.

Studies on the Reaction of Phenylmagnesium Bromide with Acetonitrile[1]

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Received February 15, 1972

Phenylmagnesium bromide is reported to react with acetonitrile to give poor yields of acetophenone except in cases where an excess of the latter reagent is employed.[3,4] It has been proposed that the acetonitrile molecule undergoes tautomerization and, in this form, can be thought of as a "pseudo-acid" which, when treated with the Grignard reagent, gives rise to considerable amounts of benzene.[5]

$$C_6H_5MgBr + CH_3C{\equiv}N \longrightarrow C_6H_6 + BrMgCH_2CN \rightleftharpoons CH_2{=}C{=}NMgBr$$

The idea of hydrogen abstraction by the Grignard reagent is supported by the fact that benzonitrile, which has no active hydrogen atom, generally gives good yields of ketone with the Grignard reagent. Propionitrile, which has a less labile hydrogen than acetonitrile, is reported to give a good yield of ketone.[6] Pivalonitrile and trifluoroacetonitrile also give excellent yields of *tert*-butyl phenyl ketone and α,α,α-trifluoroacetophenone, as are shown in Table I.

We became interested in a more detailed study of the reaction of acetonitrile with the Grignard reagent since the low yield of acetophenone suggests that a much greater "active" hydrogen effect is present than when propionitrile is used.

The first attempts were directed toward establishing the true source of benzene produced in the reaction of acetonitrile and phenylmagnesium bromide. The technique of isotopic labeling was used for this purpose. Trideuterioacetonitrile was substituted for acetonitrile, and mass spectrographic analysis of the benzene produced in the reaction with phenylmagnesium bromide

(1) This work was partially supported by a grant from the Committee on Institutional Studies and Research, Murray State University, Murray, Kentucky.

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