A Practical Route to Bisbenzylisoquinolines by an Improved Ullmann Diphenyl Ether Synthesis

Michael P. Cava* and Ali Afzali

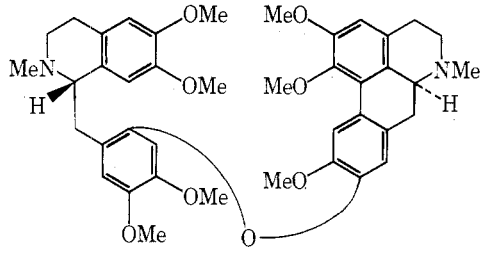
Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19174

Received January 14, 1975

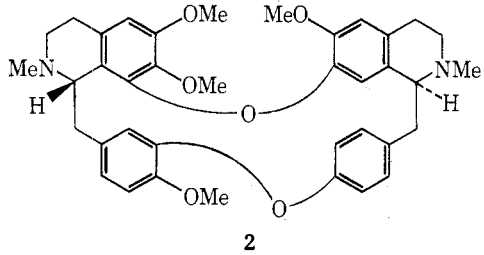
An improved Ullmann diphenyl ether synthesis is reported. In this procedure, the aromatic halide and phenol components are heated with pentafluorophenylcopper (**16**) in dry pyridine. Thus, 6′-bromolaudanosine (**4**) was condensed with phenol to give 6′-phenoxylaudanosine (**7**). Condensation of individual enantiomers of bromide **4** with the phenolic alkaloids (*S*)-armepavine (**15**), (*R*)-nuciferoline (**11**), cassythicine (**9**), and *N*-methylcassyfiline (**10**) gave the bisbenzylisoquinolines **17, 18, 19, 20,** and **21**; all yields were in the 42–54% range, based upon bromide **4**.

The significant tumor-inhibitory activity of thalicarpine (**1**) and tetrandrine (**2**) has stimulated interest in practical synthetic approaches to these compounds, and to other potentially biologically active bisbenzylisoquinolines.[1]

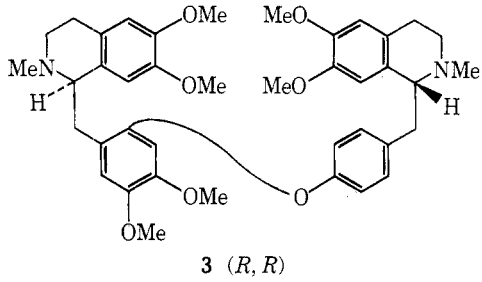
The classical Ullmann-type synthesis of a bisbenzylisoquinoline involves the direct coupling of a phenolic benzylisoquinoline with a halogenated benzylisoquinoline in the presence of copper or one of its salts or oxides. This approach has the great advantage that the two halves of the molecule may be prepared separately as pure enantiomers before the final coupling step. This advantage is usually outweighed, however, by a low yield in the final Ullmann reaction. For example, the crystalline *R,R* enantiomer (**3**) of *O*-tetramethylmagnolamine (**17**) was obtained in only 2% yield by the Ullmann coupling of (*R*)-6′-bromolaudanosine (**5**) with (*R*)-armepavine (**14**).[2] Similarly, thalicarpine (**1**) has been synthesized by the Ullmann coupling of (*S*)-6′-bromolaudanosine (**6**) with (*S*)-*N*-methyllaurotetanine (**8**);[3] the unsatisfactory nature of this reaction, however,



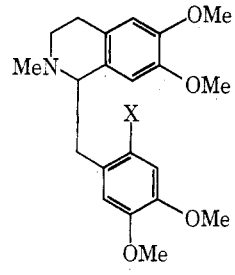
1



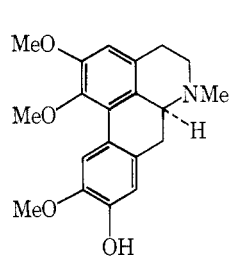
2



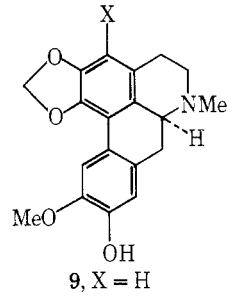
3 (*R, R*)



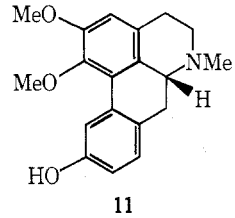
4, X = Br (*dl*)
5, X = Br (*R*)
6, X = Br (*S*)
7, X = OPh (*dl*)



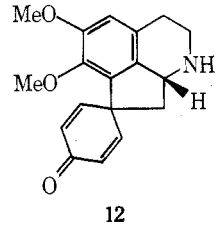
8



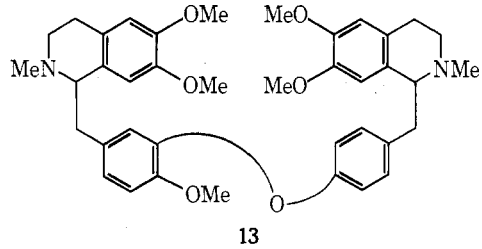
9, X = H
10, X = OMe



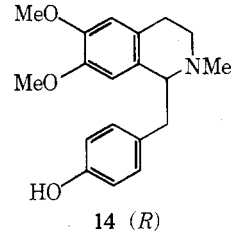
11



12



13



14 (*R*)
15 (*S*)

$(C_6F_5Cu)_4$
16

prompted an extensive study of an alternate and more practical thalicarpine synthesis in which the diphenyl ether linkage was formed at a very early stage of the synthesis.[4] The avoidance of an ultimate Ullmann step also was the key point of strategy in a recent synthesis of *dl*-*O*-methyldauricine (**13**, *R,R*, *S,S*).[1]

A 1964 kinetic study of the condensation of phenol with bromobenzene led to the proposal that cuprous phenoxide was formed as an intermediate, regardless of the oxidation state of the copper catalyst used.[5] A more recent study has given direct support to this hypothesis. In this work,[6] the reaction of phenol with phenylcopper in ether at −10° gave cuprous phenoxide as a violet precipitate which was very sensitive to both oxygen and moisture; reaction of cuprous phenoxide with bromobenzene in diglyme at 125° for 17 hr gave diphenyl ether in 38% yield, the yield being increased to 46% in the presence of pyridine. These results prompted us to investigate the utility of the relatively stable, soluble, and commercially available[7] pentafluorophenylcopper (**16**, PFPC)[8] as a condensing agent in the synthesis of bisbenzylisoquinoline-type structures.

The reaction of *dl*-6′-bromolaudanosine (**4**) with phenol was chosen as a model for our study. The best empirically determined Ullmann procedure in the benzylisoquinoline series involves the use of potassium carbonate and cupric oxide in hot pyridine for long reaction periods.[3,9] Under these conditions, crystalline 6′-phenoxylaudanosine (**7**) was obtained from phenol and bromide **4** in a maximum yield of 13%; TLC indicated that considerable debromination of **4** to laudanosine had occurred as a side reaction.

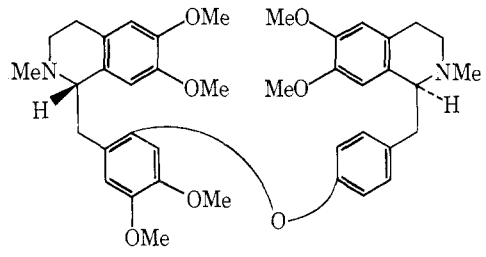
When equimolar amounts of bromide **4**, phenol, and PFPC were heated in acetonitrile, a red-brown precipitate, presumably cuprous phenoxide, soon separated. After 24 hr of refluxing, however, the precipitate had not dissolved and starting bromide was recovered in 95% yield. The desired reaction took place, however, when diglyme containing a small amount of pyridine was used as the solvent, the ether **7** being isolated in 31% yield. The yield of **7** was increased to 52% when pyridine alone was used as the solvent.

The synthesis of the natural (*S,S*) enantiomer (**17**) of *O*-tetramethylmagnolamine was next studied in order to test our procedure in the synthesis of a true bisbenzylisoquinoline. This was also a significant test case, since the classical Ullmann method is stated to give the corresponding *R,R* enantiomer **3** in only 2% yield.[2] Indeed, condensation of equimolar amounts of (*S*)-6′-bromolaudanosine (**6**), (*S*)-armepavine (**15**), and PFPC in diglyme–pyridine gave the crystalline bisbenzylisoquinoline **17** in 32% yield; the yield rose to 42% when pyridine alone was used as the solvent. When the pyridine reaction was repeated using a ratio of 1 equiv of bromide **6** to 2 equiv each of PFPC and phenol **15**, ether **17** was isolated in 53% yield, 85% of the excess (*S*)-armepavine being recovered.

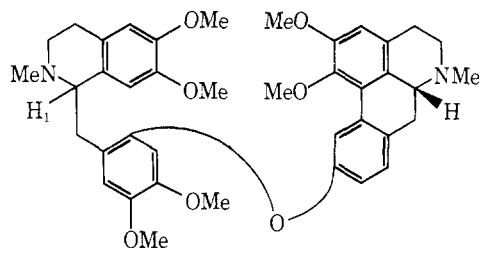
In view of the antitumor activity of thalicarpine (**1**), we chose to apply our procedure to the synthesis of some closely related unnatural benzylisoquinoline–aporphine structures, namely **18**–**21**.

(*R*)-Nuciferoline (**11**)[10] was prepared readily from natural stepharine (**12**)[11] by N-methylation, followed by a dienone–phenol rearrangement. Reaction of (*R*)-6′-bromolaudanosine (**5**) with an excess of **11** and PFPC gave the crystalline base **18** in 47% yield. Use of the enantiomeric *S* bromide **6** in this reaction gave the corresponding amorphous diastereomeric product **19** in comparable yield.

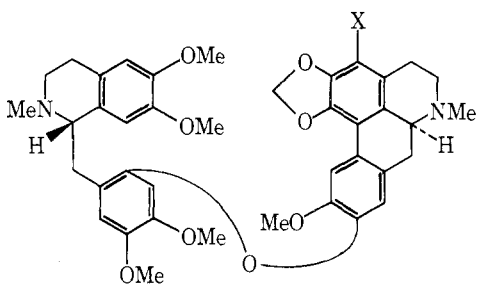
Cassythicine (**9**)[12] and *N*-methylcassyfiline (**10**)[13] were prepared from the phenolic base fraction of *Cassytha filiformis* by N-methylation, followed by countercurrent separation. Reaction of (*S*)-6′-bromolaudanosine (**6**) and PFPC with the above phenolic bases gave the crystalline thalicarpine analogs **20** and **21** in yields of 51 and 42%, respectively, based upon bromide **6**. Dimers **20** and **21**, which have the same stereochemistry as thalicarpine, are biogenetically reasonable structures which will probably be isolated eventually from natural sources.



17



18, $H_1 \cdots (R)$
19, $H_1 \blacktriangleright (S)$



20, X = H
21, X = OMe

Antitumor testing of the bisbenzylisoquinolines prepared in this work is in progress, as well as the extension of our Ullmann procedure to the synthesis of other natural and unnatural bisbenzylisoquinolines.

Experimental Section

Melting points are uncorrected. NMR spectra were determined with Varian A-60A and Varian A-100 spectrometers in $CDCl_3$ using tetramethylsilane as internal standard. Infrared spectra (KBr), ultraviolet spectra (EtOH), and mass spectra were determined using Perkin-Elmer Models 137, 202, and 270B spectrometers, respectively. Preparative TLC separations were carried out using KSGF silica plates; grade II basic alumina was used for column chromatography. The usual work-up for nonphenolic bases consisted in extraction of the total bases into 5% H_2SO_4, basification to pH 9 with ammonia, extraction into the organic solvent indicated, extraction of phenolic bases (if present) into 5% NaOH, washing the solvent (H_2O), drying ($MgSO_4$), and evaporation; recovery of any phenolic bases from the 5% NaOH wash was achieved by addition of excess NH_4Cl, followed by solvent extraction. Pentafluorophenylcopper is abbreviated as PFPC. New procedures for the resolution of laudanosine and armepavine are included, since the literature methods were, in our hands, unsatisfactory. Diglyme was distilled from $LiAlH_4$. Pyridine was dried by passing it through a 5A molecular sieve column, and stored (nitrogen) over molecular sieve. All Ullmann reactions were carried out under nitrogen in carefully dried equipment. Molecular weights of all new compounds were confirmed by mass spectrometry.

***dl*-Laudanosine and Its Resolution.** Sodium borohydride (5.0 g) was added in portions with stirring to a solution of 3,4-dihydropapaverine hydrochloride[14] (50 g) in methanol (250 ml). The solution was stirred (room temperature) for 1 hr, formalin (37%, 20 ml) was then added, and stirring was continued for an additional 1 hr.

Excess $NaBH_4$ was added, and after a further 1 hr, water (1000 ml) was added. The precipitate was filtered, dried, and crystallized from hexane to give white needles of *dl*-laudanosine (36 g, 70%), mp 114–115° (lit.[2] mp 114–115°).

A solution of *dl*-laudanosine (2.0 g) and (−)-mandelic acid (880 mg) in MeOH (20 ml) was diluted with ether (200 ml). On standing at room temperature, the salt of the *S* base (1.43 g) separated as white needles, mp 132–134°, $[\alpha]D$ +42°. Treatment of the latter with ammonia liberated (*S*)-laudanosine, which crystallized (hexane) as prisms, mp 87–88°, $[\alpha]D$ +98°.

The mother liquor from the above salt was evaporated and treated with ammonia, and the basic material was worked up as usual ($CHCl_3$). A solution of the resulting base and (+)-mandelic acid (340 mg) in MeOH (15 ml) was diluted with ether (150 ml) to give white needles of the salt, mp 133–134°, $[\alpha]D$ −42°. Ammonia treatment of the latter gave (*R*)-laudanosine, which crystallized from hexane as prisms, mp 86–87°, $[\alpha]D$ −97° (lit.[2] mp 89°, $[\alpha]D$ −97.48°).

***dl*-6′-Bromolaudanosine (4) and Its Enantiomers 5 and 6.** A solution of bromine (2.4 g) in acetic acid (30 ml) was added dropwise with stirring to an ice-cooled solution of *dl*-laudanosine (4.3 g) and sodium acetate (1.43 g) in 10% aqueous acetic acid (190 ml). The mixture was stirred for an additional 2 hr, during which time the initial yellow precipitate dissolved. After basification (KOH), the precipitate was extracted into ether. The usual work-up, followed by crystallization from $CHCl_3$–ether, gave **4** as needles (3.8 g, 76%), mp 124–125° (lit.[15] mp 128°).

Bromination of (*S*)-laudanosine and (*R*)-laudanosine was carried out in the same way, to give (*S*)-6′-bromolaudanosine (**5**) and the enantiomer **6**, both having mp 145–146° (lit.[2,3] mp 140–141°).

Resolution of *dl*-Armepavine. A mixture of *dl*-armepavine (3.43 g) and (−)-mandelic acid (1.675 g) was dissolved in hot absolute EtOH (110 ml). After cooling to room temperature and standing for a further 1 hr, the crystals which separated were filtered, washed with ether, and recrystallized from EtOH. The resulting colorless needles (1.7 g, mp 125–126°) were basified with ammonia and worked up as usual for basic material. Crystallization from acetone–ether gave (*S*)-armepavine (1.15 g), mp 136–137°, $[\alpha]D$ +108.5° (*c* 1.0, MeOH).

The mother liquor from the (−)-mandelate was evaporated, and the remaining base (2.35 g) was recovered by ammonia treatment and CH_2Cl_2 extraction. A solution of this base and (+)-mandelic acid (1.10 g) in hot EtOH (70 ml) afforded, after cooling, filtration of the solid, and recrystallization from acetone–ether, crystals (1.80 g), mp 126–127°. Regeneration of the base from this salt, followed by acetone–ether crystallization, gave (*R*)-armepavine (0.90 g), mp 136–137°, $[\alpha]D$ −107° (*c* 0.9, MeOH) (lit.[11] mp 138–139°).

(*R*)-Nuciferoline (11). A solution of stepharine[11] (5.0 g) in a mixture of 37% formalin (12 ml) and formic acid (12 ml) was heated (steam bath) for 5 hr. Ammonia basification followed by the usual work-up (CH_2Cl_2) gave alkaloidal material which was dissolved in 20% hydrochloric acid (100 ml) and heated (steam bath) for 3 hr. Ammonia basification, followed by the usual work-up (CH_2Cl_2), afforded, after crystallization from acetone, microcrystals of **11** (3.5 g, 68%), mp 229–231°, $[\alpha]D$ −140° (*c* 0.35, $CHCl_3$) (lit.[10] mp 227–229°, $[\alpha]D$ −157° (*c* 0.18, EtOH)).

Ullmann Condensation of *dl*-6′-Bromolaudanosine (4) with Phenol. A. Using Cupric Oxide. A mixture of cupric oxide (0.080 g), powdered potassium carbonate (0.150 g), bromide **4** (0.450 g), phenol (0.150 g), and pyridine (5 ml) was refluxed for 18 hr, additional cupric oxide (0.050 g) being added after the first 8 hr. Solvent evaporation, followed by the usual work-up for basic material, gave an oil which was chromatographed on alumina. Benzene elution, followed by crystallization (hexane–ether), gave white plates of *dl*-6′-phenoxylaudanosine (**7**, 0.06 g, 13%): mp 102–103°; NMR δ 2.39, 3.56, 3.80 (s, 3 H each), 3.73 (s, 6 H), 6.18, 6.65 (s, 1 H each), 6.55 (s, 2 H), and 6.9–7.15 (m, 5 H).

Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.15; H, 6.90; N, 3.11. Found: C, 72.21; H, 7.02; N, 2.85.

B. Using Pentafluorophenylcopper (PFPC) in Diglyme. A solution of phenol (0.100 g) and PFPC (0.250 g) in diglyme (4 ml) was heated at 100° for 30 min. Pyridine (2 ml) was added, followed by a solution of bromide **4** (0.435 g) in diglyme (4 ml). After heating for a further 18 hr, the mixture was poured into water (250 ml) and the product was isolated as in section A to give pure **7** (0.154 g, 34%), mp 102–103°.

C. Using PFPC in Pyridine. A solution of bromide **4** (0.440 g), phenol (0.135 g), and PFPC (0.250 g) in pyridine (10 ml) was heated at 110–115° for 6 hr. Additional PFPC (0.10 g) in pyridine (1 ml) was added and heating was continued for a further 5 hr. Work-up as in section A afforded crystalline ether **7** (0.235 g, 52%), mp 102–103°.

(*S,S*)-*O*-Tetramethylmagnolamine (17). A solution of (*S*)-6′-bromolaudanosine (**6**, 0.435 g), (*S*)-armepavine (0.650 g), and PFPC (0.500 g) in pyridine (10 ml) was heated at 115–120° for 7 hr. The mixture was poured into water (200 ml) and extracted with benzene. Work-up of the benzene phase for nonphenolic bases was followed by alumina (6 g) chromatography (1:1 chloroform–benzene elution), preparation TLC purification (7% methanol in chloroform, R_f 0.22), and hexane–ether crystallization to give white needles to ether **17** (0.351 g, 53%): mp 148–149.5°; $[\alpha]D$ +89° (*c* 0.5, MeOH) (lit.[16] mp 148–149°, $[\alpha]D$ +86.22°); NMR δ 2.42, 2.50, 3.58, and 3.60 (s, 3 H each), 3.74 (s, 6 H), 3.80 (s, 6 H), 6.12 (s, 2 H), 6.48 (s, 1 H), 6.51 (s, 2 H), 6.57 (s, 1 H), 6.73 (1 H, d, J = 8 Hz), and 6.98 (1 H, d, J = 8 Hz).

Anal. Calcd for $C_{40}H_{48}N_2O_7$: C, 71.85; H, 7.18; N, 4.19. Found: C, 71.30; H, 6.82; N, 3.97.

Unreacted excess (*S*)-armepavine (85%) was isolated from the phenolic base fraction of the original reaction mixture.

Aporphine–Benzylisoquinoline Dimer 18. A solution of (*R*)-nuciferoline (0.630 g) and PFPC (0.450 g) in pyridine (7 ml) was heated gradually to 120°. (*R*)-6′-Bromolaudanosine (**5**, 0.435 g) in pyridine (5 ml) was added and heating was continued for 5 hr. Solvent evaporation, followed by the usual nonphenolic base work-up, gave an oil which was chromatographed on alumina, the column being eluted successively with benzene and chloroform. The material eluted by chloroform was further purified by preparative TLC (10% MeOH in $CHCl_3$, R_f 0.3–0.4), followed by crystallization from hexane to give **18** as white microcrystals (0.280 g, 47%): mp 146–148°; $[\alpha]D$ −109° (*c* 0.37, MeOH); λ_{max} 208 nm (log ϵ 4.62), 230 sh (4.28), 270 (4.27), 305 (3.76); mass spectrum *m/e* (rel intensity) 668 (4), 462 (7), 437 (6), 206 (100); NMR δ 2.42, 2.50 (s, 3 H each), 3.50, 3.71, 3.76 (s, 6 H each), 6.15, 6.48, 6.53 (s, 1 H each), 6.55 (2 H, s), 6.75 (1 H, d, J = 6 Hz), 7.13 (1 H, d, J = 6 Hz), and 7.87 (1 H, s).

Anal. Calcd for $C_{40}H_{46}N_2O_7$: C, 72.07; H, 6.90; N, 4.20. Found: C, 71.86; H, 6.89; N, 4.21.

Aporphine–Benzylisoquinoline Dimer 20. A mixture of (*S*)-6′-bromolaudanosine (**6**, 0.430 g), cassythicine[12] (**9**, 0.580 g), PFPC (0.510 g), and pyridine (10 ml) was refluxed for 5 hr. The mixture was poured into water (100 ml) and the product was extracted into benzene. The usual work-up for nonphenolic bases gave an oil which was first chromatographed on a short silica column (5% MeOH in chloroform eluent), then purified further by preparative TLC (2:2:1 $CHCl_3$–EtOAc–MeOH, R_f 2.6–3.1). Crystallization from methanol gave **20** as white needles (0.340 g, 51%): mp 177–178°; $[\alpha]D$ +41° (*c* 0.2, $CHCl_3$); λ_{max} 283 nm (log ϵ 4.20), 303 (4.01); mass spectrum *m/e* (rel intensity) 680 (<2); NMR δ 2.41, 2.47, 3.77 (s, 3 H each), 3.87 (s, 6 H), 3.90 (s, 3 H), 3.98 (s, 3 H), 5.94 (s, 1 H), 5.99 and 6.17 (2 H, close doublets, $-OCH_2O-$), 6.50 (s, 3 H), 6.57 (s, 1 H), 6.62 (s, 1 H), and 7.75 (s, 1 H).

Anal. Calcd for $C_{40}H_{44}N_2O_8$: C, 67.29; H, 6.47; N, 4.11. Found: C, 66.81; H, 6.50; N, 3.78.

Aporphine–Benzylisoquinoline Dimer 21. A mixture of bromide **6** (0.500 g), *N*-methylcassyfiline[13] (**10**, 0.680 g), PFPC (0.500 g), and pyridine (10 ml) was heated at 115–120° for 5 hr. The reaction mixture was worked up as for the synthesis of base **20** (see above). Crystallization from methanol gave white needles of **21** (0.343 g, 42%): mp 197–199°; $[\alpha]D$ +28° (*c* 0.2, $CHCl_3$); λ_{max} 285 nm (log ϵ 4.47), 301 (3.95), 310 (4.14); mass spectrum *m/e* 710 (rel intensity) (1); NMR δ 2.44, 2.48, 3.58 (s, 3 H each), 3.77 (s, 6 H), 3.82, 3.94, 4.01 (s, 3 H each), 5.94 (s, 1 H), 6.00 and 6.18 (2 H, close doublets, $-OCH_2O-$), 6.54 (s, 2 H), 6.58 (s, 1 H), 6.64 (s, 1 H), and 7.70 (s, 1 H).

Anal. Calcd for $C_{41}H_{46}N_2O_9$: C, 66.35; H, 6.47; N, 3.94. Found: C, 65.92; H, 6.56; N, 3.57.

Acknowledgment. We are grateful to the National Institutes of Health for a grant (CA-11445) in support of this work. We also thank Dr. M. J. Mitchell for the *Cassytha* alkaloids used in this study, Dr. W. A. Sheppard (E. I. du Pont de Nemours and Co.) for valuable discussions of organocopper chemistry, and Dr. I. Noguchi and Mr. J. Skiles for the improved resolution of laudanosine.

Registry No.—**4**, 54712-52-6; **5**, 4829-34-9; **7**, 54677-43-9; **9**, 5890-28-8; **10**, 3984-08-5; **11**, 1862-49-3; **12**, 2810-21-1; **17**, 7283-30-9; **18**, 54677-44-0; **20**, 54677-45-1; **21**, 54677-46-2; *dl*-laudanosine, 1699-51-0; (−)-mandelic acid, 611-71-2; (*S*)-laudanosine (−)-mandelate, 54677-47-3; (*S*)-laudanosine, 2688-77-9; (+)-mandelic acid,

17199-29-0; (*R*)-laudanosine (+)-mandelate, 54677-48-4; (*R*)-laudanosine, 85-63-2; *dl*-armepavine, 5884-67-3; (*S*)-armepavine (−)-mandelate, 54677-49-5; (*S*)-armepavine, 14400-96-5; (*R*)-armepavine (+)-mandelate, 54677-50-8; (*R*)-armepavine, 524-20-9; phenol, 108-95-2; cupric oxide, 1317-38-0; pentafluorophenylcopper, 18206-43-4.

References and Notes

(1) S. M. Kupchan and H. W. Altland, *J. Med. Chem.*, **16**, 913 (1973), and references cited therein.
(2) M. Tomita and B. Ito, *Yakugaku Zasshi*, **78**, 103 (1958).
(3) M. Tomita, H. Furukawa, S. T. Lu, and S. M. Kupchan, *Chem. Pharm. Bull.*, **15**, 959 (1967).
(4) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and K. Sempuka, *J. Am. Chem. Soc.*, **95**, 2995 (1973).
(5) H. Weingarten, *J. Org. Chem.*, **29**, 3624 (1964).
(6) T. Kawaki and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **45**, 1499 (1972).
(7) Peninsular Chemical Co., Gainesville, Fla.
(8) A Cairncross and W. A. Sheppard, *J. Am. Chem. Soc.*, **90**, 2186 (1968).
(9) For the study with model compounds see M. Tomita, K. Fumitani and Y. Aoyagi, *Chem. Pharm. Bull.*, **13**, 1341 (1965).
(10) K. Bernauer, *Helv. Chim. Acta*, **47**, 2122 (1964).
(11) M. P. Cava, K. Nomura, S. K. Talapatra, M. J. Mitchell, R. H. Schlessinger, K. T. Buck, J. L. Beal, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *J. Org. Chem.*, **33**, 2785 (1968).
(12) M. P. Cava, K. V. Rao, B. Douglas, and J. A. Weisbach, *J. Org. Chem.*, **33**, 2443 (1968).
(13) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Aust. J. Chem.*, **19**, 297 (1966).
(14) W. M. Whaley and T. R. Govindacharl, *Org. React.*, **6**, 100 (1951).
(15) C. Schoepf and K. Thierfelder, *Justus Liebigs Ann. Chem.*, **537**, 143 (1939).
(16) K. Ito and T. Aoki, *Yakugaku Zasshi*, **79**, 325 (1959).

Synthesis of the Potentially Cytotoxic Compound 5-[Bis(2-chloroethyl)amino]-1,3-phenylene Biscarbamate

Mark A. Thorn,* George H. Denny, and Robert D. Babson

Merck Sharp and Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07090

Received February 6, 1975

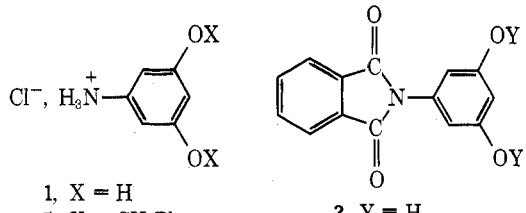
5-Aminoresorcinol hydrochloride (**1**) reacted with ethylene oxide to give **2**, which could not be converted to its bis(2-chloroethyl)amino derivative in the presence of standard reagents. Compound **1** was therefore converted to **3** by treatment with phthalic anhydride and thence to **4** by reaction with benzyl bromide under alkaline conditions. Removal of the phthalimido group with hydrazine, followed by treatment with hydrochloric acid, gave the hydrochloride **5**, which reacted with ethylene oxide to produce **6**. Bistosylation to **7**, followed by treatment with lithium chloride in acetone, afforded the mustard **8** in high yield. Removal of the blocking groups to give **9** was accomplished with refluxing trifluoroacetic acid in the presence of anisole as a benzyl cation scavenger, the product being isolated and characterized as its trifluoroacetic acid solvate. Treatment of **9** with cyanogen bromide gave the dicyanate **10** as a crude powder which underwent addition of water to give the dicarbamate **11** upon treatment with hydrochloric acid. Compounds **8**–**11** are potentially cytotoxic nitrogen mustards.

The presence of the *O*-carbamate group as a structural feature of a number of antitumor compounds[1] suggests that this group might be incorporated in concert with other structural moieties of known antitumor propensities. The synthetic objective undertaken in the present work was to incorporate two *O*-carbamate functions into the structure of an aromatic nitrogen mustard, the latter being a structural class having established antitumor activity.[2] Furthermore, it has been demonstrated in certain instances that more favorable antitumor activity was obtained with meta-substituted aromatic nitrogen mustards than with the corresponding ortho or para derivatives.[3]

Phenolic derivatives of aniline mustard have been prepared by Artico and Ross[4] and more recently by Edwards et al.[5] In addition, two nitrogen mustards of the pyrocatechol series have been described by Vasil'eva and Berlin.[6]

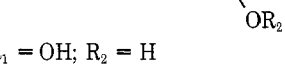
Synthetic strategy directed toward the synthesis of **11** was focused at first on schemes originating with demethylation of the known compound 1-[bis(2-chloroethyl)amino]-3,5-dimethoxybenzene.[7] Conventional reagents and conditions for demethylation of phenolic ethers, such as hot hydrochloric acid, gave consistently unsatisfactory results. Attention was next given to the synthesis of **2** as a possible substrate for mustard synthesis. The diol **2** was prepared by treating 5-aminoresorcinol hydrochloride (**1**)[8] with ethylene oxide. It was found, however, that **2** underwent extensive decomposition when attempts were made to replace the aliphatic hydroxyl groups by chloro groups using a variety of methods.

Protection of the aromatic hydroxyl groups was therefore a necessity before attempting further structural modification of **1**. This required that the amino function itself be protected at the outset. This was accomplished by phthalimidation according to a modification of the general method of Wanag,[9] using phthalic anhydride in acetic acid to provide **3**. Subsequent formation of the bisbenzyl ether **4** was undertaken with the expectation that eventual removal



1, X = H
5, X = CH_2Ph

3, Y = H
4, Y = CH_2Ph



2, R_1 = OH; R_2 = H
6, R_1 = OH; R_2 = CH_2Ph
7, R_1 = OTs; R_2 = CH_2Ph
8, R_1 = Cl; R_2 = CH_2Ph
9, R_1 = Cl; R_2 = H; CF_3COOH solvate
10, R_1 = Cl; R_2 = CN
11, R_1 = Cl; R_2 = $CONH_2$

Ph = phenyl
Ts = *p*-toluenesulfonyl