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EXPEDIENT SYNTHESIS OF (*S*)- AND (*R*)-NORCOCLAURINE FROM (*S*)- AND (*R*)-ARMEPAVINE PREPARED BY THE 1-PHENYLETHYLUREA METHOD

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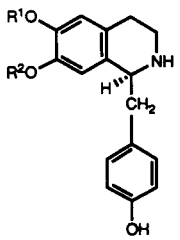
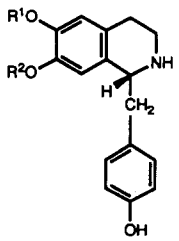
ABSTRACT.—(±)-Armepavine [**3**] prepared by Bischler-Napieralski synthesis afforded, on reaction with (*S*)-(−)-1-phenylethylisocyanate, ureas **4** and **5** which were separated and purified by crystallization from EtOH and 70% HOAc. Alcoholysis of **4** and **5** with sodium butoxide in *n*-BuOH afforded (*S*)-armepavine [**3a**] and (*R*)-armepavine [**3b**], respectively. Hplc analysis of ureas prepared from **3a** and **3b** with (*S*)-(−)-1-phenylethylisocyanate showed them to be optically pure alkaloids. Refluxing **3a** and **3b** with 48% HBr afforded the hydrobromide salts of (*S*)-norcoclaurine [**1a**] and its (*R*)-isomer **1b**, respectively.

(*S*)-Norcoclaurine [**1a**] is a central intermediate in the biosynthesis of benzylisoquinoline alkaloids (1,2). The (*R*)-enantiomer **1b** was isolated from *Nelumbo nucifera* (3), and racemic **1** occurs in *Acontium japonicum* Thunb. and was named higenamine (4). Although **1** has been prepared from (±)-coclaurine [**2**] (5–10) by demethylation with 48% HBr (3), this material does not seem suitable for a chemical resolution because of the hyper-solubility of its salts in commonly used solvents and because of the extreme sensitivity of the material to air oxygen.

Preparation of optically active isomers **1a** and **1b** was accomplished by chemical resolution of *O*-benzyl-protected precursors (11) and acid hydrolysis of the optical isomers (4). For preparing optically active **1a** and **1b** labeled at C-1 with ^{13}C, the Zenk group used the urea separation technique, separating the ureas obtained from the α-benzyl ethers and (*S*)-(−)-α-methoxybenzylisocyanate by chromatography and deprotecting the amines obtained after hydrolysis with sodium butoxide in *n*-BuOH by catalytic debenzylation (1).





1a $R^1=R^2=H$ **1b** $R^1=R^2=H$
2a $R^1=Me, R^2=H$ **2b** $R^1=Me, R^2=H$
3a $R^1=R^2=Me$ **3b** $R^1=R^2=Me$

To prepare **1a** and **1b** for a pharmacological investigation, we decided to start their synthesis with the readily available (±)-armepavine [**3**] (12–14), which occurs in nature as the (*S*)-enantiomer (15–17). It was planned to treat **3** with commercially available (*S*)-(−)-1-phenylethylisocyanate, to separate urea diastereomers, and to convert the ureas into amines by hydrolysis with sodium butoxide in *n*-BuOH, a methodology which already has been applied successfully to the synthesis of several optically active isoquinoline alkaloids (18–20). Urea diastereomers **4** and **5**, obtained from armepavine **3** and *S*-(−)-1-phenylethylisocyanate afforded, after crystallization from EtOH and two crystallizations from 70% aqueous HOAc, 17% of optically pure urea **5**, which is less polar than urea **4** obtained from the mother liquor in 12.3% yield.

Hydrolysis of **4** and **5** with sodium butoxide in *n*-BuOH afforded, after usual workup and crystallization of basic material from Me_2CO, (*S*)-norar-

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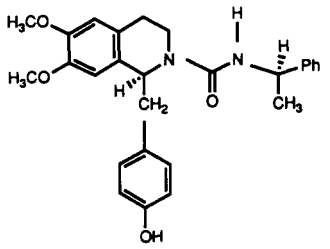

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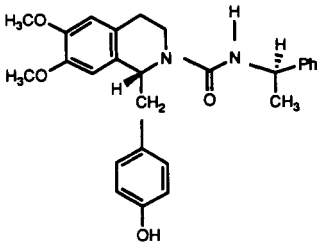

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mepavine [**3a**] and (*R*)-norarmepavine [**3b**], respectively. The antipodal alkaloids were found to be optically pure as judged after reaction with (*S*)-(−)-1-phenylethylisocyanate and hplc analysis of the ureas obtained. *O*-Demethylation of **3a** and **3b** was accomplished by refluxing 48% HBr and the hydrobromide salts of **1a** and **1b** collected after evaporation of solvent and washing the residues with iPrOH and Et_2O. Although the yields of optically pure ureas **4** and **5** were relatively low, it has to be remembered that no chromatographic method was used for their separation, leaving a lot of "useful" material in mother liquors. The physical data collected for alkaloids **1a**, **1b** and **3a**, **3b** agree reasonably well with those reported in the literature. It is well established that phenolic 1-benzylisoquinoline alkaloids tend to retain solvents of crystallization. Specific rotations in this series of compounds vary considerably when measured in different solvents and at different concentrations (21).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Fisher-Johns melting point apparatus, and optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Mass spectra were taken on a Finnigan 1015 D instrument. Elemental analysis was performed by Microlit Laboratories. Optical purity of the compounds described was measured with a Shimadzu CR601 instrument with an LC-6A solvent delivery pump and an SPD-6A spectrophotometric detector, Shimadzu Scientific Instruments, Columbia, Maryland. The column used was a Econosphere Si gel column with a particle size of 5μ and spectroscopic detection at 281 nm. The solvent system used was CH_2Cl_2-EtOAc (5:1) with a flow rate of 1.5 ml/min. Tlc analysis was performed on SiO_2 plates purchased from Analtech, Newark, New Jersey, using EtOAc-$CHCl_3$ (1:4) as a solvent system and I_2 vapors for the detection of products.

(*S*)-(−)-1-PHENYLETHYLUREA **4** AND (*R*)-(+)-1-PHENYLETHYLUREA **5** FROM (±)-NORARMEPAVINE [**3**].—(±)-Norarmepavine [6.0 g prepared from 6.75 g **3**·HCl according to Fujitani *et al.* (13)] was dissolved in CH_2Cl_2 (50 ml), and (*S*)-(−)-1-phenylethylisocyanate (2.96 g) was added. After stirring at room temperature for 1 h the solution was washed with 10% HCl and brine, dried over $MgSO_4$, and evaporated. The residue was crystallized from EtOH (100 ml) to give 5.58 g of a mixture of **4** and **5**. Crystallization from 70% HOAc (100 ml) gave 1.9 g of urea **5**, which was pure by hplc (faster moving diastereomer; retention time 15–19 min.): mp 231–233°; $[\alpha]_D$ −66° (DMF, $c = 0.49$); cims *m/z* $[M + 1]^+$ 447. *Anal.* calcd for $C_{27}H_{30}N_2O_4$ (446.55) C 72.62, H 6.77, N 6.27%; found C 72.73, H 6.76, N 6.21%.

The mother liquor of the crystallization of **5** from HOAc was evaporated to dryness and the residue crystallized from EtOH (100 ml) and 70% HOAc (100 ml) to afford 1.1 g of the more polar urea **4** (retention time 20–24 min.): mp 221–223°; $[\alpha]_D$ +121.6° (DMF, $c = 0.73$); cims *m/z* $[M + 1]^+$ 447. *Anal.* calcd for $C_{27}H_{30}N_2O_4$ (446.55), C 72.62, H 6.77, N 6.27%; found C 72.66, H 6.75, N 6.17%.

(*S*)-(−)-NORARMEPAVINE [**3a**] FROM 1-PHENYLETHYLUREA [**4**].—Urea **4** (1.24 g) was dissolved in *n*-BuOH (100 ml), Na (300 mg) was added, and the material was refluxed for 5 h. Solvent was evaporated, and the residue was dissolved in 1 N HCl (200 ml), washed with Et_2O, made alkaline with concentrated NH_4OH, and extracted with EtOAc, dried with $MgSO_4$, and evaporated. The residue, after crystallization from Me_2CO, afforded **3a** (460 mg): mp 160–161° [lit. (13) mp 153°]; $[\alpha]_D$ −38.8° ($CHCl_3$, $c = 0.44$) [lit. (16) $[\alpha]_D$ −23° ($CHCl_3$, $c = 1.3$)].

(*R*)-(+)-NORARMEPAVINE [**3b**] FROM 1-PHENYLETHYLUREA [**5**].—Similarly prepared

from urea **5** as described for the optical isomer **3a** from **4**: mp 159–160° [lit. (15) 157–158°]; $[\alpha]_D$ +30.6° ($CHCl_3$, $c=0.31$)] [lit. (15) +31.5° ($CHCl_3$, $c=2.37$)]. Optical purity of **3a** and **3b** assessed after reaction with (*S*)-(−)-1-phenylethylisocyanate and hplc analysis of ureas **4** and **5** showed that the alkaloids were optically pure.

(*S*)-(−)-NORCOCLAURINE HYDROBROMIDE (**1a**·HBr).—Isoquinoline **3a** (150 mg) was refluxed in 48% HBr (20 ml) for 18 h. After evaporation to dryness the residue was washed with iPrOH and with EtOH to afford 139 mg of beige-colored **1a**·HBr: mp 261–263° [lit. (2) for ^{13}C-labeled material, mp 269–270°]; $[\alpha]_D$ −27° (MeOH, $c=0.25$), [lit. (2) −25.4° (MeOH, $c=0.25$)]; cims *m/z* $[M+1]^+$ 272.

(*R*)-(+)-NORCOCLAURINE HYDROBROMIDE (**1b**·HBr).—Similarly prepared from isoquinoline **3b** as described above for **3a**: mp 262–263° [lit. (2) for ^{13}C-labeled material, mp 269–270°]; $[\alpha]_D$ +23.3° (MeOH, $c=0.29$)], [lit. (2) +27.6° (MeOH, $c=0.25$)]; cims $[M+1]^+$ 272.

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