of $NaNH_2$ (2 equiv), and 5.59 g of 3-chloro-*N*,*N*-dimethylpropylamine, was recrystallized from 95% EtOH in 42% yield, mp 168–170 °C. Anal. Calcd for $C_{17}H_{20}Cl_2N_2O$: C, 60.2; H, 5.94; Cl, 20.9; N, 8.26. Found: C, 60.3; H, 5.95; Cl, 20.5; N, 8.42.

The IR spectra of the above material and the product obtained by the isomerization of **4b** with 1 equiv of $NaNH_2$ in anhydrous benzene were absolutely identical. A mixture melting point was not depressed.

2-[2,5-Dichloro-*N*-[3-(dimethylamino)propyl]anilino]-phenol (6c). The product, 14.9 g (**6c**) obtained from a mixture of 13.3 g of *o*-(2,5-dichlorophenoxy)aniline (**3c**), 5.10 g of $NaNH_2$ (2 equiv), and 6.44 g of 3-chloro-*N*,*N*-dimethylpropylamine, was recrystallized from 95% EtOH in 60% yield, mp 161–163 °C. Anal. Calcd for $C_{17}H_{20}Cl_2N_2O$: C, 60.2; H, 5.94; Cl, 20.9; N, 8.26. Found: C, 60.4; H, 5.73; Cl, 21.0; N, 8.33.

2-Chloro- and 3-Chloro-10-[3-(dimethylamino)propyl]-phenoxazines (1a = 1c and 1b).[14] These compounds were prepared by cyclization of the new "phenoxyaniline" intermediates **4a**, **4c**, and **4b** and/or the isomeric "anilinophenol" intermediates **6a**, **6c**, and **6b**.

2-Chloro-10-[3-(dimethylamino)propyl]phenoxazine (1a and 1c)[14] and Hydrochloride. From 4a. Treatment of 7.33 g of **4a** and 6.10 g of K_2CO_3 in 200 mL of DMF for 18 h, under reflux using the previously described procedure including partition chromatography,[1a,b] gave 6.33 g 95% yield of **1a** as a viscous oil, bp 175–180 °C (0.5 torr); (lit.[1b] bp 176–180 °C (0.5 torr)). The hydrochloride melted at 220–222 °C. The IR spectra of **1a** was identical with that of a sample isolated from the hydrochloride preparation previously prepared[15] and reported.[1b] Elemental analyses were within acceptable limits.

From 4c. A mixture of 8.48 g of **4c** with 7.00 g of K_2CO_3 that was allowed to react as previously desribed and including partition chromatography, yielded 7.19 g (95%) of **1c** as a viscous oil. Distillation gave 5.25 g, 69% yield, of a light amber oil: bp 175–180 °C (0.5 torr); n^{25}_D 1.614 (lit.[1b] bp 176–180 °C (0.5 torr); n^{25}_D 1.614). A portion of this base was converted to the hydrochloride, mp 220–222 °C, 93% yield. A mixtur melting point of the hydrochlorides of **1a** and **1c** was not depressed, mp 220–222 °C (lit.[1a,b] mp 220–222 °C). Anal. Calcd for $C_{17}H_{19}ClN_2O$·HCl: C, 60.2; H, 5.94; Cl, 20.9; N, 8.26. Found: C, 60.4; H, 5.98; Cl, 20.9; N, 8.03.

From 6c. A mixture of 8.48 g of **6c** and 7.00 g of K_2CO_3 was allowed to react as described above. After similar workup, including partition chromatography, 7.36 g (97% yield) of **1c** was obtained as an oil; **1a** (identical with **1c**) was also prepared (in 90% yield) from **6a** by employing this procedure. The IR spectra of **1a**, prepared from **4a** and **6a**, and the IR spectra of **1c**, prepared from **4c** and **6c**, were absolutely identical, and so were the IR spectra of the corresponding hydrochlorides, mp 220–222 °C. Needless to say, mixture melting points were not depressed. Elemental analyses were within acceptable limits.

3-Chloro-10-[3-(dimethylamino)propyl]phenoxazine (1b) and Hydrochloride. From 4b. From a mixture of 4.60 g of **4b** and 2.82 g of K_2CO_3 in 50 mL of DMF, and purification of the product by partition chromatography as previously reported,[1a] 4.07 g of **1b** was obtained in 86% yield; bp 176–180 °C (0.4 torr); n^{25}_D 1.601 (lit.[1b] bp 176–180 °C (0.4 torr); n^{25}_D 1.601) (route B). The hydrochloride of **1b** was obtained in 82% yield, mp 184–185 °C (lit.[1b] mp 183–184 °C). Elemental analyses were within acceptable limits.

From 6b. From a mixture of 5.25 g of **6b** and 8.82 g of K_2CO_3 in 50 mL of DMF, and after the usual workup described above, including partition chromatography, 4.50 g (96% yield) of **1b** was obtained as an oil: bp 175–180 °C (0.4 torr); n^{25}_D 1.601 (lit.[1b] 176–180 °C (0.4 torr); n^{25}_D 1.601). The IR spectra of **1b**, prepared from **4b** and **6b**, and by route B,[1b] were identical and so were the corresponding IR spectra of the hydrochlorides, mp 184–185 °C (lit.[1b] mp 183–184 °C). A mixture melting point with a sample prepared from **4b** was not depressed. Anal. Calcd for $C_{17}H_{19}ClN_2O$·HCl: C, 60.2; H, 5.94; Cl, 20.9; N, 8.26. Found: C, 59.9; H, 5.99; Cl, 21.2; N, 7.95.

(14) In this paper 2-chloro-10-[3-(dimethylamino)propyl]phenoxazine is prepared from two separate routes and is designated **1a** and **1c** according to the designations in Scheme I of the intermediates from which it was prepared. 3-Chloro-10-[3-(dimethylamino)propyl]phenoxazine is analogously designated **1b**.

(15) We thank Dr. R. A. Hardy, Jr., of the Medical Research Division, Lederle Laboratories, American Cyanamid Company, Pearl River, NY, for samples of **1a** prepared as previously described.[1b,c]

Summary

Cyclization of (*o*-halophenoxy)anilines **4** with K_2CO_3 in DMF to form phenoxazines **1** proceeds via Smiles rearrangements of **4** to the isomeric (*o*-haloanilino)phenols **6** which cyclize to **1**.

The (*o*-haloanilino)phenol intermediates **6** were isolated and converted to the corresponding phenoxazines **1**. *N*,*N*-Dimethyl-*N*′-[2-(2,4-dichlorophenoxy)phenyl]-1,3-propanediamine (**4b**) heated with K_2CO_3 in DMF gave 3-chloro-10-[3-(dimethylamino)propyl]phenoxazine (**1b**). The intermediate in this transformation, 2-[2,4-dichloro-*N*-[3-[(dimethylamino)propyl]anilino]phenol (**6b**) was prepared from **4b** and $NaNH_2$ in benzene. Cyclization of **6b** with K_2CO_3 in DMF also gave **1b**. *N*,*N*-Dimethyl-*N*′-[2-(2,5-dichlorophenoxy)phenyl]-1,3-propanediamine (**4c**) heated with K_2CO_3 in DMF yielded 2-chloro-10-[3-(dimethylamino)propyl]phenoxazine (**1c**). The intermediate in this transformation, 2-[2,5-dichloro-*N*-[3-(dimethylamino)propyl]anilino]phenol (**6c**), prepared from **4c** and $NaNH_2$ in benzene also gave **1c** with K_2CO_3 in DMF. 2-[*o*-Chloro-*N*-[3-(dimethylamino)propyl]-anilino]-4-chlorophenol (**6a**) was prepared by the Smiles rearrangement of *N*,*N*-dimethyl-*N*′-[2-(*o*-chlorophenoxy)-5-chlorophenyl]-1,3-propanediamine (**4a**) with $NaNH_2$ in benzene. Both **4a** and **6a** gave 2-chloro-10-[3-(dimethylamino)propyl]phenoxazine (i.e., **1a** = **1c**) also, when heated with K_2CO_3 in DMF.

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Registry No. **1a**, 4418-46-6; **1a**·HCl, 89279-25-4; **1b**, 89279-24-3; **1b**·HCl, 89279-26-5; **2a**, 22544-02-1; **2b**, 38461-29-9; **2c**, 3169-76-4; **3a**, 56966-48-4; **3a**·HCl, 89279-15-2; **3b**, 26306-64-9; **3b**·HCl, 89279-16-3; **3c**, 3169-77-5; **3c**·HCl, 89279-17-4; **4a**, 89279-18-5; **4b**, 89279-19-6; **4c**, 89279-20-9; **6a**, 89279-21-0; **6b**, 89279-22-1; **6c**, 89279-23-2; 3-chloro-*N*,*N*-dimethylpropylamine, 109-54-6.

Preparation of Chirally Deuterated *N*-(Trifluoroacetyl)-β-alanine and Related Compounds

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Isotopically labeled amino acids containing a hydrogen isotope at a prochiral carbon have proven valuable for the investigation of the stereospecificity of enzymatic reactions.[1]

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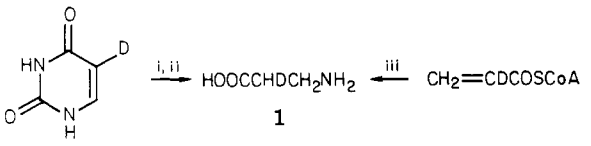
For studies in this area we required a derivative of β-alanine (1) chirally labeled with deuterium adjacent to the carboxyl group. β-Alanine is widespread in nature as a metabolite of uracil[2] and is also formed by enzymatic addition of ammonia to acrylyl coenzyme A.[3] It was anticipated that carrying out the enzymatic reduction of [5-$^2H_1$]uracil with subsequent hydrolysis, or the enzymatic amination of [2-$^2H_1$]acrylyl CoA, and determining the configuration of the [2-$^2H_1$]β-alanine formed would provide important information about the stereochemistry and mechanism of these enzymatic reactions.

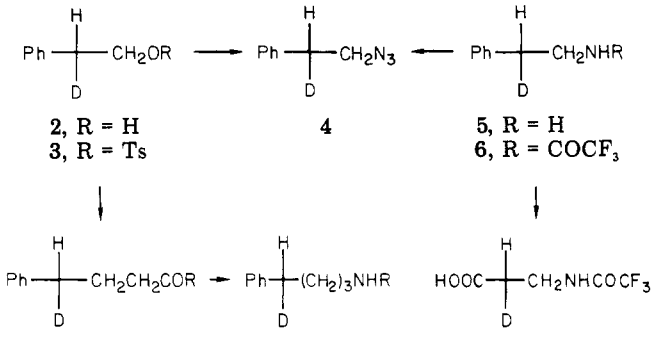


1

(i) dihydrouracil dehydrogenase, (ii) H_2O, (iii) acrylyl coenzyme A aminase

We report the preparation of a crystalline derivative of **1**, the trifluoroacetamide **7**, of known absolute configuration, starting from (*S*)-(−)-2-phenyl[2-$^2H_1$]ethanol (**2**). This useful member of the family which owes its chirality to the difference between hydrogen and deuterium[4] can be prepared in a convenient four-step sequence from mandelic acid. Elsenbaumer and Mosher have reported reaction conditions and a purification scheme that afford **2** in high optical purity.[5] The possibility of converting the hydroxyl group to other functionalities and the capacity of ruthenium tetroxide[6] to oxidize benzene rings to carboxyl groups under mild conditions that do not disturb the adjacent chiral center combine to make **2** a valuable intermediate for the synthesis of optically active α-deuterated carboxylic acids.

For the synthesis of **7**, (*S*)-**2** was converted to azide **4** by nucleophilic displacement of tosylate **3** with azide ion. A more convenient procedure is the direct conversion of **2** to **4** with a mixture of sodium azide, tri-*n*-butylphosphine, carbon tetrachloride, and a crown ether, a route patterned after Shioiri's one-pot method for conversion of alcohols to nitriles.[7] Azide **4** was reduced to amine **5** with $LiAlH_4$. Oxidation of the trifluoroacetamide **6** with ruthenium tetroxide gave the dextrorotatory amide **7** in 80% yield. A workup procedure in which excess RuO_4 is removed from the unreduced reaction mixture by rotary evaporation at 40 °C avoids the problems normally associated with adsorption of the product on precipitated RuO_2. Because none of the steps in this short sequence alters the chirality, (+)-**7** has the *R* configuration.



2, R = H; **3**, R = Ts — **4** — **5**, R = H; **6**, R = $COCF_3$

8, R = OH; **9**, R = NH_2 — **10**, R = H; **11**, R = $COCF_3$ — **7**

After this work was completed, Gani and Young[8] reported the preparation of (*R*)-(**1**), without mention of optical rotation, by decarboxylation of a stereospecifically deuterated aspartic acid, and used this sample to deduce the stereochemistry of reduction of uracil by bovine liver enzymes.

We also prepared the trifluoroacetamide **11** of 4-phenyl[4-$^2H_1$]butylamine from (*S*)-**2**. The tosylate **3** was used to alkylate malonic ester, affording (*R*)-4-phenyl[4-$^2H_1$]butanoic acid (**8**) after hydrolysis and decarboxylation. Conversion to the amide **9**, followed by hydride reduction, led to amine **10** and its trifluoroacetamide **11**. Again, no configurational change occurs during these steps, so that the levorotatory compounds **8**–**11** all have the *R* configuration.

These results illustrate the potential for converting alcohol **2** into a wide variety of optically active α-deuterated benzenes and carboxylic acids for biochemical studies.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian T-60 and EM-390 spectrometers; chemical shifts are reported as δ units, with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer. Optical rotations were measured in 1-dm cells on a Perkin-Elmer Model 141 polarimeter; *c* is expressed in g/100 mL. Mass spectrometric analyses were performed on a Finnigan 4023 gas chromatograph–mass spectrometer.

Analytical thin-layer chromatography was performed on E. Merck 2.5 × 10 cm precoated plates. Low-pressure liquid chromatography was performed on an Altex system using E. Merck silica gel, 230–400 mesh. Diethyl ether, tetrahydrofuran, and 1,2-dimethoxyethane were distilled from $LiAlH_4$ immediately prior to use. Acetonitrile and carbon tetrachloride were distilled from P_2O_5 under nitrogen. Elemental analyses were performed by Atlantic Microlabs Inc., Atlanta, GA.

(*S*)-2-Phenyl[2-$^2H_1$]ethanol (**2**) was prepared from (*S*)-(+)-mandelic acid in four steps in 49% overall yield by the procedure of Elsenbaumer and Mosher.[5] The alcohol, after purification[5] via recrystallization of the 3,5-dinitrobenzoate, mp 110–111 °C, had bp 79–80 °C (2.2 mm), lit.[5] bp 89–90 °C (2.7 mm); $[\alpha]^{25}_D$ −1.563° (neat), lit.[5] $[\alpha]^{20}_D$ 1.564° (neat) for the enantiomer.

The *tosylate* **3** was prepared as described by Elsenbaumer and Mosher[5] in 80% yield. After recrystallization from ether–hexane it formed colorless crystals, mp 37–38 °C, $[\alpha]^{28}_D$ −0.463° (*c* 12.1, ether); lit.[5] mp 37.5–38.5 °C, $[\alpha]^{20}_D$ 0.46° (*c* 11.3, ether) for the enantiomer.

(*S*)-(−)-2-Phenyl[2-$^2H_1$]ethyl Azide (**4**). (a)[9] To a solution of 1.056 g (3.812 mmol) of tosylate **3** in 10 mL of 95% ethanol at reflux was added 0.49 g (7.53 mmol) of sodium azide in 3.0 mL of water. After 1 h another 0.25-g portion of sodium azide was added and reflux was continued for 26 h. The solution was cooled, diluted with water, and extracted with ether, and the extracts

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were dried over $MgSO_4$ and concentrated. Distillation of the residue (0.52 g) in a Kugelrohr apparatus gave 0.41 g (73%) of azide; bp 130 °C (oven temperature) (20 mm), $[\alpha]^{24}_D$ −0.722° (*c* 10.52, hexane); IR (neat) 2100, 1605 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (tt, J = 7 Hz, J_{HD} = 2 Hz, 1 H, –CHD–), 3.43 (d, J = 7 Hz, 2 H, CH_2), 7.17 (m, 5 H, Ar).

(b) A mixture of 650 mg (10 mmol) of sodium azide and 132 mg of 18-crown-6 ether in 10 mL of acetonitrile was stirred for 15 min under argon. A mixture of alcohol **2** (619 mg, 5 mmol) and tri-*n*-butylphosphine (1.113 g, 5.5 mmol) in 5 mL of acetonitrile was added. A solution of carbon tetrachloride (846 mg, 5.5 mmol) in acetonitrile was added dropwise with cooling in an ice–methanol bath. The mixture was stirred at 25 °C for 72 h, diluted with ether, washed with 10% aqueous citric acid solution, diluted with 5 mL of CCl_4, washed with water and brine, and dried over $MgSO_4$. The residue left after concentration was purified by flash chromatography; elution with hexane containing 1% ethyl acetate gave 310 mg of the azide (42%), distillation of which gave 273 mg of the pure substance, $[\alpha]^{25}_D$ −0.67° (*c*, 10.2, hexane). Further elution with hexane containing 15% ethyl acetate gave 280 mg of recovered alcohol.

In four additional runs the yield of distilled azide ranged from 42% to 58%.

(*S*)-2-Phenyl[2-$^2H_1$]ethylamine (5).[10] To a suspension of $LiAlH_4$ (141 mg, 3.71 mmol) in 10 mL of ether was added 367 mg (2.48 mmol) of azide **4** in 10 mL of ether. The mixture was stirred at 25 °C for 1.5 h, and then treated cautiously with 0.15 mL of water, 0.15 mL of 15% NaOH, and 0.45 mL of water. After this mixture was stirred for 1 h, the ether layer was separated, dried over K_2CO_3, and concentrated. Distillation yielded 277 mg (91.5%) of the amine, bp 100 °C (Kugelrohr, 10 mm), $[\alpha]^{26}_D$ −1.236° (*c* 11.25, CH_3OH); IR (neat) 3360, 3280, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, 2 H, NH_2), 2.93 (m, 3 H, $-CH_2CHD-$), 7.18 (s, 5 H, Ar).

(*S*)-1-(Trifluoroacetamido)-2-phenyl[2-$^2H_1$]ethane (6). Trifluoroacetic anhydride (0.8 g) was added carefully to a solution of amine **5** (217 mg) in 8 mL of ether cooled to −15 °C. The solution was allowed to warm to room temperature, stirred 3 h, and poured into ice water. The layers were separated, the aqueous layer was extracted with ether, and the combined ether solutions were washed with saturated $NaHCO_3$ solution, water, and brine, then dried over $MgSO_4$, and concentrated. The residue (0.385 g, 99%) was recrystallized from hexane to provide fine crystals of the amide (235 mg), mp 55–56 °C (lit.[11] mp 55–56 °C), $[\alpha]^{26}_D$ +0.627° (*c* 10.2, $CHCl_3$), $[\alpha]^{26}_D$ +0.157° (*c*, 10.2, acetone); IR ($CHCl_3$) 3300, 3100, 1690 cm^{-1}; NMR ($CDCl_3$) δ 2.9 (m, 1 H, –CHD–), 3.63 (t, J = 6.5 Hz, 2 H, CH_2), 6.43 (br, 1 H, NH), 7.3 (m, 5 H, Ar); mass spectrum, m/z 218 (M^+), 163, 126, 105, 92. An additional 75 mg of the amide was recovered by chromatography of the mother liquors, bringing the total yield to 80%.

(*R*)-3-(Trifluoroacetamido)[2-$^2H_1$]propanoic Acid (7). To a yellow solution of ruthenium tetroxide, prepared from 157 mg of ruthenium dioxide and 2.0 g of sodium periodate in 50 mL of acetone and 12 mL of water, was added a solution of 223 mg of amide **6** in 8.0 mL of acetone. The mixture was stirred at room temperature for 72 h, during which time a total of 25 g of sodium periodate in 200 mL of 50% aqueous acetone was added in portions to keep the reaction mixture yellow whenever it darkened. The mixture was filtered, cooled to 0 °C for 1 h, and filtered again. The filtrate was concentrated to a volume of 100 mL and continuously extracted with ether for 36 h. After the extracts had been dried and concentrated, the residue was recrystallized from benzene–ether. Two crops of 104.5 and 47.5 mg were obtained, bringing the total yield to 80%. The acid was purified further by sublimation at 95–100 °C at 0.2 mm (90% recovery) to give the pure compound: mp 121 °C (lit.[12] mp 119–121 °C), $[\alpha]^{25}_D$ +0.533° (*c* 6.38, CH_3OH); IR (KBr) 2600–3300, 1700 cm^{-1}; NMR[13] ($CDCl_3$) δ 2.64 (m, 1 H, –CHD–), 3.66 (t, J = 6 Hz, 2 H, $-CH_2-$); mass spectrum, m/z 186 (M^+), 168, 140, 117.

(*R*)-4-Phenyl[4-$^2H_1$]butanoic Acid (8). A solution of 2.76 g (0.01 mol) of tosylate **3** in 50 mL of THF was added dropwise to a clear solution prepared by adding 3.2 g (0.02 mol) of diethyl malonate in 50 mL of dry THF to a stirred suspension of 0.36 g of NaH (0.015 mol) in THF. The reaction mixture was refluxed for 48 h, cooled, poured into 200 mL of 2 N H_2SO_4, and extracted with ether. The ether extracts were washed with water, dried over $MgSO_4$, and concentrated to afford a yellow oil, which was purifed by chromatography on silica gel, eluting with 8% ethyl acetate:hexane. Distillation afforded the colorless substituted malonic ester (2.0 g, 75%): bp 124–144 °C (2 mm) (lit.[14] bp 142–145 °C (2 mm)); α^{28}_D 0.48° (neat); IR (neat) 3000 (s), 1725 (s), 1600 (w), 1175–1200 (s), 1040 (s), 750 (s), 700 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.20 (t, J = 5 Hz, 6 H, CH_3), 2.22 (dd, J = 5 Hz, 2 H, CH_2), 2.60 (m, 1 H, CHD), 3.30 (t, J = 5 Hz, 1 H, CH), 4.15, (q, J = 5 Hz, 4 H, CH_2O), 7.10 (s, 5 H, Ar).

A solution of 1.3 g of the malonic ester and 1.0 g of KOH in 50% ethanol (13 mL) was heated under reflux for 4 h. The solution was concentrated at reduced pressure and the aqueous residue was washed twice with ether, acidified with 6 N HCl, and continuously extracted with ether for 24 h. Concentration of the dried extracts left a colorless solid, which was recrystallized from water to afford 0.95 g (90%) of the malonic acid: mp 131–132 °C (lit.[15] mp 132 °C); $[\alpha]^{24}_D$ 0.58° (*c* 10.1, acetone); IR (KBr) 3300 (br), 3000 (s), 1720 (s), 1425 (m), 1350 (s), 1225 (s) cm^{-1}; NMR (acetone-d_6) δ 2.15 (dd, J = 5 Hz, 2 H, CH_2), 2.70 (m, 1 H, CHD), 3.38 (t, J = 5 Hz, 1 H, CH), 7.20 (s, 5 H, Ar).

The diacid (0.51 g) was decarboxylated at 160 °C at 0.02 mm for 10 min and the residue distilled at 180 °C (0.02 mm). The distillate solidified to a waxy solid on cooling and was recrystallized from hexane at −78 °C to provide colorless crystals of **8** (0.36 g, 90%): mp 52–53 °C (lit.[16] mp 52 °C); $[\alpha]^{25}_D$ −0.86° (*c*, 15.2, $CHCl_3$); IR (KBr) 3400 (br), 1680 (s), 1450 (m), 1200 (m), 900 (m) cm^{-1}; NMR ($CDCl_3$) δ 2.03 (tt, J = 7 Hz, 2 H, CH_2), 2.40 (t, J = 7 Hz, 2 H, CH_2COOH), 2.70 (m, 1 H, CHD), 7.23 (s, 5 H, Ar).

(*R*)-4-Phenyl[4-$^2H_1$]butanamide (9). Oxalyl chloride (1.5 g) was added dropwise to a solution of 0.73 g of acid **8** in 50 mL of dry benzene, and the mixture was refluxed under nitrogen for 2 h and then concentrated at reduced pressure. The residue was taken up in 100 mL of ether and cooled to 0 °C for 8 h while dry ammonia was slowly bubbled in. The flask was kept stoppered overnight at 5 °C, then the solution was concentrated in vacuo, and the residue dissolved in ethyl acetate. The organic solution was washed with water and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated at reduced pressure. The residue was recrystallized from ether:hexane to afford colorless crystals of the amide (0.45 g, 62%), mp 85–86 °C (lit.[17] mp 84.5 °C); $[\alpha]^{25}_D$ −0.58° (*c* 3.0, $CHCl_3$); IR (KBr) 3400 (s), 1650 (s), 1400 (m), 1200 (m), 700 (s); NMR ($CDCl_3$) δ 2.20 (m, 4 H, CH_2CH_2), 2.61 (m, 1 H, CHD), 6.00 (s, 2 H, NH_2), 7.22 (s, 5 H, Ar).

(*R*)-4-Phenyl[4-$^2H_1$]butylamine (10). A solution of 0.38 g of amide **9** in 20 mL of THF was added to a slurry of 0.38 g of $LiAlH_4$ in 30 mL of THF, and the mixture was refluxed for 12 h. The reaction mixture was cooled to 0 °C and treated successively with 0.35 mL of water, 0.35 mL of 15% NaOH, and 1.05 mL of water. The granular precipitate was washed with THF, and the combined THF filtrate and washings were dried over $MgSO_4$ and concentrated in vacuo. Distillation of the residue afforded the amine (0.25 g, 72%) as a colorless liquid: bp 70 °C (0.2 mm) (lit.[17] bp 123–124 °C (17 mm)); $[\alpha]^{25}_D$ −0.86° (*c* 15.2, $CHCl_3$); IR (neat) 3350 (m), 2900 (s), 2850 (m), 1600 (m), 1590 (m), 1450 (m), 700 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.60 (m, 4 H, CH_2CH_2), 2.65 (m, 3 H, CHD, CH_2N), 7.20 (s, 5 H, Ar).

(*R*)-*N*-(4-Phenyl[4-$^2H_1$]butyl)trifluoroacetamide (11). A solution of 0.6 g of trifluoroacetic anhydride in 1.0 mL of dry THF was cooled to 0 °C and added to a chilled solution of amine **10** (0.7 g) in 1.0 mL of THF. The solution was kept at 0 °C for 1 h and concentrated at reduced pressure, and the residue was passed through a 10-cm column of silica gel, eluting with 3:1

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hexane:ethyl acetate. The eluant was concentrated at reduced pressure, and the residue was distilled to afford a colorless liquid (0.9 g, 79%), which solidified upon standing: bp 120 °C (0.02 mm), $[\alpha]^{25}_D$ −0.48° (c, 10.4, $CHCl_3$); IR (neat) 3300 (s), 3100 (m), 2900 (s), 1690 (s), 1550 (m), 1450 (m), 1175 (s), 735 (s), 695 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.61 (m, 4 H, CH_2CH_2), 2.60 (m, 1 H, CHD), 3.32 (m, 2 H, CH_2), 7.2 (s, 5 H, Ar).

Anal. Calcd for $C_{12}H_{14}F_3NO$: C, 58.77; H, 5.75; N, 5.71. Found: C, 58.49; H, 5.88; N, 5.63.

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Registry No. 2, 10606-75-4; 3, 89398-25-4; 4, 89398-26-5; 5, 53729-87-6; 6, 89398-27-6; 7, 87867-32-1; 8, 89398-28-7; 9, 89398-29-8; 10, 89398-30-1; 11, 89398-31-2; (S)-(+)-mandelic acid, 17199-29-0; diethyl malonate, 105-53-3; ethyl[4-$^2H_1$]4-phenyl-2-(ethoxycarbonyl)butanoate, 89398-33-4; [4-$^2H_1$]4-phenyl-2-carboxybutanoic acid, 89398-32-3.

Hydrogen-Bonded Complexes. 5. Phenol–Amine Complexes

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Our previous studies[1-3] have shown that phenols (picric acid in particular) form crystalline, hydrogen-bonded complexes with amides having phenol–amide ratios of 1:1, 1:2, and 1:3;[1] that phenols (the dihydroxybenzenes in particular) form complexes with lactams having phenol–lactam ratios of 1:1, 1:2, 1:3, and even 3:4;[2] and that phenols (both picric acid and the dihydroxybenzenes) form complexes with ureas having phenol–urea ratios of 1:1, 1:2, 2:1, and 3:1.[3]

Most investigations of hydrogen-bonded complexes are carried out by using spectroscopic measurements in solution, but this experimental approach provides no insight into the variety of stable, crystallizable complexes that can be prepared. We have focused on those complexes that can be isolated and recrystallized as solids. The gamut of available stoichiometries in these complexes is broad, and the stoichiometry in any new case is as yet unpredictable. Such an inability to predict is an indication that our knowledge is limited and that further studies are appropriate.

In a recent study of the reactions of phenols with quaternary ammonium hydroxides in water Hanson, McCulloch, and McInnes[4] demonstrated that the anion of the quaternary ammonium phenolate that formed was associated with one to four additional phenol molecules in an intricate hydrogen-bonded network. These represent a series of hydrogen-bonded complexes having phenol to phenolate anion ratios of 1:1, 2:1, 3:1, and 4:1. It was also noted in this work that pyrocatechol reacts with di-*n*-butylamine and with tri-*n*-butylamine to form complexes having phenol–amine ratios of 3:1 and 2:1, respectively. We have extended this latter pair of observations with a comprehensive study that involved the preparation of more than 30 crystalline complexes from the dihydroxybenzenes or 2,3-dihydroxynaphthalene and amines. The phenol–amine ratios observed included values of 1:1, 2:1, 3:1, and 3:2. The present report will describe the preparations and properties of these complexes and will discuss their structures.

Results and Discussion

We encountered no difficulty in repeating the reported[4] preparations, in water as the solvent, of the di-*n*-butylamine and tri-*n*-butylamine complexes of pyrocatechol. However, it was more efficient to form the complexes in organic solvents, since this greatly facilitated the isolation and drying of the products. Suitable solvents were ether, ethyl acetate, and methylene chloride. A typical preparation involved mixing the amine and phenol in the solvent of choice, warming until a clear solution resulted, and then adding just enough hexane to bring about slow crystallization. The isolated complexes were then recrystallized from the same solvents.

The complexes that were prepared are listed in Table I, where the phenol–amine ratios are given in the third column. Since all of the observed ratios were 1 or greater and since the nitrogen contents of the complexes decrease rapidly as the values of the ratios increase from 1 to 2 to 3, a nitrogen analysis determines both the empirical formula of the complex and the phenol–amine ratio. As noted previously[2] gas chromatography (GC) provides a simple and precise method for determining these ratios. The two previously reported complexes, the pyrocatechol–di-*n*-butylamine complex and the pyrocatechol–tri-*n*-butylamine complex, were used to confirm the validity of the GC procedure. The ratio for the di-*n*-butylamine product was determined to be exactly 3.00 to 1 and for the tri-*n*-butylamine complex the value found was 2.00 ± 0.006 to 1. The asterisks in column 3 indicate products whose phenol–amine ratios were either confirmed or determined by GC.

The hydroquinone–di-*n*-butylamine complex was chosen as a substrate for exploring the impact on the composition of the complex of first changing the initial concentrations of the reagents and then changing the reaction solvent. Our initial preparation resulted in a good yield of a complex having a phenol–amine ratio of 3:1. Because of the separation of the two hydroxyl groups in hydroquinone it was our hope that we would succeed in isolating the complex having a phenol–amine ratio of 1:1 and even the complex with a ratio of 1:2. This was a reasonable expectation, since in our previous study[2] of hydrogen-bonded complexes of hydroquinone with lactams we obtained a product with a phenol–lactam ratio of 1:1 with *N*-methylpyrrolidinone and products with a ratio of 1:2 with three other lactams.

These hopes were not realized. Starting with initial hydroquinone–di-*n*-butylamine ratios of 0.504:1, 1.01:1, and 2.53:1, the only product obtained was the complex with the phenol–amine ratio at 3:1 and in yields of 58%, 83%, and 93%, respectively. The solvent in these experiments was ethyl acetate. The reaction was also run in ether, a less polar solvent, and in acetonitrile, a more polar solvent. In both solvents the only product obtained was the 3:1 complex. In a similar set of experiments with the 2:1 pyrocatechol–tri-*n*-butylamine complex the product composition again proved to be insensitive to both the initial concentrations and the choice of reaction solvent.

But it would be unwise to draw general conclusions from the above results! We have encountered one case where

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