When stored in sealed vials, compounds **1**, **4b**, and **6** discolor slowly. However, decomposition was very slow when these compounds were stored in *open* vessels over KOH|H_2SO_4| paraffin shavings in a desiccator protected from light at room temperature.

Reaction of 3,3-Dichloropropenal (2).—The starting material was prepared as reported.[6]

Following the general procedure, 2.50 g (20 mmol) of **2** in 50 ml of ether was allowed to react with 15 ml (~150 mmol) of piperidine in 100 ml of ether. Work-up afforded 3.37 g (76%) of an orange oil, which was a ~7:1 mixture of **5** and **1**: nmr (CCl_4) δ 1.62 (broad and unresolved, all 12 β- and γ-piperidino H's in both products), ~3.18 (broad and distorted multiplet, all eight α-piperidino H's in both products), 4.18 (d, J = 7 Hz, α-vinyl H in **5**), 4.91 (d, J = 13 Hz, α-vinyl H in **1**), 7.14 (d, J = 13 Hz, β-vinyl H in **1**), 9.03 (d, J = 7 Hz, formyl H in **5**). The absorptions at δ 4.91 and 7.14 were enhanced on addition of authentic **1** to the mixture.

1-[3-(Piperidino)propenoyl]piperidine (1).—Distillation of 48.0 g (450 mmol) of *trans*-3-chloropropenoic acid[7a] with 82 ml (710 mmol) of benzoyl chloride through a 30-cm Vigreux column keeping the head temperature below 116°[7b] afforded 32.6 g (58%) of *trans*-3-chloropropenoyl chloride: bp 107–116° (748 mm) [lit.[7a] bp 115–115.5° (1 atm)]; nmr (neat) δ 6.22 (d, 1, J = 13 Hz, α-H), 7.32 (d, 1, J = 13 Hz, β-H). This material contained some dissolved HCl and a little benzoyl chloride but was not further purified.

Following the general procedure, 12.5 g (100 mmol) of the acid chloride in 30 ml of ether was allowed to react with 60 ml (600 mmol) of piperidine in 350 ml of ether. Work-up gave 19.3 g (87%) of crude yellow product. Two recrystallizations from ethyl acetate afforded slightly stained material, mp 98.5–99.5°. Two further recrystallizations gave near-white needles: mp 99–100°; ir (CCl_4) 1640 (s, C=O), 1572 cm^{-1} (s, C=C); nmr (CCl_4) δ 1.57 (broad, 12, β- and γ-piperidino H's), 3.10 and 3.37 (two distorted multiplets cleanly separated, 4 each, α-piperidino H's), 4.89 (d, 1, J = 13 Hz, α-vinyl H), 7.11 (d, 1, J = 13 Hz, β-vinyl H).

Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.06; H, 10.01; N, 12.44.

3,3-Bis(piperidino)-2-methylpropenal (4b).—In 40 ml of ether 7.0 g (50 mmol) of the aldehyde **3**[1] was allowed to react with 35 ml (350 mmol) of piperidine in 200 ml of ether in the usual way to give 8.71 g (74%) of crude yellow-orange solid. The reported work-up[1] and repeated recrystallization from ethyl acetate and cyclohexane gave yellow needles of **4b**: mp 127–129° (lit.[1] mp 129–131°); nmr (CCl_4) δ 1.47 (s, CH_3), 1.59 (broad, β- and γ-piperidino H's, base overlaps δ 1.47, total both 15), 3.12 (distorted poorly resolved multiplet but one envelope, 8, α-piperidino H's), 8.97 (s, 1, CHO); ir (CCl_4) 2853 (m), 2819 (m, sh), 2727 (w, sh) (possibly formyl CH),[8] 1616 (s, C=O), 1541 cm^{-1} (vs, C=C); ir (Nujol) 1604, 1535–1520 cm^{-1} (lit., 1608, 1527 cm^{-1}).

4,4-Bis(piperidino)-3-buten-2-one (6).—4,4-Dichloro-3-buten-2-one was prepared as previously described (Darzens–Friedel–Crafts acetylation of 1,1-dichloroethene)[9a,b] except that substitution of dichloromethane for carbon tetrachloride as solvent facilitates stirring.

The general procedure, using 13.9 g (100 mmol) of the dichlorovinyl ketone in 25 ml of benzene and 65 ml (650 mmol) of amine in 180 ml of the same solvent, gave 21.8 g (92%) of crude yellowish product.[10] Two recrystallizations from ethyl acetate gave 14.5 g (61%) of near-white crystals: mp 79.5–80.5° (lit.[11] mp 80–81°) [rework of the mother liquors ultimately gave a total of 19.3 g (82%) of material of mp >78°]; ir (CCl_4) 1627 (s, C=O), 1501 cm^{-1} (s, C=C); ir (Nujol) 1617, 1508 cm^{-1} (lit.[11] 1623, 1517 cm^{-1}); nmr (CCl_4) δ 1.56 (broad, 12, β- and γ-piperidino H's), 1.80 (s, 3, methyl), 3.07 (broad and distorted but one envelope, 8, α-piperidino H's), 4.23 (s, 1, vinyl H); nmr ($CDCl_3$) δ 1.60, 1.96, 3.17, 4.40 (lit.[11] δ 1.60, 1.98, 3.19, 4.41). This compound has an anise odor not abolished when stored for several months as described above.

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Registry No.—**1**, 6162-62-5; **2**, 2648-51-3; **3**, 1561-34-8; **4b**, 40428-93-1; **5**, 40428-94-2; **6**, 10099-09-9; piperidine, 110-89-4; *trans*-3-chloropropenoic acid, 2345-61-1; *trans*-3-chloropropenoyl chloride, 3721-36-6; 4,4-dichloro-3-buten-2-one, 5780-61-0.

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Synthesis of DL-3-(3,4-Dihydroxyphenyl)alanine Methyl Ester and Related Compounds

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Successful results with L-3-(3,4-dihydroxyphenyl)-alanine (L-dopa) in the treatment of Parkinson's disease[2] have stimulated efforts in both the synthesis and resolution of DL-dopa. Ring-hydroxylated α-amino acids have usually been prepared[3] by condensation of an appropriate aromatic aldehyde with an active methylene compound, such as an azlactone in the Erlenmeyer synthesis. Low to moderate yields (30–60%) of DL-dopa have been reported by these methods.

We wish to report the synthesis of DL-3-(3,4-dihydroxyphenyl)alanine methyl ester, which was carried out *via* a single-vessel process in 83% yield. Methyl isocyanoacetate[4] (**1**), a material known[5] to undergo a wide variety of carbanion condensation reactions, was used as a starting material.[6] The isocyano group, in addition to activating the α-carbon atom for proton abstraction, affords an ideal protective group for a primary amine easily regenerated by acid hydrolysis. Condensation of **1** with 3,4-dibenzyldioxybenzaldehyde (**2**) in methyl alcohol with potassium *tert*-butoxide as the catalyst yielded the alkoxide

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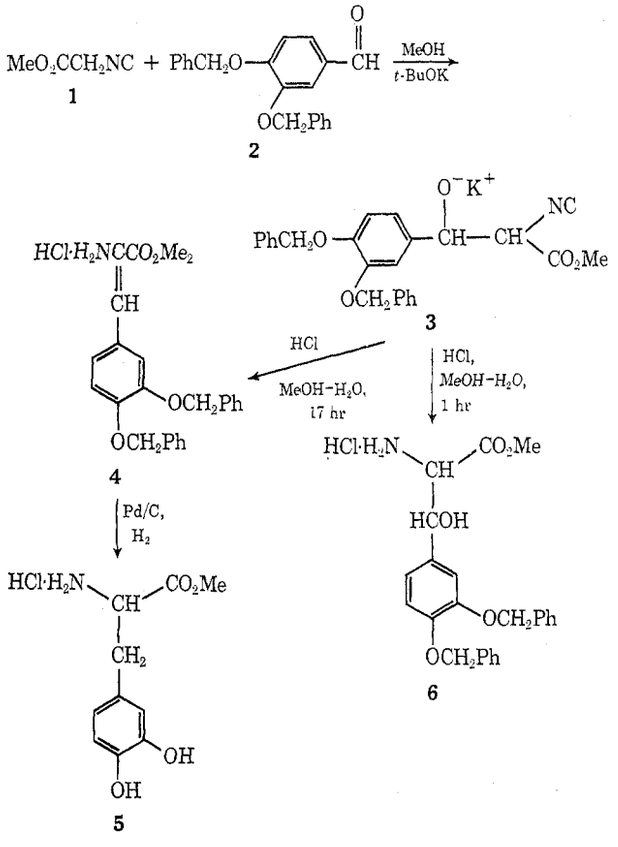
(4) We have used methyl isocyanoacetate to prepare several amino acids; U. S. patent application filed December 19, 1969, serial no. 886,748.

(5) U. Schoellkopf, *Angew. Chem., Int. Ed. Engl.*, **9**, 763 (1970), and references cited therein.

(6) Recently, Schoellkopf and coworkers and Suzuki, *et al.*, have used isocyano and isocyanopropionic esters to prepare alkyl amino acids and α-methyl-dopa by alkylation of the isocyano ester carbanions: U. Schoellkopf, D. Hoppe, and R. Jentsch, *Angew. Chem., Int. Ed. Engl.*, **10**, 331 (1971); M. Suzuki, K. Matsumoto, T. Iwasaki, and K. Okumura, *Chem. Ind. (London)*, 687 (1972).

3. Hydrochloric acid was added and the solution was heated at reflux for 17 hr to give the amine hydrochloride **4**. Catalytic hydrogenation of the mixture with 5% Pd/C at 50 psi reduced the olefinic linkage of **4**. It was critical at this step to keep the solution acidic. Neutralization of **4** before hydrogenation caused loss of the amino and ester groups, probably through condensation reactions. Vacuum evaporation of the solvent and recrystallization of the product from methanol–ether gave an 83% yield of the hydrochloride of methyl 3-(3,4-dihydroxyphenyl)alanate (**5**). Acid hydrolysis of **5** produced DL-dopa in essentially quantitative yield.



If the acidic hydrolysis of **3** is carried out for 1 hr instead of 17 hr the alcohol **6** is the predominant product. This intermediate may prove valuable for the synthesis of norepinephrine or dopamine derivatives.

The synthesis also works smoothly for other aromatic aldehydes. For example, 3,4-methylenedioxybenzaldehyde and 3,4-dimethoxybenzaldehyde were converted to **5**; however, an additional hydrolysis using boron tribromide in methylene chloride[7] was needed to remove the methylene or methyl ether groups.

Experimental Section

Methyl Isocyanoacetate (1).—The phosgene method of Ugi[8] was used for the synthesis of **1**. Methyl *N*-formylglycinate (41 g, 0.31 mol) was dissolved in a mixture of 600 ml of methylene chloride and freshly distilled triethylamine (79.2 g, 0.78 mol). Phosgene mixed with argon was then slowly bubbled through the mixture for 1–1.2 hr to maintain a temperature of 40°. The triethylamine hydrochloride was filtered and the methylene chloride was evaporated. The residue was treated with benzene and refiltered. Methyl isocyanoacetate (18 g, 0.18 mol, 58% yield) was obtained after distillation at 77.0–79.0° (2.5 mm).

Reaction of Methyl Isocyanoacetate (1) **with 3,4-Dibenzyldioxybenzaldehyde** (2).—Potassium *tert*-butoxide (2.5 g, 0.022 mol) was added to a methanolic solution of **1** (2 g, 0.02 mol) and the mixture was heated to 60°, at which time 3,4-dibenzyldioxybenzaldehyde (6.36 g, 0.02 mol) was added. The resulting solution was heated for 3 hr and cooled to room temperature and 10 ml of concentrated hydrochloric acid and 10 ml of water were added. This solution was refluxed for 17 hr, cooled to room temperature, and hydrogenated at 50 psi (Parr apparatus) for 4 hr with palladium on charcoal (5%) as a catalyst. Evaporation of the solution to dryness yielded a tan solid which on recrystallization from methanol–ether gave 4.1 g (0.017 mol, 83% yield) of the methyl ester hydrochloride of dopa (**5**). A proton nmr spectrum of **5** in DMSO-d_6 showed signals at δ 6.66 (m, 3, HAr), 4.08 [t, 1, $HC(NH_2 \cdot HCl)CO_2CH_3$], 3.70 (s, 3, H_3CCO_2–), 3.00 (d, 2, CH_2Ar). This nmr spectrum and an ir spectrum of **5** are identical with spectra of an authentic sample prepared by refluxing dopa with a methanolic solution of hydrochloric acid for 1 hr. Compound **5** can be hydrolyzed to dopa by refluxing in 6 *N* hydrochloric acid for 4 hr.

Reaction of Methyl Isocyanoacetate with 3,4-Methylenedioxybenzaldehyde.—A similar procedure was used with 3,4-methylenedioxybenzaldehyde (3.0 g, 0.02 mol) except that hydrolysis was carried out for 1 hr. The solvent was evaporated under vacuum and the residue was washed with ether to remove residual piperonal. The benzylic alcohol (type **6**) was the major product as evidenced by its infrared spectrum (plates), ~3500 (OH), 1725 cm^{-1} ($-CO_2CH_3$), and nmr spectrum (DMSO-d_6), δ 4.45 (HCOH). This material was hydrolyzed further with HCl–H_2O–MeOH and evaporated to give 4.5 g (81%) of olefinic material (type **4**): ir (KBr) 1695 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 7.12 (m, 3, HAr), 6.42 (s, 1, HC=C), 6.01 (s, 2, OCH_2O), 3.80 (s, 3, CO_2CH_3). This material was hydrogenated using platinum oxide in acetic acid to give 4.1 g (0.016 mol, 80% yield) of 3,4-methylenedioxyphenylalanine methyl ester after recrystallization from methanol–ether: mp 276–279° (lit.[9] mp 278–280°); nmr (DMSO-d_6) δ 6.90 (m, 3, HAr), 6.00 (s, 2, OCH_2O), 4.14 [t, 1, $HC(NH_2 \cdot HCl)CO_2CH_3$], 3.65 (s, 3, CO_2CH_3), 2.85 (d, 2, CH_2Ar). The product was further identified by conversion to its *N*-acetyl derivative, mp 107–108° (lit.[10] mp 107–108°). The 3,4-methylenedioxyphenylalanine methyl ester was converted to **5** by boron tribromide using the method of McOmie, *et al.*[7] To 1 g of this product was added 4 ml of boron tribromide in 50 ml of methylene chloride and the reaction mixture was refluxed for 6 hr. At the end of this period excess acetic anhydride was added and the reaction mixture was stirred for 1 hr, at which time the mixture was poured into water and hydrolyzed for 0.5 hr. The mixture was evaporated and then treated with MeOH–HCl–H_2O at reflux for 2 hr. After evaporation and recrystallization from methanol–ether, 0.3 g (35% yield) of **5** was obtained.

These experiments to produce type **4** can also be efficiently accomplished in a single-vessel process in 80% yield.

Reaction of Methyl Isocyanoacetate with 3,4-Dimethoxybenzaldehyde.—When a procedure identical with reaction of **1** with 3,4-methylenedioxybenzaldehyde was used with 3,4-dimethoxybenzaldehyde (3.3 g, 0.02 mol), methyl 3,4-dimethoxyphenylalanate hydrochloride (4.4 g, 0.016 mol, 80% yield) was obtained. Treatment of this product with excess boron tribromide in methylene chloride and acidification with hydrochloric acid in methanol gave 3.9 g (78% yield) of **5** after recrystallization from methanol–ether.

Registry No.—**1**, 39687-95-1; **2**, 5447-02-9; **4**, 40635-70-9; **5**, 40611-00-5; **6**, 40635-71-0; 3,4-methylenedioxybenzaldehyde, 120-57-0; 3,4-dimethoxybenzaldehyde, 120-14-9.

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