Synthesis of DL-2-(2,4,6-Cycloheptatrien-1-yl)glycine

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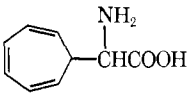
We report herein the synthesis of the title compound **4** which can be considered to be a nonbenzenoid isomer of the biologically important amino acid β-phenylalanine. The preparative route is based[2,3] on the condensation of tropylium tetrafluoroborate[4] with dimethyl formamidomalonate.[5]



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Experimental Section

Melting points are uncorrected. Optical rotations were measured in water with a Perkin-Elmer photoelectric polarimeter at 25°.

Dimethyl α-Formamido-2,4,6-cycloheptatriene-1-malonate (1).—A solution of Na (2.3 g) in 60 ml of EtOH was added dropwise and with stirring to a finely powdered mixture of dimethyl formamidomalonate[6] (17.5 g, 0.1 mole) and tropylium tetrafluoroborate[4] (17.8 g, 0.1 mole). H_2O (150 ml) was added, the solution was extracted (CH_2Cl_2) and the extracts were dried and evaporated to a pale yellow oil (20.5 g). A portion (14 g) was dissolved in boiling H_2O; the solution was filtered through charcoal and allowed to cool giving 12.7 g of the crystalline product, mp 107–108°. *Anal.* ($C_{13}H_{15}NO_5$) C, H, N.

DL-N-Formyl-2-(2,4,6-cycloheptatrien-1-yl)glycine (2).—A solution of **1** (2.65 g, 0.01 mole) in 60 ml of MeOH containing 8 g of NaOH was allowed to stir overnight at room temperature. After 20 min a precipitate was formed. The heterogeneous solution was evaporated to dryness at low temperature, the residue was dissolved (H_2O), and the pH was adjusted to 5–5.5 by the addition of Dowex-50 (H^+). Filtration and concentration of the filtrate afforded the crystalline product; yield 0.5–0.7 g. Recrystallization was effected by dissolving in MeOH–H_2O and removing most of the MeOH under reduced pressure; mp 183°, $[\alpha]_D$ 0° (*c* 2.18, MeOH). *Anal.* ($C_{10}H_{11}NO_3$) C, H, N.

Dimethyl α-acetamido-2,4,6-cycloheptatriene-1-malonate (3) was prepared essentially as described for **1**, but using dimethyl acetamidomalonate.[5] The product crystallized upon adding H_2O and it was recrystallized from MeOH to give pure material (54%), mp 165–167°. *Anal.* ($C_{14}H_{17}NO_5$) C, H, N.

DL-2-(2,4,6-Cycloheptatrien-1-yl)glycine (4).—To a suspension of **2** (3 g) in 40 ml of 3 *N* HCl were added 25 ml of DMF and 10 ml of MeOH with brief heating. The resulting solution was then treated dropwise with 1 ml of concentrated HCl and stirred at room temperature overnight. Solvent was removed by addition of *n*-BuOH and evaporation at *ca.* 60° to give a dark crystalline residue. The latter was dissolved in the minimum volume of H_2O and added to a column (2.5 × 30 cm) containing Dowex-50 (H^+) and the column was washed (H_2O) until the effluent was faintly acidic. Elution with 2 *N* NH_4OH (500 ml total) afforded a pale yellow solution which was evaporated to dryness leaving a crystalline cream-colored solid. The latter was suspended in H_2O–MeOH (1:1), filtered, and washed with the same mixture; yield 2 g of pure product: mp 246° dec; ir (KBr), 1590, 1525 (zwitterion), 2600, 2100 cm^{-1} (acid dimer); λ_{max} 256 mμ (H_2O–MeOH). *Anal.* ($C_9H_{11}NO_2$) C, H, N.

DL-N-2-(2,4,6-Cycloheptatrien-1-yl)trifluoroacetylglycine (5).—To a suspension of **4** (0.2 g) in 7 ml of H_2O was added 1.2 ml of 1 *N* NaOH. After warming briefly the homogeneous solution was cooled to room temperature and treated with 1.5 ml of ethylthio trifluoroacetate[6] with vigorous stirring. After 30 min, the solution was evaporated, and the residue was taken up in Et_2O and processed to a syrup which solidified in a small volume of cold H_2O. The product was filtered and washed (H_2O) to give 0.227 g of colorless crystals. Recrystallization was effected by dissolving in Et_2O, adding petroleum ether (bp 30–60°), and allowing the solution to evaporate slowly, mp 122–124°. *Anal.* ($C_{11}H_{10}F_3NO_3$) C, H, N.

Fragmentation of Dimethyl α-Acetamido-2,4,6-cycloheptatriene-1-malonate.—An amount of **3** (1 g) was suspended in 10 ml of 2 *N* HCl and the mixture was heated under reflux for 5 hr. The homogeneous solution was evaporated to dryness and the resulting white solid was suspended in ether and filtered; yield 0.16 g (60%), mp 230–235°. This product was identical with glycine (mixture melting point and ir spectra).

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Preparation of 3-Fluoropropane-1,2-diol from Glycidol (Hydroxymethyloxirane)[1a]

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3-Fluoropropane-1,2-diol is an intermediate in the synthesis of fluorolactic acid[2] which is a specific inhibitor of lactate dehydrogenase.[3] In contrast to previous lengthy procedures[2,4,5] the present paper describes a one-step synthesis, suitable for large-scale preparation of 3-fluoropropane-1,2-diol.

Experimental Section

2-Fluoropropane-1,2-diol.—A mixture of glycidol (100 g, 1.35 moles) and KHF_2 (106 g, 1.35 moles) in 200 ml of DMF was refluxed overnight. Solid KF was filtered off and the solvent was vacuum evaporated. The product (34.3 g, 0.37 mole, 27% yield) had bp 74–79° (4 mm). *Anal.* ($C_3H_7FO_2$) C, H.

2-Ethyl-4-fluoromethyl-2-methyl-1,3-dioxolane.—A sample of 3-fluoropropane-1,2-diol (2 g) was refluxed overnight with 2-butanone (20 ml) in the presence of toluenesulfonic acid (0.05 g). H_2O was removed from the azeotrope by refluxing in a Soxhlet extractor, charged in the cup with 10 g of Linde Molecular Sieve. After removal of the unreacted solvent under vacuum, the product was obtained by distillation (2 g), bp 145–150° (lit.[5] 146–147°).

A mixture of 1,2-propanediol and 1,3-propanediol was separated into two distinct peaks at 80° on a 4 m × 3.2 mm column, packed with 12% DEGS on Chromosorb W, indicating that this column separates isomeric diols. Both 3-fluoropropane-1,2-diol and the ketal prepared from it gave single distinct peaks.

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