

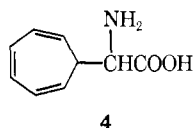
Synthesis of DL-2-(2,4,6-Cycloheptatrien-1-yl)glycine

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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 tetrafluoroborate⁴ with dimethyl formamidomalonate.⁵



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 formamidomalonate⁶ (17.5 g, 0.1 mole) and tropylium tetrafluoroborate⁴ (17.8 g, 0.1 mole). H₂O (150 ml) was added, the solution was extracted (CH₂Cl₂) and the extracts were dried and evaporated to a pale yellow oil (20.5 g). A portion (14 g) was dissolved in boiling H₂O; the solution was filtered through charcoal and allowed to cool giving 12.7 g of the crystalline product, mp 107–108°. *Anal.* (C₁₃H₁₅NO₃) 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 (H₂O), 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–H₂O and removing most of the MeOH under reduced pressure; mp 183°, [α]_D 0° (c 2.18, MeOH). *Anal.* (C₁₀H₁₁NO₃) 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 H₂O and it was recrystallized from MeOH to give pure material (54%), mp 165–167°. *Anal.* (C₁₄H₁₇NO₅) 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 H₂O and added to a column (2.5 × 30 cm) containing Dowex-50 (H⁺) and the column was washed (H₂O) until the effluent was faintly acidic. Elution with 2 N NH₄OH (500 ml total) afforded a pale yellow solution which was evaporated to dryness leaving a crystalline cream-colored solid. The latter was sus-

ended in H₂O–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 m μ (H₂O–MeOH). *Anal.* (C₉H₁₁NO₂) C, H, N.

DL-N-2-(2,4,6-Cycloheptatrien-1-yl)trifluoroacetyl-glycine (5).—To a suspension of **4** (0.2 g) in 7 ml of H₂O 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 trifluoroacetate⁶ with vigorous stirring. After 30 min, the solution was evaporated, and the residue was taken up in Et₂O and processed to a syrup which solidified in a small volume of cold H₂O. The product was filtered and washed (H₂O) to give 0.227 g of colorless crystals. Recrystallization was effected by dissolving in Et₂O, adding petroleum ether (bp 30–60°), and allowing the solution to evaporate slowly, mp 122–124°. *Anal.* (C₁₁H₁₀F₃NO₃) 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 acid² 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 KHF₂ (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.* (C₃H₇FO₂) 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). H₂O 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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