h. Excess cyclooctene was removed in vacuo and the solid residue was recrystallized from methanol to give colorless **3a:** mp 171–172 °C; 1.70 g (92%); IR 5.69 μm ($CHCl_3$); NMR ($CDCl_3$) δ 1.24 (6 H), 1.2–2.2 (14 H), 6.9–7.3 (10 H). Anal. Calcd for $C_{27}H_{30}O$: C, 87.52; H, 8.16, O, 4.32. Found: C, 87.27; H, 8.24.

Preparation of 3b. A solution of 0.26 g (0.5 mmol) of the dimer of 1 in 10 mL of 1,5-cyclooctadiene containing 50 mg of hydroquinone was heated under nitrogen at 97 °C for 23 h. Excess diene was removed in vacuo and the residue was purified by TLC (silica gel, 5% ethyl acetate–petroleum ether), followed by three recrystallizations from methanol, to give colorless prisms, **3b:** mp 124–126 °C; 0.35 g (94%); IR 5.69 μm ($CHCl_3$); NMR ($CDCl_3$) δ 1.24 (6 H), 1.5–2.6 (10 H), 5.7–6.0 (2 H), 6.9–7.3 (10 H). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66; O, 4.34. Found: C, 88.20; H, 7.68.

Preparation of 3c. A solution of 0.26 g (0.5 mmol) of the dimer of 1 in 8 mL of 1,3-cyclooctadiene containing 50 mg of hydroquinone was heated under nitrogen at 100 °C for 72 h. Column chromatography (silica gel, benzene) and recrystallization from methanol gave colorless plates, **5:** mp 144 °C; 0.31 g (84%); IR 5.69 μm ($CHCl_3$); NMR ($CDCl_3$) δ 1.08 (3 H), 1.27 (3 H), 1.3–2.4 (9 H), 3.2 (br d, 1 H), 5.3 (dd, 1 H), 5.4–4.9 (1 H), 6.8–7.2 (10 H). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66; O, 4.34. Found: C, 87.71, H, 7.81.

Hydrogenation of 3b and 3c. Hydrogenations were carried out in ethyl acetate using 5% Pd/C as a catalyst. Quantitative yields of **3a** were obtained in both cases.

Preparation of 5. A solution of 0.26 g (0.5 mmol) of the dimer of 1 in 9 mL of cyclooctatetraene containing 50 mg of hydroquinone was heated under nitrogen at 40 °C for 2 weeks (similar results were obtained by heating at 65 °C for 3 days). Evaporation of excess tetraene in vacuo followed by preparative TLC (2% ethyl acetate–petroleum ether, three elution) and recrystallization from acetone–methanol gave **5:** mp 168–169 °C; 210 mg (45%); IR 5.69 μm ($CHCl_3$). The mass spectrum of **5** had intense peaks at 468 (parent), 338, and 260 (1) in the high-mass region. Anal. Calcd for $C_{35}H_{32}O$: C, 89.70; H, 6.88; O, 3.41. Found: C, 89.69; H, 7.10.

The same adduct was made from the 76 °C dimer[6] of cyclooctatetraene by heating 2.5-mmol amounts of **1** (as the dimer) and the 76 °C dimer in 10 mL of acetone under nitrogen at 61 °C for 18 h. Evaporation of solvent and recrystallization from acetone–methanol gave **5:** mp 168–169 °C; 0.92 g (79%).

Cope Rearrangement of 5. A solution of 100 mg of **5** was heated in acetone under nitrogen for 2 h at 120 °C. Evaporation of solvent and recrystallization from acetone–methanol gave **6:** mp 233–234 °C; 85 mg (85%); IR 5.99 μm ($CHCl_3$). The mass spectrum had intense peaks at *m/e* 468 (parent), 338, and 260 (1), in the high-mass region. Anal. Calcd for $C_{35}H_{32}O$: C, 89.70; H, 6.88; O, 3.41. Found: C, 89.70; H, 7.01.

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Registry No.—1, 26307-17-5; 1 dimer, 38883-84-0; **2a,** 931-88-4; **2b,** 111-78-4; **2c,** 1700-10-3; **3a,** 63904-18-7; **3b,** 63904-19-8; **3c,** 63904-20-1; **5** isomer I, 63866-53-5; **5** isomer II, 63866-54-6; **6** isomer I, 63866-55-7; **6** isomer II, 63866-56-8; cyclooctatetraene, 629-20-9; cyclooctatetraene dimer, 14375-95-2.

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An Alternate Synthesis of 5,6-Dihydroxy-2,3-dihydroindole-2-carboxylates (Cyclodopa)

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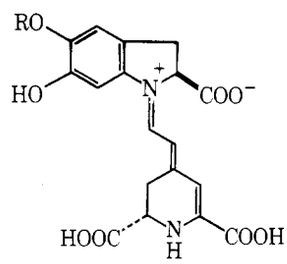
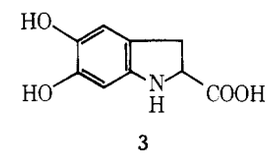
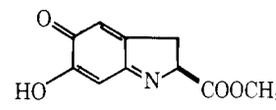
For the total synthesis of betanin (1),[1] the red-violet pigment of the beet (*Beta vulgaris*), and the corresponding aglycone betanidin (2)[1,2] an efficient synthesis of cyclodopa (3) (5,6-dihydroxy-2,3-dihydroindole-2-carboxylic acid) was required. The methyl ester of this acid was prepared previously by oxidation of dopa methyl ester (7) with potassium ferricyanide followed by reduction of the intermediate methyl 6-hydroxy-5-oxo-2,3-dihydroindole-2-carboxylate (dopachrome methyl ester) (4) with sodium dithionite.[3] This method serves poorly on a preparative scale because acceptable yields of product are obtained only when the oxidations are performed in less than 0.05 M solutions. The irreversible isomerization of dopachrome methyl ester (4) to methyl 5,6-dihydroxyindole-2-carboxylate in the basic oxidation medium creates further problems. In later work that led to a preparatively useful cyclodopa synthesis, the isomerization of dopachrome ester was avoided by performing the oxidation on dopa (6) itself rather than its esters.[4] A further improvement resulted when it was noticed that solutions of cyclodopa (3) could be stabilized by complexation with borate.[4]



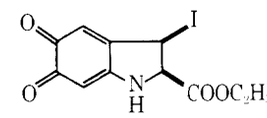
1, R = glucose
2, R = H



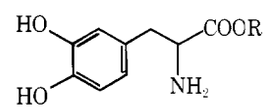
3



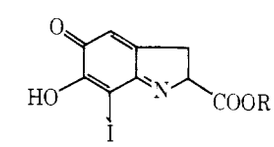
4



5



6, R = H
7, R = CH_3
8, R = C_2H_5

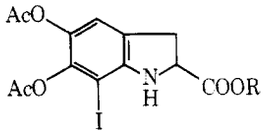


9, R = CH_3
10, R = C_2H_5

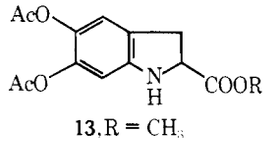
While the latter study was in progress we reinvestigated some older work of Bu'Lock and Harley-Mason.[5] They found that oxidation of dopa ethyl ester hydrochloride (8) with po-

tassium iodate in aqueous 1-butanol yielded a red, crystalline iodoquinone which was formulated as **5**.

In this laboratory their procedure gave approximately 25% of this iodoquinone, but superior yields were obtained by performing the oxidation in a two-phase system employing chloroform as the organic phase. The infrared spectrum in Nujol of the iodoquinone exhibited bands at 3100, 1740, 1673, and 1625 cm^{-1} in general agreement with structure **5**, but the NMR spectrum of the compound measured immediately after dissolution in DMSO-d_6 indicated the presence of at least three species and within 2 h anything resembling an iodoquinone had vanished. To avoid manipulation of this sensitive compound the crude iodoquinone was immediately reduced with sodium dithionite and the reduction product was stabilized further by acetylation. If the previously postulated structure **5** of the iodoquinone were correct, an *O,O,N*-triacetate should have resulted. In contradiction to this proposal, a mass spectrum of the product showed it to be a diacetate. Furthermore, the spectrum lacked both M − 1 and M − HI peaks, in better agreement with the presence of an aromatic rather than a benzylic iodide. Indeed, an NMR spectrum of this iodide exhibited a triplet (J = 1 Hz) caused by a single aromatic proton. The magnitude of the coupling constant suggests *o*- rather than *m*-benzylic coupling,[6] and the iodoquinones **9** and **10** and their reduction products **11** and **12** thus all are 7-iodo derivatives. Catalytic reduction of the iodides **11** and **12** over a palladium catalyst in ethanol containing



11, R = CH_3
12, R = C_2H_5



13, R = CH_3
14, R = C_2H_5

triethylamine afforded the racemic *O,O*-diacetylcyclodopa esters **13** and **14** in 40% overall yield based on dopa methyl ester, characterized further by crystalline hydrochlorides. Their NMR spectra show singlets and triplets (J = 1 Hz) corresponding to one aromatic proton each. The newly formed protons show no long-range coupling, while the second signals again display *o*-benzylic coupling, thus providing confirmation for the location of the iodine atom in the iodinated intermediates. The ability of potassium iodate to cause iodinations was recognized earlier[5] but whether iodination in the present case occurs before or after formation of the dihydroindole remains unknown. Treatment of cyclodopa methyl ester with potassium iodate followed by reduction with dithionite and acetylation gave iodide **11**, identical with that prepared from dopa methyl ester (**7**) using the same sequence of reactions. Earlier investigators have developed efficient methods for the hydrolysis of cyclodopa esters to cyclodopa.[3,4]

Experimental Section

Methyl 5,6-Diacetoxy-7-iodo-2,3-dihydroindole-2-carboxylate (11). To a stirred mixture of 2.5 g of racemic 3,4-dihydroxyphenylalanine (dopa) methyl ester hydrochloride (**7**), 40 mL of water, and 400 mL of chloroform was added a solution of 8.56 g of potassium iodate in 100 mL of water. After stirring for 12 min, the aqueous phase was separated and extracted twice with chloroform. The combined extracts were washed with brine and evaporated to dryness under reduced pressure at 50 °C. The residue was dissolved in 200 mL of 40% aqueous ethanol and sodium dithionite ($Na_2S_2O_4$) was added until the red color disappeared. The mixture was filtered and the filtrate was extracted three times with ether. The ether extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Treatment of the residue with 50 mL of acetic anhydride and 10 mL of pyridine for 4 h at room temperature, followed by the standard workup afforded a crude acetate (2.06 g) which was purified by chromatography over 60 g of silicic acid. Elution with CH_2Cl_2–acetone (97:3) gave the crystalline iodoacetate **11** (2.03 g). Recrystallization from methanol gave prisms: mp 126–127 °C; positive Beilstein test; UV_{max} (C_2H_5OH) 218 (ε 31 400), 245 (shoulder, ε 7710), and 307 nm (ε 4690); IR (Nujol) 3350, 3250, 1760, 1730, 1690, 1215, 935, and 883 cm^{-1}; NMR ($CDCl_3$) δ 2.17 (s, 3), 2.27 (s, 3), 3.42 (d of d, 2, J = 1, 8 Hz), 3.69 (s, 3), 4.44 (t, 1, J = 8 Hz), 4.70 (d, 1, exchangeable with D_2O), and 6.82 ppm (t, 1, J = 1 Hz). Anal. Calcd for $C_{14}H_{14}O_6NI$: C, 40.11; H, 3.37; N, 3.34; I, 30.28. Found: C, 40.22; H, 3.43; N, 3.39; I, 30.09.

Methyl 5,6-Diacetoxy-2,3-dihydroindole-2-carboxylate (13). The iodo acetate **11** (1.827 g), 360 mg of 10% palladium-on-carbon, and 0.73 mL of triethylamine in 110 mL of ethanol were stirred under hydrogen (1 atm). After reduction was complete (hydrogen uptake, 118 mL; calcd, 102 mL), the catalyst was filtered and washed with ethanol, and the filtrate was evaporated under reduced pressure. The residue was dissolved in dichloromethane, washed with aqueous sodium thiosulfate and brine, and dried (Na_2SO_4). Removal of solvent gave 1.2 g of a gum which was chromatographed on 36 g of silicic acid. Elution with CH_2Cl_2–acetone (95:5) gave pure (±)-di-*O*-acetylcyclodopa methyl ester as a gum (1.165 g, 40% from dopa methyl ester hydrochloride): NMR ($CDCl_3$) δ 2.25 (s, 6), 3.31 (d, 2, J = 8 Hz), 3.76 (s, 3), 4.43 (t, 1, J = 8 Hz), 4.36 (broad s, 1, exchangeable with D_2O), 6.55 (s, 1), and 6.95 (t, 1, J = 1 Hz).

Methyl 5,6-Diacetoxy-2,3-dihydroindole-2-carboxylate Hydrochloride. Di-*O*-acetylcyclodopa methyl ester, **13** (100 mg), was dissolved in absolute ether and the solution was saturated with dry hydrogen chloride under ice cooling to give a white precipitate. Filtration and recrystallization from methanol–ether afforded colorless prisms (81 mg): mp 117–121 °C; UV_{max} (C_2H_5OH) 244 (ε 6840) and 304 nm (ε 3810); IR (Nujol) 3060, 3040, 2500–2400, 1758, 1770, 1753, 910, 883, and 860 cm^{-1}; NMR (DMSO-d_6) δ 2.22 (s, 6), 3.27 (AB part of ABX, 2), 3.70 (s, 3), 4.66 (X part of ABX, 1), 6.69 (s, 1), and 7.03 (broad s, 1). Anal. Calcd for $C_{14}H_{16}ClNO_6$: C, 50.99; H, 4.89; Cl, 10.76; N, 4.25. Found: C, 51.05; H, 4.96; Cl, 10.65; N, 4.18.

(±)-Ethyl 5,6-Diacetoxy-2,3-dihydroindole-2-carboxylate. Di-*O*-acetylcyclodopa ethyl ester was prepared using the same method described for the methyl ester.

7-Iodo-5,6-di-*O*-acetylcyclodopa ethyl ester (**12**): mp 141–142 °C (from CH_3OH); IR (Nujol) 3380, 1770, 1745, 1730, 1600, 1580, 938, 900, and 875 cm^{-1}; NMR ($CDCl_3$) δ 1.28, (t, 3), 2.22 (s, 3), 2.30 (s, 3), 3.44 (d of d, 2, J = 1, 8 Hz), 4.17 (q, 2), 4.39 (t, 1, J = 8 Hz), 6.75 (t, 1, J = 1 Hz); mass spectrum *m/e* (rel intensity) 433 (27.7), 391 (42.6), 349 (100), 276 (66.8), and 149 (40.0). Anal. Calcd for $C_{15}H_{16}INO_6$: C, 41.60; H, 3.72; I, 29.30; N, 3.27. Found: C, 41.67; H, 3.74; I, 29.37; N, 3.23.

Di-*O*-acetylcyclodopa ethyl ester (**14**): IR ($CHCl_3$) 3360, 1760, 1730, 1668, 1620, 910, and 895 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, 3), 2.20 (s, 6), 3.26 (d, 2, J = 8 Hz), 4.13 (q, 2), 4.32 (t, 1), 6.35 (s, 1), and 6.75 (t, 1, J = 1 Hz).

Di-*O*-acetylcyclodopa ethyl ester hydrochloride: mp 121–123 °C (from CH_3OH–ether): IR (Nujol) 3040, 2500–2300, 1775, 1740, 910, 880, and 855 cm^{-1}. Anal. Calcd for $C_{15}H_{18}ClNO_6$: C, 52.43; H, 5.28; Cl, 10.31; N, 4.08. Found: C, 52.64; H, 5.39; Cl, 10.19; N, 3.99.

Methyl 6-Hydroxy-5-oxo-2,3-dihydroindole-2-carboxylate (9). The crude *o*-quinone was dissolved in acetone, filtered, and concentrated without heating until crystals had separated. These were collected and washed with ether to afford red needles: mp 118–20 °C dec and remelt at 193–194 °C; IR (Nujol) 3100, 1740, 1673, 1625, 1567, and 885 cm^{-1}; NMR (DMSO-d_6) δ 3.44 (AB part of ABX), 3.77 (s), (3.87 (s), 4.82 (X part of ABX), 6.44 (t, J = 3 Hz), 7.03 (s), 7.20 (d), and 10.48 (broad s). After 2 h, the peaks at δ 3.44, 3.77, and 6.44 had disappeared and were replaced by a very broad peak centered at 6.27 ppm.

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Registry No.—**7**, 40611-00-5; **9**, 63797-93-3; **11**, 63797-94-4; **12**, 63797-95-5; **13**, 63864-75-5; **13**·HCl, 63864-76-6; **14**, 63797-96-6; **14**·HCl, 63797-97-7.

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