Studies on the Chemical Reactivity of the Quinone Methide Derived from the Oxidative Cyclization of α-Methyl-3,4-dihydroxyphenylalanine Ethyl Ester

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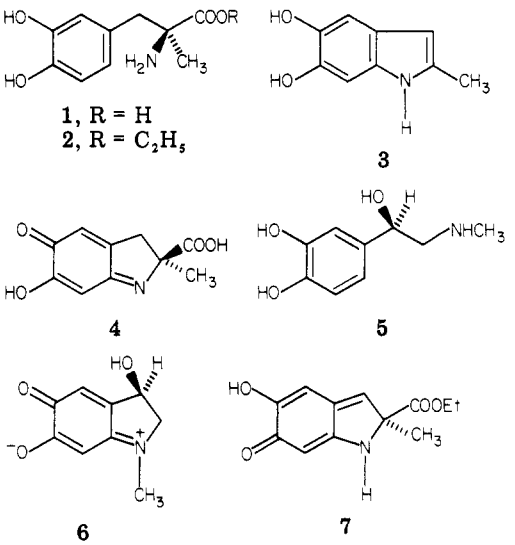
Received May 13, 1982

Air oxidation of the ethyl ester of (*S*)-α-methyl-3,4-dihydroxyphenylalanine [(*S*)-α-MeDopa] generates the corresponding cyclic quinone methide which proved to be unreactive toward nucleophiles. Under a variety of reaction conditions the quinone methide rearranged to an indole, the structure of which was established by an independent synthesis to be ethyl 5,6-dihydroxy-2-methylindole-3-carboxylate.

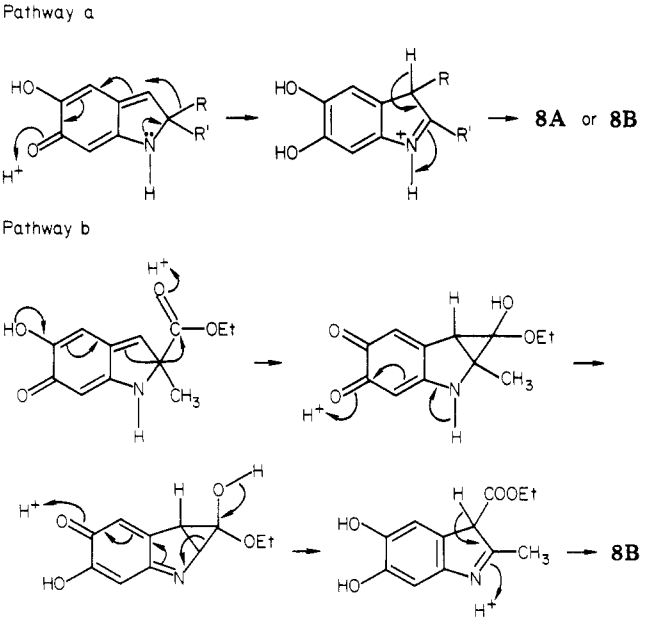
The catechol derivatives (*S*)-α-methyl-3,4-dihydroxyphenylalanine [(*S*)-α-MeDopa, **1**][1] and its ethyl ester (**2**, Chart I) are used extensively in the therapeutic management of hypertension. Occasionaly, however, severe liver damage and other undesirable side effects[3] have been noted. Some workers have postulated that the hepatic necrosis may be caused by covalent interaction between biomacromolecules and electrophilic products (semiquinones, *o*-benzoquinones, and cyclic iminoquinones) resulting from the oxidation of the catechol moiety present in these and related systems.[4] Studies on the chemical oxidation of **1** with $K_3Fe(CN)_6$ have led to the characterization of 2-methylindole-5,6-diol (**3**) the formation of which presumably proceeds via decarboxylation of the iminoquinone **4**.[5] In the case of a catecholamine such as epinephrine (**5**), the corresponding iminoquinone **6** (adrenochrome) has been isolated in crystalline form.[6] Of some interest is the recent report that adrenochrome itself will cause cardiac lesions in experimental animals.[7]

The association of cytotoxicity with oxidation products of these important biogenic amines and amino acids led us to examine the products formed from the chemical oxidation of (*S*)-α-MeDopa ethyl ester (**2**). Treatment of **2** with $K_3Fe(CN)_6$ at pH 7.4 provided a crystalline yellow product which unexpectedly proved to have the quinone methide structure **7**.[8] The present paper reports the results of some of our efforts to characterize the potential electrophilic properties of **7**. Under a variety of reaction conditions, however, **7** did not form stable adducts but rather rearranged to an indolic product, the structure of which has been established by an independent synthesis.

Chart I



Scheme I



Results and Discussion

Attempted reaction of **7** with *N*-acetylcysteine and thiophenol under mild conditions led to recovery of starting material only. Even when heated with thiophenol under reflux in ethanol, no adduct could be obtained. Instead, an isomeric product displaying spectroscopic characteristics expected of a dihydroxyindole was isolated in moderate yield. The two likely structures for this product **8** are given by **8A** and **8B**. The rearrangement

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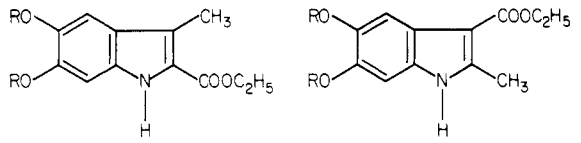


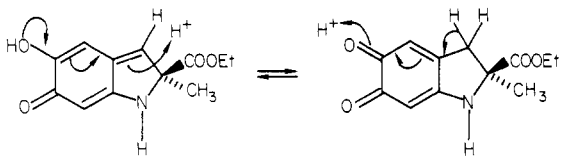
A B

8, R = H
9, R = CH_3CO
11, R = CH_3

was catalyzed by acid and also could be effected thermally by vacuum sublimation. Acetylation of 8 yielded the corresponding diacetoxy product 9. Furthermore, the direct conversion of 7 to 9 could be achieved by treatment of the quinone methide with acetic anhydride and pyridine. Treatment of 8 with diazomethane provided the corresponding dimethyl ether 11.

The two mechanistic pathways shown in Scheme I may account for the observed rearrangement. Pathway a could account for the formation of both **8A** and **8B** while pathway b can accomodate only indole **8B** as the reaction product. A mechanism analogous to that described by pathway b has been reported recently in a related system.[9]

Some useful information with respect to the behavior of quinone methide 7 was gained by examining its NMR spectrum in Me_2SO-d_6. The quinone methide displays three low-field singlets at δ 5.39, 6.19, and 6.85 attributable to the C-3, C-4, and C-7 methine protons. Addition of D_2O led to the selective exchange of the proton resonating at δ 5.39. When this deuterated analogue was made to undergo thermal rearrangement by vacuum sublimation, the NMR spectrum of the resulting indole displayed both low-field aromatic proton signals (δ 6.67 and 7.25) observed in the product obtained upon thermal rearrangement of the unexchanged quinone methide. Consequently, the C-3 proton must exchange with D_2O via the following tautomeric equilibrium between 7 and 10. The high electron

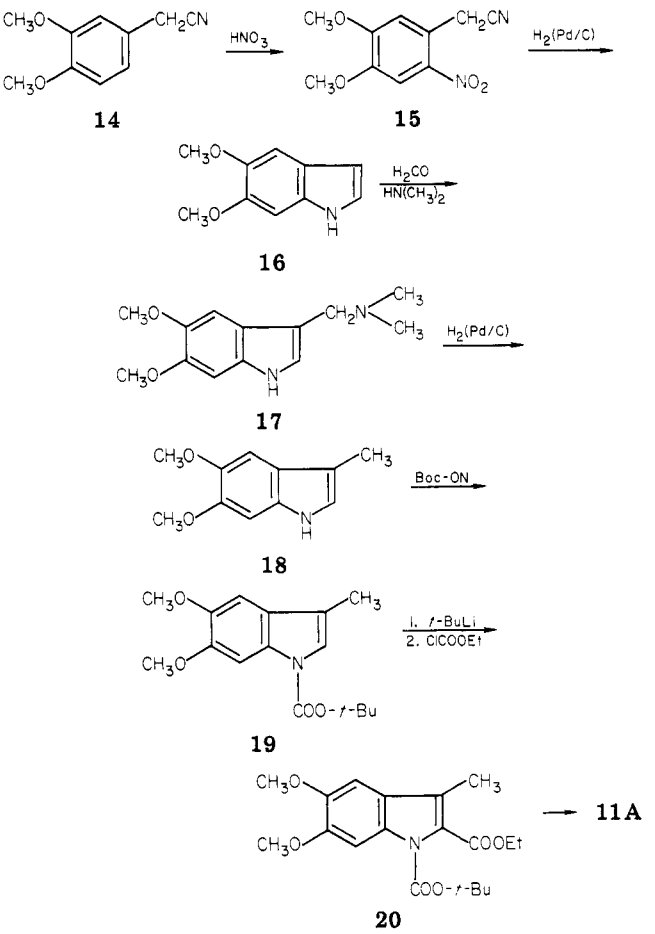


7 10

density at C-3 illustrated by this type of tautomerism may be offered as an argument in support of the mechanism illustrated in pathway b. For better definition of the chemical behavior of 7 illustrated by this rearrangement, the structure assignment of 8 was approached by synthesis.

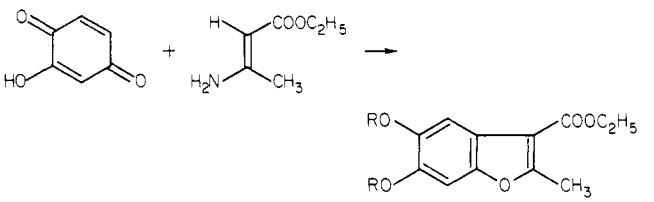
The synthesis of ethyl 5,6-dihydroxyindole-3-carboxylate (**8B**) by the condensation of hydroxy-*p*-quinone with ethyl 3-aminocrotonate was reported in 1951.[10] Unfortunately, the only characterization of this product was its decomposition point (200 °C) which was similar to that observed for the rearrangement product. In our hands this reaction yielded a white crystalline product which displayed an NMR spectrum consistent with **8B** but clearly different from the rearrangement product. In particular, the chemical shifts of the two aromatic proton signals (δ 7.22 and 6.91) did not coincide with the corresponding signals for the rearrangement product (δ 7.28 and 6.70). The melting point of this condensation product (160 °C) was significantly different from the 200 °C decomposition point

Scheme II



14 15 16 17 18 19 20 → 11A

reported for **8B**.[10] Treatment with diazomethane yielded the corresponding dimethyl ether which, on the basis of spectroscopic and melting point data, also was different from the dimethyl ether synthesized from the rearrangement product. Elemental and high-resolution mass spectral analyses established that both the condensation product and its dimethyl ether were derivatives of benzofuran, namely, compounds **12** and **13**, respectively. Despite several attempts, we were unable to isolate an indolic product from this condensation.



12, R = H
13, R = CH_3

Simultaneously we were pursuing the synthesis of **8A**. Nitration of the commercially available (3,4-dimethoxyphenyl)acetonitrile (**14**) provided (4,5-dimethoxy-2-nitrophenyl)acetonitrile (**15**) in 70% yield (Scheme II). The regiospecific nitration at C-2 was established by the NMR spectrum which displayed two singlets in the aromatic region, consistent with the para orientation of the aromatic protons. Catalytic reduction of **15** yielded the indole **16** in 83% yield. A Mannich-type reaction on **16** in the presence of aqueous formaldehyde and dimethylamine generated 5,6-dimethoxygramine (**17**) which upon catalytic reduction led to 5,6-dimethoxy-3-methylindole (**18**). Introduction of the ester group at C-2 proceeded by way of

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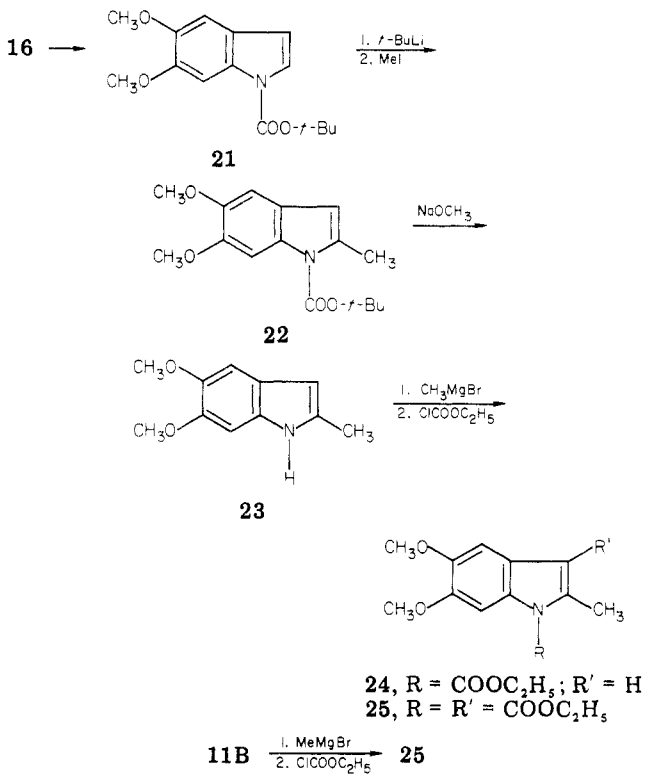
Scheme III



the *N-tert*-butoxycarbonyl intermediate **18**. Hasan et al.[11] recently have reported that the anions derived from such indole derivatives undergo regiospecific α substitution. Treatment of indole **18** with NaH follwed by [2-[[(*tert*-butoxycarbonyl)oxy]imino]phenyl]acetonitrile (Boc-ON) gave the protected indole **19** which was converted to the corresponding 2-lithio intermediate with *tert*-butyllithium at −78 °C. This intermediate was allowed to react with ethyl chloroformate to generate the blocked ester **20** which upon mild hydrolysis yielded the desired product **11A**, melting at 166–168 °C. The dimethyl ether derived from the rearangement product melted at 183–184 °C. Additionally, the NMR spectra of these two compounds were clearly different (see Experimental Section).

The results of these studies led us to develop an alternate synthesis leading to the B isomeric system. The reaciton sequence started with 5,6-dimethoxyindole (**16**) which was converted to its *N-tert*-butoxycarbonyl derivative **21** (Scheme III). Treatment of the lithio derivative of **21** with iodomethane yielded exclusively the C-2 methyl product **22** which was converted to the unprotected indole **23** with sodium methoxide in methanol. Reaction of **23** with methylmagnesium bromide to generate the indole Grignard reagent followed by reaction with ethyl chloroformate provided a mixture of products. The ^{1}H NMR spectrum of this mixture in $CDCl_3$ displayed eight low-field aromatic signals at δ 7.77, 7.74, 7.62, 6.98, 6.88, 6.81, 6.18, and 6.10 and three methyl signals at δ 2.95, 2.55, , and 2.40 in addition to signals for the ethyl ester and methoxy groups. From the NMR spectra of compounds **23** and **24** we were able to assign these eight low-field signals as follows: indole **23** δ 6.98, 6.81, and 6.10; 1-(ethoxycarbonyl)-5,6-dimethoxy-2-methylindole (**24**), δ 7.77, 6.88, and 6.18; 1,3-bis(ethoxycarbonyl)-5,6,-dimethoxy-2-methylindole (**25**), δ 7.74 and 7.62. The signals corresponding to the methyl group protons at δ 2.40, 2.55, and 2.95 were assigned to compounds **23–25**, respectively. None of the desired monoadduct **11B** could be detected in this spectrum. Variations in reaction conditions did not improve this situation. However, more vigorous reaction conditions led to a mixture which upon slow cooling yielded crystalline **25**. The identical compound (NMR, melting point, mixture melting point) was isolated from **11C** by reaction of the corresponding indole Grignard reagent with ethyl chloroformate. Thus we are able to conclude that quinone methide **7** rearranges via a 1,2-migraiton of the ethoxycarbonyl moiety, presumably according to the reaction pathway b.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. The solvent was removed with a Büchi rotary evaporator. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian FT-80 instrument. Chemical shifts are reported in part per million relative to Me_4Si ($CDCl_3$ and Me_2SO-d_6) or DSS (D_2O) as the internal standard; s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. Infrared spectra were recorded on a Perkin-Elmer 337 grating IR spectrophotometer. Chemical ionization mass spectra (CIMS) were obtained on an AEI MS-9 instrument modified for chemical ionization. High-resolution electron ionization mass spectra (HRMS) were obtained on a modified AEI MS 902 from the Bio-organic, Biomedical Mass Spectrometry Resource, Space Sciences Laboratory, University of California, Berkeley. All ultraviolet spectra were taken on a Cary Model 118 instrument by using 1-cm quartz cells.

Ethyl 5,6-Dihydroxy-2-methylindole-3-carboxylate (8B). To a solution of quinone methide **7**[8] (50 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) was added thiophenol (0.19 g, 1.73 mmol). The reaction mixture was heated under reflux for 3 h. Evaporation of the solvent with heat under a high vacuum gave 22 mg (44%) of **8B**: mp 200 °C with decomposition; UV (EtOH)λ_{max} 233 nm (log ϵ 4.74), 283 (4.05), 290 (4.00); ^{1}H NMR (Me_2SO-d_6) δ 8.46 (br s, exchanges with D_2O, 1 H, NH or OH), 8.36 (br s, exchanges with D_2O, 1 H, NH or OH), 7.25 (s, 1 H, Ar H), 6.67 (s, 1 H, Ar H), 4.19 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 2.55 (s, 3 H, CH_3), 1.34 (t, 3 H, J = 7.1 Hz, CH_2CH_3); CIMS, m/e 236 (MH^+). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.28; H, 5.53; N, 5.96. Found: C, 61.12; H, 5.59; N, 5.88.

Compound **8B** also could be obtained as a sublimate by applying a high vacuum (0.1 μm) to a melt of quinone methide **7**.

Ethyl 5,6-Diacetoxy-2-methylindole-3-carboxylate (9B). To a solution of quinone methide **7** (50 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) was added acetic anhydride (1 mL, 9.8 mmol) and pyridine (2 drops). The reaction mixture was stirred overnight at room temperature. Evaporation of the solvent left a white solid which was purified by sublimation to give 30 mg (44%) of **9B**: mp 140–141 °C; UV (EtOH) λ_{max} 215 nm (ϵ 26 800), 250 (11 150), 285 (9470); ^{1}H NMR ($CDCl_3$) δ 8.61 (br s, exchanges with D_2O, 1 H, NH), 7.62 (s, 1 H, Ar H), 6.91 (s, 1 H, Ar H), 4.32 (q, 2 H, J = 7.2 Hz, CH_3CH_2), 2.44 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3CO), 2.33 (s, 3 H, CH_3CO), 1.40 (t, 3 H, J = 7.2 Hz, CH_3CH_2); exact mass (HRMS) calcd for $C_{16}H_{17}NO_6$ (M^+) 319.1056, found 319.1043.

Ethyl 5,6-Dihydroxy-2-methylbenzofuran-3-carboxylate (12). To a solution of ethyl 3-aminocrotonate[12] (1.75 mL, 13.6 mmol, distilled) in chloroform (15 mL) was added hydroxy-*p*-quinone (0.86 g, 6.9 mmol) portionwise. This mixture was heated under reflux for 3 h. The brownish solution was allowed to stand in the refrigerator which led to the separation of an off-white solid. The product was suction filtered and sublimed to give 0.6 g (37%) of **12** as a white crystalline solid: mp 160 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.70 (br s, exchanges with D_2O, 2 H, OH), 4.30 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 2.63 (s, 3 H, CH_3), 1.35 (t, J = 7.1 Hz, 3 H, CH_2CH_3); EIMS, m/e 236 (M^+), 207, 135, 77, 63, 29. Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.33; H, 5.38.

Ethyl 5,6-Dimethoxy-2-methylbenzofuran-3-carboxylate (13). To a solution of benzofuran **12** (23 mg, 0.1 mmol) in 1 mL

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(12) Willstäter, A. *Ber. Dtsch. Chem. Ges. B* **1911**, *44*, 2180.

of a mixture of ether/ethanol (4:1) was added an ethereal solution of diazomethane (5 mL, 0.3 mmol). After being allowed to stand in a refrigerator for 24 h, the reaction was quenched by the addition of 3 drops of acetic acid. Ether (5 mL) was added, and the organic layer was washed with saturated K_2CO_3 solution, dried (Na_2SO_4), and evaporated to give a white solid. Recrystallizaiton from hot ethanol provided 20 mg (78%) of **13**: mp 118–118.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.44 (s, 1 H, Ar H), 6.98 (s, 1 H, Ar H), 4.26 (q, 2 H, J = 7.2 Hz, CH_2CH_3), 3.94 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 1.41 (t, 3 H, J = 7.2 Hz, CH_2CH_3); exact mass (HRMS) calcd for $C_{14}H_{16}O_5$ (M^+) 264.0997, found 264.1001. Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.43; H, 6.17.

5,6-Dimethoxygramine (17). To an ice-cooled solution of dimethylamine (40%, 7.4 mL, 65 mmol) was added acetic acid (8 mL) and formaldehyde (37%, 4.8 mL, 65 mmol). Indole **16**[13] (10.76 g, 61 mmol) in methanol (200 mL) was added to the above mixture, and the resulting solution was heated under reflux for 3 h. The solvent was concentrated in vacuo to 20% of its volume and the resulting mixture treated with 70 mL of water. After being washed with chloroform, the aqueous mixture was chilled, made basic with 20% NaOH, and extracted with chloroform (3 × 100 mL). The chloroform layer was dried ($MgSO_4$) and evaporated to an oil. Benzene (2 mL) was added, and the mixture was allowed to crystallize in the cold. Filtration of the crystals afforded 5.82 g (40%) of **17**. Recrystallization from benzene–ethanol provided an analytical sample: mp 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 (br s, exchanges with D_2O, 1 H, NH), 7.11 (s, 1 H, Ar H), 6.98 (d, 1 H, Ar H), 6.83 (s, 1 H, Ar H), 3.90 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.58 (s, 2 H, CH_2), 2.28 (s, 6 H, CH_3). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.95. Found: C, 67.00; H, 7.79; N, 11.59.

5,6-Dimethoxy-3-methylindole (18). A mixture of **17** (3.0 g, 12.8 mmol), 10% Pd/C (0.24 g), and ethanol (100 mL) was shaken in a Parr hydrogenator under H_2 (20 psi) for 2 h at 50 °C. The mixture was filtered through Celite and evaporated to a solid residue. A chloroform solution of this residue was washed with 5% HCl, dried (Na_2SO_4), and evaporated to yield 2.0 g (82%) of **18**: mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1 H, Ar H), 6.83 (s, 2 H, Ar H), 3.93 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 2.28 (d, J = 1 Hz, 3 H, CH_3). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.07; H, 6.85; N, 7.36. Found: C, 68.95; H, 6.89; N, 7.28.

***N*-(*tert*-Butoxycarbonyl)-5,6-dimethoxy-3-methylindole (19).** To dry THF (30 mL) in a flame-dried, 300-mL, round-bottomed flask charged with N_2 were added NaH (2.8 g, 7.0 mmol, 61% in pentane, prewashed with distilled toluene) and tetrahydrofuran (THF). To this suspension was added with stirring and cooling a solution of indole **18** (5.6 g, 29 mmol) in 50 mL of THF. The mixture was stirred for 1 h at room temperature and then brought to a reflux for 1 h. After cooling in an ice bath, Boc-ON (8.61 g, 35 mmol) was added slowly, and the resulting mixture was stirred at room temperature for 3 h. The cooled mixture was treated with water and extracted with ether (3 × 50 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to yield a brownish oil. The oil was chromatographed on an alumina column (neutral) which was eluted with a mixture of dichloromethane/hexane (10:4.5) to provide a yellowish solid. The solid was recrystallized from ethanol to yield 5.2 g (61%) of **19**: mp 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1 H, Ar H), 7.21 (d, J = 1.2 Hz, 1 H, Ar H), 5.9 (s, 1 H, Ar H), 3.94 (s, 6 H, OCH_3), 2.22 (d, J = 1.2 Hz, 3 H, CH_3), 1.65 (s, 9 H, CH_3). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.94; H, 7.26; N, 4.83. Found: C, 65.92; H, 7.19; N, 4.63.

Ethyl 5,6-Dimethoxy-3-methylindole-2-carboxylate (11A). To a solution of **19** (0.2 g, 0.69 mmol) in 10 mL of dry THF at −78 °C under nitrogen was added dropwise *t*-BuLi (1.3 M, 2.1 mL, 2.75 mmol). After the mixture was stirred for 1 h, ethyl chloroformate (0.3 mL, 2.75 mmol) was added slowly. The mixture was stirred for 10 min at −78 °C and at room temperature for 1 h. The reaction was quenched with 2 mL of water and extracted with ether (2 × 30 mL), and the combined ether extracts were dried ($MgSO_4$) and evaporated to yield 0.15 g of a yellowish solid: ^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1 H, Ar H), 6.92 (s, 1 H, Ar H), 4.38 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 3.95 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 2.37 (s, 3 H, CH_3), 1.60 (s, 9 H, CH_3), 1.39 (t, 3 H, J = 7.1 Hz, CH_2CH_3). The spectrum was fully consistent with ethyl *N*-(*tert*-butoxycarbonyl)-5,6-dimethoxy-3-methylindole-2-carboxylate (**20**). This material was used directly in the next step.

To a solution of **20** (0.15 g, 0.31 mmol) in 2 mL of dichloromethane was added 2 mL of distilled TFA. After the mixture was stirred for 4 h at room temperature, the solvent was evaporated to give an off-white solid. Recrystallization from hot ethanol provided 0.08 g of **11A**: mp 166–168 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (br s, exchanges with D_2O, 1 H, NH), 6.98 (s, 1 H, Ar H), 6.79 (s, 1 H, Ar H), 4.38 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.94 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 2.56 (s, 3 H, CH_3), 1.41 (t, J = 7.1 Hz, 3 H, CH_2CH_3). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.23; H, 6.62; N, 5.25.

Ethyl 5,6-Dimethoxy-2-methylindole-3-carboxylate (11B). To a solution of indole **8B** (30 mg, 0.13 mmol) in 5 mL of a mixture of ether/ethanol (3:1) was added an ethereal solution of diazomethane (30 mL, 0.5 mmol). The resulting mixture was stored in the refrigerator for 1 day. The cold reaction mixture was treated with the dropwise addition of 3 mL of acetic acid. The ether layer was washed with saturated K_2CO_3 solution, dried ($MgSO_4$), and evaporated to provide a solid residue. This solid was dissolved in a small volume of dichloromethane and chromatographed on an alumina column (neutral). Elution with chloroform provided 15 mg (45%) of **11B**: mp 183–184 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (br s, exchanges with D_2O, 1 H, NH), 7.63 (s, 1 H, Ar H), 6.80 (s, 1 H, Ar H), 4.39 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.95 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 2.69 (s, 3 H, CH_3), 1.43 (t, 3 H, J = 7.2 Hz, CH_2CH_3). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.66; H, 6.47; N, 5.26.

***N*-(*tert*-Butoxycarbonyl)-5,6-dimethoxyindole (21).** Indole **16** (5.0 g, 28.2 mmol), sodium hydride (8 g, 203 mmol), and Boc-ON (12 g, 48.8 mmol) were allowed to react in the same way as described for the synthesis of **20**. The reaction mixture was chromatographed on an alumina column (neutral) and the product eluted with a mixture of dichloromethane/hexane (10:4.5) as a yellowish oil. Bulb-to-bulb distillation [oven temperature 150–160 °C (0.005 mmHg)] gave a colorless oil which solidified upon being allowed to stand at room temperature to provide 5.5 g (70%) of **21**: mp 69–70 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1 H, Ar H), 7.43 (d, J = 3.6 Hz, 1 H, Ar H), 6.96 (s, 1 H, Ar H), 6.41 (d, J = 3.6 Hz, 1 H, Ar H), 3.93 (s, 3 H, OCH_3) 3.87 (s, 3 H, OCH_3), 1.64 (s, 9 H, CH_3). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.90; N, 5.07. Found: C, 64.84; H, 6.85; N, 4.98.

***N*-(*tert*-Butoxycarbonyl)-5,6-dimethoxy-2-methylindole (22).** To a solution of **21** (5.5 g, 19.9 mmol) in 250 mL of dry THF at −78 °C was added dropwise a solution of *t*-BuLi (1.3 M, 46 mL, 60 mmol) in pentane. The yellowish reaction mixture was stirred for 1 h. Iodomethane (11.3 mL, 78 mmol, 98%) was added, and the resulting mixture was stirred for 1 h at 0 °C. The reaction was quenched by addition of 20 mL of water. After being stirred for 1 h at room temperature, the mixture was extracted with ether, and the ether layer was dried ($MgSO_4$) and evaporated to give a yellowish oil. The oil was chromatographed on a neutral alumina column which was eluted with a mixture of dichloromethane/hexane (10:4.5) to give 4.8 g (83%) of **22**: ^{1}NMR ($CDCl_3$) δ 7.68 (s, 1 H, Ar H), 6.80 (s, 1 H, Ar H), 6.10 (s, 1 H, Ar H), 3.85 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 2.46 (s, 3 H, CH_3), 1.59 (s, 9 H, CH_3); exact mass (EIMS) calcd for $C_{16}H_{21}NO_4$ (M^+) 291.1470, found 291.1470.

5,6-Dimethoxy-2-methylindole (23). Dry THF (10 mL) was added to **22** (2.8 g, 9.6 mmol) to make a concentration of 0.96 M **22**. To this was added sodium methoxide (1.6 g, 29.6 mmol) in methanol (4.5 mL), and the mixture was stirred for 45 min at room temperature. To this mixture were added 5 mL of ether and 5 mL of water. The organic layer was separated, washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to an oily residue. The oil was chromatographed on an alumina column neutral with hexane/dichloromethane (1:1) containing increasing amounts of chloroform. Crystallization from ethanol of the solid material isolated from the column afforded 1.4 g (76%) of **23**: mp 86–87 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (br s, exchanges with D_2O, 1 H, NH), 6.98 (s, 1 H, Ar H), 6.81 (s, 1 H, Ar H), 6.10 (d, J = 0.6 Hz, 1 H, Ar H), 3.89 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 2.40 (d, J = 0.7 Hz, 3 H, CH_3). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.07; H, 6.85; N, 7.36. Found: C, 69.06; H, 6.79; N, 7.34.

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1,3-Bis(ethoxycarbonyl)-5,6-dimethoxy-2-methylindole (25). (a) From 5,6-dimethoxy-2-methylindole (23). To a 3 M solution of methylmagnesium bromide (0.5 mL, 1.5 mmol) in 20 mL of dry THF was added indole **23** (200 mg, 1.04 mmol) in 2 mL of dry THF. The mixture was warmed on a hot water bath for 0.5 h. The solution was cooled with an ice bath, and ethyl chloroformate (0.3 mL, 2.8 mmol) was added. The reaction mixture was heated to reflux for 5 h and after cooling was treated with 1 mL of water, dried ($MgSO_4$), and evaporated to yield an oily material. ^1H NMR revealed a 50:40:10 ratio of diester **25** to starting material (**23**) to monoester product **24**. When this material was allowed to stand at room temperature, crystals formed. These were suction filtered and washed with a cold ethanol/hexane mixture to give 81 mg (23%) of **25** as a white solid: mp 140-141 °C; ^1H NMR ($CDCl_3$) δ 7.74 (s, 1 H, Ar H), 7.62 (s, 1 H, Ar H), 4.43 (m, 4 H, CH_2CH_3) 3.95 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 2.95 (s, 3 H, CH_3), 1.50 (m, 6 H, CH_2CH_3). Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.49; H, 6.33; N, 4.08.

(b) From Ethyl 5,6-Dimethoxy-2-methylindole-3-carboxylate (11B). Indole **11B** (13 mg, 0.05 mmol), 3 M methylmagnesium bromide (0.03 mL, 0.09 mmol), and ethyl chloroformate (0.02 mL, 0.18 mmol) were allowed to react in the same way as described for the preparation of **25** from **23**. The product was crystallized from ethanol to yield 12 mg (73%) of **25**: mp 140-141 °C; ^1H NMR spectrum was identical with the product obtained from **23**.

Acknowledgment. This research was supported by Public Health Service Research Grant MH21219.

Registry No. **2**, 6014-30-8; **7**, 75014-12-9; **8B**, 83634-09-7; **9B**, 83634-10-0; **11A**, 16381-44-5; **11B**, 24608-62-6; **12**, 83634-11-1; **13**, 83634-12-2; **14**, 93-17-4; **15**, 17354-04-0; **16**, 14430-23-0; **17**, 5446-82-2; **18**, 73396-98-2; **19**, 83634-13-3; **20**, 83634-17-7; **21**, 83634-14-4; **22**, 83634-15-5; **23**, 57330-45-7; **24**, 83634-18-8; **25**, 83634-16-6; thiophenol, 108-98-5; ethyl 3-aminocrotonate, 7318-00-5; hydroxy-*p*-quinone, 2474-72-8.

Preparation and Properties of *endo,endo*-7,8-Diphenylbicyclo[4.1.1]octa-2,4-diene

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Received May 7, 1982

endo,endo-7,8-Diphenylbicyclo[4.1.1]octa-2,4-diene (**10**) has been prepared in ten steps from ϵ-truxillic acid. If the pendant phenyl substituents in this hydrocarbon could adopt conformations where they become approximately coplanar with the diene segment, the possibility for substantive electronic delocalization through the cyclobutane relay orbitals exists. Three-dimensional X-ray crystal structure analysis of **10** reveals that while the unsaturated four-carbon bridge is essentially planar, one of the aryl rings is twisted 20° out of plane because proximity factors prohibit parallel stacking. Additionally, photoelectron spectroscopic analysis of **10** and several model compounds (**17**, **18**, and **23**) shed no light on the question of through-bond interaction because of high-level interference arising from electron promotion out of the benzene rings. Nonetheless, the chemical reactivity of **10** is very high, it being very prone to thermolysis and photolysis. Interestingly, the reactions which occur under these conditions find no parallel with the behavior of lesser substituted prototype structures.

The effects of inserting one or more carbon atoms of tetrahedral geometry between the p orbital networks of classical π systems have received considerable study. In homoaromatic cations,[2,3] the resulting gap does not prohibit charge delocalization. However, decreased overlap integrals lead to substantive dropoffs in interaction, the levels of which are apparently inadequate to support homoconjugation in neutral[4] and anionic analogues.[5] When two π systems are linked together in mutually perpendicular planes, spiroconjugation can result.[6] However, such through-space electronic delocalization manifests itself only when the interacting π components have degenerate or nearly degenerate basis orbital energies. This condition stipulates that spiroconjugation should be most important in those molecules which possess identical pairs of perpendicular, planar π segments. The available experimental results are in full agreement.[6a,d,7]

In the last few years, an awareness has developed that four-membered rings are capable of strong interaction with pendant vinyl groups. By means of photoelectron spec-

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