5-Epibenzylpenicillin (*S*)- and (*R*)-Sulfoxide Benzyl Ester. 5-Epibenzylpenicillin benzyl ester[1] (1.272 g, 3 mmol) was oxidized with *m*-chloroperbenzoic acid as described for I. Owing to the instability of these sulfoxides when chromatographed on silica gel, they could not be isolated in a crystalline state, but they were obtained as a slightly impure oil, which was identified only by ^{1}H NMR spectroscopy.

(*S*)-Sulfoxide: TLC R_f 0.20; NMR ($CDCl_3$) δ 1.18 (s, CH_3), 1.39 (s, CH_3), 3.46 (s, $-CH_2CO-$), 4.03 (s, 3-H), 4.54 (d, J = 2 Hz, 5-H), 4.88 (dd, J = 2 and 7 Hz, 6-H), 5.13 (s, $-OCH_2-$), 7.19 (s, C_6H_5), 7.28 (s, C_6H_5), 7.40 (d, J = 7 Hz, CONH–).

(*R*)-Sulfoxide: TLC R_f 0.15; NMR ($CDCl_3$) δ 1.27 (s, CH_3), 1.34 (s, CH_3), 3.55 (s, $-CH_2CO-$), 3.89 (s, 3-H), 5.00 (dd, J = 2 and 7 Hz, 6-H), 5.11 (s, $-OCH_2-$), 5.20 (d, J = 2 Hz, 5-H), 7.26 (s, C_6H_5), 7.31 (s, C_6H_5), 7.41 (d, J = 7 Hz, –CONH–).

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Registry No.—I, 59034-27-4; II, 59751-74-5; III, 59751-75-6; *m*-chloroperbenzoic acid, 937-14-4; 5-epibenzylpenicillin benzyl ester 59034-28-5; 5-epibenzylpenicillin benzyl ester (*S*)-sulfoxide, 59751-76-7; 5-epibenzylpenicillin benzyl ester (*R*)-sulfoxide, 59751-77-8.

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Derivatives of 3,4-Dihydroxyphenylalanine for Peptide Synthesis

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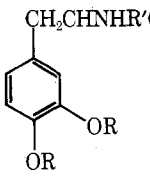
The current therapeutic use of levodopa (L-3,4-dihydroxyphenylalanine, Dopa, **1**) in Parkinsonism[1] prompted us to consider a possible improved utilization of this amino acid when in peptide or other derivatized form. Moreover, when suitably incorporated as an analogue of tyrosine or phenylalanine into peptides, Dopa could furnish peptide hormone analogues of biological interest. This communication describes the synthesis of a number of protected derivatives of Dopa designed for use in solid-phase or conventional peptide synthesis: the *p*-nitrophenyl ester of *N-tert*-butyloxycarbonyl-*O,O'*-diacetyl-3,4-dihydroxyphenylalanine [Boc-Dopa-$(Ac)_2$-ONP, **2**] and, in particular, the corresponding ester of *N-tert*-butyloxycarbonyl-*O,O'*-dibenzyl-3,4-dihydroxyphenylalanine [Boc-Dopa$(Bzl)_2$-ONP, **3**]. The chief difficulty in working with Dopa is its well-known ease of oxidation,[2] probably to the quinone, and other products, and this formed the basis for protection of the phenolic groups.



	R	R'	R"
1	H	H	OH
2	$OCCH_3$	$COOC(CH_3)_3$	$OC_6H_4NO_2$
3	$CH_2C_6H_5$	$COOC(CH_3)_3$	$OC_6H_4NO_2$
4	H	H	$OCH_3 \cdot HCl$
5	H	$COOC(CH_3)_3$	OCH_3
6	H	$COOC(CH_3)_3$	OH
7	$OCCH_3$	$COOC(CH_3)_3$	OH
8	$CH_2C_6H_5$	$COOC(CH_3)_3$	OH

Prepared as intermediates for **2** and **3** were Dopa methyl ester hydrochloride (Dopa-OCH_3·HCl, **4**), *N-tert* butyloxycarbonyl-3,4-dihydroxyphenylalanine methyl ester (Boc-Dopa-OCH_3, **5**), *N-tert*-butyloxycarbonyl-3,4-dihydroxyphenylalanine (Boc-Dopa, **6**), and its diacetyl and dibenzyl derivatives, Boc-Dopa$(Ac)_2$ (**7**) and Boc-Dopa$(Bzl)_2$ (**8**). The diacetyl compounds belong to the DL series; all other compounds were of both the L and DL series.

At the inception of this work there were few known studies relating to the incorporation of Dopa into peptides. They involved the use of phthalyl and methyl ester to protect Dopa in N- and C-terminal position, respectively, without protection of the phenolic groups, as in the synthesis of a number of dipeptides of DL-Dopa.[3] After this work was essentially complete, a route to di- and tripeptides of L-Dopa was described in which Z-Dopa$(Z)_2$, Z-Dopa$(Z)_2$-ONP, and Dopa$(Z)_2$-OBzl served as the chief intermediates.[4] The nonselective removal of protecting groups by hydrogenolysis that was employed in general limits the utility of that route to the synthesis of small peptides for Dopa in endo position. Moreover, such intermediates are not designed for Merrifield solid-phase peptide synthesis, the *N*-benzyloxycarbonyl group being too stable for deprotection with the TFA reagent and the *O*-benzyloxycarbonyl group probably too labile to various hydrolytic conditions including exposure to triethylamine. The present work extends the synthetic scope of past studies by providing for stepwise introduction of L- and DL-Dopa in suitably protected form and for selective removal of the phenolic and amino protecting groups of Dopa, namely through utilization of derivatives **3** and **8**. In addition, it demonstrates that the ordinarily labile Dopa may be subjected safely to a variety of procedures frequently employed in conjunction with peptide synthesis including treatment with sodium in liquid ammonia. Addition of a small amount of hydrazine proved particularly effective in protecting against oxidation under alkaline conditions. The utility of derivative **3** in solid-phase synthesis has recently been demonstrated in the synthesis of a protected 2-Dopa-4-threonine nonapeptide analogue of oxytocin, Z-L-Cys(Bzl)-L-Dopa$(Bzl)_2$-L-Ile-L-Thr(Bzl)-L-Asn-L-Cys(Bzl)-L-Pro-L-Leu-Glyn.[5] The synthesis of the latter and the biological properties of [2-Dopa 4-Thr] oxytocin derived from it are to be communicated elsewhere.

Boc-L-Dopa (**6**) had been prepared previously by Kaiser et al.[6] by derivatization of Dopa with Boc azide in aqueous alkali under argon. In our hands this procedure generally gave dark, insoluble material unless most stringent anaerobiosis was attained. Moreover, the published elemental analyses for **6**, both calculated and obtained, were erroneous, especially the value for carbon which is high by 1.3%. These properties led us to examine an alternate route to **6** involving derivatization

of Dopa methyl ester in nonaqueous medium to give Boc-Dopa-OCH_3 followed by deesterification.

Dopa was esterified by the general procedure of Brenner and Huber.[7] L- and DL-Dopa-OCH_3·HCl agreed in melting point with these compounds prepared by the Fischer procedure.[8,9] A similar procedure was recently employed for the DL compound.[10] Treatment with Boc azide in pyridine converted the free base obtained from **4** to Boc-Dopa-OCH_3 (**5**). On standing in aqueous methanol containing 5.6 equiv of base and a trace of hydrazine, **5** was deesterified almost quantitatively. The resulting Boc-L-Dopa (**6**) agreed in optical rotation and melting point with a sample prepared by the procedure of Kaiser et al.[6] Moreover, discrepant values for carbon we attribute to solvation were obtained also for our preparations of L- and DL-**6** unless they were subjected to unusually prolonged, exhaustive drying.

When treated with 3 equiv of acetic anhydride in $NaHCO_3$ solution at room temperature **6** formed an *O,O'*-diacetyl derivative [Boc-Dopa$(Ac)_2$, **7**]. Refluxing with 2 equiv of benzyl chloride and K_2CO_3 in the presence of NaI, essentially as described for the preparation of 3,4-dibenzyloxybutyrophenone from the catechol compound,[11] converted **6** to *N*-Boc-*O,O'*-dibenzyl-L-Dopa (**8**). **7** and **8** were converted smoothly to their respective *p*-nitrophenyl esters by treatment with *N,N'*-dicyclohexylcarbodiimide and *p*-nitrophenol in the usual way. A reaction time of at least 24 h proved advantageous for **8**. Treatment of **8** with sodium in liquid ammonia[12] followed by TFA afforded Dopa in 93% yield as determined on the amino acid analyzer.[13] Optical rotation of the isolated material agreed well with that of starting L-Dopa. In addition, application of the Manning–Moore procedure[14] as employed by Felix et al.[4] confirmed that the route to **8** is free of significant racemization. Intermediates **3** and **8** are therefore expected to be compatible with routes to peptides of L-Dopa and cysteine to be introduced via *S*-benzylcysteine.

Experimental Section

Organic extracts were dried over $MgSO_4$. Evaporations were under reduced pressure. Boc azide was purchased from Aldrich Chemical Co., Milwaukee, Wis.; DL-Dopa from Schwarz/Mann, Orangeburg, N.Y. L- and D-Dopa were obtained by resolution of DL-Dopa as described.[15]

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were taken in a 2-dm cell in a Rudolph spectropolarimeter system, Model 80Q6-34402. Amino acid analyses were performed on a Beckman/Spinco amino acid analyzer, Model 120.[13] Dopa eluted at 70 ml on the 50-cm column, pH 4.26, at 30 °C; ninhydrin color constant 19.1 compared to 22.1 for leucine. Optical purity of L-Dopa was determined essentially as described by Felix et al.[4] except that analyses were in the 50-cm resin column of the analyzer[13] with sodium citrate buffer (pH 4.25, 0.2 M) at 50 °C. Elution volumes were 34 ml (Ala), 71 ml (Dopa), 154 ml (L-Ala-D-Dopa), and 183 ml (L-Ala-L-Dopa).

L- and DL-Dopa-OCH_3·HCl (4). Dopa (10 g, 50 mmol) was added portionwise to MeOH (120 ml) containing $SOCl_2$ (20 ml) held at 0 °C. The mixture was stirred at room temperature for 18 h, then evaporated to give DL-**4** (12.2 g, 98%), mp 182–183 °C (lit.[8] mp 180–181, 179–180 °C[10]); L-**4**, 87%, mp 172–174 °C (lit.[9] mp 170–171 °C).

Boc-L- and -DL-Dopa-OCH_3 (5). A solution of Dopa-OCH_3 (7.6 g, 36 mmol), obtained from **4** as described,[8] and Boc azide (7.6 g, 50 mmol) in pyridine (70 ml) was stirred for 2 days. The solvent was evaporated and the residue was taken up in EtOAc (100 ml). Some tar was filtered off. Dilution with hexane followed by recrystallization from MeOH–H_2O gave DL-**5** (8.6 g, 76%): mp 186–188 °C; ^1H NMR (MeOD) δ 1.36 [9 H, s, $C(CH_3)_3$], 2.84 (2 H, m, β-CH_2), 3.66 (3 H, s, OCH_3), 4.23 (1 H, m, α-CH), 6.6 (3 H, m, C_6H_3).

Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.9, H, 6.80, N, 4.50. Found: C, 57.8, H, 6.95, N, 4.52.

L-**5**: 71% yield, mp 133–135 °C, $[\alpha]^{26}D$ 7.6° (*c* 1.2, MeOH).

Anal. Found: C, 57.8; H, 6.55; N, 4.46.

Boc-L- and -DL-Dopa (6). A solution of **5** (3.4 g, 10 mmol) in MeOH (30 ml) containing 2 N NaOH (28 ml, 56 mmol) and 2 drops of N_2H_4·H_2O was allowed to stand at room temperature for 4 h. The mixture was taken to dryness, diluted with H_2O, and extracted with EtOAc. The aqueous solution was adjusted to pH 2 and extracted with EtOAc. The extract was dried and concentrated to give after recrystallization from EtOAc–benzene DL-**6** (3.2 g, 98%), mp 140–142 °C. For analysis DL-**6** like L-**6** was dried at 0.2 Torr at 100 °C for 5 days.

Anal. Calcd for $C_{14}H_{19}NO_6$; C, 56.6, H, 6.44, N, 4.71. Found: C, 56.4; H, 6.45; N, 4.83.

^1H NMR (MeOD), as for L-**6**. When a sample was dried instead at 0.2 Torr at 25 °C for 24 h, an additional ^1H NMR signal at 7.3 ppm was present attributed to occluded benzene. Anal. C, 58.1; H, 6.78; N, 4.62.

L-6, recrystallized from EtOAc–cyclohexane: 92% yield; mp 142–144 °C (very rate dependent); $[\alpha]D$ +16.2° (*c* 1, MeOH) [lit.[6] mp 148 °C, $[\alpha]^{25}D$ +16.4° (*c* 1, MeOH)]. A mixture melting point with a sample of L-**6**, mp 142–144 °C, prepared as described,[6] showed no depression: ^1H NMR (MeOD) δ 1.39 [9 H, s, $C(CH_3)_3$], 2.91 (2 H, m, β-CH_2), 4.27 (1 H, m, α-CH), 4.92 (4 H, s, exchangeable H), 6.67 (3 H, m, C_6H_3).

Anal. Found: C, 56.4; H, 6.42; N, 4.89.

Boc-DL-Dopa$(Ac)_2$ (7). Acetic anhydride (6 ml, 60 mmol) was added to a solution of **6** (6 g, 20 mmol) in aqueous $NaHCO_3$ (16 g, 20 mmol) and the mixture was stirred under N_2 for 30 min at room temperature. It was extracted with ether and then was cooled and adjusted to pH 2. The gum that separated was extracted with EtOAc, and the extract was dried and concentrated. The residue was recrystallized from benzene–hexane to give **7** (6.4 g, 83%): mp 132–134 °C; ^1H NMR (Me_2SO-d_6) δ 1.3 [9 H, s, $C(CH_3)_3$], 2.24 (6 H, s, CH_3CO), 3.0 (2 H, m, β-CH_2), 4.15 (1 H, m, α-CH), 7.25 (3, m, aromatic).

Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.7; H, 6.08; N, 3.67. Found: C, 57.1; H, 6.04; N, 3.66.

Boc-Dopa$(Ac)_2$-ONP (2). A solution of **7** (3.8 g, 10 mmol) and *p*-nitrophenol (1.7 g, 12 mmol) in EtOAc (60 ml) was treated with DCCI (2.4 g, 12 mmol) for 2 h. The mixture was filtered and the solution was concentrated to give after recrystallization from benzene–hexane **2** (4.4 g, 88%), mp 109–112 °C.

Anal. Calcd for $C_{24}H_{26}N_2O_{10}$: C, 57.4; H, 5.22; N, 5.58. Found: C, 57.3; H, 5.20; N, 5.62.

Boc-Dopa$(Bzl)_2$ (8) and Its Deprotection. A solution of **6** (3.6 g, 13 mmol) and benzyl chloride (3.36 g, 26.4 mmol) in EtOH (60 ml) was refluxed with K_2CO_3 (3.69 g, 28.2 mmol) and NaI (156 mg, 1.1 mmol) for 3 h. Most of the solvent was evaporated and the residue was diluted with H_2O. The suspension at 0 °C was adjusted to pH 2. Extraction with EtOAc, drying, and concentration yielded a residue that was recrystallized from benzene–hexane to give DL-**8** (4 g, 69%), mp 140–142 °C.

Anal. Calcd for $C_{28}H_{31}NO_6$: C, 70.4; H, 6.54; N, 2.93. Found: C, 70.3; H, 6.62; N, 3.01.

L-**8** (65%): mp 105–107 °C, $[\alpha]^{25}D$ +14.2° (*c* 1, MeOH).

Anal. Found: C, 70.1; H, 6.65; N, 2.96.

A solution of L-**8** (23.5 mg, 49.4 μmol) in 4 ml of liquid NH_3 was treated with sodium until a blue color throughout the solution lasting 40 s was obtained. NH_4Cl (20 mg) was added and the solution was evaporated in a stream of N_2. To the residue TFA (1 ml) was added. After 30 min at 25 °C under N_2 the mixture was taken to dryness. The residue was dissolved in water and it contained Dopa (45.8 μmol, 93%) on amino acid analysis. Treatment with 1 equiv of L-alanine *N*-carboxyanhydride[16] followed by amino acid analysis showed 0.09% L-Ala-D-Dopa.

The aqueous solution from treatment of 120 mg of L-**8** was adjusted to pH 5 with dilute NH_3 and it was then concentrated to incipient crystallization to give L-**1** (32 mg, 64%). One recrystallization from water (1 ml) gave 23 mg, $[\alpha]^{22}D$ −32.9° (*c* 0.5, H_2O). Starting L-**1** had $[\alpha]^{22}D$ −32.9° (*c* 0.4, H_2O).

Boc-L- and -DL-Dopa$(Bzl)_2$-ONP (3). Compound **8** (4 g, 10.6 mmol) was treated with *p*-nitrophenol (2.06 g, 148 mmol) and DCCI (2.62 g, 12.7 mmol) in EtOAc (105 ml) as described for **2**. Workup and crystallization from benzene–hexane furnished DL-**3** (1.9 g, 36%): mp 132–134 °C; ^1H NMR (Me_2SO-d_6) δ 1.37 [9 H, s, $C(CH_3)_3$], 3.03 (2 H, m, β-CH_2), 4.4 (1 H, m, α-CH), 5.13 (4 H, s, OCH_2Ar), 6.75–7.73 (15 H, m, aromatic), 8.36 (2 H, d, aromatic ortho to NO_2).

Anal. Calcd for $C_{34}H_{34}N_2O_8$: C, 68.2; H, 5.72; N, 4.78. Found: C, 68.7; H, 5.77; N, 4.92.

A longer reaction time of 24 h gave L-**3** (56%), mp 142–144 °C, $[\alpha]^{25}D$ −0.97° (*c* 1, EtOAc).

Anal. Found: C, 68.0; H, 5.79; N, 4.63.

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Registry No.—L-1, 59-92-7; DL-1, 63-84-3; DL-2, 59686-53-2; L-3, 59727-96-7; DL-3, 59727-97-8; L-4, 1421-65-4; DL-4, 40611-00-5; L-5, 37169-36-1; DL-5, 59686-54-3; L-6, 30033-24-0; DL-6, 59686-55-4; DL-7, 59686-56-5; L-8, 59727-98-9; DL-8, 59727-99-0; Boc azide, 1070-19-5; acetic anhyride, 108-24-7; *p*-nitrophenol, 100-02-7; benzyl chloride, 100-44-7.

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Stabilization of Substituted Cyclobutadienes

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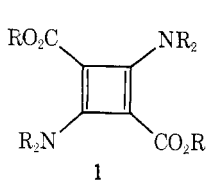
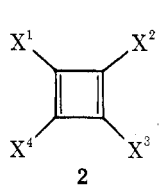
In the past several years there has been a renewed interest in the chemistry of cyclobutadiene and its derivatives.[1] Cyclobutadiene itself has been observed at low temperature;[2] but as was correctly predicted by theory,[3] is too reactive to be isolated at room temperature. A number of derivatives have been prepared which are isolable, though they generally have been found to be reactive. The stability of these derivatives has been ascribed either to the presence of bulky substituents which retard intermolecular reactions[4] or to the "push–pull" effect[5] when there are both electron-donating and electron-withdrawing groups attached to the cyclobutadiene ring.[6]

However, in the latter cases, there is a possibility that steric effects might be at least partially responsible for the increased stabilization. For example in **1**[6] the four substituents are not only of the "push–pull" type but also are relatively large groups in themselves. In order to determine to what degree the "push–pull" effect is responsible for the stabilization of substituted cyclobutadienes and also to search for other possible stable cyclobutadienes, we have carried out calculations with our successful adaptation of the Hückel method[3b,c,7] on the series **2**. The crucial feature of this modification is that



1



2

resonance energy is computed as the difference between the actual molecular energy and the energy the molecule would have, had it acted like a polyene. Following Dewar and de Llano,[8] the energy of the reference polyene is computed as the sum of bond energy terms. Results are summarized in Table I where it is seen that all compounds in which "push–pull" stabilization is possible (**2b–o**) show a decrease in antiaromaticity, thus giving support to the "push–pull" proposal. Furthermore, in all cases when electron-donating groups are placed between electron-withdrawing groups, a more stable compound is produced than when they are placed on adjacent carbons. This is in qualitative agreement with earlier calculations of Hoffmann,[9] but not with those of Weiss and Murrell,[10] who found that the position of donor and acceptor groups on the ring has little effect on stability.

Table I. Resonance Energies (RE) and Resonance Energies per π Electron (REPE) in Units of β for Substituted Cyclobutadienes

Compd	X^1	X^2	X^3	X^4	RE	REPE	REPE Aihara's method
2a	H	H	H	H	−1.07	−0.268	−0.307
2b	NH_2	NH_2	CHO	CHO	−0.65	−0.054	−0.057
2c	NH_2	CHO	NH_2	CHO	−0.33	−0.028	−0.037
2d	NH_2	NH_2	COOR	COOR	−0.64	−0.040	−0.043
2e	NH_2	COOR	NH_2	COOR	−0.32	−0.020	−0.028
2f	NH_2	NH_2	$CONH_2$	$CONH_2$	−0.66	−0.041	−0.046
2g	NH_2	$CONH_2$	NH_2	$CONH_2$	−0.32	−0.020	−0.030
2h	SH	SH	COOR	COOR	−0.64	−0.040	−0.045
2i	SH	COOR	SH	COOR	−0.36	−0.023	−0.030
2j	F[a]	F	CHO	CHO	−0.39	−0.033	−0.036
2k	F	CHO	F	CHO	−0.03	−0.002	−0.021
2l	F	F	COOR	COOR	−0.39	−0.024	−0.028
2m	F	COOR	F	COOR	−0.02	−0.001	−0.016
2n	F	F	$CONH_2$	$CONH_2$	−0.42	−0.026	−0.031
2o	F	$CONH_2$	F	$CONH_2$	−0.02	−0.001	−0.018
2p	F	F	NH_2	NH_2	−1.22	−0.101	−0.077
2q	F	NH_2	F	NH_2	−0.93	−0.078	−0.056
3a		H	H	H	−0.64	−0.160	−0.193
3b		NH_2	H	H	−0.40	−0.067	−0.093
3c		H	NH_2	H	−0.76	−0.127	−0.145
3d		NH_2	H	NH_2	−0.26	−0.032	−0.054
3e		NH_2	NH_2	NH_2	−0.46	−0.046	−0.049
3f		F	H	H	−0.18	−0.029	−0.069
3g		H	F	H	−0.69	−0.115	−0.130
3h		F	H	F	+0.05	+0.006	−0.033

[a] For the fluoro-substituted compounds $h_F = 1.5$ and $k_{C-F} = 1.33$ were used. These were obtained using thermochemical data in the same manner as previously.[7] The carbon–fluorine bond energy terms used in the calculation of the reference energies are $E_{CH-F} = 0.74021\beta$ and $E_{C-F} = 0.66491\beta$.

It is of particular interest that the most stable of the "push–pull" cyclobutadienes synthesized to date[2b,2d] is a tetramethyl derivative of **2e**, one of the most aromatic compounds in Table I. The methyl groups will enhance the stability still further, both because of their bulk and their electron-donating ability. Our main conclusion about compounds such as **1** is that the "push–pull" effect does play a major role in stabilizing the cyclobutadiene system.

We also predict that the replacement of the amino group by fluorine should give cyclobutadienes even more stable than those already synthesized: the resonance energies per π electron of compounds **2k, 2m,** and **2o** are very close to zero. That is, the very substantial antiaromaticity of cyclobutadiene has been completely removed in these systems. These results are in accord with the known electron-donating ability of fluorine bonded to an electron-demanding site. The pronounced stabilizing effect of fluorine in carbene formation is an example of this.[11] Nevertheless, the stability of **2k, 2m,** and **2o** may not be due to the "push–pull" effect alone, and hence we cannot say that fluorine is necessarily a better electron donor than the amine group.

In addition, we have computed the resonance energies of