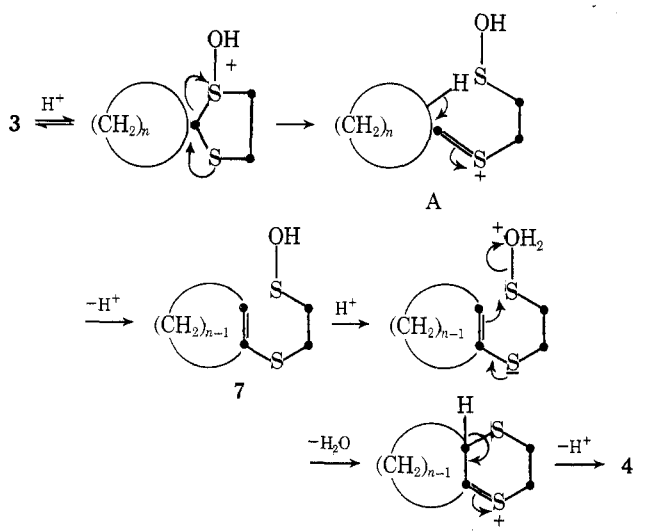
flux, 5 days), considerable tar formation prevailed and no **6** was detected. Isolation of the eight-membered monosulfoxide **3** ($n$ = 7) has also been unsuccessful owing to its lability at room temperature such that even in the absence of acid catalyst, ring transformation occurred slowly giving usually a mixture of products including **4** ($n$ = 7) as shown by mass spectrometric analysis[5] ($m/e$ 200 $M^+$ for $C_{10}H_{16}S_2$) for the crude sulfoxide **3** ($n$ = 7) ($m/e$ 218 $M^+$ for $C_{10}H_{18}OS_2$).

A possible mechanism for this interesting ring expansion reaction of spiro-1,3-dithiolane 1-oxides **3** *under acid-catalyzed condition* is shown in Scheme I. Heterolytic cleavage

**Scheme I**



of the C(2)–S bond following initial protonation of the sulfoxide moiety would generate a sulfur stabilized carbonium ion A, which on loss of proton followed by acid-catalyzed ring closure of the sulfenic acid **7** affords the annelated 5,6-dihydro-1,4-dithiins **4** as shown. Similar intermediates of structure A have been proposed in the acid hydrolysis of 2,2-diphenyl-1,3-dithiolane 1-oxide,[6] and oxidative cleavage of 1,3-dithian[7,8] and dithiolane[9] derivatives in the synthesis of ketones.

## Experimental Section[5]

The following experiments are illustrative of the general synthetic procedures.

**2,2-Undecamethylene-1,3-dithiolane (2, $n$ = 11).** A mixture of 46.5 g of cyclododecanone, 24.1 g of 1,2-ethanedithiol, and 0.75 g of PTSA·$H_2O$ in 200 ml of benzene was subjected to azeotropic distillation until the theoretical amount of water (4.6 ml) was collected. The benzene solution was concentrated in vacuo to give a solid, crude **2** ($n$ = 11), which was suitable for use in subsequent reactions.

**2,2-Undecamethylene-1,3-dithiolane 1-Oxide (3, $n$ = 11).** To an ice-cooled solution of 15 g of crude **2** in 100 ml of methylene chloride, a solution of 11.2 g of MCPBA (ca. 90% active) in 200 ml of methylene chloride was added dropwise over a 2-h period. The reaction mixture was quenched by addition of aqueous sodium carbonate and extracted twice with methylene chloride. The latter was dried ($MgSO_4$) and concentrated in vacuo to give a white solid which was recrystallized from hexanes to give 14 g (88%) of essentially pure **3** ($n$ = 11). An analytical sample (mp 107.2 °C) was obtained by further recrystallization (Table I).

**2,3-Decamethylene-5,6-dihydro-1,4-dithiin (4, $n$ = 11).** A mixture of 2 g of **3** ($n$ = 11) and 0.2 g of PTSA·$H_2O$ in 50 ml of benzene was subjected to azeotropic distillation via a Dean-Stark receiver for 18 h. The darkened benzene solution was taken up in ether and washed with sodium bicarbonate. The organic layer was separated, dried ($MgSO_4$), and concentrated to give a brown oil which was purified by short path distillation, affording 1.76 g (96%) of pure **4** ($n$ = 11) (Table II): mass spectrum $m/e$ 246 ($M^+$); NMR $\delta$ 1.0–2.0 (m, 16, carbocyclic ring protons), 2.2 (t, 4, allylic), and 3.0 ppm (s, 4, $-SCH_2CH_2S-$).

**Registry No.**—**2** ($n$ = 3), 380-90-5; **2** ($n$ = 4), 176-39-6; **2** ($n$ = 5), 177-16-2; **2** ($n$ = 6), 184-32-7; **2** ($n$ = 11), 16775-67-0; **2** ($n$ = 14), 59796-98-4.

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(5) Melting points, which were determined on a Mettler FP-1 apparatus, were uncorrected. NMR spectra were recorded in $CDCl_3$ on a Varian T-60 NMR spectrophotometer using $Me_4Si$ as internal standard and mass spectra were obtained on an AEI MS-30 mass spectrometer. Microanalyses were performed by Analytical Sciences Division, Research Laboratories, Eastman Kodak Co. Satisfactory analytical data (±0/4% for C, H, S) were reported for all compounds listed in the tables.
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# Preparation and Stereochemical Analysis of 5-Epibenzylpenicillin (*S*)- and (*R*)-Sulfoxide Esters


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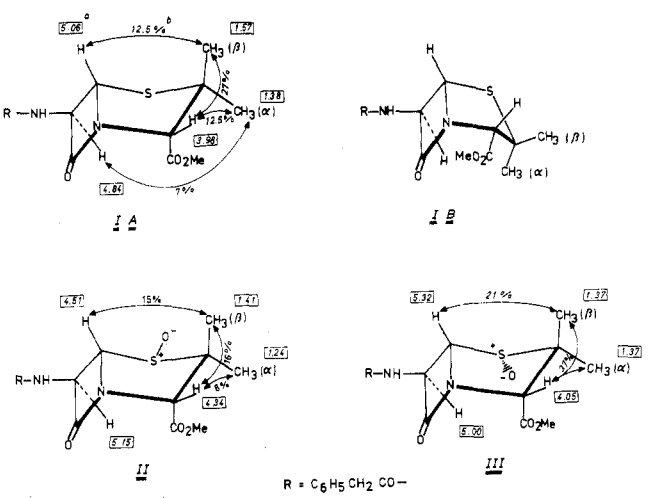
Oxidation of the 5 epimer of benzylpenicillin methyl ester[1] (I) with *m*-chloroperbenzoic acid yielded the (*S*)- and (*R*)-sulfoxide II and III in a ratio of 2:1. The isomers were isolated by column chromatography and crystallized from dry benzene. Apparently, steric control is the major directing influence in the oxidation of the 5 epimer, since neither sulfoxide configuration is likely to be stabilized by an internal hydrogen bond with the side chain amide proton,[2] as the two interacting atoms are manifestly too distant. It should be noted that natural or 6-epiphenoxymethyl- and benzylpenicillin esters yielded only the (*S*)-sulfoxide using this reagent.[2,3]

Thiazolidine ring conformation and sulfoxide configuration



[a] Chemical shifts in parts per million downfield from $Me_4Si$, for 5-H, 6-H, 3-H, 2 α-Me, and 2 β-Me, measured in dimethyl sulfoxide-$d_6$. [b] NOE values determined in dimethyl sulfoxide-$d_6$.

were defined using NMR techniques. Evidence for conformation A in the sulfide as well as in the sulfoxides was based on nuclear Overhauser effects, determined in dimethyl sulfoxide-$d_6$, a method which has been used on several occasions in studies of the penicillin series.[2-4] In 5-epibenzylpenicillin methyl ester a positive effect was observed between the low-field methyl signal and 3-H (27%) and 5-H (12.5%), whereas irradiation of the high-field methyl peak gave only 12.5% intensity increase of 3-H, a small increase of 6-H (5–10%), and no augmentation of the intensity of the 5-H signal. The (*S*)-sulfoxide (II) gave a positive effect between the low-field methyl signal and 3-H (16%) and 5-H (15%), and between the high-field methyl signal and 3-H (5–10%). In the (*R*)-sulfoxide (III) the chemical shift values of the two methyl groups are almost identical, excluding a selective irradiation. The NOE's observed for 3-H (37%) and for 5-H (21%) upon irradiation of this complex signal are thus composite values, and reflect the influence of both methyl groups, at least for 3-H. It should be noted that in neither sulfoxide a positive effect was observed between 6-H and one of the methyl groups.

From these NOE experiments, it may be concluded that the low-field methyl signal corresponds to the 2$\beta$-methyl protons, and that this group is in spatial proximity of 3-H and 5-H, a requirement inherent in conformation A, but not in B. They also indicate that the conformation of the thiazolidine ring of both sulfoxides is almost identical with that of the sulfide I. It has been shown for several penicillins and their 6 epimers that the conformation of the sulfoxide was different from that of the parent sulfide.[2,4,5]

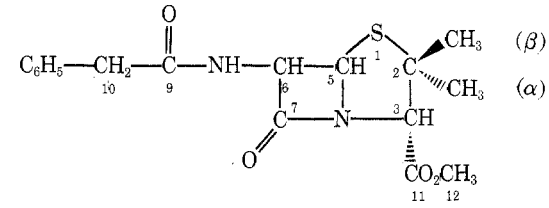
Assignments for sulfoxide configuration were made using $^{13}C$ NMR spectroscopy (Table I). In the 5-episulfide (I), as in penicillin methyl ester,[6] 2$\alpha$-Me absorbs at higher field than 2$\beta$-Me, and this can be explained on the basis of the steric proximity of 2$\alpha$-Me to the cis substituent at C-3 ($COOCH_3$).[7] Similarly, in the process sulfide → sulfoxide, it has been pointed out[6] that the upfield shifts observed for $\gamma$-situated carbons C-6, C-3, 2$\alpha$-Me, and 2$\beta$-Me were best explained if a sizable steric effect was attributed to the S=O bond, causing thus larger upfield shifts for carbons in closer proximity to the sulfoxide oxygen.

In the process 5-episulfide → 5-episulfoxide-(*S*), 2$\beta$-Me is expected to undergo a larger upfield shift than 2$\alpha$-Me, and the two Me carbons must from this fact display more similar $\delta$ values in this sulfoxide configuration than in the sulfide and in the (*R*)-sulfoxide. The *S* configuration has thus been assigned to the isomer II, having 2$\beta$-Me absorption at $\delta$ 18.25 ppm (upfield shift −11.8) and 2$\alpha$-Me absorption at $\delta$ 18.9 ppm (upfield shift −5.8). In the other sulfoxide (III), the two Me carbons absorb at $\delta$ 23.25 (2$\beta$-Me, upfield shift −6.8) and 17.85 ppm (2$\alpha$-Me, upfield shift −6.85). The 6.8 ppm upfield shift of 2$\beta$-Me carbon is difficult to rationalize on the basis of steric interaction with the sulfoxide oxygen, since the atoms are in a 1,2-trans diaxial arrangement. But from the strong NOE (21%), observed between 5-H and 2$\beta$-Me protons, it can be inferred that the 5-episulfoxide-(*R*) must be somewhat more puckered than the corresponding 5-episulfide, causing 1,3-diaxial interaction between 5-H and 2$\beta$-Me. Carbon C-6 in the azetidinone ring is also very sensitive to sulfoxide configuration, and the larger upfield shift (−8.45 ppm) measured in the (*R*)-sulfoxide (III), compared to the (*S*)-sulfoxide (II) (−4.6 ppm), is consistent with the pseudoaxial position of the exocyclic oxygen in the (*R*)-sulfoxide.

The downfield shifts observed for $\beta$-situated carbons C-2 and C-5 upon oxidation of the thiazolidine sulfur are in accord with previous observations.[6] They had been attributed to a reduction in electron density at these carbon nuclei as a result of the inductive effect of the sulfoxide group.

Oxidation of 5-epibenzylpenicillin benzyl ester with *m*-chloroperbenzoic acid also gave the two sulfoxides in a ratio of 2:1. However, the isomers were not obtained in a pure state, and were characterized only with $^1H$ NMR spectroscopy by comparison with the values of the corresponding methyl esters.

Table I. $^{13}C$ Chemical Shift Assignments[a] for 5-Epibenzylpenicillin Methyl Ester and Its Sulfoxides




| | I | II | III |
|---|---|---|---|
| $C_2$ | 64.9 | 70.2 | 73.3 |
| $C_3$ | 69.3 | 65.55 | 67.4 |
| $C_5$ | 67.05 | 80.4 | 77.6 |
| $C_6$ | 63.4 | 58.8 | 54.95 |
| 2$\beta$-$CH_3$ | 30.05[b] | 18.25[b] | 23.25 |
| 2$\alpha$-$CH_3$ | 24.7[b] | 18.9[b] | 17.85 |
| $C_{12}$ | 52.1 | 52.8 | 52.2 |
| $C_{10}$ | 41.9 | 41.8 | 41.9 |
| $C_7$ | 168.8 | 168.3 | 166.7 |
| $C_9$ | 167.2 | 168.05 | 166 |
| $C_{11}$ | 171 | 171.5 | 171.55 |

[a] 20% solution in dimethyl sulfoxide-$d_6$; chemical shifts in parts per million downfield from $Me_4Si$. [b] Assigned by selective decoupling of the corresponding protons.

## Experimental Section

Melting points were determined in open capillaries with a Büchi-Tottoli apparatus. TLC was performed on silica gel F-254 plates (Merck) with benzene–acetone (80:20) as mobile phase. The optical rotation was measured in a Thorn-NPL photoelectric polarimeter type 243. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer, and mass spectra on an AEI MS-12 apparatus. $^1H$ NMR, NOE, and $^{13}C$ NMR spectra were recorded on a Varian XL 100-15 spectrometer equipped for CW ($^1H$) and FT ($^{13}C$) operation. NOE experiments were carried out with 10% solutions flushed out with nitrogen. For $^{13}C$ spectra the central peak of the solvent ($Me_2SO$-$d_6$) was used as internal reference, and was assumed to absorb at $\delta$ 39.6 ppm vs. $Me_4Si$.[8] The concentration was 20% w/v. Initially the $^{13}C$ spectra were recorded with complete proton (noise) decoupling. Assignments of the various $^{13}C$ resonances to methyl, methylene, methine, and quaternary carbons were made by single frequency off-resonance decoupling.

**5-Epibenzylpenicillin (*S*)- and (*R*)-Sulfoxide Methyl Ester (II and III).** 5-Epibenzylpenicillin methyl ester[1] (I, 2.0 g, 5.7 mmol) was dissolved in 50 ml of anhydrous methylene chloride. The solution was chilled to 0 °C, and a solution of *m*-chloroperbenzoic acid (80%, 1.23 g, 5.7 mmol) in anhydrous methylene chloride (30 ml) was added over a period of 30 min. The mixture was stirred for 1 h at 0 °C, extracted with $KHCO_3$ (0.5 M), washed twice with water, dried ($Na_2SO_4$), and chromatographed on silica gel (50 g) using a gradient of benzene–acetone changing from 93:7 to 85:15 as eluent. From the first fractions, 0.2 g (10%) of starting product I (TLC, $R_f$ 0.52) was recovered, and from the rest of the eluate, two compounds with $R_f$ value 0.12 and 0.07 were successively isolated and identified as (*S*)- and (*R*)-sulfoxide of 5-epibenzylpenicillin methyl ester (II and III). After crystallization from dry benzene, the yield of the isomers amounted to 0.770 g (37%) for II and to 0.400 g (19%) for III.

II: mp 158.5–159.5 °C; TLC $R_f$ 0.12; $[\alpha]^{25}D$ −126.5° (*c* 1, acetone); *m/e* 364 ($M^+$); ir (KBr) 3340, 1685, 1520 (amide), 1795 ($\beta$-lactam), 1740, 1215 (ester), 1035 $cm^{-1}$ (S=O); NMR ($CDCl_3$) $\delta$ 1.36 (s, $CH_3$), 1.53 (s, $CH_3$), 3.63 (s, $CH_2$), 3.82 (s, $OCH_3$), 4.11 (s, 3-H), 4.62 (d, $J$ = 2 Hz, 5-H), 4.98 (dd, $J$ = 2 and 7.5 Hz, 6-H), 6.45 (d, $J$ = 7.5 Hz, CONH–), 7.28 (s, $C_6H_5$).

III: mp 160–161 °C; TLC $R_f$ 0.07; $[\alpha]^{25}D$ −130° (*c* 0.2, acetone); *m/e* 364 ($M^+$); ir (KBr) 3260, 1650, 1560 (amide), 1790 ($\beta$-lactam), 1755, 1200 (ester), 1050 $cm^{-1}$ (S=O); NMR ($CDCl_3$/$Me_2SO$-$d_6$) $\delta$ 1.38 (s, 6 protons, two $CH_3$), 3.50 (s, $CH_2$), 3.68 (s, $OCH_3$), 3.93 (s, 3-H), 5.00 (dd, $J$ = 2 and 8 Hz, 6-H), 5.23 (d, $J$ = 2 Hz, 5-H), 7.22 (s, $C_6H_5$), 8.78 (d, $J$ = 8 Hz, CONH–).

**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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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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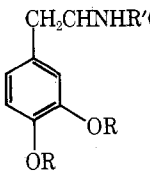
The current therapeutic use of levodopa (L-3,4-dihydroxyphenylalanine, Dopa, **1**) in Parkinsonism[1] prompted us to consider a possible improved utilization of this amino acid when in peptide or other derivatized form. Moreover, when suitably incorporated as an analogue of tyrosine or phenylalanine 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