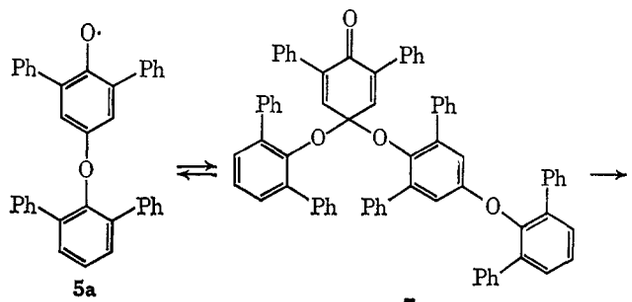

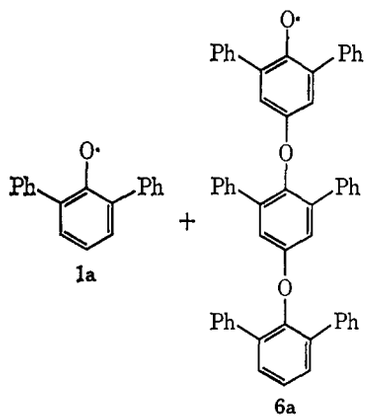

This reaction clearly demonstrates that a hindered phenoxy radical can and does react at the *para* position of another phenoxy radical. The relative ease of the redistribution of **5a** is at some variance with what might be predicted by an examination of molecular models. However, an examination of a model of the quinone ketal **7** shows that one of the pendant phenoxy rings is nearly coplanar with the cyclohexadienone ring and consequently is less hindered than the planar written form of **7** would appear.

Experimental Section

2,6-Diphenylphenol (**1**).—This material was prepared as described by Plešek.[7]

2,6-Diphenylanisole (**2**).—To a stirred solution of sodium methoxide (0.75 mol) and 2,6-diphenylphenol (88.6 g, 0.56 mol) in methanol (240 ml) under nitrogen was added slowly dimethyl sulfate (76 ml). The reaction was stirred 6 hr and the methanol was distilled. The residue was treated with water, the organics were taken up in pentane, and any phenolic material was extracted with Claisen alkali.[8] The pentane was evaporated and the residue was distilled yielding a colorless oil (bp 175–177° (2.2 mm), mp 40–41°, n^{20}D 1.6329, 63% yield).

Anal. Calcd for $C_{19}H_{16}O$: C, 88.2; H, 6.2; mol wt, 260. Found: C, 88.0; H, 6.4; mol wt, 256.

4-Bromo-2,6-diphenylanisole (**3**).—2,6-Diphenylanisole (54 g, 0.02 mol) was brominated (32 g, 0.02 mol) in glacial acetic acid (200 ml). After 4 hr at room temperature, the reaction was refluxed for 2 hr and then poured into sodium bisulfite solution (300 ml, 1%). The brown oil which formed slowly crystallized and was recrystallized from 80% ethanol giving 58.5 g (85%) of white crystals, mp 98–99°.

Anal. Calcd for $C_{19}H_{15}OBr$: C, 67.3; H, 4.4; mol wt, 339. Found: C, 67.3; H, 4.9; mol wt, 334.

4-(2,6-Diphenylphenoxy)-2,6-diphenylanisol (**4**).—Potassium *t*-butoxide (11.2 g, 0.1 mol) and dimethylformamide (DMF) (20 ml) were combined under nitrogen and a mixture of 2,6-diphenylphenol (24.6 g, 0.1 mol) in hexamethylphosphortriamide (18 g) was added. This mixture was heated until all of the *t*-butyl alcohol distilled out. The reaction was cooled and 4-bromo-2,6-diphenylanisole (33.9 g, 0.1 mol), DMF (30 ml), and cuprous bromide (2.0 g) were added. The mixture was stirred and heated to reflux while 3 ml of DMF was distilled to remove any traces of *t*-butyl alcohol. The reaction was cooled after 18 hr and a mixture of methanol (600 ml) and concentrated HCl (25 ml) was added. The reaction was filtered and the organic material was extracted with benzene. Residual 2,6-diphenylphenol was removed with Claisen alkali[8] from the benzene which was then dried and distilled. There were three fractions obtained after the benzene: 2,6-diphenylanisole,[9] 4-bromo-2,6-diphenylanisole, and 4-(2,6-diphenylphenoxy)-2,6-diphenylphenol bp 237–260°/(3 mm). This material was recrystallized from 4:1 hexane–toluene giving white crystals, 11 g, 22%, mp 149–150°.

Anal. Calcd for $C_{37}H_{28}O_2$: C, 88.1; H, 5.6; mol wt, 504. Found: C, 87.8; H, 5.4; mol wt, 470.

4-(2,6-Diphenylphenoxy)-2,6-diphenylphenol (**5**).—Anisole **4** (8.2 g, 0.016 mol) was heated to reflux under nitrogen with pyridine hydrochloride (5.5 g, 0.048 mol) for 18 hr. The residue was poured into water (150 ml). The tan solids were recrystallized from hexane–toluene giving white plates, mp 162–164°, 4.0 g, 50%. A thin layer chromatography showed that the dimer was contaminated with unreacted starting material which was separated by elution chromatography on alumina with hexane–benzene: mp 175–177°.

Anal. Calcd for $C_{36}H_{26}O_2$: C, 88.2; H, 5.3; mol wt, 490. Found: C, 87.8; H, 5.5; mol wt, 470.

Redistribution.—4-(2,6-Diphenylphenoxy)-2,6-diphenylphenol (**5**, 10 mg) in benzene (1 ml) under nitrogen at 25° was treated with the tri-*t*-butylphenoxy radical[10] (10 μl of 0.1 *M* solution). The blue color of the radical was discharged immediately and after a few minutes the orange-red color of the diphenoquinone appeared.[3] The sample was treated with bis(trimethylsilyl)acetamide and the silylated phenols were examined by tlc and vpc. A complete redistribution sequence was observed which corresponded to seeing oligomers up to 11 monomer units long. This sequence was identical with the one obtained from the reaction of 2,6-diphenylphenol, poly(2,6-diphenylphenylene oxide) and an oxidizing agent.[5]

A vpc analysis of the silylated mixture showed three components as their silyl ethers: 2,6-diphenylphenol, 4-(2,6-diphenylphenoxy)-2,6-diphenylphenol, and the trimer **6**. The monomer and dimer were shown to be identical with the known materials by retention times and by infrared spectra.

Polymerization.—Dimer **5** (0.5 g) was stirred in toluene (30 ml) with lead dioxide (5 g) for 24 hr. The colorless solution was filtered. The polymer was isolated by precipitation into methanol: yield 0.42 g, 84%. Intrinsic viscosity in $CHCl_3$, 0.97.

A sample of 2,6-diphenylphenol treated in an identical manner gave a red solution which yielded 0.35 g (70%) of polymer which had an intrinsic viscosity of 0.48.

Registry No.—**2**, 20104-40-9; **3**, 20104-39-6; **4**, 20104-41-0; **5**, 20104-42-1.

(7) J. Plešek, *Chem. Listy*, **50**, 252 (1956), reprinted in *Coll. Czech. Chem. Commun.*, **21**, 375 (1956).

(8) See L. F. Fieser "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 191.

(9) The 2,6-diphenylanisole results from debromination of the bromo compound. In spite of the fact that both the bromoanisole and the phenol are present in the reaction at this point, further addition of cuprous bromide only results in debromination and not in production of more dimer.

(10) C. D. Cook and R. C. Woodworth, *J. Amer. Chem. Soc.*, **75**, 6242 (1953).

Transesterification with an Anion-Exchange Resin

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Although the modification of esters of edible oils by alcoholysis using anion exchange resins is used commercially,[1] synthetic applications of such base-catalyzed transesterifications are rare.[2]

(1) A. T. Gros and R. O. Feuge, *J. Amer. Oil Chem. Soc.*, **26**, 97, 704 (1949).

(2) C. J. Schmidle and R. C. Mansfield, *Ind. Eng. Chem.*, **44**, 2868 (1952); M. J. Astle and J. E. Zaslowsky, *ibid.*, **44**, 2868 (1952).

TABLE I
PHYSICAL CONSTANTS OF METHYL ESTERS

Compound	Registry no.	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CBz-Gly-GlyOMe	13437-63-3	55–57	$C_{13}H_{16}N_2O_5$	55.71	5.75	10.00	55.62	5.73	10.00
D-Ala-OMe·HCl	14316-64-4	95–96	$C_4H_{10}NO_2Cl$	34.43	7.17	10.04	33.82	6.92	9.87
t-BOC-L-Val-D-AlaOMe	15136-15-9	88–90	$C_{14}H_{26}N_2O_5$	55.61	8.67	9.27	55.37	8.58	9.56
t-BOC-L-Pro-L-LeuOMe	15136-16-0	80–81	$C_{17}H_{30}N_2O_5$	59.62	8.83	8.18	59.51	8.96	8.31

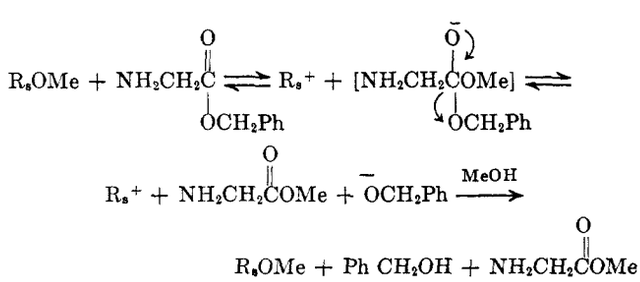
TABLE II

Compound	Registry no.	Mp or bp (mm), °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
N-Acetyl-DL-Ala-OEt	5143-72-6	72 (0.1)	$C_7H_{13}NO_3$	52.81	8.23	8.8	52.80	8.22	8.69
CBz-L-Leu-L-Ala-OEt	19817-68-6	66–67	$C_{19}H_{28}N_2O_5$	62.62	7.74	7.69	62.45	7.65	7.79
CBz-Gly-Gly-L-Ala-OEt	5673-76-7	71–73	$C_{17}H_{23}N_3O_6$	55.88	6.35	11.50	56.42	6.18	11.50
N-Benzoyl-DL-Phe-OEt	19817-70-0	83–85	$C_{18}H_{19}NO_3$	72.70	6.44	4.71	72.69	6.34	4.78
CBz-L-Met-L-Try-OEt	19842-38-7	102–104	$C_{26}H_{31}N_3O_5S$	62.77	6.23	8.45	62.91	6.34	8.51

We now report that amino acid and peptide alkyl ester derivatives as well as fatty acid esters are readily transesterified by treatment with a *strong* anion exchange resin in methanol or ethanol at room temperature. Under the experimental conditions used, the carbobenzoxy, the *t*-butyloxycarbonyl, and the O-, S-, and the imidazole-benzyl protecting groups commonly used in peptide synthesis remain intact but the ω-carboxyl functions of aspartic and glutamic residues are also transesterified. By using sterically pure L-amino acid and LL dipeptide derivatives, it was shown by gas chromatographic analysis of the products[3,4] that the reaction proceeds without detectable racemization (<1% D). Attempts to prepare higher alkyl or benzyl esters from amino acid and fatty acid methyl esters were less successful than the synthesis of ethyl esters. The formation of significant quantities of benzyl esters required refluxing in benzyl alcohol for several hours and chromatographically pure esters could be isolated only in low yields (<50%).

The presence of the resin is essential for the transesterification reaction to proceed. The absence of reactivity of methanolic solutions from which the resin, after contact for several hours, had been removed indicated that transesterification was due to the continuous replenishment of methoxide ions by the resin in the solvent. On the basis of these findings the transesterification reaction may be rationalized as in Scheme I, where R_s^+ is the resin cation. In peptide synthesis where the stability and the selective removal of protecting groups is an important consideration, it may be practically useful to remove a benzyl ester function by transesterification with retention of steric purity.

SCHEME I



(3) B. Halpern and J. W. Westley, *Biochem. Biophys. Res. Commun.*, **19**, 361 (1965).

(4) J. W. Westley and B. Halpern in "Gas Chromatography 1968," A. B. Littlewood, Ed., Institute of Petroleum, London, 1968.

Experimental Section[5]

Preparation of Anion Exchange Resin.—BIO-RAD AG I-X8 resin (50 g, (50–100 mesh, chloride form) was converted into the hydroxide form by washing with 500 ml of 1 *N* NaOH, and the excess free hydroxyl ions were removed by washing the resin with deionized water until the pH of the effluent was lower than 8. The resin was dehydrated by continuous washing with anhydrous methanol or ethanol (<0.01% H_2O). The resin suspensions were stored in the refrigerator, and under these conditions kept their activity for 1–2 weeks.

Preparation of Methyl Esters from Benzyl Esters.—Methyl esters were prepared in 80–95% yield by stirring 400–600 mg of the amino acid benzyl ester derivative with 1–2 g of anion exchange resin and 10–15 ml of methanol, at room temperature, for 30–80 min. The progress of the reaction was followed by tlc (isopropyl ether:chloroform:acetic acid 6:3:1) or glpc (5 ft × $^1/_8$ in. column of 5% trifluoropropyl methyl silicone fluid (QF-I) on Aeropack 30). The solutions were filtered, and the solvent was evaporated to yield the corresponding methyl ester. The D-AlaOMe was characterized as the hydrochloride (Table I).

Preparation of Ethyl Esters from Methyl Esters.—Several ethyl esters were prepared in 80–90% yield from methyl esters by a similar transesterification procedure using a resin which had been dehydrated with ethanol. The reactions were carried out in anhydrous ethanol (Table II).

Preparation of Methyl Esters from Ethyl Esters.—Methyl esters were prepared in 80–90% yield from ethyl esters using resins which had been dehydrated with methanol and anhydrous methanol was used as the solvent. The L-Ala-OMe and L-Leu-OMe were characterized as the hydrochlorides (Table III).

Preparation of Benzyl Esters from Methyl Esters.—Benzyl esters were prepared in <50% yield from methyl esters using resin which had been dehydrated with benzyl alcohol. Benzyl alcohol was used as solvent. The reactions were carried out at 80–90° for 24 hr. The DL-Val-OBz was characterized as the *p*-toluenesulfonate (Table IV).

Steric Analysis of Amino Acid and Peptide Derivatives.—The amino acid alkyl esters (Table I and III) were treated with TFA-L-prolyl chloride as described previously.[3] Glpc analysis of the diastereoisomers confirmed the steric homogeneity of the products (<1% of the undesirable dipeptide). Direct glpc of *t*-BOC-L-Pro-L-Leu OMe[4] also showed less than 1% of the LD dipeptide in the isolated product.

Alcoholysis of Amino Acid Esters Containing S, O, and $N^{(im)}$

(5) All melting points and boiling points are uncorrected. Glpc analyses were carried out on a Varian 600D gas chromatograph using a 5 ft × $^1/_8$ in. (5% QFI on Aeropack 30) column with a nitrogen flow of 30 ml/min. All compounds were characterized by mass spectrometry using a Finnigan 1015 quadrupole mass spectrometer.

TABLE III

PHYSICAL CONSTANTS OF METHYL ESTERS

Compound	Registry no.	Mp or bp (mm), °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
L-Ala-OMe HCl	2491-20-5	98–100	$C_4H_{10}NO_2Cl$	34.43	7.17	10.04	34.24	6.90	9.97
L-Leu-OMe HCl	7517-19-3	145–147	$C_7H_{16}NO_2Cl$	46.30	8.82	7.71	46.26	8.86	7.66
Methyl caprate	110-42-9	90–92 (4)	$C_{11}H_{22}O_2$	70.92	11.90		70.72	11.63	
Methyl stearate	112-61-8	40–41	$C_{19}H_{38}O_2$	76.45	12.83		76.72	12.79	

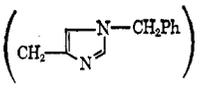
TABLE IV

PHYSICAL CONSTANTS OF BENZYL ESTERS

Compound	Registry no.	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Benzyl stearate	5531-65-7	44–45	$C_{25}H_{42}O_2$	80.15	11.30		80.39	11.44	
DL-Val-OBz *p*-toluene sulfonate	17664-92-5	134–138	$C_{19}H_{25}NO_5S$	60.02	6.59	3.77	60.15	6.64	3.76

TABLE V

CHARACTERISTIC PEAKS IN MASS SPECTRA OF TRANSESTERIFICATION PRODUCTS

Compound	Registry no.	*m/e*	Fragment
S-Bz-L-Cys-OEt (mol wt, 239)	953-18-4	239	M^+
		166	$M^+ - (COOEt)$
		102	$M^+ - (PhCH_2 - SCH_2)$
O-Bz-L-Tyr-OEt (mol wt, 299)	19842-36-5	299	M^+
		226	$M^+ - (COOEt)$
$N^{(im)}$Bz-L-HiS-OMe (mol wt, 259)	19817-75-5	200	$M^+ - COOCH_3$
		171	
t-BOC-L-Asp-β-OMe-Leu-OMe (mol wt, 374)	19817-76-6	374	M^+
		317	$M^+ - (CH_3)_3C$
		315	$M^+ - COOCH_3$
t-BOC-L-Asp-β-OMe-L-Ala-OMe (mol wt, 332)	19817-77-7	332	M^+
		301	$M^+ - OCH_3$
t-BOC-L-Thr-ε-CBz-L-Lys-OMe (mol wt, 495)	19842-37-6	394	$M^+ - (CH_3)_3COC(=O)$
		287	$M^+ - [CBz + (CH_3)_3CO]$

Benzyl, Carbobenzoxy, *t*-Butyloxycarbonyl, and Aspartic Acid β-Benzyl Ester Derivatives.—S-Bz-L-Cys-OMe, O-Bz-L-Tyr-OMe, $N^{(im)}$-Bz-L-His-OMe, *t*-BOC-L-Asp-OBz-L-Leu-OBz, *t*-BOC-L-Asp-L-Ala-OBz, and *t*-BOC-L-Thr-εCbz-L-Lys-OBz were transesterified with ethanol or methanol, respectively. The chromatographically pure product (tlc, isopropyl ether:chloroform:acetic acid 6:3:1) were examined by mass spectrometry. The results (Table V) indicated that only the β-benzyl ester function of aspartic acid had been transesterified under these conditions.

Acknowledgments.—This investigation was supported by National Aeronautics and Space Administration Grant NGR-05-020-004.