TABLE III

L-AMINO ACID 4-(METHYLTHIO)PHENYL ESTER (MTP) HYDROBROMIDES

Compd	Registry no.	Yield, %	Mp, °C	Molecular formula	Analyses, % Calcd C	Calcd H	Calcd Br	Found C	Found H	Found Br	[α]D
H-Ala	22142-39-8	87	159	$C_{10}H_{14}BrNO_2S$	41.1	4.8	27.3	41.1	4.7	27.2	[α]$^{29.0}$D +4.4° (c 2.98, MeOH)
H-Gly	22142-40-1	100	250	$C_9H_{12}BrNO_2S$	38.9	4.3	28.7	39.05	4.3	28.7	
H-Ile	22142-41-2	71	191	$C_{13}H_{20}BrNO_2S$	46.7	6.0	23.9	46.8	5.9	24.15	[α]$^{29.0}$D +29.9° (c 1.32, MeOH
H-Leu	22142-42-3	43	147	$C_{13}H_{20}BrNO_2S$	46.7	6.0	23.9	46.9	6.2	24.0	[α]$^{28.8}$D +17.3° (c 0.375, MeOH
H-Lys ε-TFA	22142-43-4	44	151	$C_{15}H_{20}BrF_3N_2O_3S$	40.5	4.5	17.9	41.2	4.8	16.8	[α]$^{28.8}$D +23.3° (c 2.38, MeOH)
H-Phe	22155-47-1	82	226	$C_{16}H_{18}BrNO_2S$	52.2	4.9	21.7	52.1	4.8	21.7	[α]$^{28.8}$D +34.7° (c 1.90, MeOH)
H-Pro	22142-44-5	81	135	$C_{12}H_{16}BrNO_2S$	45.3	5.1	25.1	45.2	4.95	25.3	[α]$^{28.8}$D −21.9° (c 1.30, MeOH)
H-Sar	22142-45-6	80	203	$C_{10}H_{14}BrNO_2S$	41.1	4.8	27.3	41.2	4.9	27.6	
H-Val	17662-76-9	69	216.5	$C_{12}H_{18}BrNO_2S$	45.0	5.7	25.0	44.95	5.7	25.2	[α]$^{29.0}$D +17.3° (c 2.40, MeOH)

bromide, a side reaction which has been observed for N-carbobenzoxymethionine.[8] This tends to indicate that this side reaction with the MTP ester occurs at a very slow rate or not at all.

From this work a new general activating procedure has been developed for the MTP esters of N-protected amino acids which has been found to extend the utility of the MTP ester for peptide synthesis to most of the sensitive amino acids and protecting groups. However, it is anticipated that this method of activation will be of little use for peptides which include the amino acid residues of methionine, cysteine, and cystine.

Experimental Section[9]

General Procedure for the Preparation of N-Carbobenzoxy-L-amino Acid 4-(Methylthio)phenyl Esters.—The general procedure is illustrated in the preparation of **N-carbobenzoxy-L-tryptophan 4-(methylthio)phenyl ester.** To an ice-cooled solution of N-carbobenzoxy-L-tryptophan (3.7 g, 12 mmol) in methylene chloride (25 ml) was added N,N'-dicyclohexylcarbodiimide (2.5 g, 12 mmol), followed by the addition of 4-(methylthio)phenol (1.5 g, 12 mmol). The reaction mixture was stirred at 0° for *ca.* 1 hr, then warmed to room temperature and stirred overnight. The solution was diluted with 25 ml of methylene chloride and the insoluble urea was filtered off and washed with 50-ml portions of methylene chloride. The filtrate and washes were combined, and the solvent was removed under reduced pressure. The oily brown residue was dissolved in ethyl acetate (250 ml) and washed with 10% citric acid solution (100 ml), 10% sodium bicarbonate solution (100 ml), and saturated sodium chloride solution (100 ml) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The thin, brown oil (6.6 g) was dissolved in chloroform (20 ml) and chromatographed on a SilicAR cc-7 column, using chloroform as the eluent. The crude oils were recrystallized from ethyl acetate–hexane to yield white, solid N-carbobenzoxy-L-tryptophan 4-(methylthio)phenyl ester (3.1 g, 56.4%), mp 108–111°. Further recrystallization from ethyl acetate–hexane gave a white solid: mp 111°; [α]^{27}D +9.3° (*c* 2.635, chloroform).

Anal. Calcd for N-carbobenzoxy-L-tryptophan 4-(methylthio)phenyl ester: C, 67.8; H, 5.3; S, 7.0. Found: C, 67.5; H, 5.5; S, 6.8.

General Procedure for the Preparation of N-Carbobenzoxy-L-amino Acid 4-(Methylsulfonyl)phenyl Esters.—The oxidation of the N-carbobenzoxy-L-amino acid 4-(methylthio)phenyl esters to their sulfone analogs was carried out as illustrated in the preparation of **N-carbobenzoxy-L-valine 4-(methylsulfonyl)-phenyl ester.** To a solution of N-carbobenzoxy-L-valine 4-(methylthio)phenyl ester (1.8 g, 5 mmol) in dioxane (25 ml) was added *m*-chloroperbenzoic acid (2.6 g, 15 mmol). The reaction mixture was stirred at room temperature for *ca.* 4 hr. The solution was then poured into a solution of sodium bicarbonate (2.1 g, 25 mmol) in water (75 ml). The resulting white suspension was extracted once with ethyl acetate (250 ml); the aqueous phase was saturated with sodium chloride and extracted again with two 150-ml portions of ethyl acetate. The combined extracts were washed with two 150-ml portions of saturated sodium chloride solution and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting solid (2.6 g) was dissolved in chloroform (15 ml) and chromatographed on a SilicAR cc-7 column, using chloroform as the eluent. The first eight fractions were recrystallized from ethyl acetate–hexane to yield white, solid N-carbobenzoxy-L-valine 4-(methylsulfonyl)-phenyl ester (1.2 g, 60%), mp 99–101°. Recrystallization from ethyl acetate–hexane a second time gave a white solid: mp 100–101°; ν_{max} 1310 and 1145 cm^{-1} (sulfone); [α]$^{27.3}$D +9.0° (*c* 2.2, chloroform).

Anal. Calcd for N-carbobenzoxy-L-valine 4-(methylsulfonyl)-phenyl ester: C, 59.2; H, 5.7; S, 7.9. Found: C, 59.2; H, 5.5; S, 7.75.

General Procedure for the Preparation of L-Amino Acid 4-(Methylthio)phenyl Ester Hydrobromides.—The general procedure for the removal of the carbobenzoxy protecting group to yield the hydrobromide salts of L-amino acid 4-(methylthio)-phenyl esters is illustrated in the preparation of **L-phenylalanine 4-(methylthio)phenyl ester hydrobromide.** To a slurry of N-carbobenzoxy-L-phenylalanine 4-(methylthio)phenyl ester (2.1 g, 5 mmol) in glacial acetic acid (10 ml) was added a solution (20 ml) of anhydrous hydrogen bromide (2.7 g, 33 mmol) in a glacial acetic acid. The resulting yellow solution was stirred at room temperature for *ca.* 35 min. The solvent and excess hydrogen bromide were then removed under reduced pressure. The residual cream-colored solid was slurried with anhydrous ethyl ether, filtered, and recrystallized from anhydrous methanol–anhydrous ethyl ether to yield white, needle-like crystals of L-phenylalanine 4-(methylthio)phenyl ester hydrobromide (1.4 g, 82%), mp 220–225°. Further recrystallization gave a white solid: mp 226°; [α]$^{28.8}$D +34.7° (*c* 1.9, methanol).

Anal. Calcd for L-phenylalanine 4-(methylthio)phenyl ester hydrobromide: C, 52.2; H, 4.9; Br, 21.7. Found: C, 52.1; H, 4.8; Br, 21.7.

Acknowledgment.—The authors are indebted to the National Science Foundation, which supported this investigation, and also to the Crown Zellerbach Corp. for samples of 4-(methylthio)phenol.

(8) S. Guttman and R. A. Boissonnas, *Helv. Chim. Acta*, **42**, 1257 (1959).

(9) Melting points were taken on a Mel-Temp apparatus and are uncorrected. Analyses were performed by Dr. S. M. Nagy, Belmont, Mass.

Acenaphthylene Oxide[1]

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In the course of preparing a series of deuterium-labeled alkylacenaphthylenes for a mass spectral investigation of phenalenium ion formation,[3] it became

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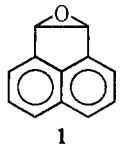
(2) National Defense Education Act Fellow, 1967–1968.

(3) T. H. Kinstle and P. J. Ihrig, Abstracts, 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967, O, 110.

necessary to synthesize 1,2-epoxyacenaphthene (**1**). Several attempted preparations of **1** or its substituted derivatives are described in the literature, but none of these were successful.[4,5] The very recent report of Richter and Silver[6] describes several additional un-



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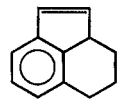


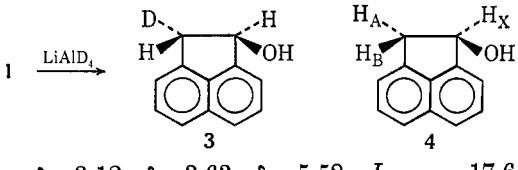
2

successful attempts to isolate **1** or the epoxide of 2,3,4,5-tetrahydroacenaphthylene (**2**). We wish to describe now a simple preparation and some of the chemical properties of **1**.

Acenaphthylene, when treated with an equimolar amount of *m*-chloroperbenzoic acid in chloroform solution at 0° for 24 hr, is converted in >90% yield to **1**. This is apparent from an nmr spectrum of the crude reaction mixture, which shows the complete absence of the olefinic acenaphthylene resonance at 6.85 ppm and the appearance of a two-proton singlet at 4.77 ppm due to the epoxide methine protons. Impurities of acenaphthenone (*ca.* 5%, methylene resonance at 3.75 ppm) and another minor, as yet unidentified component were evident in the reaction mixture.

Solutions of **1** are labile to heat and protonic media. Attempts to purify **1** by chromatography on neutral alumina or silica gel resulted in nearly quantitative conversion to acenaphthenone. This facile rearrangement is not unexpected and probably accounts for the problems previously encountered in isolation of **1** and related substances. Careful work-up followed by recrystallization gives **1** as colorless plates in 35% yield. Crystalline **1** is quite stable and exhibited no change in physical properties after 18 months.

Compound **1** undergoes several reactions characteristic of epoxides. Reaction with alkyl Grignard reagents yields 2-alkyl-1-acenaphthenols, which can be dehydrated to 1-alkylacenaphthylenes free from the isomeric alkylidenes.[7] Reaction of **1** with lithium aluminum deuteride produces *trans*-2-*d*-acenaphthenol (**3**) in quantitative yield. The stereochemical assignment in **3** follows from a comparison of its nmr spectrum with that of **4**, which shows a pattern analyzed as



3 **4**

ABX: δ_B 3.12, δ_A 3.63, δ_X 5.58, J_{AB} = 17.6 Hz, J_{AX} = ±7.3 Hz, and J_{BX} = +2.9 Hz. This assignment of H_A and H_B is consistent with the known relationship of dihedral angle and coupling constants,[9] and is in excellent agreement with the coupling constants reported for 1-bromoacenaphthene.[10]

(4) G. Wittig and K. Henkel, *Ann.*, **542**, 130 (1939).
(5) P. D. Bartlett and R. F. Brown, *J. Amer. Chem. Soc.*, **62**, 2927 (1940).
(6) H. J. Richter and S. F. Silver, *J. Org. Chem.*, **33**, 3283 (1968).
(7) Dehydration of 1-alkyl-1-acenaphthenols yields mixtures of isomers which are inseparable and which result in the loss of isotopic label in deuterio alkyl derivatives.[8]
(8) Unpublished results from the Ph.D thesis of P. J. Ihrig, Iowa State University, 1968.
(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).
(10) M. J. S. Dewar and R. C. Fahay, *J. Amer. Chem. Soc.*, **85**, 2245, 2704 (1963).

The nmr spectrum of **3** exhibits a doublet (J = 2.9 Hz, δ_X 5.58) and a broad resonance (δ_B 3.13, broadened and unresolved due to deuterium coupling) in addition to the typical aromatic proton multiplet.

Finally, compound **1** is deoxygenated by triphenylphosphine with added hydroquinone under standard reaction conditions[11] to produce acenaphthylene in 68% yield. The results of the reactions described above demonstrate that, once purified, **1** undergoes typical epoxide reactions without complications caused by prior rearrangement to acenaphthenone.

Experimental Section

1,2-Epoxyacenaphthene (**1**).—Acenaphthylene (6.08 g, 0.04 mol) was added during 5 min to a solution of *m*-chloroperbenzoic acid (10.3 g, 0.06 mol) in chloroform (100 ml) previously cooled to 0°. The mixture was allowed to stand in the refrigerator for 24 hr, during which the yellow color of acenaphthalene slowly disappeared and a precipitate of *m*-chlorobenzoic acid appeared. The acid was removed by filtration and the filtrate was poured into cold aqueous sodium bicarbonate and quickly extracted with cold chloroform. The organic phase was washed with 5% sodium thiosulfate, saturated sodium bicarbonate, and water, dried, and concentrated to 8.1 g of a yellow oil which slowly crystallized. Three recrystallizations from carbon tetrachloride afforded 1.68 g (35%) of colorless plates, mp 83–84°. The mass spectrum of this material showed an intense molecular ion peak at *m/e* 168 ($C_{12}H_8O$) and a fragmentation pattern essentially identical with that of acenaphthenone. The ir spectrum showed no carbonyl bands but showed bands at 12.34 and 12.84 μ, characteristic of epoxides. The nmr spectrum showed peaks at 4.77 (2 H, singlet) and 7.13–7.75 (6 H, multiplet).

Anal. Calcd for $C_{12}H_8O$: C, 85.69; H, 4.79. Found: C, 85.73; H, 4.83.

trans-**2-Deuterioacenaphthenol** (**3**).—A solution of **1** (0.2 g, 1.2 mmol) in anhydrous ether (6 ml) was added dropwise to a stirred slurry of lithium aluminum deuteride (0.05 g, 1.2 mmol) in ether (5 ml). The addition was complete in 30 min and stirring was continued for 1 hr. Water was added dropwise and the mixture was worked up to afford 0.20 g (100%) of colorless plates, mp 143–145°, mmp with acenaphthenol 143–145°. Low-voltage mass spectral analysis showed that only one deuterium had been incorporated into the alcohol. The nmr spectrum (described in text above) was obtained as a solution in DMSO-d_6 containing a trace of trifluoroacetic acid.

Deoxygenation of 1 with Triphenylphosphine.—Following the procedure of Wittig and Haag,[11] **1** (0.17 g, 1.0 mmol), triphenylphosphine (0.27 g, 1.0 mmol) and hydroquinone (0.03 g, 0.3 mmol) were mixed thoroughly in a small flask equipped with an efficient condenser and heated at 150° for 1 hr. Chromatography on neutral alumina (Woelm) of the crude reaction mixture and elution with hexane afforded 0.104 g (68%) of acenaphthylene, mp 89–90°, mmp 89–90°.

Registry No.—**1**, 22058-69-1.

(11) G. Wittig and W. Haag, *Ber.*, **88**, 1654 (1955).

A Facile Route to a Novel Derivative of 2,4,6,8-Nonanetetraone

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Recent studies in these laboratories[1] have shown that pyrrolidine reacts with 3-acyl-4-hydroxy-6-methyl-2-

(1) J. F. Stephen and E. Marcus, *J. Org. Chem.*, **34**, 2527 (1969).