Octahydrophenanthrene Derivatives. Stereoselective Synthesis of the Isomeric 9,10-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrenes[1]

Wendel L. Nelson* and Bob E. Sherwood

Department of Pharmaceutical Sciences, School of Pharmacy, University of Washington, Seattle, Washington 98195

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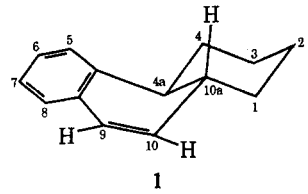
The four isomeric 9,10-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrenes were prepared. Permanganate oxidation of 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene (1) afforded the 9(e),10(a) isomer, 2. Wet Prévost conditions, followed by hydrolysis, gave the 9(a),10(e) diol, 3. Opening of the syn 9,10-epoxide, 6, using trichloracetic acid in benzene, followed by hydrolysis, afforded the 9(e),10(e) diol, 4. Aqueous acid opening of anti 9,10-epoxide (7) afforded 5, the 9(a),10(a) diol.

In previous work related to preparation of derivatives of 9,10-disubstituted octahydrophenanthrenes, addition of a number of electrophiles to 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene (1)[3] has been reported.[2] Addition of peracid, hypobromous acid, and iodine isocyanate all occur primarily from the α face of the molecules (steroid nomenclature); *i.e.*, on the side opposite the 10a hydrogen atom. With reference to other studies it was necessary to find routes to the isomeric 9,10-diols, **2**-**5**.[3] This led to an investigation of the use of other electrophiles to this olefin, as well as the openings of the isomeric epoxides, as potential routes to the isomeric diols.



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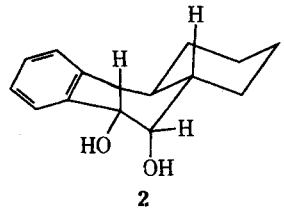

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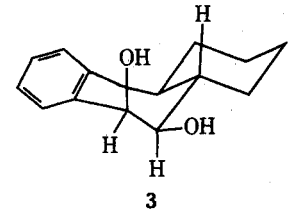

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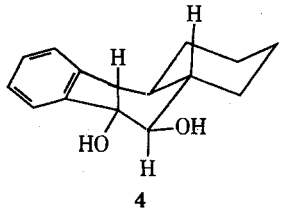

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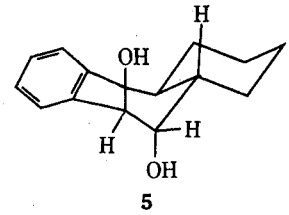

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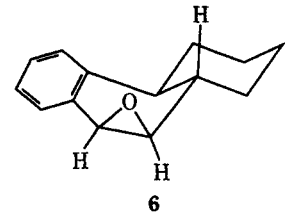
Our first approach to the desired diols involved the judicious choice of reagents for electrophilic addition to olefin 1. Permanganate oxidation afforded a single diol, which must be a cis diol,[4] which was assigned structure **2**, based on its nmr spectrum and the known net course of addition.

Structure assignments based on the nmr spectra (Table I) are extremely facile for **3** and **4**, since $J_{10,10a}$ is large, and $J_{9,10}$ varies only with the position of the 9-hydroxyl group.[5] In the 10(a)-hydroxy compounds, **2** and **5**, where $J_{10,10a} \cong 0$ and $J_{9,10}$ is relatively constant, additional evidence is required, *e.g.*, known course of addition being cis or trans.

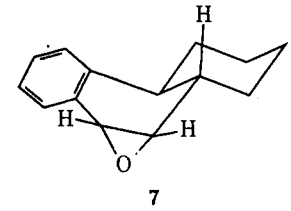
The selectivity of addition of permanganate ion and other electrophiles such as iodine isocyanate to the α face suggested use of another electrophilic iodonium ion generating reagent to prepare **3**. By using conditions of the wet Prévost reaction,[6,7] where the iodonium ion attacks the α face, it is possible to add both hydroxyl groups on the opposite side, the β face, thus affording a route to **3**.

Refluxing the intermediate iodoacetate with wet acetic acid afforded a miture of monoacetates of **3**, readily demonstrated by acetylation to a single diester, which is hydrolyzed to a single diol. The structure is readily assigned from nmr evidence (Table I), since $J_{10,10a}$ is large.

The isomeric syn and anti epoxides,[8] **6** and **7**, proved to be key intermediates in preparation of **4** and **5**, respectively. The epoxides **6** and **7** were prepared from olefin **1**. Peracid oxidation of **1** afforded **7**,[2a] and addition of hypobromous acid to **1**, followed by treatment with sodium hydroxide in methanol, gave **6**.[2a] Attack of these electrophiles also occurs from the α face of this tricyclic olefin.



6



7

Trichloroacetolysis (benzene) of the syn epoxide **6** afforded a route to diol **4**, somewhat unexpectedly. Previous openings under these conditions on substrates of *trans*-stilbene oxide,[9] and the isomeric-1-phenyl-4-*tert*-butylcyclohexane oxides,[10] had afforded products of cis opening.

Our previous experiences in opening of epoxide **6** with nucleophiles such as azide or ammonia[2a] had demonstrated regiospecific opening at the benzylic position, possibly indicative of the preferred route of opening regardless of conditions, consistent with some positive character of the benzylic carbon, C-9. The stereochemistry of the product of ring opening was readily assigned from the nmr spectrum, $J_{9,10} = 8.0$, $J_{10,10a} = 10$ Hz.

The differences in this result compared with those of Berti[10,11] may be a consequence of additional steric restraints of this system in the transition state, and/or differences in degrees of polarization compared to noncyclic systems.

Acid-catalyzed hydrolysis of the anti epoxide **7** in aqueous DMSO afforded diol **5** in excellent yield. The specific trans opening of similar epoxides under these hydrolytic conditions has been previously reported.[10,11] Only structure **5** was consistent with a small coupling constant for $J_{9,10}$.

The successful synthesis of the isomeric 9,10-epoxy-*trans*-octahydrophenanthrenes, **6** and **7**, and the cis diols, **2** and **3**, is dependent on the fact that all of the chosen electrophilic reagents *m*-chloroperbenzoic acid, potassium permanganate, silver acetate–iodine, and hypobromous acid, add stereoselectively to the α face of 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene, *i.e.*,

Table I
60-MHz Nmr Spectral Data for the Isomeric 9,10-Diols[a]

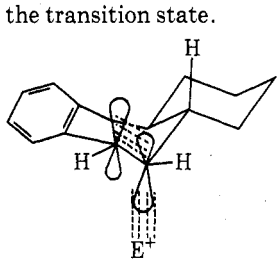
Compd	H_9 Orientation of H_9	H_9 Multiplicity and chemical shift, δ	$J_{9,10}$, Hz	H_{10} Orientation of H_{10}	H_{10} Multiplicity and chemical shift, δ	$J_{10,10a}$, Hz
2	Axial	d, 4.57	4	Equatorial	d, 3.75	~0
3	Equatorial	d, 4.55	4	Axial	dd, 3.50	9
4	Axial	d, 4.43	8	Axial	dd, 3.33	10
5	Equatorial	d, 4.30	2.5	Equatorial	d, 3.61	~0

[a] Spectra were recorded in DMSO-d_6.

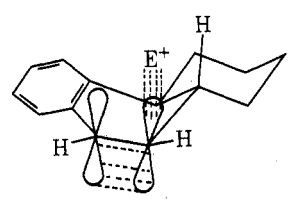
antiparallel to the axial hydrogen at C-10a. From models no great steric differences in the ease of parallel or antiparallel approach can be seen. In fact, the parallel approach (not observed) would seem to be the least sterically hindered owing to less 1,3 interaction with the hydrogens on the alicyclic rings.

The stereoselectivity observed may be explained in terms of stereotorsional control described by Garbisch.[12] Antiparallel approach would decrease torsional strain energy between proton H_{10} and the equatorial group at carbon 10a, whereas parallel approach would increase this torsional strain energy.

Stereoelectronic control of the reaction[14-16] may also be a factor contributing to the stereoselectivity of these reactions. In this case, if one assumes some degree of polarization at the benzylic position, C-9, as seems likely, an antiparallel (axial) attack at C-10 would allow maximum orbital overlap between the forming σ bond and the partial carbonium ion at C-9 with the central ring in its energetically most favorable, half-chair conformation. In contrast, parallel attack at C-10 would require a twisted boat conformation of the central ring to maintain orbital overlap in the transition state.



antiparallel



parallel

The preparation of these diols will allow for further study of epoxide openings in this system, and other related work, some of which is presently under investigation.

Experimental Section[17]

9(e),10(a)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (2). A solution of potassium permanganate, 8.69 g (0.055 mol), and sodium hydroxide, 3.0 g (0.075 mol), in 340 ml of water was cooled to 0° and added over a 30-min period to a stirred solution of 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene (1),[2a] 9.21 g (0.05 mol), in 300 ml of *tert*-butyl alcohol and 210 ml of water, maintaining the temperature below 5° with an ice bath. The solution was stirred for an additional 15 min at 0°, 10% aqueous sodium bisulfite (500 ml) was added to destroy the manganese dioxide, and the solution was continuously extracted with 300 ml of ether for 67 hr. The ether solution was dried and evaporated and the white solid remaining was recrystallized from ether to give 9(e),10(a)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (2): 7.2 g (66%); mp 97–100°; λ_{max} (H_2O) 263 nm (ϵ 325); ir (KBr) 3360 (OH), 2900 and 2840 (aliphatic CH), 1440 (CO), and 720 and 750 cm^{-1} (aromatic CH); nmr ($CDCl_3$, DMSO-d_6) δ 7.50–7.67 (m, 1, H_8), 7.17–727 (m, 3, $H_{5,6,7}$), 4.57 (d, 1, $J_{9,10}$ = 4.0 Hz, H_9), 4.12 (s, broad, 1, OH), 3.75 (d, 1, $J_{10,9}$ = 4.0, $J_{10,10a} \cong 0$ Hz, H_{10}), 1.33–2.13 (m, 10, CH_2CH envelope), D_2O was added and the nmr absorption at δ 4.12 disappeared and an absorption at δ 3.57 (s, 2, HDO) appeared; mass spectrum (70 eV) *m/e* (rel intensity, fragment) 218 (4, M^+), 201 (19, M − OH), 200 (100, M − H_2O), 182 (82, M − $2H_2O$), 171 (23, $C_{12}H_{11}O$), 157 (33, $C_{11}H_9O$), 141 (43, $C_{11}H_9$), 129 (43, $C_{10}H_9$), 115 (25, C_9H_7), 107 (18, C_7H_7O), 91 (34, C_7H_7), 77 (26, C_6H_5).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03: H, 8.31; *m/e* 218.1306. Found: C, 76.91; H, 8.08; *m/e* 218.1258.

9(a),10(e)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (3). Powdered iodine, 1.27 g (0.005 mol), was added in small portions over a 30-min period to a stirred solution of 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene (1),[2a] 921 mg (5.0 mmol), and silver acetate (J. T. Baker Chemical Co.), 1.84 g (0.011 mol), in 20 ml of glacial acetic acid (99.5%) and the stirring was continued an additional 40 min. Wet acetic acid (4% water), 20 ml, was added and the mixture was heated at 100° for 3 hr with stirring. Ether and sodium chloride were added, the mixture was filtered, and the precipitate was washed with ether. The combined ether filtrates were washed with water followed by 10% aqueous sodium bicarbonate and water, dried, and evaporated to give 1.41 g of colorless oil. The nmr spectrum of this oil contained two signals for the acetate methyl group and two sets of multiplets for H_9 and H_{10}, indicating a mixture of *cis*-9-hydroxy-10-acetoxyl and 9-acetoxy-10-hydroxyl compounds.

The oil was treated with acetic anhydride, 4.0 g (0.04 mol), and 4 drops of pyridine for 20 hr and then diluted with water and extracted with ether. The ether solution was washed with water followed by 10% aqueous sodium bicarbonate, 10% aqueous hydrochloric acid, and water, dried, and evaporated. The solid remaining was recrystallized from hexane to yield 9(a),10(e)-diacetoxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (8): 1.39 g (96%); mp 135–136°; ir (KBr) 2940 and 2870 (aliphatic CH), 1740 (C=O), 1235 (CO), and 670, 685, 735, 755, and 785 cm^{-1} (aromatic CH); nmr ($CDCl_3$) δ 7.34–7.16 (m, 4, ArH), 6.18 (d, 1, $J_{9,10}$ = 4.0 Hz, H_9), 5.00 (dd, 1, $J_{10,10a}$ = 11.0 Hz, H_{10}), and 1.00–2.68 (m, 16, CH_2CH envelope).

A solution of 9(a),10(e)-diacetoxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (8), 145 mg (0.5 mmol), and potassium hydroxide, 561 mg (0.01 mol), in 10 ml of ethanol (95%) was stirred at room temperature for 6 hr, diluted with water, and extracted with ether. The ether solution was washed with 10% aqueous hydrochloric acid followed by water, dried, and evaporated. The solid remaining was recrystallized from hexane to yield 9(a),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (3): 90 mg (83%); mp 151–153°; λ_{max} (H_2O) 263 nm (ϵ 335); ir (KBr) 3360 (OH), 2920 and 2850 (aliphatic CH), and 745 and 765 cm^{-1} (aromatic CH); nmr (DMSO-d_6) δ 7.07–7.33 (m, 4, ArH), 4.85 (d, 1, $J_{HO,9}$ = 4.5 Hz, OH), 4.47 (t, 1, $J_{9,10}$ = 4.0 Hz, H_9), 4.27 (d, 1, $J_{HO,10}$ = 7.5 Hz, HO), 3.41 (ddd, 1, $J_{10,10a}$ = 9.0 Hz, H_{10}), 1.0–2.58 (m, 10, CH_2CH envelope); nmr (DMSO-d_6, D_2O) δ 4.55 (d, 1, $J_{9,10}$ = 4.0 Hz, H_9), 3.85 (s, 2, HDO), 3.50 (dd, 1, $J_{10,10a}$ = 9.0 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 218 (27, M^+), 201 (17, M − OH), 200 (100, M − H_2O), 182 (42, M − $2H_2O$), 171 (18, $C_{12}H_{11}O$), 157 (33, $C_{11}H_9O$), 141 (35, $C_{11}H_9$)R 129 (64, $C_{10}H_9$), 115 (35, C_9H_7), 107 (37, C_7H_7O), 91 (50, C_7H_7), 77 (27, C_6H_5).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; *m/e* 218.1306. Found: C, 77.34; H, 8.35; *m/e* 218.1292.

9(e),10(e)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (4). To a solution of *syn*-9,10-epoxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (6),[2a] 500 mg (2.5 mmol), in 17 ml of benzene was added a solution of trichloroacetic acid, 490 mg (3.0 mmol), in 3.7 ml of benzene and the mixture was stored overnight at room temperature. The benzene solution was washed with 10% aqueous sodium bicarbonate, followed by water, and dried, and the organic solvent was evaporated under reduced pressure. The solid remaining was recrystallized from hexane to give 9(e)-trichloroacetoxy-10(e)-hydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (9): 385 mg (43%); mp 119–120°; ir (KBr) 3580 (OH), 2920 and 2845 (ali-

phatic CH), 1755 (C=O), 1250 (CO), and 680 and 760 cm^{-1} (aromatic CH); nmr ($CDCl_3$) δ 7.18–7.37 (m, 4, ArH), 6.13 (d, 1, $J_{9,10}$ = 8.0 Hz, H_9), 3.87 (dd, 1, $J_{10,10a}$ = 11.5 Hz, (H_{10}), and 0.67–2.70 (m, 10, CH_2CH envelope).

A solution of 9(e)-trichloroacetoxy-10(e)-hydroxy-1,2,3,4,4a,-9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (**9**), 363 mg (1.0 mmol), and potassium hydroxide, 1.34 g (0.024 mol), in 12 ml of 95% ethanol was stirred at room temperature for 3 hr. The mixture was diluted with water and extracted with several portions of ether. The combined ether solutions were dried and evaporated. The remaining solid was recrystallized from benzene to give 9(e),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (**4**): 188 mg (82%); mp 174–176°; λ_{max} (H_2O) 263 nm (ϵ 330); ir (KBr) 3340 (OH), 2910 and 2840 (aliphatic CH), 1445 and 1480 (CO), and 750 cm^{-1} (aromatic CH); nmr (DMSO-d_6) δ 7.47–7.60 (m, 1, H_8), 7.23 (m, 3, $H_{5,6,7}$), 5.20 (s, broad, 1, OH), 4.70 (s, broad, 1, OH), 4.43 (d, 1, $J_{9,10}$ = 8.0 Hz, H_9), 3.33 (t, broad, 1, $J_{10,10a} \cong$ 9 Hz, H_{10}), 1.0–2.57 (m, 10, CH_2CH envelope); nmr (DMSO-d_6, D_2O) δ 3.97 (s, 2, HDO), 3.27 (dd, 1, $J_{10,10a}$ = 10.0 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 218 (11, M^+), 201 (15, M − OH), 200 (100, M − H_2O), 182 (25, M − $2H_2O$), 171 (23, $C_{12}H_{11}O$), 157 (16, $C_{11}H_9O$), 141 (14, $C_{11}H_9$), 129 (28, $C_{10}H_9$), 115 (19, C_9H_7), 107 (21, C_7H_7O), 91 (14, C_7H_7), 77 (11, R_6H_5).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; *m/e* 218.1306. Found: C, 77.16; H, 8.06; *m/e* 218,1324.

9(a),10(a)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (5). *anti*-9,10-Epoxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**7**)[2a] 400 mg (2.0 mmol), in 90 ml of dimethyl sulfoxide (DMSO) was treated with a solution of sulfuric acid, 120 mg (1.33 mmol), in 30 ml of water (0.02 *N* H_2SO_4 in 75% aqueous DMSO) and stirred for 3 hr. The solution was diluted with water and extracted with benzene, and the benzene solution was washed with water, dried, and evaporated. The residual oil was crystallized and recrystallized from hexane–ether (2:1) to yield 9(a),10(a)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (**4**): 309 mg (71%); mp 124.5–125°; λ_{max} (H_2O) 264 nm (ϵ 340); ir (KBr) 3350 (OH), 2910 and 2850 (aliphatic CH), 980 and 1010 (CO), and 705, 720, 750, and 780 cm^{-1} (aromatic CH); nmr (DMSO-d_6) δ 7.21 (s, 4, ArH), 4.47 (m, 2, OH), 4.30 (d, 1, $J_{9,10}$ = 2.5 Hz, H_9), 3.61 (d, 1, $J_{10,9}$ = 2.5, $J_{10,10a} \cong$ 0 Hz, H_{10}), 2.37–2.63 (m, 2, ArH), 1.07–2.00 (m, 8, CH_2CH envelope); nmr (DMSO-d_6, D_2O) the broad multiplet at δ 4.47 disappears and a signal appears at δ 3.47 (s, broad, 2, HDO); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 218 (5, M^+), 201 (14, M − OH), 200 (100, M − H_2O), 171 (14, $C_{12}H_{11}O$), 157 (30, $C_{11}H_9O$), 129 (32, $C_{10}H_9$), 115 (24, C_9H_7), 107 (30, C_7H_7O), 91 (28, C_7H_7), 77 (19, C_6H_5).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; *m/e* 218.1306. Found: C, 77.14; H, 8.57; *m/e* 218.1292.

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References and Notes

(1) (a) A preliminary account of this work was presented at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, Abstract MEDI 09. (b) Taken in part from the Ph.D. Thesis of B. E. Sherwood, submitted to the Graduate School, University of Washington, Feb 1973.
(2) (a) W. L. Nelson and D. D. Miller, *J. Med. Chem.*, **13**, 807 (1970); (b) W. L. Nelson, D. D. Miller and E. Shefter, *J. Org. Chem.*, **35**, 3433 (1970).
(3) All materials are racemic, although only a single isomer is shown.
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(5) The central ring is arbitrarily assigned the half-chair conformation where the equatorial (e) and axial (a) substituents at C-9 are in fact pseudo-equatorial and pseudo-axial respectively.
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(8) Syn and anti refer to the hetero three-membered ring as being on the same side, or opposite side, of the tricyclic skeleton as the C-10a hydrogen atom.
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(17) Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on Beckman IR-5 and IR-20 spectrometers. Ultraviolet spectra were obtained on a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra were recorded on 60-MHz Varian A-60 and T-60 spectrometers in the solvent stated with tetramethylsilane (TMS) as an internal standard. In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Gas chromatographic data were determined on a Hewlett-Packard 5752 research gas chromatograph. The column and temperature utilized are stated for each determination. Mass spectral data were recorded on an Associated Electronics Industries MS-9 mass spectrometer. A Digital Equipment Corp. PDP-12 computer equipped with programs available from the Mass Spectrometry Laboratory, Department of Chemistry, University of Washington, Seattle, Wash. 98195, was used for data collection and mass spectral fragment determinations. Peaks given in the mass spectral fragmentations are within 5.0 millimass units from calculated values. Elemental microanalyses were performed by Dr. F. B. Strauss, Microanalytical Laboratories, Oxford, England, and Huffman Laboratories, Wheatridge, Colo. Unless otherwise stated, anhydrous sodium sulfate was used to dry solutions of organic solvents.