S-Cyclohexyl O,O-Dimethyl Phosphorothiolate (1, R = Methyl, R′ = Cyclohexyl, Entry 4): bp 64–68 °C (0.02 torr); IR (neat) 1258 (P=O), 1188 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04–2.51 (br, 10, CH_2), 2.98–3.56 (br, 1, CHS), 3.66, 3.88 (s, 6, CH_3).

Anal. Calcd for $C_8H_{17}O_3PS$: C, 42.85; H, 7.64. Found: C, 42.67; H, 8.03.

O,O-Dimethyl S-[2-(Methoxycarbonyl)ethyl] Phosphorothiolate (1, R = Me, R′ = CH_2CH_2COOMe, Entry 5): bp 57–62 °C (0.02 torr); IR (neat) 1740 (C=O), 1250 (P=O), 1180 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50–3.50 (m, 4, CH_2), 3.72 (s, 6, CH_3), 3.92 (s, 3, CH_3).

Anal. Calcd for $C_6H_{13}O_5PS$: C, 31.58; H, 5.74. Found: C, 31.11; H, 6.04.

O,O-Dimethyl S-(Ethoxycarbonyl)methyl Phosphorothiolate (1, R = Me, R′ = CH_2COOEt, Entry 6): bp 76–80 °C (0.01 torr) (lit.[21] bp 86 °C (0.05 torr)); IR (neat) 1740 (C=O), 1260 (P=O), 1185 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3, CH_3), 3.45, 3.72 (s, 2 CH_2), 3.72, 3.93 (s, 6, CH_3), 4.31 (q, 2, CH_2S).

S-Benzyl O,O-Diethyl Phosphorothiolate (1, R = Ethyl, R′ = Benzyl, Entry 8): bp 110–114 °C (0.02 torr) (lit.[2] bp 129–131.5 °C (0.15 torr)); IR (neat) 3055 (HAr), 1260 (P=O), 1162 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 6, CH_3), 3.81–4.40 (m, 6, CH_2), 7.11–7.53 (m, 5, HAr).

S-Butyl O,O-Diethyl Phosphorothiolate (1, R = Ethyl, R′ = Butyl, Entry 9): bp 35–40 °C (0.01 torr) (lit.[22] bp 131–133 °C (10 torr)); IR (neat) 1464 (CH_2), 1258 (P=O), 1162 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–1.10 (m, 3, CH_3), 1.10–1.93 (m, 4, CH_2), 1.33 (t, 6, CH_3), 2.53–3.10 (m, 2, CH_2S), 4.07 (q, 2, CH_2), 4.21 (q, 2, CH_2).

S-Cyclohexyl O,O-Diethyl Phosphorothiolate (1, R = Ethyl, R′ = Cyclohexyl, Entry 10): bp 67–70 °C (0.01 torr) (lit.[23] bp 99–102 °C (0.2 torr)); IR (neat) 1249 (P=O), 1155 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03–2.20 (br, 10, CH_2), 1.36 (t, 6, CH_3), 2.93–3.58 (br, 1, CHS), 4.09 (q, 2, CH_2), 4.23 (q, 2, CH_2).

O,O-Diethyl S-[2-(Methoxycarbonyl)ethyl] Phosphorothiolate (1, R = Et, R′ = CH_2CH_2COOMe, Entry 11): bp 67–70 °C (0.02 torr) (lit.[24] bp 137 °C (3.0 torr)); IR (neat) 1738 (C=O), 1248 (P=O), 1160 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, 6, CH_3), 2.50–3.40 (m, 4, CH_2), 3.70 (s, 3, CH_3), 4.09 (q, 2, CH_2), 4.24 (q, 2, CH_2).

O,O-Diethyl S-(Ethoxycarbonyl)methyl Phosphorothiolate (1, R = Et, R′ = CH_2COOEt, Entry 12): bp 70–75 °C (0.005 torr) (lit.[25] bp 78–81 °C (0.01 torr)); IR (neat) 1738 (C=O), 1258 (P=O), 1160 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12–1.58 (m, 9, CH_3), 3.45, 3.70 (s, 2, CH_2S), 3.92–4.49 (m, 6, CH_2).

O,O-Diisopropyl S-Phenyl Phosphorothiolate (1,[19] R = Isopropyl, R′ = Phenyl, Entry 13): bp 88–92 °C (0.02 torr); IR (neat) 3048 (HAr), 1388, 1378, 1256 (P=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24, 1.34 (dd, 12, CH_3), 4.48–5.04 (m, 2, CH), 7.26–7.66 (m, 5, HAr).

S-Benzyl O,O-Diisopropyl Phosphorothiolate (1, R = Isopropyl, R′ = Benzyl, Entry 14): bp 90–95 °C (0.01 torr) (lit.[26] bp 126 °C (0.04 torr)); IR (neat) 3056 (HAr), 1390, 1380, 1258 (P=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26, 1.36 (dd, 12, CH_3), 3.96, 4.17 (s, 2, CH_2), 4.41–4.97 (m, 2, CH_2), 7.10–7.50 (m, 5, HAr).

S-Cyclohexyl O,O-Diisopropyl Phosphorothiolate (1, R = Isopropyl, R′ = Cyclohexyl, Entry 15): bp 60–65 °C (0.005 torr); IR (neat) 1452 (CH_2), 1386, 1376, 1246 (P=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95–2.35 (br, 10, CH_2), 1.28, 1.38 (dd, 12, CH_3), 2.95–3.53 (br, 1, CHS), 4.43–4.99 (m, 2, CH).

Anal. Calcd for $C_{12}H_{25}O_3PS$: C, 51.41; H, 8.99. Found: C, 51.12; H, 9.08.

O,O-Diphenyl S-Phenyl Phosphorothiolate (1, R = Phenyl, R′ = Phenyl, Entry 16): bp 106–110 °C (0.02 torr); IR (neat) 3048 (HAr), 1274 (P=O), 1190 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95–7.65 (m, 15, HAr).

Anal. Calcd for $C_{18}H_{15}O_3PS$: C, 63.15; H, 4.42. Found: C, 63.16; H, 4.49.

S-Benzyl O,O-Diphenyl Phosphorothiolate (1, R = Phenyl, R′ = Benzyl, Entry 17): mp 64–66 °C (lit. mp 65–67 °C); IR (Nujol) 3040 (HAr), 1278 (P=O), 1194 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03, 4.25 (s, 2, CH_2), 7.07–7.40 (m, 15, HAr).

S-Cyclohexyl O,O-Diphenyl Phosphorothiolate (1, R = Phenyl, R′ = Cyclohexyl, Entry 18): bp 102–105 °C (0.01 torr); IR (neat) 3050 (HAr), 1485 (CH_2), 1262 (P=O), 1190 (PO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.40 (br, 10, CH_2), 3.10–3.80 (br, 1, CHS), 7.30 (br, s, 10, HAr).

Anal. Calcd for $C_{18}H_{21}O_3PS$: C, 62.06: H, 6.08. Found: C, 62.03; H, 6.36.

Electrolysis of 3 (R′ = Phenyl) and NaBr in MeCN. A mixture of **3** (R′ = phenyl, 218 mg, 1 mmol) and NaBr (129 mg, 1.25 mmol) in MeCN (20 mL) containing Et_4NClO_4 (100 mg) was electrolyzed at 3 V (applied voltage), 4–3 mA/cm^2, at 29–30 °C for 2.5 h. After 2×10^{-3} faraday of electricity was passed and the solvent was removed, chromatography (SiO_2, hexane/benzene) gave **4** (R′ = phenyl, 11 mg, 4%) and recovered **3** (195 mg, 89%).

Electrolysis of 2 (R = Et) and NaBr in MeCN. A mixture of **2** (R = Et, 141 mg, 1 mmol) and NaBr (129 mg, 1.25 mmol), in MeCN (20 mL), was electrolyzed at 3 V (applied voltage), 1.4–1 mA/cm^2, at 27–28 °C for 6 h. After 1×10^{-3} faraday of electricity was passed and the solvent was removed, chromatography (SiO_2, $CHCl_3$/AcOEt) gave **5** (R = Et, 63 mg) and recovered **2** (37 mg). IR and ^1H NMR spectra of **5** were identical with those of authentic sample.

Electrolysis of a Mixture of 2 and 3 without Using Halide Salts. A solution of **2** (R = Et, 320 mg, 2.3 mmol) and **3** (R′ = phenyl, 222 mg, 1 mmol) in MeCN (20 mL) containing Et_4NClO_4 (100 mg) was electrolyzed at a constant voltage of 3 V (anode potential 1.0–1.2 V vs. $Ag/AgClO_4$), giving 2.8–0.1 mA/cm^2, at 19–25 °C. After passage of 3.5×10^{-3} faraday of electricity during 60 h, the mixture was concentrated in vacuo and the residue was chromatographed (SiO_2, hexane/benzene/AcOEt) to give **1** (R = Et, R′ = phenyl, 117 mg, 23%), **2** (117 mg, 37%), **3** (19 mg, 9%), and **4** (R′ = phenyl, 54 mg, 22%).

Registry No. **1** (R = Me, R^1 = phenyl), 4237-00-7; **1** (R = Me, R^1 = benzyl), 7205-16-5; **1** (R = Me, R^1 = butyl), 26901-83-7; **1** (R = Me, R^1 = cyclohexyl), 70550-08-2; **1** (R = Me, R^1 = CH_2CH_2COOMe), 70550-09-3; **1** (R = Me, R^1 = CH_2COOEt), 2088-72-4; **1** (R = Et, R^1 = phenyl), 1889-58-3; **1** (R = Et, R^1 = benzyl), 13286-32-3; **1** (R = Et, R^1 = butyl), 20195-07-7; **1** (R = Et, R^1 = cyclohexyl), 26437-23-0; **1** (R = Et, R^1 = CH_2CH_2COOMe), 70550-10-6; **1** (R = Et, R^1 = CH_2COOEt), 2425-25-4; **1** (R = isopropyl, R^1 = phenyl), 15267-38-6; **1** (R = isopropyl, R^1 = benzyl), 26087-47-8; **1** (R = isopropyl, R^1 = cyclohexyl), 70550-11-7; **1** (R = phenyl, R^1 = phenyl), 70562-38-8; **1** (R = phenyl, R^1 = benzyl), 13879-47-5; **1** (R = phenyl, R^1 = cyclohexyl), 70550-12-8; **2** (R = Me), 868-85-9; **2** (R = Et), 762-04-9; **2** (R = isopropyl), 1809-20-7; **2** (R = phenyl), 4712-55-4; **3** (R^1 = phenyl), 882-33-7; **3** (R^1 = benzyl), 150-60-7; **3** (R^1 = butyl), 629-45-8; **3** (R^1 = cyclohexyl), 2550-40-5; **3** (R^1 = $(CH_2)_2COOMe$), 15441-06-2; **3** (R^1 = CH_2COOEt), 1665-65-2; **4** (R^1 = phenyl), 1212-08-4; **5** (R = Et), 107-49-3.

(21) Nguyen-Thanh-Thuong French Patent 1 450 400 (Cl. C 07f, A 01N), 1966; *Chem. Abstr.* **1967**, *66*, 94695.

(22) Petrov, K. A.; Bliznyuk, N. K.; Mansurov, I. Yu. USSR Patent, 130 156, 1960; *Chem. Abstr.* **1961**, *55*, 6374*f*.

(23) Sallmann, R. Swiss Patent 323 228 (Cl. 36o), 1957; *Chem. Abstr.* **1958**, *52*, 14959*d*.

(24) Arbuzov, B. A.; Yarmukhametova, D. Kh. *Izvt. Akad. Nauk SSSR, Otd. Khim. Nauk* **1960**, 1881; *Chem. Abstr.* **1961**, *55*, 16410*g*.

(25) Schlör, H.; Schrader, G. German Patent 1 083 809 (Cl. 12o), 1960; *Chem. Abstr.* **1961**, *55*, 17500*c*.

(26) Kado, M. *Yuki Gosei Kagaku Kyokai Shi* **1971**, *29*, 197; *Chem. Abstr.* **1972**, *76*, 21819.

Convenient Synthesis of 9-Methylbenzo[*a*]pyrene[1]

John W. Lyga and John A. Secrist III*

The Ohio State University, Department of Chemistry, Columbus, Ohio 43210

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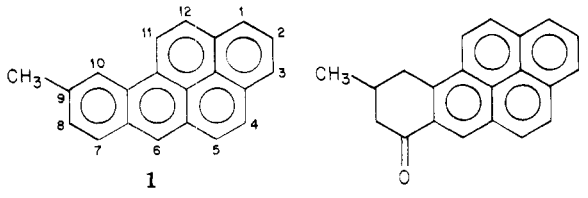
In connection with some studies concerning the diol epoxide mechanism of carcinogenesis for polycyclic aromatic hydrocarbons, we required a convenient synthesis

(1) In the earlier literature, this is referred to as 2′-methyl-3,4-benzpyrene; see "The Ring Index", 2nd Ed.; The American Chemical Society: Washington D.C.; 1960, p 922, entry 6399 for the presently accepted numbering.

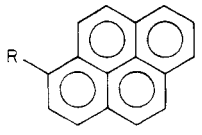
0022-3263/79/1944-2941$01.00/0

of 9-methylbenzo[a]pyrene (1) by way of its known precursor 7-keto-9-methyl-7,8,9,10-tetrahydrobenzo[a]pyrene (2). The only literature procedure leading to 1[2] requires



1

2



3

a, R = H
b, R = CHO
c, R = CH=C(SCH$_3$)CH$_3$
d, R = CH$_2$COCH$_3$
e, R = CH$_2$C(CH$_3$)=CHCO$_2$CH$_2$CH$_3$
f, R = CH$_2$CH(CH$_3$)CH$_2$CO$_2$H

13 steps from pyrene and is quite laborious. We have developed a seven step synthesis of **2** from pyrene (going through several of the same intermediates) which improves the overall yield and which also should prove useful for the synthesis of other substituted polycyclic aromatic hydrocarbons.

The simplest approach to attaching the 9-methylated benzo ring to pyrene (**3a**) would employ a standard Friedel–Crafts strategy utilizing methylsuccinic anhydride. However, this provided exclusively the isomer leading to 8-methylbenzo[a]pyrene.[3] Our approach was to utilize two successive condensation reactions, each incorporating two carbons, to build up the required five carbons unambiguously from 1-formylpyrene (**3b**).[4]

The preparation of **3b** was accomplished with a substantial increase in yield simply by omitting the solvent from the standard Vilsmeier–Haack conditions.[5] Condensation of **3b** with diethyl (1-methylthio)ethylphosphonate[6] produced the vinyl sulfide **3c**, which was readily hydrolyzed with mercuric ion to the ketone **3d** (68% overall yield from **3b**).[7] The last two carbons were incorporated by treatment of **3d** with the anion derived from ethyl trimethylsilylacetate[9] to produce the α,β-unsaturated ester **3e** in 80% yield.[10] Saponification of **3e** followed by catalytic hydrogenation afforded 3-methyl-4-(1-pyrenyl)butanoic acid (**3f**), which was converted to the acid chloride with PCl_5 and cyclized to **2** with $SnCl_4$.[2] Conversion of **2** to **1** was accomplished in much improved yield by reduction with $NaBH_4$ and aromatization with palladium on charcoal.[2]

Experimental Section[11]

1-Formylpyrene (3b). The literature procedure[5] was followed except that the solvent (dichlorobenzene) was deleted. From 50 g of pyrene, 44.5 g (78%) of **3b** was obtained after recrystallization from 95% ethanol, mp 125–126 °C (lit. mp 126 °C[5]).

2-(Methylthio)-1-(1-pyrenyl)-1-propene (3c). To a solution of 14.6 g (0.069 mol) of diethyl 1-(methylthio)ethylphosphonate[6] in 300 mL of THF at −70 °C under nitrogen was added 31.5 mL (0.063 mol) of 2 M *n*-BuLi in hexane over 15 min. After stirring 3–4 h, 14.4 g (0.063 mol) of **3b** in 100 mL of THF was added over 30 min. The resulting solution was stirred for 30 min at −70 °C, and allowed to warm up to room temperature. After addition of 200 mL of saturated NH_4Cl, the mixture was extracted with 1:1 ether–benzene (2 × 100 mL). The organic extracts were washed with saturated $NaHCO_3$ solution (100 mL) and saturated NaCl (100 mL) and gravity filtered through a cone of anhydrous $MgSO_4$. Removal of solvent under reduced pressure left ca. 20 g of crude yellow **3c**, sufficiently pure for the next step. Analytically pure material was produced by recrystallization twice from acetone: mp 95.5–96 °C; ^1H NMR ($CDCl_3$) δ 1.90 (d, J = 1 Hz, 3, CH_3C=C), 2.35 (s, 3, CH_3S), 6.63 (br s, 1, CH=C), 7.52–8.10 (m, 9, ArH); exact mass calcd m/e 288.0973, found 288.0981.

Anal. Calcd for $C_{20}H_{16}S$: C, 83.29; H, 5.59. Found: C, 83.05; H, 5.60.

1-(1-Pyrenyl)-2-propanone (3d). A solution of 20 g (0.069 mol, used directly) of crude **3c** in 550 mL of 3.5:1:1 acetone–H_2O–acetonitrile was heated at reflux for 36 h, decolorized, and filtered through Celite. The solution was neutralized with saturated $NaHCO_3$ (100 mL), concentrated, and extracted with 1:1 ether–benzene (2 × 100 mL). The organic extracts were washed with 1 N aqueous KI (100 mL) and saturated $NaHCO_3$ (100 mL), then gravity filtered through a cone of anhydrous $MgSO_4$. Removal of solvent in vacuo left a yellow solid which was recrystallized from ether to yield 9.2 g (68% from **3b**) of **3d**; ^1H NMR ($CDCl_3$) δ 1.98 (s, 3, CH_3), 4.15 (s, 2, CH_2), 7.55–8.11 (m, 9, aromatic); exact mass calcd m/e 258.1045, found 258.1050.

Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.18; H, 5.43.

(Z)- and (E)-Ethyl 3-Methyl-4-(1-pyrenyl)-2-butenoate (3e). To 31.2 g (0.172 mol) of dicyclohexylamine in 500 mL of THF under N_2 at −70 °C was added 82 mL (0.172 mol) of 2.1 N *n*-butyllithium in hexane over 10 min. The solution was stirred for 15 min, and 27.5 g (0.172 mol) of ethyl trimethylsilylacetate[9] in 200 mL of THF was added over 15 min. After a total of 30 min, 22.2 g (0.086 mol) of **3d** in 350 mL of THF was added over 30 min. The cloudy yellow solution (deep red in some runs where **3d** was not rigorously purified) was stirred at −70 °C for 1 h, and then allowed to warm to room temperature. The solution was quenched with 150 mL of saturated NH_4Cl and 150 mL of 1 N HCl, and filtered through Celite to remove the amine hydrochloride. After concentration to remove THF, the aqueous solution was extracted with 1:1 ether–benzene (2 × 75 mL). The organic extracts were washed with 1 N HCl (100 mL), saturated NH_4Cl, and saturated NaCl, and gravity filtered through a cone of anhydrous $MgSO_4$ and charcoal. Removal of solvent left a pale green-yellow oil which was of sufficient purity to carry on to the next step (22.7 g, 80%). An analytical sample of the mixture was prepared by preparative TLC (silica gel, elution with 1:4 ether–petroleum ether) followed by molecular distillation [165 °C (0.02 mm)]. Partial isomer separation was possible with repeated elutions: ^1H NMR ($CDCl_3$) more polar isomer, δ 1.26 (t, 3, OCH_2CH_3), 2.31 (d, 3, J < 1 Hz, CH_3C=C), 4.09 (q, 2, OCH_2CH_3), 4.41 (s, 2, CCH_2C), 5.50 (m, 1, CH=C), 7.75–8.35 (m, 9, aromatic); less polar isomer δ 1.35 (t, 3, OCH_2CH_3), 1.70 (d, 3, J = 1.5 Hz, CH_3C=C), 4.33 (q, 2, OCH_2CH_3), 4.80 (s, 2, CCH_2C), 5.91 (m, 1,

(2) Bachmann, W. E.; Carmack, M. *J. Am. Chem. Soc.* **1941**, *63*, 2494–2499.
(3) Winterstein, A.; Vetter, H.; Schön, K. *Chem. Ber.* **1935**, *68*, 1079–1085.
(4) Approaches incorporating all four carbons at once, for example with a Grignard reagent, did not work.
(5) Vollmann, H.; Becker, H.; Corell, M.; Streeck, H. *Justus Liebigs Ann. Chem.* **1937**, *531*, 1–159.
(6) Corey, E. J.; Shulman, J. I. *J. Org. Chem.* **1970**, *35*, 777–780.
(7) The carbanion derived from (α-chloroethyl)trimethylsilane is a recently developed reagent which can be used for this reductive nucleophilic acylation.[8] In our hands the yields for this procedure were significantly poorer than with the phosphonate reagent.
(8) Cooke, F.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1977**, 513.
(9) Shimoji, K.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620–1621.
(10) (Carbomethoxymethyl)triphenylphosphorane, the anion derived from dimethyl(carbomethoxymethyl)phosphonate, and lithium *tert*-butylacetate all afforded inferior yields of product.
(11) Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are corrected. ^1H NMR spectra were measured with a Varian EM-360 instrument; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded with an AEI-MS9 spectrometer at 70 eV. Microanalyses were done by Galbraith Laboratories, Inc. Tetrahydrofuran was dried by distillation from sodium and benzophenone or calcium hydride. The ultraviolet absorption spectrum (in nm) was recorded on a Cary 15 ultraviolet absorption spectrophotometer.

CH=C), 7.80–8.45 (m, 9, aromatic); exact mass calcd m/e 328.1464, found 328.1468.

Anal. Calcd for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14. Found: C, 83.85; H, 5.89.

3-Methyl-4-(1-pyrenyl)butanoic Acid (3f). A mixture of 19.5 g (59.3 mmol) of **3e**, 150 mL of 40% aqueous KOH, and 50 mL of ethanol was heated at reflux for 3 h (alcoholic KOH is equally acceptable), cooled, and acidified with 6 N HCl. The precipitate was filtered off and recrystallized from benzene–ether to yield 16.0 g (89%) of the α,β-unsaturated acids (**3f**). A solution of 11.16 g (36.9 mmol) of **3f** and 1.7 g of 10% Pd/C in 150 mL of 9:1 ethyl acetate–acetic acid was hydrogenated (Parr shaker) at 3.5 atm for 24 h. Removal of catalyst by filtration and solvent under reduced pressure followed by recrystallization of the residue from benzene–petroleum ether afforded 9.9 g (87%) of **3g**: mp 124–129 °C (lit. mp 125–135 °C[2]); exact mass calcd m/e 302.1307, found 302.1314.

9-Methylbenzo[*a*]pyrene (1). The conversion of **3f** to **2** was accomplished as described[2] in 93% yield, mp 175.5–176 °C (lit. mp 176.5–177.5 °C[2]). To ketone **2** (7.0 g, 24.6 mmol) in 300 mL of 1:1 THF–ethanol was added 0.6 g (15.8 mmol) of $NaBH_4$ in three portions. After 20 h, hydrolysis was accomplished with saturated NH_4Cl, and the solution was concentrated. Extraction with 1:1 ether–benzene (2 × 100 mL) followed by washing the organic extracts with saturated NaCl, decolorization, gravity filtration through a cone of $MgSO_4$, and evaporation of the solvent afforded a yellow solid (one spot by TLC) which was used directly (4.79 g, 68%). Aromatization was accomplished as described[2] with 10% Pd/C (25% by weight), purifying by vacuum distillation directly from the reaction mixture followed by recrystallization from benzene–methanol. From 0.32 g of alcohol, 0.23 g of **1** was isolated (77%): mp 139–140 °C (lit. mp 139–140 °C[2]); ^1H NMR ($CDCl_3$) δ 2.62 (s, 3, CH_3), 7.08, 7.34, 7.48, 7.72, 7.88, 7.97, 8.03, 8.13, 8.22, 8.58, 8.70, 8.87 (m, 11, aromatics); UV (EtOH) λ_{max} (ϵ) 407 (6400), 386 (20 800), 384 (20 300), 379 (26 200), 367 (20 500), 350 sh (11 300), 335 sh (5200), 298 (57 200), 286 (44 200), 273 (30 500), 267 (48 900), 256 (37 700), 228 (24 700), 222 (23 100).

Registry No. **1**, 70644-19-8; **2**, 70644-20-1; **3a**, 129-00-0; **3b**, 3029-19-4; **3c**, 70644-21-2; **3d**, 70644-22-3; (*E*)-**3e**, 70644-23-4; (*Z*)-**3e**, 70644-24-5; **3f**, 70644-25-6; 7-hydroxy-9-methyl-7,8,9,10-tetrahydrobenzo[*a*]pyrene, 70644-26-7; diethyl 1-(methylthio)ethylphosphonate, 22966-40-1; ethyl trimethylsilylacetate, 4071-88-9.

Stereospecific Synthesis of *threo*- and *erythro*-1-(Aryloxy)-3-(alkylamino)butan-2-ols

Howard Tucker

Imperial Chemical Industries Limited, Pharmaceuticals Division, Mereside Alderley Park, Macclesfield Cheshire, England SK10 4TG

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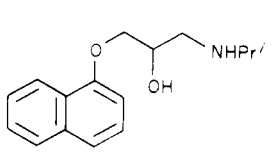
There is an extensive literature on the biological consequences of α-alkyl substitution in the ethanolamine moiety of β stimulants related to isoproterenol[1] and related β antagonists.[2] By contrast, relatively little structure–activity work has been reported on the effects of α-alkyl substitution on the biological properties of the medicinally important β antagonists related to propranolol (**1**). In



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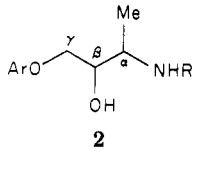
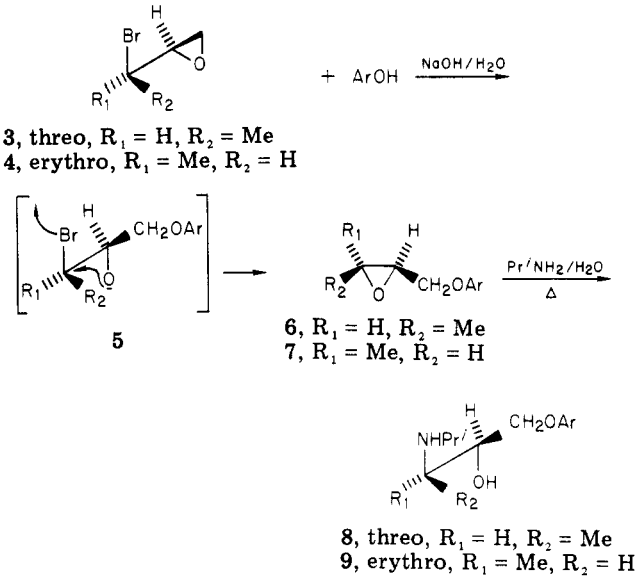


2

(1) R. T. Brittain, D. Jack, and A. C. Ritchie, *Adv. Drug Res.*, **5**, 197 (1970).

(2) R. Howe, *J. Med. Chem.*, **12**, 642 (1969), and references cited therein.

Scheme I



studying this problem we devised a route for the stereoselective synthesis of the threo and erythro isomers of 1-(aryloxy)-3-(alkylamino)butan-2-ols (**2**) starting from the simple precursors *cis*- and *trans*-crotyl alcohol. Recent reports on the synthesis of α- and γ-methyl(aryloxy)propanolamines[3,4] have prompted us to report our own findings.

We discovered that phenols reacted with both *threo*- and *erythro*-(1-bromoethyl)oxirane[5] (**3** and **4**, respectively) under basic conditions at room temperature to give in each case a single oxirane product to which we have assigned the cis and trans structures **6** and **7** (see reaction Scheme I). The *threo*-(1-bromoethyl)oxirane (**3**) was prepared from *trans*-crotyl alcohol as described by Hiskey et al.;[6] the erythro isomer (**4**) was obtained from *cis*-crotyl alcohol by an analogous method. In practice, **3** and **4** are considerably less reactive than the related demethyl analogue chloromethyloxirane, and there is still ca. 10% phenol present after 3 days' stirring. We usually stopped the reaction at this stage and the excess phenol was easily removed by extraction with dilute caustic soda.

In principle the reaction of oxirane **3** with a nucleophile can occur at carbon atoms 1, 2, or 3. Attack at carbon 2 was ruled out since this could not yield an oxirane and moreover there is ample precedent[7] that nucleophiles attack oxiranes at the least substituted carbon atom. A direct S_N2 attack on carbon 3 with displacement of the bromine atom would have given a terminal oxirane whereas the ^1H NMR spectra of the products **6a–c** clearly show signals for two vicinal oxirane protons and for the OCH_2 group. Attack at carbon 1 is consistent with the findings of Hiskey et al.,[6] who showed that **3** reacted with sodium acetylide at carbon 1, and also of Waters et al.,[8] who showed that sodium methoxide attacked (1-bromoethyl)oxirane at carbon 1. Interestingly Waters et al.

(3) G. Shtacher, R. Rubenstein, and P. Somani, *J. Med. Chem.*, **21**, 678 (1978).

(4) T. L. Lemke, R. L. Boblitt, G. A. Capiton, L. A. Cates, and G. E. Martin, *J. Org. Chem.*, **43**, 2079 (1978).

(5) A more precise nomenclature for *threo*-(1-bromoethyl)oxirane (**3**) is 2(*SR*)-[1(*SR*)-bromoethyl]oxirane and likewise the erythro isomer (**4**) is 2(*SR*)-[1(*RS*)-bromoethyl]oxirane.

(6) C. F. Hiskey, H. L. Slates, and N. L. Wendler, *J. Org. Chem.*, **21**, 429 (1956).

(7) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(8) R. C. Waters and C. A. Van Der Werf, *J. Am. Chem. Soc.*, **76**, 709 (1954).

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