96 (47), 94 (100), 83 (54), 79 (82); NMR δ 5.98 (br, 1 H), 5.40 (vbr, 1 H), 4.36 (br, 1 H), 1.97 (s, 3 H), 0.7-2.0 (m, 12 H). Anal. Calcd for $C_9H_{15}NO$: C, 70.56; H, 9.86. Found: C, 70.32; H, 9.64.

**2-(1-Hydroxyethyl)-1-methylcyclohexanol (6).** Hydroboration of 1.0 g of **1c** was carried out by using a commercial solution of borane in tetrahydrofuran (Alfa), followed by alkaline hydrogen peroxide workup to afford 1.10 g (97%) of diol **6**: mp 81.0-84.0 °C; NMR δ 4.26 (br, 1 H) 1.25-1.95 (m, 11 H), 1.22 (s, 3 H), 1.18 (d, 3 H).

**Registry No. 1a** (isomer 1), 83528-99-8; **1a** (isomer 2), 83529-00-4; **1b**, 771-98-2; **1c**, 79828-21-0; **1c** α-naphthylurethane, 83529-06-0; **1d**, 591-49-1; **2**, 83529-01-5; **3**, 83529-02-6; **4**, 83529-03-7; **5**, 83529-04-8; **6**, 83529-05-9; mercuric nitrate, 10045-94-0.

## Convenient Synthesis of *meso*-Azobis(α-phenylethane)

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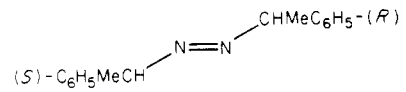
We had the need to develop a method of synthesis of *meso*-azobis(α-phenylethane) [*meso*-bis(1-phenylethyl)-diazene, **1**] which could be used to prepare large quantities (100 g-1 kg) of pure material.




**1**

The synthesis of **1** has been reported,[1-7] and in all cases the starting material of choice has been acetophenone azine (**2**). Catalytic reduction of **2** over Pt or Pd/C in glacial acetic acid[2,3] (ethanol[4] or dioxane[5]) afforded the substituted hydrazine **3** as a mixture of racemic and meso forms. Oxidation of the isolated hydrazines to **1** was accomplished by treatment of **3** with hydrogen peroxide in the presence of aqueous $NaHCO_3$[2a] (34% yield), oxygen gas over a heptane solution of **3**[4] (72% yield), air over **3** as a neat oil[3] (73% yield), or mercuric oxide in an ether[6] or benzene[2b] solution of **3** (47% yield). The method of Scheppele[7] involved the addition of 1 mol of chlorine to **2** followed by reduction with lithium aluminum hydride (or deuteride) to afford **1** (or **1**-$d_2$) in 52% yield. In some of these reported syntheses, the description of the procedures was vague[1-5] and lacked the necessary detail to allow one to synthesize **1** in reasonable quantity and quality without considerable experimental study. In others, the use of expensive reagents (mercuric chloride,[2b,6] lithium aluminum hydride[7]) discourage their use in preparing larger quantities of **1**.

In our hands, the reduction of the azine **2** (20 g) in glacial acetic acid (200 mL) with hydrogen (~40-50 psi) and 5% or 10% Pd/C proceeded readily to give **3** contaminated with an appreciable amount of side product,[8] *dl*-α-phenylethylamine, which remained unchanged in the oxidation step (using either mercuric oxide, oxygen, or air).

The hydrogenation of the azine **2** in ethyl acetate over 10% Pd/C proceeded at a reasonable rate at 30-50 psi and ambient temperature to afford a colorless solution of **3** (single spot by TLC) after removal of the catalyst. This solution can be directly treated (15 min) with dry freshly prepared mercuric oxide to afford **1** (~50% yield after workup); however, it was more convenient to oxidize **3** to **1** by stirring the ethyl acetate solution of **3** under an atmosphere of oxygen at ambient temperature (1.5-3 h) to give **I** in ~50% isolated yield. The procedure described here can be successfully used to prepare **1** on a scale of 10-100 g of isolated crystalline product (mp 72-73 °C) in less than 2 days.

### Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The $^1H$ NMR spectrum of **1** was measured on a Varian Model FT-80 spectrometer. Reactions were monitored and product purity was checked by thin-layer chromatography on precoated silica gel plates (EM Laboratories, 60F-254) by using 3:1 toluene/EtOAc as the developing solvent. The compounds and their approximate $R_f$ values were as follows: **1**, 0.80; **2**, 0.76; **3**, 0.26.

**Acetophenone Azine (2).** The azine **2** was prepared essentially according to the procedure described by Cohen[2a] by using acetophenone (350 mL, 3.0 mol), 95+% hydrazine[9] (48 mL, 1.5 mol), 95% EtOH (1500 mL), and glacial HOAc (6 mL) in a 3-L Erlenmeyer flask equipped with a reflux condenser and magnetic stirrer. After the mixture was refluxed for 3.5 h, the reaction was complete (TLC), and after the mixture cooled, 336 g of acetophenone azine (95% yield) was collected as bright yellow prisms, mp 122-123 °C. An additional 11 g of **2** of equal quality could be obtained by concentration of the mother liquor (to 400 mL) for a total yield of 98%.

***meso*-Azobis(α-phenylethane) (1).**[10] A 2-L Parr hydrogenation bottle was charged with acetophenone azine (mp 122-123 °C; 200.0 g, 846 mmol), EtOAc (1000 mL),[11] and 10% Pd/C (5.0 g) and shaken with $H_2$ on a Parr Model 3921 low-pressure hydrogenation apparatus at 30-50 psi for 10 h, at the end of which time the absorption of hydrogen ceased, and 2 equiv of $H_2$ had been absorbed. The reaction mixture was filtered through a pad of Celite (suction) to remove the catalyst. The colorless filtrate (TLC, single spot, $R_f$ 0.26, 3:1 toluene/EtOAc) was placed in a 2-L round-bottomed flask equipped with a magnetic stirrer, and the system was flushed with oxygen and connected to a reservoir of oxygen (balloon). After 0.5 h, the solution had turned pale yellow and warmed slightly. After 3 h, the oxidation was complete (TLC, single spot, $R_f$ 0.80, 3:1 toluene/EtOAc). Most of the EtOAc was removed on a rotary evaporator at 30 °C (25 mmHg) to give 240 g of a pale yellow oil (product plus EtOAc) to which was added 100 mL of MeOH. The resulting solution was cooled to 0 °C and stored for several hours in an ice bath, after which time **1** was collected as colorless crystals which were washed with two 20-mL portions of cold (ice bath) MeOH.[12] The air-dried product (105 g, 52% yield; mp 68-70 °C) was recrystallized from 230 mL of

(1) Schulze, W. A.; Lochte, H. L. *J. Am. Chem. Soc.* **1926**, *48*, 1031.
(2) (a) Cohen, S. G.; Groszos, S. J.; Sparrow, D. B. *J. Am. Chem. Soc.* **1950**, *72*, 3947. (b) Cohen, S. G.; Wang, C. H. *Ibid.* **1955**, *77*, 2457.
(3) Gibian, M. J.; Corley, R. C. *J. Am. Chem. Soc.* **1972**, *94*, 4178.
(4) Robertson, J. A. *Chem. Abstr.* **1952**, *45*, P1384g; U.S. Patent 2520339 (to Du Pont), Aug 29, 1950.
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(6) Shelton, J. R.; Liang, C. K. *Synthesis* **1971**, 204.
(7) Grizzle, P. L.; Miller, D. W.; Scheppele, S. E. *J. Org. Chem.* **1975**, *40*, 1902.

(8) The side product (7.6 g) was isolated after oxidation of the crude **3** in ether solution with oxygen (1.5 days) by extraction with 5% aqueous HCl from which it was liberated with aqueous KOH. It was shown to be identical with *dl*-α-phenylethylamine (formed by hydrogenolysis of the NH-NH bond in **3**) by comparison with an authentic sample ($^1H$ NMR, IR, and benzamide melting point, 120-121 °C).
(9) The use of 99% hydrazine hydrate (73 mL, 1.5 mol) could be employed with equal success.
(10) This procedure has also been carried out on smaller scales by using the same proportions of **2** (160, 40, or 20 g) to EtOAc (800, 200, or 100 mL) and 10% Pd/C (4, 1, or 0.5 g) with the same overall percent yields of pure **1**.
(11) The amount of azine used is only partly soluble in this amount of EtOAc but dissolves as the hydrogenation proceeds.
(12) The mother liquor from this crystallization contained only azo compound (TLC, $R_f$ 0.80) which was shown by $^1H$ NMR analysis to have the composition of approximately 7 parts of racemic **1** to 1 part of *meso*-**1**.

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MeOH to give 88.0 g (44% overall yield from 2) of pure *meso*-azobis(α-phenylethane) [mp 72–73 °C (lit.[2a] mp 72–73 °C)], after being drying to constant weight at 0.5 mmHg. The $^1$H NMR spectrum was consistent with that reported for 1.[6,13]

**Acknowledgment.** This work was supported in part by Contract 16-9135 from Sandia National Laboratories, Albuquerque, NM.

**Registry No.** *meso*-1, 65026-52-0; *dl*-1, 65026-53-1; 2, 729-43-1; *meso*-3, 83587-18-2; *dl*-3, 83587-19-3; acetophenone, 98-86-2; hydrazine, 302-01-2; *dl*-α-phenylethylamine, 618-36-0.

(13) Personal communication from Professor Frederick D. Greene, Department of Chemistry, MIT.

## Selectivity in the Hydrogenation of 20(22)-Dehydro Steroids

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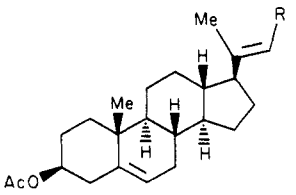
Attachment of the steroid side chain onto tetracyclic steroid starting materials to yield products with the natural C-20(R) configuration has been the subject of investigation by several research groups. The impetus for this work has been provided by a need for synthetic methods for elaboration of the functionalized side chains present in a variety of ecdysones (insect moulting hormones),[1] vitamin D metabolites,[2] and unusual marine sterols.[3] Of all the known methods of side-chain introduction,[4] the Wittig olefination of 20-oxo steroids followed by selective hydrogenation,[4b-d] is one of the simplest and most versatile since it takes advantage of the ready availability of 20-oxo steroids. It has been amply demonstrated, and is now generally accepted, that 20-oxo steroids can be efficiently condensed with Wittig reagents to yield exclusively (*E*)-20(22)-dehydro steroids.[4b-d] The success of this method therefore is dependent only on specific, or at least selective, hydrogenation of the 20(22)-dehydro intermediates. The older literature[5] and even a recent report by Piraux and co-workers[4b] suggest this can be accomplished with complete specificity. More recent reports by McMorris and Schow,[4c,d] however, indicate this to be only a fairly selective process. Other recent work by Uskokovic,[4e] Nes,[6] and their co-workers suggests the near absence of selectivity. In order to resolve this controversy, a study was initiated to determine the effects of experimental parameters on reduction selectivity.

The two 20(22)-dehydro steroids which have been most studied, with regard to hydrogenation selectivity, are 20-(22)-dehydrocholesteryl acetate (1) and 20(22)-dehydro-25-oxo-27-norcholesteryl acetate (2).[7] In this earlier work, the selectivity estimates are in question, due either to the absence of a precise analytical method of quantitation or to the likely possibility of incomplete resolution of all components on gas–liquid phase chromatography (GLC). High-resolution GLC, on wall-coated open tubular (WCOT) columns, was used in the present work to provide rapid and precise estimates of reaction aliquot and product compositions. The results of a study employing authentic samples of 1, and the expected reduction products 3 and 4[8] as well as the tetrahydro compound 5,[9] on commercially available OV-1, SE-54, and SP-2250 WCOT GLC columns showed that only the SP-2250 column is of use in this analysis. Only this medium-polarity column allows complete resolution of diene 1 from cholesteryl acetate (3) such that reduction of 1 to 3 and 4 can be easily followed to the consumption of all 1. The capacity factor ($k'$) and separation factor ($\alpha$) values were determined as described by Jennings.[10] For the SP-2250 column (10 m, 250 °C), the $k'$ values were as follows: 1, 30.6; 3, 28.9; 4, 25.7; 5, 29.0. The $\alpha$ values were as follows: 1/3, 1.06; 1/4, 1.19; 3/5, 1.00.[11] Analogous results were obtained on GLC analysis




1, R = $CH_2CH_2CH(CH_3)_2$
2, R = $CH_2CH_2COCH_3$

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(1) (a) Nakanishi, K. *Pure Appl. Chem.* **1971**, *25*, 167. (b) Hikino, H.; Hikino, Y. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 256.

(2) (a) Deluca, H. F.; Schnoes, H. K. *Annu. Rev. Biochem.* **1976**, *45*, 631. (b) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 85.

(3) (a) Nes, W. R.; McKean, M. L. "Biochemistry of Steroids and Other Isoprenoids"; University Park Press: Baltimore, MD, 1977. (b) Minale, L.; Sodano, G. In "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Plenum Press: New York, 1977; p 87.

(4) (a) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. (b) Schmit, J. P.; Piraux, M.; Pilette, J. F. *J. Org. Chem.* **1975**, *40*, 1586. (c) McMorris, T. C.; Schow, S. R. *Ibid.* **1976**, *41*, 3759. (d) Schow, S. R.; McMorris, T. C. *Ibid.* **1979**, *44*, 3760. (e) Narwid, T. A.; Cooney, K. E.; Uskokovic, M. R. *Helv. Chim. Acta* **1974**, *57*, 771. (f) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630. (g) Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (h) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3445. (i) Tanabe, M.; Hayashi, K. *Ibid.* **1980**, *102*, 862. (j) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172. (k) Dauben, W. G.; Brookhart, T. *J. Am. Chem. Soc.* **1981**, *103*, 238. (l) Marino, J. P.; Abe, H. *Ibid.* **1981**, *103*, 2907. (m) Midland, M. M.; Kwon, Y. C. *J. Org. Chem.* **1981**, *46*, 229. (n) Kyler, K. S.; Watt, D. S. *Ibid.* **1981**, *46*, 5182.

(5) (a) Hershberg, E. P.; Oliveto, E. P.; Gerold, C.; Johnson, L. *J. Am. Chem. Soc.* **1951**, *73*, 5073. (b) Bergmann, E. D.; Rabinowitz, M.; Levinson, Z. H. *Ibid.* **1959**, *81*, 1239.

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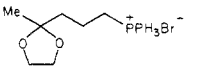
(7) This compound was prepared by modification of the procedure of ref. 4c, which involving Wittig condensation of the ylide derived from phosphonium salt i with pregnenolone. The literature procedure (Crombie, L.; Hemesley, P.; Pattenden, G. *J. Chem. Soc. C* **1969**, 1016) for preparation of i from the corresponding bromide (benzene, 80 °C, 48 h) was found not to be very useful, giving i in only 9% yield. Reaction at 120 °C for 144 h in xylene, however, gave i in 86% yield. Higher temperatures with shorter reaction times resulted in decomposition of i. The condensation of the ylide derived from i with pregnenolone is reported to require a large excess (6–8 equiv) of ylide for high yields of olefin. In the present work, a 71% yield of olefin was obtained from a reaction which employed only 2.2 equiv. of Wittig reagent.




i

(8) An authentic sample was prepared by acetylation ($Ac_2O$, pyr) of 20-isocholesterol, a sample of which was generously provided by Dr. M. Tanabe, SRI International.

(9) Reduction of 20(22)-dehydrocholesterol over $PtO_2$ in dioxane–HOAc has been reported to result in 28% conversion to the C-20 isomeric cholestanol derivatives (see ref 6a).

(10) Jennings, W. "Gas Chromatography with Capillary Columns", 2nd ed.; Academic Press: New York, 1980; Chapter 1.

(11) For the OV-1 column (10 m, 240 °C), the $k'$ values were as follows: 1, 12.1; 3, 12.1, 4, 11.0. The $\alpha$ values were as follows: 1/3, 1.00; 1/4, 1.11. For the SE-54 column (15 m, 270 °C), the $k'$ values were as follows: 1, 12.2; 3, 12.2; 4, 11.0; 5, 12.5; 6, 11.2. The $\alpha$ values were as follows: 1/3, 1.00; 1/4, 1.10; 3/5, 1.02; 4/6, 1.02.

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