cyclohexyl ketone oxime, 6316-03-6; acetophenone oxime, 613-91-2; benzophenone oxime, 574-66-3; *p*-tolyl *tert*-butyl ketone oxime, 31007-19-9; 2',4'-dichloroacetophenone oxime, 71516-67-1; 3',4'-dichloroacetophenone oxime, 71516-68-2; 2',5'-dichloroacetophenone oxime, 71516-69-3; 2-thienyl methyl ketone oxime, 1956-45-2; cyclopropyl ketone oxime, 1453-52-7; 4'-nitroacetophenone oxime, 10342-64-0; 3'-nitroacetophenone oxime, 7471-32-1; 4'-methoxyacetophenone oxime, 2475-92-5; 2',4'-dimethoxyacetophenone oxime, 23997-80-0; 4'-chloroacetophenone oxime, 1956-39-4; 2-(diethylamino)ethyl ketone oxime, 71516-70-6; acetone, 67-64-1; 3-pentanone, 96-22-0; cyclohexyl ketone, 1121-37-5; acetophenone, 98-86-2; benzophenone, 119-61-9; *p*-tolyl *tert*-butyl ketone, 30314-44-4; 2',4'-dichloroacetophenone, 2234-16-4; 3',4'-dichloroacetophenone, 2642-63-9; 2',5'-dichloroacetophenone, 2476-37-1; 2-thienyl methyl ketone, 88-15-3; cyclopropyl ketone, 1121-37-5; 4'-nitroacetophenone, 100-19-6; 3'-nitroacetophenone, 121-89-1; 4'-methoxyacetophenone, 100-06-1; 2',4'-dimethoxyacetophenone, 829-20-9; 4'-chloroacetophenone, 99-91-2; 2-(diethylamino)ethyl ketone, 71516-71-7; dichloromethane, 75-09-2.

Reduction of Diphenylethylenes and Related Compounds with Magnesium in Methanol

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Diphenylethylenes and diphenylethanes appear rather frequently in the chemical literature, particularly within realms of medicinal interest, either in the open-chained forms or as closed-ring analogues.[1] In many cases, the syntheses of particular diphenylethylene derivatives and their dihydro analogues were carried out independently by parallel reaction schemes with different starting materials;[2] thus it would appear that, at least in some cases, the synthesis of diphenylethane derivatives could have been facilitated if an efficient method were available for the reduction of the corresponding diphenylethylenes.

The most commonly used reduction procedures for simple diphenylethylenes include catalytic hydrogenation over palladium or platinum,[3] which allows rapid reduction of the 1,1-diphenylethylenes but reduces the stilbenes less readily;[4] furthermore, the course of reduction could be inhibited by the presence of a bivalent sulfur[5] or nitrogen atom,[6] as in the case of iminostilbenes. Sodium borohydride in trifluoroacetic acid has been reported to reduce 1,1-diphenylethylene in good yield, yet it fails to saturate the olefinic double bonds in a dibenzo[*a*,*d*]cyclohepten-5-ylidene derivative.[7] Lithium–ammonia has been used successfully in reducing the central double bond of phenanthrene;[8] metal–ammonia reductions of simple 1,1-diphenylethylenes, however, tend to give large amounts of dimeric products.[9] Numerous other methods of reduction have also shown merit in specific examples, but their general applicability has not been demonstrated.[10]

In connection with our work directed toward the synthesis of some dihydrodibenz[*b*,*f*]oxepins and dihydrodibenzo[*b*,*f*]thiepins, we have discovered that the use of magnesium in methanol can effectively reduce a variety of 1,1- and 1,2-diphenylethylenes as well as related compounds. Previously, magnesium in methanol (or other alcohols) has only been used in the reduction of carbon–heteroatom double bonds[11,12] and nitrogen oxides,[13] and, more recently, its success in selective reduction of various α,β-unsaturated nitriles has been demonstrated.[14] Under somewhat modified conditions,[15] we have found that the reduction of diphenylethylenes can proceed in virtually quantitative yields, except in cases where the double bond is part of an aromatic ring. Results of this study are summarized in Table I.

In addition to its efficiency, economy, and convenience, the magnesium in methanol reduction also offers the advantage of being applicable to systems incorporating nuclear halogen substituents and heteroatoms, such as a bivalent sulfur, oxygen, and basic nitrogen, as demonstrated by the reduction of **8a** in Table I.[15,16]

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. The vapor-phase chromatographic (VPC) analyses were performed using either a 2 mm i.d. × 6 ft 3% OV-17 on 60/80 Gas Chromosorb Q silanized glass column or a 4 mm i.d. × 6 ft 3% OV-1 on 100/120 Chromosorb W-H.P. stainless steel column in a Perkin-Elmer Model 3920B gas chromatograph with a flame ionization detector. All percent-composition values are reported as relative peak areas without correction for relative detector response. Infrared spectra were recorded on a Perkin-Elmer Model 727 grating spectrometer. ^{1}H NMR spectra were obtained on a JEOL C60-HL spectrometer; chemical shifts (δ) are reported relative to Me_4Si. Mass spectra were obtained using a Finnigan Model 4000 quadrupole mass spectrometer at 70 eV, equipped with the INCOS data system; when chemical ionization was used, methane was the reagent gas.

In all workup procedures, "brine" refers to saturated sodium chloride solution. The drying process involved standing the solution over $MgSO_4$ and filtering it prior to evaporation. Magnesium shavings were obtained from Matheson Coleman and

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(2) (a) E. L. Engelhardt, H. C. Zell, W. S. Saari, M. E. Christy, and C. D. Colton, *J. Med. Chem.*, **8**, 89 (1965); (b) E. L. Engelhardt, U. S. Patent 3014911 (1961); *Chem. Abstr.*, **56**, 10112h (1962).

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(4) When magnesium in methanol is used, the order of ease of reduction seems to be reversed though both examples are conveniently reduced.

(5) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 15.

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(10) (a) W. L. Jolly and K. A. Strom, *J. Org. Chem.*, **36**, 3649 (1971); (b) N. J. Cusack, C. B. Reese, A. C. Risius, and B. Roozpeikar, *Tetrahedron*, **32**, 2157 (1976); (c) L. G. Humber, F. Herr, and M.-P. Charest, *J. Med. Chem.*, **14**, 982 (1975); Limpricht and Schwanert, *Justus Liebigs Ann. Chem.*, **145**, 334 (1868); F. Toda and M. Kanno, *Bull. Chem. Soc. Jpn.*, **49**, 2643 (1976); R. Fischer, F. M. Kungle, and J. Schmutz, Swiss Patent 593965 (1977); (d) D. D. Phillips, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 313; R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, 1965, p 75; L. F. Fieser and W. S. Johnson, *J. Am Chem. Soc.*, **61**, 168 (1939); J. R. Durland and H. Adkins, ibid., **60**, 1501 (1938); G. Schroeter, H. Muller, and J. Y. S. Huang, *Chem. Ber.*, **62**, 645 (1929).

(11) L. Zechmeister and P. Rom, *Justus Liebigs Am. Chem.*, **468**, 117 (1929). Zechmeister and Rom also reported that chlorobenzene was not dehalogenated by magnesium in methanol but iodobenzene and bromobenzene were; in addition, an example of the addition of four hydrogen atoms to an α,β-unsaturated ketone was reported.

(12) (a) V. Hahn, R. Hansal, I. Markovcic, and D. Vargazon, *Ark. Kemi*, **26**, 21 (1954); *Chem. Abstr.*, **50**, 292f (1956); (b) R. Hansal, D. Vargazon, and V. Hahn, *Ark. Kemi*, **27**, 33 (1955); *Chem. Abstr.*, **50**, 4894i (1956).

(13) C. P. Joshua and P. K. Ramdas, *Synthesis*, 873 (1974).

(14) (a) J. A. Profitt, D. S. Watt, and E. J. Corey, *J. Org. Chem.*, **40**, 127 (1975); (b) D. S. Watt and M. L. Raggio, *ibid*, **41**, 1873 (1976); (c) R. W. Freerksen, W. E. Pabst, M. L. Raggio, S. A. Sherman, R. R. Wroble, and D. S. Watt, *J. Am. Chem. Soc.*, **99**, 1536 (1977); (d) P. Camps, R. M. Ortuno, and F. Serratosa, *Tetrahedron*, **32**, 2583 (1976); (e) D. J. Aberhart and C-T. Hsu, *J. Org. Chem.*, **43**, 4374 (1978); (f) D. S. Watt, *Diss. Abstr. B*, **33** (10)8 4699 (1970).

(15) Conditions have not been completely optimized.

(16) Unpublished results by J. A. Profitt and H. H. Ong.

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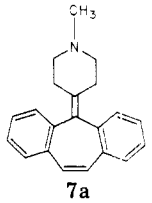
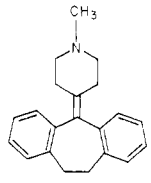
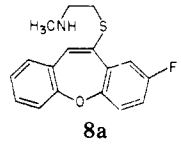
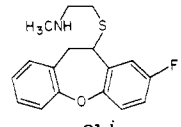
Table I. Reduction of Diphenylethylenes and Related Compounds

starting material	product	conditions[j] (equiv of Mg, temp, time)	% reduction[a]
trans-stilbene (1a)	1,2-diphenylethane (1b)	A[b]	100,[c] 99[d]
cis-stilbene (2)	1b	A	100[c]
1,1-diphenylethylene (3a)	1,1-diphenylethane (3b)	A	91,[c] 91[d]
		B[e]	100,[c] 99+[d]
5*H*-dibenz[*b*,*f*]azepine (4a)	10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (4b)	A	100,[c] 100[d]
2-phenylindole (5a)	2-phenylindoline (5b)	A	0,[c] 0[d]
		B	0,[c] 0[d]
phenanthrene (6a)	9,10-dihydrophenanthrene (6b)	A	4,[c] 2[d]
		B	28,[c] 28[d]
		(20.0, reflux, 90)	50,[c] 52[d,f]
 7a	 7b	(10.0, RT, 180)	78,[c] 85[d]
		(10.0, 50, 180)	94,[c] 97[d]
 8a	 8b[i]	(40.0, RT, 120)	85,[g] 67[h]

[a] The remainder of the crude material is starting material unless otherwise indicated. [b] 10.0 mol equiv of Mg, RT, 90 min. [c] As determined by ^{1}H NMR integration. [d] As determined by VPC. [e] 10.0 mol equiv of Mg, 50 °C, 90 min. [f] An impurity of 1.3%, possibly arising from further reduction of **6b**, was apparent by VPC. [g] Isolated yield; TLC indicated complete reduction to **8b**. [h] Isolated yield of the maleate salt of **8b**. [i] The free base was converted to a crystalline maleate in ether, mp 118–120 °C. Anal. Calcd for $C_{21}H_{22}FNO_5S$: C, 60.14; H, 5.29; N, 3.34; F, 4.53. Found: C, 60.11; H, 5.19; N, 3.19; F, 4.80. [j] (Equivalents of Mg, temperature in °C, time in minutes).

Bell and were of the type specified for Grignard reaction. The methanol was obtained from Mallinckrodt and was sold as "Karl Fischer Methanol". Cyproheptadine hydrochloride (**7a**) was a gift from Merck, Sharp and Dohme Research Laboratories. Other starting materials were obtained from Aldrich Chemical Co. and were used without further purification.

1,2-Diphenylethane (1b). Method A. To 1.00 g (0.0056 mol) of *trans*-stilbene, **1a** (97%), in 55.5 mL of methanol was added 1.35 g (0.056 mol) of magnesium shavings in one portion. The reaction was stirred in a room temperature water bath for 90 min, then the methanol was decanted from any remaining shavings with 10 mL of methanol as a rinse. The combined methanolic solution was cooled in ice, treated with 30 mL of 6 N hydrochloric acid, and diluted with 150 mL of water. The mixture was extracted three times with chloroform. The combined chloroform solution was washed with water and brine and dried to give 1.04 g of a white crystalline solid: mp 48–52 °C (mp of authentic sample (Aldrich) 50–53 °C); VPC analysis (OV-1, 250 °C) indicated a purity >99%; NMR ($CDCl_3$) was identical with the reported spectrum;[17a] IR ($CHCl_3$) was identical with that obtained with an authentic sample of **1b**; MS *m*/*e* (rel intensity) 182, (17, M^+), 91 (100).

cis-Stilbene (97%) (1.00 g) was reduced to give 1.02 g of a white crystalline solid using the same procedure outlined in method A: mp 51–52.5 °C; IR ($CHCl_3$), NMR ($CDCl_3$), and mass spectrum of this compound were identical with those of **1b** obtained after reduction of *trans*-stilbene.

1,1-Diphenylethane (3b). Method B. To 1.00 g (0.0056 mol) of 1,1-diphenylethylene (**3a**, 97%) in 55.5 mL of methanol in a 50 °C oil bath was added 1.35 g (0.056 mol) of magnesium shavings. The reaction was stirred at 50 °C for 90 min then worked up as described in method A to give 1.03 g of a clear oil: VPC analysis (135 °C, OV-17) indicated >99% purity; IR (TF) 3.20–3.41, 6.22, 6.68, 6.84, 7.22, 9.7, and 10.9 μm; NMR ($CDCl_3$) δ 7.5 (s, 10 H, aromatic), 4.16 (q, J = 7.5 Hz, 1 H, $CHCH_3$), and 1.64 (d, J = 7.5 Hz, 3 H, $CHCH_3$); MS *m*/*e* (rel intensity) 182 (40, M^+), 167 (100).[19a]

10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepine (4b). Iminostilbene (1.00 g; 0.0052 mol) in 52 mL of methanol was reduced with 1.26 g (0.052 mol) of magnesium and worked up as in method A, except that the combined chloroform solution was shaken with 10% sodium hydroxide solution before washing it with water, to give 0.99 g of a lilac-colored solid: mp 104.5–105.5 °C (mp of authentic sample (Aldrich) 105–106.5 °C); VPC analysis (OV-17, 190 °C) indicated 100% conversion; IR (Nujol) was identical with the reported spectrum;[18] NMR ($CDCl_3$) was identical with the reported spectrum;[17b] MS *m*/*e* (rel intensity) 195 (100, M^+).

Partial Reduction of Phenanthrene (6a) to 9,10-Dihydrophenanthrene (6b). To 1.00 g (0.0056 mol) of phenanthrene (98%) in 56 mL of methanol at reflux was added 2.72 g (0.112 mol) of magnesium shavings. The reaction was refluxed for 90 min then worked up as in method A to give 1.02 g of a semisolid material: VPC analysis (OV-17, 160 °C) indicated 50% reduction to **6b** (determined by coinjection with authentic **6b** (Aldrich)) and approximately 1.3% of an unidentified product; NMR ($CDCl_3$) of the reaction mixture, δ 8.50–8.95 (m, **HC=CH** of **6a**), 7.0–8.2 (m, aromatic), and 2.85 (s, CH_2 of **6b**)[17a,19c] [the magnitudes of the δ 2.85 and 8.50–8.95 integrations were compared to indicate 52% reduction]; MS (chemical ionization) *m*/*e* (rel intensity) 181 (97.4, MH^+ of **6b**), 179 (100.0, MH^+ of **6a**).

4-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-methylpiperidine (7b). Cyproheptadine hydrochloride was converted to the free base with aqueous base, extracted, and dried to give 4-(5-dibenzo[*a*,*d*]cycloheptenylidene)-1-methylpiperidine (**7a**).

To 503 mg (0.00175 mol) of **7a** in 17.5 mL of methanol in a 50 °C oil bath was added 426 mg (0.0175 mol) of magnesium shavings. The reaction was stirred at 50 °C for 3 h and monitored by VPC (OV-17, 215 °C). Approximately 10–90% of the reduction oc-

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(18) C. J. Pouchart, "The Aldrich Library of Infrared Spectra", 2nd ed, Aldrich Chemical Co., Inc. Milwaukee, Wis., 1975, p 695.

(19) (a) "CRC Atlas of Spectral Data and Physical Constants for Organic Compounds", J. G. Grasselli, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1973, Part B p 506; (b) *ibid.*, Part B, p 748; (c) *ibid*, Part B p 749.

curred between the first and second hours of reaction.[20] The methanolic solution, with 2 mL of methanol as a rinse, was treated with 10 mL of 6 N hydrochloric acid, diluted with 55 mL of water, and extracted three times with chloroform. The chloroform solution was shaken with 10% sodium hydroxide solution, washed with water and brine, and dried to give 508 mg of a clear oil which crystallized on standing: VPC analysis (OV-17, 215 °C) indicated 97% conversion; IR (KBr) 3.23–3.78, 6.72, 6.81, 6.92, 7.02, 7.18, 7.76, 7.98, 8.78, and 8.83 μm; NMR ($CDCl_3$) δ 7.11 (s, aromatic) and 1.90–3.70 (m, alkyl), with δ 7.20–7.33 (m, aromatic of **7a**) and 6.92 (S, **HC=CH** of **7a**) [comparison of the integrations in the δ 6.9–7.4 region indicated 94% reduction]; MS *m/e* (rel intensity) 289 (22, M^+), 58 (100).

2-Fluoro-10,11-dihydro-11-[(β-(methylamino)ethyl)-thio]dibenz[*b,f*]oxepin (8b). To 0.50 g (0.0017 mol) of 2-fluoro-11-[(β-(methylamino)ethyl)thio]dibenz[*b,f*]oxepin (**8a**)[21] in 16 mL of methanol at room temperature was added 1.59 g (0.066 mol) of magnesium shavings. The reaction was stirred at room temperature for 2 h, and complete conversion was indicated by TLC (25% methanol–benzene, silica gel; R_f of **8a** 0.35; R_f of **8b** 0.22). The methanolic solution was decanted from any undissolved magnesium, treated with 36 mL of 6 N hydrochloric acid, and extracted with chloroform. The chloroform solution was shaken consecutively with 10% sodium hydroxide solution, water, and brine and dried to give an oil. The oil was triturated with hot pentane, and the pentane was evaporated to give 0.43 g (85% of theory) of **8b**. An ethereal solution of **8b** was treated with ethereal maleic acid, and the resulting salt was washed with ether to give 0.47 g (67% of theory overall) of a white powder: mp 115.5–117.5 °C; IR (KBr) 2.75–3.10, 3.10–4.20, 5.90, 6.38, 6.78, 7.25, 7.40, 8.00, 8.17, and 8.40 μm; NMR ($CDCl_3$) δ 13.5–8.0.(m, 2 H, CO_2**H**), 7.45–6.60 (m, 7 H, aromatic), 6.28 (s, 2 H, olefinic of maleic acid), 4.63–4.30 (m, 1 H, $SCHCH_2$), and 3.90–2.40 (m, 10 H, $ArCH_2CH + S(CH_2)_2NHCH_3$); MS (chemical ionization) *m/e* (rel intensity) 304 (29.4, MH^+).[22]

Registry No. **1a**, 103-30-0; **1b**, 103-29-7; **2**, 645-49-8; **3a**, 530-48-3; **3b**, 612-00-0; **4a**, 256-96-2; **4b**, 494-19-9; **5a**, 948-65-2; **6a**, 85-01-8; **6b**, 776-35-2; **7a**, 129-03-3; **7b**, 50603-12-8; **8a**, 71316-84-2; **8b**, 71316-85-3; **8b** maleate, 71316-86-4; magnesium, 7439-95-4.

(20) An induction period for reductions with magnesium in alcohols has been reported previously: M. Sclar and M. Kilpatrick, *J. Am. Chem. Soc.*, **59**, 584 (1937); also see ref 14a,d.

(21) The synthesis, properties, and pharmacological activity of **8a**, **8b**, and related compounds are the topic of a future publication.

(22) We wish to thank Mr. Marc N. Agnew for spectroscopic determinations and Eve Memoli for assistance in preparation of this manuscript.

Facile Synthesis of 3β-Hydroxy-5α-cholest-8(14)-en-15-one 3-Acetate

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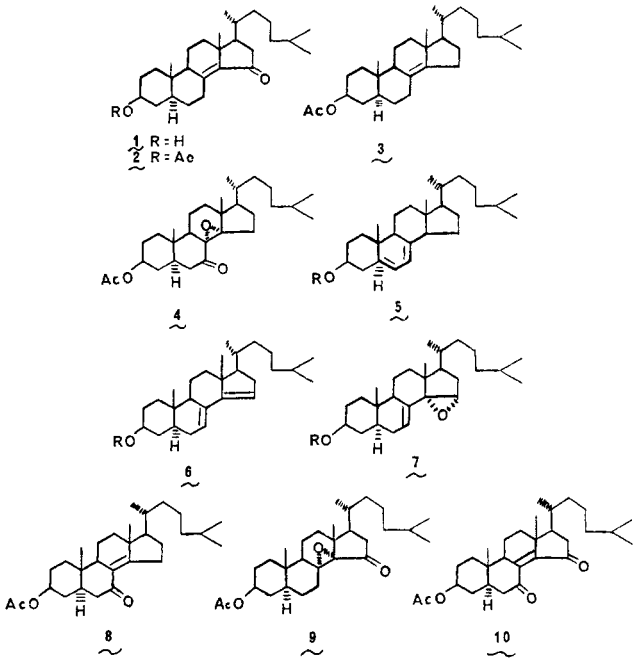
Cholesterol biosynthesis, a process common to nearly all mammalian cells because of the necessity of this sterol in membrane structure, is dependent on the rate-limiting enzyme HMG CoA reductase.[1] Recent investigations have revealed the ability of various oxygenated sterols to suppress the activity of this enzyme in a wide variety of cell systems.[2] Included in this study was the series of 15-oxygenated sterols[3] of previous interest for their role as intermediates in the biosynthesis of cholesterol.[4] In this series the ability of 3β-hydroxy-5α-cholest-8(14)-en-15-one (**1**) to lower serum cholesterol levels in vivo was particularly noteworthy[5] since it represents the first example of such an effect by this type of inhibitor of sterol biosynthesis.

Our desire to study the unique biological activity of **1** in various assays prompted an investigation into its synthesis. Past work on the chromic acid oxidation of 5α-cholest-8(14)-en-3β-ol 3-acetate (**3**) by Wintersteiner and Moore had produced the desired compound directly as its acetate ester **2**, but only in low (6–10%) yield.[6] The



major product of this reaction was the 7-keto-8(14)-epoxide **4** obtained in 16–25% yield along with other components. More recent preparation of **1** had utilized acid-catalyzed isomerization of 7-dehydrocholesterol ester (**5**; R = benzoate) to the 7,14-dienol ester **6** (R = benzoate) which, when treated with peracids, provided the 14-epoxide **7**. Acid hydrolysis then gave the desired 15-keto compound. Since the isomerization reaction is not particularly clean[7,8] and the subsequent reactions produced the desired product in only modest overall yield (ca. 25%),[7] we investigated alternate routes.[18]

A direct oxidation of the readily accessible olefin **3** was appealing, and therefore a study of this approach using some of the more recently developed oxidizing agents was pursued. Initially, **3**, prepared from 7-dehydrocholesterol

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(3) G. J. Schroepfer, Jr., E. J. Parish, H. W. Chen, and A. A. Kandutsch, *J. Biol. Chem.*, **252**, 8975 (1977).

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