Treatment of **12** with aq NaOH gave the free base: mp 246–250°; nmr ($CDCl_3$) δ 1.83 (m, 4, $\overline{NCH_2(CH_2)_2CH_2}$), 2.24 (s, 1, OH?; exchanged with D_2O), 2.65 (m, 4, $\overline{NCH_2(CH_2)_2CH_2}$), 2.90 (t, 2, OCH_2CH_2N), 3.27 (s, 3, CH_3O?), 4.08 (t, 2, OCH_2CH_2), 4.14 (s, 1, unknown), 6.5–7.3 (m, 12, arom); mass spect (70 eV) *m/e* (rel intensity) 443 (M^+) (43), 442 (98), 345 (32), 98 (41), 84 (100). A mol wt detd in soln (DMF; Mechrolab osmometer) indicated that the free base was monomeric; tlc in several solvents indicated homogeneity. *Anal.* ($C_{28}H_{29}NO_2S$) calcd mol wt: 443. Found: 540 (osmometer).

D. Thiapyrans. 3-(*m*-Methoxyphenylthio)-2-phenylpropionic Acid (13).—A mixt of atropic acid (10.45 g, 0.07 mole) and *m*-methoxythiophenol (9.88 g, 0.07 mole) was heated under N_2 at 125° for 20 hr.

The product was dissolved in Et_2O and the resultant soln was washed with 0.1 *N* I_2–KI soln and then was extd with NaOH. Acidification of the basic exts gave an oil which was extd into Et_2O. Washing, drying, and subsequent evapn of the Et_2O gave the acid **13** (15.59 g, 77%) as an oil; nmr indicated the addn to have occurred on the β-C; the product was used directly in the next step without further characterization.

7-Methoxy-3-phenyl-4-thiochromanone (14) and 5-methoxy-3-phenyl-4-thiochromanone (15).—A mixt of the acid **13** (39.9 g) and PPA[15] (798 g) was heated at 80–86° for 1 hr. The mixt was poured onto ice and then was extd with $CHCl_3$. The $CHCl_3$ exts were washed with aq $NaHCO_3$. Drying and evapn left an oil; recrystn (THF–Skellysolve B) gave **14** (11.0 g), mp 147–150°; further recrystn (EtOAc–Skellysolve B) gave mp 151–152.5°; nmr (DMSO-d_6) shows a downfield ortho-coupled doublet (δ 7.7, J = 7 Hz), consistent for the C-5 H deshielded by the adjacent C=O in support of the structural assignment **14**. *Anal.* ($C_{16}H_{14}O_2S$) C, H; S: calcd, 11.86; found, 11.18.

Concn of the mother liquors yielded an addl 9 g of **14** (contaminated by **15** and other impurities). The product from the remaining mother liquors was chromatog (alumina; elution with PhMe) to yield a semisolid (6.2 g); recrystd several times (MeCN) to yield **15** (2.0 g), mp 128.5–132°; nmr arom multiplicity and absence of a downfield doublet in 7.5–8.0 region support the structural assignment **15**. *Anal.* ($C_{16}H_{14}O_2S$) C, H, S.

3,4-Dihydro-7-methoxy-3-phenyl-4-hydroxy-4-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}-2*H*-1-benzothiapyran·HCl (16).—Prepd from **14** (9.35 g) and *N*-[2-(*p*-bromophenoxy)ethyl]pyrrolidine (9.35 g) as described above for **11a**: yield of **16**, 2.11 g (12%); mp 172–173° dec (CH_3OH–Et_2O); uv max (EtOH), 222 (log ε 4.62), 258 (4.21), 280 (sh) (3.92), 296 (sh) (3.63); ir (Nujol) 3320 cm^{-1} (OH). *Anal.* ($C_{28}H_{31}NO_3S$·HCl) C, H, N, S.

7-Methoxy-3-phenyl-4-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}-2*H*-1-benzothiapyran·HCl (17).—The alcohol **16** (1.70 g) was dehydrated by the procedure used for **12**: yield of **17**, 1.05 g (64%); mp 224–226° (CH_2Cl_2–EtOAc); uv max (EtOH), 250 (log ε 4.49), 262 (sh) (4.46), 319 (4.10); ir (Nujol) shows no OH absorption. *Anal.* ($C_{28}H_{29}NO_2S$·HCl) C, H, Cl, N, S.

E. Dibenzothiepins.—2-(*m*-Methoxybenzylthio)benzoic acid (18) was obtained from equimolar amts of *m*-methoxybenzylchloride and *o*-mercaptobenzoic acid in refluxing aq EtOH contg 2 equiv of $NaHCO_3$; mp 199–201° (Me_2CO–Skellysolve B). *Anal.* ($C_{15}H_{14}O_3S$) C, H, S.

8-Methoxydibenzo[*b,e*]thiepin-11(6*H*)-one (19) was prepd from the acid **18** (18.3 g) following the procedure described above for the isothiochromanone **10**: yield, 12.2 g (72%); mp 110–111°. *Anal.* ($C_{15}H_{12}O_2S$) C, H, S.

8-Methoxy-11-hydroxy-11-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}-6,11-dihydrodibenzo[*b,e*]thiepin·HCl (20) was prepd from the ketone **19** (4.80 g) and *N*-[2-(*p*-bromophenoxy)ethyl]pyrrolidine (5.05 g) as described above for **11a**: yield of **20**, 3.10 g (34%); mp 183° dec. *Anal.* ($C_{27}H_{29}NO_3S$·HCl) C, H, Cl, S.

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17α-Propadienyl-19-nortestosterone and Related Compounds. A New Series of Potent Orally Active Progestogens[1]

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The synthesis of a series of 17α-propadienyl (allenyl) steroids in the 19-nortestosterone and estradiol series is described. 17β-Hydroxy-17α-propadienylestr-4-en-3-one (**3a**) and its 18-Me homolog (**3c**), the most active compounds of the former group, show oral progestational potencies 10 and 12 times 17α-ethynyl-19-nortestosterone, respectively.

The 17α-ethynyl-19-norsteroids are the first progestationally active compounds to receive widespread acceptance as oral contraceptive agents.[3] Replacement of the 17α-ethynyl group in the 19-nortestosterone series by vinyl or allyl substituents leads to compounds with progestational activities comparable to their 17α-ethynyl counterparts. However, these latter substances also show androgenic and anabolic activity in experimental animals.[4] A number of other 17α substituents such as 17α-cyclopropyl,[5] 17α-haloethynyl,[6] 17α-trihalovinyl,[6] and 17α-butadiynyl[7] have been incorporated into the 19-nortestosterone molecule. The chloroethynyl grouping showed the greatest activity enhancement relative to the 17α-ethynyl substituent, the progestational potency of 17α-chloroethynyl-19-nortestosterone being 2–3 times the parent 17α-ethynyl-19-nortestosterone (norethindrone).[6] This paper describes the synthesis and biological activity of a variety of 17α-propadienyl steroids in the estradiol and 19-nortestosterone series.[8] The 17α-propadienyl-19-nor-

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(3) See V. Petrow in "Essays in Biochemistry," Vol. 2, Academic Press, New York, N. Y., 1966, p 117.

(4) J. F. Sanders, F. B. Colton, and V. A. Drill, *Proc. Soc. Exp. Biol. Med.*, **94**, 717 (1957); D. A. McGinty and C. Djerassi, *Ann. N. Y. Acad. Sci.*, **71**, 500 (1958).

(5) H. G. Lehmann, H. Muller, and R. Wiechert, *Chem. Ber.*, **98**, 1470 (1965); J. W. Dean, G. O. Potts, and R. G. Christiansen, *J. Med. Chem.*, **10**, 795 (1967).

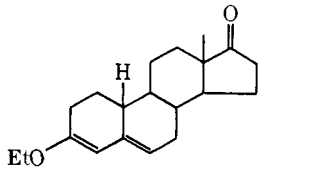
(6) J. H. Fried, T. S. Bry, A. E. Oberster, R. E. Beyler, T. B. Windholz, J. Hannah, L. H. Sarett, and S. L. Steelman, *J. Amer. Chem. Soc.*, **83**, 4664 (1961).

(7) J. N. Gardner, O. Gnoj, A. S. Watnick, and J. Gibson, *Steroids*, **4**, 801 (1964); C. Burgess, D. Burn, P. Feather, M. Howarth, and V. Petrow, *Tetrahedron*, **21**, 1197 (1965).

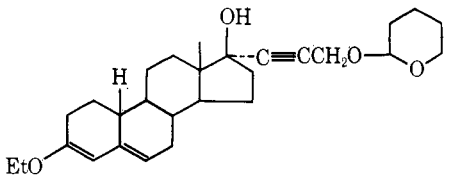
(8) The synthesis of 17α-propadienyl steroids in the pregnane series has been reported by R. Vitali and R. Gardi, *Gazz. Chim. Ital.*, **96**, 1125 (1966).

testosterones are orally active progestogens and a number of these steroidal allenes exhibit progestational potencies greater than their 17α-ethynyl counterparts.

Several methods have been reported in the patent literature for the synthesis of 17α-propadienyl steroids starting with 17α-dihalocyclopropyl precursors.[9] Herein we report two additional methods for the synthesis of 17α-propadienyl steroids from 17α-(1-tetrahydropyranyloxy- and 1-chloroprop-2-yn-3-yl)estranes. In our experience the procedure involving the reduction of the monotetrahydropyranyloxy ether **2** with



1



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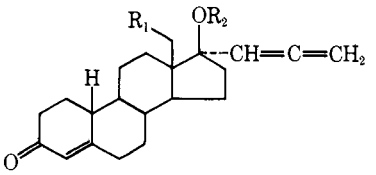
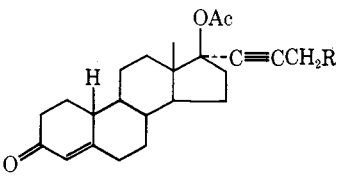
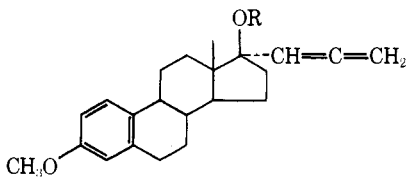


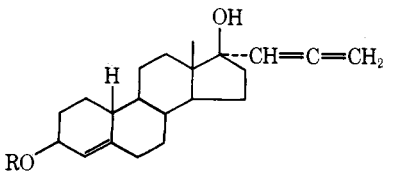
3a, $R_1 = R_2 = H$
b, $R_1 = H; R_2 = Ac$
c, $R_1 = CH_3; R_2 = H$



4a, R = OH
b, R = Cl



5a, R = H
b, R = Ac



6a, R = H
b, R = $COCH_3$

LAH proved to be a most efficient method.[10] The requisite acetylenic tetrahydropyranyl ether **2** was prepared by treating 3-ethoxyestra-3,5-dien-17-one (**1**)[11] with 3-tetrahydropyran-2′-yloxyprop-1-ynyl-magnesium bromide.[12] The crude propynyl carbinol **2** was treated sequentially with LAH in Et_2O to form the 17α-propadienyl group and with dil HCl in MeOH to regenerate the Δ⁴-3-keto chromophore. Purification of the resulting product by preparative tlc over silica gel afforded 17β-hydroxy-17α-propadienylestr-4-en-3-one (**3a**) in 48% overall yield from **1**. The ir spectrum of **3a** showed the characteristic allene band at 1955 cm^{-1},[13] and its nmr spectrum exhibited resonances centered at 5.43 ppm (t, J = 6.5 Hz) and 4.94 ppm (d, J = 6.5 Hz) for the vinyl and exomethylene protons, resp, of the allene system. These spectroscopic criteria were used for the identification of all 17α-allenyl steroids described in the sequel (see Table I).

The second approach utilized the 17α-chloropropynyl intermediate **4b** which was prepared by treating **1** with the tetrahydropyranyloxypropynyl Grignard reagent followed by addition of Ac_2O (to acetylate the intermediate Mg alkoxide at C-17) and hydrolysis with dil acid to remove the pyranyl ether and enol ether protecting groups. Conversion of **4a** to the requisite chloride **4b** was accomplished by reaction with CCl_4–$(Ph)_3P$ in hot DMF solution.[14] Reductive dechlorination of the chloropropynyl compound **4b** with Zn–Cu couple in boiling MeOH produced the 17β-acetoxyallene **3b** in 30% yield from **4b**.[15] Exposure of the latter acetate (**3b**) to dil NaOMe in MeOH provided the corresponding 17β-alcohol identical with the allenic carbinol **3a** obtained by the hydride reduction process.

Since introduction of an 18-Me substituent into 17α-ethynyl-19-nortestosterone results in a substantial increase in oral progestational activity,[16] the synthesis of the 18-methyl propadiene **3c** was undertaken. It was also of interest to prepare a 17α-allene in the estradiol series since 17α-ethynyl estradiol 3-methyl ether is a potent oral estrogen.[17] Accordingly, (−)-17β-hydroxy-17α-propadienyl-13-ethylgon-4-en-3-one (**3c**),[18] 3-methoxy-17α-propadienylestra-1,3,5(10)-trien-17β-ol (**5a**),[19] and its corresponding 17-acetate **5b** were prepared by the LAH and Zn dechlorination procedures, resp. Finally the Δ⁴-3-ketone **3a** was transformed into the 3β-hydroxy and 3β-acetoxy derivatives **6a**,**b** by Li(*tert*-BuO)$_3$AlH reduction and acetylation.

Biological Activities.—The oral progestational and antiestrogenic potencies of the various 17α-propadienyl-19-nortestosterones are summarized in Table II relative to norethindrone.

17β-Hydroxy-17α-propadienylestr-4-en-3-one (**3a**) has an oral progestational potency 10 × norethindrone.

(9) See J. A. Edwards and L. H. Knox, U. S. Patents 3,392,165 and 3,392,166 (1968); *Chem Abstr.*, **69**, 97011 (1968); *ibid.*, **70**, 4385 (1969).

(10) J. S. Cowie, P. G. Landor, and S. R. Landor, *Chem. Commun.*, 541 (1969), report a similar reaction in an unrelated series of compounds.

(11) C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Amer. Chem. Soc.*, **76**, 4092 (1954).

(12) P. D. Landor, S. R. Landor, and E. S. Pepper, *J. Chem. Soc. C*, 185 (1967).

(13) See L. J. Bellamy in "The Infrared Spectra of Complex Molecules," Methuen & Co., Ltd., London, 1956, p 52.

(14) We wish to thank Drs. B. Berkoz, J. P. Verheyden, and J. G. Moffatt for providing these unpublished experimental conditions.

(15) See T. L. Jacobs, E. G. Teach, and D. Weiss, *J. Amer. Chem. Soc.*, **77**, 6254 (1955), and ref cited therein for a similar reaction in an unrelated series of compounds.

(16) H. Smith, *et al.*, *Experientia*, **19**, 394 (1963).

(17) R. I. Dorfman and F. A. Kincl, *Acta Endocrinol.*, **52**, 619 (1966).

(18) The starting material, (+)-18-ethylgon-4-ene-3,17-dione, obtained from Roussel-Uclaf, Paris, has converted into the 3-ethoxy-$\Delta^{3,5}$ derivative for conversion into the propadiene (**3c**).

(19) Estrone 3-methyl ether was the starting material for this synthesis.

TABLE I

No.	Steroid	Mp, °C	[α]D, deg	νmax[a] cm⁻¹	Formula[g]
3a	17β-Hydroxy-17α-propadienylestr-4-en-3-one	137–140[b]	−30	1955	$C_{21}H_{28}O_2$
3b	17β-Acetoxy-17α-propadienylestr-4-en-3-one	71–74[c]	+5	1955	$C_{23}H_{30}O_3 \cdot 0.5H_2O$
6a	17α-Propadienylestr-4-ene-3β,17β-diol	58–60[d]	−20	1950	$C_{21}H_{30}O_2$
6b	3β-Acetoxy-17α-propadienylestr-4-en-17β-ol	106–108[e]	−55	1960	$C_{23}H_{32}O_3 \cdot 0.5H_2O$
3c	(−)-17β-Hydroxy-17α-propadienyl-13-ethylgon-4-en-3-one	148–150[f]	−30	1950	$C_{22}H_{30}O_2$
5a	3-Methoxy-17α-propadienylestra-1,3,5(10)-trien-17β-ol acetate	94–97[b]	+94	1940	$C_{24}H_{30}O_3$
5b	3-Methoxy-17α-propadienylestra-1,3,5(10)-trien-17β-ol	130–132[f]	+52	1955	$C_{22}H_{28}O_2$

[a] Allene stretching vibration. [b] Recrystd from Et_2O–hexane. [c] Recrystd from Me_2CO–H_2O. [d] Recrystd from Et_2O–hexane. [e] Recrystd from MeOH–H_2O. [f] Recrystd from Me_2CO–hexane. [g] All compds were analyzed for C, H.

TABLE II

Steroid	Oral progestational potency[a] (norethindrone = 1)	Oral antiestrogenic potency[b] (norethindrone = 1)
3a	10	4
3c	12	10–15
6a	4	5
6b	5	7
3b	2	5

[a] M. K. McPhail, *J. Physiol. (London)*, **83**, 145 (1934). [b] R. I. Dorfman, F. A. Kincl, and H. J. Ringold, *Endocrinology*, **68**, 43 (1961).

The optically active 18-methyl-Δ^4-3-keto propadienyl compound **3c** is 12 × norethindrone in the Clauberg assay. Reduction of the 3-ketone to the 3β-alcohol reduces progestational potency by a factor of *ca.* 2, the 17α-propadienylestr-4-ene-3β,17β-diol (**6a**) being 4 × norethindrone. The corresponding 3-acetate **6b** is roughly equivalent to the alcohol **6a**. In the propadienyl series, acetylation of the 17-hydroxyl group causes a marked reduction in progestational potency. Thus, 17β-acetoxy-17α-propadienylestr-4-en-3-one (**3b**) is 2 × norethindrone.

Interestingly, antiestrogenic potency is unaffected by acetylation at C-17 in the propadiene series. Thus, 17β-hydroxy-17α-propadienylestr-4-en-3-one (**3a**) and its 17-acetate **3b** exhibit approximately the same antiestrogenic potency.

The oral estrogenic potencies of the two 17α-propadienyl estradiol compounds **5a** and **5b** are 2.0 and 0.6 times estrone, resp.

Experimental Section[20]

17β-Hydroxy-17α-propadienylestr-4-en-3-one (3a).—Method **A.**—A soln of 3-tetrahydropyran-2′-yloxyprop-1-yne (12.0 g) in dry THF (100 ml) was added to a soln of EtMgBr prepd from EtBr (8.2 g) and Mg turnings (1.8 g) in THF (150 ml). The reaction mixt was heated under reflux for 5 min and after being allowed to stand at room temp for 2 hr it was treated with a soln of 3-ethoxyestra-3,5-dien-17-one (**1**; 10.0 g) in dry THF (150 ml). After 2 hr the reaction mixt was poured into satd NH_4Cl soln and the product was isolated by extn with CH_2Cl_2.

A suspension of LAH (10.0 g) in 200 ml of dry Et_2O was heated under reflux for 1 hr, cooled to room temp, and treated dropwise with stirring with a soln of 10.0 g of **2** in 200 ml of dry Et_2O. The resulting suspension was heated under reflux with stirring for 2.5 hr, and after cooling the reaction mixt, the excess of hydride was decompd by the addn of Me_2CO. Satd Na_2SO_4 soln and solid Na_2SO_4 were added to ppt the metal salts. The resulting mixt was filtered, and the collected solids were washed with CH_2Cl_2. The filtrate was dried (Na_2SO_4) and evapd to yield a solid which was hydrolyzed by treatment with a soln of 1% HCl in MeOH (200 ml) for 15 min at room temp. H_2O (2 l.) was added, and the resulting mixt was extd exhaustively with CH_2Cl_2. The pooled org exts were washed with H_2O, dried (Na_2SO_4), and evapd to yield crude **3** which was purified by preparative tlc [EtOAc–hexane (2:3)]. This yielded 2.4 g of **3a**, mp 128–130° (see Table I).

Method B.—A soln of 3-tetrahydropyran-2′-yloxyprop-1-yne (7.1 g) in dry THF (50 ml) was added to a soln of EtMgBr prepd from EtBr (4.0 g) and Mg turnings (0.9 g) in THF (75 ml). The reaction mixt was heated under reflux for 5 min, and, after being allowed to stand at room temp for 30 min, it was treated with a soln of 3-ethoxyestra-3,5-dien-17-one (1; 5.0 g) in dry THF (65 ml). After 8 hr, AcCl (20 ml) was added, and the reaction mixt was kept at room temp for 18 hr and then poured into H_2O. The crude product, isolated by extn with CH_2Cl_2, was dissolved in MeOH (15 ml) contg 0.25 ml of concd HCl, and the resulting soln was heated under reflux for 10 min. Addn of H_2O (200 ml) and isolation by extn with CH_2Cl_2 furnished a cryst solid which was purified by chromatog over Florisil (200 g). Elution with EtOAc–hexane (1:4) gave 3.5 g of the acetoxy alcohol **4a**, mp 175–179°, after crystn from Et_2O)

17β-Acetoxy-17α-(1-chloroprop-2-yn-3-yl)estr-4-en-3-one (4b).—A soln of alcohol **4a** (3.5 g) and $(Ph)_3P$ (4.2 g) in DMF (26.7 ml) contg CCl_4 (1.1 ml) was heated at 110° for 15 min and then the solvent was evapd under reduced pressure. The residue was dissolved in hexane–Et_2O (3:1) and chromatogd on 140 g of silica gel. Elution with Et_2O–hexane (2:1) and crystn of the pooled cryst fractions from hexane furnished **4b** (2.8 g): mp 104–107°; $[\alpha]_D$ −24°; λ_{max} 239–240 mμ (log ε 4.23); ν_{max} 1725, 1675 cm⁻¹. *Anal.* ($C_{23}H_{29}ClO_3$) C, H, Cl.

17β-Acetoxy-17α-propadienylestr-4-en-3-one (3b).—A soln of chloride **4b** (2.8 g) in abs MeOH (50 ml) was heated under reflux with Zn–Cu couple (18.7 g) for 1 hr. The couple was prepd by treating 21.0 g of Zn dust with 1.2 g of $Cu(OAc)_2$ in 30 ml of hot AcOH at 90° for 3 min followed by cooling, removal of the AcOH by decantation, and successive washings with dry Et_2O (3 × 75 ml) and abs MeOH (2 × 75 ml). The cooled soln was filtered, concd to *ca.* 20 ml, and dild with H_2O, and the product was isolated by extn with CH_2Cl_2. A soln of the resulting solid (2.2 g) dissolved in hexane–Et_2O (2:1) was adsorbed on a column of silica gel (110 g). Elution with hexane–Et_2O (3:2) afforded 0.9 g of pure allene **3b**, mp 71–74°, and 0.7 g of **3b** admixed with 15% of an unknown impurity.

Compd 3a.—A soln of **3b** (0.45 g) in MeOH (10 ml) was treated with 1.9 *N* NaOMe in MeOH (1 ml), and after 24 hr the resulting soln was neutralized with AcOH. The solvent was evapd under reduced pressure and the resulting residue was purified by prep tlc to give 0.18 g of **3a**, mp 137–140° after crystn from Et_2O–hexane.

3β-Hydroxy- and 3β-Acetoxy-Δ^4-propadienes (6a,b).—A soln of the steroid **3a** (0.35 g) and Li(*tert*-BuO)$_3$AlH (2.0 g) in anhyd THF (20 ml) was heated under reflux for 16 hr, cooled, and dild with H_2O. The resulting mixt was extd with several portions of CH_2Cl_2, and the combined exts were washed with H_2O, dried (Na_2SO_4), and evapd. Purification of the resulting product by prep tlc afforded 0.26 g of **6a**, mp 58–60°. Treatment of **6a** (0.20 g) with 2.5 ml of Ac_2O-Py (1:4) for 18 hr at room temp provided the 3-acetate **6b**, mp 106–108° (see Table I for additional constants of **6a** and **6b**).

(20) Mp are uncorrected and were taken on a Fisher-Johns apparatus. Uv spectra were measured in EtOH on a Beckman DU Model 2400 spectrometer. Ir spectra were measured as KBr disks on a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were recorded on a Varian A-60 spectrometer using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (ppm) relative to TMS on the δ scale to the nearest 0.01 ppm. We wish to thank Mrs. P. Nelson, Analytical Department, Syntex Research, Palo Alto, Calif., for assistance with these measurements.