devoid of any activity on normal behavior of mice, the most active being IIb and IIc, whereas the substituted cinnamic acid derivatives were practically ineffective. This selective inhibition of conditioned avoidance response could be of great relevance. We are continuing studies of IIb because of its low toxicity, its efficacy on conditioned behavior in rats, and its neuropsychopharmacological effects in various animal species,[22] in view of a preliminary clinical trial.

Experimental Section‡

Method A. 2-(4-Acetoxy-3,5-dimethoxybenzoyl)isoxazolidine (IIc). A soln of 11 g (42.5 mmoles) of 4-acetoxy-3,5-dimethoxybenzoyl chloride in 50 ml of CH_2Cl_2 was added dropwise with stirring to a suspension of 4.65 g (42.5 mmoles) of isoxazolidine·HCl[13] in 85 ml of CH_2Cl_2 contg 14.2 ml (102 mmoles) of Et_3N. Stirring was contd for 1 hr at room temp, then for 2 hr at reflux. After washing with dil HCl, dil aqueous $NaHCO_3$, and H_2O, the organic phase was dried (Na_2SO_4) and evapd. The residue was purified by crystn from EtOH.

Method B. *trans*-3-(3,4,5-Trimethoxycinnamoyl)-1,3-oxazolidine (IIIb). A soln of 5.8 g (22.6 mmoles) of *trans*-3,4,5-trimethoxycinnamoyl chloride in 50 ml of CH_2Cl_2 was added dropwise with stirring to a cooled (−5°) soln of 3.45 g (47.2 mmoles) of freshly distd oxazolidine[15] in 150 ml of the same solvent. The reaction mixt was kept at 0° for 3 hr, then it was washed with dil HCl, dil aqueous $NaHCO_3$, and H_2O. The organic soln was dried (Na_2SO_4), the solvent was evapd, and the residue was crystd from PhH.

Method C. 2-(3,5-Dimethoxy-4-hydroxybenzoyl)isoxazolidine (IId). A suspension of 4 g (13.5 mmoles) of 2-(4-acetoxy-3,5-dimethoxybenzoyl)isoxazolidine (IIc) in 58 ml of H_2O and 32 ml of EtOH contg 6.4 ml of concd NH_4OH was heated at 60° for 5 min. The soln was neutralized with dil HCl to pH 6.5–7 and concd *in vacuo* until all the EtOH had evapd.§ After cooling overnight at 4°, the ppt was collected, dried *in vacuo* over P_2O_5, and crystd from 60% EtOH.

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‡The determination of melting points was carried out with a Büchi capillary melting point apparatus and mps are uncorrected. Ir spectra were recorded on a Perkin-Elmer spectrophotometer Model 137 in Nujol mulls, and nmr spectra were measured on a Varian A-60 spectrometer in $CDCl_3$ (TMS). These spectra were as expected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical value.

§Compd IIg directly crystallized from the ethanolic solution.

Synthesis and Anticholinergic Properties of 1-Adamant-1-yl-1-phenyl-3-*N*-pyrrolidino-1-propanol Hydrochloride[1,†]

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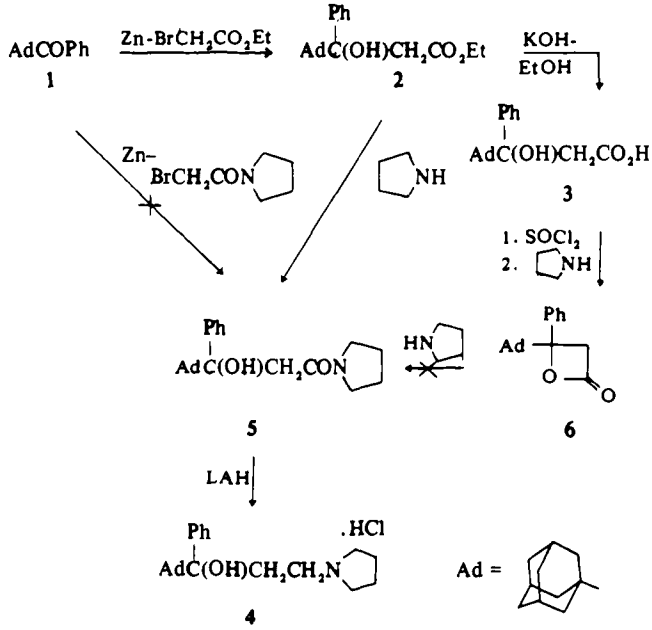
The 1-adamantanecarboxylic ester of scopolamine has potent peripheral anticholinergic activity,[2] while 1-adamantanamine hydrochloride (Amantadine) has a central action in the form of activity in Parkinson's disease.[3] It was of interest to synthesize the adamantane analog of procyclidine hydrochloride, which acts in Parkinson's disease by a central anticholinergic effect.[4] Replacement of the cyclohexyl group gave the title compound, **4**.

Chemistry. Reformatsky reactions of adamantyl phenyl ketone (**1**) with *N*-(bromoacetyl)pyrrolidine failed to yield amide **5**,[5] but gave ester **2** with ethyl bromoacetate. Formation of **5** *via* the β-lactone **6** was unsuccessful, but **5** was eventually made by extended reflux of ester **2** with excess pyrrolidine and a catalytic amount of *tert*-BuOK. Reduction of **5** with LAH gave the desired amine, which was isolated as the hydrochloride **4**.

Biological Testing. Compound **4** showed mydriatic activity in mice at 100 mg/kg orally or intraperitoneally (ip). General depression of the central nervous system also occurred at these doses and deaths were observed at 800

Scheme I



†Chemistry of Adamantane. 5.

and 200 mg/kg ip. These results indicate relatively weak peripheral anticholinergic activity and this was confirmed *in vitro* on the guinea pig isolated ileum when a pA_2[6] of 6.7 for acetylcholine was obtained. Central anticholinergic activity was assessed by measuring the ability of **4** to antagonize the tremors induced by oxotremorine.[7] Compd **4** was given orally at 50, 100, and 200 mg/kg to groups of 8 mice (CFW) 1 hr before the iv injection of 150 μg/kg of oxotremorine, and symptoms were observed for 20 min. A control group treated with oxotremorine alone was tested concurrently; 50 mg/kg of **4** caused a 40% reduction in tremor compared with the controls, but the effect was not increased at the higher doses. Almost complete inhibition of the salivation and lachrymation caused by the oxotremorine occurred at all doses used, reflecting the peripheral anticholinergic effect of **4**. A selective central anticholinergic effect of **4** was not demonstrated therefore.

Experimental Section‡

2-Ethoxycarbonyl-1-adamant-1-yl-1-phenylethanol (2). A soln of phenyl adamant-1-yl ketone[8] (24.03 g, 0.1 mole) and ethyl bromoacetate (11.15 ml, 0.1 mole) in 150 ml of a 2:1 mixture of C_6H_6 and toluene was added over 45 min to 6.9 g of Zn–Cu couple and was allowed to come to reflux. Two further equivalents of Zn–Cu couple and ester were added at 30-min intervals and reflux was continued for 1 hr. The solid, after extn and removal of solvent, was recrystd from MeOH to give 24.6 g of **2** (75%); mp 110.5–111°. *Anal.* ($C_{21}H_{28}O_3$) C, H, O.

***N*-(2-Adamant-1-yl-2-hydroxy-2-phenylpropionyl)pyrrolidine (5).** Compd **2** (7.0 g, 21 mmoles) and approx 50 mg of *tert*-BuOK were refluxed with 70 ml of pyrrolidine for 72 hr. The cream-colored solid left after evapn was recrystd from C_6H_6–hexane to give 4.9 g of **5** (65%); mp 168–169°. *Anal.* ($C_{23}H_{31}NO_2$) C, H, N, O.

1-Adamant-1-yl-1-phenyl-3-*N*-pyrrolidino-1-propanol Hydrochloride (4). Compd **5** (2.0 g, 5.7 mmoles) reduced with LAH (THF) for 20 hr after extn gave the amine which was sepd as the HCl salt and recrystd from EtOH, to give 1.1 g of **4** (52%); mp 278°. *Anal.* ($C_{23}H_{34}ClNO$) C, H, Cl, N, O.

3-Adamant-1-yl-3-hydroxy-3-phenylpropionic Acid (3). Compd **2** (1.64 g, 5 mmoles), sapond with KOH (1.65 g) in 90% aqueous EtOH (35 ml), after recrystn from MeOH–H_2O, gave 1.35 g (90%); mp 210°. *Anal.* ($C_{19}H_{24}O_3$) C, H, O.

4-Adamant-1-yl-4-phenyl-2-oxetanone (6). Compd **3** (1.0 g, 3 mmoles), warmed with 5 ml of $SOCl_2$ and 2 drops of pyridine for 30 min, after extn, gave a residue which was unchanged after reflux with pyrrolidine in ether for 15 min. The residue was recrystd from *n*-hexane to give 0.9 g of **6** (95%); mp 112–112.5°, ir C=O (β-lactone), 1830 cm^{-1}; mass spectrum M^+ 282. No amide **5** was detected by tlc. *Anal.* ($C_{19}H_{22}O_2$) C, H, O.

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‡All new compounds give satisfactory nmr and ir spectra. Melting points were taken on a Kofler hot-stage microscope and are uncorrected.

17α-Propadienyl, 17α-Propynyl, and 17α-Trifluoropropynyl Analogs of 6,6-Difluoronorethindrone†

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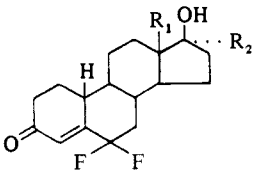
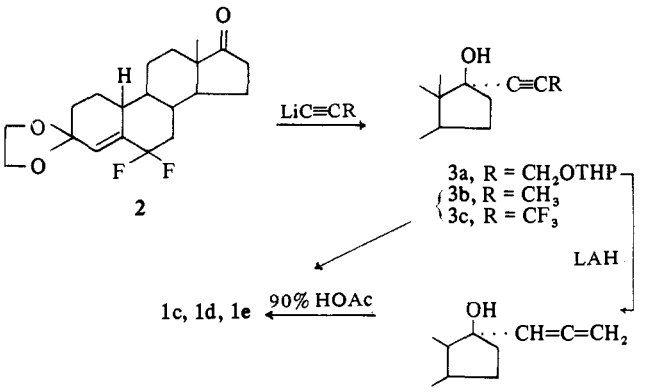
The synthesis of 6,6-difluoronorethindrone (**1a**), a progestational agent with enhanced activity, was recently reported.[1-5] As an extension of this discovery, the syntheses of (±)-6,6-difluoronorgestrel (**1b**),[6,7] 17β-hydroxy-6,6-difluoro-17α-propadienyl-4-estren-3-one (**1c**), 17β-hydroxy-6,6-difluoro-17α-(1-propynyl)-4-estren-3-one (**1d**), and 17β-hydroxy-6,6-difluoro-17α-(3,3,3-trifluoropropynyl)-4-estren-3-one (**1e**) have been completed. Each of these compounds is a potent oral progestational agent (Table I). Comparison of this data with that for related compounds[1-7,‡] clearly shows the extent of enhancement in both 17α-ethynyl- and 17α-propadienyl-17β-ols of the Δ^4-estren-3-one series. The 6,6-*gem*-difluoro group is an important means of enhancing the progestational activity of the parent compounds.



1a, $R_1 = CH_3$; $R_2 = C{\equiv}CH$
1b, $R_1 = C_2H_5$; $R_2 = C{\equiv}CH$
1c, $R_1 = CH_3$; $R_2 = CH{=}C{=}CH_2$
1d, $R_1 = CH_3$; $R_2 = C{\equiv}CCH_3$
1e, $R_1 = CH_3$; $R_2 = C{\equiv}CCF_3$



Compounds **1c**, **1d**, and **1e** were prepared from a common precursor, 6,6-difluoro-4-estrene-3,17-dione 3-ethylene ketal (**2**), first used in the synthesis[1-5] of **1a**. When the 17-keto group of **2** reacts with the lithium derivative of the appropriate acetylene, the intermediate ethynylated ketals **3a**, **3b**, and **3c** are produced. LAH reduction of **3a** converts the 17α-(3-tetrahydropyranyloxypropynyl) derivative to the 17α-propadienyl 3-ethylene ketal derivative‡,9,§ **4**. Mild acid cleavage of the ethylene ketal function in the inter-

†Contribution No. 1835.

‡Biollaz, *et al.*,[8] describe the reaction of acetylenic Grignard reagents with steroidal 17-ketones.

§Cowie, *et al.*,[10] report a similar reaction in an unrelated series of compounds.