ene–Skelly B gave pure **30** in 14% yield, mp 91–92 °C. Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

Biological Assay. Adult (3 months old) female Sprague-Dawley rats (wt 270–300 g) were housed in group cages (four per cage) with free access to food and water. The animal room had a 14 h light/10 h dark cycle (lights on at 0400 h) and was illuminated by "Vita lights" (Duro-Test Corp., North Berger, N.J.). Daily vaginal smears were recorded, and the rats were selected for experimentation after they had demonstrated at least two consecutive 4-day estrus cycles.

Animals were selected for ovulation studies on the day of proestrus. The melatonin analogues were administered (1) intravenously, dissolved in 0.2 mL of 50% Me_2SO, or (2) orally, in 0.4 mL of PEG 400. All doses were given at 1200 h. The rats were killed on the day of estrus, and the oviducts were removed and searched for ova by microscopic examination. Groups of control rats received only vehicle.

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Hypobetalipoproteinemic Agents. 2. Compounds Related to 4-(1-Adamantyloxy)aniline

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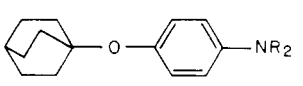
While the previously used displacement reaction of sodium 1-adamantyl oxide on 4-fluoronitrobenzene was applicable to the preparation of 4-(1-adamantyloxy)aniline and several related compounds, certain derivatives were not easily accessible by this route. Thus the recently reported ortho alkylation of anilines and the dicyclohexylcarbodiimide-promoted coupling of 1-adamantanol with phenols were useful in the preparation of aromatic-substituted derivatives. Furthermore, addition of phenylmagnesium bromide to 1-cyanoadamantane provided entry to the 4-(1-adamantylmethyl)aniline series. 4-(1-Adamantyloxy)aniline (**3**) is herein reported to be a more potent hypobetalipoproteinemic agent than the previously reported bicyclooctyloxy analogue. Replacement of the oxygen atom of **3** with sulfur (**74**) or methylene (**62**), but not nitrogen (**71**), results in active compounds. In the oxygen series derived from **3**, the widest scope of substitution on nitrogen resulting in activity is found. The *N*-ethoxycarbonyl (**5**), acetyl (**6**), methyl (**12**), ethyl (**13**), *N*-methyl-*N*-(2-hydroxyethyl) (**19**), *N*-methyl-*N*-formyl (**22**), *N*,*N*-dimethyl (**26**), pyrrolidine (**14**), and piperidine (**15**) derivatives are active. Aromatic ring substitution also provided the active 3-chloro (**44b**), 2-fluoro (**41b**, **42**, and **43**), and 2-methylthiomethyl (**48**) compounds. Thus these active compounds are identified for further development as hypobetalipoproteinemic agents.

In the first paper of this series we showed that 4-(1-bicyclo[2.2.2]octyloxy)aniline (1, R = H) and appropriately



1

substituted derivatives exhibited activity in both the standard lipid lowering assay and a new assay aimed specifically at measuring the effect of agents on the atherogenic lipoproteins.[2] The previous work suggested the need for a compact lipophilic moiety on the oxygen atom at the para position of the aniline. We, thus, turned our attention to analogues of 1 bearing an adamantyl group.

Synthesis. As in the earlier work, nucleophilic aromatic substitution provided entry to this series.[2] Thus, reaction of the anion from 1-adamantanol with *p*-fluoronitrobenzene afforded the ether **2** (Scheme I). Catalytic reduction gave the primary amine **3**. Acylation of this amine with acetic anhydride gave **6**; the sulfonamides **7** and **8** were obtained by reaction of the amine with the corresponding sulfonyl chlorides. Condensation of **3** with the appropriate heterocumulenes gave the substituted ureas

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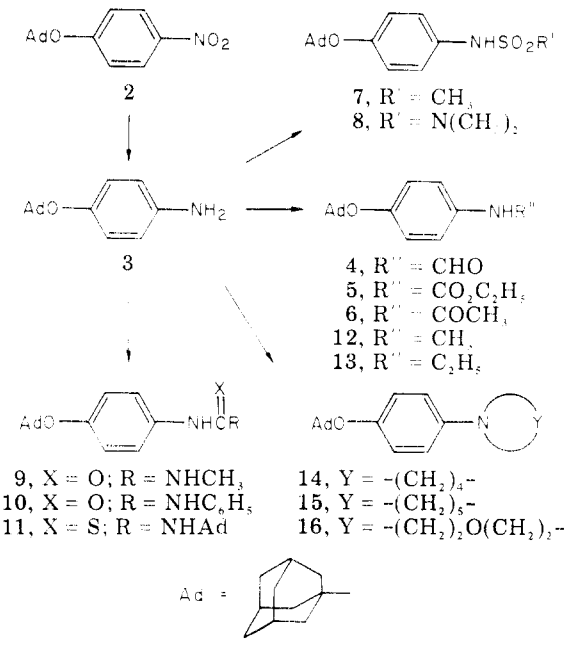
Scheme I



2

7, R' = CH_3
8, R' = $N(CH_3)_2$

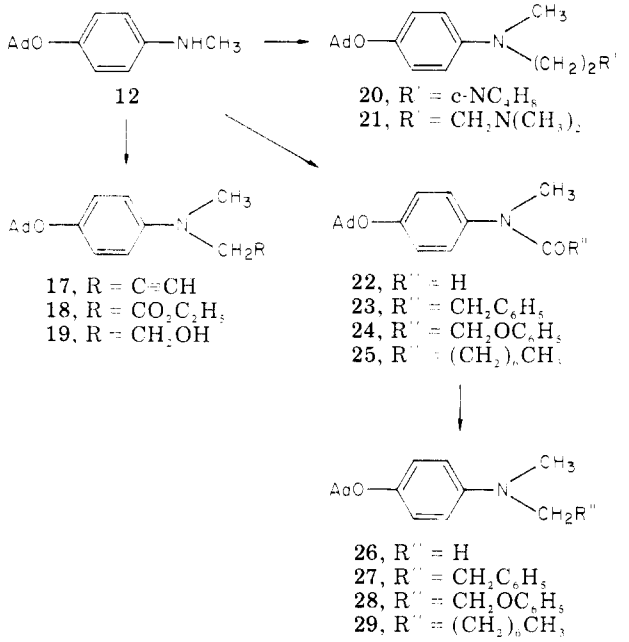
3

4, R'' = CHO
5, R'' = $CO_2C_2H_5$
6, R'' = $COCH_3$
12, R'' = CH_3
13, R'' = C_2H_5

9, X = O; R = $NHCH_3$
10, X = O; R = NHC_6H_5
11, X = S; R = NHAd

14, Y = $-(CH_2)_4-$
15, Y = $-(CH_2)_5-$
16, Y = $-(CH_2)_2O(CH_2)_2-$

Scheme II



12

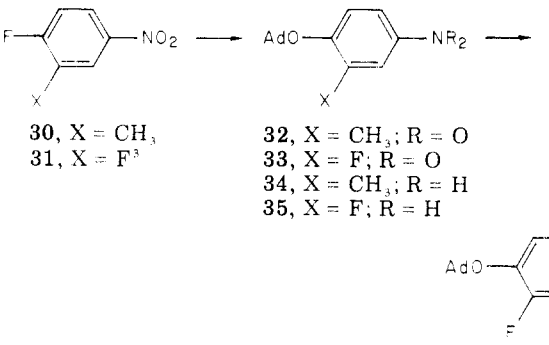
20, R' = c-NC_4H_8
21, R' = $CH_2N(CH_3)_2$

17, R = C≡CH
18, R = $CO_2C_2H_5$
19, R = CH_2OH

22, R'' = H
23, R'' = $CH_2C_6H_5$
24, R'' = $CH_2OC_6H_5$
25, R'' = $(CH_2)_6CH_3$

26, R'' = H
27, R'' = $CH_2C_6H_5$
28, R'' = $CH_2OC_6H_5$
29, R'' = $(CH_2)_6CH_3$

Scheme III

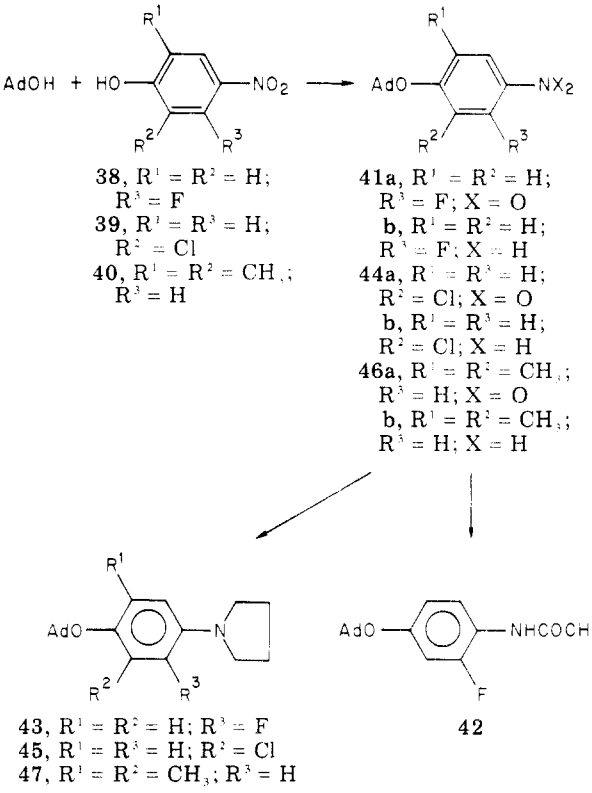


30, X = CH_3
31, X = F[3]

32, X = CH_3; R = O
33, X = F; R = O
34, X = CH_3; R = H
35, X = F; R = H

36, R' = $NHCOCH_3$
37, R' = c-NC_4H_8

Scheme IV



38, $R^1 = R^2 = H$; $R^3 = F$
39, $R^1 = R^3 = H$; $R^2 = Cl$
40, $R^1 = R^2 = CH_3$; $R^3 = H$

41a, $R^1 = R^2 = H$; $R^3 = F$; X = O
b, $R^1 = R^2 = H$; $R^3 = F$; X = H
44a, $R^1 = R^3 = H$; $R^2 = Cl$; X = O
b, $R^1 = R^3 = H$; $R^2 = Cl$; X = H
46a, $R^1 = R^2 = CH_3$; $R^3 = H$; X = O
b, $R^1 = R^2 = CH_3$; $R^3 = H$; X = H

43, $R^1 = R^2 = H$; $R^3 = F$
45, $R^1 = R^3 = H$; $R^2 = Cl$
47, $R^1 = R^2 = CH_3$; $R^3 = H$

42

9–11.[2] The *N*-formyl derivative **4** was obtained in good yield by reaction of the primary amine with ethyl formate. Reduction of the acyl derivatives ($LiAlH_4$) then afforded the secondary amines **12** and **13**. Alkylation of the primary amine with the appropriate α,ω-dihalides gave the heterocyclic derivatives **14**–**16**.

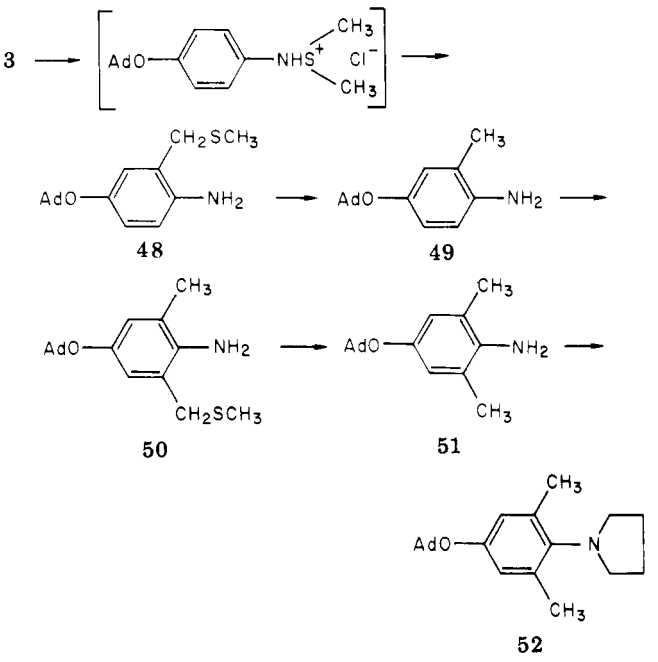
The activity exhibited by those analogues bearing basic nitrogen then prompted a further study of the SAR in this series. Alkylation of the *N*-methyl derivative **12** with activated halides afforded the tertiary amines **17** and **18** (Scheme II); the amino ester **18** was reduced to the amino alcohol **19** without prior purification. While attempted alkylation of **12** with unactivated halides proved fruitless, preformation of the anion of **12** (lithium counterion) followed by reaction with such halides provided the desired products **20** and **21** in workable yields. In an alternate approach to tertiary amine derivatives, **12** was acylated with ethyl formate and the appropriate acid chlorides to afford **22**–**25**. Reaction of these derivatives with $LiAlH_4$ led largely to acyl cleavage products. Use of diborane as the reducing agent circumvented this difficulty, affording **26**–**29**.

The nucleophilic attack–catalytic hydrogenation route was also used in the preparation of the compounds in Scheme III. Further use of this sequence was hampered by the relative inaccessibility of appropriate starting materials. Additional ring substitution was achieved as described in Schemes IV and V.

The recently reported coupling of admantanol with phenols[4] provided access to compounds not otherwise easily obtained. Thus, reaction of adamantanol with DCC and Cu_2Cl_2 (18 h at 80 °C) followed by addition of a *p*-nitrophenol (**38**, **39**, or **40**; 24 h at 100 °C) afforded the respective nitro compounds **41a**, **44a**, and **46a** in low yield (Scheme IV). Catalytic reduction afforded anilines **41b**, **44b**, and **46b** which were derivatized as shown.

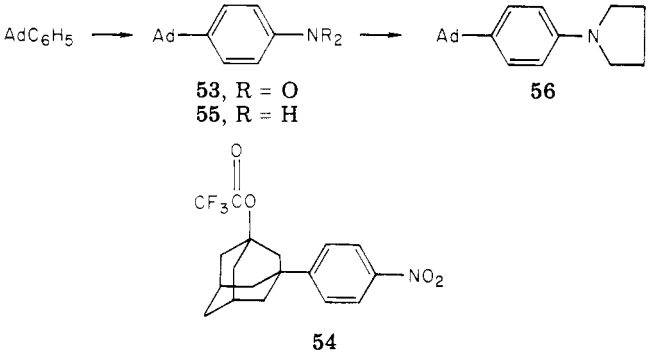
Not surprisingly, attempted displacement on 5-fluoro-2-nitrotoluene failed to afford any of the desired product because of steric inhibition of resonance. The procedure developed by Gassman and co-workers for the ortho alkylation of anilines[5,6] provided access to analogues bearing alkyl substitution at the 2 and 2,6 positions.

Scheme V



Treatment of **3** with chlorodimethylsulfonium chloride at −70 °C followed by addition of sodium methoxide gave the sulfide **48** (Scheme V). Desulfurization with Raney nickel afforded the monomethyl analogue **49** which was subjected to the same sequence to afford, in turn, **50** and **51**. Aniline **51** was then converted to pyrrolidine **52**.

Several modifications of the bridge between the adamantyl moiety and the aromatic ring were achieved as follows. Nitration of 1-phenyladamantane under mild

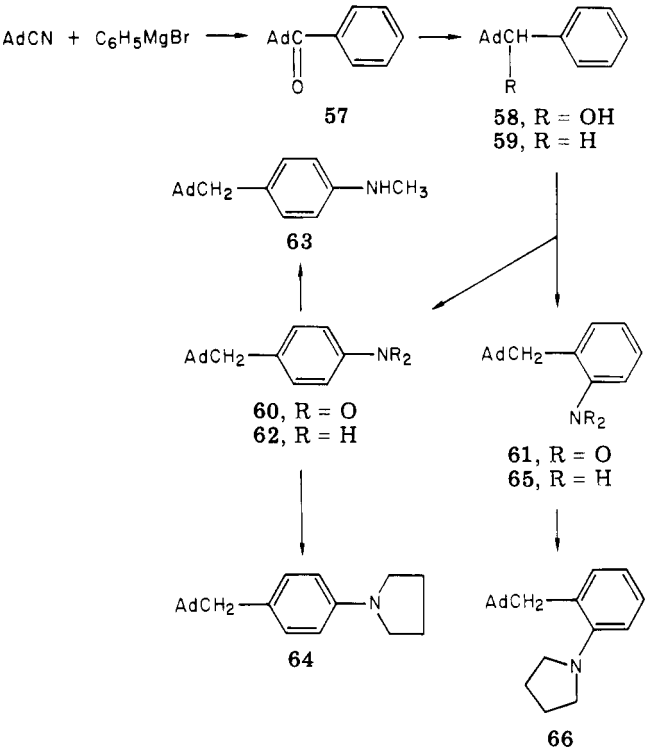


conditions (HNO_3–CF_3CO_2H at 0 °C) produced **53**, which lacks the bridging atom. (In a single instance where control of temperature was lost, there was obtained, as well, a considerable amount of the product of a free radical reaction, the ester **54**.) Reduction afforded the amine **55** from which the pyrrolidine **56** was obtained.

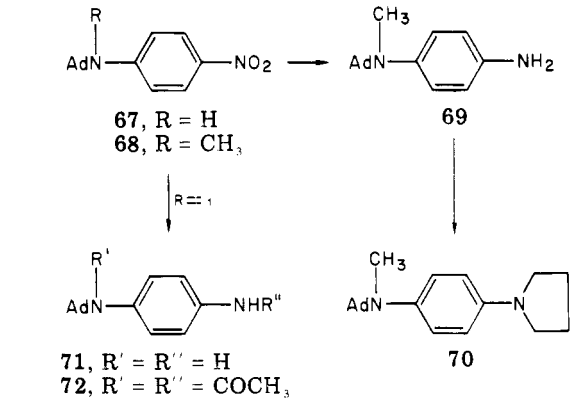
Condensation of phenylmagnesium bromide with 1-cyanoadamantane afforded ketone **57** upon acidic workup (Scheme VI). Sodium borohydride reduction yielded **58**, and acetylation and Birch reduction gave the desired hydrocarbon **59**.[7] In contrast to the nitration of phenyladamantane itself, reaction of **59** under the same conditions gave a 1:1 mixture of the ortho and para isomers. Each of these was then reduced to the corresponding aniline (**62** and **65**) which was then derivatized in the usual way.

The key to entry into the nitrogen-bridged series proved to be the use of HMPA as solvent. Thus, reaction of 1-adamantylamine with *p*-fluoronitrobenzene in HMPA gave a good yield of the nitroaniline **67**. Further transformations of **67** are shown in Scheme VII.

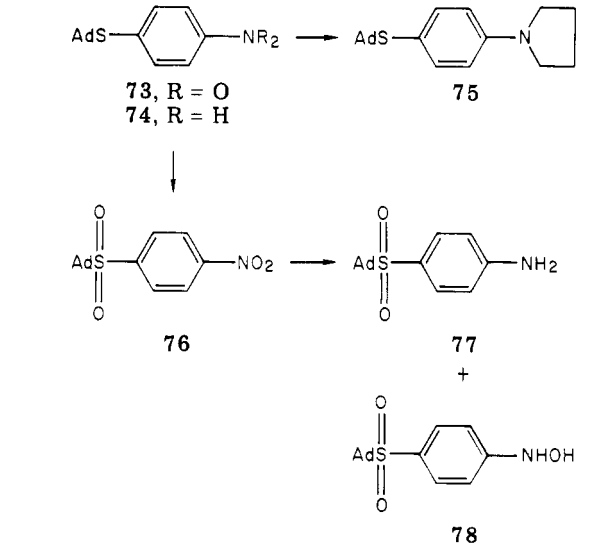
Scheme VI



Scheme VII

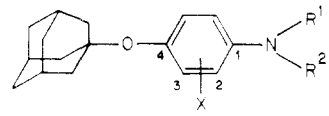


Scheme VIII



Reaction of the anion from 1-adamantanethiol with *p*-fluoronitrobenzene gave the sulfur-bridged starting material **73** which was elaborated to **74** and **75** (Scheme

Table I. Hypobetalipoproteinemic Activity of [*p*-(1-Adamantyloxy)phenyl]amines in Diet-Induced Hypercholesterolemic Rats[a]



compd no.	X	R^1	R^2	CHOL, T/C	HPL, T/C	HPL/CHOL, T/C
1	see text for structure			0.80*	0.72*	0.90
3	H	H	H	0.54*	0.35*	0.65*
4	H	H	CHO	0.71*	0.78	1.09
5	H	H	$CO_2C_2H_5$	0.57*	0.42*	0.74*
6	H	H	$COCH_3$	0.66*	0.50*	0.76*
7	H	H	SO_2CH_3	1.51*	1.30	0.85*
9	H	H	$CONHCH_3$	1.06	0.96	0.91
10	H	H	$CONHC_6H_5$	1.18	1.23	1.05
11	H	H	CSNHAd	0.88	0.91	1.03
12[d]	H	H	CH_3	0.52*	0.32*	0.63*
13[d]	H	H	C_2H_5	0.49*	0.36*	0.72*
14	H		$-(CH_2)_4-$	0.65*	0.52*	0.80*
15	H		$-(CH_2)_5-$	0.44*	0.25*	0.58*
16	H		$-(CH_2)_2O(CH_2)_2-$	0.92	0.87	0.94
17[d]	H	CH_3	$CH_2C{\equiv}CH$	0.57*	0.60*	1.05
19	H	CH_3	$(CH_2)_2OH$	0.63*	0.55*	0.88*
20[d]	H	CH_3	$(CH_2)_2$-c-NC_4H_8	1.26*	1.22	0.97
21[d]	H	CH_3	$(CH_2)_3N(CH_3)_2$	0.98	0.99	1.01
22	H	CH_3	CHO	0.51*	0.36*	0.72*
26[d]	H	CH_3	CH_3	0.46*	0.34*	0.73*
27[d]	H	CH_3	$(CH_2)_2C_6H_5$	1.09	1.07	0.98
28	H	CH_3	$(CH_2)_2OC_6F_5$	1.03	1.06	1.03
29[d]	H	CH_3	$(CH_2)_5CH_3$	1.15	1.04	0.91
34[d]	3-CH_3	H	H	0.52*	0.31*	0.60*[b]
35	3-F	H	H	0.57*	0.52*	0.92
36	3-F	H	$COCH_3$	1.15	1.07	0.93
37	3-F		$-(CH_2)_4-$	0.80	0.82	1.02
41b	2-F	H	H	0.35*	0.24*	0.68*
42	2-F	H	$COCH_3$	0.62*	0.35*	0.55*
43	2-F		$-(CH_2)_4-$	0.58*	0.30*	0.51*
44b[d]	3-Cl	H	H	0.63*	0.43*	0.68*
45	3-Cl		$-(CH_2)_4-$	1.08	1.07	0.98
46b[d]	3,5-$(CH_3)_2$	H	H	0.86	0.80	0.93
47	3,5-$(CH_3)_2$		$-(CH_2)_4-$	0.81	0.78	0.96
48	2-(CH_2SCH_3)	H	H	0.49*	0.38*	0.76*
49	2-CH_3	H	H	0.64*	0.25*	0.38*[c]
50	2-CH_3, 6-(CH_2SCH_3)	H	H	0.88	0.85	0.96
51	2,6-$(CH_3)_2$	H	H	0.77*	0.72	0.93
52	2,6-$(CH_3)_2$		$-(CH_2)_4-$	1.18	1.28	1.08
1-adamantanol				0.94	0.98	1.04
p-hydroxyaniline				0.94	0.98	1.04

[a] CHOL = total serum cholesterol; HPL = heparin precipitating lipoproteins; T/C signifies the mean value for the treated rats divided by that for the control rats; an asterisk denotes a response significantly different ($p < 0.05$) from control means; dose 50 mg/kg [a range of 0.11 (compound 11) to 0.21 (compound 3) (mmol/kg)/day]; food intake and weight gain were considered normal unless specifically noted by footnotes *b* or *c*. [b] Animals showed a weight gain of <63% of control during the experiment. [c] Animals showed a weight gain of <63% and a food intake of <73% of control values during the experiment. [d] Data reported for the hydrochloride salt.

VIII). Oxidation of **73** with *m*-chloroperbenzoic acid gave the sulfone **76**. Catalytic reduction of **76** gave an unexpectedly complex mixture from which there was isolated the amine **77**, the hydroxylamine **78**, and a trace of the azoxy compound.

We decided also to assess the importance of the position of attachment to the adamantyl nucleus. Accordingly, *p*-fluoronitrobenzene was reacted with the anions of both 2-adamantanol and 2-methyl-2-adamantanol, since there was some evidence indicating that the best activity resulted when the ether oxygen was that of a tertiary polycyclic alcohol. Each of the resulting nitro ethers was then reduced and derivatized (Scheme IX).

Pharmacology. Each compound was assayed (in 0.25% aqueous methylcellulose vehicle) for hypobetalipoproteinemic activity in a group of four to six diet-induced hypercholesteremic rats at 50 mg/kg po,[8] corresponding to a dose range of 0.11 (compound 11) to 0.21 (compound 3) (mmol/kg)/day. Serum cholesterol and heparin precipitating lipoproteins (HPL) were determined as described previously.[8] The effects of the compounds on these serum constituents as well as on the HPL–cholesterol ratio are summarized in Tables I–III. Unless specifically noted, weight gain and food intake were considered normal (>63 and >73% of control values, respectively).

The data in Tables I–III are compiled from numerous individual test runs from our screening assay for hypobetalipoproteinemic agents.[8] All active compounds were retested to verify activity. Data from each run were analyzed statistically as a one-way classification.[9a] All values were transformed to logarithms to achieve more homogeneity within group variances. The mean response for each test compound was compared with the mean observed in control animals with the LSD test.[9b] An

Scheme IX

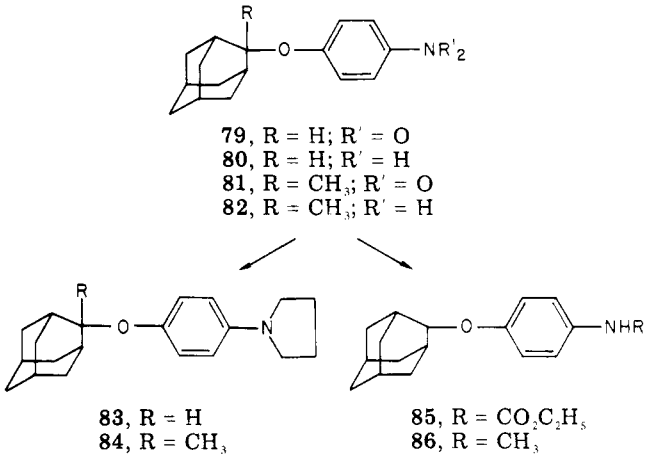
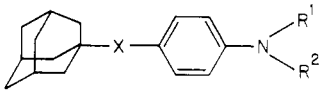


Table II. Hypobetalipoproteinemic Activity of [(1-Adamantyl-X)phenyl]amines in Diet-Induced Hypercholesterolemic Rats[a]



compd no.	X	isomer	R^1	R^2	CHOL, T/C	HPL, T/C	HPL/CHOL, T/C
55[d]		para	H	H	141*	1.40*	0.99
56		para	-$(CH_2)_4$-		1.17	0.90	0.77
62[d]	CH_2	para	H	H	0.45*	0.23*	0.50*
63[d]	CH_2	para	H	CH_3	0.55*	0.45*	0.82*
64	CH_2	para	-$(CH_2)_4$-		0.82	0.87	1.06
65[d]	CH_2	ortho	H	H	0.86	0.89	1.03
66	CH_2	ortho	-$(CH_2)_4$-		1.39*	1.40*	1.01
69[d]	NCH_3	para	H	H	0.84	0.82	0.98[c]
70	NCH_3	para	-$(CH_2)_4$-		0.93	1.02	1.10[b]
71	NH	para	H	H	0.94	0.85	0.90[b]
72	$NCOCH_3$	para	H	$COCH_3$	1.00	0.98	0.98
74	S	para	H	H	0.51*	0.45*	0.87*
75	S	para	-$(CH_2)_4$-		0.83	0.95	1.14*
77	SO_2	para	H	H	1.12	1.07	0.95
78	SO_2	para	H	OH	1.06	1.10	1.04

[a-d] See corresponding footnotes to Table I.

asterisk in the tables indicates that a test mean was significantly ($p \leq 0.05$) different than the control mean.

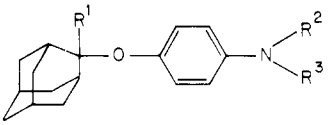
According to our operational definition,[10] an agent is an active hypobetalipoproteinemic drug when it significantly reduces the HPL and also the HPL/cholesterol ratio. Significant reduction of serum cholesterol is not required for hypobetalipoproteinemic activity. However, all of the compounds reported herein to be hypobetalipoproteinemic are indeed also hypocholesterolemic except for **80**. Two compounds (**4** and **51**) are only hypocholesterolemic, and two (**7** and **20**) are hypercholesterolemic under the test conditions.

Discussion

Subsequent to the work of our initial report on the hypobetalipoproteinemic activity of **1** (R = H),[2] we have discovered that replacement of the bicyclooctyl moiety with the 1-adamantyl group affords the more active aniline **3**. While **1** (R = H) is active at 90 mg/kg,[2] it does not lower the HPL/CHOL ratio at 50 mg/kg (Table I) as **3** does. Several other tertiary ethers were previously prepared and found to be inactive,[2] suggesting that some unique feature of **1** (R = H) and **3** is necessary for activity.

Our animal test system was designed to discover agents which reduce atherogenic lipoproteins as determined by a decrease in HPL (heparin precipitating lipoproteins) and the HPL to cholesterol (CHOL) ratio. Since our first report, ultracentrifugation studies[10] on one member of this new class, namely, the piperidine **15**, have in fact demonstrated not only the desired decrease in the atherogenic lower density ($d < 1.040$ g/mL) lipoproteins but also an increase in the high density ($1.040 < d < 1.21$ g/mL) lipoprotein, which may well be antiatherogenic.[11-13]

Table III. Hypobetalipoproteinemic Activity of [p-(2-Adamantyloxy)phenyl]amines in Diet-Induced Hypercholesterolemic Rats[a]



compd no.	R^1	R^2	R^3	CHOL, T/C	HPL, T/C	HPL/CHOL, T/C
80	H	H	H	0.82	0.67*	0.82*
82	CH_3	H	H	0.58*	0.45*	0.77*[b]
83	H	-$(CH_2)_4$-		1.07	1.07	1.01
84	CH_3	-$(CH_2)_4$-		1.04	1.03	0.99
86[d]	H	H	CH_3	0.83	0.87	1.04

[a,b,d] See corresponding footnotes to Table I.

In the ensuing discussion, the terms "active" and "activity" are used to denote hypobetalipoproteinemic activity. It is important to note that the "best" compounds are not selected based solely on the data reported herein. Rather, these data are used to select compounds for further development to identify the best compounds.

In contrast to the results obtained with **1** (R = H),[2] a wider scope of substitution on the nitrogen of **3** results in active compounds. For example, while the *N*-methyl, ethyl, acetyl, and *N,N*-diethyl derivatives of **1** are inactive,[2] the *N*-ethoxycarbonyl (**5**), acetyl (**6**), methyl (**12**), ethyl (**13**), *N*-methyl-*N*-(2-hydroxyethyl) (**19**), *N*-methyl-*N*-formyl (**22**), and *N,N*-dimethyl (**26**) derivatives of **3** are active. When the nitrogen is incorporated into a five- or six-membered ring, the piperidine from **1** is active but the pyrrolidine from **1** is not. In the adamantyloxy series both **14** and **15** are active. The morpholine is, however, inactive. The ureas and thioureas prepared in either series are likewise inactive.

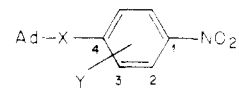
Introduction of either methylene (**62**) or sulfur (**74**) as the bridge between the adamantyl and phenyl rings leads to active compounds. In the methylene series the *N*-methyl derivative **63** is active but the pyrrolidine **64** is not, indicating that activity in this series is more sensitive to substitution on nitrogen than in the oxygen series. The ortho compounds **65** and **66** are inactive. In the sulfur series, the pyrrolidine **75** and the sulfones **77** and **78** are inactive.

Of the several 2-adamantyl derivatives prepared (Table III), only **80** was active. In this case alkyl substitution on nitrogen eliminates activity.

Within the oxygen series, aromatic ring substitution has variable affects. The 3-chloroaniline **44b** is active but the 3-chloropyrrolidine **45** is not. The 3-fluoro (**35**, **36**, and **37**), 3-methyl (**34**), and 3,5-dimethyl (**46b** and **47**) compounds are inactive. The 2-fluoroaniline (**41b**), -acetanilide (**42**), and -pyrrolidine (**43**) are active as is the 2-(methylthiomethyl) compound (**48**).

The question arises as to the nature of the active principle of **3**. We have tested 1-adamantanol and *p*-hydroxyaniline and found them to be inactive (Table I). These results and the fact that the methylene compound **62** is active would seem to suggest that the intact (adamantyloxy)aniline moiety is necessary for activity.

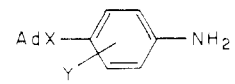
Table IV. 4-[Adamantyl(oxy, thio, and amino)]nitrobenzenes



compd no.	Ad	X	Y	method	yield, %	chromatogr solvent	recrystn solvent	mp, °C	formula
2	1-Ad[a]	O	H	A			SSB[b]	135-137	$C_{16}H_{19}NO_3$
32	1-Ad	O	3-CH_3	A	36	25% SSB in CH_2Cl_2	SSB	89.5-91	$C_{17}H_{21}NO_3$
33	1-Ad	O	3-F	A	68	CH_2Cl_2		115-121	$C_{16}H_{18}FNO_3$
41a	1-Ad	O	2-F	C	c	CH_2Cl_2		88-89	$C_{16}H_{18}FNO_3$
44a	1-Ad	O	3-Cl	C	5	CH_2Cl_2	Me_2CO-SSB	84-85	$C_{16}H_{18}ClNO_3$
46a	1-Ad	O	3,5-$(CH_3)_2$	C	c	CH_2Cl_2		139-155	$C_{18}H_{23}NO_3$
67	1-Ad	NH	H	B	67		Me_2CO-cyhex[d]	188-189	$C_{16}H_{20}N_2O_2$
73	1-Ad	S	H	A	73		CH_2Cl_2-cyhex	145-147	$C_{16}H_{19}NO_2S$
79	2-Ad[e]	O	H	A	50	1:1 C_6H_6-SSB	SSB	120-122.5	$C_{16}H_{19}NO_3$
81	2-Me-2-Ad[f]	O	H	A	71	1:1 SSB-CH_2Cl_2		83.0-85.3	$C_{17}H_{21}NO_3$

[a] 1-Adamantyl. [b] SSB = Skellysolve B. [c] The product was obtained admixed with an unknown amount of bis(1-adamantyl) ether. [d] cyhex = cyclohexane. [e] 2-Adamantyl. [f] 2-Methyl-2-adamantyl.

Table V. 4-(Adamantyl-X)anilines



compd no.	Ad	X	Y	method	yield, %	recrystn solvent	mp, °C	formula
3	1-Ad[a]	O	H	D	95	MeOH-H_2O	175-177	$C_{16}H_{21}NO$
34	1-Ad	O	3-CH_3	D	77	CH_2Cl_2-EtOAc[b]	201-202	$C_{17}H_{24}ClNO$
35	1-Ad	O	3-F	D	79	CH_2Cl_2-hex[c]	180-190.5	$C_{16}H_{20}FNO$
41b	1-Ad	O	2-F	D	9[d,e]	CH_2Cl_2-SSB[m]	152-154	$C_{16}H_{20}FNO$
44b	1-Ad	O	3-Cl	D	39	EtOH-EtOAc[b]	179-185	$C_{16}H_{21}Cl_2NO$
46b	1-Ad	O	3,5-$(CH_3)_2$	D	4[d,e]		196.7-197	$C_{18}H_{26}ClNO$
48	1-Ad	O	2-CH_2SCH_3	E	52	CH_2Cl_2-SSB	62-65	$C_{18}H_{25}NOS$
49	1-Ad	O	2-CH_3	F	21	CH_2Cl_2-SSB	143.5-145	$C_{17}H_{23}NO$
50	1-Ad	O	2-CH_3, 6-CH_2SCH_3	E	8	b	202-203.5	$C_{19}H_{28}ClNOS$
51	1-Ad	O	2,6-$(CH_3)_2$	F	10		136.6-139	$C_{18}H_{25}NO$[f]
55	1-Ad		H	D	59	MeOH-EtOAc[b]	263-265	$C_{16}H_{22}ClN$
62	1-Ad	CH_2	H	D	63	MeOH-EtOAc[b]	250-253	$C_{17}H_{24}ClN$
65	1-Ad	CH_2[g]	H	D	58	MeOH-EtOAc[b]	230-235	$C_{17}H_{24}ClN$[h]
69	1-Ad	NCH_3	H	D	88	MeOH-EtOAc[b]	228-230	$C_{17}H_{26}Cl_2N_2 \cdot 0.5H_2O$
71	1-Ad	NH	H	D	88	MeOH-H_2O	153-156	$C_{16}H_{22}N_2$[i]
74	1-Ad	S	H	D	80	MeOH-H_2O	148-151	$C_{16}H_{21}NS$
80	2-Ad[k]	O	H	D	79	pet. ether[j]	88-89.5	$C_{16}H_{21}NO$
82	2-Me-2-Ad[l]	O	H	D	64	CH_2Cl_2-SSB	95.6-97.9	$C_{17}H_{23}NO$

[a] 1-Adamantyl. [b] Hydrochloride salt. [c] Hexane. [d] The yield is for three steps. [e] The yield is based on the starting phenol. [f] Analysis corrected for 1.47% CH_2Cl_2 found by melt solvate. [g] Ortho isomer. [h] Anal. C: calcd, 73.49; found, 73.01. [i] Anal. C: calcd, 79.28; found, 78.72. [j] Petroleum ether. [k] 2-Adamantyl. [l] 2-Methyl-2-adamantyl. [m] SSB = Skellysolve B.

However, these naive experiments by no means answer this complex question.

From the foregoing extensive, but not exhaustive, examination it is clear that numerous changes of structure 3 can be made without eliminating the activity. It remains for further evaluation to show which compounds are suitable for continued development as hypobetalipoproteinemic agents.

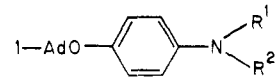
Experimental Section

Melting points are uncorrected and are reported as obtained on either a Thomas-Hoover or a capillary melting point apparatus. NMR spectra were determined on a Varian A-60D or XL-100 instrument. The authors are indebted to the Department of Physical and Analytical Chemistry Research of The Upjohn Co. for elemental analyses and other analytical services. The presence of an empirical formula means that the compound was analyzed for C, H, and N and the values were within ±0.4% of theory. Preparative LC was conducted using silica gel of predominately 30–50 μm particle size. In general methods A–O, specific mention is not made when solids were recrystallized or when amines were converted to hydrochloride salts, since it is apparent from the Tables IV–VIII when these manipulations were done.

4-[Adamantyl(oxy, thio, and amino)]nitrobenzenes (Table IV). Method A. To a solution of 35 mmol of the appropriate adamantanol (or thiol) in 40 mL of DMF and 80 mL of C_6H_6 there was added 1 equiv (1.46 g) of a 56% dispersion of NaH in mineral oil. The mixture was stirred at reflux for 15 min and allowed to cool. Following the addition of 35 mmol of the desired fluoronitrobenzene, the mixture was heated at reflux for 5 h and then allowed to cool. The mixture was then washed thoroughly with H_2O, concentrated, and chromatographed if necessary.

Method B. A mixture of 1.51 g (10 mmol) of 1-adamantanamine, 1.41 g of *p*-fluoronitrobenzene, and 1.38 g of K_2CO_3 in 10 mL of HMPA was stirred for 17 h in an oil bath at 135 °C. The

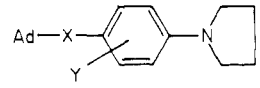
Table VI. Amides, Carbamates, and Ureas from 4-(Adamantyloxy)anilines



compd no.	R^1	R^2	method	yield, %	recrystn solvent	mp, °C	formula
4	H	CHO	K	87	Me_2CO-cyhex[d]	149-150	$C_{17}H_{21}NO_2$
5	H	$CO_2C_2H_5$	H	87	MeOH	116.5-118	$C_{19}H_{25}NO_3$
6	H	$COCH_3$	G	88	MeOH	167-168.5	$C_{18}H_{23}NO_2$
7	H	SO_2CH_3	H	89	MeOH-H_2O	167-169	$C_{17}H_{23}NO_3S$
8	H	$SO_2N(CH_3)_2$	H	67	MeOH-H_2O	197.5-199.5	$C_{18}H_{26}N_2O_3S$
9	H	$CONHCH_3$	J	85	MeOH-H_2O	210-211	$C_{18}H_{24}N_2O_2$
10	H	$CONHC_6H_5$	J	67	Me_2CO-H_2O	223-224.5	$C_{23}H_{26}N_2O_2$
11	H	CSNH(1-Ad)	J	55	(THF)[f]	203.8-205.3	$C_{27}H_{36}N_2OS$
22	CH_3	CHO	K	70	Me_2CO-cyhex[d]	106-108.1	$C_{18}H_{23}NO_2$
23	CH_3	$COCH_2C_6H_5$	I	79	SSB[g]	89-91	$C_{25}H_{29}NO_2$
24	CH_3	$COCH_2OC_6H_5$	I	91	SSB	108-110	$C_{25}H_{29}NO_3$
25	CH_3	$CO(CH_2)_6CH_3$	I	90	e		
36	H	$COCH_3$[a]	G	85	MeOH	227-231	$C_{18}H_{22}FNO_2$
42	H	$COCH_3$[b]	G	70	MeOH	173.2-175	$C_{18}H_{22}FNO_2$
85	H	$CO_2C_2H_5$[c]	I	81	Et_2O-SSB	113-115	$C_{19}H_{25}NO_3$

[a] 3-F. [b] 2-F. [c] 2-Adamantyloxy analogue. [d] Cyclohexane. [e] Amorphous gum. [f] Not recrystallized; compound was pure as isolated from the reaction solvent THF. [g] SSB = Skellysolve B.

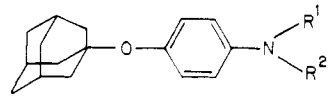
Table VII. [4-(Adamantyl-X)phenyl]pyrrolidines



compd no.	Ad	X	Y	yield, %	recrystn solvent	mp, °C	formula
14	1-Ad[a]	O	H	72	MeOH	120-122	$C_{20}H_{27}NO$
37	1-Ad	O	3-F	15	b	149-155	$C_{20}H_{26}FNO$
43	1-Ad	O	2-F	54	b	99-106	$C_{20}H_{26}FNO$
45	1-Ad	O	3-Cl	39	c	157.2-158.3	$C_{20}H_{26}ClNO$
47	1-Ad	O	3,5-$(Me)_2$	87	c	93-102.5	$C_{22}H_{31}NO$
52	1-Ad	O	2,6-$(Me)_2$	17	b	184.4-185.6[d]	$C_{22}H_{32}ClNO$[e]
56	1-Ad		H	67	Me_2CO-H_2O	167-169	$C_{20}H_{27}N$
64	1-Ad	CH_2	H	64	EtOH	147-148.5	$C_{21}H_{29}N$
66	1-Ad	CH_2	H[f]	32[c,d]	CH_2Cl_2-EtOH	188-191	$C_{21}H_{30}ClN$
70	1-Ad	NCH_3	H	66	MeOH	128-129.5	$C_{21}H_{30}N_2$
75	1-Ad	S	H	49[c]	SSB[i]	159-162	$C_{20}H_{27}NS$
83	2-Ad[g]	O	H	29[c]	pet. ether[j]	101.5-102.5	$C_{20}H_{27}NO$
84	2-CH_3-2-Ad[h]	O	H	69		119.1-121.2	$C_{21}H_{29}NO$

[a] 1-Adamantyl. [b] Compound purified by LC (elution with 0.5% Me_2CO-CH_2Cl_2). [c] Compound purified by chromatography. [d] Hydrochloride salt. [e] Analysis calculated for 1.08% Et_2O and 1.85% CH_2Cl_2 determined by melt solvate. [f] Ortho isomer. [g] 2-Adamantyl. [h] 2-Methyl-2-adamantyl. [i] SSB = Skellysolve B. [j] Petroleum ether.

Table VIII. Secondary and Tertiary Amines from 4-(1-Adamantyloxy)aniline



compd no.	R^1	R^2	method	yield, %	recrystn solvent	mp, °C	formula
12	CH_3	H	L	64	CH_2Cl_2-EtOAc	207.5-208.5[a]	$C_{17}H_{24}ClNO$
13	C_2H_5	H	L	7.9[b]	CH_2Cl_2-EtOAc	185-187.5[a]	$C_{18}H_{26}ClNO$
15	-$(CH_2)_5$-		c	19	pet. ether	72-73.5	$C_{21}H_{29}NO$
16	-$(CH_2)_2O(CH_2)_2$-		d	19	CH_2Cl_2-SSB[g]	146.0-150.1	$C_{20}H_{27}NO_2$[f]
17	CH_3	$CH_2C{\equiv}CH$	N	77	CH_2Cl_2-EtOAc	180-181[a]	$C_{21}H_{28}ClNO$
19	CH_3	$(CH_2)_2OH$	N, L	80	Me_2CO-SSB	94-99	$C_{19}H_{27}NO_2$
20	CH_3	$(CH_2)_2$-c-NC_4H_8	O	55	CH_2Cl_2-CH_3CN	189-190[a]	$C_{23}H_{36}Cl_2N_2O{\cdot}2H_2O$[e]
21	CH_3	$(CH_2)_3N(CH_3)_2$	O	53	MeOH-CH_3CN	221-223[a]	$C_{22}H_{36}Cl_2N_2O{\cdot}H_2O$
26	CH_3	CH_3	L	15	CH_2Cl_2-EtOAc	214-216[a]	$C_{18}H_{26}ClNO{\cdot}0.5H_2O$
27	CH_3	$(CH_2)_2C_6H_5$	M	65	CH_2Cl_2-EtOAc	213-214[a]	$C_{25}H_{32}ClNO$
28	CH_3	$(CH_2)_2OC_6H_5$	M	76	MeOH	108-109	$C_{25}H_{31}NO_2$
29	CH_3	$(CH_2)_7CH_3$	M	66	EtOAc	144-148[a]	$C_{25}H_{30}ClNO$

[a] Hydrochloride salt. [b] Chromatographed on silica gel (C_6H_6-NH_4OH). [c] From alkylation of aniline with $I(CH_2)_5I$. [d] From alkylation of aniline with $Cl(CH_2)_2O(CH_2)_2Cl$. [e] Anal. H: calcd, 8.69; found, 8.15. [f] Satisfactory analysis for C could not be obtained. [g] SSB = Skellysolve B.

mixture was allowed to cool, diluted with H_2O, and extracted with C_6H_6. The organic layer was washed thoroughly with H_2O and then brine and taken to dryness.

Method C. Dicyclohexylcarbodiimide (100 g, 0.485 mol) was added to an initimate mixture of 73.8 g of 1-adamantanol and 4.9 g of Cu_2Cl_2 warmed in an oil bath at 80 °C. Following 18 h of heating, there was added 0.485 mol of the appropriate nitrophenol. The mixture was heated at about 100 °C for an additional 24 h and allowed to cool. The dark mass was taken up in CH_2Cl_2, separated from some precipitated solid, and washed in turn with 10% NaOH and brine. The residue which remained when the organic layer was taken to dryness was chromatographed on silica gel. In two cases the product was obtained admixed with an unknown amount of bis(1-adamantyl) ether. These mixtures were used in the next step without further purification, since separation after reduction was more easily achieved.

4-(1-Adamantyl)nitrobenzene (53) and 4-[3-(Trifluoroacetoxy)-1-adamantyl]nitrobenzene (54). To an ice-cooled suspension of 4.31 g (0.020 mol) of 1-phenyladamantane in 30 mL of TFA there was added dropwise 6 mL of HNO_3. At the end of 2 h the cooling bath was removed. After an additional 1 h of stirring, the mixture was poured onto ice H_2O. The precipitated oil was extracted with C_6H_6. The organic layer was washed with H_2O, $NaHCO_3$, and brine and taken to dryness. The residue was chromatographed on 290 g of silica gel (elution with 1:1 CH_2Cl_2 SSB). There was obtained first the desired nitro compound **53** which was recrystallized from SSB to give 0.73 g of solid: mp 119.5–120.5 °C. Anal. ($C_{16}H_{19}NO_2$).

This was followed by a more polar fraction. Recrystallization from SSB afforded 0.49 g of **54**: mp 93–97 °C; ν_{max} 1720 cm^{-1}; *m/e* 369. Anal. ($C_{18}H_{20}F_3NO_4$) C, H; N: calcd, 3.79; found, 4.38.

In a subsequent run, where the temperature was carefully kept below 10 °C, the same reaction afforded the desired nitro compound, mp 123–126 °C, in 46% yield as the sole identifiable product.

1-Benzoyladamantane (57). A solution of 5.0 g (0.031 mol) of 1-cyanoadamantane in 80 mL of Et_2O was added to 20 mL of 2.85 M C_6H_5MgBr in Et_2O. Following 18 h of stirring at room temperature, the mixture was cooled in ice and treated with 100 mL of 2.5 N HCl in Et_2O and 500 mL of H_2O. The mixture was then allowed to stir at room temperature for 4 h. The organic layer was then washed with H_2O, $NaHCO_3$, and brine and taken to dryness. The residue was recrystallized from a small amount of MeOH to afford 5.80 g (76%) of the ketone **57**: mp 48–50 °C; ν_{max} 1680 cm^{-1}. Anal. ($C_{17}H_{20}O$) C, H.

α-(1-Adamantyl)benzyl Alcohol (58). To a warm solution of 5.80 g (0.024 mol) of **57** in 60 mL of 95% *i*-PrOH there was added 1.0 g of $NaBH_4$. At the end of 5 h of stirring at room temperature the solvent was removed in vacuo. The residue was dissolved in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was recrystallized from petroleum ether (cooling in freezer) to give 5.04 g (86%) of alcohol **58**: mp 52–53 °C. Anal. ($C_{17}H_{22}O$) C, H.

1-Benzyladamantane (59). From 58. A solution of 5.04 g (0.021 mol) of the alcohol **58** in 10 mL of Ac_2O and 20 mL of pyridine was allowed to stand at room temperature for 7 h. The mixture was then poured onto ice H_2O and extracted with Et_2O. The extract was then washed in turn with H_2O, 2.5 N HCl, H_2O, and brine and taken to dryness. The crude acetate (5.60 g) was obtained as an amorphous gum.

Ammonia (200 mL) was distilled into a solution of the above product and 7.6 mL of *t*-BuOH in 50 mL of THF. There was then added 0.56 g of Li metal in two portions; as soon as the last color faded (5 min), there was added 5 g of NH_4Cl, and the solvent was evaporated under a stream of N_2. The residue was dissolved in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. There was obtained 4.29 g (91%) of **59**: mp 41–42 °C; NMR and IR consistent with structure. This material could not be satisfactorily recrystallized.

From 57. To crude **57** from 5.0 g (0.031 mol) of 1-cyanoadamantane in 300 mL of triethylene glycol was added (after flushing the system with nitrogen) 31.0 g (0.620 mol) of hydrazine hydrate in one portion, followed by 22.7 g (0.378 mol) of acetic acid. The mixture was heated for 16 h in a 105 °C oil bath. The mixture was allowed to cool somewhat and then 35 g (0.62 mol) of pulverized potassium hydroxide was added. The reflux condenser was replaced with a distillation apparatus, and the temperature was slowly raised to 185 °C and maintained there for 6.5 h. The distillate was mixed with water and extracted with ether, and the ether solution was dried ($MgSO_4$) and concentrated to give 0.9 g of white solid. The reaction mixture was diluted with an equal volume of water and extracted three times with ether. The combined ether layers were washed with water and brine, dried ($MgSO_4$), and concentrated to give 6.7 g of a yellow oil which was combined with the 0.9 g of solid and chromatographed on 100 g of silica gel, eluting with hexane and taking 75-mL fractions. Fractions 4–6 contained 5.3 g (75%) of white solid **59**: mp 41.6–43 °C. Sublimation (80 °C, 0.2 mm) afforded analytically pure **59**: mp 42.8–44.3 °C. Anal. ($C_{17}H_{22}$) C, H.

α-(1-Adamantyl)-*p*-nitrotoluene (60) and α-(1-Adamantyl)-*o*-nitrotoluene (61). Nitric acid (6 mL) was added quickly to an ice-cooled suspension of 4.29 g (0.019 mol) of **59** in 30 mL of TFA. The mixture was stirred in the cold until all solid had dissolved (3 h) and then poured into ice H_2O. The precipitate was extracted with C_6H_6, and this solution was washed in turn with H_2O, $NaHCO_3$, and brine. The solid which remained when the extract was taken to dryness was chromatographed on 240 g of silica gel (elution with 25% CH_2Cl_2 in SSB) to give (in order of elution) the following. (1) **61**: 1.71 g (33%); mp 71–73 °C (from MeOH); NMR δ 7.82 (dd, J = 7, 2.5 Hz, 1 H, ortho to nitro), 7.38 (m, 3 H, aromatic). Anal. ($C_{17}H_{21}NO_2$) C, H, N. (2) **62**: 1.65 g (32%); mp 101–112 °C; NMR δ 7.85, 6.95 (AA'BB', 4 H, aromatic). Anal. ($C_{17}H_{21}NO_2$) C, H, N.

***N*-(1-Adamantyl)-*N*-methyl-*p*-nitroaniline (68).** To a solution of 4.08 g (0.015 mol) of **67** in 15 mL of DMF and 60 mL of C_6H_6 there was added 0.63 g of 56% NaH. Following 3 h of stirring at reflux, 10 mL of CH_3I was added; at the end of an additional 2 h, 5 mL of CH_3I was added and the mixture heated 2 h more. The reaction was then diluted with C_6H_6 and washed well with H_2O. The residue was chromatographed on 290 g of silica gel (elution with 10% Me_2CO in SSB). The fractions containing product were combined and recrystallized from petroleum ether (cooling in freezer) to yield 3.31 g (77%) of **68**: mp 60–61 °C (sublimes at 55 °C). Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

[Adamantyl(oxy, methylene, and amino)]anilines (Table V). Method D. A mixture of 10 mmol of the nitro compound and 0.20 g of 10% Pd on charcoal in 150 mL of EtOAc was shaken under H_2 until the theoretical gas uptake was observed. The catalyst was removed on a filter and the filtrate taken to dryness.

Method E. To 12.5 g (0.18 mol) of Cl_2 in 180 mL of CH_2Cl_2 cooled to −70 °C was added a precooled solution of 11.4 g (0.18 mol) of dimethyl sulfide in 40 mL of CH_2Cl_2 at such a rate as to produce a 5 °C exotherm. To this there was then added a solution of 0.176 mol of **3** and 17.8 g of Et_3N in 1 L of CH_2Cl_2. Following 2 h of stirring in the cold the mixture was treated with 51.8 g of a 25% solution of NaOMe in MeOH. The reaction was allowed to warm slowly, and it was stirred overnight, washed with H_2O, and taken to dryness. The residual gum was chromatographed over silica gel (elution with 1–4% Me_2CO in CH_2Cl_2).

Method F. A Raney nickel sludge (W-5 activity) containing approximately 96 g of the alloy was rinsed five times with EtOH. This was then added to 76.4 mmol of the sulfide in 80 mL of EtOH. Following 2 h of stirring, the metal was collected on a filter and the filtrate taken to dryness. The residue was chromatographed on silica gel (elution with 1–3% Me_2CO in CH_2Cl_2).

1-Adamantyl *p*-Nitrophenyl Sulfone (76). Solid *m*-$ClC_6H_4CO_3H$ (3.44 g) was added to an ice-cooled solution of 2.89 g (0.01 mol) of **73** in 100 mL of CH_2Cl_2. The mixture was allowed to come to room temperature and stirred for 5 h. The solution was washed twice with $NaHCO_3$ and taken to dryness. The residue was recrystallized from Me_2CO–H_2O to give 2.49 g (78%) of sulfone **76**: mp 222–225 °C. Anal. ($C_{16}H_{19}NO_4S$) C, H, N.

Catalytic Reduction of 1-Adamantyl *p*-Nitrophenyl Sulfone (77 and 78). A mixture of 2.49 g of **76** and 0.25 g of 10% Pd/C in 150 mL of EtOAc was shaken under H_2. After 3 h an additional 0.25 g of Pd/C was added. At the end of a total of 7 h of reaction time, the catalyst was collected on a filter and the filtrate taken to dryness. The residue was chromatographed on 120 g of silica gel (elution with 5% Me_2CO–CH_2Cl_2) to give (in order of elution) the following. (1) The azoxide: 0.07 g (from CH_2Cl_2); mp >300 °C; *m/e* 594. (2) Aniline **77**: 0.30 g; mp 255–259

°C (from EtOAc-cyclohexane); *m/e* 291. Anal. ($C_{16}H_{21}NO_2S$) C, H, N. (3) Hydroxylamine **78**: 0.72 g; mp 255 °C (from EtOAc-cyclohexane); *m/e* 307. Anal. ($C_{16}H_{21}NO_3S$) C, H, N.

Amides, Carbamates, and Ureas from 4-(Adamantyloxy)anilines (Table VI). Method G. Acetylation was conducted using Ac_2O as previously described.[2]

Method H. A solution of 5.7 mmol of the aniline in 15 mL of ice-cold pyridine was treated with an excess of the appropriate acid halide. Following 18 h of standing at room temperature the mixture was diluted with water, precipitating the product.

Method I. To an ice-cooled solution of the amine (7.8 mmol) and 1.08 g of Et_3N in 40 mL of THF there was added 1.1 equiv of the acid chloride. Following 3 h of stirring at room temperature the solvent was removed in vacuo and the mixture worked up as in method H.

Method J. A solution of 0.82 mol of the aniline and an excesss of the heterocumulene in 40 mL of THF was allowed to stand at room temperature overnight. The mixture was diluted with water, precipitating the product.

Method K. A suspension of 41 mmol of the aniline in 60 mL of ethyl formate was stirred at reflux for 48 h. The mixture was taken to dryness.

***N*-(1-Adamantyl)-*N*,*N*'-(1,4-phenylene)bis[acetamide] (72).** The diamine (**70**, 2.86 g) was acetylated by method G. There was obtained 1.90 g of product (32%): mp 245–346 °C. Anal. ($C_{20}H_{26}N_2O_2$) C, H, N.

***N*-[(Adamantyl-X)phenyl]pyrrolidines** (Table VII) were prepared as previously described.[2]

Secondary and Tertiary Amines Derived from 4-(1-Adamantyloxy)anilines (Table VIII). Method L. $LiAlH_4$ reductions were conducted as previously described.[2]

Method M. To an ice-cold solution of 4.8 mmol of the amide in 20 mL of THF there was added 10 mL of 1 N B_2H_6 in THF. Following 18 h of standing in the cold there was added 1 mL of H_2O. The bulk of the solvent was then removed in vacuo and the residue stirred for 5 h with 40 mL of 2.5 N HCl. The mixture was then made strongly basic and extracted with Et_2O. The extract was taken to dryness and the residue treated with ethereal HCl.

Method N. A mixture of 7.9 mmol of the amine, 1.07 g of K_2CO_3, and 8 mmol of the halide in 10 mL of DMF and 40 mL C_6H_6 was heated at reflux for 17 h. The mixture was allowed to cool, washed with water and brine, and taken to dryness.

Method O. To a solution of 7.8 mmol of the secondary amine in 20 mL of THF cooled in an ice–MeOH bath there was added 4.75 mL of 1.64 N BuLi in pentane. A solution of 1 equiv of a 1:1 mixture of the chloroamine and toluene in 20 mL of THF was then added. The mixture was stirred in the cold for 1 h and at reflux for 18 h. The mixture was allowed to cool and then worked up as in method M.

***N*-Methyl-α-(1-adamantyl)-*p*-toluidine Hydrochloride (63).** The free base from amine **62** (2.77 g, 10 mmol) was converted to the carbamate by method H. There was obtained 1.68 g of product (SSB): mp 130–132 °C. Anal. ($C_{20}H_{27}NO_2$) C, H, N.

This was reduced by means of $LiAlH_4$ and the product worked up as in method L. The gum was chromatographed on silica gel (30% CH_2Cl_2–SSB/NH_4OH) and converted to the hydrochloride salt. There was obtained 0.15 g (CH_2Cl_3–EtOAc) of **63**: mp 208–210 °C. Anal. ($C_{18}H_{26}ClN$) H, N; C: calcd, 71.85; found, 71.41.

***p*-(2-Adamantyloxy)-*N*-methylaniline Hydrochloride (86).** The carbamate **85** (2.0 g, 6.4 mmol) was reduced and worked up as in method L. The gum was chromatographed as above and the product recrystallized (MeOH–Et_2O) as its hydrochloride salt. There was obtained 0.71 g (38%) of **86**: mp 223–227.5 °C. Anal. ($C_{17}H_{24}ClNO$) C, H, N.

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2-Indanpropionic Acids: Structural Leads for Prostaglandin $F_{2\alpha}$ Antagonist Development[1]

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A rationale is presented for the development of prostaglandin $F_{2\alpha}$ receptor antagonists. The target analogue, 5,6-(dibenzyloxy)-1-oxo-2-propyl-2-indanpropionic acid (**3**), was shown to have selective activity for antagonism of $PGF_{2\alpha}$ when compared to the antagonism of acetylcholine and KCl on the mouse ileum, whereas other 2-indanpropionic acids (**1**, **2**, **4**), not substituted with benzyl functions, were considerably less active and nonselective. The results suggest that **3** may serve as a lead compound for further drug development.

H_1-receptor antihistamines generally have basic amino functions, presumably capable of interacting with an anionic site as does histamine, but also have two aryl groups, generally β or γ to the amino function, which replace the imidazole ring of the agonist and are thought to provide increased affinity with a loss of intrinsic activity.[2-4] Hence, we reasoned[5] that antiprostaglandins might be constructed having carboxyl groups capable of interacting with a cationic site. Aryl functionality located approximately at the position of the cyclopentanediol grouping of $PGF_{2\alpha}$ similarly might be expected to provide increased affinity with a loss of intrinsic activity during receptor binding.[5] Thus, for our preliminary studies a series of carboxylic acids (**1**–**4**) was synthesized and

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