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

Daniel Lednicer,[1] William E. Heyd,* D. Edward Emmert, Ruth E. TenBrink, Paul E. Schurr, and Charles E. Day

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001. Received February 13, 1978

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
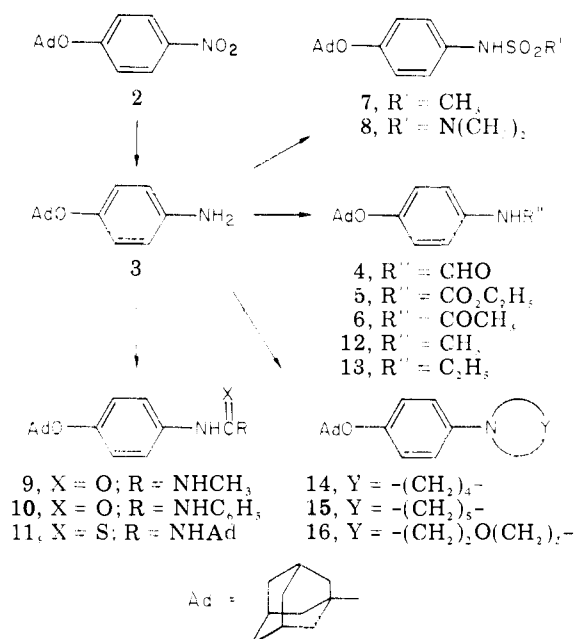

1
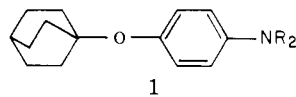
substituted derivatives exhibited activity in both the standard lipid lowering assay and a new assay aimed specifically at measuring the effect of agents on the atherogenic lipoproteins.[2] The previous work suggested the need for a c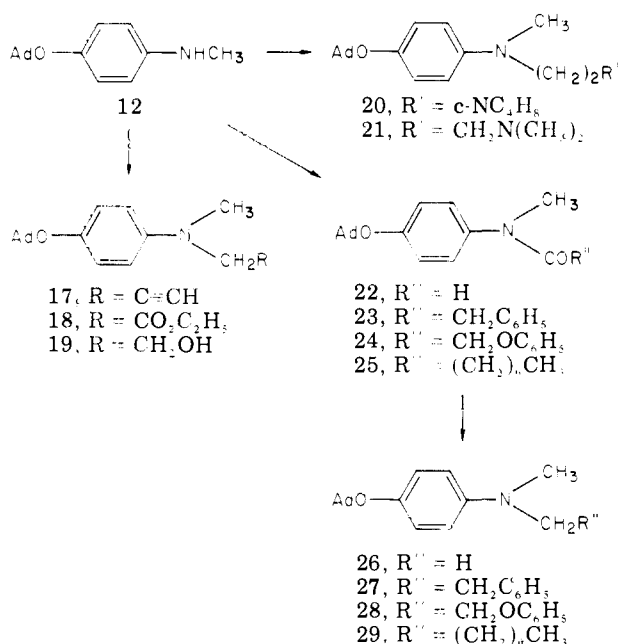ompact lipophilic moiety on the oxygen atom at the para position of the aniline. We, thus, turned our attention to analogues of **1** bearing an adamantyl group.

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
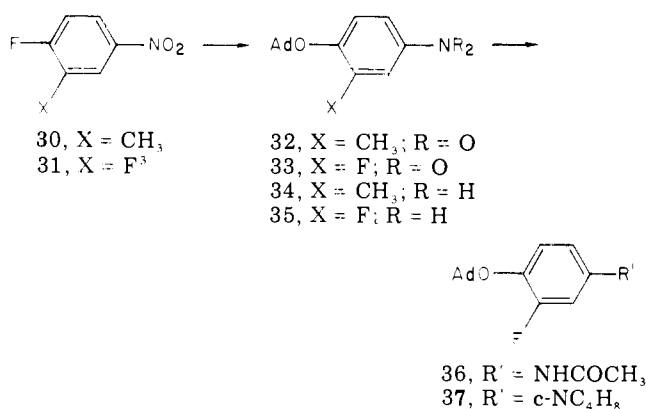
Scheme I

2

7, R' = CH₃
8, R' = N(CH₃)₂

3

4, R'' = CHO
5, R'' = CO₂C₂H₅
6, R'' = COCH₃
12, R'' = CH₃
13, R'' = C₂H₅

9, X = O; R = NHCH₃
10, X = O; R = NHC₆H₅
11, X = S; R = NHAd

14, Y = -(CH₂)₄-
15, Y = -(CH₂)₅-
16, Y = -(CH₂)₂O(CH₂)₂-

Ac =

Scheme II

12

20, R' = c-NC₄H₈
21, R' = CH₂N(CH₃)₂

17, R = C≡CH
18, R = CO₂C₂H₅
19, R = CH₂OH

22, R'' = H
23, R'' = CH₂C₆H₅
24, R'' = CH₂OC₆H₅
25, R'' = (CH₂)₄CH₃

26, R'' = H
27, R'' = CH₂C₆H₅
28, R'' = CH₂OC₆H₅
29, R'' = (CH₂)₄CH₃

Scheme III

30, X = CH₃
31, X = F

32, X = CH₃; R = O
33, X = F; R = O
34, X = CH₃; R = H
35, X = F; R = H

36, R' = NHCOCH₃
37, R' = c-NC₄H₈

Scheme IV

AdOH + HO—⟨ ⟩—NO₂ → AdO—⟨ ⟩—NX₂

38, R¹ = R² = H;
R³ = F
39, R¹ = R³ = H;
R² = Cl
40, R¹ = R² = CH₃;
R³ = H

41a, R¹ = R² = H;
R³ = F; X = O
b, R¹ = R² = H;
R³ = F; X = H
44a, R¹ = R³ = H;
R² = Cl; X = O
b, R¹ = R³ = H;
R² = Cl; X = H
46a, R¹ = R² = CH₃;
R³ = H; X = O
b, R¹ = R² = CH₃;
R³ = H; X = H

43, R¹ = R² = H; R³ = F
45, R¹ = R³ = H; R² = Cl
47, R¹ = R² = CH₃; R³ = 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 (LiAlH₄) 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 LiAlH₄
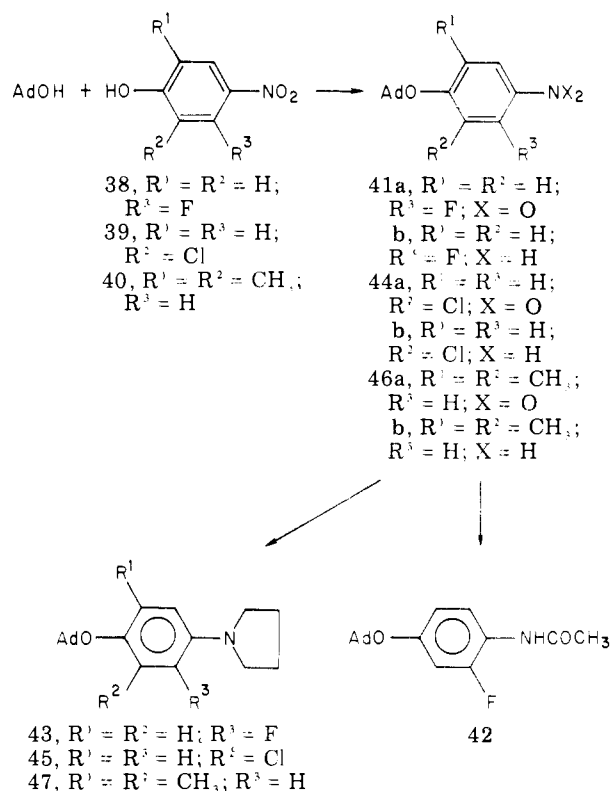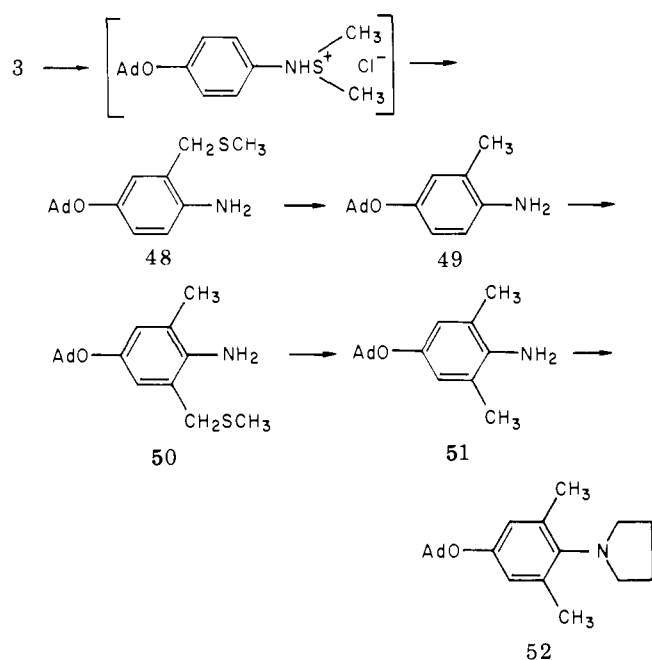
led largely to acyl cleavage products. Use of diborane as the reducing agent circumvented this difficulty, affording 26-29.

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 phenols⁴ provided access to compounds not otherwise easily obtained. Thus, reaction of adamantanol with DCC and Cu₂Cl₂ (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.
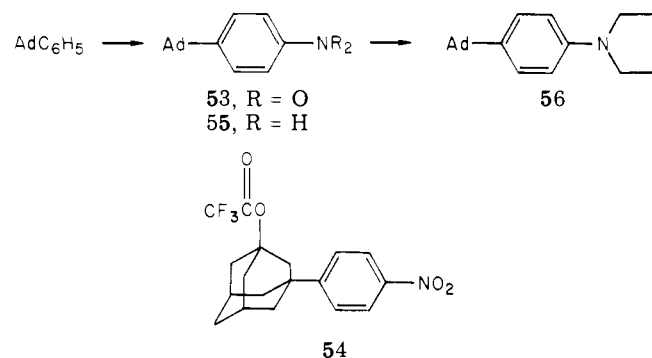
Not surprisingly, attempted displacement on 5-fluoro-2-nitrotoluene failed to afford any of the desired product because of steric inhibition of resonance. The procedure developed by Gassman and co-workers for the ortho alkylation of anilines⁵,⁶ provided access to analogues bearing alkyl substitution at the 2 and 2,6 positions.

Scheme V

48

49

50

51

52

Scheme VI

$AdCN + C_6H_5MgBr \longrightarrow AdC\overset{O}{C}C_6H_5 \longrightarrow AdCH(R)C_6H_5$

57

58, R = OH
59, R = H

63

60, R = O
62, R = H

61, R = O
65, R = H

64

66

Scheme VII

67, R = H
68, R = CH₃

69

71, R' = R'' = H
72, R' = R'' = COCH₃

70

Scheme VIII

73, R = O
74, R = H

75

76

77

+

78

53, R = O
55, R = H

56

54

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 ada-
mantyl moiety and the aromatic ring were achieved as
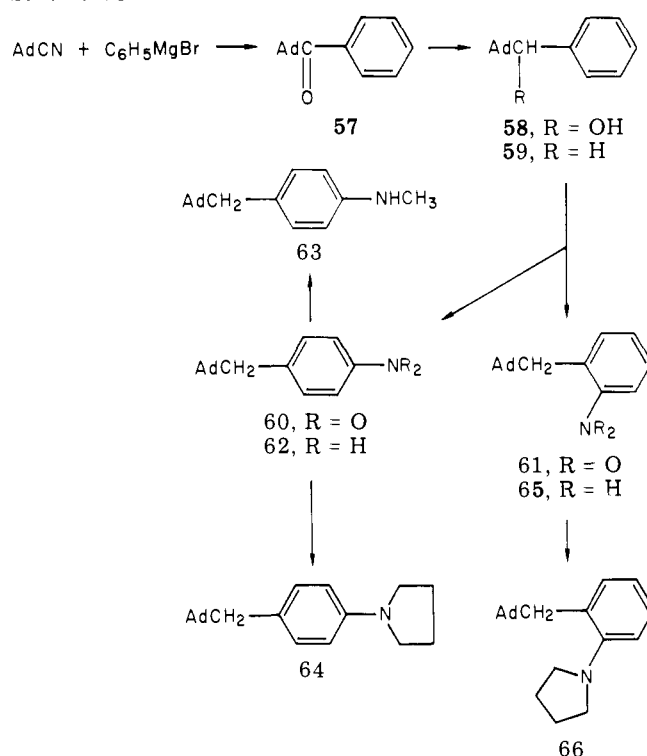follows. Nitration of 1-phenyladamantane under mild
conditions (HNO_3–CF_3CO_2H at 0 °C) produced **53**, which
lacks the bridging atom. (In a single instance where control
of temperature was lost, there was obtained, as well, a
considerable amount of the product of a free radical re-
action, the ester **54**.) Reduction afforded the amine **55**
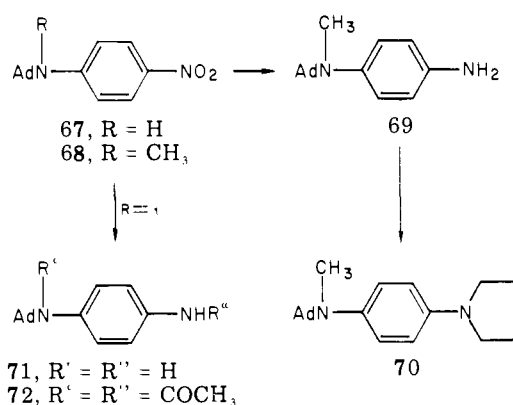from which the pyrrolidine **56** was obtained.

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**. In contrast to the nitration of phen-
yladamantane itself, reaction of **59** under the same con-
ditions 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 trans-
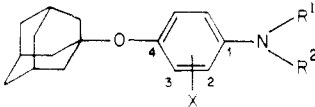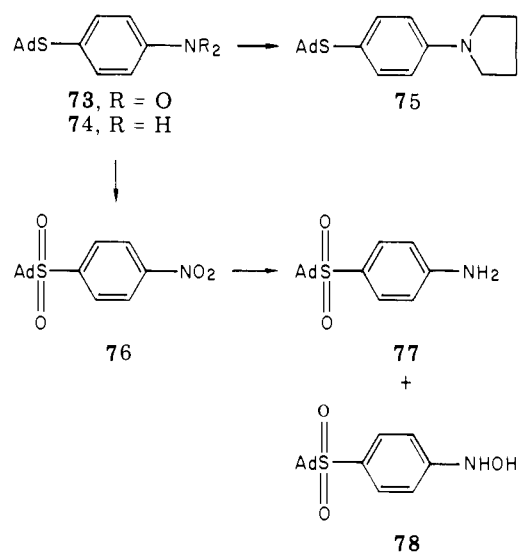formations of **67** are shown in Scheme VII.

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	R¹	R²	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	$CH_2C≡CH$	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	$(CH_2)_2N(CH_3)_2$	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[f]	H	CH_3	$(CH_2)_3C_6H_5$	1.09	1.07	0.98
28	H	CH_3	$(CH_2)_2OC_6H_5$	1.03	1.06	1.03
29[d]	H	CH_3	$(CH_2)_2CH_3$	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		-$(CH_2)_5$-	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		-$(CH_2)_5$-	1.08	1.07	0.98
46b[d]	3,5-$(CH_3)_2$	H	H	0.86	0.80	0.93
47	3,5-$(CH_3)_2$		-$(CH_2)_5$-	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.[9h] An
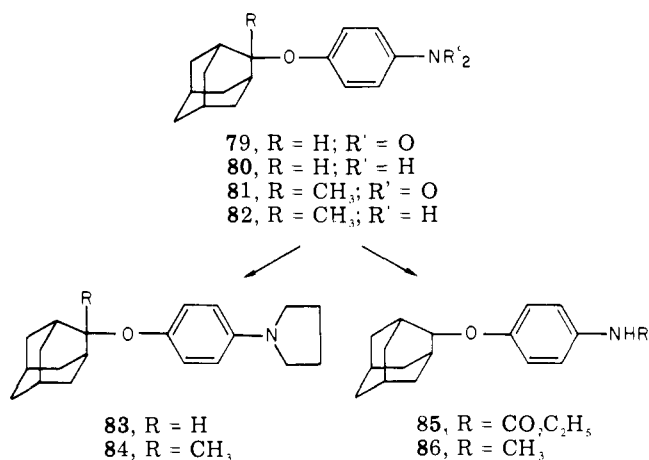
Scheme IX

79, R = H; R' = O
80, R = H; R' = H
81, R = CH₃; R' = O
82, R = CH₃; R' = H

83, R = H
84, R = CH₃

85, R = CO₂C₂H₅
86, R = CH₃

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

compd no.	X	isomer	R¹	R²	CHOL, T/C	HPL, T/C	HPL/ CHOL, T/C
55[d]		para	H	H	141*	1.40*	0.99
56		para		-(CH₂)₄-	1.17	0.90	0.77
62[d]	CH₂	para	H	H	0.45*	0.23*	0.50*
63[d]	CH₂	para	H	CH₃	0.55*	0.45*	0.82*
64	CH₂	para		-(CH₂)₄-	0.82	0.87	1.06
65[d]	CH₂	ortho	H	H	0.86	0.89	1.03
66	CH₂	ortho		-(CH₂)₄-	1.39*	1.40*	1.01
69[d]	NCH₃	para	H	H	0.84	0.82	0.98[c]
70	NCH₃	para		-(CH₂)₄-	0.93	1.02	1.10[b]
71	NH	para	H	H	0.94	0.85	0.90[b]
72	NCOCH₃	para	H	COCH₃	1.00	0.98	0.98
74	S	para	H	H	0.51*	0.45*	0.87*
75	S	para		-(CH₂)₄-	0.83	0.95	1.14*
77	SO₂	para	H	H	1.12	1.07	0.95
78	SO₂	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 ($p \le 0.05$) 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

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

compd no.	R¹	R²	R³	CHOL, T/C	HPL, T/C	HPL/ CHOL, T/C
80	H	H	H	0.82	0.67*	0.82*
82	CH₃	H	H	0.58*	0.45*	0.77*[b]
83	H	-(CH₂)₄-		1.07	1.07	1.01
84	CH₃	-(CH₂)₄-		1.04	1.03	0.99
86[d]	H	H	CH₃	0.83	0.87	1.04

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

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]

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-CH₃	A	36	25% SSB in CH₂Cl₂	SSB	89.5-91	$C_{17}H_{21}NO_3$
33	1-Ad	O	3-F	A	68	CH₂Cl₂		115-121	$C_{16}H_{18}FNO_3$
41a	1-Ad	O	2-F	C	c	CH₂Cl₂		88-89	$C_{16}H_{18}FNO_3$
44a	1-Ad	O	3-Cl	C	5	CH₂Cl₂	Me₂CO-SSB	84-85	$C_{16}H_{18}ClNO_3$
46a	1-Ad	O	3,5-(CH₃)₂	C	c	CH₂Cl₂		139-155	$C_{18}H_{23}NO_3$
67	1-Ad	NH	H	B	67		Me₂CO-cyhex[d]	188-189	$C_{16}H_{20}N_2O_2$
73	1-Ad	S	H	A	73		CH₂Cl₂-cyhex	145-147	$C_{16}H_{19}NO_2S$
79	2-Ad[e]	O	H	A	50	1:1 C₆H₆-SSB	SSB	120-122.5	$C_{16}H_{19}NO_3$
81	2-Me-2-Ad[f]	O	H	A	71	1:1 SSB-CH₂Cl₂		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-H₂O	175-177	$C_{16}H_{21}NO$
34	1-Ad	O	3-CH₃	D	77	CH₂Cl₂-EtOAc[b]	201-202	$C_{17}H_{24}ClNO$
35	1-Ad	O	3-F	D	79	CH₂Cl₂-hex[c]	180-190.5	$C_{16}H_{20}FNO$
41b	1-Ad	O	2-F	D	9[d,e]	CH₂Cl₂-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-(CH₃)₂	D	4[d,e]		196.7-197	$C_{18}H_{26}ClNO$
48	1-Ad	O	2-CH₂SCH₃	E	52	CH₂Cl₂-SSB	62-65	$C_{18}H_{25}NOS$
49	1-Ad	O	2-CH₃	F	21	CH₂Cl₂-SSB	143.5-145	$C_{17}H_{23}NO$
50	1-Ad	O	2-CH₃, 6-CH₂SCH₃	E	8	b	202-203.5	$C_{19}H_{28}ClNOS$
51	1-Ad	O	2,6-(CH₃)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	CH₂	H	D	63	MeOH-EtOAc[b]	250-253	$C_{17}H_{24}ClN$
65	1-Ad	CH₃[g]	H	D	58	MeOH-EtOAc[b]	230-235	$C_{17}H_{24}ClN^h$
69	1-Ad	NCH₃	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-H₂O	153-156	$C_{16}H_{22}N_2{}^i$
74	1-Ad	S	H	D	80	MeOH-H₂O	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	CH₂Cl₂-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% CH₂Cl₂ 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.
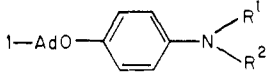
Experimental Section

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 C₆H₆ 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 H₂O, 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 K₂CO₃ in 10 mL of HMPA was stirred for 17 h in an oil bath at 135 °C. The
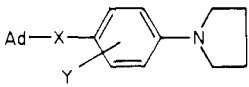
Table VI. Amides, Carbamates, and Ureas from 4-(Adamantyloxy)anilines

compd no.	R[1]	R[2]	method	yield, %	recrystn solvent	mp, °C	formula
4	H	CHO	K	87	Me₂CO-cyhex[d]	149-150	C₁₇H₂₁NO₂
5	H	CO₂C₂H₅	H	87	MeOH	116.5-118	C₁₉H₂₅NO₄
6	H	COCH₃	G	88	MeOH	167-168.5	C₁₈H₂₃NO₂
7	H	SO₂CH₃	H	89	MeOH-H₂O	167-169	C₁₇H₂₃NO₃S
8	H	SO₂N(CH₃)₂	H	67	MeOH-H₂O	197.5-199.5	C₁₈H₂₆N₂O₃S
9	H	CONHCH₃	J	85	MeOH-H₂O	210-211	C₁₈H₂₄N₂O₂
10	H	CONHC₂H₅	J	67	Me₂CO-H₂O	223-224.5	C₁₉H₂₆N₂O₂
11	H	CSNH(1-Ad)	J	55	(THF)[f]	203.8-205.3	C₂₇H₃₆N₂OS
22	CH₃	CHO	K	70	Me₂CO-cyhex[d]	106-108.1	C₁₈H₂₃NO₂
23	CH₃	COCH₂C₆H₅	I	79	SSB[g]	89-91	C₂₅H₂₉NO₂
24	CH₃	COCH₂OC₆H₅	I	91	SSB	108-110	C₂₅H₂₉NO₃
25	CH₃	CO(CH₂)₆CH₃	I	90	e		
36	H	COCH₃[a]	G	85	MeOH	227-231	C₁₈H₂₂FNO₂
42	H	COCH₃[b]	G	70	MeOH	173.2-175	C₁₈H₂₂FNO₂
85	H	CO₂C₂H₅[c]	I	81	Et₂O-SSB	113-115	C₁₉H₂₅NO₃

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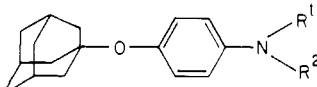
Table VII. [4-(Adamantyl-X)phenyl]pyrrolidines

compd no.	Ad	X	Y	yield, %	recrystn solvent	mp, °C	formula
14	1-Ad[a]	O	H	72	MeOH	120-122	C₂₀H₂₇NO
37	1-Ad	O	3-F	15	b	149-155	C₂₀H₂₆FNO
43	1-Ad	O	2-F	54	b	99-106	C₂₀H₂₆FNO
45	1-Ad	O	3-Cl	39	c	157.2-158.3	C₂₀H₂₆ClNO
47	1-Ad	O	3,5-(Me)₂	87	c	93-102.5	C₂₂H₃₁NO
52	1-Ad	O	2,6-(Me)₂	17	b	184.4-185.6[d]	C₂₂H₃₂ClNO[e]
56	1-Ad		H	67	Me₂CO-H₂O	167-169	C₂₀H₂₇N
64	1-Ad	CH₂	H	64	EtOH	147-148.5	C₂₁H₂₉N
66	1-Ad	CH₂	H[f]	32[c,d]	CH₂Cl₂-EtOH	188-191	C₂₁H₃₀ClN
70	1-Ad	NCH₃	H	66	MeOH	128-129.5	C₂₁H₃₀N₂
75	1-Ad	S	H	49[c]	SSB[i]	159-162	C₂₀H₂₇NS
83	2-Ad[g]	O	H	29[c]	pet. ether[j]	101.5-102.5	C₂₀H₂₇NO
84	2-CH₃-2-Ad[h]	O	H	69		119.1-121.2	C₂₁H₂₉NO

[a] 1-Adamantyl. [b] Compound purified by LC (elution with 0.5% Me₂CO-CH₂Cl₂). [c] Compound purified by chromatography. [d] Hydrochloride salt. [e] Analysis calculated for 1.08% Et₂O and 1.85% CH₂Cl₂ 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	CH₃	H	L	64	CH₂Cl₂-EtOAc	207.5-208.5[a]	C₁₇H₂₄ClNO
13	C₂H₅	H	L	7.9[b]	CH₂Cl₂-EtOAc	185-187.5[a]	C₁₈H₂₆ClNO
15	-(CH₂)₄-		c	19	pet. ether	72-73.5	C₂₀H₂₉NO
16	-(CH₂)₂O(CH₂)₂-		d	19	CH₂Cl₂-SSB[g]	146.0-150.1	C₂₀H₂₇NO₂[f]
17	CH₃	CH₂C≡CH	N	77	CH₂Cl₂-EtOAc	180-181[a]	C₂₀H₂₈ClNO
19	CH₃	(CH₂)₂OH	N, L	80	Me₂CO-SSB	94-99	C₁₉H₂₇NO₂
20	CH₃	(CH₂)₂-c-NC₄H₈	O	55	CH₂Cl₂-CH₃CN	189-190[a]	C₂₃H₃₆Cl₂N₂O·2H₂O[e]
21	CH₃	(CH₂)₃N(CH₃)₂	O	53	MeOH-CH₃CN	221-223[a]	C₂₂H₃₆Cl₂N₂O·H₂O
26	CH₃	CH₃	L	15	CH₂Cl₂-EtOAc	214-216[a]	C₁₈H₂₆ClNO·0.5H₂O
27	CH₃	(CH₂)₂C₆H₅	M	65	CH₂Cl₂-EtOAc	213-214[a]	C₂₅H₃₂ClNO
28	CH₃	(CH₂)₂OC₆H₅	M	76	MeOH	108-109	C₂₅H₃₁NO₂
29	CH₃	(CH₂)₇CH₃	M	66	EtOAc	144-148[a]	C₂₅H₄₀ClNO

[a] Hydrochloride salt. [b] Chromatographed on silica gel (C₆H₆-NH₄OH). [c] From alkylation of aniline with I(CH₂)₄I. [d] From alkylation of aniline with Cl(CH₂)₂O(CH₂)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 H₂O, and extracted with C₆H₆. The organic layer was washed thoroughly with H₂O 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 Cu₂Cl₂ 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 CH₂Cl₂, 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 HNO₃. At the end of 2 h the cooling bath was removed. After an additional 1 h of stirring, the mixture was poured onto ice H₂O. The precipitated oil was extracted with C₆H₆. The organic layer was washed with H₂O, NaHCO₃, and brine and taken to dryness. The residue was chromatographed on 290 g of silica gel (elution with 1:1 CH₂Cl₂ 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. (C₁₆H₁₉NO₂).

This was followed by a more polar fraction. Recrystallization from SSB afforded 0.49 g of 54: mp 95–97 °C; ν_max 1720 cm⁻¹; m/e 369. Anal. (C₁₈H₁₈F₃NO₃) C, H, N: calcd, 3.79; found, 4.58.

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 Et₂O was added to 20 mL of 2.85 M C₆H₅MgBr in Et₂O. 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 Et₂O and 500 mL of H₂O. The mixture was then allowed to stir at room temperature for 4 h. The organic layer was then washed with H₂O, NaHCO₃, 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. (C₁₇H₂₀O) 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 NaBH₄. At the end of 5 h of stirring at room temperature the solvent was removed in vacuo. The residue was dissolved in H₂O and Et₂O. The organic layer was washed with H₂O 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. (C₁₇H₂₂O) C, H.

1-Benzyladamantane (59). From 58. A solution of 5.04 g (0.021 mol) of the alcohol 58 in 10 mL of Ac₂O and 20 mL of pyridine was allowed to stand at room temperature for 7 h. The mixture was then poured onto ice H₂O and extracted with Et₂O. The extract was then washed in turn with H₂O, 2.5 N HCl, H₂O, 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 NH₄Cl, and the solvent was evaporated under a stream of N₂. The residue was dissolved in H₂O and Et₂O. The organic layer was washed with H₂O 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 (MgSO₄) 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 (MgSO₄), 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. (C₁₇H₂₂) C, H.

α-(1-Adamantyl)-p-nitrotoluene (60) and α-1-(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 H₂O. The precipitate was extracted with C₆H₆, and this solution was washed in turn with H₂O, NaHCO₃, and brine. The solid which remained when the extract was taken to dryness was chromatographed on 240 g of silica gel (elution with 25% CH₂Cl₂ 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. (C₁₇H₂₁NO₂) 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. (C₁₇H₂₁NO₂) 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 C₆H₆ there was added 0.63 g of 56% NaH. Following 3 h of stirring at reflux, 10 mL of CH₃I was added; at the end of an additional 2 h, 5 mL of CH₃I was added and the mixture heated 2 h more. The reaction was then diluted with C₆H₆ and washed well with H₂O. The residue was chromatographed on 290 g of silica gel (elution with 10% Me₂CO 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. (C₁₇H₂₂N₂O₂) 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 H₂ 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 Cl₂ in 180 mL of CH₂Cl₂ cooled to –70 °C was added a precooled solution of 11.4 g (0.18 mol) of dimethyl sulfide in 40 mL of CH₂Cl₂ 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 Et₃N in 1 L of CH₂Cl₂. 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 H₂O, and taken to dryness. The residual gum was chromatographed over silica gel (elution with 1–4% Me₂CO in CH₂Cl₂).

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% Me₂CO in CH₂Cl₂).

1-Adamantyl p-Nitrophenyl Sulfone (76). Solid m-ClC₆H₄H₃CO₃H (3.44 g) was added to an ice-cooled solution of 2.89 g (0.01 mol) of 73 in 100 mL of CH₂Cl₂. The mixture was allowed to come to room temperature and stirred for 5 h. The solution was washed twice with NaHCO₃ and taken to dryness. The residue was recrystallized from Me₂CO–H₂O to give 2.49 g (78%) of sulfone 76: mp 222–225 °C. Anal. (C₁₆H₁₉NO₄S) 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 H₂. 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% Me₂CO–CH₂Cl₂) to give (in order of elution) the following. (1) The azoxide: 0.07 g (from CH₂Cl₂): 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_2–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.

References and Notes

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2-Indanpropionic Acids: Structural Leads for Prostaglandin F₂α Antagonist Development[1]

Donald T. Witiak,* Sunil V. Kakodkar, Timothy P. Johnson, John R. Baldwin, and Ralf G. Rahwan

Divisions of Medicinal Chemistry and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210. Received August 2, 1978

A rationale is presented for the development of prostaglandin F₂α 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 PGF₂α 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 PGF₂α 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