(40 g, 0.22 mol, Pierce Chemical Co.) was converted to the phenol, in 63% yield, in the manner described above: bp 91–93 °C (20 mm); n^{24}_D 1.4440 [lit.[3] bp 92 °C (25 mm); n^{25}_D 1.4469].

Acknowledgment. We are grateful to Drs. H. A. Musallam, R. O. Pick, E. A. Steck, and T. R. Sweeney of WRAIR for assistance, suggestions, and enthusiasm during the course of our research, to Drs. David E. Davidson, Arba Ager, John L. Brown, Frank D. Chapple, Richard E. Whitmire, and Leon Schmidt for performing biological tests, to Drs. H. A. Musallam of WRAIR and P. Blumbergs of Ash Stevens, Inc., for making available 5-chloro-6-methoxy-3-methyl-8-nitroquinoline and 5-chloro-6-methoxy-4-methyl-8-nitroquinoline and to Janice Conlon, Beth Bauer, and Suzanne Olivieri for technical assistance. This investigation was supported by the U.S. Army Medical Research and Development Command under Contract No. DADA 17-70-C-0101 and is Contribution no. 1644 to the Army Research Program on Antiparasitic Drugs.

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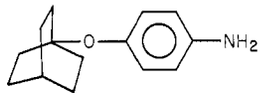
Hypobetalipoproteinemic Agents. 3. Variation of the Polycyclic Portion of 4-(1-Adamantyloxy)aniline

William E. Heyd,* Larry T. Bell, James R. Heystek, Paul E. Schurr, and Charles E. Day

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001. *Received January 4, 1982*

We have replaced the adamantyl moiety of the hypobetalipoproteinemic 4-(1-adamantyloxy)aniline (**2**) with 1- and 4-diamantyl, *cis*- and *trans*-9-decalyl, and 1,1-dimethylbutyl, -hexyl, and -octyl. The compounds were easily accessible by our previous route. Only the diamantyl compounds, **8** and **11**, were active, suggesting that some as yet unidentified, special geometrical and/or associative (electronic) aspects of the tertiary bi- and polycyclooxyanilines are required for the hypobetalipoproteinemic activity of these agents.

We have previously reported the hypobetalipoproteinemic activity of agents related to 4-(1-bicyclo[2.2.2]-octyloxy)aniline (**1**)[1] and the more potent 4-(1-adamantyloxy)aniline (**2**).[2] This activity consists of a reduction of the atherogenic heparin precipitating lipoproteins (HPL) and also the HPL to cholesterol ratio in the cholesterol–cholic acid fed rat.[3] Ultracentrifugation studies with the piperidine **3** have demonstrated that not only are the atherogenic, lower density (d <1.040 g/mL) lipoproteins reduced as desired, but the high density lipoproteins (1.040 < d < 1.21 g/mL), which may well be antiatherogenic,[4-6] are increased. The extensive investigation of compounds related to **2** included variation in the bridging oxygen atom and substitution on the aromatic ring and on nitrogen.[2] Two other changes in the polycyclooxy portion of **1** and **2** produced compounds **4**[1] which were inactive, **5a**[2] which was active, and **5b**[2] the activity of which is considered indeterminant due to subnormal weight gain. Thus, there seemed to be some unique structural characteristic of the bicyclic and tricyclic portions of **1** and **2**, respectively, responsible for their hypo-



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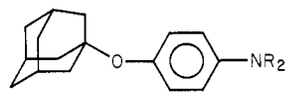
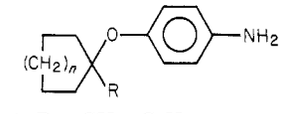


2, R = H
3, R = $(CH_2)_5$

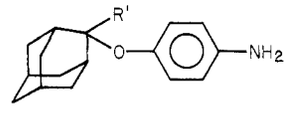
Table I. Hypobetalipoproteinemic Activity of *p*-Aminophenyl Ethers in Diet-Induced Hypercholesterolemic Rats[a]

no.	dose, (mmol/kg)/day	T/C		
		Chol	HPL	HPL/Chol
8	0.17	0.53*	0.35*	0.66*
11	0.17	0.31*	0.19*	0.62*
14[b]	0.18	0.92	0.89	0.97
17[b]	0.18	1.38*	1.24	0.90*
20[b]	0.22	0.84	0.78	0.92
23[b]	0.19	1.02	0.96	0.94
26[b]	0.17	0.98	0.84	0.86*

[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; compounds were dosed at 50 (mg/kg)/day. Food intake and weight gain were considered normal (>73% and >63% of control values, respectively) during the experiments. [b] Data reported for the hydrochloride salt.



4, R = CH_3, C_2H_5, n = 1, 2



5a, R′ = H
b, R′ = CH_3

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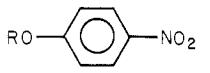
Table II. *p*-Nitrophenyl Ethers



no.	yield, %	purification solvent: chromatogr	purification solvent: recrystn	mp, °C	formula	anal.
7	57		C_2H_5OH	140.5-142	$C_{20}H_{23}NO_3$	C, H, N
10	41	30% CH_2Cl_2 in hexane		152-173	$C_{20}H_{23}NO_3$	C, H, N
13	70	benzene		oil	$C_{16}H_{21}NO_3$	C, H, N
16	41	benzene		79.0-81.0	$C_{16}H_{21}NO_3$	C, H, N
19	76	benzene		oil	$C_{12}H_{17}NO_3$	C, H, N
22	88	benzene		oil	$C_{14}H_{21}NO_3$	C, H, N
25	90	benzene		oil	$C_{16}H_{25}NO_2$	C, H, N

betalipoproteinemic activity. We describe herein the further exploration of this novel feature.

Chemistry and Pharmacology. Nucleophilic displacement of the fluoride of *p*-fluoronitrobenzene by the appropriate tertiary alkoxide provided the requisite nitro compounds, which were hydrogenated to the corresponding anilines (Scheme I).[1,2] Thus, the adamantyl group of **2** has been replaced by 1-diamantyl (**8**), 4-diamantyl (**11**), *cis*- (**14**) and *trans*-9-decalyl (**17**), 1,1-dimethylbutyl (**20**), 1,1-dimethylhexyl (**23**), and 1,1-dimethyloctyl (**26**).

Each compound was assayed (in 0.25% aqueous methylcellulose vehicle) for hypobetalipoproteinemic activity at 50 (mg/kg)/day, and the data were analyzed statistically as previously described.[2] Active compounds were retested to confirm activity. Total serum cholesterol (Chol), HPL, and the HPL to cholesterol ratio are reported in Table I. The nitro compounds were also tested, and none exhibited hypobetalipoproteinemic activity.

Discussion

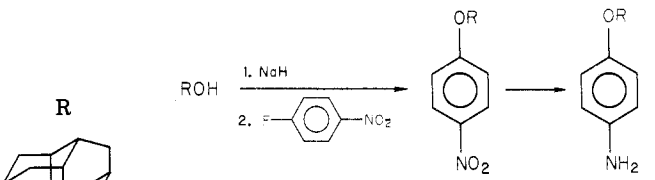
The striking result is that only the diamantyl analogues (**8** and **11**) of **2** show hypobetalipoproteinemic activity. Both **8** and **11** are adamantylogues of **2**. Aniline **8** may also be considered an adamantylogue of the secondary 4-(2-adamantyloxy)aniline (**5a**),[2] which was found to be hypobetalipoproteinemic but not hypocholesterolemic. The formal addition of four carbon atoms to **2** to generate **11** occurs remote to the oxyaniline function and, therefore, provides minimal perturbation of the oxyaniline environment. Because of the relation of **8** to both **2** and **5a**, the formal site of homologation relative to the oxyaniline function is ambiguous, but the environment of this group is surely different for **8** as compared with **2** and **11**. Nevertheless, **2**, **8**, annd **11** are all active compounds, precluding any definitive statement about the magnitude of this environmental effect.

The decalyl derivatives offer alternative cyclic tertiary C_{10} systems with quite different geometry. The acyclic amine **23** was calculated to be approximately isolipophilic to **2**, and the lower and higher homologues (**20** and **26**) were prepared as well. None of these compounds was hypobetalipoproteinemic. It seems unlikely that differences in lipophilicity are the only factors responsible for the inactivity of these compounds and those (**4**) mentioned above. Thus, we have further strengthened our original notion that some as yet unidentified, special geometrical and/or associative (electronic)aspects of the tertiary bicyclooctyl, adamantyl, and now 1- and 4-diamantyl moieties are required for the hypobetalipoproteinemic activity of these agents.

Experimental Section

Melting points are uncorrected and were obtained on either a Thomas-Hoover or capillary melting point apparatus. NMR spectra were determined on a Varian A60D or XL-100 instrument.

Scheme I



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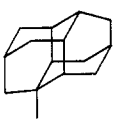
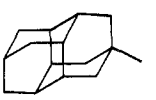
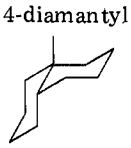
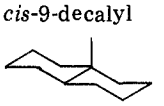
 1-diamantyl	6	7	8
 4-diamantyl	9	10	11
 *cis*-9-decalyl	12	13	14
 *trans*-9-decalyl	15	16	17
$CH_3(CH_2)_nC(CH_3)_2$			
$n = 2$	18	19	20
$n = 4$	21	22	23
$n = 6$	24	25	26

2-Methyl-2-pentanol, 2-methyl-2-heptanol, and 2-methyl-2-nonanol were purchased from Aldrich Chemical Co.; 4-fluoronitrobenzene was purchased from Eastman. 1-Diamantanol (**6**) was prepared by bromination[8] of diamantane,[9] followed by hydrolysis.[10] 4-Diamantanol (**9**) was prepared from tetrahydro-Binor-S[9] as described.[11] *cis*-9-Decalol (**12**) and *trans*-9-decalol (**15**) were prepared as described.[12]

The nitro compounds (Table II) were prepared from the appropriate alcohol, sodium hydride, and *p*-fluoronitrobenzene as described previously.[1] The anilines (Table III) were prepared by hydrogenation over platinum or 10% palladium on carbon in ethyl acetate solution, filtration from the catalyst, concentration, and recrystallization or conversion to the hydrochloride using HCl in absolute diethyl ether.

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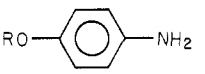
Table III *p*-Aminophenyl Ethers



no.	yield, %	recrystn solvent	mp, °C	formula	anal.
8	74	CH_2Cl_2/hexane then C_2H_5OH	128.8–135.8	$C_{20}H_{25}NO$	C, H, N
11	29	CH_2Cl_2, then ethanol	231.1–238.8	$C_{20}H_{25}NO$	C, H, N
14[a]	57	$(CH_3)_2CHOH$	>250 dec	$C_{16}H_{24}ClNO$	C, H, N, Cl
17[a]	17	C_2H_5OH	205 dec	$C_{16}H_{24}ClNO$	C, H, N, Cl
20[a]	92	$(C_2H_5)_2O$[b]	112.1–114.3	$C_{12}H_{20}ClNO$	C, H, N; Cl[c]
23[a]	97	$(C_2H_5)_2O$	94.8–96.1	$C_{14}H_{24}ClNO$	C, H, N, Cl
26[a]	74	1:1 benzene/Skelly B	92.0–94.2	$C_{16}H_{28}ClNO$	C, H, N, Cl

[a] Data reported are for the hydrochloride salt. The yield is based on the corresponding nitro compound. [b] The salt was generated in ether but not recrystallized. [c] Cl: calcd, 15.43; found, 15.95.

Acknowledgment. The authors are indebted to P. E. Marlatt and M. C. Moerman for the preparation of 4-diamantanol, R. L. Pederson for the preparation of *cis*- and *trans*-9-decalols, M. A. Rebenstorf for the hydrogenation reactions, Dr. W. Morozowich for helpful discussion on the isolipophilicity of compounds **2** and **23**, R. C. Anderson and D. J. Liggett for microanalyses, B. Story, H. Sanders, G. Louthan, T. A. Scahill, and P. A. Meulman for other analytical work, and J. K. Woods for typing the manuscript.

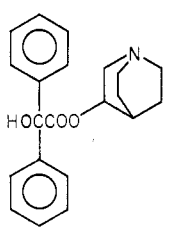
Analogues of 3-Quinuclidinyl Benzilate

W. J. Rzeszotarski,* R. E. Gibson, W. C. Eckelman, D. A. Simms, E. M. Jagoda, N. L. Ferreira, and R. C. Reba

Radiopharmaceutical Chemistry, George Washington University Medical Center, Washington, DC 20037.
Received August 10, 1981

A number of analogues of 3-quinuclidinyl benzilate (QNB) have been synthesized and their affinities to muscarinic receptor from rat or dog ventricular muscle measured. We have determined that the muscarinic receptor can to a different degree accomodate either a halogen in the ortho, meta, or para position of one phenyl ring or the replacement of one phenyl ring with an alkyl group. Our in vitro competition studies show that the affinities lie within a 270-fold range, from the highest affinity compound, 3-quinuclidinyl α-hydroxy-α-cyclopentylphenylacetate (**2**), to the lowest affinity compound, 3-quinuclidinyl α-hydroxy-α-2-propargylphenylacetate (**11**).

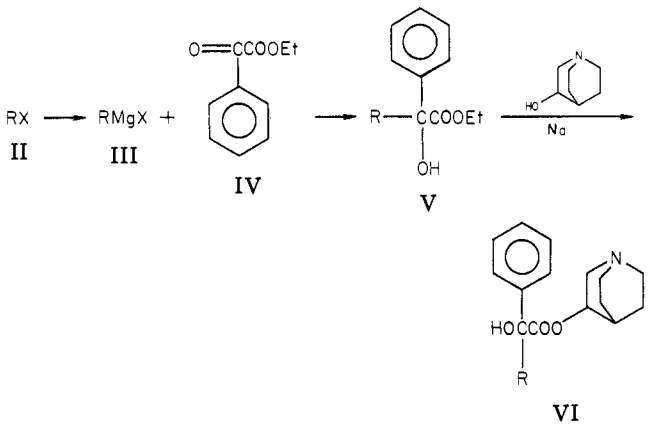
3-Quinuclidinyl benzilate (QNB, I), synthesized by



I

Sternbach and Kaiser,[1] is one of the most potent muscarinic antagonists.[2] Recently,[3,4] our group disclosed the potential use of QNB analogues for myocardial imaging. The proposed[5] "three points of attachment" model of the interaction of the muscarinic antagonist with the receptor explains neither the role of the second aromatic ring nor the role of substitution in the ring. Some impairment of binding has been reported at the receptor level due to ring substitution.[6] It has also been reported that the replacement of one of the aromatic rings with the cyclopentyl or cyclohexyl[7,8] group does not change the biological activity when tested in an intact animal[2] or isolated tissue preparations.[7,8] Recently, we reported a halogenated QNB

Scheme I



II III IV V VI

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