couragement throughout the course of this work and to Dr. H. Uno and K. Natsuka for good discussion in preparation of this manuscript. Thanks are also due to T. Yoshida and S. Motoyoshi for assistance in this work and to members of the analytical section of these laboratories for elemental and spectral measurements.

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Synthesis and Evaluation of the Antiovulatory Activity of a Variety of Melatonin Analogues

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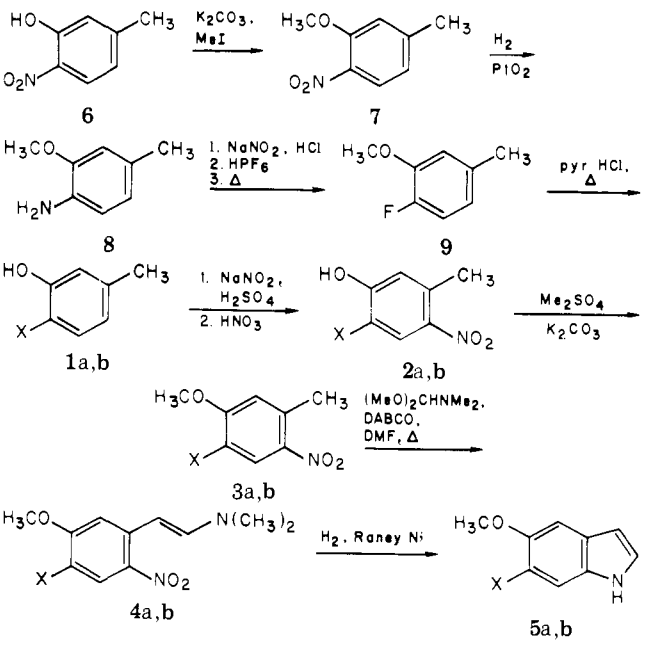
A series of melatonin analogues was synthesized and examined for ovulation-blocking activity. Deviation from the 5-methoxy group or substitution of the 1 position prevented activity. Activity was not particularly sensitive to minor variations in the *N*-acyl group nor was it significantly altered by methylation of position 2 or the α-methylene; however, a pronounced enhancement resulted from halogenation of the 6 position.

Since the first isolation of melatonin (**15a**) in 1959,[1] interest in this hormone has grown steadily. Of particular interest are the reports that melatonin has the ability to inhibit LH secretion.[2] A major difficulty in assessing the physiological properties of melatonin is its very rapid metabolism. This rate of metabolism combined with the polyphasic nature of the process complicates estimation of a biological half-life for melatonin. Kopin et al.[3] estimate that exogenously administered melatonin disappears from whole mice with a half-life of about 2 min through the first 10 min following injection but that after 40 min the half-life has grown to about 35 min. In this same report, data are presented indicating a plasma half-life in rats through the first 30 min of about 15 min. Maickel et al.[4] have estimated the plasma half-life in rats to be about 12 min through the first 2 h following administration.

We undertook the synthesis of a variety of melatonin analogues with the intention of producing compounds with similar physiological properties but greater resistance to metabolism. A more general goal was to establish which features of the melatonin molecule are essential for activity and which sites will tolerate structural modification. In view of the evidence that the major route in the metabolism of melatonin is hydroxylation at the 6 position,[3] we were particularly interested in synthesizing analogues bearing substituents in that position.

Chemistry. The synthetic work is described in three parts: (1) preparation of the indoles, (2) attachment of the side chain at the 3 position, and (3) preparation of analogues starting from serotonin.

Scheme I



a, X = Cl; b, X = F

Indoles. The versatile indole synthesis developed by

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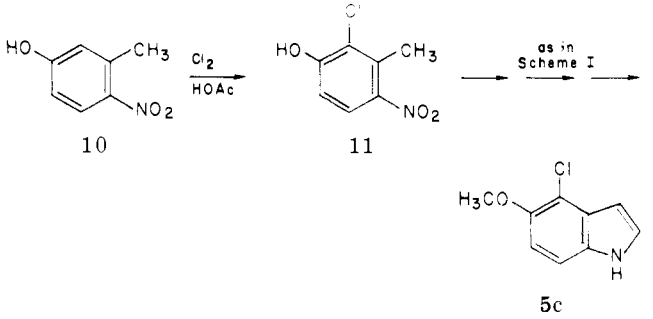
Scheme II



Batcho and Leimgruber[5] was adopted for the preparation of the three haloindoles **5a–c** (Schemes I and II). The requisite benzenoid substrate was readily prepared in the case of the chloro compound **3a**, but synthesis of the fluoro compound **3b** was somewhat more involved.

Nitrosation of **1a** followed by mild oxidation with HNO_3 afforded **2a** as the only isomer. This very selective nitration is an adaptation of the method of Hodgson et al.[6] Methylation of **2a** provided **3a**, which was then condensed with dimethylformamide acetal, and the resultant enamine **4a** was reductively cyclized to **5a**.

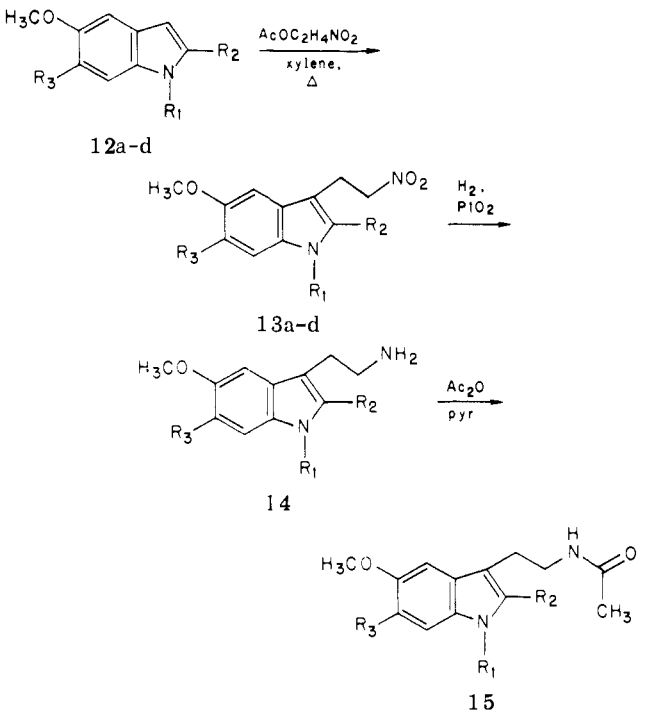
The starting point for the 6-fluoro-*m*-cresol (**1b**) was the corresponding nitrocresol **6**. Following conversion to the anisole **7**, the nitro group was reduced catalytically. The resulting amino group was then replaced by fluorine using a modified Schiemann reaction.[7] It was then necessary to cleave the methoxy group in order to continue with the nitrosation–oxidation procedure used in the case of the chloro compound. From this point, the synthesis of **5b** was identical to that of **5a**.

The preparation of the 4-chloroindole **5c** (Scheme II) was a spinoff from an earlier synthesis of **5a**. A reported preparation of **3a** involves the direct chlorination of **10**.[8] A byproduct, indeed the major product, in this reaction is **11**. Complete separation of **2a** from **11** is rather troublesome, so the synthesis was continued using a 4:1 mixture of **11** and **2a**. The mixture of **5c** and **5a** which ultimately resulted was readily separated.

Attachment of the Side Chain. The more reactive indoles **12a–d** were alkylated at the 3 position by reaction with nitroethene generated in situ by thermolysis of nitroethyl acetate (Scheme III).[9] The nitroethyl acetate used for this purpose was prepared by acetylation of nitroethanol with acetic anhydride using NaOAc as a catalyst. These conditions constitute a substantial improvement over literature methods.[10] Reduction of the nitroethylated indoles **13a–d** by hydrogenation over PtO_2, followed by acetylation of the resulting tryptamines with acetic anhydride–pyridine, completed the synthesis of **15a–d**.

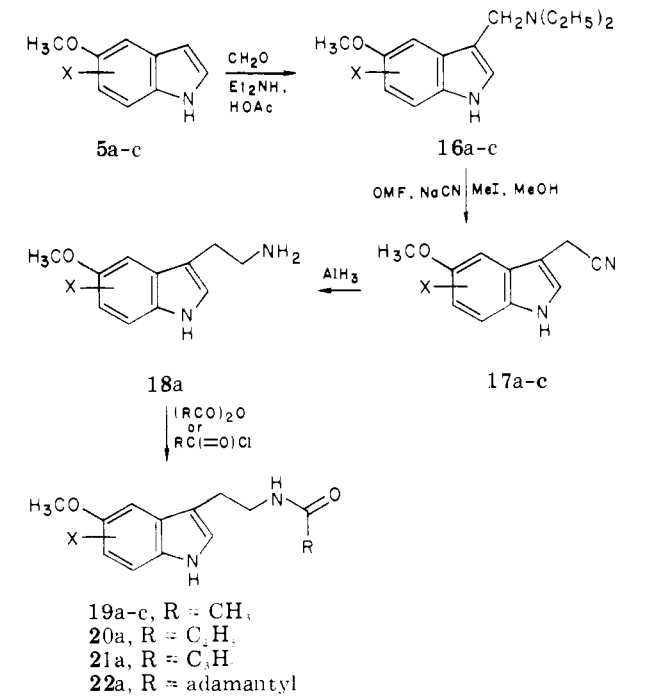
The halogenated indoles were apparently too unreactive for condensation with nitroethene in the manner described above. The compounds were, therefore, converted to the corresponding tryptamines by the method of Henbest et al.[11] (Scheme IV); that is, the indoles were alkylated under Mannich reaction conditions and the resulting gramines **16a–c** were quaternized in the presence of cyanide ion. It was found that the yield from this cyanation process was considerably improved by the addition of some DMF to the solvent system. The overall yields for the conversion of the indoles **5a–c** to their respective indole-3-acetonitriles **17a–c** ranged from 45 to 50%. The syntheses were completed by reducing the nitriles with AlH_3 and acylating the resulting tryptamines **18a–c** with acetic anhydride–pyridine or with other acylating combinations.[12]

Scheme III



a, R_1, R_2, R_3 = H; **b**, R_1 = CH_3, R_2, R_3 = H; **c**, R_1, R_3 = H, R_2 = CH_3; **d**, R_1, R_2 = H, R_3 = CH_3

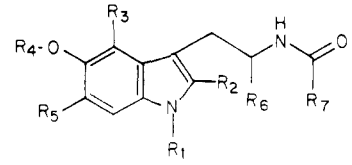
Scheme IV



The α-methylated analogue **26** was prepared by a method similar to that employed by Heinzelman et al.[13] (Scheme V). The aldehyde **23** was produced by formylation of **5a** using $POCl_3$–DMF. Condensation of **23** with nitroethane gave the nitronate **24** which was reduced with AlH_3 and then acylated with acetic anhydride–pyridine.

Analogues Starting from Serotonin. *N*-Acetylserotonin (**28**) was prepared by selective hydrolysis of *N*,*O*-diacetylserotonin (**27**) (Scheme VI). Alkylation of **28** with ethyl bromide and with cyclopentyl bromide af-

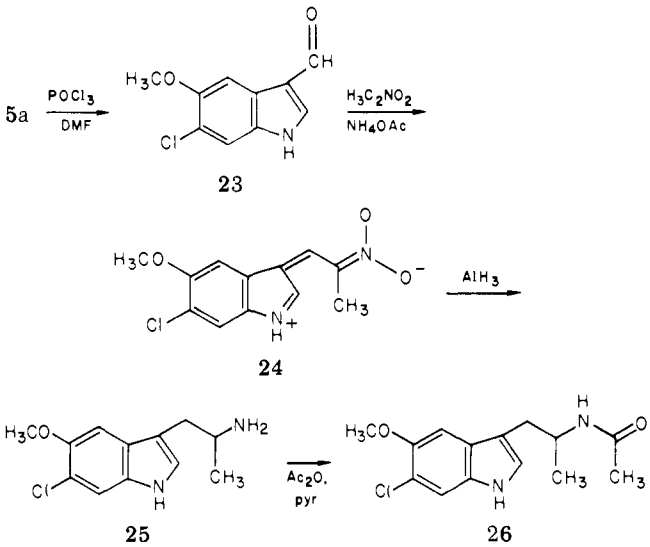
Table I. Ovulation-Blocking Activity of Melatonin and Derivatives



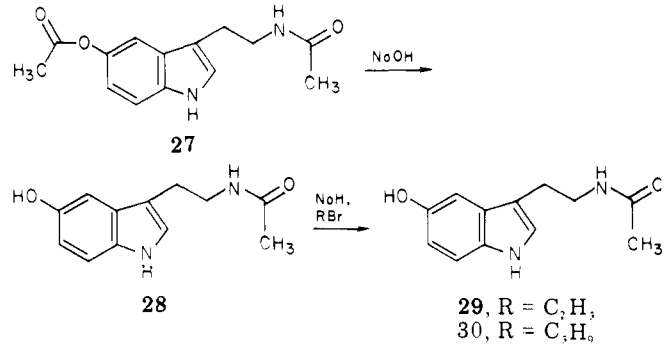
compd	R_1	R_2	R_3	R_4	R_5	R_6	R_7	dose, mg/rat[a]	rte of admin[b]	act.,[c] no. of rats ovulating/ no. of rats treated
15a	H	H	H	Me	H	H	Me	8	iv	1/10
								5	iv	4/5
								8	oral	1/3
15b	Me	H	H	Me	H	H	Me	8	oral	3/3
15c	H	Me	H	Me	H	H	Me	8	oral	1/6
								4	oral	2/3
15d	H	H	H	Me	Me	H	Me	8	oral	4/4
19a	H	H	H	Me	Cl	H	Me	4	iv	0/3
								1	iv	1/6
								5	oral	0/6
								4	oral	1/6
								1	oral	3/6
19b	H	H	H	Me	F	H	Me	2	oral	1/6
								1	oral	2/4
19c	H	H	Cl	Me	H	H	Me	8	oral	3/3
20a	H	H	H	Me	Cl	H	Et	4	oral	0/3
21a	H	H	H	Me	Cl	H	*n*-Pr	4	oral	1/6
22a	H	H	H	Me	Cl	H	Ad[d]	8	oral	3/3
26	H	H	H	Me	Cl	Me	Me	8	oral	1/3
27	H	H	H	Ac	H	H	Me	8	oral	3/3
								8	iv	3/3
28	H	H	H	H	H	H	Me	8	oral	3/3
								8	iv	3/3
29	H	H	H	Et	H	H	Me	8	oral	3/3
30	H	H	H	C_3H_9	H	H	Me	8	oral	3/3

[a] Weight of rats was 270–300 g. [b] Vehicle: iv in 50% Me_2SO; oral in PEG 400. [c] Control rats (vehicle only) invariably ovulated. [d] Ad = adamantyl.

Scheme V



Scheme VI



forded the respective melatonin analogues **29** and **30**.

Biological Results and Discussion. Rats selected for their uniform 4-day estrus cycles were dosed with compound at 12:00 noon on the day of proestrus. The doses were thus timed so that an optimal drug effect was realized from 2 to 4 p.m., i.e., the time during which a surge in LH normally occurs. Failure of the rats to ovulate by the following day was taken as evidence of a successful blockage of the LH surge. A detailed description of the assay is given in the Experimental Section. The results of these experiments are presented in Table I.

Simply measuring the ovulation-inhibiting activity of these compounds does not distinguish between inherent melatonin-like properties and an enhancement of the level of endogenous melatonin through an antimetabolic action. On the other hand, compound **19a** has been subjected to the "tadpole blanching" test, a very sensitive bioassay for melatonin-like activity,[14] and found to give a positive response.[15] Further, the general pattern of the SAR seems more consistent with a direct action of the compounds. Note, for example, the inactivity of all of the derivatives involving a deviation from the 5-methoxy group (compounds **27–30**). It is also evident that methylation at position 2 or the α-methylene (compounds **15c** and **26**) has no significant effect on activity, but methylation of the 1 and 6 positions (compounds **15b** and **15d**) appears to prevent (or greatly reduce) activity. The apparent inactivity of 6-methylmelatonin is rather surprising in view of the activity of the 6-halo compounds. Possibly the

inductive effect of the methyl group is inviting attack by electrophilic enzymes. The 1-methyl group might be exerting a similar effect. It is quite clear from the activities of compounds **20a** and **21a** that the nature of the amide moiety is not critical, although the acetamide function does appear to be optimal.

Obviously the most important substituent effect that was realized is the pronounced enhancement of activity that results from halogenation of the 6 position (compounds **19a** and **19b**). For reasons stated earlier, it was anticipated that these derivatives would be more slowly metabolized than melatonin. The serum half-life of **19a** was found to be 27 min through the first 2 h following iv administration[16]—considerably longer than the 12- to 15-min half-life reported for melatonin. The effect of chlorination of the 6 position, while significant, is, nevertheless, somewhat limited. Metabolism of **19a** still appears to be relatively rapid. It might be argued that the chloro group lacks effectiveness as a blocking group because hydroxylation accompanied by an "NIH shift" could still take place,[17] but florination of the 6 position gives virtually the identical result. In any case, it is evident that interfering with hydroxylation by substituting the 6 position with halogen can result in a reduced rate of metabolism.

If one accepts the persuasive evidence that the *major* metabolic fate of melatonin is 6-hydroxylation[3,18] and that 6-halogenation effectively blocks that path, it follows that the secondary route of metabolism cited by Kopin et al.[3] is also quite facile and is itself capable of disposing of melatonin in a relatively short time. In all probability, this alternate route involves attack of the indole moiety by pyrrolase. The importance of this enzyme in the metabolism of melatonin in the brain of the rat has recently been established.[19]

In terms of practical utility, the 6-halomelatonins, although still rather rapidly metabolized, are agents with a duration of effect which should greatly facilitate the investigation of the physiological properties of this intriguing class of compounds. Such investigations are in progress.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting-point apparatus. Neither melting points nor boiling points are corrected. Although only selected spectral data are provided herein, all new compounds exhibited IR, UV, and NMR spectra consistant with the reported structures. IR spectra were determined with a Beckman IR 4250 or a Perkin-Elmer 457A spectrometer. UV spectra were run on a Cary Model 15 spectrometer. NMR spectra were determined using a Varian Associates A-60A or HA-100 spectrometer with Me_4Si as an external standard. Unless otherwise indicated, all new compounds were subjected to elemental analysis, and the results were within ±0.4% of theoretical values.

6-Chloro-4-nitro-*m*-cresol (2a). A mixture of 142 g (1.1 mol) of 6-chloro-*m*-cresol in 300 mL of HOAc and 40 mL of concentrated H_2SO_4 was stirred at 8–12 °C (ice–salt bath) as a solution of 70 g of $NaNO_2$ in 200 mL of H_2O was added over a period of 100 min. The mixture was stirred for another 30 min following the addition and then poured into a large volume of cold H_2O. The crude nitroso compound was collected and partially dried. It was then added in portions to a stirred solution of 100 mL of 70% HNO_3 and 300 mL of H_2O maintained at a temperature of 40–50 °C. Heating and stirring were continued until the evolution of brown fumes ceased. The mixture was diluted with additional H_2O, and the product was collected. The yield of **2a** after recrystallization from EtOH–H_2O was 155 g (83%), mp 142–143 °C (lit. 143–144 °C).[8]

2-Chloro-5-methyl-4-nitroanisole (3a). A mixture of 150 g (0.8 mol) of **2a**, 120 g (0.87 mol) of K_2CO_3, and 84 mL (112 g, 0.89 mol) of Me_2SO_4 in 3 L of absolute EtOH was refluxed for 2 h. An additional 100 g of K_2CO_3 and 30 mL of Me_2SO_4 was added, and refluxing was continued for another 2 h. The cooled mixture was poured into a large volume of H_2O, and after chilling for a few hours the product was collected. The yield of **3a** was 134 g (83%), mp 117–118 °C. After recrystallization from EtOH–H_2O: mp 118–119 °C. Anal. ($C_8H_8ClNO_3$) C, H, N, Cl.

6-Chloro-5-methoxyindole (5a). (A) Without Isolation of the Intermediate Styrylamine 4a. A solution of 15.1 g (0.075 mol) of **3a**, 10.7 g (0.09 mol) of dimethylformamide dimethyl acetal, and 1.0 g of DABCO in 100 mL of DMF was heated overnight at 120 °C in a distillation apparatus under a gentle nitrogen sweep. The resulting deep-red solution was hydrogenated over 0.4 g of Raney nickel at 15 psi. The catalyst was filtered off, and the filtrate was added to 500 mL of H_2O containing 10 mL of HOAc. The product was extracted into CH_2Cl_2. The extracts were washed with NaCl solution and dried (Na_2SO_4). The solvent was removed, and the crude product was sublimed (4-mm pressure and 130 °C). The colorless sublimate was recrystallized from MeOH–H_2O to give 6.1 g (45%) of **5a**: mp 126–128 °C; NMR ($CDCl_3$) δ 3.90 (s, 3 H, OCH_3), 6.45 (m, 1 H, 3-H), 7.13 (br s, 2 H, 2- and 4-H), 7.35 (s, 1 H, 7-H), 8.1 (br s, 1 H, N-H). Anal. (C_9H_8ClNO) C, H, N, Cl.

(B) Isolating Intermediate Styrylamine 4a. The condensation of **3a** with dimethylformamide dimethyl acetal was carried out as in procedure A. The DMF was removed from the deep-red solution in vacuo with gentle warming. The residue was washed with hot Skelly B, and the resulting solid was recrystallized from MeOH to give a 78% yield of **4a**: mp 140–141 °C; UV (EtOH) λ_{max} 326 nm (ϵ 13300), 462 (4500). Anal. ($C_{11}H_{13}ClN_2O_3$) C, H, N, Cl.

The styrylamine **4a** was hydrogenated in benzene over Raney nickel. After filtering, the solution was washed with 1% H_3PO_4 solution and then with NaCl solution and dried (Na_2SO_4). Removal of the solvent gave crude **5a**, which was sublimed and recrystallized as in procedure A. The yield based on **4a** was 46%.

5-Methyl-2-nitroanisole (7). A mixture of 306 g (2 mol) of 6-nitro-*m*-cresol, 300 g (2.17 mol) of K_2CO_3, 500 mL of DMF, 500 mL of H_2O, and 3 L of EtOH was warmed with mechanical stirring. After the exothermic reaction subsided, 150 mL (342 g, 2.4 mol) of MeI was added, and the mixture was refluxed overnight. The mixture was concentrated to half volume under reduced pressure and then added to 6 L of cold H_2O. The precipitated product was collected, washed with H_2O, and dried: yield 331 g (99%); mp 55–56.5 °C (lit. 55 °C).[20]

2-Methoxy-4-methylaniline (8). An ethanolic solution of 331 g (2.0 mol) of **7** was hydrogenated over 5% Pd/C. After filtration and removal of the solvent, the product was distilled. The colorless distillate weighed 259 g (95%), bp 88–94 °C (4 mm) [lit. bp 88–94 °C (3 mm)].[21]

2-Fluoro-5-methylanisole (9). The conversion of the aniline **8** to **9** was accomplished by a modified Schiemann reaction essentially identical to that described in *Organic Syntheses*.[7] The precautions and notations cited therein should be carefully observed. Thus, 69 g (0.5 mol) of **8** in a solution of 136 mL of concentrated HCl and 930 mL of H_2O at −5 °C was treated with a solution of 42 g (0.61 mol) of $NaNO_2$ in 110 mL of H_2O. After addition of 75 mL (0.6 mol) of 65% HPF_6, the salt was collected and washed with 400 mL of H_2O and a solution of 120 mL of MeOH and 460 mL of Et_2O as prescribed. The dried salt weighed 155 g (96%). The entire quantity of salt was thermolyzed by portionwise addition to 500 mL of mineral oil at 165 °C over a 45-min period. The reaction was mildly exothermic. Upon cooling, 400 mL of 10% Na_2CO_3 solution was added, and steam distillation was carried out as in the published procedure. Distillation of the crude product afforded 34 g (45%) of colorless **9**, bp 93–95 °C (30 mm). Anal. (C_8H_9FO) C, H.

6-Fluoro-*m*-cresol (1b). A flask containing 200 g of pyridine hydrochloride was preheated under nitrogen to 180 °C to drive off any moisture. After cooling to 150 °C, 34 g (0.24 mol) of **8** was added. The temperature was raised to 220 °C (bath temperature) for 3 h. After cooling, the mixture was taken up in a large volume of H_2O and extracted with CH_2Cl_2. Evaporation of the solvent gave a crude product containing 5% **8** (by NMR). A solution of the crude product in 1 M NaOH was washed with CH_2Cl_2, acidified with HCl, and extracted again with CH_2Cl_2. Evaporation of these extracts and distillation gave 26.6 g of **1b**, bp 86–93 °C (30 mm). Although this product gave an unsatis-

factory analysis, TLC showed only one spot and the NMR spectrum was unequivocal: NMR ($CDCl_3$) δ 2.28 (s, 3 H, CH_3), 5.13 (br s, 1 H, OH), 6.8 (m, 3 H, Ar H). Anal. (C_7H_7FO) H; C: calcd, 66.7; found, 65.1.

6-Fluoro-4-nitro-*m*-cresol (2b). Following the procedure described for the preparation of **2a**, 26.6 g (0.21 mol) of **1b** was nitrosated and then oxidized to **2b**. The yield of recrystallized product was 25.4 g (70%), mp 110–111.5 °C. Anal. ($C_7H_6FNO_3$) C, H, N, F.

2-Fluoro-5-methyl-4-nitroanisole (3b). Methylation of **2b** was carried out according to the procedure described for the preparation of **3a**. An 82% yield of **3b** was obtained after recrystallization from MeOH–H_2O, mp 95–95.5 °C. Anal. ($C_8H_8FNO_3$) C, H, N, F.

6-Fluoro-5-methoxyindole (5b). Conversion of **3b** to **5b** was carried out using procedure B described for the preparation of **5a**. The intermediate styrylamine **4b** was obtained in 64% yield, mp 116–117 °C. Anal. ($C_{11}H_{13}FN_2O_3$) C, H, N, F. The yield of **5b** based on **4b** was 54%, mp 73–74 °C. Anal. (C_9H_8FNO) C, H, N, F.

4-Chloro-5-methoxyindole (5c). Using the method of Raiford,[8] 4-nitro-*m*-cresol was chlorinated. To avoid a tedious fractional crystallization, the crude 2-chloro-4-nitro-*m*-cresol (11), which contained 20% of the 6-chloro isomer **2a**, was directly methylated according to the procedure for the preparation of **3a**. The resulting 2-chloro-5-methyl-4-nitroanisole was isolated in 90% yield as a mixture containing 20% **3a**. This mixture was then used to prepare **5c** following procedure A for the preparation of **5a**. In this case, the temperature of the condensation with dimethylformamide acetal was increased to 145 °C. The separation of **5c** from the **5a** produced was readily accomplished by crystallization from benzene–hexane using seeds of pure **5c**, isolated by silica gel chromatography. The yield of pure **5c**, based on the starting anisole, was 39%, mp 109–111 °C. Anal. (C_9H_8ClNO) C, H, N, Cl.

5-Methoxy-1-methylindole (12b). 5-Methoxyindole was methylated in 68% yield using the procedure for the N-methylation of indole described in *Organic Syntheses*,[22] mp 102–103 °C. Sundberg and Parton[23] have since reported the preparation of **12b** using NaH–Me_2SO and MeI (reported mp 103–104 °C).

2-Nitroethyl Acetate. A solution of 25 g of NaOAc in 120 mL (130 g, 1.27 mol) of Ac_2O was maintained at a temperature of 35 °C using a cold H_2O bath, as 100 g (1.1 mol) of 2-nitroethanol was added over a period of 30 min. (*Caution*: The temperature of this reaction must be carefully controlled. If allowed to exceed 60 °C, a violent decomposition may occur.) When the reaction temperature no longer tended to rise, the bath was removed and the solution was allowed to stir overnight. The solution was then poured into a large volume of cold H_2O and extracted with three portions of CH_2Cl_2. The extracts were washed with NaCl solution and dried over Na_2SO_4. Evaporation of the solvent followed by distillation at reduced pressure gave 119 g (81%) of pure 2-nitroethyl acetate: bp 51–55 °C (0.5 mm); NMR ($CDCl_3$) δ 2.12 (s, 3 H, CH_3), 4.69 (s, 4 H, CH_2's).

5-Methoxy-3-(2-nitroethyl)indole (13a). A mixture of 20 g (0.14 mol) of 5-methoxyindole, 20 g (0.15 mol) of 2-nitroethyl acetate, and 0.5 g of *tert*-butylcatechol in 100 mL of xylene was refluxed under nitrogen for 3 h. The xylene was evaporated from the dark mixture under reduced pressure, and the residue was chromatographed on a column of silica gel that was eluted with 2% EtOAc in C_6H_6. Crystallization of the product from benzene–hexane gave 20 g (67%) of **13a**: mp 74–75.5 °C; NMR ($CDCl_3$) δ 3.44 (t, J = 7 Hz, 2 H, β-CH_2), 3.87 (s, 3 H, OCH_3), 4.65 (t, J = 7 Hz, 2 H, α-CH_2), 7.1 (m, 4 H, Ar H), 8.1 (br s, 1 H, NH). Anal. ($C_{11}H_{12}N_2O_3$) C, H, N.

5-Methoxy-1-methyl-3-(2-nitroethyl)indole (13b). Nitroethylation of **12b** according to the above procedure gave a 66% yield of **13b**, mp 85–87 °C (from MeOH–H_2O). Anal. ($C_{12}H_{14}N_2O_3$) C, H, N.

5-Methoxy-2-methyl-3-(2-nitroethyl)indole (13c). Nitroethylation of 5-methoxy-2-methylindole according to the above procedure gave a 51% yield of **13c**, mp 94–95 °C (from benzene–hexane). Anal. ($C_{12}H_{14}N_2O_3$) H, N; C: calcd, 61.5; found, 61.0.

5-Methoxy-6-methyl-3-(2-nitroethyl)indole (13d). Nitroethylation of 5-methoxy-6-methylindole according to the above procedure gave a 58% yield of **13d**, mp 82–84 °C (from benzene–hexane). Anal. ($C_{12}H_{14}N_2O_3$) C, H, N.

5-Methoxytryptamine (14a). Hydrogenation of **13a** was carried out using the same conditions employed by Noland and Hovden,[24] i.e., using PtO_2 and EtOH as the solvent. The product, **14a**, was isolated as the free base in 84% yield, mp 119–122 °C (from C_6H_6) (lit.[25] 121–122 °C).

5-Methoxy-1-methyltryptamine (14b). Hydrogenation of **13b** as above gave **14b** in 83% yield. The product was isolated as the free base which was an oil: UV (EtOH) λ_{max} 228 nm (ϵ 24 000), 282 (6400), 305 (5000); NMR ($CDCl_3$) δ 1.48 (br s, 2 H, NH_2), 2.93 (d, J = 5 Hz, 2 H, CH_2), 2.99 (d, J = 5 Hz, 2 H, CH_2), 3.68 (s, 3 H, 1-CH_3), 3.83 (s, 3 H, OCH_3), 7.0 (m, 4 H, Ar H). Anal. ($C_{12}H_{16}N_2O$) C, H, N.

5-Methoxy-2-methyltryptamine (14c). Hydrogenation of **13c** as above gave a 65% yield of **14c**, mp 104–106 °C (from benzene–hexane). Anal. ($C_{12}H_{16}N_2O$) C, H, N.

Melatonin (15a). A solution of 1.0 g (52 mmol) of **14a** in 8 mL of C_6H_6 and 2 mL of pyridine was cooled with ice, as 1 mL of Ac_2O was added. The ice bath was removed and the solution stirred for 3 h. The volatile materials then were removed under vacuum. The residue was taken up in $CHCl_3$ and washed with 5% $NaHCO_4$ solution followed by saturated NaCl solution. After drying over Na_2SO_4, the solvent was evaporated and the product was recrystallized from C_6H_6. The yield of **15a** was 1.11 g (91%): mp 118–119 °C (lit.[11b] 116–118 °C); IR and UV identical with those reported by Szmuszkovicz et al.[11b]

1-Methylmelatonin (15b). Acetylation of **14b** as in the above procedure produced 0.96 g (80%) of **15b** after recrystallization from benzene–hexane: mp 101–102 °C; IR (KBr) ν 3300 cm^{-1} (NH), 1640 (amide I), 1560 (amide II); UV (MeOH) λ_{max} 226 nm (ϵ 26 400), 282 (6400), 304 (5000), 315 sh (4000); NMR ($CDCl_3$) δ 1.90 (s, 3 H, Ac), 2.90 (t, J = 6.5 Hz, 2 H, β-CH_2), 3.55 (qt, J = 6.5 Hz, 2 H, α-CH_2), 3.70 (s, 3 H, 1-CH_3), 3.85 (s, 3 H, OCH_3), 5.9 (br s, 1 H, NH), 6.85 (s, 1 H, 2-H), 6.92 (qt, J = 2 and 9 Hz, 1 H, 6-H), 7.06 (d, J = 2 Hz, 1 H, 4-H), 7.21 (d, J = 9 Hz, 1 H, 7-H). Anal. ($C_{14}H_{18}N_2O_2$) C, H, N.

2-Methylmelatonin (15c). Acetylation of **14c** as in the above procedure afforded 0.46 g (38% yield) of **15c**, isolated as a viscous oil which refused to crystallize, even after chromatography over 30 g of silica gel (eluted with EtOAc): NMR ($CDCl_3$) δ 1.87 (s, 3 H, 2-CH_3), 2.32 (s, 3 H, Ac), 2.87 (t, J = 6.5 Hz, 2 H, β-CH_2), 3.48 (qt, J = 6.5, 2 H, α-CH_2), 3.84 (s, 3 H, OCH_3), 5.7 (br s, 1 H, NH), 6.78 (qt, J = 2 and 8.5 Hz, 1 H, 6-H), 7.00 (d, J = 2 Hz, 1 H, 4-H), 7.17 (d, J = 8.5 Hz, 1 H, 7-H), 8.3 (br s, 1 H, NH). Anal. ($C_{14}H_{18}N_2O_2$) C, H, N.

6-Methylmelatonin (15d). Acetylation of **14d** as in the previous procedure afforded 0.94 g (79% yield) of **15d** after recrystallization from benzene–hexane, mp 108–109 °C. Anal. ($C_{14}H_{18}N_2O_2$) C, H, N.

6-Chloro-5-methoxy-3-indoleacetonitrile (17a). A solution of 14 mL of 60% HOAc and 4.8 g (66 mmol) of Et_2NH was prepared and cooled to about 5 °C. To this solution was added 5.1 mL of formalin (37%). After stirring for 10 min at 5 °C, this solution was poured into a chilled solution (15 °C) of 10 g (55 mmol) of **5a** in 20 mL of EtOH. The resulting solution was allowed to warm to room temperature and then stirred for 1 h. The mixture was then poured into 200 mL of cold 1 N NaOH and extracted with three portions of Et_2O. The extracts were washed with NaCl solution. After drying over Na_2SO_4, the Et_2O was evaporated, leaving the intermediate amino compound **16a** as a viscous oil.

The crude **16a** was taken up in a solution of 200 mL of MeOH, 10 mL of DMF, 10 mL of H_2O, and 13.3 g (270 mmol) of NaCN. A dropwise addition of 21 mL (48 g, 340 mmol) of MeI was then made over a period of 1 h. After stirring for a second hour, the mixture was poured into a large volume of cold H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was recrystallized from benzene–hexane. The yield of **17a** was 6.1 g (50% based on **5a**): mp 136–137 °C; NMR ($CDCl_3$) δ 3.80 (s, 2 H, CH_2), 3.94 (s, 3 H, OCH_3), 7.01 (s, 1 H, 4-H), 7.14 (d, J = 2 Hz, 1 H, 2-H), 7.33 (s, 1 H, 7-H), 8.2 (br s, 1 H, NH). Anal. ($C_{11}H_9ClN_2O$) C, H, N, Cl.

6-Fluoro-5-methoxy-3-indoleacetonitrile (17b). Using the procedure described above, **5b** was converted to **17b** in 45% yield, mp 97–98 °C (from benzene–hexane). Anal. ($C_{11}H_9FN_2O$) C, H, N, F.

6-Chloro-5-methoxytryptamine (18a). A solution of AlH_3 in THF was prepared by dropwise addition of a solution of 5.2 mL (9.8 g, 100 mmol) of 100% H_2SO_4 in 40 mL of THF to a mixture of 7.6 g (200 mmol) of $LiAlH_4$ and 200 mL of THF. Without removing the precipitated Li_2SO_4, a solution of 6.0 g (27 mmol) of **17a** in 40 mL of THF was added over a 30-min period. After stirring for another hour, the excess hydride was destroyed by the addition of small chips of ice. Most of the supernatant THF solution was decanted. (Setting aside most of the THF at this point greatly reduces emulsion formation in the subsequent extractions.) The precipitated aluminum salts were treated with cold 20% NaOH, and the resulting cloudy solution was extracted with $CHCl_3$. These extracts were combined with the THF solution, washed with NaCl solution, and dried over Na_2SO_4. The solvents were removed, and the residue was triturated with Et_2O–pentane. The crystalline product was washed with hot Et_2O–Skelly B and dried, giving 5.0 g (83%) of pure **18a**, mp 124–126 °C. Anal. ($C_{11}H_{13}ClN_2O$) C, H, N, Cl.

6-Fluoro-5-methoxytryptamine (18b). Reduction of **17b** according to the procedure described above gave **18b** in 88% yield, mp 120–121 °C (from benzene–hexane). Anal. ($C_{11}H_{13}FN_2O$) C, H, N, F.

6-Chloromelatonin (19a). The tryptamine **18a** was acetylated with Ac_2O in benzene–pyridine as described in the above procedures. The residue from evaporation of the reaction mixture was taken up in a 1:1 mixture of $CHCl_3$ and EtOAc. This solution was then washed with $NaHCO_3$ and NaCl solutions. The crude product left, after evaporation of the solvents, was purified by boiling in C_6H_6. The yield of pure **19a** was 87%, mp 149.5–150 °C. Anal. ($C_{13}H_{15}ClN_2O_2$) C, H, N, Cl.

6-Fluoromelatonin (19b). Acetylation of **18b** according to the above procedure resulted in a 90% yield of **19b**, mp 158–159 °C (lit.[32] 152–154 °C). Anal. ($C_{13}H_{15}FN_2O_2$) C, H, N, F.

4-Chloromelatonin (19c). Using the procedures described above for the preparation of **19a** and **19b**, **5c** was converted to **19c**. The intermediate nitrile **17c** and tryptamine **18c** were used without complete purification (mp of **17c**, 128–135 °C; mp of **18c**, 92–96 °C). The overall yield of **19c** based on **5c** was 30%, mp 159.5–160 °C. Anal. ($C_{13}H_{15}ClN_2O_2$) C, H, N, Cl.

***N*-[2-(6-Chloro-5-methoxy-3-indolyl)ethyl]propionamide (20a).** In a similar manner to the tryptamine acetylations described above, **18a** was acylated with propionic anhydride. The yield of **20a** was 90%, mp 100–101 °C (from benzene–hexane). Anal. ($C_{14}H_{17}ClN_2O_2$) C, H, N, Cl.

***N*-[2-(6-Chloro-5-methoxy-3-indolyl)ethyl]butyramide (21a).** In a similar manner to the above acylations, **18a** was acylated with butyryl chloride. The product could not be crystallized until it was chromatographed on a short silica gel column. The yield of **21a** was 62%, mp 98–98.5 °C (from benzene–hexane). Anal. ($C_{15}H_{19}ClN_2O_2$) C, H, N, Cl.

***N*-[2-(6-Chloro-5-methoxy-3-indol)ethyl]-1-adamantanecarboxyamide (22a).** A solution of 0.25 g (1.1 mmol) of **18a** in 5 mL of $CHCl_3$ was stirred with a slurry of 0.125 g of Na_2CO_3 in 0.6 mL of H_2O while a solution of 0.25 g (1.3 mmol) of 1-adamantanecarboxylic acid chloride in 1 mL of $CHCl_3$ was slowly added. After stirring for 1 h, the mixture was washed successively with cold H_2O, cold 1 M HCl, and NaCl solution. The $CHCl_3$ solution was dried over Na_2SO_4, and the solvent was evaporated. The crude product was recrystallized from benzene–hexane. The yield of **22a** was 0.32 g (75%), mp 200–202 °C. Anal. ($C_{22}H_{27}ClN_2O_2$) C, H, N, Cl.

6-Chloro-5-methoxy-3-indolecarboxaldehyde (23). Maintaining a temperature of 10–20 °C, 19 mL of DMF was treated dropwise with 5.5 mL (9.2 g, 60 mmol) of $POCl_3$. After 15 min, a solution of 10 g (55 mmol) of **5a** in 5 mL of DMF was added slowly, keeping the temperature at 20–30 °C. Following the addition, the temperature was maintained at 35 °C for 1 h. The solution was then poured onto crushed ice, and the resulting mixture was treated with three quarters of a solution of 10.5 g of NaOH in 50 mL of H_2O—added gradually so that an acidic pH was maintained. The remainder of the NaOH solution was added at once, and the mixture was boiled for 1 min. After cooling, the product was collected, washed with H_2O, and recrystallized from EtOH–H_2O. A yield of 7.28 g (63%) of **23** resulted: mp 253–255 °C; IR (mull) ν 3200 cm^{-1} (NH), 1640 (C=O); NMR (Me_2SO-d_6) δ 3.91 (s, 3 H, OCH_3), 7.53 (s, 1 H, 7-H), 7.73 (s, 1 H, 4-H), 8.09 (s, 1 H, 2-H), 9.81 (s, 1 H, CHO), 12.0 (NH, very broad). Anal. ($C_{10}H_8ClNO_2$) C, H, N.

6-Chloro-5-methoxy-α-methyl-β-indolenideniumethyl-nitronate (24). A mixture of 2.5 g (12 mmol) of **23**, 10 mL of nitroethane, and 0.5 g of NH_4OAc was refluxed until all the starting material had dissolved. After an additional 30 mL of reflux, the mixture was allowed to cool, and the product was collected. Chilling the filtrate produced a small second crop. The product was washed with hot H_2O and then recrystallized from MeOH. The yield of **24** was 1.48 g (47%): mp 179–180 °C; UV (MeOH) λ_{max} 222 nm (ϵ 27 600), 291 (9900), 395 (16 100); NMR (Me_2SO-d_6) δ 2.48 (s, 3 H, α-CH_3), 3.95 (s, 3 H, OCH_3), 7.57 (s, 2 H, 4- and 7-H), 7.97 (s, 1 H, 2-H), 8.52 (s, 1 H, 3-H) (NH exchanged). Anal. ($C_{12}H_{11}ClN_2O_3$) C, H, N.

6-Chloro-5-methoxy-α-methyltryptamine (25). The reduction of **24** with AlH_3 in THF was carried out in the same manner as the other AlH_3 reductions described above. The product **25** was a very viscous oil obtained in 97% yield: UV (EtOH) λ_{max} 225 nm (ϵ 22 900), 298 (6500), 301 (6400), 313 sh (4000). Anal. ($C_{12}H_{15}ClN_2O$) C, H, N.

6-Chloro-5-methoxy-α-methylmelatonin (26). Acetylation of **25** in the manner described in the above procedures resulted in a 75% yield of **26**, mp 163.5–165.5 °C. Anal. ($C_{14}H_{17}ClN_2O_2$) C, H, N, Cl.

***N*,*O*-Diacetylserotonin (27).** A mixture of 10 g (25 mmol) of serotonin creatinine sulfate, 10 g of Na_2CO_3, 1 mL of H_2O, and 100 mL of $CHCl_3$ was stirred vigorously as 20 mL of Ac_2O was added. Stirring was continued for 2.5 h. This mixture was then stirred slowly for 1 h with 500 mL of 10% Na_2CO_3 solution. The $CHCl_3$ layer was separated and dried over Na_2SO_4. Removal of the $CHCl_3$ left a quantitative yield of **27** as a viscous oil. The product was spectrally identical with that reported by Ayer and Browne.[26]

***N*-Acetylserotonin (28).** A mixture of 13 g (50 mmol) of **27** and 100 mL of 1 M NaOH was diluted with sufficient MeOH to produce a clear solution. After allowing to stand overnight, the solution was poured into a large volume of saturated NaCl solution and extracted several times with EtOAc. The extracts were dried over Na_2SO_4, and the solvent was removed under vacuum. The residue was chromatographed on 300 g of silica gel (Woelm, activity I), which was eluted with EtOAc. Evaporation of the eluant left 8.1 g (74%) of **28** as a hygroscopic, viscous oil. Repeated efforts to secure a satisfactory elemental analysis were unsuccessful; however, the product appeared quite clean by spectral examination: IR (KBr) ν 3450 cm^{-1} (NH, OH), 1640 (amide I), 1560 (amide II); UV (EtOH) λ_{max} 223 nm (ϵ 21 900), 278 (6100), 298 sh (4600), 312 sh (3500); NMR (Me_2SO-d_6) δ 1.89 (s, 3 H, Ac), 2.81 (t, J = 6.5 Hz, 2 H, β-CH_2), 3.41 (qt, J = 6.5 Hz, 2 H, α-CH_2), 6.65 (qt, J = 2 and 8 Hz, 1 H, 6-H), 6.92 (d, J = 2 Hz, 1 H, 2-H), 6.96 (d, J = 2 Hz, 1 H, 4-H), 7.15 (d, J = 8 Hz, 1 H, 7-H), 7.5 (br s, 1 H, NH), 7.8 (s, 0.5 H, OH), 8.4 (br s, 0.5 H, OH), 10.1 (br s, 1 H, NH). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 64.46; H, 6.57; N, 12.29.

***N*-Acetyl-*O*-ethylserotonin (29).** A solution of 750 mg (3.4 mmol) of **28** in 40 mL of DMF was stirred at 5 °C as 82 mg (3.4 mmol) of NaH was added. After allowing to stir for 20 min, 0.77 mL (1.1 g, 10 mmol) of EtBr was added. Stirring was continued overnight. The mixture was then poured into a large volume of H_2O and extracted with CH_2Cl_2. The extracts were washed with NaCl solution and dried over Na_2SO_4. Evaporation of the solvent left a viscous oil, which was chromatographed on 30 g of silica gel that was eluted with C_6H_6–EtOAc. The yield of **29**, a viscous oil, was 354 mg (42%): NMR ($CDCl_3$) δ 1.42 (t, J = 7 Hz, 3 H, OEt), 1.91 (s, 3 H, Ac), 2.91 (t, J = 6.5 Hz, 2 H, β-CH_2), 3.57 (qt, J = 6.5 Hz, 2 H, α-CH_2), 4.07 (qt, J = 7 Hz, 2 H OEt), 5.6 (br s, 1 H, NH), 6.85 (qt, J = 2 and 9 Hz, 1 H, 6-H), 6.98 (d, J = 2 Hz, 1 H, 2-H), 7.04 (d, J = 2 Hz, 1 H, 4-H), 7.24 (d, J = 9 Hz, 1 H, 7-H), 8.2 (br, s, 1 H, NH). Anal. ($C_{14}H_{18}N_2O_2$) C, H, N.

***N*-Acetyl-*O*-cyclopentylserotonin (30).** Alkylation of **28** with cyclopentyl bromide was carried out according to the procedure described above. The product, following silica gel chromatography, was crystalline. Recrystallization from benz-

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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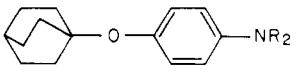
While the previously used displacement reaction of sodium 1-adamantyl oxide on 4-fluoronitrobenzene was applicable to the preparation of 4-(1-adamantyloxy)aniline and several related compounds, certain derivatives were not easily accessible by this route. Thus the recently reported ortho alkylation of 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



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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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