4-Substituted-1,2,3,4-tetrahydro-3,3-dimethylisoquinolines. II. (1)

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A practical synthesis (Scheme I) is described for the preparation of a series of 4-substituted-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolines (**3**). Treatment of α-(1-amino-1-methylethyl)arylmethanols or α-(1-amino-1-methylethyl)heteroarylmethanols (**5**) with aromatic aldehydes gave imines **7** from which amino alcohols **8** were derived by reduction with potassium borohydride. Acid catalyzed cyclization of **8** yielded **3**. An acyl substituent was installed by Friedel-Crafts acylation as a final step. The biological activities of **3a** (1) are briefly described.

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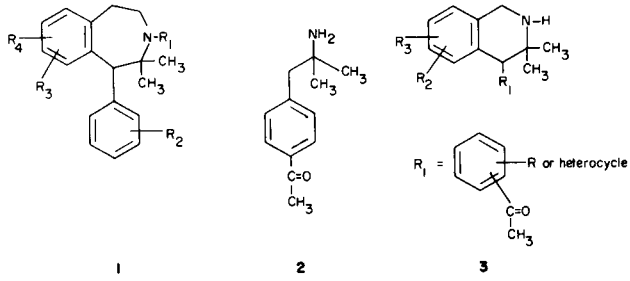
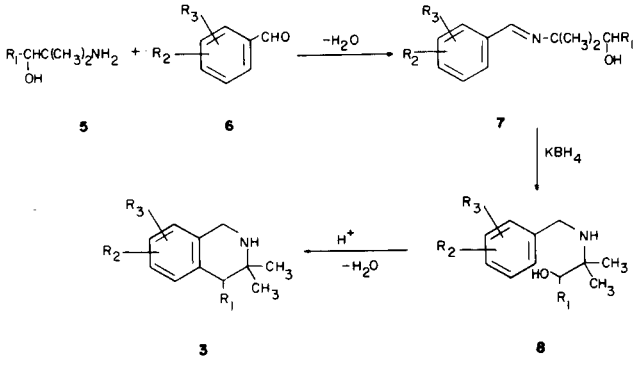
In the previous paper (2) we had described the synthesis of 2,3,4,5-tetrahydro-1*H*-1,3-benzazepines **1** which exhibited anti-arrhythmic activities. 4-Acetylphentermine **2** (3) was shown to lower 5-hydroxytryptophan (serotonin) in the mouse brain. It was hoped that a new class of compounds of formula **3**, having a fused six-membered ring in place of a seven-membered ring (2), but combining elements of both **1** and **2**, might show enhanced biological activity.



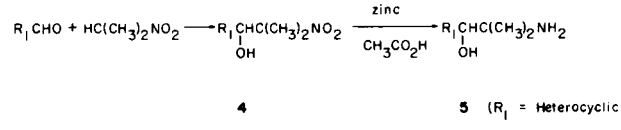
In this paper we describe the synthetic methods for the target compounds **3** using readily obtainable starting materials and intermediates. The sequence of reactions is presented in Scheme I.

Scheme I



Condensation of **5** with arylaldehydes **6** under azeotropic conditions gave the imino derivatives **7**. The latter were reduced with potassium borohydride yielding the secondary alcohol amines **8** (Table II). Finally, treatment of **8** with acidic cyclizing agents gave the target compounds **3** (Table III).

The intermediate amino alcohols **5a-c** (where R_1 = aryl) were reported previously (1,2). Their heteroaromatic analogs **5d-h** were prepared from the corresponding heteroaromatic aldehydes and 2-nitropropane according to methods used formerly (1,2,4) giving the nitro alcohols **4**. The latter on reduction with zinc in acetic acid gave α-(1-amino-1-methylethyl)substituted-methanols **5** (Table I).



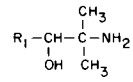
As with their aromatic analogs (1,2), the heterocyclic amino alcohols **5** and nitro alcohol precursors **4** exhibit nonequivalency of the *geminal* methyl groups in their proton magnetic resonance (pmr) spectra with a separation of signals of up to 0.30 ppm. Similarly, 1,2,3,4-tetrahydro-3,3-dimethylisoquinolines **3** display a signal separation of the *geminal* methyl groups of up to 0.45 ppm.

In the preceeding papers (1,2) it was shown that concentrated sulfuric acid is a very effective cyclizing agent in the temperature range of 25 to 85°. However, in the presence of groups prone to hydrolytic cleavage (*eg*, OCH_3), polyphosphoric acid (PPA, Method A) or boron trifluoride etherate (Method B) have been found preferable.

The heteroaromatic secondary amines **8** (where R_1 is pyridinyl or furanyl) did not cyclize to give tetrahydroisoquinoline derivatives **3** under conditions which were successful where R_1 was aryl. The 2-furanyl derivatives **8f** gave tar-like decomposition products, while the 3-, 4-, or

Table I

α-(1-Amino-1-methylethyl)heteroarylmethanols **5**

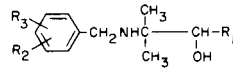


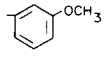
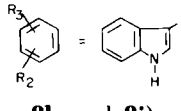
5	R_1	Mp °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
5d		230-231 (b)	47	$C_8H_{13}NO_2$ (a)	47.05	6.91	6.86	47.09	6.84	6.87
5e		71-72 (c)	53	$C_8H_{13}NOS$	56.11	7.65	8.18	55.88	7.68	8.07
5f		112-113	69	$C_9H_{14}NO_2$	65.03	8.49	16.85	64.97	8.57	16.74
5g		130-131	71	$C_9H_{14}NO_2$	65.03	8.49	16.85	64.84	8.52	16.79
5h		120-121	57	$C_9H_{14}NO_2 \cdot HOAc$	58.39	8.02	12.39	58.24	7.92	12.41

(a) Characterized as a hemisulfate. (b) Melts with decomposition. (c) Melting point of hydrochloride, 214-215° dec.

Table II

α-[1-[(Arylmethyl)amino]-1-methylethyl]substituted-methanols **8**



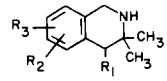
8	R_1	R_2	R_3	Mp °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
8a	C_6H_5	3-OCH_3	H	91-92	95	$C_{18}H_{23}NO_2$	75.75	8.12	4.91	75.99	8.28	4.86
8b		3-OCH_3	4-OCH_3	81.5-83	74	$C_{20}H_{27}NO_4$	69.54	7.88	4.05	69.66	7.82	4.00
8c	C_6H_5	H	4-OCH_3	87-88	86	$C_{18}H_{23}NO_2$	75.75	8.12	4.91	75.83	8.10	5.10
8d		3-NH_2	H	129-130	49	$C_{21}H_{24}N_2O$	78.72	7.55	8.74	78.71	7.45	8.87
8e		R_2,R_3 = 3, 4-		216-217 dec	74	$C_{19}H_{21}NOS \cdot HCl$	65.59	6.37	4.02	65.75	6.63	3.85
8f		H	H	102-103	49	$C_{15}H_{19}NO_2$	73.44	7.81	5.71	73.2	7.90	5.69
8g		H	H	94-95	71	$C_{16}H_{20}N_2O$	74.75	8.07	10.93	74.96	7.85	10.90
8h		R_2,R_3 = 3, 4-OCH_2O-		136-137	63	$C_{17}H_{20}N_2O_3$	67.98	6.71	9.33	68.02	6.81	9.18
8i		H	H	202-203	78	$C_{17}H_{20}N_2O_3 \cdot 2HCl$	58.37	6.74	8.51	58.24	6.78	8.80
8j	C_6H_5			170-171 dec	76	$C_{19}H_{22}N_2O$	77.52	7.53	9.52	77.80	7.70	9.44

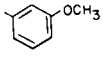
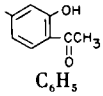
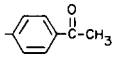
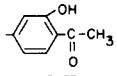
2-pyridinyl analogs (**8g**, **8h** and **8i**) gave either starting materials (boron trifluoride etherate at 100°) or black, water-soluble polymers (concentrated sulfuric acid, or methanesulfonic acid at 25°, or PPA at 100°). Similarly, an attempt to cyclize **8j** where R_1 is 1*H*-indol-3-yl was also unsuccessful. Under moderate conditions (100-120°), **8j** was recovered unchanged, while more stringent conditions (130-150°) gave dark, water-soluble unidentifiable products. We were able to effect cyclization of the 2-thienyl analog **8e** to give 1,2,3,4-tetrahydro-2,2-dimethyl-1-(2-thienyl)benz[*f*]isoquinoline (**3l**) in 60% yield.

Friedel-Crafts acetylation of compounds **3** usually occurred at the least hindered site. Thus, when both aromatic rings were unsubstituted, acetylation took place on the 4-position of the isolated ring, the fused aromatic ring remained unaffected. However, when the fused aromatic ring contained an electron-releasing group, such as amino or methoxy, the acyl group was introduced into a neighboring position of the fused ring, leaving the pendant ring unaffected. As a rule, the methoxy group was cleaved to the phenolic compound, giving a product with a strongly chelated system. In one instance we were able to

Table III

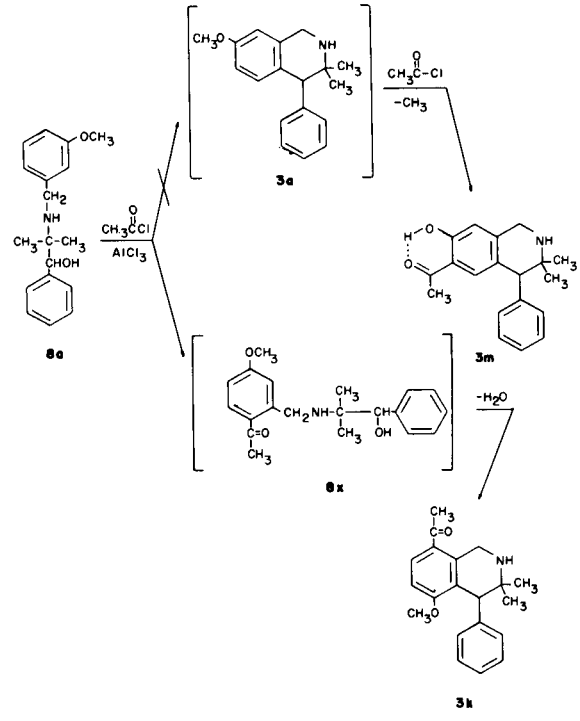
4-Substituted-1,2,3,4-tetrahydro-3,3-dimethylisoquinolines **3**



3	R_1	R_2	R_3	Mp °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3a	C_6H_5	H	7-OCH_3	264-265 dec	72	$C_{18}H_{21}NO{\cdot}HCl$	71.16	7.30	4.61	71.06	7.43	4.43
3b		6-OCH_3	7-OCH_3	261-262 dec	76	$C_{20}H_{25}NO_3{\cdot}HCl$	66.02	7.20	3.85	65.75	7.40	3.58
3c	C_6H_5	6-OCH_3	H	230-231 dec	30	$C_{18}H_{21}NO{\cdot}HCl$	71.16	7.30	4.61	71.30	7.46	4.44
3d	C_6H_5	H	8-NO_2	104.5-105.5	45	$C_{17}H_{18}N_2O_2$	72.32	6.43	9.92	72.11	6.57	9.87
3e		H	7-NH_2	149-150	24	$C_{21}H_{22}N_2$	83.40	7.33	9.27	83.12	7.49	9.13
3f		H	H	250-251 dec	45	$C_{19}H_{21}NO_2{\cdot}HCl$	68.77	6.68	4.22	68.68	6.89	4.14
3g	C_6H_5	6-OH	7-(CO)-CH_3	292-293 dec	44	$C_{19}H_{21}NO_2{\cdot}HCl$	68.77	6.68	4.22	68.82	6.94	4.14
3h		H	H	186-187 dec	17 (a)	$C_{19}H_{21}NO$ (c)	63.68	6.20	2.97	63.70	6.43	3.06
3i	C_6H_5	7-(CO)-CH_3	8-NH_2	135-136	51	$C_{19}H_{22}N_2O$	77.52	7.53	9.52	77.37	7.65	9.32
3j		6-Cl	H	286-287 dec	45	$C_{19}H_{20}ClNO_2{\cdot}HCl$	62.30	5.78	3.82	62.42	5.85	3.78
3k	C_6H_5	5-OCH_3	8-(CO)-CH_3	145-146	52	$C_{20}H_{23}NO_2$	77.64	7.49	4.53	77.46	7.46	4.45
3l		R_2,R_3 = 5, 6-		111-112	60	$C_{19}H_{19}NS$	77.77	6.53	4.77	77.68	6.58	4.56

(a) The low yield of isolated product is due to its great solubility in crystallization solvents. (b) Compound **3k** was obtained from the same precursor (**8a**) as **3a** by the direct acylation-cyclization of **8a** under Friedel-Crafts reactions conditions. (c) Isolated and analyzed as monocitrate.

effect both the cyclization and simultaneous acylation of secondary amine **8a** under normal Friedel-Crafts reaction conditions. The unexpected substitution pattern of the cyclized product **3k** may have resulted from acetylation of **8a** *para* to the methoxy function to give **8x** followed by normal cyclization with elimination of water. If cyclization to **3a** were to occur first, followed by acetylation, the expected product would be **3m**.



Compound **3k** was the only product resulting from the Friedel-Crafts reaction which had the methoxy function intact.

Compounds of formula **3** were found to exhibit antiarrhythmic activity both in the *ouabain*-induced arrhythmia test (**5**) and in the coronary ligated Harris dog (**6**) test in the range at about 3 to 15 mg/kg. The best activity was shown by 1,2,3,4-tetrahydro-7-methoxy-3,3-dimethyl-4-phenylisoquinoline (**3a**) and 1,2,3,4-tetrahydro-3,3-dimethyl-4-(2-napthalenyl)-7-isoquinolinamine (**3e**) which were active at 3 mg/kg in the *ouabain*-induced arrhythmia test and at 10 mg/kg in the coronary ligated Harris dog test.

EXPERIMENTAL

Physical constants, yields, and analytical values for the compounds below are reported in Tables I-III. Melting points were determined using a Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam spectrograph. Unless otherwise stated, the former were determined as solution in 95% ethanol and the latter as Nujol mulls. The pmr spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Thin layer chromatography was carried out on silica gel G (Stahl) using a mixture of toluene, acetone and heptane in varying proportions, as the eluent. The chromatograms were developed in an iodine chamber.

The proton magnetic resonance spectra (pmr) for aromatic or heteroaromatic protons were included only in those instances when their assignment was essential to the elucidation of the substitution pattern. Sometimes, the resonance peaks of lone protons were not assigned when the resolution was poor or if they were hidden under an envelope of other aliphatic protons.

α-(1-Amino-1-methylethyl)arylmethanols **5a**, **5b** and **5c** have been reported previously (1,2). The preparation of heteroaromatic analogues **5d**-**5h** (Table I) and their precursors, α-(1-methyl-1-nitroethyl)-substituted-methanols **4a**, **4b** and **4e** is described here. Since the conditions of reactions and work-up methods are somewhat different for each case, the preparation of compounds **4** and **5** is described in detail in the sequential order.

α-(1-Amino-1-methylethyl)-2-furanmethanol (**5d**).

To a stirred solution of 35.6 g (0.4 mole) of 2-nitropropane and 16.2 g (0.3 mole) of sodium methoxide in 120 ml of methanol was added 19.2 g (0.2 mole) of furan-2-carboxaldehyde (freshly distilled) dropwise at 10° and the resulting solution allowed to stir at room temperature overnight. Acetic acid was added to *p*H 6.0 at 0°, the sodium salts were removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. Water was added to the residue and the product was extracted twice with 150 ml of ethyl acetate. The combined extracts were washed with aqueous saturated sodium chloride solution, dried over sodium sulfate, and evaporated exhaustively *in vacuo* giving 24.1 g (68% yield) of analytically pure α-(1-methyl-1-nitroethyl)-2-furanmethanol (**4a**) as light yellow oil, bp 112-113° (3.0 mm); pmr (carbon tetrachloride): δ 1.42, 1.57 (6H, *gem* methyls), 3.61 (1H, C*H*OH, deuterium oxide-exchangeable), 5.17 (1H, CHOH) ppm.

Anal. Calcd. for $C_8H_{11}NO_4$: C, 51.88; H, 5.99; N, 7.56. Found: C, 52.13; H, 6.22; N, 7.62.

To a rapidly stirred solution of 23.8 g (0.13 mole) of α-(1-methyl-1-nitroethyl)-2-furanmethanol (**4a**) in 150 ml of glacial acetic acid was added 60 g of zinc dust portionwise at 15 to 25° and allowed to stir overnight at room temperature. The salts and excess zinc were filtered off and the filtrate was evaporated *in vacuo*. The residue was taken up with ice-water, made basic with potassium carbonate, and extracted three times with 150 ml of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and evaporated to dryness *in vacuo* giving 9.5 g (47% yield) of the oily product having only one spot on tlc. To a solution of the base in warm 2-propanol was added concentrated sulfuric acid in 2-propanol to *p*H 2.0. After standing overnight at room temperature, analytically pure α-(1-amino-1-methylethyl)-2-furanmethanol (**5d**) crystallized out as a hemisulfate, mp 230-231° dec; uv λ max (ethanol): nm (ε) 211 (9600); ir (chloroform): 3610, 1030 (OH), 3420, 3390, 1580 (NH_2) cm^{-1}.

Anal. Calcd. for $C_8H_{13}NO_2 \cdot 0.5\ H_2SO_4$: C, 47.05; H, 6.91; N, 6.91; S, 7.85. Found: C, 47.09; H, 6.84; N, 6.87; S, 7.86.

α-(1-Amino-1-methylethyl)-2-thiophenemethanol (**5e**).

To a stirred solution of 35.6 g (0.4 mole) of 2-nitropropane and 16.2 g (0.3 mole) of sodium methoxide in 150 ml of methanol was added 15.0 g (0.134 mole) of 2-thiophenecarboxaldehyde dropwise at 15-20° and the solution was stirred overnight at room temperature. Acetic acid was added to *p*H 6.5 and the solvent and excess 2-nitropropane were removed *in vacuo*. To the resude was added 120 ml of saturated sodium bisulfite solution and 150 ml of ethyl acetate. The two-phase mixture was stirred vigorously for 30 minutes and separated. The organic phase was washed with saturated sodium chloride, dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was crystallized from cyclohexane giving 67.0 g (33% yield) of pure α-(1-methyl-1-nitroethyl)-2-thiophenemethanol (**4b**) as white crystals, mp 59-60°; uv λmax (ethanol): nm (ε) 231 (8500), 276-285 plateau (1800); pmr (deuteriochloroform): δ 1.50, 1.69 (6H, *gem* methyls), 2.79 (1H, CHO*H*, deuterium oxide-exchangeable), 5.52 (1H, C*H*OH) ppm.

Anal. Calcd. for $C_8H_{11}NO_3S$: C, 47.75; H, 5.51; N, 6.96. Found: C, 47.75; H, 5.48; N, 7.02.

To a rapidly stirred suspension of 30.0 g (0.15 mole) of α-(methyl-1-nitroethyl)-2-thiophenemethanol (**4b**) in 300 ml of methanol and 50 ml of concentrated hydrochloric acid was added 90.0 g of zinc dust portionwise at 15° over 15 minutes and the mixture was allowed to stir overnight at room temperature. Hyrdrochloric acid (75 ml) was added and the mixture was stirred for 30 hours at 50°. The salts and excess zinc were removed by filtration and the filtrate was evaporated *in vacuo*. The residue was taken up with ice-water, made basic with potassium carbonate, and extracted three times with 200 ml of ethyl acetate. The combined extracts were washed with aqueous sodium chloride, dried over sodium sulfate, and concentrated *in vacuo* to about 75 ml. At this point dry hydrogen chloride was passed through the solution to *p*H 2.0 to give, on cooling, 21.0 g of the hydrochloride, mp 214-215° dec. The free base was regenerated by dissolving in cold water, treating with potassium carbonate, extracting with ethyl acetate, and evaporating to dryness *in vacuo*. Crystallization of the residue from cyclohexane gave 13.0 g (53% yield) of α-(1-amino-1-methylethyl)-2-thiophenemethanol (**5e**) as white crystals of analytical purity, mp 71-72°; uv λ max (ethanol): nm (ε) 234 (8400); ir (chloroform): 3640 (OH), 3420, 3390, 1575 (NH_2) cm^{-1}; pmr (deuteriochloroform): δ 1.01, 1.21 (6H,m *gem* methyls), 2.20 (3H, s, O*H*, NH_2, deuterium oxide-exchangeable), 4.60 (C*H*OH) ppm.

Anal. Calcd. for $C_8H_{13}NOS$: C, 56.11; H, 7.65; N, 8.16. Found: C, 55.88; H, 7.68; N, 8.07.

α-(1-Amino-1-methylethyl)-3-pyridinemethanol (**5f**).

α-(1-Methyl-1-nitroethyl)-3-pyridinemethanol (**4c**) was obtained in 86% yield following published procedure (4). This nitro alcohol derivative (9.8 g, 0.05 mole) in 100 ml of methanol was saturated with dry hydrogen chloride. To a stirred solution was added 30 g of zinc dust portionwise at 20° over a period of 15 minutes and the mixture was allowed to stir overnight at room temperature. The salts and excess zinc were removed by filtration and the filtrate was evaporated *in vacuo* at 28°. The residue was taken up with ice-water, made basic with potassium carbonate, and extracted three times with a mixture of 75 ml of ethyl acetate-1-butanol. The combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from acetonitrile gave 5.7 g (69% yield) of α-(1-amino-1-methylethyl)-3-pyridinemethanol (**5f**) as white crystals of analytical purity, mp 112-113°.

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.97; H, 8.57; N, 16.74.

α-(1-Amino-1-methylethyl)-4-pyridinemethanol (**5g**).

α-(1-Methyl-1-nitroethyl)-4-pyridinemethanol (**4d**) (4) in 75% yield as white crystals, mp 130-131°, by following the precedure used to prepare the 3-pyridyl analog, **5f**; pmr (deuteriochloroform): δ 0.92, 1.18 (6*H*, *gem* methyls), 2.50 (3H, CHO*H* and NH_2, deuterium oxide-exchangeable), 4.27 (1H, C*H*OH) ppm.

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.82; H, 8.52; N, 16.79.

α-(1-Amino-1-methylethyl)-2-pyridinemethanol, Monoacetate Salt (**5h**).

To a stirred solution of 4.4 g (0.11 mole) of sodium hydroxide and 1 mg

of hydroquinone in 30 ml of water was added 9.8 g (0.11 mole) of 2-nitropropane at 25° over 30 minutes. To this pink colored solution was added a solution of 10.7 g (0.1 mole) of 2-pyridinecarboxaldehyde in 15 ml of glacial acetic acid at 50° over 15 minutes. During that time the off-white precipitate began to separate. After 2 hours, 100 ml of water was added and the light orange crystals (13.6 g, 69% crude yield) were collected by filtration, mp 93-94°. Recrystallization from 2-propanol gave 10.8 g (55% yield) of α-(1-methyl-1-nitroethyl)-2-pyridinemethanol (**4e**) as off-white crystals of analytical purity, mp 94-95°; uv λ max (ethanol): nm (ε) 255 sh (3150), 260 (3400), 266 sh (2560): pmr (deuteriochloroform): δ 0.96, 1.14 (6H *gem* methyls), 4.70 (1H, broad, deuterium oxide-exchangeable, O*H*), 5.26 (1H, C*H*OH) ppm.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.35; H, 6.27; N, 14.08.

To a rapidly stirred solution of 9.8 g (0.05 mole) of α-(1-methyl-1-nitroethyl)-2-pyridinemethanol (**4e**) in 200 ml of glacial acetic acid was added 35 g of zinc dust portionwise over 30 minutes at 20° and allowed to stir overnight at room temeperature. Fifteen g of zinc was added and continued to stir for 6 hours. The salts and excess zinc were removed by filtration and the filtrate was evaporated *in vacuo*. The residue was taken up with ice-water, made basic with potassium carbonate and extracted three times with 125 ml of ethyl acetate-1-butanol. The combined organic extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate and evaporated *in vacuo*. The semisolid residue (7.1 g) was crystallized from acetonitrile containing 3 ml of acetic acid to give 6.4 g (57% yield of α-(1-amino-1-methylethyl)-2-pyridinemethanol monoacetate salt (**5h**) as nearly white crystals, mp 119-120°. An analytical sample, mp 120-121°, was obtained by recrystallization from ethyl acetate; uv λ max (ethanol): nm (ε) 256 sh (2900), 260 (3200), 267 sh (2380); pmr (DMSO-d_6): δ 0.98, 1.14 (6H, *gem* methyls), 1.80 (3H, CH_3-C=O), 4.55 (1H, C*H*OH), 6.80 (4H, s, $^+NH_3$, CHO*H*, all protons deuterium oxide-exchangeable) ppm.

Anal. Calcd. for $C_9H_{14}N_2O{\cdot}CH_3CO_2H$: C, 58.39; H, 8.02; N, 12.39. Found: C, 58.24; H, 7.96; N, 12.41.

α-[1-[(Arylmethyl)amino]-1-methylethyl]substituted-methanols **8**. (Table II).

The four examples for the preparation of compounds **8f**, **8g**, **8h** and **8j** illustrate general procedures of obtaining both aromatic (R_1 = aryl) and heteroaromatic (R_1 = heterocycle) analogs.

α-[1-Methyl-1-[(phenylmethyl)amino]ethyl]-2-furanmethanol (**8f**).

A solution of 5.7 g (0.03 mole) of crude α-(1-amino-1-methylethyl)-2-furanmethanol (**5d**) and 3.2 g (0.03 mole) of benzaldehyde in 75 ml of benzene was refluxed until the theoretical volume of water was collected, and the infrared spectrum showed absence of the carbonyl function (3 hours). After the solvent was evaporated, the residual imino derivative was taken up with 40 ml of methanol and treated with 1.5 g of potassium borohydride for 2 hours with stirring at room temperature. Glacial acetic acid was added at 15° to *p*H 6.5 and the solvent was evaporated *in vacuo*. The residue was taken up with cold water and extracted twice with 75 ml of dichloromethane. The combined extracts were dried over sodium sulfate and evaporated to dryness. Two recrystallizations of the residue gave 3.4 g (49% yield) of pure α-[1-methyl-1-[(phenylmethyl)amino]ethyl]-2-furanmethanol (**8f**) as white crystals, mp 102-103°; uv λmax (ethanol): nm ε) 210 sh (3400), 257 (150), pmr (carbon tetrachloride): δ 1.00, 1.18 (6H, *gem* methyls), 3.67 (2H, ArCH_2N), 4.35 (1H, s, C*H*OH), 6.20 [2H, 3-H, 4-H, (furyl)], 7.25 [6H, s, 5-*H* (furyl) and 5 aromatic protons] ppm.

α-[1-Methyl-1-[(phenylmethyl)amino]ethyl]-3-pyridinemethanol (**8g**).

A solution of 8.3 g (0.05 mole) of α-(1-amino-1-methylethyl)-3-pyridinemethanol (**5e**) and 5.8 g (0.55 mole) of benzaldehyde in 200 ml of benzene was refluxed for 3 hours, while 0.9 ml of water separated in a Dean-Stark trap. The solvent was removed. The residual imino derivative was taken up with 75 ml of methanol and treated with 2.5 g of potassium borohydride at room temperature with stirring. After 1 hour the solvent was evaporated *in vacuo* at 30°, the residue taken up with cold water, and extracted twice with 150 ml of ethyl acetate. The combined extracts were washed, dried over sodium sulfate, and evaporated *in vacuo*. The yellowish solid residue was recrystallized from acetonitrile giving 7.8 g of analytically pure **8g** as white crystals, mp 94-95°. Concentration of the filtrate to a low volume gave 1.6 g (total yield: 74%) of additional product **8g**, mp 93-94°; pmr (deuteriochloroform): δ 0.99, 1.30 (6H, *gem* methyls), 4.23 (2H, s, ArCH_2N), 4.58 (Py-C*H*OH) ppm.

α-[1-[(1,3-Benzodioxol-5-ylmethyl)amino]-1-methylethyl]-4-pyridinemethanol (**8h**).

A solution of 6.0 g (0.036 mole) of α-(1-amino-1-methylethyl)-4-pyridinemethanol (**5g**) and 5.8 g (0.036 mole) of 1,3-benzodioxole-5-carboxaldehyde in 150 ml of benzene was refluxed until the theoretical volume of water had separated in a Dean-Stark trap. After the solvent was removed, the residue was taken up with 75 ml of methanol and treated with 2.5 g of potassium borohydride at 23° for 2 hours. The solvent was removed *in vacuo* at 25°. The residue was taken up with cold water, extracted twice with 120 ml of ethyl acetate, the extracts dried over sodium sulfate and evaporated *in vacuo*. Crystallization of the residue from 2-propanol gave 6.8 g (63% yield) of α-[1-[(1,3-benzodioxol-5-ylmethyl)amino]-1-methylethyl]-4-pyridinemethanol (**8h**) as white crystals of analytical purity, mp 136-137°; uv λ max (ethanol): nm (ε) 209 (7300), 220 (7500); ir (chloroform): 3390 (OH, NH) cm^{-1}; pmr (deuteriochloroform): δ 0.91, 1.20 (6H, *gem* methyls), 3.00 (2H, broad, N*H*, O*H*, deuterium oxide-exchangeable), 3.69 (2H, ArCH_2N), 4.48 (1H, C*H*OH), 5.95 (2H, O-CH_2-O) ppm.

α-[1-[(1*H*-Indol-3-ylmethyl)amino]-1-methylethyl]benzenemethanol (**8j**).

A solution of 8.25 g (0.05 mole) of α-(1-amino-1-methylethyl)benzenemethanol (**5a**) (1) and 7.2 g (0.05 mole) of 1*H*-indole-3-carboxaldehyde in 150 ml of benzene was refluxed for 2 hours while 0.9 ml of water separated in a Dean Stark trap. The solvent was removed, the residue was taken up with 100 ml of methanol, and treated with 2.5 g of potassium borohydride at room temperature for 2 hours. The resulting white preciptiate (8.5 g, mp 168-169° dec), was recovered by filtration. The filtrate was evaporated to dryness *in vacuo* at 30°. The residue was taken up with water, and the white solid (13.8 g, mp 166-168° dec) was collected and washed with water. Recrystallization of the combined crops from methanol gave 11.7 g (76% yield) of analytically pure α -[1-[(-*H*-3-ylmethyl)amino]-1-methylethyl]benzenemethanol (**8j**) as white crystals, mp 170-171° dec; uv λ max (ethanol): nm (ε) 217 (43,500), 280 (6150), 288 sh (5000); ir (nujol): 3520, 3100 (OH, NH) cm^{-1}; pmr (DMSO-d_6): δ 1.01, 1.10 (6H, *gem* methyls), 1.60 (1H, broad, aliphatic N*H*), 3.98 (2H, CH_2), 4.61 (1H, C*H*OH), 5.36 (1H, broad, CHO*H*, deuterium oxide-exchangeable), 10.68 (1H, indole N*H*) ppm.

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(3-methoxyphenyl)-3,3-dimethylisoquinoline Hydrochloride (**3b**). Method A. (Table III).

A stirred solution of 29.0 g (0.084 mole) of α-[1-[[(3,4-dimethoxyphenyl)-methyl]amino]-1-methylethyl]-3-methoxybenzenemethanol (**8b**) in 250 ml of polyphosphoric acid was heated at 80° for 4 hours. The solution was poured onto ice, made basic with sodium hydroxide, and extracted twice with 500 ml of dichloromethane. The extracts were washed, dried over sodium sulfate and evaporated to dryness. To the residue, dissolved in 300 ml of 2-propanol, was introduced dry hydrogen chloride to *p*H 2.0. After standing for 20 hours at room temperature, 23.0 g (76% yield) of **3b** hydrochloride as white crystals of analytical purity was obtained, mp 261-262° dec; uv λ max (ethanol): nm (ε) 215 (22,000), 266 (12,000); pmr (DMSO-d_6): δ 1.15, 1.40 (6H, *gem* methyls), 3.50 (3H, 3-OCH_3), 3.75, 3.80 [6H, 3,4-(OCH_3)$_2$] ppm.

1,2,3,4-Tetrahydro-3,3-dimethyl-8-nitro-4-phenylisoquinoline (**3d**).

In a similar manner (Method A) 9.0 g (0.03 mole) of α-[[[(2-nitrophenyl)methyl]amino]-1-methylethyl]benzenemethanol (1) gave 3.8 g (48% yield) of pure **3d** as off-white crystals after crystallization from cyclohexane, mp 104.5-105.5°; uv λ max (ethanol): pmr (ε) 265 (5400); pmr (deuteriochloroform): δ 0.92, 1.30 (6H, *gem* methyls), 1.80 (1H, N*H*, deuterium oxide-exchangeable), 3.92 (1H, ArC*H*Ar), 4.55 (2H, ArCH_2N) ppm.

1,2,3,4-Tetrahydro-3,3-dimethyl-4-(2-naphthalenyl)-7-isoquinolinamine (**3e**).

Using Method A, 20.0 g (0.062 mole) of α-[1-[[(3-aminophenyl)methyl]-amino]-1-methylethyl]-2-napthalenemethanol (**8d**) gave 9.1 g of crude **3e** after crystallization from cyclohexane, mp 141-142°. Final recrystallization from ethyl acetate gave 4.5 g (24% yield) of **3e** as tan crystals of analytical purity, mp 149-150°; uv λ max (ethanol): nm (ε) 226 (15,000); pmr (deuteriochloroform): δ 0.92, 1.30 (6H, *gem* methyls), 3.30 (3H, broad, ArNH_2 and ArCH$_2$N*H*R, deuterium oxide-exchangeable), 3.90 (1H, ArC*H*Ar), 4.15 (2H, ArCH_2NHR) ppm.

1,2,3,4-Tetrahydro-7-methoxy-3,3-dimethyl-4-phenylisoquinoline, Hydrochloride (**3a**). Method B.

A stirred solution of 11.4 g (0.04 mole) of α-[1-[(3-methoxyphenylmethyl)amino-1-methylethyl]benzenemethanol (**8a**) in 75 ml of boron trifluoride etherate was refluxed for 4 hours. After cooling, the solution was poured onto ice, made basic with ammonium hydroxide, and extracted twice with 150 ml of ethyl acetate. The combined extracts were washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated to *ca.* 50 ml. At this point dry hydrogen chloride was passed into the warm solution to *p*H 2.0 and allowed to stand at 23° overnight. The resulting white precipitate of the hydrochloride (9.9 g, mp 262-263° dec) was collected by filtration and recrystallized from ethyl acetate-2-propanol (1:1) giving 8.5 g (70% yield) of analytically pure, white crystals of 1,2,3,4-tetrahydro-7-methoxy-3,3-dimethyl-4-phenylisoquinoline hydrochloride (**3a**), mp 264-265° dec; uv λ max (ethanol): nm (ε) 205 (16,750), 280 (2000), 287 (2000); pmr (DMSO-d$_6$): δ 1.21, 1.41 (6H, *gem* methyls), 3.59 (3H, ArOCH_3), 4.42 (2H, ArCH_2N), 4.47 (1H, ArC*H*Ar) ppm.

1,2,3,4-Tetrahydro-6-methoxy-3,3-dimethyl-4-phenylisoquinoline, Hydrochloride (**3c**).

Following the above procedure (Method B), 57.0 g (0.2 mole) of α-[1-[[(4-methoxyphenyl)methyl]amino]-1-methylethyl]benzenemethanol (**8c**) yielded 22.5 g of **3c** hydrochloride after recrystallization from ethyl acetate, mp 227-228° dec. Final recrystallization from acetonitrile gave 17.8 g (30% yield) of analytically pure, off-white crystals of **3c** hydrochloride, mp 230-231° dec; uv λ max (ethanol): nm (ε) 204 (16,800), 279 (2000), 287 (2000); pmr (DMSO-d$_6$): δ 1.20, 1.40 (6H, *gem* methyls), 3.60 (3H, ArOCH_3), 4.41 (3H, ArC*H*Ar, ArCH_2 NHR) ppm.

1,2,3,4-Tetrahydro-2,2-dimethyl-1-(2-thienyl)benz[*f*]isoquinoline (**3l**).

Using Method B, 15.0 g (0.04 mole) of α-[1-methyl-1-[[(2-naphthalenyl)-methyl]amino]-1-methylethyl]-2-thiophenemethanol (**8e**) gave 8.1 g (60% yield) of pure **3l** after recrystallization from dichloromethane, mp 111-112; uv λ max (ethanol): nm (ε) 225 (69,200), 268-276 plateau (6200), 278 (6500), 290 sh (4700); pmr (deuteriochloroform): δ 1.06 , 1.25 (6H, *gem* methyls), 2.00 (1H, N*H*, deuterium oxide-exchangeable), 4.31 (2H, ArCH_2N), 4.61 (1H, ArC*H*-thiophene) ppm.

1-[2-Hydroxy-4-(1,2,3,4-tetrahydro-3,3-dimethyl-4-isoquinolyl)phenyl]-ethanone Hydrochloride (**3f**).

A slurry of 9.0 g (0.03 mole) of 1,2,3,4-tetrahydro-4-(3-methoxyphenyl)-3,3-dimethylisoquinoline hydrochloride (1) in 100 ml of 1,2-dichloroethane was added dropwise with stirring and cooling to a solution of 26.5 g (0.2 mole) of aluminum chloride and 16.0 g (0.2 mole) of acetyl chloride in 150 ml of 1,2-dichloroethane. After the mixture was stirred for 20 hours at room temperature and then for 5 hours at 45°, it was poured onto ice, made basic with ammonium hydroxide, and separated. The aqueous phase was reextracted with 200 ml of 1,2-dichloroethane, the combined extracts were washed, dried over sodium chloride, and evaporated to dryness *in vacuo*. The residue was dissolved in 100 ml of 2-propanol and treated with dry hydrogen chloride to *p*H 2.0. On standing for 20 hours at 25°, 6.1 g of **3f** hydrochloride was obtained, mp 247-248°. Recrystallization from 2-propanol gave 4.5 g (45% yield) of **3f** as off-white crystals of analytical purity, mp 250-251° dec; uv λ max (ethanol): 217 (33,600), 258 (13,200), 326 (4400); ir (nujol): 1650 (C=O) cm^{-1}; pmr (DMSO-d$_6$): δ 1.20, 1.45 (6H, *gem* methyls), 2.65 (3H, COCH_3), 4.40 (3H, broad, ArC*H*Ar, ArCH_2N), 7.95 (1H, d, J = 9.0 Hz, 6′-*H*), 11.85 (1H, O*H*, deuterium oxide-exchangeable) ppm.

1-(1,2,3,4-Tetrahydro-6-hydroxy-3,3-dimethyl-4-phenyl-7-isoquinolinyl)-ethanone Hydrochloride (**3g**).

In a similar manner 12.7 g (0.042 mole) of 1,2,3,4-tetrahydro-6-methoxy-3,3-dimethyl-4-phenylisoquinoline hydrochloride (**3c**) gave 6.1 g (44% yield) of **3g** hydrochloride as off-white crystals of analytical purity (after recrystallization from 2-propanol), mp 292-293° dec; uv λ max (ethanol): nm (ε) 219 (32,000), 261 (11,600), 328-340 plateau (36000); ir (nujol): 1660 (C=O) cm^{-1}; pmr (DMSO-d$_6$): δ 1.25, 1.45 (6H, *gem* methyls), 2.68 (3H, COCH_3), 4.40 (2H, ArCH_2N), 4.50 (1H, ArC*H*Ar), 6.33 (1H, s, 5-*H*), 7.91 (1H, s, 8-*H*), 12.45 (1H, O*H*, deuterium oxide-exchangeable) ppm.

1-[4-(1,2,3,4-Tetrahydro-3,3-dimethyl-4-isoquinolinyl)phenyl]ethanone Monocitrate (**3h**).

A solution of 35.6 g (0.13 mole) of 1,2,3,4-tetrahydro-3,3-dimethyl-4-phenylisoquinoline hydrochloride (1) in 250 ml of dichloromethane was added with stirring to a solution of 120 g (0.90 mole) of anhydrous aluminum chloride and 70.5 g (0.90 mole) of acetyl chloride in 1000 ml of dichloromethane and allowed to stir 20 hours at room temperature. The dark mixture was poured onto ice, made basic with sodium hydroxide, and separated. The aqueous phase was extracted with 300 ml of dichloromethane, the organic extracts were washed, dried, and evaporated to dryness. The residue was chromatographed on 300 g of Florisil, ether being used as an eluent. The combined fractions were evaporated, dissolved in 2-propanol, and treated with one equivalent of citric acid at 50°. After standing at room temperature, 10.5 g (17% yield) of **3h** as a monocitrate of analytical purity was obtained, mp 186-187° dec; uv λ max (ethanol): nm (ε) 252 (14,200); ir (nujol): 1720, 1700 (C=O) cm^{-1}; pmr (DMSO-d$_6$): δ 1.10, 1.35 (6H, *gem* methyls), 4.38 (3H, s, ArC*H*Ar, ArCH_2N), 8.00 (2H, d, J = 8.5 Hz, 2′-*H*, 6′-*H*) ppm.

1-(8-Amino-1,2,3,4-tetrahydro-3,3-dimethyl-4-phenyl-7-isoquinolinyl)-ethanone (**3i**).

Using the same procedure as for the preparation of **3f**, 12.6 g (0.05 mole) of 1,2,3,4-tetrahydro-3,3-dimethyl-4-phenyl-8-isoquinolinamine dihydrochloride (1) gave 10.0 g of crude **3i**, after recrystallization from diethyl ether, mp 129-130°. Final recrystallization from cyclohexane gave 7.5 g (51% yield) of analytically pure white crystals, mp 135-136°; ir (chloroform): 3400, 3280 (NH), 1680 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 0.80, 1.15 (6H, *gem* methyls), 1.60 (1H, ArCH$_2$N*H*R), 2.10 (3H, COCH_3), 3.70 (1H, ArC*H*Ar), 4.00 (2H, ArCH_2N), 6.60-7.40 (8H, m, aniline NH_2 and aromatic protons) ppm.

1-[4-(6-Chloro-1,2,3,4-tetrahydro-3,3-dimethyl-4-isoquinolinyl)-2-hydroxyphenyl]ethanone Hydrochloride (**3j**).

Using similar reaction conditions as for the preparation of **3f**, 12.3 g (0.036 mole) of 6-chloro-1,2,3,4-tetrahydro-4-(3-methoxyphenyl)-3,3-dimethylisoquinoline hydrochloride (1) gave 8.6 g of crude **3j** as a hydrochloride, mp 284-285° dec. Final recrystallization from methanol gave 6.0 g (45% yield) of pure **3j**, mp 286-287° dec; uv λ max (ethanol): 216 (35,000), 259 (13,700), 326 (4600): ir (nujol): 1695 (C=O) cm^{-1}; pmr (DMSO-d$_6$): δ 1.25, 1.45 (6H, *gem* methyls), 2.70 (3H, COCH_3), 4.40 (2H, ArCH_2N), 4.50 (1H, ArC*H*Ar), 7.83 (1H, d, J = 8.5 Hz, 6′-*H*), 11.30 (2H, broad NH$_2$), 12.95 (1H, O*H*, deuterium oxide-exchangeable) ppm.

1-(1,2,3,4-Tetrahydro-5-methoxy-3,3-dimethyl-4-phenyl-8-isoquinolinyl)-ethanone (**3k**).

To a stirred solution of 42.0 g (0.31 mole) of aluminum chloride and 24.7 g (0.31 mole) of acetyl chloride in 400 ml of dichloromethane was added a slurry of α-[1-[[(3-methoxyphenyl)methyl]amino]-1-methylethyl]-benzenemethanol [**8a**, 25.0 g (0.078 mole)] in 150 ml of dichloromethane dropwise, with cooling. After the mixture was stirred for 70 hours at room temperature, it was poured onto ice, made basic with sodium hydroxide, and separated. The organic phase was washed with saturated

aqueous sodium chloride solution, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from ether-ethyl acetate (1:1) gave 12.7 g (52% yield) of pure **3k** as white crystals, mp 145-146°; uv λ max (ethanol): nm (ε) 225 (22,800), 274 (14,000); ir (chloroform): 1680 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 0.80, 1.25 (6H, *gem* methyls), 1.80 (1H, N*H*, deuterium oxide-exchangeable), 2.60 (3H, $COCH_3$), 4.00 (1H, ArC*H*Ar), 4.60 (2H, d, J = 7.0 Hz, $ArCH_2N$), 6.65 (1H, d, J = 8.5 Hz, 6-*H*), 6.90-7.25 (5H, m, phenyl group), 7.84 (1H, d = 8.5 Hz, 7-*H*) ppm.

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