Preparation of 4-Aryl-1,2,3,4-tetrahydro-3,3-dimethylisoquinolines and 1,2,3,4-Tetrahydro-3,3-dimethyl-4-phenylbenz[*h*]isoquinolines

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Synthetic procedures to prepare a number of 4-aryl-1,2,3,4-tetrahydro-3,3-dimethylisoquinolines and their benzo-homogues **3** through a series of intermediates are described. The condensation of α-(1-amino-1-methylethyl)arylmethanols **5** with arylaldehydes **6** gave imino derivatives **7** which on reduction with borohydride gave secondary amines **8**. The treatment of **8** with mineral acids gave the target compounds **3**. Biological activities of **3** are briefly discussed.

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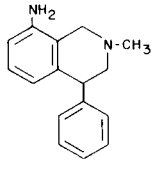
There has been considerable interest in compounds having antidepressant activity. 8-Amino-1,2,3,4-tetrahydro-2-methyl-4-phenylisoquinoline (**1**), was reported (1) to exhibit antidepressant activity in cats and rats. 4-Acetylphentermine **2** was shown (2) to lower 5-hydroxytryptophan (serotonin) in the mouse brain and was active as an antidepressant. It was hoped that a new class of compounds of generic formula **3**, which combined elements of both **1** and **2**, might show enhanced biological properties.



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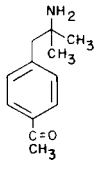

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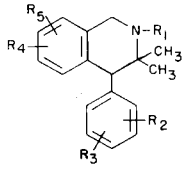
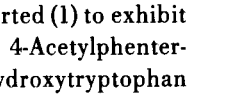


3

In this paper, we describe synthetic methods for the target compounds **3** using simple and readily obtainable starting materials and intermediates. The general method represents the reduction of α-(1-methyl-1-nitroethyl)arylmethanols **4** (3) with zinc dust in acetic acid or in methanol and hydrochloric acid to give α-(1-amino-1-methylethyl)-arylmethanols **5** (3). Condensation of **5** with properly substituted arylaldehydes **6** under azeotropic conditions gave the imino derivatives **7**. These (**7**), which are usually semi-solids, were not isolated but directly reduced by potassium borohydride to give α-[1-[(arylmethyl)amino]-1-methylethyl]arylmethanols **8** (Table I). Compounds **8** are characterized by the nonequivalency of their geminal methyl groups whose resonance signals are separated of up to 0.20 ppm.

Attempts to convert the imines **7** into 1-aryl-1,2,3,4-tetrahydro-3,3-dimethylisoquinolin-4-ols **9** were unsuccessful. Starting amino alcohols **5** and arylaldehydes **6** were instead recovered as a result of hydrolysis of **7** in the aqueous acidic media during work-up.

Various acids were tried as agents to effect the cyclization of **8** into 4-aryl-1,2,3,4-tetrahydro-3,3-dimethylisoquinolines of formula **3** (Table II). Schwan and co-workers (4) had used 48% hydrobromic acid to cyclize α-[1-[(arylmethyl)amino]ethyl]benzenemethanols of the general formula  into the corresponding tetrahydro-4-phenylisoquinolines. This agent was ineffective with our compounds **8** in which the geminal methyl groups cause considerably greater steric hindrance at the reaction site.

We have found other acids, however, which are effective in giving reasonably good yields of **3**. These include concentrated sulfuric acid (Method A), methanesulfonic acid (Method A'), 60% sulfuric acid (Method A", where the cyclization was effected with simultaneous hydrolysis of the amido group), polyphosphoric acid (Method B), and borontrifluoride etherate (Method C).

The above authors (4) had reported on the difficulty in effecting the cyclization of α-[1-[[[4-(dimethylamino)-phenyl]methyl]amino]ethyl]benzenemethanol into 6-(dimethylamino)-1,2,3,4-tetrahydro-3-methyl-4-phenylisoquinoline by using hydrobromic acid or polyphosphoric acid. In our case compounds **8**, having amino or amido substituents in various positions, cyclized readily into the corresponding isoquinolines **3** in yields ranging from 70 to 80% by treatment with concentrated sulfuric acid at room temperature (**3k, 3l, 3n, 3p**) or at 85° (**3i, 3j**).

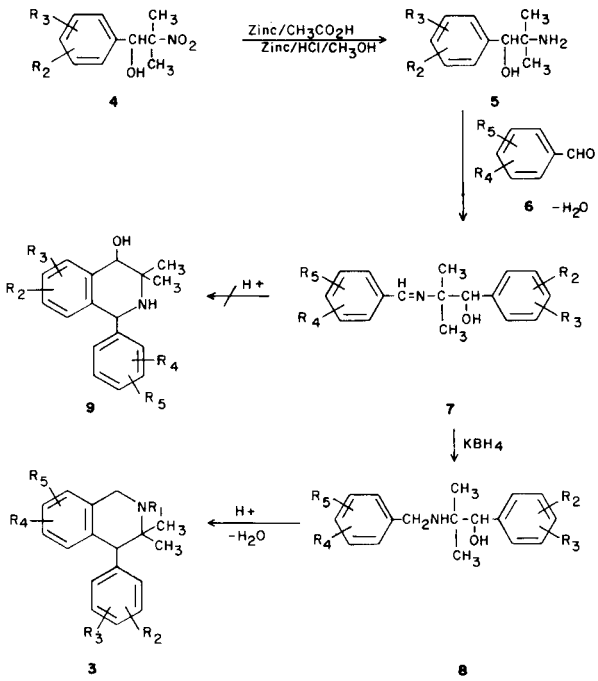
The introduction of an *N*-methyl group by the Eschweiler-Clark method was usually accomplished after the cyclization step was complete. The nonequivalency of geminal methyl groups in compounds **3** is even more pronounced than in their precursors **8**, displaying a signal separation of up to 0.50 ppm.

The synthetic sequence of reactions is presented in Scheme I.

Compounds of formula **3** were found to exhibit antisecretory activity within a dose range of 20 mg./kg. down to 2.5 mg./kg. when administered by varied routes (*i.e.*, intraperitoneal, intraduodenal and oral) in the 4 hour Shay rat gastric anti-secretory assay (5). The best activity was shown by compounds **3l** (5 mg./kg.), **3g** (1 mg./kg.) **3n** (2.5 mg./kg.), **3d**, (10 mg./kg.) and **3j** (5 mg./kg.).

0022-152X/80/071563-06$02.25

Scheme I



EXPERIMENTAL

Physical constants, yields, and analytical values for the compounds below are reported in Tables I and II. 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 was 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 methanol-acetonitrile-acetone in varying proportions, as the eluent. The chromatograms were developed in an iodine chamber.

The completeness of transformations of α-[1-[(arylmethyl)amino]-1-methylethyl]arylmethanols **8** into 4-aryl-1,2,3,4-tetrahydro-3,3-dimethylisoquinolines **3** was usually determined by thin layer chromatography. The low yields of some compounds **3** were due to their great solubilities in the crystallization solvents, and no attempts were made to use more involved operational techniques like column chromatography to isolate more products. The pmr for the aromatic protons were not included. Occasionally, the resonance peaks of lone protons were not assigned when the resolution was insufficient and if they were buried under an envelope of other aliphatic protons.

α-[1-Methyl-1-nitroethyl]arylmethanols (**4**).

Amino alcohols **4a**, **4b**, **4c** and **4d** were reported previously (3). The preparation of 4-chloro-α-(1-methyl-1-nitroethyl)benzenemethanol (**4e**) and α-(1-methyl-1-nitroethyl)-2-napthalenemethanol (**4f**) is described here.

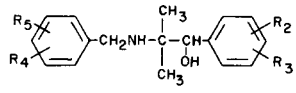
4-Chloro-α-(1-methyl-1-nitroethyl)benzenemethanol (**4e**).

To a stirred solution of 27.0 g. (0.5 mole) of sodium methoxide (Ventron Co., 97%) in 200 ml. of methanol was added 59.0 g. (0.667 mole) of 2-nitropropane dropwise at 25° over a period of 40 minutes. While the temperature of the reaction flask was maintained at 0°, 46.8 g. (0.33 mole) of 4-chlorobenzaldehyde (Aldrich Co.) was added over 30 minutes and the stirring was continued for 20 hours at room temperature. Glacial acetic acid was added at 0° to *p*H 6.5 and the solvent and excess 2-nitropropane were removed *in vacuo*. The white residue was taken up with water and extracted twice with 200 ml. of dichloromethane. The combined extracts were washed, dried over sodium sulfate, and evaporated to dryness. Crystallization of the residue from cyclohexane-isopropyl ether gave 21.0 g. (28% yield) of **4e** as white crystals, m.p. 78.5-79.5°; ir (chloroform): 3580 (OH), 1549, 1350 (NO_2) cm^{-1}; pmr (deuteriochloroform): δ 1.42, 1.59 (6H, nonequivalent *gem* methyls), 2.64 (1H, d, J = 4.0 Hz, *OH*, deuterium oxide-exchangeable), 5.26 (1H, d, J = 4.0 Hz, C*H*OH) ppm.

Anal. Calcd. for $C_{10}H_{12}ClNO_3$: C, 52.30; H, 5.27; N, 6.10. Found: C, 52.40; H, 5.43; N, 6.05.

Table I

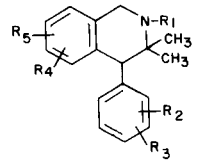
α-[1-[(Arylmethyl)amino]-1-methylethyl]arylmethanols **8**



Compound No.	R_2	R_3	R_4	R_5	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Method
8a	H	H	H	H	107-108	82	$C_{17}H_{21}NO$	79.96	8.28	5.49	79.99	8.18	5.50	A
8b	H	H	3-OH	H	130-131	77	$C_{17}H_{21}NO_2$	75.24	7.80	5.16	75.07	7.83	5.06	A
8c	3-OCH_3	H	H	H	63-65	55	$C_{18}H_{23}NO_2$	75.75	8.12	4.91	75.52	8.20	4.80	A
8d	4-Cl	H	H	H	125-126	98	$C_{17}H_{20}ClNO$	70.46	6.96	4.83	70.60	7.07	4.83	B
8e	H	H	4-Cl	H	107-108	90	$C_{17}H_{20}ClNO$	70.46	6.96	4.83	70.40	6.93	4.96	B
8f	3-OCH_3	H	4-Cl	H	96.5-97.5	65	$C_{18}H_{22}ClNO_2$	67.60	6.93	4.38	67.47	6.94	4.64	B
8g	H	H	4-$NHCOCH_3$	H	145-146	70	$C_{19}H_{24}N_2O_2$	73.04	7.74	8.97	72.85	7.87	8.84	A
8h	H	H	3-NH_2	H	125-126	33	$C_{17}H_{22}N_2O$	75.52	8.20	10.36	75.31	8.17	10.20	C
8i	4-Cl	H	3-NH_2	H	129-130	60	$C_{17}H_{21}ClN_2O$	66.99	6.94	9.19	66.87	7.15	9.18	C
8j	H	H	4-$N(CH_3)_2$	H	89-90	81	$C_{19}H_{26}N_2O$	76.47	8.78	9.39	76.32	8.82	9.37	A
8k	3-Cl	H	3-NH_2	4-Cl	107-108	42	$C_{17}H_{20}Cl_2N_2O$	60.19	5.94	8.26	60.28	5.98	8.23	C
8l	H	H	R_4, R_5 = 3,4-		104-105	90	$C_{21}H_{23}NO$	82.58	7.59	4.59	82.58	7.59	4.77	B
8m	R_2, R_3 = 3,4-		R_4, R_5 = 3,4-		157-158	89	$C_{25}H_{25}NO$	84.47	7.09	3.94	84.63	7.13	3.91	B
8n	H	H	R_4, R_5 = 2,3-		131-132	84	$C_{21}H_{23}NO$	82.58	7.59	4.59	82.68	7.76	4.48	A
8o	H	H	2-NO_2	H	125-126	78	$C_{17}H_{20}N_2O_3$	67.98	6.71	9.33	68.20	6.82	9.55	B
8p	H	H	2-NH_2	H	105-106	69	$C_{17}H_{22}N_2O$	75.52	8.20	10.36	75.42	8.31	10.26	C

Table II

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



Compound No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3a	H	H	H	H	H	299-300 (b)	72	$C_{17}H_{19}N \cdot HCl$	74.57	7.36	5.12	74.55	7.65	4.97
3b	CH_3	H	H	H	H	246-247 (b)	80	$C_{18}H_{21}N \cdot HCl$	75.11	7.70	4.87	75.02	7.87	4.81
3c	H	3-OCH_3	H	H	H	261-262 (b)	71	$C_{18}H_{21}NO \cdot HCl$	71.16	7.30	4.61	71.12	7.28	4.80
3d	H	H	H	H	7-OH	207-208 (b)	86	$C_{17}H_{19}NO$	80.57	7.57	5.53	80.75	7.87	5.76
3e	H	H	4-Cl	H	H	299-300.5 (b)	86	$C_{17}H_{18}ClN \cdot HCl$	66.24	6.21	4.54	66.31	6.42	4.47
3f	CH_3	H	4-Cl	H	H	108.5-109.5	78	$C_{18}H_{20}ClN$	75.64	7.05	4.90	75.59	7.07	4.87
3g	H	H	H	6-Cl	H	276-277 (b)	73	$C_{17}H_{18}ClN \cdot HCl$	66.24	6.21	4.54	66.14	6.14	4.59
3h	CH_3	H	H	6-Cl	H	84.5-85.5	66	$C_{18}H_{20}ClN$	75.64	7.05	4.90	75.47	7.03	4.67
3i	H	H	H	6-NH_2	H	164-165 (b)	73	$C_{17}H_{20}N_2$	80.91	7.99	11.10	80.72	8.16	11.00
3j	H	H	H	6-$NHCOCH_3$	H	152-153	80	$C_{19}H_{22}N_2O$	77.52	7.53	9.52	77.68	7.65	9.69
3k	H	H	H	H	7-NH_2	142-143	73	$C_{17}H_{20}N_2$	80.91	7.99	11.10	80.82	8.11	11.06
3l	H	H	H	H	8-NH_2	211-212	78	$C_{17}H_{20}N_2$	80.91	7.99	11.10	80.81	8.07	11.13
3m	H	3-OCH_3	H	6-Cl	H	159-160	43	$C_{18}H_{20}NO \cdot HCl$ (a)	61.46	6.45	3.98	61.47	6.39	3.88
3n	H	H	4-Cl	H	7-NH_2	115-116	75	$C_{17}H_{19}ClN_2$	71.19	6.68	9.77	71.12	6.77	10.06
3o	H	3-Cl	H	6-Cl	7-NH_2	349-350 (b)	30	$C_{17}H_{16}Cl_2N_2 \cdot HCl$	56.76	5.32	7.77	56.99	5.42	7.79
3p	H	H	H	6-$N(CH_3)_2$	H	104-105	72	$C_{19}H_{24}N_2$	81.38	8.63	9.91	81.30	8.79	9.99
3q	CH_3	H	H	6-$N(CH_3)_2$	H	78-79	73	$C_{20}H_{26}N_2$	81.58	8.98	9.52	81.88	9.13	9.49
3r	H	H	H	R_4, R_5 = 5,6-		139-140	74	$C_{21}H_{21}N$	87.76	7.37	4.87	87.54	7.59	4.84
3s	CH_3	H	H	R_4, R_5 = 5,6-		105-106	55	$C_{22}H_{23}N$	87.66	7.69	4.65	87.53	7.61	4.58
3t	H	H	H	R_4, R_5 = 7,8-		287-288 (b)	68	$C_{21}H_{21}N \cdot HCl$	77.88	6.85	4.33	77.72	7.00	4.21
3u	CH_3	H	H	R_4, R_5 = 7,8-		119-120	77	$C_{22}H_{23}N$	87.66	7.69	4.65	87.52	7.86	4.54
3v	H	R_2, R_3 = 3,4-		R_4, R_5 = 5,6-		174-175	50	$C_{22}H_{23}N$	88.98	6.87	4.15	88.78	6.88	4.09

(a) The compound analyzed having 0.75 mole of water of crystallization, the presence of which was determined by the Karl Fischer method. (b) Melts with decomposition.

α-(1-Methyl-1-nitroethyl)-2-napthalenemethanol (**4f**).

The above method was followed. Thus, by using 15.5 g. (0.1 mole) of 2-naphthalenecarboxaldehyde (other conditions being similar to the preparation of **4e**), 13.2 g. of crude **4f** was obtained as nearly white cake. Crystallization from ethyl acetate-cyclohexane (1:1) gave 9.8 g. (41% yield) of pure **4f** as white crystals, m.p. 96-97°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.60; H, 6.40; N, 5.99.

α-(1-Amino-1-methylethyl)arylmethanols (**5**).

The amino alcohols **5a**, **5b** and **5c** were reported previously (3). The preparation of **5d** and **5e** is described here.

α-(1-Amino-1-methylethyl)-4-chlorobenzenemethanol (**5d**).

To a stirred solution of 208.0 g. (0.91 mole) of 4-chloro-α-(1-methyl-1-nitroethyl)benzenemethanol (**4e**) in 2 liters of methanol was added 820 ml. (4.0 mole) of concentrated hydrochloric acid at 10° followed by the addition of 650 g. of zinc dust portionwise over a period of 2 hours. After the mixture was stirred for 20 hours at room temperature, the excess zinc and salts were filtered off and washed with methanol. The filtrate was evaporated to dryness *in vacuo*, the residue was taken up with ice and made basic with sodium hydroxide. The product was extracted twice with 1.5 liters of ethyl acetate. The combined extracts were dried over sodium sulfate and evaporated to dryness *in vacuo*. The yellow oily residue was crystallized from Skelly B giving 130.0 g. (72% yield) of **5d** as white crystals, m.p. 96.5-97.5°; uv (ethanol): λ max nm (ε) 221 (12,000); pmr (deuteriochloroform): δ 0.90, 1.10 (6H, nonequivalent *gem* methyls), 2.20 (3H, NH_2, *OH*, deuterium oxide-exchangeable), 4.31 [1H, Ar*CH*(OH)R] ppm.

Anal. Calcd. for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07; N, 7.02. Found: C, 60.15; H, 7.11; N, 6.98.

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

To a vigorously stirred solution of 51.0 g. (0.2 mole) of α-(1-methyl-1-nitroethyl)-2-naphthalenemethanol (**4f**) in 400 ml. of glacial acetic acid was added 140 g. of zinc dust portionwise at 20-25° over a period of 20 minutes. After the stirring was continued for 20 hours at room temperature, the excess zinc and salts were removed by filtration and the filtrate was evaporated *in vacuo*. The residue was taken up with ice-water, made basic with sodium hydroxide, and extracted twice with 300 ml. of ethyl acetate. The combined extracts were washed with aqueous saturated sodium chloride, dried over sodium sulfate, and concentrated to *ca.* 40 ml. giving 27.5 g. of analytically pure **5e**, m.p. 121-122°. Further concentration of the filtrate to a low volume and cooling gave 6.7 g. (total yield: 76%) of additional product as white crystals, m.p. 121-122°.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.10; H, 8.05; N, 6.58.

α-[1-[(Arylmethyl)amino]-1-methylethyl]benzenemethanols **8**.

The imino derivatives (Schiff bases of type **7**) have been prepared by the refluxing of an amino alcohol **5** and arylaldehyde **6** under azeotropic conditions (Method A), or in refluxing methanol or ethanol in the presence of anhydrous potassium carbonate (Method B). The Schiff bases prepared by Method A were reduced to **8** by potassium borohydride in methanol (after benzene was first removed), while those obtained by Method B were reduced directly in the same reaction medium. In the presence of the nitro groups, the imino derivatives were usually reduced first by borohyride and the subjected to the catalytic hydrogenation to give diamino derivatives **8** (Method C). The three methods described here will illustrate general procedure of obtaining **8** (Table I).

α-[1-[[(4-Chlorophenyl)methyl]amino]-1-methylethyl]benzenemethanol (**8e**).

Method A.

A solution of 33.0 g. (0.2 mole) of α-(1-amino-1-methylethyl)benzenemethanol (**5a**) and 31.0 g. (0.22 mole) of 4-chlorobenzaldehyde in 300 ml. of benzene was refluxed for 4 hours, while 3.6 ml. of water separated in a Dean-Stark trap. After the solvent was evaporated, the residue was taken up with 500 ml. of methanol and treated with 5.4 g. (0.1 mole) of potassium borohydride. After 20 hours at room temperature, 500 ml. of water was added and the resulting white crystalline precipitate (55.0 g., 90% yield) of analytical purity was collected by filtration, m.p. 107-108°; uv (ethanol): λ max nm (ε) 207 (7000), 217 (7400); pmr (deuteriochloroform): δ 0.95, 1.15 (6H, nonequivalent *gem* methyl groups), 3.80 (2H, ArC*H*$_2$NHR), 4.55 [1H, ArC*H*(OH)R], 4.70 (1H, O*H*, deuterium oxide-exchangeable) ppm.

α-[1-Methyl-1-[[(2-nitrophenyl)methyl]amino]ethyl]benzenemethanol (**8o**).

Method B.

A stirred mixture of 49.5 g. (0.3 mole) of α-(1-amino-1-methylethyl)-benzenemethanol (**5a**), 45.3 g. (0.3 mole) of 2-nitrobenzaldehyde and 60.0 g. (0.42 mole) of potassium carbonate in 400 ml. of methanol was refluxed for a period of 4 hours. After cooling to 23°, the solid was filtered off and discarded. To the filtrate, containing a Schiff base **7**, was added 10.8 g. (0.2 mole) of potassium borohydride at 25° and continued to stir at this temperature for 3 hours. The precipitated solid was collected, washed with water and methanol giving 78.0 g. (78% yield) of α-[1-methyl-1-[[(2-nitrophenyl)methyl]amino]ethyl]benzenemethanol (**8o**) m.p. 122-123°. An analytical sample, recrystallized from ethanol, melted at 125-126°.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.20; H, 6.82; N, 9.55.

α-[1-[[(2-Aminophenyl)methyl]amino]-1-methylethyl]benzenemethanol (**8p**).

Method C.

A solution of 60.0 g. (0.2 mole) of the above crude nitro derivative **8o** in 200 ml. of methanol and 100 ml. of glacial acetic acid was hydrogenated over 2.0 g. of palladium-on-charcoal (10%) using a Parr hydrogenation apparatus until the hydrogen uptake ceased (45 minutes). The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was taken up with ice, made basic with ammonium hydroxide, and extracted twice with 200 ml. of ethyl acetate. The combined organic extracts were dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from cyclohexane gave 42.7 g. (69% yield) of α-[1-[[(2-aminophenyl)methyl]amino-1-methylethyl]-benzenemethanol (**8p**) as off-white crystals of analytical purity, m.p. 105-106°; uv (ethanol): λ max nm (ε) 285 (7000); pmr (deuteriochloroform): δ 1.00, 1.15 (6H, nonequivalent *gem* methyls), 3.35 [4H, broad, ArCHN*H*$_2$, RN*H*CH$_2$Ar, ArCH(O*H*)R, deuterium oxide-exchangeable], 3.75 (2H, ArC*H*$_2$N), 4.55 [1H, ArC*H*(OH)] ppm.

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.42; H, 8.31; N, 10.26.

1,2,3,4-Tetrahydro-3,3-dimethyl-4-arylisoquinolines (**3**).

A variety of acidic agents were tried to effect the cyclization of α-[1-[(arylmethyl)amino]-1-methylethyl]arylmethanols **8** into **3**. While, occasionally, two different agents were equally effective, as exemplified by the formation of **3a**, more often one method was considerably better than others and as such is described here for individual compounds.

1,2,3,4-Tetrahydro-3,3-dimethyl-4-phenylisoquinoline Hydrochloride (**3a**).

Hydrobromic Acid Method.

A solution of 7.7 g. (0.03 mole) of α-[1-methyl-1-[(phenylmethyl)amino]-ethyl]benzenemethanol (**8a**) in 48% hydrobromic acid (12 ml.) was heated for 6 hours at 100°. After standing overnight at room temperature, 8.1 g. (80% yield) of the hydrobromide of **8a** was recovered, m.p. 225-226° dec. The filtrate, on concentration to a low volume, gave 1.2 g. of additional hydrobromide of **8a** (total recovery: 92%), m.p. 224-225°. No product **3a** was detected in the filtrate.

Method A.

Compound **8a** (10.3 g., 0.04 mole) was dissolved in 30 ml. of concentrated sulfuric acid with external cooling and then allowed to stand for 20 hours at room temperature. The yellowish syrupy contents were poured over crushed ice, made basic with sodium hydroxide, and extracted twice with 150 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from ethyl acetate-cyclohexane (1:1) gave 5.6 g. (79% yield) of **3a** base, m.p. 79-80°.

Anal. Calcd. for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.09; H, 7.98; N, 5.86.

Method C.

A solution of 59.0 g. (0.23 mole) of **8a** in 400 ml. of borontrifluoride etherate was heated at 85° for 40 hours and then refluxed (128°) for 30 hours. After cooling to 25°, the solution was poured over ice, made basic with sodium hydroxide, and extracted twice with 500 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue was dissolved in 300 ml. of 2-propanol followed by the addition of dry hydrogen chloride to *p*H 2.0 to give, on standing, 48.0 g. (72% yield) of 1,2,3,4-tetrahydro-3,3-dimethyl-4-phenylisoquinoline, hydrochloride (**3a**), m.p. 299-300° dec.; pmr (DMSO-d_6): δ 0.90, 1.20 (6H, nonequivalent *gem* methyls), 4.30 (3H, ArC*H*Ar, ArC*H*$_2$NHR) ppm.

1,2,3,4-Tetrahydro-2,3,3-trimethyl-4-phenylisoquinoline Hydrochloride (**3b**).

A solution of 5.1 g. (0.02 mole) of 1,2,3,4-tetrahydro-3,3-dimethyl-4-phenylisoquinoline (**3a**) in 17 ml. of 97% formic acid and 5 ml. of 36% aqueous formaldehyde was refluxed for 2 hours. Hydrochloric acid (10%, 25 ml.) was then added and the reaction mixture was heated at 100° for 15 minutes. The contents were poured onto ice, made basic with ammonium hydroxide, and extracted twice with 75 ml. of ethyl acetate. The combined extracts were dried over sodium sulfate and concentrated *in vacuo* to *ca.* 25 ml. At this point dry hydrogen chloride was introduced to *p*H 2.0. After standing at room temperature for 20 hours, 4.6 g. (80% yield) of 1,2,3,4-tetrahydro-2,3,3-trimethyl-4-phenylisoquinoline hydrochloride (**3b**) of analytical purity crystallized as off-white crystals, m.p. 246-247° dec.; pmr (DMSO-d_6): δ 1.23, 1.38 (6H, *gem* methyls), 2.92 (3H, N-C*H*$_3$) ppm.

1,2,3,4-Tetrahydro-3,3-dimethyl-4-(3-methoxyphenyl)isoquinoline Hydrochloride (**3c**). Method B.

A stirred solution of 20.0 g. (0.07 mole) of 3-methoxy-α-[1-methyl-1-[(phenylmethyl)amino]ethyl]benzenemethanol (**8c**) in 200 ml. of polyphosphoric acid (PPA) was heated at 100° for 2 hours. Subsequently it was poured onto ice, made basic with sodium hydroxide, and extracted twice with 300 ml. of dichloromethane. The combined extracts were dried over sodium sulfate and evaporated to dryness. The residue was taken up with 200 ml. of 2-propanol and treated with dry hydrogen chloride to *p*H 2.0. On standing for 20 hours at room temperature, 15.1 g. (71% yield) of product **3c** hydrochloride crystallized as off-white solid of analytical purity, m.p. 261-262° dec.; uv (ethanol): λ max nm (ε) 204 (18,600), 274 (2400), 282 (2200); pmr (DMSO-d_6): δ 1.20, 1.40 (6H, *gem* methyls), 3.75 (3H, ArOC*H*$_3$), 4.45 (3H, ArC*H*Ar, ArC*H*$_2$NHR), 10.4 (2H, $^+$N*H*$_2$) ppm.

1,2,3,4-Tetrahydro-3,3-dimethyl-4-phenyl-7-isoquinolinol (**3d**).

A solution of α-[1-[[(3-hydroxyphenyl)methyl]amino]-1-methylethyl]-benzenemethanol (**8b**, 1.0 g.) in 5 ml. of concentrated sulfuric acid was heated at 80° for 7 hours and then poured onto ice. On addition of ammonium hydroxide to *p*H 8.5, 0.8 g. of white precipitate had separated, m.p. 203-204° dec. Two recrystallizations from 2-propanol gave analytically pure white crystals of **3d**, m.p. 207-208° dec.; uv (ethanol): λ max nm (ε) 220 sh (7500), 282 (1990), 228 sh (1820); pmr (DMSO-d_6): δ 0.74, 1.12 (3H, *gem* methyls), 1.88 (1H, broad N*H*), 3.64 (1H, s, ArC*H*Ar), 3.96 (2H, ArC*H*$_2$N), 9.30 (O*H*) ppm.

4-(4-Chlorophenyl)-1,2,3,4-tetrahydro-3,3-dimethylisoquinoline Hydrochloride (**3e**). Method C.

A solution of 50.5 g. (0.17 mole) of **8d** in 350 ml. of borontrifluoride

etherate was refluxed for 11 hours, poured onto ice, made basic with sodium hydroxide, and extracted twice with 500 ml. of ethyl acetate. The combined extracts were washed, dried, and concentrated to *ca.* 400 ml. *in vacuo*. At this point dry hydrogen chloride was introduced to *p*H 2.0 causing 49.6 g. of crude hydrochloride to separate, m.p. 295-296° dec. Recrystallization from 2-propanol gave 45.0 g. (86% yield) of **3e** hydrochloride of analytical purity as white crystals, m.p. 299-300° dec.; pmr (DMSO-d_6): δ 1.20, 1.40 (6H, *gem* methyls) ppm.

4-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,3,3-trimethylisoquinoline (**3f**).

A solution of 14.0 g. (0.05 mole) of **3e** in 40 ml. of 97% formic acid and 10 ml. of 36% formaldehyde was refluxed for 2 hours. Hydrochloric acid (75 ml., 10%) was added and the solution was heated for 30 minutes on a steam bath. The solution was poured onto ice, made basic with ammonium hydroxide, and extracted twice with 150 ml. of ether. The extracts were washed, dried over sodium sulfate, and evaporated to dryness. Crystallization of the residue from 2-propanol gave 11.2 g. (78% yield) of analytically pure, white crystals of **3f**, m.p. 108.5-109.5°; uv (ethanol): λ max nm (ε) 203 (31,600); pmr (deuteriochloroform): δ 0.90, 1.05 (6H *gem* methyls), 2.35 (3H, N-CH_3), 3.80 (3H, ArC*H*Ar, ArCH_2N, J = 5.0 Hz) ppm.

6-Chloro-1,2,3,4-tetrahydro-3,3-dimethyl-4-phenylisoquinoline Hydrochloride (**3g**).

α-[1-[[(4-Chlorophenyl)methyl]amino]-1-methylethyl]benzenemethanol [**8e**, 52.5 g. (0.18 mole)] was dissolved in 35 ml. of concentrated sulfuric acid with external cooling and allowed to stand for 20 hours at room temperature. The solution was poured onto ice, made basic with sodium hydroxide, and extracted twice with 400 ml. of ethyl acetate. The extracts were washed, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue was dissolved in 400 ml. of isopropyl ether and introduced dry hydrogen chloride to *p*H 2.0 giving 46.0 g. of crude hydrochloride, m.p. 270-272° dec. Recrystallization from 2-propanol gave 40.0 g. (73% yield) of analytically pure hydrochloride of **3g** as white crystals, m.p. 276-277° dec.; pmr (DMSO-d_6): δ 1.20, 1.40 (6H, *gem* methyls) ppm.

6-Chloro-1,2,3,4-tetrahydro-2,3,3-trimethyl-4-phenylisoquinoline (**3h**).

A solution of 14.0 g. (0.05 mole) of **3g** in 40 ml. of 97% formic acid and 10 ml. of 36% aqueous formaldehyde was refluxed for 2 hours. Hydrochloric acid (75 ml., 10%) was added and the solution was heated at 100° for 30 minutes. The contents were poured onto ice, made basic with ammonium hydroxide, and extracted twice with 150 ml. of ethyl acetate. The extracts were washed, dried over sodium sulfate, and evaporated *in vacuo*. Crystallization of the residue from 2-propanol gave 9.5 g. (66% yield) of **3h** as white crystals of analytical purity, m.p. 84.5-85.5°; uv (ethanol): λ max nm (ε) 205 (34,200); pmr (deuteriochloroform): δ 0.87, 1.03 (6H, *gem* methyls), 2.35 (3H, N-CH_3), 3.70 (2H, ArCH_2NR), 3.85 (1H, ArC*H*Ar) ppm.

1,2,3,4-Tetrahydro-3,3-dimethyl-4-phenyl-6-isoquinolinamine (**3i**). Method A'.

A stirred solution of 7.8 g. (0.025 mole) of *N*-[4-[[(2-hydroxy-1,1-dimethyl-2-phenylethyl)amino]methyl]phenyl]acetamide (**8g**) in 28 ml. of 90% sulfuric acid was heated at 85° for 4 hours. Water (7 ml.) was then added *cautiously* to make about 60% acid solution, and the heating was continued for 2 hours longer. The contents were poured onto ice, made basic with sodium hydroxide, and extracted twice with 200 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from isopropyl ether gave 4.6 g. (73% yield) of pure **3i** as off-white crystals, m.p. 164-166° dec.; uv (ethanol): λ max nm (ε) 208 (19,100), 240 (7700), 294 (1930); ir (chloroform): 3450, 3400, 1626 (NH); pmr (deuteriochloroform): δ 0.85, 1.25 (6H, *gem* methyls), 2.79 (3H, broad, NH, deuterium oxide-exchangeable), 3.65 (1H, ArC*H*Ar), 4.08 (2H, ArCH_2N) ppm.

N-(1,2,3,4-Tetrahydro-3,3-dimethyl-4-phenyl-6-isoquinolinlyl)acetamide (**3j**). Method A".

A stirred solution of 9.4 g. (0.03 mole) of *N*-[4-[[(2-hydroxy-1,1-dimethyl-2-phenylethyl)amino]methyl]phenyl]acetamide (**8g**) in 25 ml. of methanesulfonic acid was heated at 85° for 5 hours. After cooling to 25°, the yellow syrupy solution was poured onto ice, made basic with ammonium hydroxide, and extracted twice with 250 ml. of ethyl acetate. The extracts were washed, dried over sodium sulfate, and evaporated *in vacuo*. The residue was crystallized from diethyl ether-isopropyl ether giving 7.1 g. (80% yield) of nearly white, analytically pure crystals of **3j**, m.p. 152-153°; uv (ethanol): λ max nm (ε) 208 sh (36,200), 247 (15,000); ir (nujol): 3350 (NH), 1662, 1540 (NHC=O) cm^{-1}; pmr (deuteriochloroform): δ 1.14, 1.26 (6H, *gem* methyls), 1.75 (1H, s, basic N*H*), 2.00 (3H, COCH_3), 3.76 (1H, ArC*H*Ar), 4.17 (2H, ArCH_2N), 7.67 (N*H*COCH$_3$) ppm.

1,2,3,4-Tetrahydro-3,3-dimethyl-4-phenyl-7-isoquinolinamine (**3k**).

α-[1-[[(3-Aminophenyl)methyl]amino]-1-methylethyl)benzenemethanol [**8h**, 16.0 g., (0.06 mole)] was dissolved in 50 ml. of concentrated sulfuric acid with external cooling and allowed to stand for 20 hours at room temperature. The solution was poured onto ice, made basic with sodium hydroxide, and extracted twice with 300 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate, and concentrated to *ca.* 100 ml. On standing for 20 hours at room temperature, 11.1 g. (73% yield) of **3k** as off-white crystals was obtained, m.p. 142-143°; uv (ethanol): λ max nm (ε) 240 (11,000), 294 (1600); pmr (deuteriochloroform): δ 0.80, 1.25 (6H, *gem* methyls), 3.00 (3H, ArNH_2, ArCH$_2$N*H*, deuterium oxide-exchangeable), 3.65 (1H, ArC*H*Ar), 4.05 (2H, ArCH_2N) ppm.

1,2,3,4-Tetrahydro-3,3-dimethyl-4-phenyl-8-isoquinolinamine (**3l**).

A solution of 29.5 g. (0.098 mole) of α-[1-[[(2-aminophenyl)methyl]-amino]-1-methylethyl]benzenemethanol (**8p**) in 200 ml. of concentrated sulfuric acid was allowed to stand 24 hours at room temperature. The contents were poured onto ice, made basic with sodium hydroxide, and the resulting white precipitate was collected and crystallized from acetonitrile giving 21.3 g. of **3l**, m.p. 210-211°. Recrystallization from 2-propanol gave 19.2 g. (78% yield) of analytically pure, white crystals, m.p. 211-212°; uv (ethanol): λ max nm (ε) 286 (2200): ir (nujol): 3480, 3430, 3300, 3200 (NH) cm^{-1}; pmr (DMSO-d_6): δ 0.70, 1.07 (6H, *gem* methyls), 1.85 (1H, RN*H*R), 3.60 (1H, ArC*H*Ar), 3.75 (2H, ArCH_2N), 4.70 (2H, ArNH_2) ppm.

6-Chloro-1,2,3,4-tetrahydro-3,3-dimethyl-4-(3-methoxyphenyl)isoquinoline Hydrochloride Hydrate (**3m**). Method A'.

A solution of 40.0 g. (0.125 mole) of α[1-[[(4-chlorophenyl)methyl]-amino]-1-methylethyl]-3-methoxybenzenemethanol (**8f**) in 135 ml. of methanesulfonic acid was heated at 80° for 12 hours. The solution was poured onto ice, made basic with sodium hydroxide, and extracted twice with 400 ml. of ethyl acetate. The extracts were washed with aqueous saturated sodium chloride, dried over sodium sulfate and concentrated to *ca.* 400 ml. *in vacuo*. To this solution was introduced dry hyrogen chloride and the resulting crude precipitate (26.0 g., m.p. 156-157°) was collected by filtration. Recrystallization from water gave 19.0 g. (43% yield) of **3m** hydrochloride containing 0.75 mole of water, m.p. 159-160°; uv (ethanol): λ max nm (ε) 274 (2200); ir (chloroform): 3400 (N*H*, OH) cm^{-1}; pmr (deuteriochloroform): δ 1.30, 1.60 (6H, *gem* methyls), 3.80 (3H, ArOCH_3), 4.40 (3H, ArCH_2NHR, ArC*H*R) ppm.

4-(4-Chlorophenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-7-isoquinolamine (**3n**).

A solution of 17.0 g. (0.056 mole) of α-[1-[[(3-aminophenyl)methyl]-amino]-1-methylethyl]-4-chlorobenzenemethanol (**8i**) in 50 ml. of concentrated sulfuric acid was allowed to stand for 20 hours at 23°. The contents were poured onto ice, made basic with sodium hydroxide, and extracted twice with 250 ml. of ethyl acetate. The extracts were washed, dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from diethyl ether gave 12.1 g. (75% yield) of **3n** as off-white crystals of analytical purity, m.p. 115-116°; uv (ethanol): λ max nm (ε) 295 (1600); ir (chloroform): 3480, 3400, 3200 (NH) cm^{-1}; pmr (deuteriochloroform): δ 0.88, 1.22 (6H, *gem* methyls), 3.50 (3H, broad, ArNH_2, ArCH$_2$N*H*R, deuterium oxide-exchangeable), 3.70 (1H, ArC*H*Ar), 4.10 (2H, ArCH_2NHR) ppm.

6-Chloro-4-(3-chlorophenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-7-isoquinolamine Hydrochloride (**3o**).

Polyphosphoric acid (50 ml.) was heated to 95°. α-[1-[[(3-Amino-4-chlorophenyl)methyl]amino]-1-methylethyl]-3-chlorobenzenemethanol [**8k**, 13.0 g. (0.038 mole)] was added portionwise with stirring and the solution was heated at 150° for 3 hours. The contents were poured onto ice, made basic with sodium hydroxide, and extracted twice with 200 ml. of ethyl acetate. The combined extracts were washed, dried over sodium chloride and concentrated to 200 ml. At this point dry hydrogen chloride was passed through the solution to *p*H 2.0 and the crude hydrochloride (6.3 g., m.p. 245-247° dec.) was collected by filtration. Recrystallization from 2-propanol gave 4.5 g. (30% yield) of **3o** as a monohydrochloride of analytical purity, m.p. 349-350° dec.; uv (ethanol): λ max nm (ε) 212 (46,600), 247 (11,600), 305 (2800); pmr (DMSO-d_6): δ 1.10, 1.30 (6H, *gem* methyls), 4.20 (3H, ArC*H*Ar and ArCH_2NHR), 5.40 (2H, broad, ArNH_2), 9.90 (2H, ArCH$_2$N$\overset{+}{H}_2$R) ppm.

1,2,3,4-Tetrahydro-*N,N*-3,3-tetramethyl-4-phenyl-6-isoquinolinamine (**3p**).

A solution of 12.0 g. (0.02 mole) of α-[1-[[[(4-dimethylamino)phenyl]-methyl]amino]-1-methylethyl]benzenemethanol (**8j**) in 60 ml. of concentrated sulfuric acid was allowed to stand for 20 hours at 23°. The yellowish solution was poured onto ice, made basic with ammonium hydroxide, and extracted twice with 200 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate, and evaporated *in vacuo*. The residue was crystallized from 2-propanol giving 8.1 g. (72% yield) of analytically pure, white crystals of **3p**, m.p. 104-105°; uv (ethanol): λ max nm (ε) 208 (32,850), 259 (11,250), 302-312 plateau (2100); pmr (deuteriochloroform): δ 0.82, 1.21 (6H, *gem* methyls), 1.62 (N*H*, deuterium oxide-exchangeable), 2.78 [6H, H(CH_3)$_2$], 3.70 (ArC*H*Ar), 408 2H, ArCH_2N) ppm.

1,2,3,4-Tetrahydro-*N,N*-2,3,3-pentamethyl-4-phenyl-6-isoquinolamine (**3q**).

A solution of 6.0 g. (0.0216 mole) of **3p** in 18 ml. of 88% formic acid and 6.0 ml. of 37% formaldehyde was refluxed for 3 hours. After the solution was evaporated *in vacuo*, the residue was taken up with ice, made basic with ammonium hydroxide, and extracted twice with 75 ml. of ethyl acetate. The extracts were washed, dried over sodium sulfate, and evaporated *in vacuo* to dryness. Two recrystallizations from 2-propanol gave 4.6 g. (73% yield) of **3q** as light yellow crystals, m.p. 78-79°; uv (ethanol): λ max nm (ε) 208 (29,550), 257 (11,800), 304-311 plateau (2200); pmr (deuteriochloroform): δ 0.88, 1.05 (6H, *gem* methyls), 2.31 [3H, 2-(N-CH_3)], 2.72 [6H, Ar-N(CH_3)$_2$] ppm.

1,2,3,4-Tetrahydro-2,2-dimethyl-1-phenylbenz[*f*]isoquinoline (**3r**). Method B.

A stirred solution of 52.0 g. (0.17 mole) of α-[1-methyl-1[(2-naphthalenylmethyl)amino]ethyl]benzenemethanol (**8l**) in 250 ml. of polyphosphoric acid was heated at 110° for 1 hour, poured onto ice, made basic with sodium hydroxide, and extracted twice with 400 ml. of ethyl acetate. The combined extracts were washed, dried over sodium chloride, and concentrated to *ca.* 250 ml. giving 35.3 g. (74% yield) of **3r** as white crystals of analytical purity, m.p. 139-140°; uv (ethanol): λ max nm (ε) 228 (68,000), 280 (6500); pmr (deuteriochloroform): δ 0.90, 1.30 (6H, *gem* methyls), 1.81 (1H, N*H*), 4.35 (3H, ArC*H*Ar, ArCH_2NHR) ppm.

1,2,3,4-Tetrahydro-2,3,3-trimethyl-1-phenylbenz[*f*]isoquinoline (**3s**).

A solution of 8.0 g. (0.028 mole) of **3r** in 35 ml. of 97% formic acid and 10 ml. of 37% formaldehyde was refluxed for 2 hours. After the addition of 75 ml. of 10% hydrochloric acid, the solution was heated for 30 minutes at 100°, poured onto ice, and made basic with ammonium hydroxide. The product was extracted twice with 150 ml. of ethyl acetate, the extracts were washed, dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from 2-propanol gave 4.6 g. (55% yield) of **3s** as white crystals of analytical purity, m.p. 105-106°; uv (ethanol): λ max nm (ε) 223 (61,500), 280 (7500); pmr (deuteriochloroform): δ 0.95, 1.05 (6H, *gem* methyls), 2.30 (3H, NCH_3), 3.90 (1H, ArC*H*Ar), 4.15 (2H, g., J = 8.0 Hz, ArCH_2N) ppm.

1,2,3,4-Tetrahydro-3,3-dimethyl-4-phenylbenz[*h*]isoquinoline Hydrochloride (**3t**).

α-[1-Methyl-1-[(1-naphthalenyl)amino]ethyl]benzenemethanol [**8n**, 20.4 g. (0.068 mole)] was dissolved in 200 ml. of polyphosphoric acid at 100° and the heating (with stirring) was continued for 1 hour. The solution was poured onto ice, made basic with sodium hydroxide, and extracted twice with 300 ml. of ethyl acetate. The extract was washed, dried over sodium sulfate, and evaporated *in vacuo*. To the residue, dissolved in 150 ml. of 2-propanol, was added dry hydrogen chloride to *p*H 2.0 to give, on standing at room temperature, 15.0 g. (68% yield) of **3t** hydrochloride as off-white crystals of analytical purity, m.p. 287-288° dec.; pmr (DMSO-d_6): δ 1.25, 1.50 (6H, *gem* methyls), 4.60 (1H, ArC*H*Ar), 4.85 (2H, ArCH_2N), 10.25, 10.60 (2H, ArCH$_2$N*H*, *H*Cl) ppm.

1,2,3,4-Tetrahydro-2,3,3-trimethyl-4-phenylbenz[*h*]isoquinoline (**3u**).

A solution of 8.0 g. (0.028 mole) of **3t** in 30 ml. of 87% formic acid and 15 ml. of 36% formaldehyde was refluxed for 2 hours and then for 30 minutes after the addition of 50 ml. of 10% hydrochloric acid. The solution was poured onto ice, made basic with ammonium hydroxide, and extracted twice with 200 ml. of dichloromethane. The combined extracts were washed, dried over sodium sulfate and evaporated to dryness. Crystallization of the residue from 2-propanol gave 6.5 g. (77% yield) of **3u** as off-white crystals, m.p. 119-120°; uv (ethanol): λ max nm (ε) 230 (81,000); pmr (deuteriochloroform): δ 0.95, 1.15 (6H, *gem* methyls), 2.50 (3H, N-CH_3), 3.90 (1H, ArC*H*Ar), 4.25 (2H, q, J = 14.0 Hz, ArCH_2N) ppm.

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

A stirred solution of 10.0 g. (0.028 mole) of α-[1-methyl-1-[(2-naphthalenyl)amino]ethyl]-2-naphthalenemethanol (**8m**) in 50 ml. of polyphosphoric acid was heated at 100° for 30 minutes. The contents were poured onto ice, made basic with sodium hydroxide, and extracted twice with 250 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate, and evaporated *in vacuo*. Two crystallization of the residue from 2-propanol gave 4.7 g. (50% yield) of **3v** as off-white crystals of analytical purity, m.p. 174-175°; uv (ethanol): λ max nm (ε) 224 (115,000), 270-282 plateau (12,000); pmr (deuteriochloroform): δ 1.00, 1.40 (6H, *gem* methyls), 1.92 (1H, ArCH$_2$N*H*R, deuterium oxide-exchangeable), 4.45 (2H, ArCH_2N), 4.55 (1H, ArC*H*Ar) ppm.

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