Substituted 2,3,4,5-Tetrahydro-1*H*-3-benzazepine and 2,3,4,5-Tetrahydro-1*H*-naphth[1,2-*d*]azepine Derivatives

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The multi-step synthetic procedures to prepare a number of 2,3,4,5-tetrahydro-1*H*-benzazepine derivatives **1** through a series of intermediates are described. The condensation of arylaldehydes **2** with 2-nitropropanes **3** gave nitroalcohols **4** which were reduced to alcohol amines **5**. The condensation of **5** with arylacetaldehydes **6** gave imino derivatives **7** which on reduction with borohydride gave secondary amines **8**. By employing different methods, alcohol amines **5** were condensed with arylacetic acids **9** to give amides **10** which were then reduced to amines **8**. On treatment with mineral acids, amines **8** were cyclized to the target compounds **1**. Biological activities of **1** are also briefly discussed.

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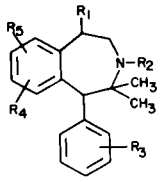
In this paper, we are describing synthetic methods towards the target compounds of the general formula **1**



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using simple or readily obtainable starting materials and intermediates. One method represented an improved procedure of Hays and Vithal Shetty (1) in which aromatic aldehydes **2** are condensed with 2-nitropropane (**3**) in the presence of sodium alkoxide giving nitroalcohols **4** (Table I). Some of the nitroalcohols (*e.g.*, **4e**, **4f**) in Table I were obtained indirectly by the selectively controlled catalytic hydrogenation of dinitro alcohol **4d** (since hydrogenation of the aromatic nitro group to the anilino derivative is very rapid and that of aliphatic one is rather slow).

The aryl nitroalcohols **4** are characterized by the nonequivalency of the *gem*-methyl groups with the resonance peaks separated by 0.1 to 0.3 ppm.

The reduction of nitroalcohols **4** with excess zinc (1) in glacial acetic acid or catalytically gave α-(1-amino-1-methylethyl)arylmethanols **5** in 70 to 85% yields (Table II).

The condensation of alcohol amines **5** with arylacetaldehydes **6** under azeotropic conditions gave the corresponding imino derivatives **7**, which, being usually semi-solids, were not characterized but reduced by borohydride directly to the secondary amines **8** (Table III).

When the properly substituted aldehydes were not available, the alternative route was used in which substituted arylacetic acids **9** are condensed with alcohol amines **5** to give amides **10** (Table IV). Reduction

Scheme I

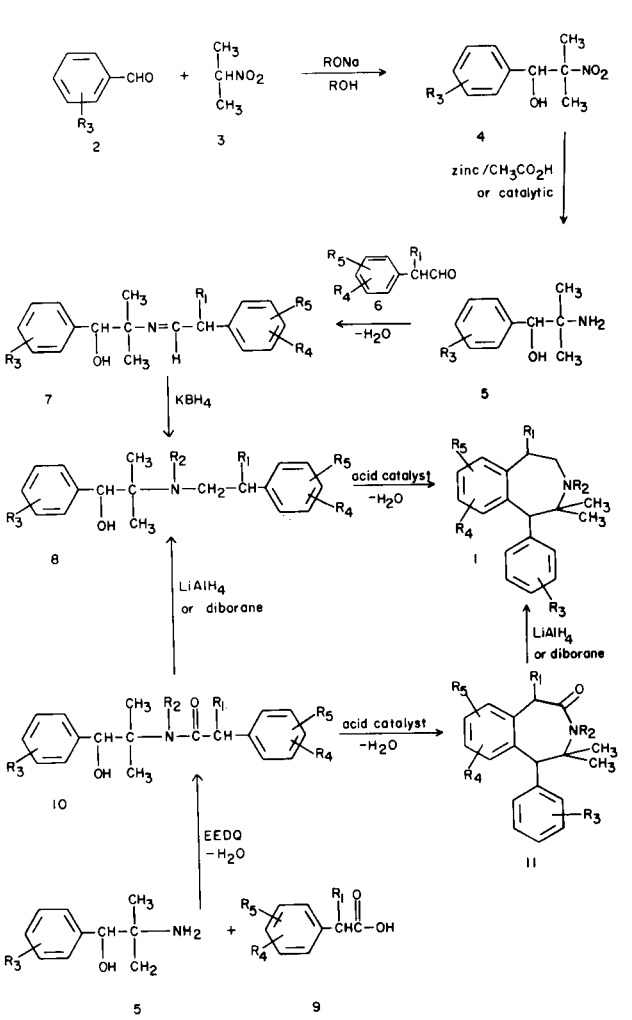

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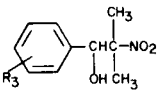
Table I

α-(1-Methyl-1-nitroethyl)arylmethanols **4**

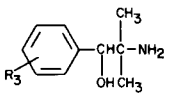


4	R_3	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4a	H	66-67 (a)	58 (b)	$C_{10}H_{13}NO_3$	61.52	6.71	7.18	61.48	6.72	7.16
4b	3-OCH_3	54-55	64	$C_{11}H_{15}NO_4$	58.65	6.71	6.22	58.59	6.66	6.41
4c	3-Cl	90-91	40 (c)	$C_{10}H_{12}ClNO_3$	52.30	5.27	6.10	52.20	5.30	6.03
4d	3-NO_2	155-156	91	$C_{10}H_{12}N_2O_5$	50.00	5.04	11.66	50.00	5.13	11.56
4e	3-NH_2	158-159 (d)	81	$C_{10}H_{14}N_2O_3$	57.13	6.71	13.32	57.00	6.77	13.16
4f	3-$NHCOCH_3$	157-158 (d)	82	$C_{12}H_{16}N_2O_4$	57.13	6.39	11.10	57.08	6.45	11.21

(a) Reference (1) m.p. 68-70°; (b) Reference (1) 12.8%. (c) Due to difficulty of crystallization, a considerable abount of **4c** (about 30% remained in the mother liquor. (d) Melts with decomposition.

Table II

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



5	R_3	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
5a	H	101-102 (a)	81 (b)	$C_{10}H_{15}NO$	72.69	9.15	8.48	72.57	9.09	8.49
5b	3-OCH_3	93-94	76	$C_{11}OH_{17}NO_2$	67.66	8.78	7.17	67.69	8.97	6.99
5c	3-Cl	97-98	78	$C_{10}H_{14}ClNO$	60.15	7.07	7.02	60.17	7.11	6.86
5d	3-NH_2	107-108	32	$C_{10}H_{16}N_2O$	66.63	8.95	15.54	66.68	9.06	15.59
5e	3-$NHCOCH_3$	147-148	73	$C_{12}H_{18}N_2O_2$	64.84	8.16	12.60	64.87	8.09	12.49

(a) Reference (1) m.p. 96-99°; (b) References (1) 46.5% yield.

of amides **10** with lithium aluminum hydride or diborane gave amines **8**. By employing acidic cyclizing agents, like concentrated sulfuric acid, methanesulfonic acid or polyphosphoric acid (PPA), the secondary amines **8** were converted into corresponding 2,3,4,5-tetrahydro-1*H*-3-benzazepines and 2,3,4,5-tetrahydro-1*H*-naphth[1,2-*d*]-azepines of formula **1** (2) (Table V) in the temperature range of 25 to 135°. The nitrogen substituent (R_2) was usually introduced after the cyclization step was complete.

Occasionally, the amides **10** were first cyclized with acidic agents to the 7-membered ring lactams **11** which were then reduced to compounds of formula **1**. The synthetic sequence of reactions is presented in Scheme I.

Compounds of formula **1** were found to exhibit anti-arrhythmic activity in an ouabain-induced arrhythmia (3) and the coronary ligated Harris dog (**4**) in the range at about 3 to 15 mg./kg. The best activity was shown by 2,3,4,5-tetrahydro-7,8-dimethoxy-1-(3-methoxyphenyl)-2,2-dimethyl-1*H*-3-benzazepine hydrochloride (**1i**) and 2,3,4,5-tetrahydro-3,4,4-trimethyl-5-phenyl-1*H*-naphth-[1,2-*d*]azepine (**1k**) which were active at 3 mg./kg. in the ouabain-induced arrhythmia test and 10 mg./kg. in the coronary ligated Harris dog test.

The basic nitrogen in compounds of formula **1** is absolutely necessary for activity, since the formation of amides (**1c** and **1e**) or urea (**1d**) rendered inactive products.

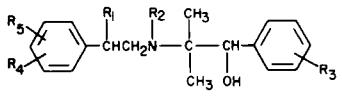
The sequence of reactions is presented in Scheme I.

EXPERIMENTAL

Physical constants, yields, and analytical values for the compounds below are reported in Tables I-V. 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

Table III

α-[1-[(2-Arylethyl)amino]-1-methylethyl]arylmethanols **8**

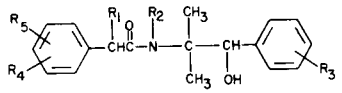


									Calcd.			Found		
8	R_1	R_2	R_3	R_4	R_5	M.p. °C	% Yield	Empirical Formula	C	N	N	C	H	N
8a	H	H	H	H	H	105-106	78	$C_{18}H_{23}NO$	80.26	8.61	5.20	80.50	8.77	5.28
8b		H	H	H	H	236-237 (d)	65	$C_{24}H_{27}NO.HCl$	75.47	7.39	3.67	75.38	7.42	3.70
8c	H	H	H	3-OCH_4	4-OCH_3	125-126	85	$C_{20}H_{27}NO_3$	72.92	8.26	4.25	73.20	8.18	4.12
8d	H	H	3-OCH_3	3-OCH_3	4-OCH_3	185-186 (d)	39	$C_{21}H_{29}NO_4 \cdot H$	63.71	7.64	3.54	63.97	7.87	3.58
8e	H	H	H	H	4-OCH_3	111-112	82	$C_{19}H_{25}NO_2$	76.22	8.42	4.68	76.03	8.43	4.73
8f	H	H	H	R_4, R_5 = 2,3-		241-242 (d)	74	$C_{22}N_{25}NO \cdot HCl$	74.25	7.36	3.94	74.09	7.43	3.85
8g	H	H	H	2-NH_2	H	110-111	61	$C_{18}H_{24}N_2O$	76.02	8.51	9.85	75.92	8.55	9.84
8h	H	CH_3	H	H	H	206-207	74	$C_{19}H_{25}NO$	71.34	8.19	4.38	71.53	8.17	4.38
8i	H	H	H	H-NHC_2H_5	H	99-100	56	$C_{20}H_{28}N_2O$	76.88	9.03	8.97	76.59	9.06	9.05

(d) Melts with decomposition.

Table IV

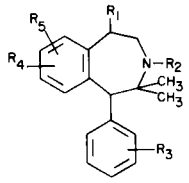
N-(2-Aryl-2-hydroxy-1,1-dimethylethyl)arylacetamides **10**

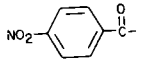
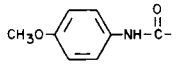
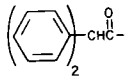


									Calcd.			Found		
10	R_1	R_2	R_3	R_4	R_5	M.p. °C	% Yield	Empirical Formula	C	H	N	C	H	N
10a	H	H	H	3-OCH_3	4-OCH_3	123-124	81	$C_{20}H_{25}NO_4$	69.95	7.33	4.08	70.20	7.23	4.22
10b	H	H	3-OCH_3	3-OCH_3	4-OCH_3	99-100	72	$C_{21}H_{27}NO_5$	67.54	7.29	3.75	67.26	7.31	3.82
10c	H	H	H		4-NO_2	180-181	55	$C_{18}H_{20}N_2O_4$	65.84	6.14	8.53	65.73	6.01	8.59
10d	H	H	H	H	4-NH_2	140-141	63	$C_{18}H_{22}N_2O_2$	72.45	7.43	9.39	72.43	7.61	9.55
10e	H	H	H	H	4-Cl	121-122	82	$C_{18}H_{20}NO_2Cl$	68.03	6.34	4.41	68.06	6.34	4.49
10f	H	H	H	R_4, R_5 = 2,3-		106-107	77	$C_{22}H_{23}NO_2$	79.25	6.95	4.20	79.19	7.10	4.23
10g	H	H	H	H	2-NH_2	127-128	69	$C_{18}H_{22}N_2O_2$	72.45	7.43	9.39	72.37	7.53	9.26

Table V

5-Aryl-2,3,4,5-tetrahydro-4,4-dimethyl-1*H*-3-benzazepines **1**



1	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
1a	H	H	H	H	H	99-100	66	$C_{18}H_{21}N$	86.01	8.42	5.57	85.76	8.43	5.60
1b	H	CH_3	H	H	H	92-93	76	$C_{19}H_{23}N$	85.98	8.72	5.28	85.94	8.88	5.47
1c	H		H	H	H	163-164	47	$C_{25}H_{24}N_2O_3$	74.98	6.04	7.00	74.82	6.18	6.92
1d	H		H	H	H	146-147	55	$C_{26}H_{28}N_2O_2$	77.97	7.05	7.00	77.67	7.14	6.92
1e	H		H	H	H	119-120	85	$C_{32}H_{31}NO$	86.25	7.01	3.14	86.20	7.09	3.13
1f		H	H	H	H	147-148	75	$C_{24}H_{25}N$	88.03	7.70	4.28	87.85	7.96	4.23
1g		CH_3	H	H	H	137-138	86	$C_{25}H_{27}N$	87.93	7.97	4.10	87.97	7.83	4.03
1h	H	H	H	7-OCH_3	8-OCH_3	286-287 (d)	58	$C_{20}H_{25}NO_2$·HCl	69.05	7.53	4.03	68.76	7.71	4.28
1i	H	H	3-OCH_3	7-OCH_3	8-OCH_3	285-286 (d)	53	$C_{21}H_{27}NO_3$·HCl	66.74	7.47	3.71	66.67	7.55	3.59
1j	H	H	H	7-OH	H	209-210 (d)	27	$C_{18}H_{21}NO$	80.86	7.92	5.24	80.70	7.98	5.51
1k	H	CH_3	H	R_4, R_5 = 8,9-		140-141	26	$C_{23}H_{25}N$	87.57	7.99	4.44	87.63	8.20	4.30
1l	H	H	H	7-NH_2	H	73-74	21	$C_{18}H_{22}N_2$	81.16	8.33	10.52	80.95	8.37	10.48

(d) Melts with decomposition.

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. No attempts were made to resolve the *d,l* mixtures of compounds **1** into optical isomers.

Preparation of α-(1-Methyl-1-nitroethyl)arylmethanols **4** (Table I).

This general procedure illustrates the preparation of compounds **4a** to **4c**.

α-(1-Methyl-1-nitroethyl)benzenemethanol (**4a**).

To a stirred solution of 81.0 g. (1.5 moles) of sodium methoxide (Ventron Co., 97%) in 500 ml. of methanol was added 178.0 g. of 2-nitropropane dropwise at 25° over a period of 30 minutes and allowed to stir for additional 15 minutes. While the temperature of the reaction flask was maintained at 0 to 5°, 105.0 g. (1.0 mole) of benzaldehyde (chlorine-free, Aldrich Co.) was added over 30 minutes and the reaction mixture was continued to stir for 20 hours at room temperature. Glacial acetic acid was added at 20° to *p*H 6.6 and the solvent and excess 2-nitropropane were removed *in vacuo*. The resulting white residue was taken up with water and extracted twice with 500 ml. of dichloromethane. The combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate and evaporated *in vacuo*. The oily residue was taken up with 200 ml. of hot cyclohexane-skelly B (1:1) and, after standing overnight at 5°, 86.4 g. of pure nitroalcohol **4a** was collected. The filtrate was evaporated to dryness, taken up with 100 ml. of dichloromethane and a solution of 60 g. of sodium bisulfite in 150 ml. of water. The two-phase solution was stirred for 90 minutes, the aldehyde-bisulfite complex was filtered through the coarse funnel and washed with dichloromethane. The two layers of the filtrate were separated, the organic phase was dried over sodium sulfate and evaporated. The oily residue (now practically free from benzaldehyde) was directly crystallized from cyclohexane giving 26.1 g. of additional product **4a** (total yield, 58%), m.p. 66-67°; uv λ max (ethanol): nm (ε) 256 (360); 264 (340); ir (nujol): 3600 (OH), 1540, 1350, (NO_2) cm^{-1}; ir (chloroform): 3580 (OH), 1548, 1350 (NO_2) cm^{-1}; pmr (deuteriochloroform): δ 1.43, 1.58 (6H, non-equivalent methyl groups), 2.61 (1H, d, J = 4.0 Hz, O*H*, deuterium oxide-exchangeable), 5.23 (1H d, J = 4.0 Hz, C*H*OH), 7.24 (5H, s, aromatic protons) ppm.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.48; H, 6.72; N, 7.16.

The bisulfite treatment was also applied to compounds **4b** and **4c**. In case of compound **4d** (3-nitro), it was not necessary since the formation of **4d** was quantitative.

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

A solution of 24.0 g. (0.1 mole) of α-(1-methyl-1-nitroethyl)-3-nitrobenzenemethanol (**4d**) in 100 ml. of tetrahydrofuran, 30 ml. of ethanol and 20 ml. of glacial acetic acid was hydrogenated over 2.0 g. of 10% palladium-on-charcoal using a Paar hydrogenation apparatus until the uptake of 3 molar equivalents of hydrogen ceased temporarily (1 hour). The thin layer chromatography (tlc; silica gel, methanol-acetonitrile, 1:3) showed one slower moving spot (Rf = 0.45) than that of starting dinitro derivative (Rf = 0.52). After the catalyst was filtered off, the filtrate was evaporated to dryness *in vacuo*. The solid residue was triturated with hot ethyl acetate to give, on cooling, 18.3 g. of off-white crystals, m.p. 151-153°. Recrystallization from acetonitrile gave 17.2 g. (82% yield) of 3-amino-α-(1-methyl-1-nitroethyl)benzenemethanol derivative **4e**, m.p. 158-159°, dec.; uv λ max (ethanol): nm (ε) 235 (9400), 292 (2050); ir (potassium bromide): 3520 (OH) 3400, 3320, 3180, 1605 (NH_2), 1540, 1350 (NO_2) cm^{-1}; pmr (DMSO-d_6): δ 1.34, 1.44 (6H, non-equivalent *gem*-methyls), 4.90 (1H, d, J = 4.5 Hz, C*H*OH), 5.00 (2H, s, N*H*$_2$), 5.83 (1H, d, J = 4.5 Hz, CHO*H*), 6.38-6.68 (3H, m, 3 aromatic protons), 6.82-7.03 (1H, m, 5-H aromatic proton) ppm.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.00; H, 6.77; N, 13.16.

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

The preparation of α-(1-amino-1-methylethyl)benzenemethanol (**5a**) illustrates general methods to obtain compounds of type **5**.

Method A.

To a vigorously stirred solution of 30.0 g. (0.154 mole) of α-(1-methyl-1-nitroethyl)benzemethanol (**4a**) in 350 ml. of glacial acetic acid was added 100 g. of zinc dust portionwise at 20-25° (ice-water cooling) over a period of 20 minutes. After 16 hours of stirring at room temperature, additional quantity of 20 g. of zinc was added and continued to stir for three hours. The subsequent tlc (methanol-acetonitrile, 1:1) showed complete reaction, the new amino derivative having slower mobility (Rf = 0.18) than the starting nitro compound (Rf = 0.6). The solid was filtered off, washed with acetic acid, and the filtrate was evaporated *in vacuo*. The residue was taken up with ice, made basic with concentrated sodium hydroxide and extracted twice with 300 ml. of ethyl acetate. The combined extracts were washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated to about 40 ml. After 20 hours at room temperature 20.5 g. (81% yield) of pure α-(1-amino-1-methylethyl)-benzemethanol (**5a**) was obtained as white crystals, m.p. 101-102°. [Lit. (1), m.p. 96-99°]; uv λ max (ethanol): nm (ε) 221 (12,000), 251-267 plateau (320); ir (chloroform): 3630 (OH), 3430-3380, 1602, 1559 (NH_2) cm^{-1}; pmr (deuteriochloroform): δ 0.91, 1.12 (6H, nonequivalent *gem*-methyl groups), 2.22 (3H, s, O*H* and N*H*$_2$, deuterium oxide-exchangeable), 4.29 (1H, s, C*H*OH), 7.22 (5H, aromatic protons) ppm.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.57; H, 9.09; N, 8.49.

Method B.

A solution of 9.75 g. (0.05 mole) of **4a** in 60 ml. of ethanol and 20 ml. of glacial acetic acid was hydrogenated over 1.5 g. of 10% palladium-on-charcoal using a Paar hydrogenation apparatus and 48 psi for 2 days. After the catalyst was filtered off, the solution was evaporated *in vacuo*. The residue was made basic with ammonium hydroxide at 0° and extracted twice with 150 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and evaporated under reduced pressure. Crystallization of the residue from ethyl acetate-isopropyl ether (2:1) gave 6.3 g. (75% yield) of **5a**, m.p. 101-102°. This product is identical in all respects with one obtained by Method A.

3-Amino-α-(1-amino-1-methylethyl)benzenemethanol (**5d**).

To a rapidly stirred suspension of 15.0 g. (0.0625 mole) of α-(1-methyl-1-nitroethyl)-3-nitrobenzenemethanol (**4d**) in 250 ml. of glacial acetic acid was added 40 g. of zinc dust over a period of 30 minutes. After the mixture was stirred for 20 hours at room temperature, 20 g. of zinc was added and continued to stir for 24 hours. The thin layer chromatography (methanol-acetonitrile, 4:1) showed complete reaction, the new diamino derivative having much slower mobility (Rf = 0.15) than the starting **5d**

(Rf = 0.7). The unreacted zinc and salts were removed by filtration and the filtrate was evaporated *in vacuo* at 30°. The residue was taken up with ice, made basic with ammonium hydroxide and extracted twice with 250 ml. of ethyl acetate. The aqueous layer was saturated with sodium chloride and re-extracted with 150 ml. of 1-butanol. The combined extracts were dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was taken up with 100 ml. of hot ethyl acetate, filtered and concentrated to a low volume to give 5.6 g. of off-white crystals m.p. 105-108°. Recrystallization from ethyl acetate-isopropyl ether gave 4.3 g. (32%) of pure 3-amino-α (1-amino-1-methylethyl)benzenemethanol (**5d**) as off-white crystals, m.p. 108-109°; uv λ max (ethanol): nm (ε) 236 (8050), 288(1850); ir(nujol): 3500 (OH), 3370, 3220 (NH), 1635, 1605, 1588; (chloroform): 3620 (OH), 3500 sh, 3400 (NH), 1625 (NH_2); pmr (DMSO-d_6): δ 0.81, 0.90 (6H, nonequivalent *gem*-methyls), 1.10-1.80 (3H, broad, CHO*H* and aliphatic NH_2, deuterium oxide-exchangeable), 4.05 (1H, s, C*H*OH), 4.82 (2H, s, aromatic NH_2, deuterium oxide-exchangeable), 6.30-6.58 (3H, m, aromatic), 6.78-6.96 (1H, m, 5-H aromatic) ppm.

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54. Found: C, 66.68; H, 9.06; N, 15.59.

1-Aryl-2,3,4,5-tetrahydro-4,4-dimethyl-1*H*-benzazepines and 2,3,4,5-Tetrahydro-3,4,4-trimethyl-5-phenyl-1*H*-naphth[1,2-*d*]azepine **1** (Table V).

The imino derivatives (Schiff bases of type **7**) were not isolated but reduced directly by potassium borohydride to the secondary amines **8**. Both the amines **8** (Table III) and amides **10** (Table IV) are described as part of the preparation of target compounds **1** (Table V) and are identified by names and numbers. Physical and spectral data are also given in experimental procedures.

2,3,4,5-Tetrahydro-2,2-dimethyl-1-phenyl-1*H*-3-benzazepine **1a** (Table V).

A solution of 6.6 g. (0.03 mole) of α-(1-amino-1-methylethyl)-benzenemethanol (**5a**) and 4.8 g. (0.03 mole) of benzeneacetaldehyde in 75 ml. of benzene was refluxed for 1 hour while 0.7 ml. of water separated in a Dean-Stark trap. The infrared absorption spectrum showed absence of C=O function and presence of strong C=N band at 1650 cm^{-1}. The solvent was removed *in vacuo*. The residue of the imino derivative was taken up with 60 ml. of methanol and added (with stirring) 1.6 g. of potassium borohydride at 20-25°. After 20 hours the solution was evaporated *in vacuo*. The residue was taken up with cold water, and the resulting crystalline product (6.8 g., 85% crude yield, m.p. 103-104°) was collected by filtration. Recrystallization from methanol gave pure α-(1-methyl-1-[(2-phenylethyl)amino]-ethyl]benzenemethanol (**8a**, Table III) as white crystals, m.p. 105-106°; uv λ max (ethanol): nm (ε) 2065 (8840), 252 (290), 256 (350), 264 sh (265); ir (chloroform): 3340 (NH,OH), 1043 (OH) cm^{-1}; pmr (deuteriochloroform): δ 0.87, 1.10 (6H, nonequivalent *gem*-methyls) ppm.

Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.50; H, 8.77; N, 5.28.

This product **8a** (13.5 g., 0.05 mole) was dissolved in 40 ml. of concentrated sulfuric acid with external cooling and allowed to stand 48 hours at room temperature. The yellowish syrupy solution was poured onto crushed ice, made basic with sodium hydroxide and extracted twice with 200 ml. of ethyl acetate. The combined organic extracts were washed, dried over sodium sulfate and evaporated *in vacuo*. The residual cake was triturated with hot 2-propanol to give, on cooling, 8.3 g. (66% yield) of 2,3,4,5-tetrahydro-2,2-dimethyl-1-phenyl-1*H*-3-benzazepine (**1a**) as white crystals, m.p. 99-100°. An analytical sample, also melting at 99-100°, was obtained by recrystallization from isopropyl ether; uv λ max (ethanol): nm (ε) 259 (410); pmr (deuteriochloroform): δ 1.10, 1.22 (6H, nonequivalent *gem*-methyls, 1.55 (NH), 4.15 (1H, ArC*H*) ppm.

Anal. Calcd. for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.76; H, 8.43; N, 5.60.

2,3,4,5-Tetrahydro-2,3,4-trimethyl-1-phenyl-1*H*-3-benzazepine (**1b**).

A solution of 2,3,4,5-tetrahydro-2,2-dimethyl-1-phenyl-1*H*-3-benzazepine (**1a**) (7.54 g., 0.03 mole) and 15 ml. of 36% aqueous formaldehyde in 25 ml. of 90% formic acid was refluxed for 8 hours. After the solution was concentrated to a low volume, ice and potassium carbonate were added to *p*H 8.5 and extracted twice with 50 ml. of ethyl acetate. The combined organic extracts were washed, dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from 2-propanol gave 6.0 g. (75% yield) of pure product **1b** as white crystals, m.p. 92-93°; uv λ max (ethanol): nm (ε) 254-260, plateau (620); pmr (deuteriochloroform): δ 0.90, 1.22 (6H, *gem*-methyls) 2.47 (3H, N-CH_3), 4.12 (1H, ArC*H*) ppm

Anal. Calcd. for $C_{19}H_{23}N$: C, 85.98; H, 8.74; N, 5.28. Found: C, 85.94; H, 8.88; N, 5.47.

2,3,4,5-Tetrahydro-2,2-dimethyl-3-(4-nitrobenzoyl)-1-phenyl-1*H*-3-benzazepine (**1c**).

To a vigorously stirred solution of 6.3 g. (0.025 mole) of 2,3,4,5-tetrahydro-2,2-dimethyl-1-phenyl-1*H*-3-benzazepine (**1a**) and 10 ml. of 15% sodium hydroxide in 50 ml. of dichloromethane was added a solution of 5.1 g. (10% excess) of 4-nitrobenzoyl chloride in 100 ml. of dichloromethane over 20 minutes at 0°. After an additional stirring for 40 minutes, the two layers were separated; the organic phase was washed, dried over sodium sulfate and evaporated. Trituration of the residue with hot 2-propanol and cooling gave 4.7 g. (47% yield) of **1c** as white crystals, m.p. 162-163°. An analytical sample, m.p. 163-164°, was obtained by recrystallization from 2-propanol-ethyl acetate; uv λ max (ethanol): nm (ε) 267 (9450); ir (nujol): 1640 (C=O) 1520 (NO_2) cm^{-1}.

Anal. Calcd. for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 74.82, H, 6.18; N, 6.92.

1,2,4,5-Tetrahydro-*N*-(4-methoxyphenyl)-2,2-dimethyl-1-phenyl-3*H*-3-benzazepine-3-carboxamide (**1d**).

A solution of 5.03 g. (0.02 mole) of 2,3,4,5-tetrahydro-2,2-dimethyl-1-phenyl-1*H*-3-benzazepine (**1a**) and 4.4 g. (0.022 mole) of 4-methoxyphenyl isocyanate and 2 drops of triethylamine in 50 ml. of dry tetrahydrofuran was refluxed for 3 hours and then evaporated to dryness *in vacuo*. The resulting cake was crystallized from acetonitrile to give 3.7 g. (55% yield) of pure product **1d** as white crystals, m.p. 146-147°; uv λ max (ethanol): nm (ε) 239 (17,600), 276-288 plateau (2000) ir (chloroform): 3400 (NH), 1658 (C=O), 1503 (CONH) cm^{-1}; pmr (deuteriochloroform): δ 1.50 (6H, equivalent *gem*-methyls), 3.70 (3H, OCH_3), 4.53 (1H, ArC*H*) ppm.

Anal. Calcd. for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05; N, 7.00. Found: C, 77.67; H, 7.14; N, 6.92.

3(Diphenylacetyl)-2,3,4,5-tetrahydro-2,2-dimethyl-1-phenyl-1*H*-3-benzazepine (**1e**).

To a rapidly stirred solution of 7.0 g. (0.0278 mole) of 2,3,4,5-tetrahydro-2,2-dimethyl-1-phenyl-1*H*-3-benzazepine (**1a**) and 10 ml. of 12% aqueous sodium hydroxide in 75 ml. of dichloromethane was added a solution of 9.3 g. (0.04 mole) of diphenylacetyl chloride (Organic/Inorganic Chemical Corp.) in 65 ml. of

the same solvent over 1 hour at 5°. After an additional stirring for 2 hours at 5°, the organic phase was washed, dried over sodium sulfate and evaporated. Crystallization from isopropyl ether gave 11.2 g. (85% yield) of pure product **1e** as white crystals, m.p. 119-120°; uv λ max (ethanol): nm (ε) 260 (1100); ir (chloroform): 1652 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 1.53, 1.66 (6H, *gem*-methyls), 3.09 (2H, t, J = 6.5 Hz, ArCH_2), 3.82 (2H, t, J = 6.5 Hz, CONCH_2), 4.68 (1H, ArC*H*), 5.08 (1H, COC*H*) ppm.

Anal. Calcd. for $C_{32}H_{31}NO$: C, 86.25; H, 7.01; N, 3.14. Found: C, 86.20; H, 7.09; N, 3.13.

2,3,4,5-Tetrahydro-2,2-dimethyl-1,5-diphenyl-1*H*-3-benzazepine (**1f**).

A solution of 19.1 g. (0.1 mole) of α-phenylbenzeneacetaldehyde and 16.5 g. (0.1 mole) of α-(1-amino-1-methylethyl)-benzenemethanol in 180 ml. of dry benzene was refluxed for 2 hours while 1.8 ml. water separated. The infrared spectrum showed absence of the carbonyl function. After benzene was removed *in vacuo*, the residue was taken up with 150 ml. of methanol and treated (stirring) with 5.8 g. of potassium borohydride for 5 hours at 25°. The solution was concentrated to a low volume *in vacuo*. The mixture was treated with cold water and extracted twice with 150 ml. of ether. The combined extracts were washed, dried over sodium sulfate and evaporated. The residue was taken up with 60 ml. of chloroform and treated with dry hydrogen chloride to *p*H 2.5 giving, after cooling, 16.8 g. of white crystals, m.p. 234-235°, dec. Further concentration of the mother liquor to a low volume gave 10.2 g. (68% overall yield) of additional product, m.p. 235-236°, dec. An analytical sample of α-[1-[(2,2-diphenylethyl)amino-1-methylethyl]benzenemethanol hydrochloride (**8b**) was obtained by recrystallization from acetonitrile, m.p. 236-237°, dec.; uv λ max (ethanol): nm (ε) 251 (490), 257 (560), 264, sh (440); ir (nujol): 3330, 3220 (NH, OH).

Anal. Calcd. for $C_{24}H_{27}NO.HCl$: C, 75.47; H, 7.39; N, 3.67. Found: C, 75.38; H, 7.42; N, 3.70.

This amino derivative **8b** (14.0 g., 0.037 mole) was added portionwise to 85 g. of polyphosphoric acid (preheated to 110°) over 45 minutes. Subsequently, the temperature was increased to 135° and maintained at this point for 3 hours to complete the cyclization. The contents were poured onto ice-water, made basic with sodium hydroxide and extracted twice with 300 ml. of methylene chloride. The combined extracts were washed, dried over sodium sulfate and evaporated. Crystallization of the residue from 2-propanol gave 9.9 g. (75% yield) of pure 2,3,4,5-tetrahydro-2,2-dimethyl-1,5-diphenyl-1*H*-3-benzazepine (**1f**), m.p. 147-148°, dec.; uv λ max (ethanol): nm (ε) 252-260 plateau (740), 270 (480); pmr (deuteriochloroform): δ 1.10, 1.20 (6H, *gem*-methyls), 1.73 (NH), 3.43 (2H, d, J = 6.5 Hz, CH_2N), 4.53 (2H, m, ArC*H*) ppm.

Anal. Calcd. for $C_{24}H_{25}N$: C, 88.03; H, 7.70; N, 4.28. Found: C, 87.85; H, 7.96; N, 4.23.

2,3,4,5-Tetrahydro-2,2,3-trimethyl-1,5-diphenyl-1*H*-3-benzazepine (**1g**).

A solution of 6.0 g. (0.0184 mole) of 2,3,4,5-tetrahydro-2,2,3-trimethyl-1,5-diphenyl-1*H*-3-benzazepine (**1f**) and 20 ml. of 37% aqueous formaldehyde in 25 ml. of 70% formic acid was refluxed for 6 hours and then concentrated to a low volume. Ice was added; the mixture was made basic with potassium carbonate and extracted twice with 100 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and evaporated *in vacuo*. The solid residue was crystallized from 2-propanol giving 5.6 g. (86% yield) of analytically pure **1g** as white crystals, m.p. 137-138°; uv λ max (ethanol): nm (ε) 205 (9500), 260 sh (360); pmr (deuteriochloroform): δ 1.08, 1.30 (6H, *gem*-methyls), 2.68 (NCH_3) ppm.

Anal. Calcd. for $C_{25}H_{27}N$: C, 87.93; H, 7.97; N, 4.10. Found: C, 87.97; H, 7.83; N, 4.03.

2,3,4,5-Tetrahydro-7,8-dimethoxy-2,2-dimethyl-1-phenyl-1*H*-3-benzazepine Hydrochloride (**1h**).

A solution of 8.3 g. (0.05 mole) of α-(1-amino-1-methylethyl)-benzenemethanol, 9.8 g. (0.05 mole) of 3,4-dimethoxybenzeneacetic acid and 13.6 g. (0.055 mole) of EEDQ (Aldrich Chem. Co.) in 300 ml. of tetrahydrofuran-ethanol was refluxed for 45 minutes and then allowed to stand for 20 hours at 25°. The solution was evaporated *in vacuo*. The residue was taken up with 250 ml. of ethyl acetate, washed with dilute hydrochloric acid, followed by washing with aqueous sodium bicarbonate. Subsequently, the extract was washed with aqueous sodium chloride, dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from ether gave 14.0 g. (82% yield) of pure *N*-(2-hydroxy-1,1-dimethyl-2-phenylethyl)-3,4-dimethoxybenzeneacetamide (**10a**, Table IV), m.p. 123-124°; ir (chloroform): 3420, 3360 (NH, OH), 1645 (C=O), 1517 (NHCO) cm^{-1}.

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 70.20; H, 7.23; N, 4.22.

To a solution of this amide **10a** (12.0 g., 0.035 mole) was added 50 ml. of 1 molar solution of diborane in tetrahydrofuran dropwise over 30 minutes and allowed to stand for 24 hours. Hydrochloric acid (15 ml.) was added cautiously, and the solution was briefly heated on a steam bath to destroy excess diborane. The solution was concentrated *in vacuo* to a low volume, made basic with sodium hydroxide at 0° and extracted twice with 200 ml. of ethyl acetate. The combined extracts were washed with aqueous sodium chloride, dried over sodium sulfate and concentrated to a low volume giving 9.5 g. (85% yield) of pure α-[1-[[2-(3,4-dimethoxyphenyl)ethyl]amino-1-methylethyl]benzenemethanol (**8c**), m.p. 125-126; uv λ max (ethanol): nm (ε) 215 sh (12,800), 226 sh (9500), 279 (2820), 286 sh (2300); ir (chloroform): 3400 broad (NH, OH) cm^{-1}.

Anal. Calcd. for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.20; H, 8.18; N, 4.12.

The above amino derivative **8c** (8.2 g., 0.025 mole) was dissolved (with external cooling) in 30 ml. of concentrated sulfuric acid and allowed to stand at 25° for 48 hours. The syrupy solution was poured onto ice, made basic with sodium carbonate and extracted twice with 175 ml. of ethyl acetate. The combined extracts were dried over sodium sulfate and evaporated *in vacuo*. To the residue was added 50 ml. of absolute ethanol, and dry hydrogen chloride was introduced to *p*H 2.5. After three days at 25°, 8.1 g. (58% yield) of pure 2,3,4,5-tetrahydro-7,8-dimethoxy-2,2-dimethyl-1-phenyl-1*H*-3-benzazepine hydrochloride (*1h*) as white crystals was obtained, m.p. 286-287°, dec.; uv λ max (ethanol): nm (ε) 235 (7810), 270 sh (1600), 284 (1920).

Anal. Calcd. for $C_{20}H_{25}NO_2.HCl$: C, 69.05; H, 7.53; N, 4.03; Cl^-, 10.19. Found: C, 68.76; H, 7.71; N, 4.28; Cl^-, 10.00.

2,3,4,5-Tetrahydro-7,8-dimethoxy-1-(3-methoxyphenyl)-2,2-dimethyl-1*H*-benzazepine Hydrochloride (**1i**).

A solution of 50.0 g. (0.26 mole) of 3,4-dimethoxybenzeneacetic acid, 68.0 g. (0.28 mole) of EEDQ and 50.0 g. (0.26 mole) of α-(1-amino-1-methylethyl)-3-methoxybenzenemethanol in 450 ml. tetrahydrofuran was stirred for three days at 25°, and then it was heated for 5 hours at 65°. The solvent was removed, the residue was acidified with sulfuric acid at 0° to *p*H 2.0, and the

amide was extracted twice with 500 ml. of ethyl acetate. The combined extracts were washed with dilute potassium bicarbonate, dried over sodium sulfate and evpaorated to dryness *in vacuo*. The semi-solid residue was crystallized from ether giving 70.0 g. (72% yield) of *N*-[2-hydroxy-2-(3-methoxyphenyl)-1,1-dimethyl ethyl]-3,4-dimethoxybenzeneacetamide (**10b**) as white crystals of analytical purity, m.p. 99-100°; uv λ max (ethanol): nm (ε): 277 (4400); ir (chloroform): 3450, 3370 (NH), 1650 (C=O); 1520 (NHCO) cm^{-1}; pmr (deuteriochloroform): δ 1.15, 1.40 (6*H*, *gem*-methyls), 3.40 (2H, ArC*H*$_2$-C=O), 3.75, 3.80, 3.85 [9H, $(OCH_3)_3$], 4.50 [1H, ArC*H*(OH)R], 5.70 (2H, N*H*CO, ArCH(O*H*)R] ppm.

Anal. Calcd. for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.26; H, 7.31; N, 3.82.

To a stirred solution of 45.0 g. (0.12 mole) of amide **10b** in 500 ml. of dry tetrahydrofuran was added 200 ml. of 1 molar solution of diborane in tetrahydrofuran (0.2 mole) over a period of 30 minutes at 0° and the stirring was continued at 25° overnight. Water was added dropwise with caution at 0° until effervescence ceased, followed by the addition of hydrochloric acid to *p*H 1.0. The acidified solution was heated 1 hour at 65° to destroy excess diborane. Ice was added, the mixture was made basic with ammonium hydroxide and extracted twice with 900 ml. of ethyl acetate. The combined organic extracts were washed, dried with sodium sulfate and concentrated to about 250 ml. At this point, dry hydrogen chloride was introduced to *p*H 2.0 to give, on cooling, 25.0 g. of crude hydrochloride, m.p. 181-183°. Recrystallization from isopropanol gave 18.5 g. (39% yield) of analytically pure α-[1-[[2-(3,4-dimethoxyphenyl)-ethyl]amino]-1-methylethyl]-3-methoxybenzenemethanol hydrochloride (**8d**) as white crystals, m.p. 185-186°, dec.; uv λ max (ethanol): nm (ε) 216-224 plateau (11,400), 274-281 plateau (3800); ir (nujol): 3280 (NH); pmr (DMSO-d_6): δ 1.20 (6H, equivalent *gem*-methyls), 4.90 [1H, ArC*H*(OH)R], 8.90 (2H, $\overset{\oplus}{N}H_2$) ppm.

Anal. Calcd. for $C_{12}H_{29}NO_4$.HCl: C, 63.71; H, 7.64; N, 3.34. Found: C, 63.97; H, 7.87; N, 3.59.

The above amine hydrochloride **8d** was added portionwise to 125 ml. of polyphosphoric acid (preheated to 95°) over 30 minutes and continued to stir for 1 hour at 95°. Subsequently, the hot fluid was poured onto ice-water, made basic with sodium hydroxide and extracted twice with 500 ml. of ethyl acetate. The combined extracts were dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was dissolved in warm 2-propanol (150 ml.) and treated with dry hydrogen chloride to *p*H 2.0. On standing at room temperature overnight, 9.8 g. (53% yield) of 2,3,4,5-tetrahydro-7,8-dimethoxy-1-(3-methoxyphenyl)-2,2-dimethyl-1*H*-benzazepine hydrochloride (**1i**) of analytical purity crystallized out as white crystals, m.p. 285-286°, dec.; uv λ max (ethanol): nm (ε) 281 (4800); pmr (DMSO-d_6): δ 1.25 (6H, equivalent *gem*-methyls), 4.80 (1H, Ar$_2$C*H*R), 9.50 (2H, $\overset{\oplus}{N}H_2$ ppm.

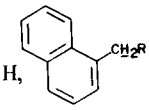
Anal. Calcd. for $C_{21}H_{27}NO_3$.HCl: C, 66.74; H, 7.47; N, 3.71; Cl, 9.38. Found: C, 66.67; H, 7.55; N, 3.59; Cl, 9.28.

2,3,4,5-Tetrahydro-4,4-dimethyl-5-phenyl-1*H*-3-benzazepin-7-ol (**1j**).

A stirred solution of 8.0 g. (0.0268 mole) of α-[1-[[2-(4-methoxyphenyl)ethyl]amino]-1-methylethyl]benzenemethanol (**8e**) in 30 ml. of methanesulfonic acid was heated for 11 hours at 83°. The brown solution was poured onto ice, made basic with ammonium hydroxide and extracted twice with 150 ml. of ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate and evaporated *in vacuo*. Trituration of the residue with hot acetonitrile and cooling gave 1.7 g. (27%) of 7-hydroxybenzazepine derivative **1j** (as a result of cyclization with simultaneous cleavage of the methoxy function), m.p. 208-209°, dec. An analytical sample melting at 209-210°, dec., was obtained by recrystallization from acetonitrile; uv λ max (ethanol): nm (ε) 204.5 (33,200), 280 (2200), 288 sh (2000); pmr (DMSO-d_6): δ 1.00, 1.07 (6H, *gem*-methyls), 2.86 (4H, broad, C*H*$_2$C*H*$_2$), 2.97 (NH), 3.86 (1H, ArC*H*), 8.90 (OH) ppm.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.70; H, 7.98; N, 5.51.

2,3,4,5-Tetrahydro-3,4,4-trimethyl-5-phenyl-1*H*-naphth[1,2-*d*]azepine (**1k**).

A solution of 74.5 g. (0.4 mole) of 1-naphthaleneacetic acid, 111.0 g. (0.45 mole) od EEDQ and 66.0 g. (0.4 mole) of α-(1-amino-1-methylethyl)benzenemethanol (**5a**) in 1 liter tetrahydrofuran was stirred and heated at 65° for 2 hours and then was allowed to stand overnight at room temperature. The solvent was removed, the residue was taken up with ice and adjusted to *p*H 2.0 with dilute sulfuric acid. The amide was extracted twice with 750 ml. of ethyl acetate. The combined extracts were washed with aqueous sodium bicarbonate, dried over sodium sulfate and evaporated to dryness *in vacuo*. The oily residue was crystallized from isopropyl ether to give 101.0 g. (77% yield) of pure *N*-(2-hydroxy-1,1-dimethyl-2-phenylethyl)-1-naphthaleneacetamide (**10f**) as off-white crystals, m.p. 106-107°; uv λ max (ethanol): nm (ε) 224 (72,000), 281 (7000); ir (chloroform): 3440, 3000 (NH), 1650 (C=O), 1510 (NHCO); pmr (deuteriochloroform): δ 1.05, 1.35 (6H, nonequivalent *gem*-methyls), 4.00 (2H, 

), 4.55 [1H, ArC*H*(OH)R], 5.40 [2H, ArCH(O*H*)R, N*H*CO] ppm.

Anal. Calcd. for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.19; H, 7.10; N, 4.23.

To a solution of 41.0 g. (0.12 mole) of the above amide **10f** in 500 ml. of dry tetrahydrofuran was added 175 ml. of 1 molar solution of diborane in tetrahydrofuran (0.175 mole) over 30 minutes at 0° and allowed to stir overnight at room temperature. Water was added at 0° dropwise *with caution*, followed by the addition of dilute hydrochloric acid to *p*H 1.0. The solution was then heated at 65° for ½ hour to destroy excess diborane, cooled, and made basic with ammonium hydroxide. The amine was extracted twice with 750 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and concentrated to a low volume giving, after cooling, 30.0 g. of crude amorphous base. This product (10.0 g.) was purified by dissolving in hot 2-propanol and adding dry hydrogen chloride to *p*H 2.0 to give 8.5 g. of analytically pure α-[1-methyl-1-[[2-(1-naphthalenyl)-ethyl]amino]ethyl]benzenemethanol hydrochloride (**8f**) as white crystals, m.p. 241-242°, dec.; uv λ max (ethanol): nm (ε) 223 (84,000), 281 (6500); ir (nujol): 3290, 3230 (NH,OH) cm^{-1}; pmr (DMSO-d_6): δ 1.25 (6H, equivalent *gem*-methyls), 4.95 [1H, ArC*H*(OH)R], 6.45 [1H, ArCH(O*H*)R], 9.00, 9.70 (2H, N*H*, *H*Cl) ppm.

Anal. Calcd. for $C_{22}H_{25}NO$.HCl: C, 74.25; H, 7.36; N, 3.94; Cl, 9.96. Found: C, 74.09; H, 7.43; N, 3.85; Cl, 9.95.

A solution of 10.0 g. of the impure base **10f** made above in 10 ml. of 36% aqueous formaldehyde and 40 ml. of 88% formic acid was refluxed for 15 hours. Thereupon, dilute hydrochloric acid was added to *p*H 1.0 and the solution was heated on a steam bath for 45 minutes. The reaction mixture was poured onto ice, made basic with ammonium hydroxide and extracted twice

with 250 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and evaporated *in vacuo*, giving α[1-methyl-[[methyl[2-(1-naphthalenyl)ethyl]amino]ethyl]benzenemethanol as an amber oil. This oily product was refluxed in 20 ml. of borontrifluoride etherate solution for 5 hours, poured onto ice and made basic with ammonium hydroxide. The basic mixture was extracted twice with 150 ml. of ethyl acetate, dried over sodium sulfate and concentrated to a low volume. On cooling, 2.5 g. (26% yield) of pure 2,3,4,5-tetrahydro-3,4,4-trimethyl-5-phenyl-1*H*-naphth[1,2-*d*]azepine (**1k**) of analytical purity crystallized as white solid, m.p. 140-141°; uv λ max (ethanol): nm (ε) 232 (86,000), 286 (10,500); pmr (deuteriochloroform): δ 1.00, 1.51 (6H, nonequivalent *gem*-methyls), 2.50 (3H, N-CH_3), 4.20 (1H, R-C*H*(Ar)-Naphth) ppm.

Anal. Calcd. for $C_{23}H_{25}N$: C, 87.57; H, 7.99; N, 4.44. Found: C, 87.63; H, 8.20; N, 4.30.

7-Amino-1,3,4,5-tetrahydro-4,4-dimethyl-5-phenyl-2*H*-3-benzazepine-2-one (**11a**).

A solution of 28.4 g. (0.157 mole) or 4-nitrobenzeneacetic acid, 40.0 g. (0.162 mole) of EEDQ (Aldrich Chem. Co.) and 26.0 g. (0.157 mole) of α(1-amino-1-methylethyl)benzenemethanol in 300 ml. of absolute ethanol and 600 ml. of tetrahydrofuran was stirred for 20 hours at room temperature, after which time it was heated for 5 hours at 65°. The reaction mixture was concentrated to about 500 ml. and on standing, 30 g. of solid material was obtained. Recrystallization from 300 ml. of absolute ethanol gave 28.5 g. (55% yield) of *N*-(2-hydroxy-1,1-dimethyl-2-phenylethyl)-4-nitrobenzeneacetamide **10c**, as an orange crystalline solid of analytical purity, 180-181° dec.; uv λ max (ethanol): nm (ε) 272 (9600); ir (nujol): 3430 (NH), 1660 (C=O), 1520 (NHCO) cm^{-1}; pmr (DMSO-d_6): δ 1.10, 1.40 (6H, nonequivalent *gem*-methyls), 3.6 (2H, ArCH_2CONH, 4.95 [1H ArC*H*(OH)R], 5.60 [1H, ArCH(O*H*)R] ppm.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.73; H, 6.01; N, 8.59.

A solution of the above acetamide **10c** (28.0 g.) in 150 ml. of glacial acetic acid, 50 ml. of tetrahydrofuran and 100 ml. of ethanol was hydrogenated over 1.5 g. of palladium-on-charcoal (10%) using a Paar hydrogenation apparatus until the hydrogen uptake ceased after 0.16 mole of hydrogen was consumed. The actual time of shaking was about 30 minutes, but the reaction had to be stopped twice to prevent over-heating. The catalyst was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was taken up with ice-water, made basic with ammonium hydroxide and extracted twice with 250 ml. of ethyl acetate. The combined organic extracts were washed, dried with sodium sulfate, and concentrated to *ca.* 100 ml. giving 15.0 g. of product, m.p. 138-139°. Recrystallization from ethyl acetate gave 11.7 g. (63% yield) of pure 4-amino-*N*-(2-hydroxy-1,1-dimethyl-2-phenylethyl)benzeneacetamide (**10d**) as tan crystals, m.p. 140-141° dec.; uv λ max (ethanol): nm (ε) 242 (10,600), 289 (1400); ir (chloroform): 3400, 3300 (NH), 1640 (C=O), 1520 (NHCO) cm^{-1}; pmr (deuteriochloroform): δ 1.10, 1.40 (6H, nonequivalent *gem*-methyls) 3.40 (2H, ArCH_2COR), 3.60 (2H, ArNH_2), 4.55 (1H, ArC*H*(OH)R], 5.80 [1H, ArCH(O*H*)R] ppm.

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.43; H, 7.61; N, 9.55.

A solution of 25.1 g. (0.084 mole) of the above amide **10d** was dissolved portionwise in 100 ml. of concentrated sulfuric acid and stirred at 80° for 5 hours. The solution was then poured onto ice, made basic with sodium hydroxide and extracted twice with 1 liter of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and evaporated to dryness *in vacuo*. The gummy residue was crystallized from diethyl ether to give 6.3 g. (28%) of pure 7-amino-1,3,4,5-tetrahydro-4,4-dimethyl-5-phenyl-2*H*-3-benzazepin-2-one (**11a**, R_1, R_2, R_3, R_4 = H; R_5 = 7-NH_2) as off-white crystals, m.p. 105-106°; uv λ max (ethanol): nm (ε) 241 (11,200), 288 (1600); ir (chloroform): 3500, 3400, 3350 (NH), 1670 (C=O), 1520 (NHCO) cm^{-1}; pmr (deuteriochloroform): δ 0.70, 1.40 (6H, nonequivalent *gem*-methyls), 3.60 [5H, ArCH_2CON*H*R, ArN*H*2], 5.05 (1H ArC*H*R) ppm.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.08; H, 7.28; N, 9.85.

2,3,4,5-Tetrahydro-4,4-dimethyl-5-phenyl-1*H*-3-benzazepin-7-amine (**11l**).

A solution of 4.5 g. (0.015 mole) of 7-amino-1,3,4,5-tetrahydro-4,4-dimethyl-5-phenyl-2*H*-3-benzazepin-2-one (**11a**, R_1 = R_2 = R_3 = R_4 = H; R_5 = 7-NH_2) in 25 ml. of tetrahydrofuran was added dropwise to a stirred suspension of 2.5 g. of lithium aluminum hydride in 25 ml. of tetrahydrofuran at 0° over 15 minutes and continued to stir at room temperature for 2 hours. The infrared spectrum showed absence of the carbonyl function at 1660 cm^{-1}. Ethyl acetate (50 ml.) was added with caution at 0° followed by the addition of cold water. The two layers were separated and the aqueous phase was re-extracted with 50 ml. of ethyl acetate. The combined organic extracts were washed with saturated sodium chloride, dried over sodium sulfate and evaporated to dryness *in vacuo*. Trituration of the gummy reisude with hot acetonitrile and cooling gave 0.9 g. (21% yield) of off-white crystals, m.p. 71-73°. Recrystallization from 2-propanol-isopropyl ether gave 0.7 g. of pure 2,3,4,5-tetrahydro-4,4-dimethyl-5-phenyl-1*H*-3-benzazepin-7-amine (**11l**) as off-white crystals, m.p. 73-74°; uv λ max (ethanol): nm (ε) 271 (9500); ir (chloroform): 3450, 3380, 1605 (NH) cm^{-1}; pmr (DMSO-d_6): δ 0.71, 1.38 (6H, nonequivalent *gem*-methyls), 3.1 (1H, NH aliphatic), 4.95 (2H, ArNH_2), 5.03 (1H, ArC*H*R), 6.70-7.10 (8H, m, aromatic protons) ppm.

Anal. Calcd. for $C_{18}H_{22}N_2$: C, 81.16; H, 8.33; N, 10.52. Found: C, 81.03; H, 8.41; H, 10.49.

N-(2,3,4,5-Tetrahydro-4,4-dimethyl-2-oxo-5-phenyl-1*H*-3-benzazepin-7-yl)acetamide (**11b**).

A solution of 1.3 g. of 7-amino-2,3,4,5-tetrahydro-4,4-dimethyl-5-phenyl-2*H*-3-benzazepin-2-one (**11a**) and 5 ml. of acetic anhydride in 40 ml. of ethyl acetate containing 5 drops of triethylamine was allowed to stand 20 hours at room temperature. The infrared spectrum (nujol) showed two carbonyl bands of equal intensity, corresponding to the acetamide at 1694 cm^{-1} and the lactam at 1666 cm^{-1}. The solution was stirred with cold water to destroy excess anhydride, made basic at 0° with sodium bicarbonate and separated. The organic phase was washed, dried over sodium sulfate and evaporated *in vacuo*. Crystallization of the residue from ethyl acetate-isopropyl ether gave 0.9 g. of pure *N*-(2,3,4,5-tetrahydro-4,4-dimethyl-2-oxo-5-phenyl-1*H*-3-benzenepin-7-yl)acetamide (**11b**) as off-white crystals, m.p. 139-140°; uv λ max (ethanol): nm (ε) 205 (33,800), 247 (18,350); ir (chloroform): 3420, 3300 (NH), 1690-1668 (broad, both carbonyl groups overlapping), 1518 (NH) cm^{-1}; (nujol): 3220, 3180 3180 (NH) 1694, 1667 (C=O), 1547, 1515 (NHCO) cm^{-1}; pmr (deuteriochloroform): δ 0.82, 1.43 (6H nonequivalent *gem*-methyls), 2.09 (3H, COCH_3), 3.60 (3H, s, ArCH_2CON*H*R), 5.06 (1H, Ar_2C*H*R), 7.10 to 7.50 (8H, m, aromatic protons), 8.12 (1H, CH_3CON*H*) ppm.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.22; H, 6.91; N, 8.74.

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REFERENCES AND NOTES

(1) E. E. Hayes and B. Vithal Shetty, U. S. Patent 3,084,099 (1963).

(2) G. Bobowski, J. M. Gottlieb and J. Shavel, Jr., U. S. Patent Application filed.

(3a) H. R. Kaplan and R. D. Robson, *J. Pharmacol. Exp. Ther.*, 175, 169 (1970); (b) *ibid.*, 145, 286-291 (1964).

(4) A. S. Harris, *Circulation*, 1, 1318-1328 (1950).