**1,1-Diphenyl-2-methyl-3-(1-pyrrodidinyl)propane·HCl (169).**—To a suspension of 29.5 g (0.1 mole) of **15** in 600 ml of liq $NH_3$ and 15.4 ml of EtOH was slowly added during 2.5 hr 6.92 g (0.3 g-atom) of Na (spheres). The mixt was then stirred for an addl 1.5 hr and allowed to evap overnight. Ice water was added and the mixt was extd with $Et_2O$. The $Et_2O$ soln was washed ($H_2O$, satd NaCl) and dried ($Na_2SO_4$). Filtn and removal of the solvent gave 28.2 g of nearly colorless oil. This was dissolved in 250 ml of hexane and chromatogd on a column of 1 kg of neutral $Al_2O_3$ (Woelm) and eluted with 1-l. portions of hexane contg increasing amounts of abs $Et_2O$. The bulk of the product came off with solvent contg 2% $Et_2O$ giving 15.4 g of oil. This was dissolved in $Et_2O$ and acidified with ethanolic HCl, yielding 18.85 g (57%) of white solid, mp 214.5–217°.

The same compd (**169**) was obtained in poor yield by treating **16** with $SOCl_2$, removing the solvent, and hydrogenating the resulting crude 3-chloro-3,3-diphenyl-2-methylpropyl-1-pyrrolidine·HCl in the presence of Pd/C. *Anal.* ($C_{20}H_{26}ClN$) C, H, Cl, N.

**Acknowledgments.**—The authors wish to thank our Physical and Analytical Chemistry Unit for analytical and spectral data, Mr. R. F. Tripp for technical assistance, and Dr. R. V. Heinzelman for guidance.

# Central Nervous System Agents. 2. Synthesis of Diphenyl Primary and Secondary Aminopropanols

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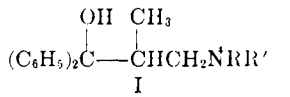
A series of 1,1-diaryl-2-methyl-3-[(primary and secondary)amino]propanols (I, R and/or R′ = H) were prepared for testing as CNS agents (anticonvulsants, anorexigenics, and their effect on simple reflexes). The primary amines were prepared by reduction of the corresponding nitriles and most of the secondary amines by reductive alkylation of the primary amines. A new cleavage of β-amino esters by Grignard reagents is described. The primary amine (1,1-diphenyl-2-methyl-3-aminopropanol) was resolved into its optical isomers and the *l* isomer was tested in man.

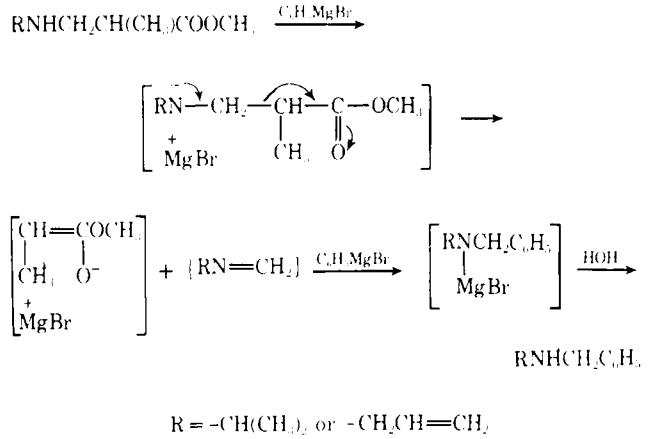
The interesting CNS stimulating effects accompanied by low anticholinergic side effects found for the tertiary amines[1] (I) have encouraged us to expand the series to



I

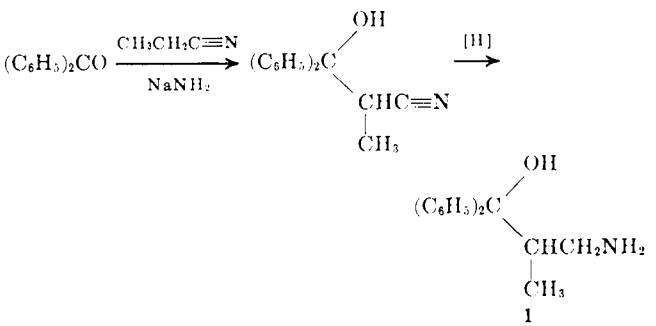
include primary and secondary amines (I, R and/or R′ = H) (Table I). These could not be satisfactorily prepared by the methods used for the tertiary amines. Although some workers[2] have successfully prepared similar primary or secondary amino alcohols by the Grignard reaction on β-amino esters or β-amino ketones, we found these methods unsatisfactory for our compounds. When methyl β-(isopropylamino)isobutyrate or β-(allylamino)isobutyrate were added to PhMgBr or PhLi under conditions that worked well with tertiary amino esters[1] none of the desired amino alcohols were isolated but instead about a 50% yield of *N*-isopropyl-or *N*-allylbenzylamine was obtained. This might be formulated as a reverse condensation reaction and explained by cleavage of the anion formed by initial abstraction of the proton from N, followed by addition of more PhMgBr to the formal compound.

Of course, PhMgBr may also add to the ester prior to, simultaneously with, or subsequent to the cleavage. This novel reaction may prove useful for the preparation of benzylamines from aromatic Grignard reagents. When the Grignard reaction was carried out at −20° as suggested by Adamson[2a] a small yield of the desired *N*-isopropylamino alcohol **28** was obtained. However,



this was much better obtained by reductive alkylation of the primary amine.

The primary amine **1** was obtained in good yield by the method Henecka, *et al.*,[3] used for analogous amino alcohols. This involved condensation of benzophenone with propionitrile in the presence of $NaNH_2$ and reduction of the resulting nitrile either with LAH or by catalytic hydrogenation.



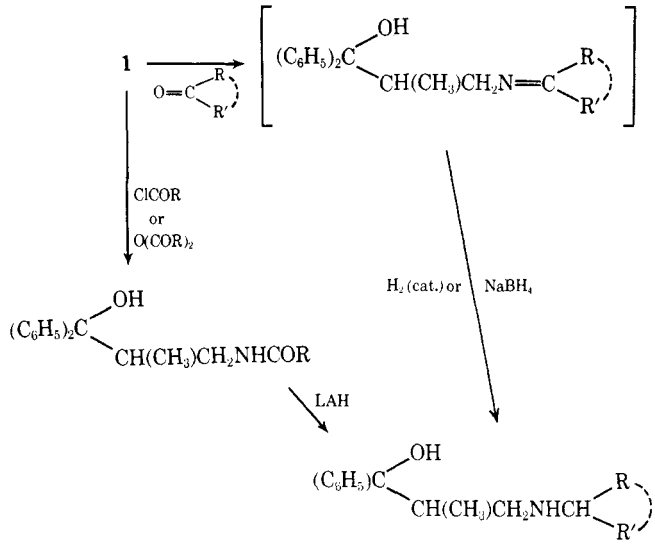
**1**

(1) Article 1: R. B. Moffett, R. E. Strube, and L. L. Skaletzky, *J. Med. Chem.*, **14**, 1088 (1971).

(2) (a) D. W. Adamson, *J. Chem. Soc., Suppl.*, **1**, S144 (1949); (b) K. Takagi, Y. Kasuya, and K. Hottori, *Yakugaku Zasshi*, **72**, 1592 (1952); *Chem. Abstr.*, **47**, 9312b (1953); (c) H. S. Mosher, M. B. Frankel, and M. Gregory, *J. Amer. Chem. Soc.*, **75**, 5326 (1953); (d) J. English and A. D. Bliss, *ibid.*, **78**, 4057 (1956).

(3) H. Henecka, R. Lorenz and R. Gösswald, British Patent 811,659 (1959); *Chem. Abstr.*, **54**, 424a (1960).

A variety of secondary amines were prepared from the primary amine **1** by either of the two methods indicated.



The *N*-methyl compounds **17** and **19** were prepared by hydrogenolysis of the corresponding *N*-benzyl-*N*-methylamines.[1]

The primary amine **1** proved to have very interesting CNS stimulating properties in animals[4] and was therefore resolved into its *d* and *l* forms. This was accomplished by crystallizing its *d*-tartrate salt to furnish the *l* isomer and its *l*-tartrate salt to give the *d* isomer. The levo rotating isomer (**6**) proved to be the more potent although the *d* isomer (**9**) also had interesting properties, being half as active on some parameters but only 0.2 as active on others.[4] The *l* isomer (**6**) was sent to the clinic for testing in humans afflicted with various mental diseases. However, undesirable side effects were encountered which may limit its use as an antidepressant.

## Experimental Section[5]

**1,1-Diphenyl-2-methyl-3-aminopropanol (1).**—To a mixt of 113.5 g (2.91 moles) of $NaNH_2$[6] and 1.75 l. of abs $Et_2O$ was slowly added with stirring a soln of 500 g (2.75 moles) of $Ph_2CO$ and 330 ml (6 moles) of EtCN in 2 l. of abs $Et_2O$. After refluxing for 3 hr and standing overnight the mixt was poured into 6 l. of ice water. The aq soln was extd with $Et_2O$ and the $Et_2O$ solns were washed ($H_2O$, dil HCl, $H_2O$, satd NaCl) and dried ($Na_2SO_4$). After filtn, the $Et_2O$ soln of the crude nitrile was concd to 4 l. and slowly added with vigorous stirring to 343 g (9 moles) of LAH and 500 ml of abs $Et_2O$. The $Et_2O$ gently refluxed during the 3.5 hr which was required for the addn. The mixt was then stirred under reflux overnight and cooled with an ice bath. To the reaction mixt was carefully added dropwise 360 ml of $H_2O$ and then 54 g of NaOH in 1.5 l. of $H_2O$. After thorough mixing, the mixt was filtd and the solid was well extd with $Et_2O$. The $Et_2O$ filtrates were extd with several portions of dil HCl and the acid exts were washed ($Et_2O$). The aq solns were basified with cold dil NaOH and the cryst free base was collected, washed ($H_2O$), and dried, giving 313 g of white crystals, mp 122.5–124.5°. This was recrystd from 1.7 l. of *i*-PrOH, yielding 266.7 g of white crystals, mp 125–126.5°.

**Hydrochloride 2.**—An *i*-PrOH soln of 20 g (0.083 mole) of the base (**1**) was acidified with a slight excess of ethanolic HCl. Diln of the soln with abs $Et_2O$ gave 17.5 g of white crystals, mp 213° dec.

**Maleate 3.**—A warm soln of 1.2 g (0.01 mole) of maleic acid in 10 ml of EtCOMe was added to a warm soln of 2.4 g (0.01 mole) of the base **1** in 15 ml of the same solvent. The maleate salt crystd almost immediately, giving 3.5 g of white crystals, mp 179–181.5°.

**Alternate Method[7] for 1,1-Diphenyl-2-methyl-3-aminopropanol (1).**—A soln of 6.232 kg (26.2 moles) of 2-(α-benzhydrol)propionitrile[8] in 28 l. of 95% EtOH and 3.85 l. of $NH_4OH$ (29% $NH_3$) was hydrogenated in a 120-l. autoclave with 1.5 l. of Raney Ni at 75° and 70.3 kg/cm². The hydrogenation was complete in about 30 min. The product was washed from the autoclave with EtOH and $CH_2Cl_2$, filtd, and concd under reduced pressure. The residual oil was dissolved in PhH and extd with dil HCl. The aq soln was washed ($Et_2O$) and basified with cold dil NaOH giving 6.04 kg of crude base. This was recrystd from 40 l. of *i*-PrOH, yielding 5.135 kg (81%) of white crystals, mp 124.5–126.5°.

***l*-1,1-Diphenyl-2-methyl-3-aminopropanol *d*-Tartrate (4).**—A mixt of 326.4 g (1.35 moles) of the base **1** and 202.5 g (1.35 moles) of *d*-tartaric acid was recrystd first from 6 l. of 85% (by vol) of aq $Me_2CO$ and then from 2.5 l. of $H_2O$ giving 169 g of white crystals, mp 154–158° dec. A sample dried at 60° (0.1 mm) was found by Karl Fischer anal. to cont 0.6 mole of water, $[\alpha]^{25}D$ −19 ± 1° in $H_2O$ (α −0.352 ± 0.02°, *c*, 0.9368 g/100 ml, *l* = 2).

***l*-1,1-Diphenyl-2-methyl-3-aminopropanol (5).**—The above *l* base *d*-tartrate (**4**) was dissolved in warm $H_2O$ and basified with NaOH. The cryst solid was collected, dried, and recrystd from 600 ml of *i*-PrOH, yielding 86.5 g of *l* base, mp 148–149.5°, $[\alpha]^{25}D$ −15.8°. A sample recrystd from *i*-PrOH had mp 148.5–150°, $[\alpha]^{25}D$ −18.5° ± 1° in MeOH (α −0.305, *c*, 0.8204 g/100 ml, *l* = 2).

***l*-1,1-Diphenyl-2-methyl-3-aminopropanol·HCl (6).**—The *l* base (**5**) was dissolved by warming in 240 ml of *i*-PrOH contg a slight excess of ethanolic HCl. On cooling cryst hydrochloride sepd giving 85.8 g of white crystals, mp 193–196°, resolidified at about 197°, and remelted at 205–215°, $[\alpha]^{27}D$ −41.6 ± 1° in $H_2O$ (α −0.75, *c*, 0.902 g/100 ml, *l* = 2); $[\alpha]^{27}D$ −38.25 ± 1° in MeOH (α 0.65, *c*, 0.860 g/100 ml, *l* = 2).

By reworking various filtrates, a small addl yield of pure **6** was obtained. The total overall yield for the resoln was 51% of the theoretical yield (one-half of the starting [*dl*] material).

***d*-1,1-Diphenyl-2-methyl-3-aminopropanol *l*-Tartrate (7).**—The filtrates from the prepn of the above *l* base *d*-tartrate (**4**) were evapd to dryness and all fractions having rotation $[\alpha]D$ +23° to +29° were combined (about 300 g). This was dissolved in $H_2O$ and basified with NaOH. The solid base was collected, washed well ($H_2O$), and dissolved in 3 l. of hot 85% aq $Me_2CO$ contg a slight excess of *l*-tartaric acid. On cooling, crude *d* base *l*-tartrate crystd and was recrystd from 1.7 l. of $H_2O$, yielding 192.2 g of white crystals, mp 152–158°. A sample was dried at 40° (0.1 mm), $[\alpha]^{25}D$ +19.0 − 1° in $H_2O$ (α = +0.342°, *c*, 0.881 g/100 ml, *l* = 2). Karl Fischer anal. indicated only 0.38% $H_2O$. *Anal.* ($C_{20}H_{25}NO_7$) Calcd: C, 61.37; H, 6.44; N, 3.58. Found: C, 59.87; H, 6.93; N, 3.55.

***d*-1,1-Diphenyl-2-methyl-3-aminopropanol (8).**—The above *d* base *l*-tartrate (**7**) was dissolved in warm $H_2O$ and basified with NaOH, the cryst solid was collected, dried, and recrystd from 800 ml of *i*-PrOH, yielding 104.1 g of *d* base, mp 148–149.5°, $[\alpha]D$ +17.7 ± 1° in MeOH (α +0.340°, *c*, 0.9606 g/100 ml, *l* = 2).

***d*-1,1-Diphenyl-2-methyl-3-aminopropanol·HCl (9).**—A soln of 10.2 g of the *d* base **8** in 65 ml of warm *i*-PrOH was acidified with ethanolic HCl giving 8.7 g of white crystals, mp 191–192°, resolidified, and remelted at 205–210°, $[\alpha]^{26}D$ +42.2 ± 1° in $H_2O$ (α +0.70°, *c*, 0.8216 g/100 ml, *l* = 2); $[\alpha]^{25}D$ +38.45 ± 1° in MeOH (α +0.648°, *c*, 0.8426 g/100 ml, *l* = 2).

**1,1-Diphenyl-3-aminobutanol[9] (10).**—A soln of 510 ml (1.53 moles) of 3 *M* PhMgBr was cooled to −20° and a soln of 2.5 g (0.19 mole) of ethyl 3-aminobutyrate in 100 ml of abs $Et_2O$ was slowly added with stirring at −20°. The mixt was stirred at −20° for 2 hr, then at 0° for 2 hr, and poured into ice water contg a slight excess of HBr. The aq layer (contg a little gummy hydro-

(4) The pharmacology of these compounds is reported in article 3 of this series, H. H. Keasling and R. B. Moffett, *J. Med. Chem.*, **14**, 1106 (1971).

(5) Mps were taken in capillary tubes with a partial immersion thermometer. Calibration of the app against standard compds showed no need for correction. Absorption peaks of spectra (ir and in selected cases nmr on a Varian A-60 instrument) were as expected. Where anal. are indicated only by symbols of the elements, anal. results obtained for these elements were within ±0.4% of the theor values.

(6) Free-flowing powder from Farchan Research Laboratories, Wickliffe, Ohio.

(7) This method was developed by Mr. Melvin A. Rebenstorf of our high pressure laboratory.

(8) H. Lettre and K. Wick, *Justus Liebigs Ann. Chem.*, **603**, 189 (1957).

(9) A. T. Austin and J. Howard [*J. Chem. Soc.*, 3278 (1961)] report (without details) an optically active (+) isomer of this compound.

Table I: Diarylamino Alcohols and Derivatives

$Ar_2C(OH)ANHR \cdot HX$

| No.[a] | Structure | ·HX | Method of prepn | Yield, %[b] | Mp, °C | Crystallizing solvent | Formula | Anal. |
|---|---|---|---|---|---|---|---|---|
| 1 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NH_2$ | Base | *c* | 40 | 125–126.5 | *i*-PrOH | $C_{16}H_{19}NO$ | C, H, N |
| 2 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NH_2$ | HCl | *c* | 76 | 213 dec | *i*-PrOH–$Et_2O$ | $C_{16}H_{20}ClNO$ | C, H, Cl, N |
| 3 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NH_2$ | $C_4H_4O_4$[d] | *c* | 97 | 179.5–181.5 | MeEtCO | $C_{20}H_{23}NO_5$ | C, H, N |
| 4 | *l*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2NH_2$ | *d*-$C_4H_6O_6$[e] | *c* | 62 | 154–158 | $H_2O$ | $C_{20}H_{25}NO_7 \cdot 0.6H_2O$ | C, H, N |
| 5 | *l*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2NH_2$ | Base | *c* | 78 | 148–149.5 | *i*-PrOH | $C_{16}H_{19}NO$ | C, H, N |
| 6 | *l*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2NH_2$ | HCl | *c* | 86 | 193–215[f] | *i*-PrOH | $C_{16}H_{20}ClNO$ | C, H, Cl, N |
| 7 | *d*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2NH_2$ | *l*-$C_4H_6O_6$[g] | *c* | 79 | 152–158 | $H_2O$ | $C_{20}H_{25}NO_7 \cdot xH_2O$[f] | C, H, N |
| 8 | *d*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2NH_2$ | Base | *c* | 81 | 148–149.5 | *i*-PrOH | $C_{16}H_{19}NO$ | C, H, N |
| 9 | *d*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2NH_2$ | HCl | *c* | 74 | 191–210[f] | *i*-PrOH | $C_{16}H_{20}ClNO$ | C, H, Cl, N |
| 10 | $(C_6H_5)_2C(OH)CH_2CH(CH_3)NH_2$ | Base | *c* | 3.2 | 156.5–157.5 | *i*-PrOH | $C_{16}H_{19}NO$ | C, H, N |
| 11 | $(C_6H_5)_2C(OH)CH(CH_2CH_3)CH_2NH_2$ | Base | *h* | 72 | 131–132 | *i*-PrOH | $C_{17}H_{21}NO$ | C, H, N |
| 12 | $(C_6H_5)_2C(OH)CH(CH_2CH_3)CH_2NH_2$ | HCl | *i* | 90 | 182.5–183.5 | *i*-PrOH–$Et_2O$ | $C_{17}H_{22}ClNO$ | C, H, Cl, N |
| 13 | $(C_6H_5)_2C(OH)CH[CH(CH_3)_2]CH_2NH_2$ | HCl | *j* | 68 | 232–232.5 | EtOH | $C_{18}H_{24}ClNO$ | C, H, Cl, N |
| 14 | $(p\text{-}CH_3C_6H_4)_2C(OH)CH(CH_3)CH_2NH_2$ | Base | *k* | 26 | 137–138.5 dec | Me cyclohexane | $C_{18}H_{23}NO$ | C, H, N |
| 15 | $(m\text{-}FC_6H_4)_2C(OH)CH(CH_3)CH_2NH_2$ | $C_4H_4O_4$[d] | *l*, *m* | 28 | 176–177 dec | 95% EtOH | $C_{20}H_{21}F_2NO_5$ | C, H, F, N |
| 16 | $(m\text{-}ClC_6H_4)_2C(OH)CH(CH_3)CH_2NH_2$ | HCl | *l*, *n* | 18 | 203.5–204.5 dec | MeEtCO | $C_{16}H_{18}Cl_3NO$ | C, H, Cl, N |
| 17 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_3$ | Base | *c* | 81 | 112–114 | *i*-PrOH | $C_{17}H_{21}NO$ | C, H, N |
| 18 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_3$ | HCl | *o* | 83 | 221–222 dec | EtOH | $C_{17}H_{22}ClNO$ | C, H, Cl, N |
| 19 | $(C_6H_5)_2C(OH)CH_2CH(CH_3)NHCH_3$ | Base[p] | *q* | 74 | 158.5–160 | EtOAc | $C_{17}H_{21}NO$ | C, H, N |
| 20 | $(C_6H_5)_2C(OH)CH_2CH(CH_3)NHCH_3$ | HCl | *r* | 88 | 190.5–191.5 dec | *i*-PrOH | $C_{17}H_{22}ClNO$ | C, H, Cl, N |
| 21 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCOCH_3$ | | *c* | 96 | 158–159 | *i*-PrOH | $C_{18}H_{21}NO_2$ | C, H, N |
| 22 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2CH_3$ | Base | *c* | 57 | 103–104 | *i*-PrOH | $C_{18}H_{23}NO$ | C, H, N |
| 23 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2CH_3$ | HCl | *s* | 71 | 187–188 | *i*-PrOH | $C_{18}H_{24}ClNO$ | C, H, Cl, N |
| 24 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCOCH_2CH_3$ | | *t* | 29 | 119–121 | *i*-PrOH | $C_{19}H_{23}NO$ | C, H, N |
| 25 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NH(CH_2)_2CH_3$ | $C_4H_4O_4$[d] | *c* | 43 | 145–146.5 | EtOAc | $C_{23}H_{29}NO_5$ | C, H, N |
| 26 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2N{=}C(CH_3)_2$ | Base | *c* | 79 | 135.5–137.5 | $Me_2CO$ | $C_{19}H_{23}NO$ | C, H, N |
| 27 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH(CH_3)_2$ | Base | *c* | 100 | 95–99.5 | *i*-PrOH | $C_{19}H_{25}NO$ | C, H, N |
| 28 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH(CH_3)_2$ | HBr | *u* | | 186–188 | $H_2O$ | $C_{12}H_{26}BrNO$ | C, H, Br, N |
| 29 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCO(CH_2)_2CH_3$ | | *c* | 55 | 107–109 | $Et_2O$ | $C_{20}H_{25}NO$ | C, H, N |
| 30 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NH(CH_2)_3CH_3$ | Base | *v* | 70 | 80–82 | *i*-PrOH | $C_{20}H_{27}NO$ | C, H, N |
| 31 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NH(CH_2)_3CH_3$ | $C_4H_4O_4$[d] | *w* | 79 | 148–148.5 | *i*-PrOH | $C_{20}H_{23}NO$ | C, H, N |
| 32 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCOCHCH_2CH_2$ | Base | *x* | 72 | 152–154 | *i*-PrOH | $C_{20}H_{23}NO_2$ | C, H, N |
| 33 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2CHCH_2CH_2$ | Base | *v* | 42 | 100.5–102 | $Et_2O$ | $C_{20}H_{25}NO$ | C, H, N |
| 34 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2N{=}C(CH_3)CHCH_2CH_2$ | Base | *y*, *z* | 70 | 120.5–122.5 | MeOH | $C_{21}H_{25}NO$ | C, N, N |
| 35 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH(CH_3)CHCH_2CH_2$[aa] | Base | *c* | 30 | 99–101 | Pentane | $C_{21}H_{27}NO$ | C, N, N |
| 36 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH(CH_3)CHCH_2CH_2$[aa] | HCl | *r* | 79 | 189–190.5 | *i*-PrOH | $C_{21}H_{28}ClNO$ | C, H, Cl, N |
| 37 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH(CH_3)CHCH_2CH_2$[bb] | Base | *c* | | 68–71 | 50% *i*-PrOH–$H_2O$ | $C_{21}H_{27}NO$ | C, H, N |
| 38 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCHCH_2CH_2CH_2$ | HCl | *c* | 30 | 199.5–201.5 | *i*-PrOH | $C_{20}H_{26}ClNO$ | C, H, Cl, N |
| 39 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH(CH_2)_3CH_2$ | Base | *cc* | 86 | 108–109.5 | EtOH | $C_{21}H_{27}NO$ | C, H, N |
| 40 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH(CH_2)_3CH_2$ | HCl | *dd* | 98 | 215–217 | MeOH–*i*-PrOH | $C_{21}H_{28}ClNO$ | C, H, Cl, N |

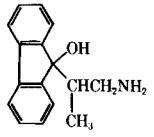
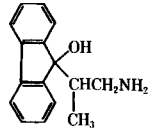
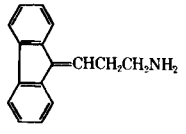
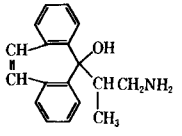
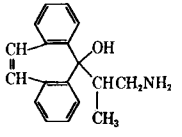
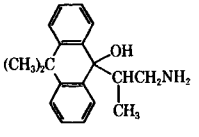
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 41 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2N{=}CHC_6H_5$ | Base | *c* | 90 | 132–136 | *i*-PrOH | $C_{23}H_{23}NO$ | C, H, N |
| 42 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2C_6H_5$ | Base | *c* | 96 | 106–108 | *i*-PrOH | $C_{23}H_{25}NO$ | C, H, N |
| 43 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2[3,4,5\text{-}(OCH_3)_3C_6H_2]$ | Base | *c* | 76 | 120–123 | EtOH | $C_{26}H_{31}NO_4$ | C, H, N |
| 44 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2[3,4,5\text{-}(OCH_3)_3C_6H_2]$ | HCl | *ee* | 57 | 155.5–157.5 | MeEtCO–*i*-PrOH | $C_{26}H_{32}ClNO_4$ | C, H, Cl, N |
| 45 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2N{=}CHC{=}CHCH{=}CHO$ | Base | *y* | 88 | 122–123.5 | *i*-PrOH | $C_{21}H_{21}NO_2$ | C, H, N |
| 46 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2C{=}CHCH{=}CHO$ | Base | *ff* | 97 | 94.5–96 | *i*-PrOH | $C_{21}H_{23}NO_2$ | C, H, N |
| 47 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2C{=}CHCH{=}CHO$ | $C_4H_4O_4$[d] | *gg* | 97 | 167.5–169.5 | $Me_2CO$ | $C_{25}H_{27}NO_6$ | C, H, N |
| 48 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2N{=}CHC{=}CHCH{=}CHS$ | Base | *y* | 90 | 125.5–127.5 | *i*-PrOH | $C_{21}H_{21}NOS$ | C, H, N, S |
| 49 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2C{=}CHCH{=}CHS$ | Base | *ff* | 96 | 107–108.5 | *i*-PrOH | $C_{21}H_{23}NOS$ | C, H, N, S |
| 50 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2C{=}CHCH{=}CHS$ | $C_4H_4O_4$[d] | *gg* | 96 | 177.5–178.5 | $Me_2CO$ | $C_{25}H_{27}NO_5S$ | C, H, N, S |
| 51 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCH_2C(CH_3)_2COOH$ | | *c* | 41 | 233.5–235.5 | DMF | $C_{21}H_{27}NO_3$ | C, H, N |
| 52 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCHCH_2CH_2N(CH_3)CH_2CH_2$ | Base | *hh* | 92 | 118.5–120 | 60% aq EtOH | $C_{22}H_{30}N_2O$ | C, H, N |
| 53 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHCHCH_2CH_2N(CH_3)CH_2CH_2$ | 2HCl | *o* | 96 | 253–254 dec | EtOH | $C_{22}H_{32}Cl_2N_2O$ | C, H, Cl, N |
| 54 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2NHSO_2(p\text{-}CH_3C_6H_4)$ | | *c* | 40 | 140–141 | PhH | $C_{23}H_{25}NO_3S$ | C, H, N, S |
| 55 | $(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2CH{=}CH_2)SO_2C_6H_5$ | | *c* | 75 | 122–124 | *i*-PrOH | $C_{25}H_{27}NO_3S$ | C, H, N, S |
| 56 |  | Base | *l* | *ii* | 135–136 | *i*-PrOH | $C_{16}H_{17}NO$ | C,[ii] H, N |
| 57 |  | HCl | *ii* | 4[ii] | 232–234 | *i*-PrOH | $C_{16}H_{18}ClNO$ | C, H, Cl, N |
| 58 |  | HBr | *c* | 3.5 | 252–255 dec | $H_2O$ | $C_{16}H_{16}BrN$ | C, H, Br, N |
| 59 |  | Base | *c* | | 178.5–179.5 | $CH_3(C_6H_{11})$[ii] | $C_{18}H_{19}NO$ | C, H, N |
| 60 |  | HCl | *c* | 18 | 280–281 | EtOH | $C_{18}H_{20}ClNO$ | C, H, Cl, N |
| 61 |  | $C_4H_4O_4$[d] | *l*, *m* | 47 | 154–155 dec | *i*-PrOH | $C_{23}H_{27}NO_5$ | C, H, N |

TABLE I (*Continued*)

[a] Compds in this article are numbered consecutively for easy reference in the following article[4] on the pharmacology of this series. [b] Unless otherwise indicated, the yields of primary amines are based on the starting diaryl ketone. Yields of compds prepared from primary amines are based on these primary amines. Yields of salts are based on the free amines. Unless otherwise indicated yields are reported for material melting not lower than 2° below the highest mp obtained. [c] The prepn of this compd is described in the Experimental Section and the yield is based on the starting material specified. [d] Maleic acid salt. [e] *l* (levo rotating) base *d*-tartrate salt. [f] See Experimental Section. [g] *d* (dextro rotating) base *l*-tartrate salt. [h] Prepared by LAH reduction of 2-(α-benzhydrol)butyronitrile [W. Chodkiewicz, P. Cadiot, A. Willemart, and S. Prevost, *Bull. Soc. Chim. Fr.*, 1586 (1958)] by the procedure described for **1**. The method reported by W. Heinrich and W. Heigel [German Patent 1,122,514 (1962)] (hydrogenation over Pt) failed in our hands. [i] Prepd from the base as described for **2**. [j] Prepd from the nitrile **62** by the method used for **1**. The free base was not isolated but the $Et_2O$ soln from the work-up of the LAH reduction was treated with dil HCl. [k] Prepd as described for **1** except anhyd KOH was used in place of $NaNH_2$. [l] Prepd by procedure described for **1** except $LiN(Et)_2$ (equimolar amounts of $C_4H_9Li$ and $Et_2NH$) was used in place of $NaNH_2$. An excess of LAH was added to the reaction mixt without sepg the nitrile. [m] The free base was not cryst. It was converted to the maleate salt in $Et_2O$. [n] The free base was not cryst. It was converted to the hydrochloride in $Et_2O$. [o] The free base in EtOH was converted to the hydrochloride with ethanolic HCl. [p] This free base has been prepd by Takagi, Kasuya, and Hattori [*Yakugaku Zasshi*, **71**, 1328 (1951); *Chem. Abstr.*, **46**, 2752*c* (1952); Japan Patent 4483 (1952); *Chem. Abstr.*, **48**, 8264 (1954)] in unspecified yield using $C_6H_5MgBr$ on ethyl β-(methylamino)butyrate. It is erroneously called the hydrochloride in *Chem. Abstr.*, **46**, 2752*c* (1952). [q] Prepd by hydrogenolysis of 1,1-diphenyl-3-(*N*-benzyl-*N*-methylamino)butanol (ref 1) as described for **17**. The hydrogenation went much more slowly even with 7 g of catalyst for a 0.05 mole run. [r] Prepd from the base in *i*-PrOH with ethanolic HCl. [s] Prepd from the base in $Et_2O$ with ethanolic HCl. [t] Prepd as described for **21** using $(EtCO)_2O$ in place of $Ac_2O$. [u] The base was dissolved in hot $H_2O$ containing a slight excess of HBr. The salt crystd on cooling. [v] Prepd by method described for **22**. [w] The maleate was prepd by mixing equimolar ethanolic solns of the base **30** and maleic acid. [x] Prepd by method described for **29**. [y] Prepd by method described for the benzylidene compd (**41**). [z] Two days reflux with the Dean–Stark trap was required to remove all $H_2O$. [aa] Racemate A. [bb] Racemate B. [cc] Prepd by the method described for **27**, using 0.2 mole of cyclopentanone per 0.1 mole of **1** in 100 ml of abs EtOH and no AcOH. Solid sepd during the hydrogenation and redissolved on warming before filtration from the catalyst. [dd] Prepd from the base in EtCOMe with ethanolic HCl. [ee] Prepd from the base in EtOAc with ethanolic HCl. [ff] Prepd as described for **42**. [gg] Prepd by mixing warm $Me_2CO$ solns of the base **46** and of maleic acid and cooling. [hh] Prepd by the method described for **27**, using 0.15 mole of *N*-methyl-4-piperidone per 0.1 mole of **1** in 120 ml of EtOH and no AcOH. [ii] Only a small sample of the free base was purified for anal., C: Calcd, 80.30; found, 79.50. The bulk of the crude base in EtOH was converted to the hydrochloride with ethanolic HCl and dild with $Et_2O$, and recryst from *i*-PrOH. The overall yield is based on 9-fluorenone. [jj] Methylcyclohexane.

bromide) was washed ($Et_2O$) and basified with NaOH. The mixt was well extd with $Et_2O$ and the exts were washed ($H_2O$, sat NaCl) and dried ($Na_2SO_4$). Filtn and evapn of the solvent *in vacuo* gave gummy solid which was crystd twice from *i*-PrOH, yielding 1.47 g of cryst solid, mp 156.5–157.5°.

**2-(α-Benzhydrol)-3-methylbutyronitrile (62).**—To 20.17 g (0.53 mole) of $NaNH_2$[6] in 200 ml of abs $Et_2O$ was slowly added with stirring a soln of 91.0 g (0.5 mole) of $Ph_2CO$ and 90.5 g (1.09 moles) of isovaleronitrile in 300 ml of abs $Et_2O$. After stirring under reflux for 3 hr, the mixt was cooled and poured into ice water. The aq layer was extd with $Et_2O$ and the $Et_2O$ solns were washed ($H_2O$, dil HCl, $H_2O$, satd NaCl). After drying ($Na_2SO_4$) and filtg, the $Et_2O$ was evapd giving 134 g of crude nitrile. This was crystd from 400 ml of PhH, yielding 66.7 g (50%) of white crystals, mp 167–169°. *Anal.* ($C_{18}H_{19}NO$) C, H, N.

**1,1-Diphenyl-2-methyl-3-(methylamino)propanol (17).**—A soln of 34.5 g (0.1 mole) of 1,1-diphenyl-2-methyl-3-(*N*-benzyl-*N*-methylamino)propanol[1] in 200 ml of MeOH was hydrogenated with 2 g of 10% Pd/C at 3.5 kg/cm² and room temp. The theoretical amt of $H_2$ was absorbed in 3 hr. Filtn and evapn *in vacuo* gave white cryst solid which was recrystd from 125 ml of *i*-PrOH, yielding 20.7 g of white crystals, mp 112–114°.

***N*-(3,3-Diphenyl-3-hydroxy-2-methylpropyl)acetamide (21).**—A soln of 30.3 g (0.12 mole) of **1** in 1.2 l. of $Et_2O$ was added with stirring to a mixt of 10.2 g (0.13 mole) of pyridine and 13.3 g (0.13 mole) of $Ac_2O$ in 100 ml of $Et_2O$. After refluxing for 2 hr the mixt was poured into ice water. The product remained insol in both layers yielding 33 g of white crystals, mp 158–159°. Recrystn from *i*-PrOH did not raise the mp.

**1,1-Diphenyl-2-methyl-3-(ethylamino)propanol (22).**—A soln of 24 g (0.12 mole) of amide **21** in 300 ml of THF was slowly added with stirring to 9.1 g (0.24 mole) of LAH in 100 ml of THF. After refluxing overnight most of the solvent was distd and replaced by $Et_2O$. There was then slowly added in succession 9.1 ml of $H_2O$, 9.1 ml of 20% NaOH, and 27.3 ml more of $H_2O$. The mixt was filtd and the solids were well extd with $Et_2O$. The $Et_2O$ solns were extd with dil HCl and the aq acid extract was basified with NaOH. The free base was recrystd from *i*-PrOH, yielding 18.3 g of white solid, mp 103–104°.

**1,1-Diphenyl-2-methyl-3-(propylamino)propanol Maleate (25).**—A 0.1-g sample of $PtO_2$ in 50 ml of EtOH was hydrogenated to Pt. Then were added 24.1 g (0.1 mole) of **1** in 150 ml of EtOH and 6.4 g (0.1 mole) of EtCHO. This was hydrogenated at 3.5 kg/cm² and room temp. About 75% of the theor amt of $H_2$ was absorbed in 5 hr by which time the uptake was very slow. The soln was filtd and evapd giving 28.9 g of nearly colorless oil. This crude free base was dissolved in EtOAc and a soln of 11.6 g (0.1 mole) of maleic acid was added. This soln was dild to turbidity with $Et_2O$ and on standing crystals sepd, yielding 33.7 g of white solid, mp 116–135°. By repeated fractional crystn from EtOAc the desired product was sepd from the less sol maleate of the starting amine **3**, yielding 17.3 g of white crystals, mp 145–146.5°.

**α-[2-(Isopropylideneamino)-1-methylethyl]benzhydrol (26).**—A soln of 12.1 g (0.05 mole) of **1** was dissolved in 75 ml of $Me_2CO$ at the bp. The soln was filtd and concd by boiling to 50 ml, giving, on cooling, 11.1 g of white crystals, mp 135.5–137.5°.

**1,1-Diphenyl-2-methyl-3-(isopropylamino)propanol (27).**—A soln of 24.1 g (0.1 mole) of **1**, 36.8 ml (0.5 mole) of $Me_2CO$, and 28.7 ml (0.5 mole) of AcOH in 75 ml of EtOH was hydrogenated with 1 g of $PtO_2$ at 3.5 kg/cm² and room temp. The theoretical amt of $H_2$ was absorbed in 5 min. The soln was filtd, evapd, dissolved in dil HCl, and washed ($Et_2O$). The aq soln was basified with NaOH and extd with $Et_2O$. After washing ($H_2O$, satd NaCl) and drying ($Na_2SO_4$) the $Et_2O$ was removed giving 28.4 g of white crystals, mp 95–99.5°. Recrystn from *i*-PrOH raised the mp to 101–102°. In another run Raney Ni was successfully used (without AcOH) in place of the $PtO_2$.

**PhMgBr on Methyl β-(Isopropylamino)isobutyrate.**—To 1 l. (3 moles) of ethereal 3 *M* PhMgBr in 1.2 l. of THF was added 79.5 g (0.5 mole) of methyl β-(isopropylamino)isobutyrate[10] in 800 ml of THF. After refluxing for 3.5 hr about two-thirds of the solvent was distd, and the residue was poured into ice water contg a slight excess of HBr. The aq soln was washed ($Et_2O$) and basified with NaOH. The suspension of $Mg(OH)_2$ was well extd with $Et_2O$ which was washed ($H_2O$, satd NaCl) and dried ($Na_2SO_4$). After filtn and evapn of the solvent, 70 g of crude liquid free

(10) R. C. Smith and S. B. Binkley, *J. Org. Chem.*, **24**, 249 (1959).

base was obtd. This was dissolved in 200 ml of hexane and after standing in the refrigerator was filtd from a small amount of cryst solid to unknown structure, mp 139–141°. The hexane filtrate was evapd to dryness *in vacuo*, the residual oil was dissolved in $Et_2O$ and acidified with ethanolic HCl. The resulting hydrochloride was collected, washed ($Et_2O$), and dried, giving 66.7 g of crude hydrochloride, mp 167–172°. This was recrystd from *i*-PrOH, yielding 40.4 g (43.6%) of salt, mp 192–193°. Recrystn from abs EtOH gave 27.5 g of crystals, mp 192–194°. This was found by ir, nmr, anal., and mmp with an authentic sample to be *N*-benzylisopropylamine·HCl.[11]

Another run, using 0.6 mole of PhMgBr and 0.2 mole of methyl β-(isopropylamino)isobutyrate in $Et_2O$, was stirred below −20° for 2 hr and below 0° for an additional 2 hr. It was decompd with ice and aq $NH_4Cl$ giving 3 layers. The oily middle layer was strongly acidified with aq HBr and washed ($Et_2O$). Crystals sepd giving 13.13 g of solid, mp 169–174°. This was recrystd first from *i*-PrOH and then from $H_2O$, yielding 6.66 g (9.3%) of white crystals, mp 186–188°. This was identical with the hydrobromide **28** (Table I).

A run using PhLi in place of PhMgBr at 0° to 5° gave as the only product isolated a 50% yield of *N*-benzylisopropylamine·HCl.

***N*-Benzylisopropylamine·HBr (63).**—An $Et_2O$ soln of 5 g (0.033 mole) of *N*-benzylisopropylamine was acidified with 48% aq HBr giving 5.6 g (72%) of the salt, mp 213–215°. This was recrystd from *i*-PrOH, yielding 4.6 g of white crystals, mp 214–216°. *Anal.* ($C_{10}H_{16}BrN$) C, H, Br.

**PhMgBr on Methyl β-(Allylamino)isobutyrate.**—In a similar way 39.2 g (0.25 mole) of methyl β-(allylamino)isobutyrate[12] and PhMgBr were allowed to react in $Et_2O$ at reflux temp for 5 hr. The reaction mixt was worked up as above and the crude free base in $Et_2O$ was converted to the hydrochloride with ethanolic HCl giving 34.3 g of crude salt, mp 125–129°. Recrystn from EtCOMe yielded 22.7 g (50%) of white crystals of *N*-allylbenzylamine·HCl,[13] mp 145–146°.

***N*-(3,3-Diphenyl-3-hydroxy-2-methylpropyl)butyramide (29).**—To 24.1 g (0.1 mole) of **1** and 9 ml (0.108 mole) of $Et_3N$ in 1 l. of abs $Et_2O$ was added dropwise 17 ml (17 g, 0.108 mole) of PrCOCl. After stirring under reflux for 2 hr, the reaction mixt was poured into ice water and acidified with HCl. The $Et_2O$ layer was sepd, washed (dil NaOH, $H_2O$), and dried ($K_2CO_3$). The $Et_2O$ soln was concd and on standing crystd, giving 18.8 g of white solid, mp 107–109°.

**1,1-Diphenyl-2-methyl-3-(1-cyclopropylethylamino)propanol (Racemate A) (35).**—A mixt of 12.1 g (0.0394 mole) of **34** and 1.9 g (0.05 mole) of $NaBH_4$ in 125 ml of MeOH was allowed to stand for 2.5 hr and then heated under reflux for 2 hr. Most of the MeOH was evapd *in vacuo*. The residue was dissolved in cold dil HCl and washed well ($Et_2O$). The aq soln was basified with NaOH and the resulting oil was extd with $Et_2O$. The exts were washed ($H_2O$, satd NaCl) and dried ($Na_2SO_4$). After filtn and removal of the $Et_2O$, the free base was crystd from 30 ml of pentane, yielding 3.7 g of cryst base, mp 92.5–96.5°. Recrystn from pentane raised the mp to 99–101°. Ir and nmr indicate this is essentially one isomer (racemate A).

**1,1-Diphenyl-2-methyl-3-(1-cyclopropylethylamino)propanol (Racemate B) (37).**—The filtrate from base **35** was concd to a very small vol, giving cryst of a second racemate which was recrystd from 50% *i*-PrOH, mp 68–71°. Ir and nmr spectra are very similar to but not identical with those of racemate A, indicating this is essentially the other racemate.

**1,1-Diphenyl-2-methyl-3-(cyclobutylamino)propanol·HCl (38).**—A soln of 24.1 g (0.1 mole) of **1** and 14.0 g (0.2 mole) of cyclobutanone in 15 ml of PhH was refluxed with a Dean–Stark trap for 20 min. The soln was evapd *in vacuo* giving crude α-[2-(cyclobutylideneamino)-1-methylethyl]benzhydrol as a waxy solid. This was dissolved in 250 ml of MeOH and 7.6 g (0.2 mole) of $NaBH_4$ was slowly added portionwise. After refluxing for 3 hr, most of solvent was evapd *in vacuo*, and the residue was shaken with $Et_2O$ and cold dil HCl. An oily hydrochloride remained insol in both layers. The aq layer and oil were sepd, washed ($Et_2O$), and basified with NaOH. The free base sepd as an oil which soon crystd giving 29 g of white solid, mp 70–90°. Recrystn from *i*-PrOH–$H_2O$ gave 20.2 g of white solid, mp 86–96°. A soln of this base in 300 ml of $Et_2O$ acidified with ethanolic HCl gave gummy hydrochloride. This was recrystd from 300 ml of *i*-PrOH, yielding 10.3 g of white crystals, mp 199.5–201.5°.

**α-[2-(Benzylideneamino)-1-methylethyl]benzhydrol (41).**—A soln of 24.1 g (0.1 mole) of **1** and 13.2 g (0.12 mole) of PhCHO in 100 ml of PhH was refluxed with a Dean–Stark trap for 45 min by which time the theoretical amt of $H_2O$ had sepd. The soln was evapd to dryness *in vacuo* giving a cryst residue which was recrystd from 250 ml of *i*-PrOH yielding 29.4 g of white needles, mp 132–136°.

**1,1-Diphenyl-2-methyl-3-(*N*-benzylamino)propanol (42).**—To a suspension of 33 g (0.1 mole) of Schiff's base **41** in 250 ml of MeOH, 7.6 g (0.2 mole) of $NaBH_4$ was added portionwise with stirring under reflux. The mixt was heated for 1.5 hr more and the MeOH was evapd. The solid residue was mixed with $H_2O$ and $Et_2O$ and acidified with HCl. An oily hydrochloride remained insol in both layers. The oil and the aq layer were sepd from the $Et_2O$ soln and the $Et_2O$ was repeatedly extd with dil HCl. The combined aq soln and oil were basified with NaOH giving 31.7 g of white solid, mp 104.5–106.5°. This was recrystd from 175 ml of *i*-PrOH yielding 30.0 g of white crystals, mp 106–108°.

**1,1-Diphenyl-2-methyl-3-(3,4,5-trimethoxybenzylamino)propanol (43).**—A soln of 12.05 g (0.05 mole) of **1** and 9.81 g (0.05 mole) of 3,4,5-trimethoxybenzaldehyde in 100 ml of PhH was refluxed with a Dean–Stark trap until the theor amt of $H_2O$ was collected (about 0.5 hr). The PhH soln was evapd giving the benzylidene compound as a yellow gum. This was dissolved in 150 ml of abs EtOH and hydrogenated with 0.1 g of $PtO_2$ and 2 g of 10% Pd/C at 3.5 kg/cm² and room temp. After 22 hr, the theor amt of $H_2$ had been absorbed, the soln was warmed to dissolve a little solid and was filtd. The filtrate was concd to 130 ml, giving 15.9 g of white solid, mp 119–122°. This was recrystd from 100 ml of EtOH, yielding 14.9 g of white crystals, mp 120–123°.

***N*-(3,3-Diphenyl-2-methyl-3-hydroxypropyl)-α,α-dimethyl-β-alanine (51).**—A soln of 12.06 g (0.05 mole) of **1** and 5.0 g (0.05 mole) of pivalolactone[14] in 100 ml of MeOH was allowed to stand at room temp for 3 days and then evapd *in vacuo*. The residue was boiled with 110 ml of *i*-PrOH and the product was recrystd from 75 ml of DMF giving 7.0 g of white solid, mp 233.5–235.5°.

***N*-(3-Hydroxy-2-methyl-3,3-diphenylpropyl)-*p*-toluenesulfonamide (54).**—A soln of 24.1 g (0.1 mole) of **1** in 1 l. of $Et_2O$ was added to a mixt of 21 g (0.11 mole) of TsCl in 100 ml of $Et_2O$ and 4.4 g (0.11 mole) of NaOH in 50 ml of $H_2O$. The mixt was stirred under reflux for 3 hr, cooled, and washed (dil HCl and dil NaOH). Evapn of the $Et_2O$ gave nearly white solid which was recrystd from MeOH, then from EtOAc, and finally from PhH, yielding 16 g of white solid, mp 140–141°. Even though this is a monosubstituted sulfonamide, it is nearly insol in dil NaOH.

***N*-Allyl-*N*-(3,3-diphenyl-2-methyl-3-hydroxypropyl)benzenesulfonamide (55).**—To a soln of 24.1 g (0.1 mole) of **1** in 500 ml of dioxane was slowly added with stirring 35.3 g (0.2 mole) of $PhSO_2Cl$ during 30 min. During this addn 131 ml (0.25 mole) of 50% NaOH, dild with 200 ml of $H_2O$, was added in 4 portions. After stirring for an addl 30 min, 30 g (0.25 mole) of allyl bromide was added. The soln was refluxed for 2 hr more and concd to a small vol in *vacuo*, giving 48.5 g of crude product, mp 110–118°. This was dissolved in $Et_2O$, washed (dil NaOH, $H_2O$, satd NaCl), dried ($Na_2SO_4$), and evapd. The residue was crystd from 200 ml of *i*-PrOH yielding 31.6 g of white crystals, mp 122–124°.

**Fluorene-Δ⁹,γ-propylamine·HBr (58).**—Crude β-(9-hydroxyfluoren-9-yl)propionitrile was prepared by the method of Campbell and Fairfull.[15] It failed to crystallize but was reduced with LAH as described for **1**. Attempts to isolate the expected 3-(9-hydroxy-9-ylfluoren)propylamine either as the free base of hydrochloride failed but conversion of the crude free base to the hydrobromide gave a small yield of the dehydrated product. This was recrystd from EtOH and twice from $H_2O$, yielding 3.3% overall of light brown crystals, mp 252–255° dec.

**5-(2-Amino-1-methylethyl)-2*H*-dibenzo[*a*,*d*]cyclohepten-5-ol·HCl (60)** was prepd by the method used for **1** using 0.4 mole of $LiNEt_2$[16] in place of $NaNH_2$, 70 g (0.34 mole) of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one in place of $Ph_2CO$, and 22 ml (0.4 mole) of EtCN in 500 ml of $Et_2O$. The crude nitrile was reduced with

(11) R. E. Lutz, P. S. Bailey, R. J. Rowlett, J. W. Wilson, R. K. Allison, M. T. Clark, N. H. Leake, R. H. Jordan, R. J. Keller, and K. C. Nicodemus, *J. Org. Chem.*, **12**, 760 (1947).

(12) A. Sh. Sharifkanov and P. S. Ibranov, *Khim. Khim. Tekhnol., Alma-Ata*, **1**, 6 (1963); *Chem. Abstr.*, **61**, 13274*f* (1964).

(13) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Amer. Chem. Soc.*, **81**, 3728 (1959).

(14) Thanks to Eastman Chemical Products Co. for a sample.

(15) N. Campbell and A. E. S. Fairfull, *J. Chem. Soc.*, 1239 (1949).

(16) Prepared *in situ* by mixing equamolar amts of Bu Li and $Et_2NH$.

16.8 g (0.46 mole) of LAH, and treatment of the $Et_2O$ soln of the crude free base with 5% aq HCl gave cryst hydrochloride insol in both layers. It was collected, dried, and recrystd first from a mixt of *i*-PrOH and EtOH and then from EtOH yielding 18.5 g of white crystals, mp 280–281°.

**Free Base 59.**—A sample of the hydrochloride was converted to the free base with NaOH and recrystd from methylcyclohexane giving white crystals, mp 178.5–179.5°.

**9-(2-Amino-1-methylethyl)-10,10-dimethyl-9-anthrol maleate (61)** was prepd from 22 g (0.1 mole) of 10,10-dimethyl-9-anthrone and 6.6 g (0.123 mole) of EtCN by the method used for **1** using 0.12 mole and $LiNEt_2$[16] in place of the $NaNH_2$. The crude free base was isolated as an oil, dissolved in $Et_2O$, and acidified with a slight excess of ethanolic maleic acid. The resulting maleate salt was recrystd from 100 ml of *i*-PrOH, yielding 18.8 g of light tan crystals, mp 154–155° dec.

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# Central Nervous System Agents. 3.[1] Structure–Activity Relationship of a Series of Diphenylaminopropanols

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A series of diphenylaminopropanols was evaluated for acute toxicity, anticonvulsant, anorexigenic, and anticholinergic activity as well as effect on simple reflexes. Therapeutic ratio was maximized in 1,1-diphenyl-2-methyl-3-aminopropanol·HCl (II-2). Anticholinergic activity was minimized by the presence of a 2-Me group. In general, tertiary amines were less active as anticonvulsants and on simple reflexes, than primary or secondary amines. Also increasing the size of the substituents on the amine decreased activity. Substitution on the Ph rings decreased activity except for the *m*-F derivative which was more active than II-2 but also more toxic. The optical isomers of II-2 were resolved and the *l* isomer (II-6) was no more toxic but markedly superior in activity.

The synthesis of a series of diphenyl aminopropanols which we have studied is reported in the two preceding communications.[1] Our interest in the compounds was due to their unique dose-related spectrum of pharmacologic activity. Administration of one of the more potent analogs to a variety of species produces apparent stimulation at low doses. At slightly higher doses the effect is one of mixed stimulation and depression with marked motor incoordination. In this dose range some of the compounds appeared to be potent anticonvulsants. Still higher doses produce convulsions in rats and mice and an apparent paralysis with ocassional clonic twitching in cats and dogs. Because of this spectrum of effects, structure–activity studies had to include a broad spectrum of tests. For this reason, testing included effects of the compounds on anticonvulsant and anorexigenic end points as well as effects on several simple reflexes. Anticholinergic testing was also included since many diphenyl aminopropanols are known cholinergic blocking agents.[2] Although it is not known which, if any, of the CNS effects are mediated by a cholinergic mechanism, it was hoped useful compounds could be found by maximizing the CNS effects while minimizing the peripheral effects.

**Methods.**—Male albino mice of the Carworth Farms strain (18–22 g) and adult mongrel dogs were used in all studies. For studies in mice, compounds were suspended or dissolved in 0.25% aq methylcellulose and administered ip. At least 3 dose levels spaced at a 0.3 log interval were used for each end point. The effective dose ($ED_{50}$) was calcd by the Spearman and Karber method.[3]

Procedures for measuring acute toxicity ($LD_{50}$), antagonism of nicotine seizure ($N_{50}$), and antagonism of isolation-induced stress ($FM_{50}$) have been described.[4] The same source also describes methods for evaluation of compounds on simple behavioral reflexes—traction

(1) Articles 1 and 2: R. B. Moffett, R. E. Strube, and L. L. Skaletzky, *J. Med. Chem.*, **14**, 1088 (1971); and R. B. Moffett and T. L. Pickering, *ibid.*, **14**, 1100 (1971). The numbering of compounds in this article refers to that used in the preceding articles. I refers to Table I in article I. II refers to Table I in article II. Compounds designated III have been previously reported (see ref 2 and footnotes in tables).

(2) (a) J. J. Denton, H. P. Schedl, W. B. Neir, and V. A. Lawson, *J. Amer. Chem. Soc.*, **71**, 2054 (1949); (b) R. W. Cunningham, B. K. Hained, M. C. Clark, R. R. Cosgrove, N. S. Daugherty, C. H. Hine, R. E. Vessey, and N. N. Yda, *J. Pharmacol. Exp. Ther.*, **96**, 151 (1949); (c) D. W. Adamson, *J. Chem. Soc., Suppl.*, **5**, 144 (1949).

(3) D. J. Finney, "Statistical Methods in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952.

(4) G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DaVanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964).