Central Nervous System Agents. 1. Synthesis of Diphenyl-*tert*-aminopropanols

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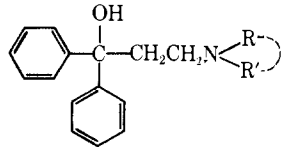
In the search for useful CNS drugs, a large series of 1,1-diaryl-2-methyl-3-*tert*-aminopropanols (II) were prepared. Most of these were prepared by a Grignard reaction with β-*tert*-amino esters, but several alternate methods are described. To round out the structure–activity relationships of their anticonvulsant, anticholinergic anorexigenic, etc., properties a number of derivatives and other related compounds were made.

It is well known that many anticholinergics have strong CNS effects which are undesirable side effects when peripheral activity is desired. Also, many CNS drugs have undesirable peripheral anticholinergic components. It is widely postulated that many CNS nerve impulses are transmitted by cholinergic mechanisms and drugs that would enhance or block these impulses might be useful in mental disease if they could be divorced from their peripheral effects.

In the past, a large number of aminopropanols of the general structure I have been investigated for their anticholinergic properties.[1] Previous workers[1f] have noted



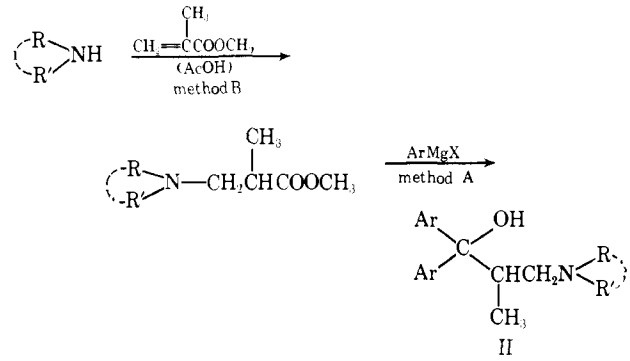
I

that branching (for example with a Me group) on C-2 of the propanol chain markedly decreased the anticholinergic properties. Probably for this reason, these branched-chain compounds have been little investigated.

This observation has been confirmed in these laboratories[2] but surprisingly the CNS effects, as exemplified by anticonvulsant and anorexigenic action on simple reflexes, were equal to or greater than those of the unbranched analogs. We have, therefore, prepared a large number of branched compounds (Table I) for study as CNS agents.

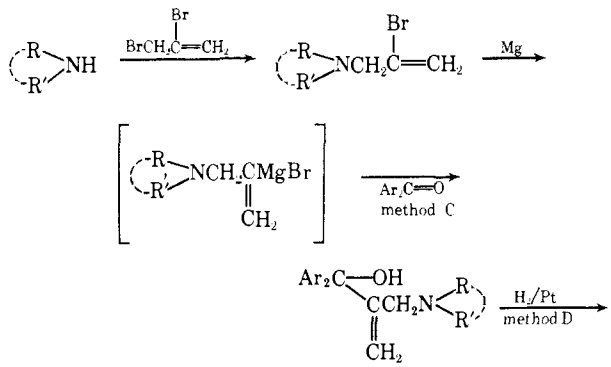
In most cases, these compounds were prepared by the action of an aryl Grignard reagent on β-*tert*-aminoisobutyrate ester (method A). These esters were made by the addition of a secondary amine to methyl methacrylate (method B). Reactive amines (*e.g.*, pyrrolidine) give excellent yields by simply mixing, but less reactive or hindered amines often require many days at room temp and even then the yields may be low. A small amount of AcOH (*e.g.*, 10 mole %) greatly facilitates these difficult reactions (Table II).

In the case of the very hindered $(i\text{-Pr})_2NH$ even the use of AcOH catalyst failed to give a practical yield of



II

the amino ester **124**. The preparation of 1,1-diphenyl-2-methyl-3-(diisopropylamino)propanol·HCl (**7**) was achieved by the elegant method of Ficini, *et al.*,[3] which involves the use of 3-(*tert*-amino)propene 2-magnesium bromide (methods C and D) as follows



This method is also useful when the requisite ArMgX is not available and the diaryl ketone is (*e.g.*, with 9-fluorenone).

An alternate method (methods F and G) for preparing compounds of this series from diaryl ketones involves condensation of an N,N-disubstituted amide with the ketone[4] followed by LAH reduction. In our hands lithium dialkyl amides[5] or $NaNH_2$ seemed to be superior to anhyd KOH as the condensing agent.

A few compounds were prepared with groups other than Me on C-2 of the propanol chain, by a Grignard reaction on the appropriately substituted 3-*tert*-aminopropiophenone (method H). This is the method of

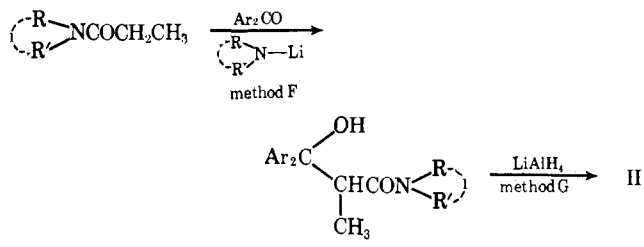
(1) (a) J. J. Denton, H. P. Schedl, W. B. Neier, and V. A. Lawson, *J. Amer. Chem. Soc.*, **71**, 2054 (1949); (b) R. W. Cunningham, B. K. Harned, M. C. Clark, R. R. Cosgrove, N. S. Daugherty, C. H. Hine, R. E. Vessey, and N. N. Yuda, *J. Pharmacol. Exp. Ther.*, **96**, 151 (1949); (c) D. W. Adamson, *J. Chem. Soc., Suppl.*, **1**, S 144 (1949); (d) A. W. Ruddy and J. S. Buckley, *J. Amer. Chem. Soc.*, **72**, 718 (1950); (e) A. C. White, A. F. Green, and A. Hudson, *Brit. J. Pharmacol. Chemother.*, **6**, 560 (1951); (f) A. M. Lands and F. P. Luduena, *J. Pharmacol. Exp. Ther.*, **116**, 177 (1956).

(2) Pharmacology of these compds is reported in article 3 of this series: H. H. Krasling and R. B. Moffett, *J. Med. Chem.*, **14**, 1106 (1971).

(3) (a) J. Ficini, G. Sarrade-Loucheur, and H. Normant, *Bull. Soc. Chim. Fr.*, 1219 (1962); (b) A. Marxer, U. S. Patent 3,458,906 (1969).

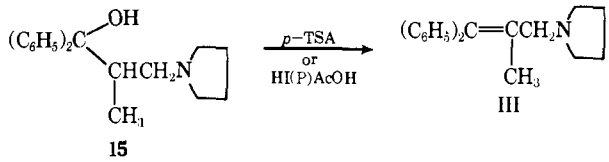
(4) W. Chodkiewicz, P. Cadiot, A. Willemart, and S. Prévost, *Bull. Soc. Chim. Fr.*, 1586 (1958).

(5) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **75**, 2415 (1953).



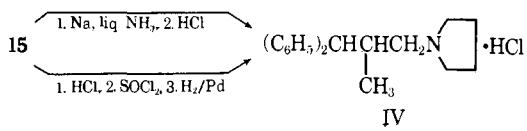
choice if two different aryl groups are desired in the molecule.

In order to test the biological effects of removing the OH group it was desired to make both the unsaturated (III) and saturated (IV) analogs. 1,1-Diphenyl-2-methyl-3-(1-pyrrolidinyl)propanol (**15**) was easily dehydrated with acids giving III.



An attempt to reduce **15** to the saturated compound IV using P–HI by the procedure of Ruddy and Buckley[1d] gave III instead. The unsaturated structure was confirmed by ir, uv, and especially nmr spectra. Since this shed doubt on the structure of the compounds reported by Ruddy and Buckley, their work was repeated in the case of the corresponding piperidine compound giving materials that essentially checked their melting points for free base and hydrochloride. Spectra indicated this was the unsaturated rather than the saturated structure reported.[1d] The same hydrochloride was obtained by dehydrating the carbinol with HCl in AcOH, a procedure that could not lead to reduction. Our melting point (226.5–229°) agrees fairly well with that reported by Kjaer and Petersen[6] (mp 222°), who prepared it by a different method. The saturated 1,1-diphenyl-2-methyl-3-(1-piperidinyl)propane·HCl has been reported by Bockmühl and Ehrhart[7] (mp 206–208°), who prepared it by 2 unambiguous methods. The compound, mp 211–212°, reported by Bockmühl, *et al.*,[8] is probably the isomeric 1,1-diphenyl-3-methyl-3-(1-piperidinyl)butane·HCl, which was also prepared by the same workers[8b] and reported, mp 214°. It is not known whether the other *N*-(3-phenylpropyl)piperidines reported by Ruddy and Buckley[1d] in their Table II are correctly formulated or not.

The desired saturated pyrrolidine IV was finally made by 2 methods. The best yields were obtained by the method of Beckett, *et al.*[9] using Na and liq NH_3 to reduce the carbinol **15**. The same compound was obtained by replacing OH by Cl which was then removed by hydrogenation.



Attempts to hydrogenate the unsaturated compound III failed to give any H_2 uptake under conditions that would not hydrogenate the benzene rings.

Experimental Section[10]

Method A. 1,1-Diphenyl-2-methyl-3-(1-pyrrolidinyl)propanol (15).[11]—To 5.34 l. (16 moles) of 3 *M* PhMgBr in Et_2O was slowly added with stirring a soln of 684 g (4 moles) of methyl β-(1-pyrrolidyl)isobutyrate[12] in 4.3 l. of abs Et_2O. The mixt was stirred under reflux for 2 hr more, cooled, and poured into ice water contg an excess of HCl[13] giving white cryst salt, insol in bath layers, which was collected and washed (H_2O, Et_2O). This was converted to the free base by dissolving it in 20 l. of boiling H_2O and adding a slight excess of aq NaOH. The free base was collected, washed (H_2O), and dried giving 1.094 kg of light tan solid, mp 115.5–117°. This was recrystd from 7.5 l. of 95% EtOH, filtd hot, and cooled yielding 975.4 g of white cryst solid, mp 117–118.5°.

Methobromide (17).—To a cold soln of 44.3 g (0.15 mole) of the free base **15** in 400 ml of EtCOMe was added 28.5 g (0.3 mole) of cold MeBr. The flask was stoppered, clamped, and allowed to stand at room temp for 3 days. The resulting crystals were collected, washed (EtCOMe, abs Et_2O), and dried giving 58.35 g of white crystals, mp 234–237° dec.

***l*-1,1-Diphenyl-2-methyl-3(1-pyrrolidinyl)propanol *d*-Tartrate (18).**—A soln of 29.5 g (0.1 mole) of the *dl* free base **15** and 15.0 g (0.1 mole) of *d*-tartaric acid in 350 ml of Me_2CO contg about 10 ml of H_2O was concd *in vacuo* to 150 ml during which considerable white solid separated. This solid was collected, washed with moist Me_2CO, and dried giving 27.1 g of white solid, mp 63–70°, $[\alpha]^{25}D$ + 36.5° (H_2O). The sample used for the rotation was evapd *in vacuo* and added to the rest of the solid which was recrystd 6 times from 80% *i*-PrOH giving 9.9 g of white cryst solid, mp 68–97°; $[\alpha]^{25}D$ + 46.9 ± 0.5° (α 1.09; *c*, 0.2903 g in 25 ml of water, *l* = 2). Karl Fischer anal. showed 1.40% H_2O. The sample for anal. was further dried but still seemed to contain some H_2O. *Anal.* ($C_{24}H_{31}NO_7$) Calcd: C, 64.70; H, 7.01; H, 3.14; found: C, 64.26; H, 7.58; N, 2.91.

***d*-1,1-Diphenyl-2-methyl-3-(1-pyrrolidinyl)propanol *l*-Tartrate (19).**—The above Me_2CO filtrate was evapd to dryness giving 24 g of a gummy solid ($[\alpha]^{25}D$ −25.6°). This was dissolved in H_2O, filtd, and converted to the free base with NaOH. The cryst crude base was collected, washed (H_2O), and dried giving 13.85 g of nearly white solid, mp 127–135°, $[\alpha]^{25}D$ +32.7° ($CHCl_3$). This crude *d* base was suspended in 80 ml of *i*-PrOH and 7.05 g of *l*-tartaric acid in 20 ml of H_2E was added. The mixt was warmed to effect soln and on cooling, crystals sepd. The crystals were collected and recrystd twice more from 80% *i*-PrOH giving 13.1 g of white cryst solid, mp 86–97°; $[\alpha]^{25}D$ −48.2° ± 0.5° (α 1.09°; *c*, 0.2827 g in 25 ml of water, *l* = 2). Karl Fischer anal. showed 1.52% H_2O. The sample for anal. was further dried but still seemed to cont some H_2O. *Anal.* ($C_{24}H_{31}NO_7$) Calcd: C, 64.70; H, 7.01; N, 3.14; found: C, 64.19; H, 7.68; N, 3.05.

***l*-1,1-Diphenyl-2-methyl-3-(1-pyrrolidinyl)propanol (20).**—An aq soln of 17 g of *l* base *d*-tartrate (**18**) ($[\alpha]^{25}D$ +47) was basified with NaOH and the resulting cryst base was collected, washed (H_2O), and dried giving 9.37 g of white solid, mp 133.5–137°, $[\alpha]^{25}D$ −39.0. This was recrystd from 100 ml of *i*-PrOH yielding 8.8 g of white crystals, mp 135–137.5°, $[\alpha]^{25}D$ −38.9 ± 0.5° (α 0.92 ± 0.01°; *c*, 0.2952 g in 25 ml of $CHCl_3$, *l* = 2).

***d*-1,1-Diphenyl-2-methyl-3-(1-pyrrolidinyl)propanol·HCl (21).**—The above *l* free base (**20**) (8.5 g) was dissolved in 60 ml of warm EtOH and acidified with 4 ml of about 7.1 *N* ethanolic HCl.

(6) A. C. Kjaer and P. V. Petersen, *Acta Chem. Scand.*, **5**, 1145 (1951).

(7) M. Bockmühl and C. Ehrhart, *Justus Liebigs Ann. Chem.*, **561**, 52 (1948).

(8) M. Bockmühl, G. Ehrhart, O. Eisleb, and L. Stein, U. S. Patent 2,446,522 (1948); (b) German Patent 766,207 (1952); *Chem. Abstr.* **52**, 7356c (1958).

(9) A. H. Beckett, G. Kirk, and R. Thomas, *J. Chem. Soc.*, 1386 (1962).

(10) Mps were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compds showed no need for correction. Absorption peaks of spectra on a Varian A-60 instrument (ir and in selected cases nmr) 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.

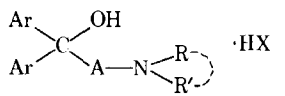
(11) Reported by R. Geoffrey, W. Spickett, and H. F. Ridley, S. Africa Patent Specification, 1909 (1962), but without details of prep or anal.

(12) R. B. Moffett, *J. Org. Chem.*, **14**, 862 (1949).

(13) In most cases when a bromide Grignard reagent was used, the reaction mixt was decompd with HBr to avoid a mixt of anions. Often the hydrobromide was sufficiently insol in both the aq and Et_2O layers to be sepd by filtn or decantation and recrystd without going through the free base.

TABLE I

1,1-DIARYLAMINO CARBINOLS



No.[a]	Structure	·HX	Method of prepn	Yield, %[b]	Mp, °C	Crystallizing solvent	Formula	Anal.
1	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_3)CH_2CH_3$	HBr	A	67[c]	175.5–176.5	EtOH-*i*-PrOH	$C_{19}H_{26}BrNO$	C, H, Br, N
2	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_3)CH_2CH_2CH_3$	HBr	*d*	57.3[d]	157–159	EtOAc	$C_{20}H_{28}BrNO$	C, H, Br, N
3	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_3)CH(CH_3)_2$	HBr	A	41[c]	191.5 dec	EtOH	$C_{20}H_{28}BrNO$	C, H, Br, N
4	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2CH_2CH_3)_2$	HCl	*d*	65[d]	171–172.5	MeEtCO	$C_{22}H_{32}ClNO$	C, H, Cl, N
5	$(C_6H_5)_2C(OH)C(=CH_2)CH_2N[CH(CH_3)_2]_2$	Base	C	60	89–90.5	*i*-PrOH	$C_{22}H_{29}NO$	C, H, N
6	$(C_6H_5)_2C(OH)C(=CH_2)CH_2N[CH(CH_3)_2]_2$	HCl	E	100	182–184 dec	EtOH–Et_2O	$C_{22}H_{30}ClNO$	C, H, Cl, N
7	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N[CH(CH_3)_2]_2$	HCl	D	64[e]	226–227.5 dec	*i*-PrOH	$C_{22}H_{32}ClNO$	C, H, Cl, N
8	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N[(CH_2)_3CH_3]_2$	HBr	A	68[f]	145.5–147	EtOH	$C_{24}H_{36}BrNO$	C, H, Br, N
9	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N[CH_2CH(CH_3)_2]_2$	Base	A	50	86–87	95% EtOH	$C_{24}H_{35}NO$	C, H, N
10	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_3)CH_2CH{=}CH_2$	HBr	A[e]	14[c,g]	158–160	*i*-PrOH	$C_{20}H_{28}BrNO$	C, H, Br, N
11	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_3)CH_2CH{=}CH_2$	HCl	E[e]	40[g]	179–180.5	*i*-PrOH–Et_2O	$C_{29}H_{26}ClNO$	C, H, Cl, N
12	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2CH{=}CH_2)_2$	HCl	A	81[c]	165.5–167	MeEtCO	$C_{22}H_{28}ClNO$	C, H, Cl, N
13	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_3)CH(CH_2)_3CH_2$	Maleate	A[h]	82[c]	129–131	*i*-PrOH	$C_{26}H_{33}NO_5$	C, H, N
14	$(C_6H_5)_2C(OH)CH(CH_3)CH_2NCH_2CH_2CH_2$	HBr	A	32[c]	167–170	EtOH	$C_{19}H_{24}BrNO$	C, H, Br, N
15	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	Base[i]	A[d]	93	118–119	95% EtOH	$C_{20}H_{25}NO$	C, H, N, O
16	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	HCl	E[i]	75	235–236	H_2O	$C_{20}H_{26}ClNO$	C, H, Cl, N
17	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	CH_3Br	*d*	100	234–237 dec	MeEtCO	$C_{21}H_{28}BrNO$	C, H, Br, N
18	*l*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$[k]	*d*-Tartrate	*d*	44[l]	86–97	80% *i*-PrOH	$C_{24}H_{31}NO_7 \cdot xH_2O$[d]	C, H, N[l]
19	*d*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$[m]	*l*-Tartrate	*d*	58[l]	86–97	80% *i*-PrOH	$C_{24}H_{31}NO_7 \cdot xH_2O$[d]	C, H, N[l]
20	*l*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$[k]	Base	*d*	85[d]	135–135.5	*i*-PrOH	$C_{20}H_{25}NO$	C, H, N
21	*d*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$[k]	HCl	*d*	96[d]	235–236	EtOH	$C_{20}H_{26}ClNO$	C, H, Cl, N
22	*d*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$[m]	Base	*d*	100[d]	135–137.5	*i*-PrOH	$C_{20}H_{25}NO$	C, H, N
23	*l*-$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$[m]	HCl	*d*	96[d]	234–235.5	EtOH	$C_{20}H_{26}ClNO$	C, H, Cl, N
24	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(\rightarrow O)(CH_2)_3CH_2$	Base	*d*	55[d]	161.5–164	C_6H_6	$C_{20}H_{25}NO_2$	C, H, N, O
25	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(\rightarrow O)(CH_2)_3CH_2$	HCl	E	50	190.5–192.5	*i*-PrOH	$C_{20}H_{26}ClNO_2$	C, H, Cl, N
26	$(C_6H_5)_2C(OH)C(=CH_2)CH_2N(CH_2)_3CH_2$	Base	C[n]	69	112.5–113.5	*i*-PrOH	$C_{20}H_{23}NO$	C, H, N
27	$(C_6H_5)_2C(OH)C(=CH_2)CH_2N(CH_2)_3CH_2$	HCl	E	92	210.5–211	EtOH–Et_2O	$C_{20}H_{24}ClNO$	C, H, Cl, N
28	$(C_6H_5)_2C(OH)CH(CH_2CH_3)CH_2N(CH_2)_3CH_2$	HCl	H[o]	83[o]	212	*i*-PrOH–Et_2O	$C_{21}H_{28}ClNO$	C, H, Cl, N
29	$(C_6H_5)_2C(OH)CH[CH(CH_3)_2]CH_2N(CH_2)_3CH_2$	HCl	H[p]	90[p]	209–210 dec	EtOH–Et_2O	$C_{22}H_{30}ClNO$	C, H, Cl, N
30	$(C_6H_5)_2C(OH)CH(C_6H_5)CH_2N(CH_2)_3CH_2$	Base	H[d]	93	173–173.5	*n*-BuOH	$C_{25}H_{27}NO$	C, H, N

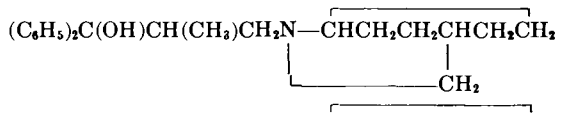
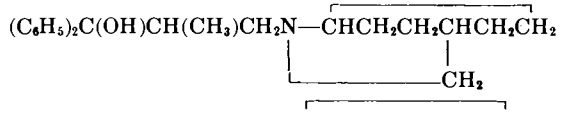
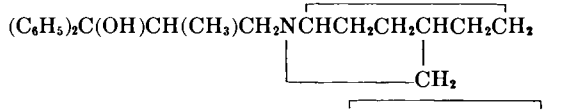
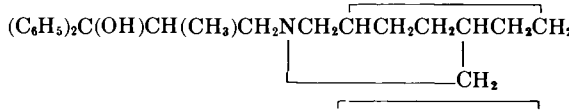
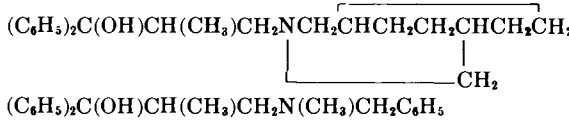
31	$(C_6H_5)_2C(OH)CH(C_6H_5)CH_2N(CH_2)_3CH_2$	HCl	C	74	229–230	MeOH–Et_2O	$C_{25}H_{28}ClNO$	C, H, Cl, N
32	$(C_6H_5)_2C(OH)C(CH_3)_2CH_2N(CH_2)_3CH_2$	HBr	H[q]	63[q]	228.5	95% EtOH	$C_{21}H_{28}BrNO$	C, H, Br, N
33	$(C_6H_5)_2C(OH)CH_2CH(CH_3)N(CH_2)_3CH_2$	Base	A[r]	45[r]	123.5–126	95% EtOH	$C_{20}H_{25}NO$	C, H, N
34	$(C_6H_5)_2C(OH)CH_2CH(CH_3)N(CH_2)_3CH_2$	HCl	E	80	210–211.5	EtOH	$C_{20}H_{26}ClNO$	C, H, Cl, N
35	$(C_6H_5)_2C(OH)CH_2CH_2CH_2N(CH_2)_3CH_2$	HCl	C[s,t]	54	179[t]	EtOH–Et_2O	$C_{20}H_{26}ClNO$	C, H, Cl, N
36	$(C_6H_5)_2C(OH)CH_2CH(CH_3)CH_2N(CH_2)_3CH_2$	HCl	C[s]	71	179	*i*-PrOH–Et_2O	$C_{21}H_{28}ClNO$	C, H, Cl, N
37	$(C_6H_5)_2C(OH)CH(CH_3)CH_2CH_2N(CH_2)_3CH_2$	HCl	C[s]	0.86	238	*i*-PrOH–Et_2O	$C_{21}H_{28}ClNO$	C, H, Cl, N
38	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CHCH_3$	Base	A	21	86–88	95% EtOH	$C_{21}H_{27}NO$	C, H, N
39	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CHCH_3$	HCl	E	60	243–245	MeOH	$C_{21}H_{28}ClNO$	C, H, Cl, N
40	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CHCH_3$	HBr	*u*	70	231.5	MeOH	$C_{21}H_{28}BrNO$	C, H, Br, N
41	$(C_6H_5)_2C(OH)CH(CH_3)CH_2NCH(CH_3)(CH_2)_2CHCH_3$	HBr	A	36	199–200	H_2O	$C_{22}H_{30}BrNO$	C, H, Br, N
42	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3C(CH_3)_2$	Base	A	57	126–127.5	95% EtOH	$C_{22}H_{29}NO$	C, H, N, O
43	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3C(CH_3)_2$	HCl	E	81	250 dec	MeOH	$C_{22}H_{30}ClNO$	C, H, Cl, N
44	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3C(CH_3)_2$	HBr	*u*	52	236.5 dec	MeOH	$C_{22}H_{30}BrNO$	C, H, Br, N
45	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_4CH_2$	HBr	A	90	206 dec	EtOH	$C_{21}H_{28}BrNO$	C,[v] H, Br, N
46	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2)_3C(CH_2)_4CH_2$	HBr	A	12	220–221 dec	MeOH	$C_{25}H_{34}BrNO$	C, H, Br, N
47		HBr	A	50	214–216 dec	EtOH	$C_{23}H_{30}BrNO$	C, H, Br, N
48		Base	*w*	57[w]	170–171.5	MeEtCO	$C_{23}H_{29}NO$	C, H, N
49		HCl	E	82	254–255.5 dec	EtOH	$C_{23}H_{30}ClNO$	C, H, Cl, N
50		Base	A	55	156.5–157.5	$C_6H_{11}CH_3$[x]	$C_{24}H_{31}NO$	C, H, N
51		HCl	E	43	221–222.5	*i*-PrOH	$C_{24}H_{32}ClNO$	C, H, Cl, N
52	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_3)CH_2C_6H_5$	Base	A	71	86–89	*i*-PrOH	$C_{24}H_{27}NO$	C, H, N
53	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_3)CH_2C_6H_5$	HCl[w]	E	56	171–173	*i*-PrOH–EtOAc	$C_{24}H_{28}ClNO$	C, H, Cl, N
54	$(C_6H_5)_2C(OH)CH_2CH(CH_3)N(CH_3)CH_2C_6H_5$	HBr	A	41	186.5 dec	*i*-PrOH	$C_{24}H_{28}BrNO$	C, H, Br, N
55	$(C_6H_5)_2C(OH)CH_2CH(CH_3)N(CH_3)CH_2C_6H_5$	Base	*z*	84	91–93	*i*-PrOH	$C_{24}H_{27}NO$	C, H, N
56	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)CH_2C_6H_5$	HCl	A	13[c]	169.5–171	MeEtCO	$C_{25}H_{30}ClNO$	C, H, Cl, N
57	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2C_6H_5)_2$	HCl	A[aa]	32[c]	171–173	EtOAc	$C_{30}H_{32}ClNO$	C, H, Cl, N

Table I (*Continued*)

No.[a]	Structure	HX	Method of prepn	Yield, %[b]	Mp, °C	Crystallizing solvent	Formula	Anal.
58	$(C_6H_5)_2C(OH)CH(CH_3)CON(CH_2C_6H_5)_2$		F[bb,cc]	25	122–123	Pentane	$C_{30}H_{29}NO_2$	C, H, N
59	$(C_6H_5)_2C(OH)CH(CH_3)CON(CH_2C_6H_5)(CH_2)_5CH_3$		F[bb,dd]	41	108–110	EtOAc	$C_{29}H_{35}NO_2$	C, H, N
60	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_2CH_2OCH_3)_2$	HCl	A[ee]	70[c]	107.5–109	EtOAc	$C_{22}H_{32}ClNO_3$	C, H, Cl, N
61	$(C_6H_5)_2C(OH)CH(CH_3)CH_2NCH_2CH(CH_3)OCH(CH_3)CH_2$	HBr	A[ff]	60	191–194 dec[ff]	EtOH	$C_{22}H_{30}BrNO_2$	C, H, Br, N
62	$(C_6H_5)_2C(OH)CH(CH_3)CH_2NCH_2CH(CH_3)OCH(CH_3)CH_2$	HCl	E[gg]	60[gg]	200–202 dec	*i*-PrOH	$C_{22}H_{30}ClNO_2$	C, H, Cl, N
63	$(C_6H_5)_2C(OH)CH(CH_3)CH_2NCH(CH_3)CH_2OCH_2CHCH_3$	CH_3SO_3H	A[hh]	13[c]	213 dec	EtOH	$C_{23}H_{33}NO_5S$	C, H, N, S
64	$(C_6H_5)_2C(OH)CH(CH_3)CH_2NCH_2CH_2SCH_2CH_2$	HBr	A	80	190–191	95% EtOH	$C_{20}H_{26}BrNOS$	C, H, Br, N, S
65	$(C_6H_5)_2C(OH)CH(CH_3)CH_2N(CH_3)CH_2CH_2N(CH_3)_2$	2HCl	A[ee]	18[c,ii]	226 dec	MeOH	$C_{21}H_{32}Cl_2N_2O$	C, H, Cl, N
66	$(C_6H_5)_2C(OH)CH(CH_3)CH_2NCH_2CH_2N(CH_3)CH_2CH_2$	Base[i]	A[ee,jj]	89	139.5–141	Et_2O	$C_{21}H_{28}N_2O$	C, H, N
67	$(C_6H_5)_2C(OH)CH(CH_3)CH_2NCH_2CH_2N(CH_3)CH_2CH_2$	2HCl	E	100	244–245	EtOH	$C_{21}H_{30}Cl_2N_2O$	C, H, Cl, N
68	$(C_6H_5)_2C(OH)CHCH_2N(CH_3)CH_2CH_2$	Base	*d*		71.5–72.5	Hexane	$C_{18}H_{21}NO$	C, H, N
69	$(C_6H_5)_2C(OH)CHCH_2N(CH_3)CH_2CH_2$	HCl[kk]	E[ll]	73[ll]	234–236	MeOH–Et_2O	$C_{18}H_{22}ClNO$	C, H, Cl, N
70	$(C_6H_5)_2C(OH)CHCH_2NCH_2CH_2CHCH_2CH_2$	HBr	A[mm]	66	271–272 dec	EtOH	$C_{20}H_{24}BrNO$	C, H, Br, N
71	$(4\text{-}CH_3C_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	HCl	A[nn]	50[c]	181–182	*i*-PrOH–MeEtCO	$C_{22}H_{32}ClNO$	C, H, Cl, N
72	$(2\text{-}CH_3C_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	HBr[oo]	A	15	210–211 dec	EtOH	$C_{22}H_{30}BrNO$	C, H, Br, N
73	$(4\text{-}C_6H_5C_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	HBr	A	72	222–223 dec	MeOH	$C_{32}H_{36}BrNO$	C, H, Br, N
74	$(3\text{-}FC_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	HBr	A	4[pp]	137.5–139	EtOAc	$C_{20}H_{26}BrF_2N$	C, H, Br, F, N
75	$(3\text{-}FC_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	Base	*pp*	65[pp]	63–65	EtOH–H_2O	$C_{20}H_{25}F_2NO$	C, H, F, N
76	$(3\text{-}FC_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	HCl	E		154.5–156	MeEtCO	$C_{20}H_{26}ClF_2NO$	C, H, Cl, F, N
77	$(3\text{-}FC_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	HBr	A	88	221.5–222	95% EtOH	$C_{20}H_{24}BrF_2NO$	C, H, Br, F, N
78	$(3\text{-}ClC_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	HCl	A	56[c]	215–217	EtOH	$C_{20}H_{26}Cl_3NO$	C, H, Cl, N
79	$(4\text{-}ClC_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	HCl	A	56[c]	224–225	MeOH	$C_{20}H_{26}Cl_3NO$	C, H, Cl, N
80	$(2\text{-}ClC_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	HCl	A	26[c]	252–253	95% EtOH	$C_{20}H_{24}Cl_3NO$	C, H, Cl, N
81	$(3\text{-}BrC_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	HCl	A	25[c]	213.5–215.5	*i*-PrOH	$C_{20}H_{26}Br_2ClNO$	C, H, Cl, N
82	$(4\text{-}BrC_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	HCl	*qq*	4[c]	231–232	MeOH	$C_{20}H_{26}Br_2ClNO$	C, H, Cl, N
83	$(3\text{-}CF_3C_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	HCl	A	26[c]	206.5–208	*i*-PrOH–Et_2O	$C_{22}H_{24}ClF_6NO$	C, H, Cl, F, N
84	$[3,5(CF_3)_2C_6H_3]_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	Base	A	94	100.5–101.5	*i*-PrOH	$C_{24}H_{21}F_{12}NO$	C, H, F,[rr] N
85	$[3,5(CH_3)_2C_6H_3](C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	HCl	E	100	298–299 dec	MeOH	$C_{24}H_{22}ClF_{12}NO$	C, H, Cl, F, N
86	$(2\text{-}OCH_3C_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	HBr	A	79	235–236	95% EtOH	$C_{22}H_{30}BrNO_3$	C, H, Br, N
87	$(3\text{-}OCH_3C_6H_4)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	HBr	A	72	207–209 dec	MeOH	$C_{22}H_{30}BrNO_3$	C, H, Br, N
88	$[3,4\text{-}(OCH_3)_2C_6H_3]_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	Base	A[ss]	16	83.5–84.5	EtOAc–hexane	$C_{24}H_{35}NO_5$	C, H, N
89	$[(3,4\text{-}OCH_2O\text{-})C_6H_3]_2C(OH)CH(CH_3)CH_2N(CH_2CH_3)_2$	Base	A[ss]	66	97–99	*i*-PrOH	$C_{22}H_{27}NO_5$	C, H, N
90	$[4\text{-}N(CH_3)_2C_6H_4]_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$	Base	A[ee,tt]	81	179.5	EtOAc	$C_{24}H_{35}N_3O$	C, H, N
91	$3,4,5(OCH_3)_3C_6H_2C(OH)(C_6H_5)$ $\lvert$ $CH_2CH_2N(CH_3)_2$	Base	*d*	22[d]	129–130	MeOH	$C_{20}H_{27}NO_4$	C, H, N
92	$3,4,5(OCH_3)_3C_6H_2C(OH)(C_6H_5)$ $\lvert$ $CH_2CH_2N(CH_3)_2$	HCl	E	46	172.5–173	MeEtCO	$C_{20}H_{28}ClNO_4$	C, H, Cl, N

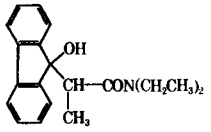
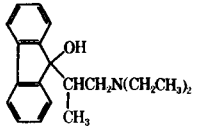
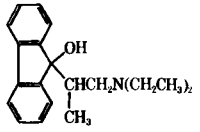
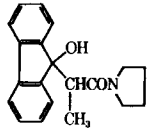
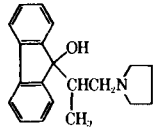
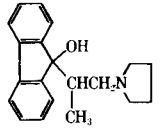
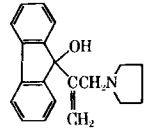
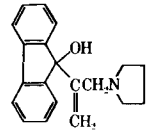
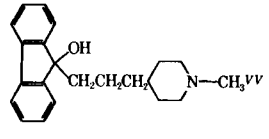
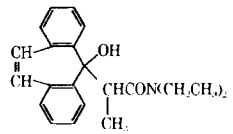
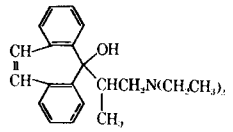
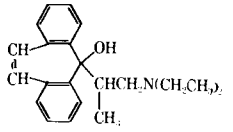
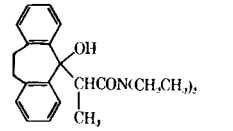
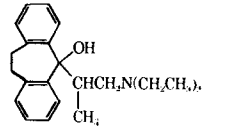
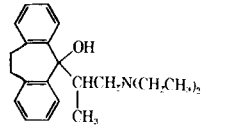
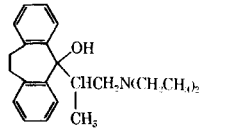
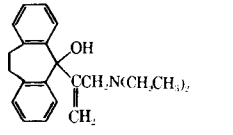
93	$(2\text{-}C_4H_3S)_2C(OH)CH(CH_3)CH_2N(CH_2)_3CH_2$[uu]	HBr	A	80	135–137	H_2O	$C_{16}H_{22}BrNOS_2$	C, H, Br, N, S
94	$(4\text{-}C_5H_4)_2C(OH)(CH_2)_4N(CH_2CH_3)_2$[vv,ww]	Base	*d*	69[d]	110–111	$C_6H_{11}CH_3$[z]	$C_{19}H_{27}N_3O$	C, H, N
95			F	63	86–87	*i*-PrOH	$C_{20}H_{23}NO_2$	C, H, N
96		Base	G	88	89–90.5	Petr ether	$C_{20}H_{25}NO$	C, H, N
97		HCl	E	89	198–200	EtOH–Et_2O	$C_{20}H_{26}ClNO$	C, H, Cl, N
98			F	56	152–153	*i*-PrOH	$C_{20}H_{21}NO_2$	C, H, N
99		Base	G	45	106–107	Hexane	$C_{20}H_{23}NO$	C, H, N
100		HCl[xx]	E	100	253 dec	EtOH	$C_{20}H_{24}ClNO$	C, H, Cl, N
101		Base	C[n,yy]	27	93–93.5	Hexane	$C_{20}H_{21}NO$	C, H, N
102		HCl	E	100	195–196	*i*-PrOH	$C_{20}H_{22}ClNO$	C, H, Cl, N
103		Base	C[zz]	54	152.5–154	C_6H_6	$C_{22}H_{27}NO$	C, H, N

Table I (*Continued*)

No.[a]	Structure	·HX	Method of prepn	Yield, %[b]	Mp, °C	Crystallizing solvent	Formula	Anal.
104			F[d]	64	127–128	*i*-PrOH–hexane	$C_{22}H_{25}NO_2$	C, H, N
105		Base	G[d]	60[d]	97–98	Hexane	$C_{22}H_{27}NO$	C, H, N
106		HCl	E	109	231–232	EtOH–Et_2O	$C_{22}H_{28}ClNO$	C, H, Cl, N
107			F	56	91–92	Hexane	$C_{22}H_{27}NO_2$	C, H, N
108		Base	G	31	80.5–81.5	Heptane	$C_{22}H_{29}NO$	C, H, N
109		HCl	E	84	237–238	EtOH	$C_{22}H_{30}ClNO$	C, H, N
110		Base	C[n,vv,aaa]	24	75.5–77	*i*-PrOH	$C_{22}H_{27}NO$	C, H, N
111		HCl	E	63	183–184	EtOH–MeEtCO	$C_{22}H_{28}ClNO$	C, H, Cl, N

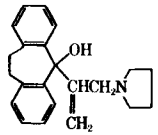
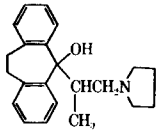
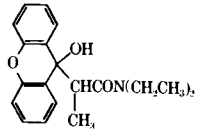
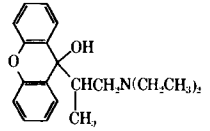
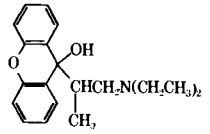
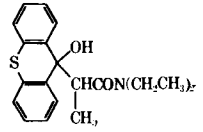
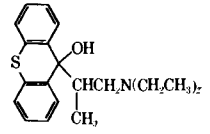
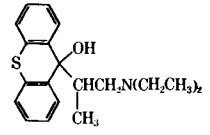
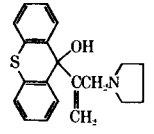
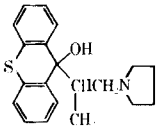
112		HBr	C[a,bbb]	48	228–229	95% EtOH	$C_{22}H_{26}BrNO$	C, H, Br, N
113		HBr	D[ccc]	58	216–217	95% EtOH	$C_{22}H_{26}BrNO$	C, H, Br, N
114			F	64	123–124	*i*-PrOH	$C_{20}H_{23}NO_3$	C, H, N
115		Base	G	63	94.5–98.5	$C_6H_{11}CH_3$[e]	$C_{20}H_{25}NO_2$	C, H, N
116		Maleate	*d*	80[d]	152–153	Et_2O	$C_{24}H_{29}NO_6$	C, H, N
117			F	60	139–140.5	*i*-PrOH	$C_{20}H_{23}NO_2S$	C, H, N
118		Base	G	57	85–87	*i*-PrOH	$C_{20}N_{25}NOS$	C, H, N
119		HCl	E	89	202–203	EtOH–Et_2O	$C_{20}H_{26}ClNOS$	C, H, Cl, N
120		HBr	C[a,bbb]	53	183–184	MeOH[ddd]	$C_{20}H_{22}BrNOS$	C, H, BrN, S,

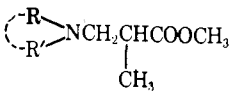
TABLE I (*Continued*)

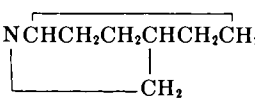
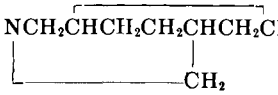
No.[a]	Structure	·HX	Method of prepn	Yield, %[b]	Mp, °C	Crystallizing solvent	Formula	Anal.
121		HBr	D	35	177–178	EtOH[ddd]	$C_{20}H_{24}BrNOS$	C, H, Br, N, S

[a] All compds are numbered consecutively for easy reference in article 3 (ref 2) on the pharmacology of this series. [b] Unless otherwise indicated, the yields of free bases are based on the methyl β-(*tert*-amino)isobutyrate (method A), the diaryl ketone (methods C and F), the 2-methylene-1,1-diphenyl-3-(*tert*-amino)propanol (method D), the *N*,*N*-dialkyl-α-(diphenylmethanol)propionamide (method G), or the β-aminopropiophenone (method H). Yields of salts are based on the free amines. Unless otherwise indicated yields are reported for material melting not less than 2° below the highest mp obtd. [c] The free base was not isolated. The yield is based on the methyl β-(*tert*-amino)isobutyrate. [d] The prepn of this compd is described in the Experimental Section and the yield is based on the starting material specified. [e] The free base was not isolated; the yield is based on the 2-methylene-1,1-diphenyl-3-(*tert*-amino)propanol·HCl. [f] Methyl-β-(dibutylamino)isobutyrate was prepd by method H [bp 64° (0.05 mm)] but was not obtained anal. pure. The yield is based on this impure ester. [g] Part of this product was isolated as the hydrobromide **10**. The filtrates were converted to the free base with NaOH and extd with Et_2O. The oily base was converted to the hydrochloride **11** in the usual way. The total yield was 54%. [h] The free base was not cryst. It was dissolved in Et_2O and acidified with ethanolic maleic acid. The resulting maleate salt was recrystd from *i*-PrOH. [i] See ref 11. [j] The free base was converted to the hydrochloride by dissolving in hot water contg a slight excess of HCl. The hydrochloride crystd on cooling. [k] *l*- (levo) rotating base. The levo base gives dextro rotating salts. [l] Caled on the basis that the theoretical yield of the isolated isomer is 0.5 of the starting material. Even after drying the product contained some H_2O. See Experimental Section. [m] *d*-(dextro) rotating base. The dextro base gives levo rotating salts. [n] No EtBr was needed in the formation of the Grignard reagent, but a few drops of MeMgBr were added to start the reaction. Since completion of this work, this compd and its hydrochloride (**27**) have been reported by Marxer,[3b] however, he reported somewhat lower mp's than we obtained. He gave no anal. [o] The hydrochloride of the Mannich ketone was used in place of the free base with an extra equiv of PhLi. The free base of the product was not isolated but was converted to the hydrochloride in Et_2O. The yield is calcd from the Mannich base·HCl. [p] The free base was not isolated but was converted to the hydrochloride in Et_2O. The yield is calcd from the starting Mannich base. [q] PhMgBr was used in place of PhLi. The Grignard reaction was decompd with ice and HBr giving the hydrobromide as a white solid insol in both layers. The free base was not prepd so the yield is based on the starting Mannich base. Attempts to prep this compd *via* α,α-dimethyl-β,β-diphenyl-β-hydroxypropionylpyrrolidine failed when the attempted condn (method F) gave back starting material. [r] The starting methyl β-(1-pyrrolidinyl)butyrate was prepd in 99% yield by the method of D. W. Adamson, *J. Chem. Soc.*, 885 (1950); bp 97° (16 mm) n^{25}D 1.4585. On reaction with PhMgBr and decompn with ice and HBr, the hydrobromide was obtd as a cryst solid but was not purified. [s] Only a few drops of EtBr was needed to start the Grignard reaction. The free base was not isolated but its Et_2O soln was converted to the hydrochloride with ethereal HCl. [t] The Grignard reagent was made from 1-(3-chloropropyl)pyrrolidine [F. F. Blicke and E. B. Hotelling, *J. Amer. Chem. Soc.*, **76**, 5099 (1954)]. 1,1-Diphenyl-4-(1-pyrrolidinyl)butanol·HCl is reported by J. A. Gautier and C. C. Farnoux [*Bull. Soc. Chim. Fr.*, 2145 (1964)], mp 149°. [u] A soln of 1 g of the free base in 15 ml of hot MeOH was acidified with 48% aq HBr and cooled. [v] C: Calcd, 64.61; found, 64.09. [w] Crude hydrobromide (**47**) was converted to the free base with NaOH and extd with CH_2Cl_2. After washing (H_2O) and drying (Na_2SO_4), the solvent was removed and the base was crystd from EtCOMe. The yield is based on starting methyl β-(2-azabicyclo[2.2.2]octane)-isobutyrate. [x] $C_6H_{11}CH_3$ = methylcyclohexane. [y] The oxalate hemihydrate of this compd was reported (without details or anal.) by Geoffrey, *et al.*[11] [z] The hydrobromide (**54**) was converted to the free base with NaOH, extd with $CHCl_3$ and Et_2O; washed (H_2O), dried (Na_2SO_4), filtd, evapd, and recrystd. [aa] Methyl β-(dibenzylamino)isobutyrate was prepd by method B [bp 127° (0.005 mm)] but was not obtd anal. pure. The yield is based on this impure ester. [bb] Pyrrolidine was used in place of Et_2NH giving *N*-pyrrolidinyllithium which was the condensing agent. [cc] The crude product was crystd first from *n*-BuOH, then from hexane and finally from pentane. [dd] *N*-Benzyl-*N*-(*n*-hexyl)propionamide was prepd as described for *N*,*N*-dibenzylpropionamide. It was distd, bp 121° (0.005 mm), and was used in this prepn although not obtd anal. pure. [ee] The hydrobromide was sol in the aq layer from the decompd Grignard reaction. It was basified with NaOH and the suspension of $Mg(OH)_2$ was well extd with Et_2O. [ff] Starting methyl β-*N*-(2,6-dimethylmorpholino)isobutyrate was obtained from K and K Laboratories, Inc., Plainview, N. Y. [gg] This hydrobromide did not seem to be of high purity. It was converted to its free base with NaOH which was combined with more free base obtd by basifying and extd the aq layer from the Grignard reaction. The free base was converted to hydrochloride by method E. The yield is based on starting ester. [ff] [hh] Crude gummy hydrobromide, insol in both layers of the decompd Grignard reaction, was converted to free base and extd with Et_2O. After washing (H_2O) and drying (Na_2SO_4) the Et_2O was evapd. The oily free base was dissolved in EtOAc and acidified with $MeSO_3H$. Crystals sepd slowly and were recrystd first from EtOAc and then from EtOH. [ii] Methyl β-[*N*-(dimethylaminoethyl)-*N*-methylamino]isobutyrate was prepd by method B [bp 43° (0.005 mm)] but was not obtd anal. pure. The yield is based on this impure water. [jj] Prepd from methyl α,4-dimethyl-1-piperazinepropionate [French Patent 1,167,510 (1958); *Chem. Abstr.*, **55**, 8443*c* (1961)]. [kk] The authors are indebted to Dr. J. B. Wright and Mr. A. J. Lallinger who first prepd this compd in these laboratories. [ll] Crude cryst free base was used to prep the hydrochloride, which was crystd first from EtOH–EtCOMe and then from MeOH–Et_2O. A yield of 75% (mp 231–232° or higher) based on starting 3-(hydroxydiphenylmethyl)-1-methyl-2-pyrrolidinone was obtained. [mm] The starting 3-carbomethoxyquinuclidine·HCl [C. A. Grob and E. Renk, *Helv. Chim. Acta*, **37**, 1689 (1954)] was added to the PhMgBr as slurry in THF. [nn] The hydrochloride was prepd from crude free base by passing HCl gas into an Et_2O soln. The solvent was decanted and the gummy hydrochloride was crystd from 3% *i*-PrOH in EtCOMe. [oo] The free base of this compd was reported (without details or anal.) by Geoffrey, *et al.*[11] [pp] A small amount of cryst hydrobromide remained insol in both layers of decompd Grignard reaction mixt. It was recrystd giving this hydrobromide. The bulk of the product remained in the aq layer which was basified with NaOH and the resulting $Mg(OH)_2$ suspension was extd with Et_2O. Drying (Na_2SO_4) the Et_2O soln, filtn, and removal of the solvent gave cryst free base, which was recrystd from 75% EtOH. The total yield was 69%. [qq] This compd crystd very slowly. It was crystd in succession from *i*-PrOH, H_2O, EtOH, and MeOH. [rr] F: Calcd, 40.18; found, 40.89. [ss] The corresponding organolithium compd was prepd by the method of G. R. Pettit and D. S. Alkalay, *J. Org. Chem.*, **25**, 1363 (1960), and used in place of the Grignard reagent in method A. [tt] The *p*-dimethylaminophenylmagnesium bromide was prepd in THF and the ester was added in the same solvent. [uu] 2-Thienyl in place of the Ph groups. [vv] The authors are indebted to Dr. R. S. P. Hsi of these laboratories for the prepn of this compd. [ww] 4-Pyridyl in place of the Ph groups. [xx] This compd was also prepd (in approximately the same overall yield from 9-fluorenone) by the hydrogenation of the CH_2 compd **102**; method D. [yy] The Grignard reaction mixt was decompd with ice and HBr in place of NH_4Cl. [zz] The Grignard reagent was prepd from 4-(3-chloropropyl)-1-methylpiperidine [A. W. Ruddy and H. W. Bishop, *J. Amer. Chem. Soc.*, **74**, 1949 (1952)]. [aaa] The Grignard reagent was prepd from 2-bromo-3-(diethylamino)propene [Ficini, *et al.*[3]]. [bbb] When the reaction was complete most of the THF was distd *in vacuo* and replaced with Et_2O. The mixt was decompd with ice and HBr giving crude hydrobromide as a solid insol in both layers. [ccc] The uptake of H_2 was quite slow requiring about 2 days. [ddd] Soln treated with Darco G-60 prior to crystn.

TABLE II

METHYL β-AMINOISOBUTYRATES



No.	—N(R)(R′)	Yield, %[a]	Bp (mm) or mp, °C	$n^{25}D$	Formula	Anal.
122	$N(CH_3)CH_2CH_3$	65[b]	66 (13)	1.4201	$C_8H_{17}NO_2$	C, H, N
123	$N(CH_3)CH(CH_3)_2$	54	77 (13)	1.4253	$C_9H_{19}NO_2$	C, H, N
124	$N[CH(CH_3)_2]_2$	0.5	56 (0.2)		$C_{11}H_{23}NO_2$	C, H, N
125	$N[CH_2CH(CH_3)_2]_2$	15	54 (0.005)	1.4324	$C_{13}H_{27}NO_2$	C, H, N
126	$N(CH_3)CH_2CH{=}CH_2$	61[c]	78 (15)	1.4345	$C_9H_{17}NO_2$	C, H, N
127	$N(CH_2CH{=}CH_2)_2$	57	97 (17)	1.4488	$C_{11}H_{19}NO_2$	C, H, N
128	$N(CH_3)CH(CH_2)_3CH_2$	71	112 (15)	1.4533	$C_{11}H_{21}NO_2$	C, H, N
129	$NCH_2CH_2CH_2$	57	77 (14)	1.4378	$C_8H_{15}NO_2$	C, H, N
130	$N(CH_2)_3CHCH_3$	70[c]	95 (15)	1.4431	$C_{10}H_{19}NO_2$	C, H, N[e]
131	$NCH(CH_3)(CH_2)_2CHCH_3$	46[c,d]	95 (18)	1.4441	$C_{11}H_{21}NO_2$	C, H, N
132	$N(CH_2)_3C(CH_3)_2$	70[c]	102 (13)	1.4459	$C_{11}H_{21}NO_2$	C, H, N
133	$N(CH_2)_3C(CH_2)_4CH_2$	46	88 (0.005)	1.4780	$C_{14}H_{25}NO_2$	C, H, N
134	$N(CH_2)_3C(CH_2)_4CH_2\cdot HCl$	84[f]	172.5 dec		$C_{14}H_{25}ClNO_2$	C, H, Cl, N
135		74	78 (0.025)	1.4725	$C_{12}H_{21}NO_2$	C, H, N
136		54[c,i]	175–176		$C_{13}H_{24}ClNO_2$	C, H, N
137	$N(CH_3)CH_2C_6H_5$	81	83 (0.005)	1.4940	$C_{13}H_{19}NO_2$	C, H, N
138	$N(CH_3)CH_2C_6H_5\cdot HCl$	89[j]	148–150		$C_{13}H_{20}ClNO_2$	C, H, N
139	$N(CH_2CH_3)CH_2C_6H_5$[k]	25	84 (0.025)	1.4913	$C_{14}H_{21}NO_2$	N
140	$N(CH_2CH_2OCH_3)_2$	23	76 (0.025)[l]	1.4370	$C_{11}H_{23}NO_4$	C,[m] H, N
141	$NCH(CH_3)CH_2OCH_2CHCH_3$	35	68 (0.005)	1.4473	$C_{11}H_{21}NO_3$	C, H, N
142	$NCH_2CH_2SCH_2CH_2$	53	100 (0.075)	1.4919	$C_9H_{17}NO_2S$	C, H, N, S[n]
143	$NCH_2CH_2SCH_2CH_2\cdot HCl$	100[o]	171–172		$C_9H_{18}ClNO_2S$	C,[p] H, Cl, N, S

[a] Prepd by method B; the yield is based on the secondary amine. [b] Free EtNHMe was liberated from its hydrochloride with 45% KOH and distd directly into methyl methacrylate, contg a few drops of AcOH. The yield is based on the EtNHMe·HCl. [c] No AcOH (catalyst) was used in this prepn. [d] The reaction mixt was allowed to stand at room temp for 7 months and then distd. It is probable that AcOH would have greatly speeded the reaction. [e] N: Calcd, 7.56; found, 8.03. [f] Hydrochloride prepd by method E and recrystd from EtCOMe. [g] Prepd from 2-azabicyclo[2.2.2]octane [W. Schneider and R. Dillmann, *Chem. Ber.*, **96**, 2377 (1963)]. [h] Prepd from 3-azabicyclo[3.2.2]nonane (Eastman Chemical Products, Inc.). [i] The free base was not isolated but was converted to the hydrochloride with ethanolic HCl. The product was fractionally crystd from the hydrochloride of the starting material first from EtCOMe and then from *i*-PrOH. [j] Hydrochloride prepd by method E and recrystd first from EtCOMe and then from *i*-PrOH. [k] Hydrolysis of a small sample of this ester yielded β-(*N*-benzyl-*N*-ethylamino)isobutyric acid (**170**), mp 103.5–104.5° (from *i*-PrOH). *Anal.* ($C_{13}H_{19}NO_2$) C, H, N. [l] Vpc indicated about 93% purity for this compd. [m] C: Calcd, 56.63; found, 56.07. [n] S: Calcd, 15.77; found, 15.31. [o] Hydrochloride prepd by method E and recrystd from *i*-PrOH. [p] C: Calcd, 45.08; found, 45.54.

On cooling the hydrochloride crystd. This was collected, washed (EtOH and Et_2O), and dried giving 9.2 g of white crystals, mp 235–236° dec, $[\alpha]^{25}D$ + 39 ± 1° (α 0.545°; *c*, 0.7010 g/100 ml of MeOH, *l* = 2).

***d*-1,1-Diphenyl-2-methyl-3-(1-pyrrolidinyl)propanol (22).**—An aq soln of 13 g of *d* base *l*-tartrate (**19**) ($[\alpha]^{25}D$ −48°) was basified with NaOH. The resulting cryst free base was collected, washed (H_2O), and dried giving 8.8 g of white solid, mp 135–137.5°, $[\alpha]^{25}D$ + 38.1 ± 0.5° (α 0.94 ± 0.01°; *c*, 0.3084 g in 25 ml of $CHCl_3$; *l* = 2).

***l*-1,1-Diphenyl-2-methyl-3-(1-pyrrolidinyl)propanol·HCl (23).**—The *d* free base (**22**) (8.05 g) was dissolved in 60 ml of warm EtOH and acidified with 4 ml of about 7.1 *N* ethanolic HCl. On cooling the hydrochloride crystd. This was collected, washed with EtOH and Et_2O, and dried giving 8.7 g of white crystals, mp 234–235.5° dec, $[\alpha]^{25}D$ −41° (α 0.5222; *c*, 0.6442 g/100 ml of MeOH, *l* = 2).

1,1-Diphenyl-2-methyl-3-(1-pyrrolidinyl)propanol *N*-Oxide (24).—A soln of 29.5 g (0.1 mole) of **15** in 100 ml of AcOH and 32 ml of 30% H_2O_2 was heated at 70° for 9 hr and allowed to stand at room temp for 2 days. The soln was evapd to dryness *in vacuo* below 40° giving a glassy residue which appeared by ir to be the acetate salt. This was dissolved in 90% MeOH and passed through a column contg 100 ml of Amberlite IR 45 c.p. (weakly basic) ion-exchange resin. The soln was evapd *in vacuo* and the residue crystd from EtOAc giving 17 g (55%) of crude cryst free base, mp 152–155°. A sample repeatedly recrystd from MeOH, H_2O, and PhH gave white solid, mp 161.5–164°.

Method B. Methyl β-(*N*-Benzyl-*N*-methylamino)isobutyrate (137).—A soln of 200.2 g (2 moles) of methyl methacrylate, 243.6 g (2 moles) of benzylmethylamine, and 6.0 g (0.1 mole) of AcOH was heated on a steam bath for 2 days. The mixt was cooled, dild with Et_2O, and extd with cold dil HCl. The acid soln was washed (Et_2O) and basified with cold NaOH. The free base was extd with Et_2O which was washed (H_2O) and dried (Na_2SO_4). After filtn and removal of the solvent, the product was distd giving 338.6 g of colorless liquid, bp 81–93° (0.025 mm).

Methyl β-(*N*-benzyl-*N*-methylamino)butyrate (144) was prepd by method B from 200.2 g (2 moles) of methyl crotonate, 242 g (2 moles) of benzylmethylamine, and 11.5 ml (0.2 mole) of AcOH.

The product was distd through a helices packed column yielding 200 g (45%) of colorless liquid, bp 107° (0.1 mm), $n^{25}D$ 1.5014. *Anal.* ($C_{13}H_{19}NO_2$) C, H, N.

1,1-Diphenyl-2-methyl-3-(methylpropylamino)propanol·HBr (2).—A soln of 10.6 g (0.0282 mole) of **10** in 150 ml of MeOH was hydrogenated with 0.1 g of PtO_2 at 3.5 kg/cm² and room temp. The theoretical amt of H_2 was absorbed in 3 min and the uptake was stopped. The soln was filtd and evapd to dryness, giving a gum. This was crystd from EtOAc yielding 6.1 g (57.3%) of white crystals, mp 157–159°.

1,1-Diphenyl-2-methyl-3-(di-*n*-propylamino)propanol·HCl (4).—A soln of 12.1 g (0.05 mole) of 1,1-diphenyl-2-methyl-3-aminopropanol,[14] 11.6 g (0.2 mole) of propionaldehyde, and 11.5 (0.2 mole) of AcOH in 120 ml of abs EtOH was hydrogenated at 3.5 kg/cm². The theoretical amount of H_2 was absorbed in 1 hr and the soln was filtd from catalyst and evapd to dryness. The residue was treated with $PhSO_2Cl$ and NaOH under Hinsberg's procedure but no appreciable primary or secondary amines were indicated. An Et_2O soln of the product was shaken with dil HCl and on standing cryst solid sepd. After cooling this solid was collected, washed (H_2O, Et_2O), and dried giving 11.8 g of cryst hydrochloride, mp 170–172°. This was recrystd from 250 ml of EtCOMe, yielding 10.6 g of white crystals, mp 171–172.5°.

2-Bromo-3-(diisopropylamino)propene (145).—To a refluxing soln of 101 g (1.0 mole) of $(i\text{-Pr})_2NH$ in 250 ml of EtOH was slowly added with stirring during 75 min a soln of 100 g (0.5 mole) of 2,3-dibromopropene in 200 ml of EtOH. After stirring under reflux for 2.5 hr, the solvent was removed, and the residue was dissolved in dil HCl. The aq soln was extd with Et_2O and basified with NaOH. The product was extd with Et_2O, dried ($MgSO_4$), filtd, and distd, yielding 55.6 g of liquid, bp 83–87° (16 mm). *Anal.* ($C_8H_{18}BrN$) C, H, Br, N.

Method C. α-{1-[(Diisopropylamino)methyl]vinyl}benzhydrol (5).—To a mixt of 6.8 g (0.28 g-atom) of Mg turnings and 20 ml of THF was added 1 g (0.01 mole) of EtBr and a crystal of I_2. When the reaction had started, a soln of 44.0 g (0.20 mole) of **145** and 7.0 g (0.07 mole) of EtBr in 20 ml of THF was added dropwise at 40–45°. After stirring for 2 hr at this temp most of the Mg had reacted and a soln of 36.4 g (0.20 mole) of Ph_2CO in 50 ml of THF was slowly added. The mixt was heated at 65–70° for 6 hr, cooled, and poured into 400 ml of 10% NH_4Cl contg 3 ml of NH_4OH. The mixt was extd with Et_2O and the Et_2O soln was extd with cold dil HCl. The aq acid soln was washed (Et_2O) and basified with NaOH giving 44.7 g of brown solid, mp 83–88°. This was recrystd from 100 ml of *i*-PrOH, yielding 36.3 g of white crystals, mp 89–90.5°.

Method D. 1,1-Diphenyl-2-methyl-3-(diisopropylamino)propanol·HCl (7).—A soln of 16.2 g (0.05 mole) of **5** in 140 ml of MeOH was acidified with methanolic HCl and hydrogenated with 0.5 g of PtO_2 at 3.5 kg/cm² and room temp. The theoretical amount of H_2 was absorbed in 3 hr. The soln was filtd and evapd to dryness *in vacuo* giving a colorless gum. This was crystd from 100 ml of *i*-PrOH yielding 11.5 g of white crystals, mp 226–227.5° dec.

2-Bromo-3-(1-pyrrolidinyl)propene (146).[8b]—To 42.6 g (0.6 mole) of pyrrolidine was added dropwise with stirring at 25–40° 60 g (0.3 mole) of 2,3-dibromopropene. The mixt was heated on a steam bath for 2 hr, cooled, poured into ice water, and acidified with HCl. The aq soln was washed (Et_2O) and basified with NaOH, and the product was extd with Et_2O. After washing (H_2O) and drying ($MgSO_4$), the soln was filtd and distd, yielding 41.7 g of liquid, bp 61–63° (13 mm). *Anal.* ($C_7H_{12}BrN$) C, H, N.

Method E. Procedure for Preparing Hydrochlorides.—The free base was dissolved in a suitable solvent. Et_2O was used for the more sol hydrochlorides, an alcohol for the less sol, and EtOAc or EtCOMe for those of intermediate solubility. This soln was acidified by a slight excess of alcoholic HCl. In some cases the hydrochloride crystd from the soln and needed no further purification. In other cases, the product was recrystd from the solvent indicated in the tables.

2-Phenylacrylophenone (147).[15]—A soln of 3.8 ml of piperidine in 75 ml of MeOH was slowly added to a mixt of 147 g (0.75 mole) of deoxybenzoin, 560 ml of MeOH, and 183 g (2.3 moles) of 37% CH_2O. After stirring under reflux for 3 hr the mixt was cooled, dild with 750 ml of H_2O, and extd twice with Et_2O. The Et_2O soln was washed (dil HCl, H_2O, 5% $NaHCO_3$, and H_2O). After drying ($CaCl_2$) the solvent was removed, and the product was distd giving 123.2 g (80%) of colorless liquid, bp 189–194° (15 mm). This product slowly dimerizes[15] on standing at room temp or in the refrigerator but may be kept at −30°. The monomer can be easily regenerated from the dimer by distn at 15 mm pressure.

2-Phenyl-3-(1-pyrrolidinyl)propiophenone (148).[16]—To 123.2 g (0.63 mole) of **147** was slowly added with cooling 49.5 ml (0.63 mole) of pyrrolidine. Heat was evolved and on standing the mixt crystd. After standing overnight the solid was recrystd from 250 ml of *i*-PrOH giving 139.8 g of white crystals, mp 97–99°. *Anal.* ($C_{19}H_{21}NO$) C, H, N.

Hydrochloride 149.—This was prepd from 12.5 g (0.045 mole) of the base **148** by method E in Et_2O and recrystd from EtCOMe, yielding 11 g of white crystals, mp 163–164°. *Anal.* ($C_{19}H_{22}ClNO$) C, H, Cl, N.

Method H. 1,1,2-Triphenyl-3-(1-pyrrolidinyl)propanol (30).—To a stirred soln of 77 ml (0.15 mole) of 2 *M* PhLi in Et_2O–PhH at 0–5° was added over 30 min a soln of 14.0 g (0.05 mole) of **148** in 300 ml of dry Et_2O. The mixt was stirred at 0–5° for 3 hr, allowed to stand at room temp overnight, and then heated at reflux for 2 hr. The react mixt was poured into ice water, and the mixt was extd with $CHCl_3$. The org layer was washed (H_2O), dried ($MgSO_4$), and concd *in vacuo* to a cream-colored solid. This was recrystd from *n*-BuOH, yielding 16.6 g of white solid, mp 173–173.5°.

2,2-Dimethyl-3-(1-pyrrolidinyl)propiophenone (150).—A mixt of 74.0 g (0.5 mole) of isobutyrophenone, 53.5 g (0.5 mole) of pyrrolidine·HCl, 15 g (0.5 mole) of $(CH_2)_x$, 0.8 ml of concd HCl, and 500 ml of dioxane was heated on the steam bath with stirring for 3 hr and then an addl 5 g (0.15 mole) of $(CH_2O)_x$ was added. After heating for an addl 16 hr, the mixt was evapd *in vacuo* nearly to dryness. The resulting syrup was dissolved in H_2O washed (Et_2O), and basified with NaOH. The free base was extd with Et_2O which was washed (H_2O, satd NaCl) and dried (K_2CO_3). After filtn and removal of the solvent the free base was distd through a short column, yielding 36.1 g (31.3%) of colorless liquid, bp 98° (0.005 mm), $n^{24}D$ 1.5206. *Anal.* ($C_{15}H_{21}NO$) C, H, N.

Hydrochloride 151.—A soln of 4.39 g (0.019 mole) of this free base **150** in EtOAc was acidified with ethanolic HCl and dild to cloudiness with Et_2O. Crystals slowly sepd giving 6.3 g of crystals, mp 129–137°. This was recrystd from *i*-PrOH, yielding 4.2 g of white crystals, mp 148.5–150°. *Anal.* ($C_{14}H_{22}ClNO$) C, H, Cl, N.

2-Ethyl-3-(1-pyrrolidinyl)propiophenone·HCl (152) was prepd by the above procedure from 60 g (0.4 mole) of butyrophenone, 14 g (0.5 mole) of $(CH_2O)_x$, 54 g (0.5 mole) of pyrrolidine·HCl, 1 ml of concd HCl, and 50 ml of dioxane. The crude oily free base in Et_2O was converted to hydrochloride and recrystd from EtCOMe yielding 20 g of white crystals, mp 158–159°. *Anal.* ($C_{15}H_{22}ClNO$) C, H, Cl, N.

2-Isopropyl-3-(1-pyrrolidinyl)propiophenone (153) and Hydrochloride (154).—This was prepd by the above procedure from 81 g (0.5 mole) of isovalerophenone, 15 g (0.5 mole) of $(CH_2O)_x$, 54 g (0.5 mole) of pyrrolidine·HCl, and 50 ml of dioxane. The yield of distd oily free base was 33 g, bp 118–121° (0.5 mm). A sample for anal. was converted to the hydrochloride in Et_2O and recrystd from EtCOMe giving white solid, mp 159–159.5°. *Anal.* ($C_{16}H_{24}ClNO$) C, H, Cl, N.

1-(3-Chloro-2-methylpropyl)pyrrolidine (155).—The free base was liberated from crude hydrochloride[17] with 25% KOH, extd with Et_2O, washed (satd NaCl), and dried (K_2CO_3). After filtn and removal of the solvent the base was distd giving an 88% yield of colorless oil, bp 83–84° (14 mm).

1-(3-Chlorobutyl)pyrrolidine (156) and Hydrochloride (157).—A soln of 85 g (0.49 mole) of 1-(1-pyrrolidinyl)-3-butanol[12] in 100 ml of $CHCl_3$ was added with stirring during 2 hr to a soln of 85 g (0.71 mole) of $SOCl_2$ in 300 ml of $CHCl_3$ at 0–10°. The mixt was heated under reflux for 3 hr and the solvent was evapd *in vacuo*.

(14) Described in the second article of this series, R. B. Moffett and T. L. Pickering, *J. Med. Chem.*, **14**, 1100 (1971).

(15) J. Matti, A. Laval-Verges, and I. Emod, *Bull. Soc. Chim. Fr.*, 1176 (1963).

(16) This compd was reported (without anal.) by C. F. Huebner, U. S. Patent 3,203,962 (1964). He reportedly prepd it by several methods, all of which gave material with exactly the same mp (89–90°). This was 9° lower than the mp of our material. None of his methods was as convenient as that described herein.

(17) H. G. Kolloff, J. H. Hunter, E. H. Woodruff, and R. B. Moffett, *J. Amer. Chem. Soc.*, **71**, 3988 (1949).

The residue was treated with cold 25% KOH and well extd with Et_2O. The Et_2O soln was washed (satd NaCl) and dried (K_2CO_3). After filtn and removal of the solvent the product was distd yielding 60 g of colorless liquid, bp 83–85° (15 mm). This base was converted to the hydrochloride in Et_2O and recrystd from *i*-PrOH–Et_2O yielding 48.1 g of white solid, mp 184–185°. *Anal.* ($C_8H_{17}Cl_2N$) C, H, Cl, N.

***N,N*-Dibenzylpropionamide (158).**—To a soln of 395 g (2 moles) of $(PhCH_2)_2NH$ in 600 ml of PhH was slowly added with vigorous stirring and cooling (ice bath), a soln of 93 g (1 mole) of EtCOCl in 600 ml of PhH. The mixt was allowed to stand overnight at room temp and filtd. The solid was well extd with PhH and the combined PhH soln were distd yielding 204 g of colorless liquid, bp 156–158° (0.15 mm). *Anal.* ($C_{17}H_{18}NO$) C, H, N.

1-Propionylpyrrolidine (159).—By a similar procedure this was prepd from 710 g (10 moles) of pyrrolidine and 462.5 g (5 moles) of EtCOCl in 2 l. of PhH. The product was distd yielding 465 g of colorless liquid, bp 126° (26 mm). *Anal.* ($C_7H_{13}NO$) C, H, N.

1-Isobutyrylpyrrolidine (160).—By a similar procedure this was prepd from 282 g (4 moles) of pyrrolidine and 200 g (1.9 moles) of *i*-PrCOCl in 200 ml of abs Et_2O. The product was distd through a 12-in. helices packed column yielding 231 g of colorless liquid, bp 107° (13 mm), $n^{25}D$ 1.4691. *Anal.* ($C_8H_{15}NO$) C, H, N.

Method F. *N,N*-Diethyl-5-hydroxy-α-methyl-5*H*-dibenzo[*a,d*]cycloheptene-5-acetamide (104).—To a soln of 65 ml (0.1 mole) of a 15% soln of BuLi in hexane and 35 ml of abs Et_2O were slowly added with stirring a soln of 8 g (0.11 mole) of Et_2NH in 15 ml of Et_2O and 12.9 g (0.1 mole) of $EtCONEt_2$ in 20 ml of abs Et_2O. Then was carefully added a soln of 30.6 g (0.1 mole) of 5*H*-dibenzo[*a,d*]cyclohepten-5-one in 400 ml of abs Et_2O. After refluxing for 3 hr, the mixt was cooled and acidified with dil HCl. The solid was dissolved in Et_2O and washed (dil HCl, dil $NaHCO_3$, H_2O). After drying ($MgSO_4$), the soln was filtd and evapd *in vacuo* giving 31 g of crude solid. This was recrystd from *i*-PrOH–hexane yielding 21.3 g of solid, mp 127–218°.

Method G. 5-[2-(Diethylamino)-1-methylethyl]-5*H*-dibenzo[*a,d*]cycloheptene-5-ol (105).—To 4.5 g (0.12 mole) of LAH in 50 ml of THF was slowly added with stirring a soln of 20.1 g (0.06 mole) of **104** in 100 ml of THF. The mixt was refluxed for 19 hr and cooled and there was then added carefully 5.5 ml of H_2O, 3.5 ml of 20% NaOH, and 16 ml of H_2O successively. The solid was collected and well extd with THF. Evapn of the solvent and recrystn of the residue from hexane gave 11.6 g of solid, mp 97–98°.

1-Methyl-α,α-diphenyl-3-pyrrolidinemethanol (68).—A mixt of 33.0 g (8.5 moles) of LAH and 3.3 l. of abs Et_2O was refluxed through a Soxhlet extractor contg 120 g (0.44 mole) of 3-(hydroxydiphenylmethyl)-1-methyl-2-pyrrolidinone.[18] When all the pyrrolidinone had been extd into the flask the reaction mixt was decompd by very slowly adding with vigorous stirring 33 ml of H_2O, 33 ml of 15% NaOH, and 99 ml of H_2O successively. The mixt was filtd and the solid was well extd with Et_2O. The Et_2O soln was dried (Na_2SO_4), filtd, and evapd giving 112 g of crude solid. A sample was recrystd 3 times from hexane giving white crystals, mp 71.5–72.5°.

1-(3,4,5-Trimethoxyphenyl)-1-phenyl-3-dimethylaminopropanol (91).—The free base was liberated from 88 g (0.29 mole) of 3-dimethylamino-3′,4′,5′-trimethoxypropiophenone·HCl[19] with NaOH and extd with Et_2O. After drying (K_2CO_3) the soln was filtd and evapd *in vacuo* giving 80.6 g of oily free base. This was dissolved in abs Et_2O and slowly added with vigorous stirring to 200 ml (0.6 mole) of 3 *M* PhMgBr in 400 ml of abs Et_2O. After heating under reflux for 3 hr, the mixt was cooled and poured into ice water contg 151 g (0.9 mole) of 48% HBr. The aq layer was washed (Et_2O) and basified with NaOH. The suspension of $Mg(OH)_2$ was well extd with Et_2O and the ext was washed (H_2O) and dried (Na_2SO_4). Filtn and removal of the solvent gave gummy crystals which were recrystd from EtOAc yielding 22 g of white crystals, mp 126–129°. A small sample was recrystd from MeOH, mp 129–130°.

1,1-Bis(4-pyridyl)-5-diethylaminopentanol (94).—4-Pyridyllithium was prepd by slowly adding 46.8 g (0.296 mole) of 4-bromopyridine to 0.6 mole of BuLi in 450 ml of dry Et_2O at −60°. Then a soln of 14 g (0.075 mole) of methyl 5-diethylaminovalerate[20] in 120 ml of dry Et_2O was slowly added with stirring at −68° and the mixt was kept at −45° overnight. After warming to room temp, 40 ml of satd NH_4Cl soln was added dropwise followed by 200 ml of H_2O. Stirring was contd for 2 hr. The aq layer was well extd with Et_2O, and the Et_2O solns were washed (satd NH_4Cl). Removal of Et_2O gave a red oil which was dissolved in dil HCl, washed (Et_2O), and basified with NaOH. The product layer was extd with Et_2O which was dried ($MgSO_4$) and evapd *in vacuo*. The resulting red oil crystd on standing and was triturated with hexane giving 16.3 g of crystals, mp 105.5–108.5°. Recrystn twice from PhH–hexane, once from PhH and once from methylcyclohexane, with Darco G-60 treatment, yielded 11 g of crystals, mp 110–111°.

9-[2-(Diethylamino)-1-methylethyl]xanthen-9-ol Maleate (116).—A mixt of 7.0 g (0.0224 mole) of the free base **115** in Et_2O and 2.6 g (0.224 mole) of maleic acid in Et_2O was cooled in the refrigerator yielding 7.7 g of the salt, mp 152–153° dec.

1-Acetoxy-1,1-diphenyl-2-methyl-3-diethylaminopropane·HCl (161).—A soln of 29.7 g (0.1 mole) of 1,1-diphenyl-2-methyl-3-(diethylamino)propanol[17] in 200 ml of AcCl was allowed to stand at room temp overnight. The soln was filtd from hydrochloride of the starting material and dild to turbidity with abs Et_2O (vol of soln about 500 ml). On standing crystals slowly sepd, giving 19.76 g of nearly white solid which was recrystd from 200 ml of EtCOMe, yielding 13.6 g of white crystals, mp 156.5–158°. *Anal.* ($C_{22}H_{30}ClNO_2$) C, H, Cl, N.

1,1-Diphenyl-2-methyl-3-(1-pyrrolidine)propylene *p*-Toluenesulfonate (162).—To a hot soln of 114.1 g (0.6 mole) of *p*-TsOH·H_2O in 300 ml of xylene was slowly added with vigorous stirring under reflux with a Dean–Stark water trap a warm soln of 147.7 g (0.5 mole) of **15** in 300 ml of xylene. The refluxing was contd for 4.5 hr during which time the ther amount of H_2O was collected and the solid all dissolved. On cooling, the cryst product sepd and was collected, washed (xylene, Et_2O), and dried giving 190.6 g of nearly white crystals, mp 173–175°. Diln of the xylene filtrate with Et_2O yielded an addl 25.5 g of salt, mp 163–170°. A sample of the first crop recrystd from *i*-PrOH had the same mp. *Anal.* ($C_{27}H_{31}NO_3S$) C, H, N, S.

Free Base 163.—A suspension of 188.6 g (0.42 mole) of this salt (**162**) in 1.5 l. of H_2O was basified with NaOH. The free base was extd with Et_2O, washed (H_2O satd NaCl), and dried (Na_2SO_4). After filtn and removal of the solvent 117.5 g of nearly white solid was obtained, mp 67.5–69.5°. This was recrystd from *i*-PrOH giving 102.7 g of white solid, mp 68.5–70°. *Anal.* ($C_{20}H_{23}N$) C, H, N.

Hydrochloride 164.—A soln of 27.7 g (0.1 mole) of the free base **163** in 500 ml of Et_2O was acidified with ethanolic HCl giving 31.0 g of white solid, mp 178–182.5°. A 1-g sample was recrystd from 15 ml of EtCOMe giving 0.5 g of white crystals, mp 181–183°. *Anal.* ($C_{20}H_{24}ClN$) C, H, Cl, N.

Hydriodide 165.—Treatment of 29.5 g (0.1 mole) of **15** with red P and 47% HI by the procedure of Ruddy and Buckley[1d] gave 35.1 g of the hydriodide of the unsatd amine rather than the expected satd compd, mp 168–171°. *Anal.* ($C_{20}H_{24}IN$) C, H, I, N.

A sample converted to the free base gave material identical with **163** above, as shown by ir and mixt mp.

1,1-Diphenyl-2-methyl-3-(1-piperidine)propylene·HI (166).—A soln of 12.3 g of 1,1-diphenyl-2-methyl-3-(1-piperidine)propanol,[1d] obtained from the hydrobromide **45**, in AcOH, was treated with red P and 47% HI as described by Ruddy and Buckley.[1d] An 88.7% yield of hydriodide was obtained, mp 206–208° dec. *Anal.* ($C_{21}H_{26}IN$) C, H, I, N.

Free Base 167.—This hydriodide **166** was converted to the free base with NaOH and extd with Et_2O. Removal of the Et_2O and recrystn from *i*-PrOH gave an 88.3% yield of white crystals, mp 100–101.5°, which agrees with mp 99–100° reported by Ruddy and Buckley[1d] for the satd compd. Nmr confirmed the propylene structure. *Anal.* ($C_{21}H_{25}N$) C, H, N.

Hydrochloride 168.—An EtOAc soln of 8.7 g (0.023 mole) of this base (**167**) was converted to the HCl with ethanolic HCl yielding 9.7 g of white crystals, mp 223–228° dec. This is undoubtedly the same compd that Ruddy and Buckley[1d] considered to be satd 2-methyl-3,3-diphenylpropyl-1-piperidine·HCl (reported, mp 218–220°).

To confirm the structure this compd was also prepd by passing a little HCl gas into a suspension of 3.5 g (0.01 mole) of 1,1-diphenyl-2-methyl-3-(1-piperidine)propanol·HCl in 35 ml of AcOH. The solid dissolved and the soln was heated under reflux for 4 hr. The soln was dild with abs Et_2O to 250 ml giving 2.02 g of white crystals, mp 226.5–229°. Ir and mmp show this to be identical with **168**. *Anal.* ($C_{21}H_{26}ClN$) C, H, Cl, N.

(18) Chodkiewicz, *et al.*,[4] except $NaNH_2$ was used in place of KOH.

(19) E. Haggett and S. Archer, *J. Amer. Chem. Soc.*, **71**, 2255 (1949).

(20) V. M. Solov'ev, A. P. Arendaruk, and A. P. Skoldinov, *Zh. Obshch. Khim.*, **31**, 2577 (1961); *J. Gen. Chem. USSR*, **31**, 2405 (1961).

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.

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

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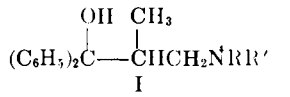
A series of 1,1-diaryl-2-methyl-3-[(primary and secondary)amino]propanols (I, R and/or R′ = H) were prepared for testing as CNS agents (anticonvulsants, anorexigenics, and their effect on simple reflexes). The primary amines were prepared by reduction of the corresponding nitriles and most of the secondary 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.

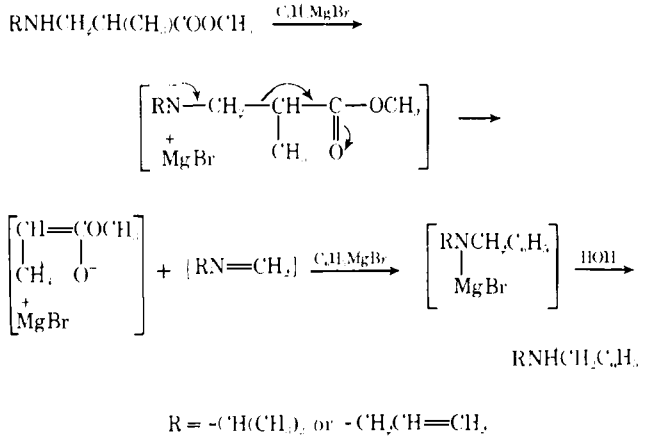
The interesting CNS stimulating effects accompanied by low anticholinergic side effects found for the tertiary amines[1] (I) have encouraged us to expand the series to



I

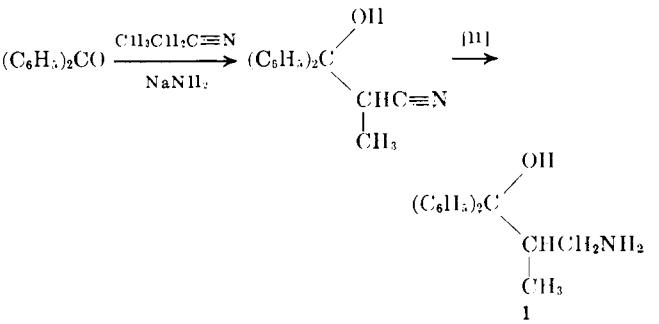
include primary and secondary amines (I, R and/or R′ = H) (Table I). These could not be satisfactorily prepared by the methods used for the tertiary amines. Although some workers[2] have successfully prepared similar primary or secondary amino alcohols by the Grignard reaction on β-amino esters or β-amino 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).