2-Aminomethyl-benzhydrols

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A series of 2-aminomethyl-benzhydrols (**3**) was prepared by different methods; starting with substituted isoindolines (**1**), phthalides (**4**), or cyanobenzophenones (**7**).

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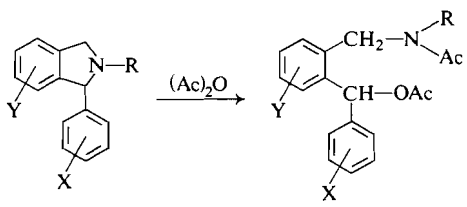
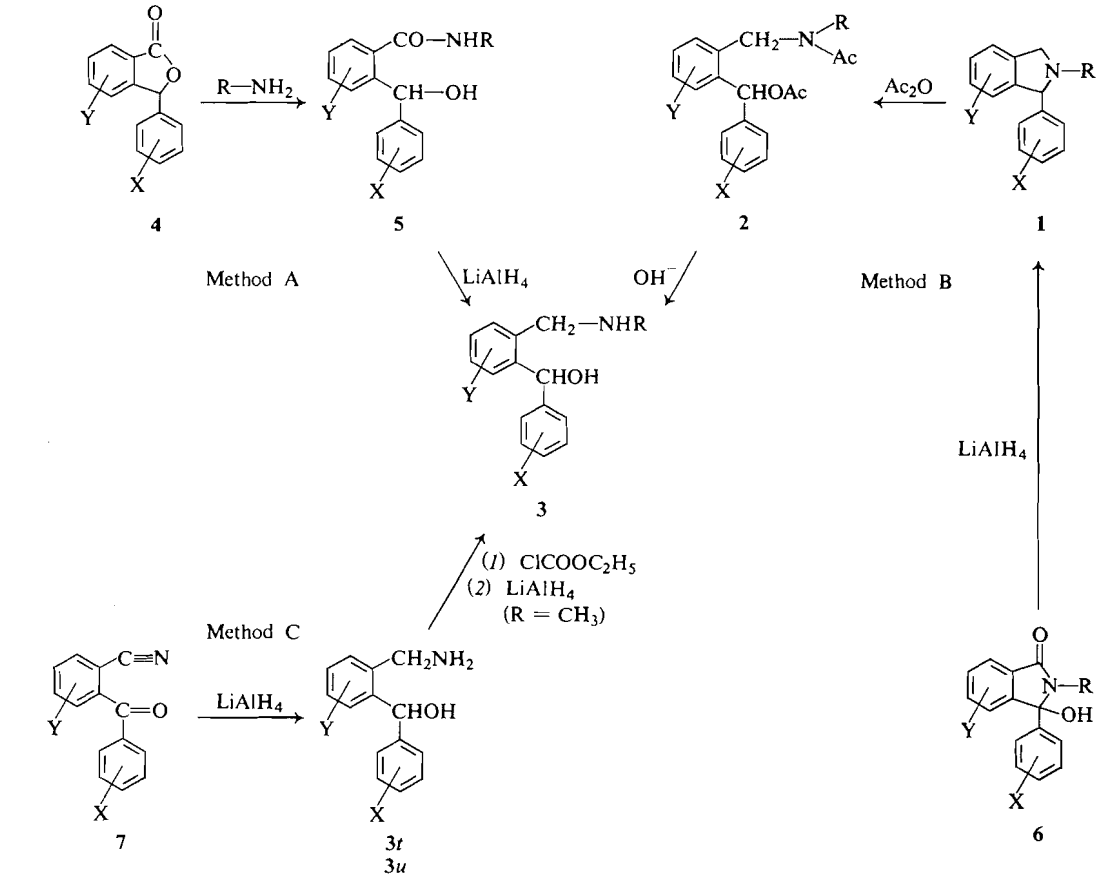
In the course of our studies on the ring cleavage of suitably substituted heterocycles, we investigated the reaction of 1-aryl-*N*-alkylisoindolines (**1**) with acetic anhydride (eq. [1]).

[1] 

1 **2**

In line with the results obtained with 1-aryl-tetrahydro-β-carbolines (1), 1-aryl-tetrahydro-isoquinolines (2), and 1-aryl-dihydroisobenzofurans (3) this reaction yielded *O*,*N*-diacetyl-2-aminomethylbenzhydrols (**2**). Rather unexpectedly, these compounds exhibited anorexigenic activity (4) which was especially pronounced in the secondary amines (**3**) resulting from saponification of **2**. This property was so far attributed only to derivatives of phenethylamine (5). This interesting finding caused a detailed study of alternate pathways of synthesis (see Scheme 1) as well as a study of structural modifications.



SCHEME 1

A rather general method for the preparation of **3** comprises the reaction of phenylphthalides (**4**) with amines and subsequent reduction of the amides (**5**) with lithium aluminum hydride (method A). This procedure fails, however, with ammonia.

In cases where the benzoylbenzoic acid necessary for the preparation of the phthalide (**4**) was not easily accessible, as for example, for the preparation of **3***i*, (X = $3CF_3$, 4-Cl; Y = H) the original isoindoline cleavage proved advantageous (method B). The isoindolines (**1**) were obtained via standard procedure from phthalimides and phenylmagnesium halides, followed by reduction of the 1-aryl-1-hydroxy-3-oxoisoindolines (**6**). On refluxing with acetic anhydride, the isoindoline ring was opened to the *N*,*O*-diacetyl compounds (**2**), which were generally saponified with potassium hydroxide without purification to yield **3**. Ring cleavage could not be achieved with the unsubstituted 1-phenyl-2-methylisoindoline.

Method B is also unsuitable for the preparation of the primary amines (**3***t* and *u*).

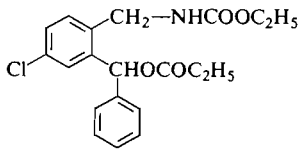
These compounds were obtained via Sandmeyer reaction of *o*-amino-*p*′-chlorobenzophenone and lithium aluminum hydride reduction of the nitrile (**7**) (method C). Compound **3***t* could be converted to **3***c* with chloroformate and subsequent reduction.

Table 1 indicates the methods used for the preparation of a number of substituted aminomethyl-benzhydrols (**3**).

Recently, a further method for the preparation of similar compounds was described (10); this procedure is limited to the preparation of tertiary amines, which exhibit anti-inflammatory properties according to the patent claims.

Compound **3***c* was separated into the enantiomers with di-*p*-toluoyl tartaric acid as described in the experimental section.

On partial saponification of **8** the carbamate **9** was obtained.



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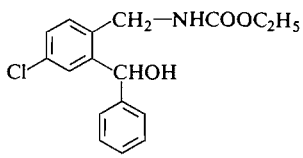
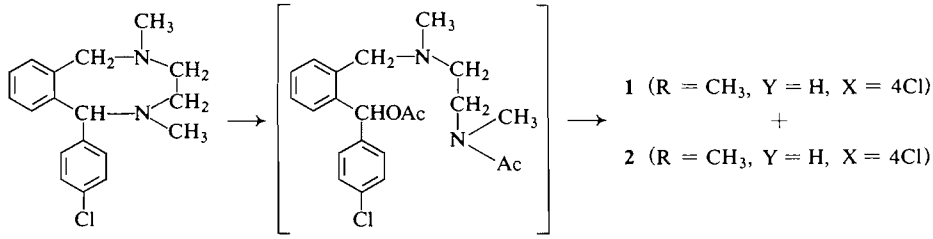


9

[2]



10 **11**

1 (R = CH_3, Y = H, X = 4Cl)
+
2 (R = CH_3, Y = H, X = 4Cl)

Ring cleavage of the diazocine (**10**) did not yield the acetylaminoethyl derivative (**11**); instead, **2** and the isoindoline (**1**) were isolated as the only reaction products (eq. [2]), most likely due to a Hoffman-Type elimination of *N*-vinyl-*N*-methylacetamide.

Compounds **12** to **15** were prepared by standard procedures to obtain information on the structure-activity relationship, which will be discussed elsewhere (4).

Experimental

Melting points were taken on a Fisher–Johns apparatus and are uncorrected. The microanalyses were performed by Dr. C. Daesslé, Montreal, and Dr. A. B. Gygli, Toronto.

Method A

(*a*) The appropriate phthalide **4** (8) (0.05 mole) was dissolved in 500 ml of benzene, saturated with methylamine, or containing a 5 times molar excess of the corresponding larger amine. The mixture remained at room temperature until no more starting material could be identified on thin-layer chromatography (t.l.c.), generally 48 h, and was then evaporated to dryness *in vacuo*. The residue was crystallized.

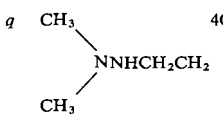
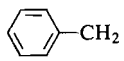
(*b*) The amide **5** (0.05 mole), dissolved in 100 ml of tetrahydrofuran/50 ml of ether, was added to a refluxing suspension of 0.1 mole of lithium aluminum hydride in 200 ml of ether. After 3 h of reflux, sodium hydroxide and water were added and the liquid phase removed by suction. The cake was repeatedly washed with ether. The ether was dried over potassium carbonate and evaporated to dryness *in vacuo*. The ethanol solution of the residue

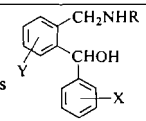
TABLE 1

Preparation and properties of 2-aminomethyl-benzhydrols

3*	R	X	Y	Method	Yield† (%)	Melting point (°C)	Crystallization solvent	Formula	Analysis											
									Calculated						Found					
									C	H	N	Cl	F	S	C	H	N	Cl	F	S
a	CH_3	H	H	A	73	224–225	Ethanol	$C_{15}H_{17}NO \cdot HCl$	68.30	6.88	5.31	13.44	—	—	68.54	7.06	5.44	13.50	—	—
b	CH_3	4F	H	A B	72 60	231	Ethanol	$C_{15}H_{16}FNO \cdot HCl$	63.94	6.08	4.97	12.58	6.74	—	63.87	6.12	4.82	12.89	6.68	—
c	CH_3	4Cl	H	A B C	71 60 92‡	226–227	Ethanol/ Ether	$C_{15}H_{16}ClNO \cdot HCl$	60.42	5.75	4.70	23.78	—	—	60.56	5.69	4.63	23.80	—	—
d	CH_3	2Cl	H	B	61	205	Ethanol/ Ether	$C_{15}H_{16}ClNO \cdot HCl$	60.42	5.75	4.70	23.78	—	—	61.05	5.81	4.79	23.70	—	—
e	CH_3	3Cl	H	B	15	174	Ethanol/ Ether	$C_{15}H_{16}ClNO \cdot HCl$	60.42	5.75	4.70	23.78	—	—	60.57	5.90	4.70	23.94	—	—
f	CH_3	4Br	H	A	65	206–207	Methanol/ Ether	$C_{15}H_{16}BrNO \cdot HCl$	52.57	5.00	4.09	—	—	—	52.09	5.42	4.11	—	—	—
g	CH_3	$3CF_3$	H	A	53	160–162	Ethanol/ Ether/ Pet. ether	$C_{16}H_{16}F_3NO \cdot HCl$	57.92	5.16	4.22	10.69	17.18	—	57.94	5.29	4.36	11.15	17.48	—
h	CH_3	$4CH_3S$	H	A	62	184	Ethanol/ Ether	$C_{16}H_{19}NOS \cdot HCl$	62.02	6.51	4.52	11.44	—	10.35	62.05	6.44	4.48	11.45	—	10.60
i	CH_3	4Cl $3CF_3$	H	B	45	253	Ethanol/ Ether	$C_{16}H_{15}ClF_3NO \cdot HCl$	52.48	4.40	3.82	19.36	15.56	—	52.58	4.48	3.66	19.53	15.50	—
k	CH_3	$4CH_3$	H	B	40	218–219	Ethanol/ Ether	$C_{16}H_{19}NO \cdot HCl$	69.18	7.26	5.04	—	—	—	69.55	7.38	5.07	—	—	—
l	CH_3	$4CH_3O$	H	B	81	179	Ethanol/ Ether	$C_{16}H_{19}NO_2 \cdot HCl$	65.41	6.86	4.78	—	—	—	65.17	6.98	5.05	—	—	—
m	C_2H_5	4Cl	H	A	65	209	Methanol/ Ether	$C_{16}H_{18}ClNO \cdot HCl$	61.55	6.13	4.48	22.71	—	—	61.21	6.11	4.39	22.60	—	—
n	n-C_4H_9	4Cl	H	B	24	102–105	Ethanol/ Ether	$C_{18}H_{22}ClNO \cdot HCl$	63.53	6.81	4.12	20.84	—	—	63.67	6.86	4.31	20.78	—	—
o	$CH_2CH(CH_3)_2$	4Cl	H	B	15	154	Ethanol/ Ether	$C_{18}H_{22}ClNO \cdot HCl$	63.53	6.81	4.12	20.84	—	—	63.86	7.05	4.30	20.46	—	—

TABLE 1 (*Concluded*)

3*	R	X	Y	Method	Yield† (%)	Melting point (°C)	Crystallization solvent	Formula	Analysis											
									Calculated						Found					
									C	H	N	Cl	F	S	C	H	N	Cl	F	S
p	$HOCH_2CH_2$	4Cl	H	A	42	157–161	Ethanol/ Ether	$C_{16}H_{18}ClNO_2 \cdot HCl$	58.55	5.84	4.27	21.60	—	—	58.38	6.39	4.42	21.37	—	—
q		4Cl	H	A	40	184–187	Ethanol/ Ether	$C_{18}H_{24}ClN_3O \cdot HCl$	53.15	6.43	10.33	26.15	—	—	53.39	6.79	10.16	25.78	—	—
		4Cl	H	A	42	200–202	Ethanol/ Petroleum ether	$C_{21}H_{20}ClNO \cdot HCl$	67.39	5.65	3.74	18.94	—	—	67.65	5.84	3.81	18.70	—	—
s		4Cl	H	A	47	198–201	Ethanol/ Petroleum ether	$C_{20}H_{24}ClNO \cdot HCl$	65.63	6.88	3.82	19.37	—	—	65.64	7.16	3.81	19.29	—	—
t	H	4Cl	H	C	82	194–196	Ethanol/ Ether	$C_{14}H_{14}ClNO \cdot HCl$	59.17	5.32	4.93	24.95	—	—	59.11	5.21	5.10	24.85	—	—
u	H	H	5Cl	C	54	169–170	IPA/ Ether	$C_{14}H_{14}ClNO \cdot HCl$	59.17	5.32	4.93	24.95	—	—	59.18	5.42	5.03	25.03	—	—
v	CH_3	H	5Cl	C	81§	190–192	Ethanol/ Ether	$C_{15}H_{17}ClNO \cdot HCl$	60.42	5.75	4.70	23.78	—	—	60.69	5.68	4.68	23.68	—	—
w	CH_3	Cl	4′,5′ di-OCH_3	A	60	190–192	Ethanol/ Ether	$C_{17}H_{20}ClNO_3 \cdot HCl$	51.00	5.91	3.91	19.80	—	—	51.20	5.89	3.67	19.61	—	—
x	H	H	H	‖	59‖	216	Ethanol/ Ether	$C_{14}H_{15}NO \cdot HCl$	67.30	6.47	5.61	14.20	—	—	67.36	6.50	5.70	14.08	—	—

*The general structure is 

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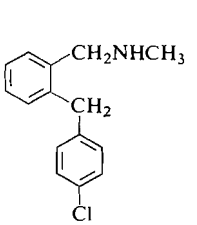
†Calculated for the sequences 5 → 3 (Method A), 1 → 3 (Method B) and 7 → 3 (Method C).
‡92% from 3*t* → 3*c*.
§81% from 3*u* → 3*v*.
‖Hydrogenolysis of 3*r*; see experimental section.



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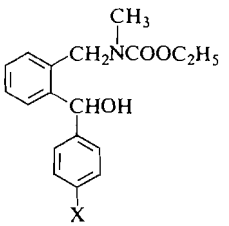
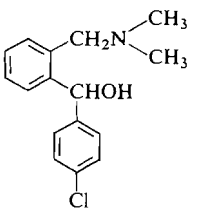


13*a* (X = Cl)
13*b* (X = F)



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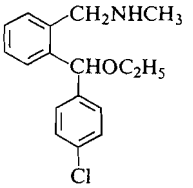

15

was acidified with hydrogen chloride in ether. The material was recrystallized from appropriate solvents (see Table 1).

Method B

(*a*) The appropriate 1-aryl-*N*-methylisoindoline (**1**) (7) (0.2 mole) was refluxed in 500 ml of acetic anhydride for 16 h. The solution was concentrated *in vacuo* and left to crystallize at 0 °C. The diacetate was filtered by suction, washed with ether, and dried.

(*b*) The diacetate (0.1 mole) was refluxed for 1 h in 125 ml of 50% aqueous potassium hydroxide/250 ml of ethylene glycol. The solution was cooled, diluted with 1000 g of ice and extracted five times with 200 ml of ether. The combined extracts were washed with sodium carbonate solution, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The ethanol solution of the residue was acidified with hydrogen chloride in ether. The material was recrystallized from appropriate solvents.

Method C

The substituted 2-cyanobenzophenone (**7**) (9) (0.02 mole), dissolved in 125 ml tetrahydrofuran, was added dropwise to a refluxing suspension of 0.05 mole of lithium aluminum hydride in 150 ml of ether. After 2 h refluxing, sodium hydroxide solution (2 *N*) was added and the liquid phase removed by suction. The cake and the aqueous phase were repeatedly washed with ether. The ether extracts were combined, dried over potassium carbonate, and evaporated to dryness *in vacuo*. The residue was dissolved in ethanol and acidified with hydrogen chloride in ether. The material was recrystallized from ethanol/ether.

4-Chloro-2′-methylaminomethyl-benzhydrol (3c) from 3t and 5-Chloro-2-methylaminomethyl-benzhydrol (3v) from 3u

(*a*) Ethyl chloroformate (0.1 mole) was added dropwise, with external cooling, to the solution of 0.01 mole of the primary amines **3***t* and *u*, as free bases, in 200 ml of pyridine. After 2 h at room temperature the pyridine was removed *in vacuo* and the residue chromatographed on silicic acid. The major fractions eluting with 2.5% chloroform in benzene were combined, filtered through a glass sinter funnel, evaporated to dryness, and dried in high vacuum. The oil was homogeneous on t.l.c., and analyzed properly.

(*b*) The carbonate-urethane (0.03 mole) in 100 ml of ether was added dropwise to a refluxing suspension of 0.1 mole of lithium aluminum hydride in 200 ml of ether. After 4 h of refluxing, the hydrochloride was isolated in the usual way (properties see Table 1).

Separation of 4-Chloro-2′-methylaminomethyl-benzhydrol (3c) into Enantiomers

The hot concentrated solution of 90 g of di-*p*-toluoyl-*l*-tartaric acid in ethanol was added to a hot concentrated solution of 61 g of 4-chloro-2′-methylaminomethyl-benzhydrol in ethanol. The mixture was left to crystallize overnight at room temperature. The crystals were filtered by suction and the mother liquors were concentrated. A second crystalline fraction was obtained. The first fraction was recrystallized from ethanol. The mother liquors of this fraction were used for the recrystallization of the second fraction.

This procedure was systematically repeated 4 times. The final two crystalline fractions were combined and the free base was liberated with 2 *N* sodium hydroxide solution and extracted with ether. After drying and evaporation of the ether, the residue was recrystallized 4 times from ether/petroleum ether. Yield: 13 g (43%), m.p. 71–74°; $[\alpha]_D^{25°} = +78.4°$ (ethanol).

Anal. Calcd. for $C_{15}H_{16}ClNO$: C, 68.81; H, 6.16; N, 5.35. Found: C, 69.36; H, 6.46; N, 5.60.

The mother liquors of the above recrystallizations were combined, evaporated to dryness, and the base was liberated with 2 *N* sodium hydroxide solution and extracted with ether. The ether solution was dried over potassium carbonate and evaporated to dryness, 27 g of resin remained as residue.

The hot concentrated solution of 40 g di-*p*-toluoyl-*d*-tartaric acid in ethanol was added to the hot concentrated solution of 27 g resin in ethanol. The same procedure was repeated as described for the first enantiomer. Yield: 10.6 g (35%), m.p. 71–74 °C; $[\alpha]_D^{25°} = -80.1°$ (ethanol).

Anal. Calcd. for $C_{15}H_{16}ClNO$: C, 68.81; H, 6.16; N, 5.35. Found: C, 68.55; H, 6.43; N, 5.43.

2-Aminomethyl-benzhydrol (3x)

Palladium-on-charcoal (5%), (2 g), was added to a solution of 8 g 4-chloro-2′-(benzylaminomethyl)-benzhydrol (**3***r*). The mixture was shaken in an atmosphere of hydrogen at room temperature. When the hydrogen uptake came to a standstill after about 48 h, the catalyst was removed by filtration and the solution was evaporated *in vacuo* to dryness. The resulting residue was chromatographed on a silica column using chloroform–methanol–ammonia (90:9.5:0.5) as eluant. The main fraction was converted to the hydrochloride and recrystallized from ethanol/ether (properties see Table 1).

5-Chloro-2-ethoxycarbonylaminomethyl-benzhydrol (9)

5-Chloro-O-ethoxycarbonyl-2-ethoxycarbonylaminomethyl-benzhydrol (17.3 g) (**8**) (preparation see **3***v* from **3***u*, step (*a*)), was dissolved in 25 ml of 95% ethanolic

2 *N* sodium hydroxide solution. After 2 h at room temperature the mixture was diluted with water, adjusted to p*H* 6 with 1 *N* hydrochloric acid, and extracted 3 times with chloroform. The combined chloroform extracts were dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was chromatographed on silicic acid. The major fractions eluting with 1% methanol/benzene were combined, treated with charcoal, filtered through a glass sinter funnel, evaporated to dryness, and dried in high vacuum. 10.7 g (76%) of a colorless oil remained.

Anal. Calcd. for $C_{17}H_{18}ClNO_3$: C, 63.84; H, 5.67; N, 4.38; Cl, 11.08. Found: C, 64.05; H, 6.13; N, 4.27; Cl, 10.81.

*1-(p-Chlorophenyl)-2,5-dimethyl-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine (**10**)*

A mixture of 2.7 g 1-(*p*-chlorophenyl)-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine (6), 4 ml 40% formaldehyde solution, and 10 ml formic acid was heated to reflux for 6 h. The solution was poured over ice and made basic with concentrated ammonia. The mixture was extracted with three 100 ml portions of ether. The combined ether extracts were washed, dried over magnesium sulfate, and evaporated to dryness. The residue was converted to the dihydrochloride by addition of ethereal hydrochloric acid and recrystallized from ethanol/water. Yield: 2.4 g (65%), m.p. 265–266°.

Anal. Calcd. for $C_{18}H_{21}ClN_2 \cdot 2HCl$: C, 57.85; H, 6.21; Cl, 28.45; N, 7.50. Found: C, 58.16; H, 6.52; Cl, 27.99; N, 7.45.

The free base, liberated from the dihydrochloride, could be crystallized from hexane and melted at 83°.

*4-Chloro-2′-(N-methyl-N-acetylaminomethyl)-O-acetylbenzhydrol (**2**, R = CH_3, Y = H, X = 4-Cl)*

The free base **10** (10 g) was heated to reflux in 100 ml of acetic anhydride for 12 h. The mixture was poured on ice–ammonia and extracted with three 200 ml portions of ether. The combined ether extracts were washed with 4 *N* hydrochloric acid. The aqueous, acidic layer yielded, after basification and extraction, a small amount of crystals which were identical in all respects with 1-(4-chlorophenyl)-2-methylisoindoline (**1**, R = CH_3, Y = H, X = 4-Cl). The ether layer was dried over magnesium sulfate and evaporated to dryness. The oily residue crystallized from ethanol. Yield: 8 g (69%), m.p. 132–135°.

Anal. Calcd. for $C_{19}H_{20}ClNO_3$: C, 66.01; H, 5.78; N, 4.05. Found: C, 66.07; H, 5.75; N, 4.20.

*4-Chloro-2′-methylaminomethyl-diphenylmethane (**12**)*

o-(*p*-Chlorobenzyl)-benzoic acid (49 g) was refluxed for 2 h with 75 ml of thionyl chloride. Excess reagent was removed *in vacuo* and the residue dissolved in 500 ml of benzene. Methylamine was introduced in excess under ice cooling. The mixture remained at room temperature for 2 h and was then distributed between water and benzene/chloroform. The organic layer was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to a crystalline slurry. The amide was recrystallized from ethanol. Yield: 36.5 g (70%).

The above amide (29 g) was dissolved in 250 ml of tetrahydrofuran and added dropwise into a refluxing suspension of 12 g lithium aluminum hydride in 350 ml of tetrahydrofuran. The mixture was refluxed for 8 h. Excess lithium aluminum hydride was destroyed with 2 *N* sodium hydroxide. The solids were filtered by suction and washed repeatedly with tetrahydrofuran. The filtrate and the washings were combined and dried over potassium carbonate and evaporated to dryness *in vacuo*. The resulting resin was dissolved in ethanol, and hydrogen chloride was introduced under ice cooling. On addition of ether, crystals separated, which were recrystallized from ethanol/ether. Yield: 17.4 g (63.5%), m.p. 201–205°.

Anal. Calcd. for $C_{15}H_{16}ClN \cdot HCl$: C, 63.82; H, 6.07; N, 4.96; Cl, 25.13. Found: C, 64.00; H, 6.17; N, 5.03; Cl, 25.18.

*4-Chloro-2′-[(N-methyl-N-ethoxycarbonylamino)-methyl]-benzhydrol (**13a**)*

4-Chloro-2′-(methylaminomethyl)-benzhydrol (**3***c*) (5.1 g) was dissolved in 50 ml of dry pyridine and ethyl chloroformate (2.1 g) was added under external cooling. The mixture was allowed to stand at room temperature for 24 h and was then evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was washed with dilute hydrochloric acid, water, sodium carbonate solution, and finally dried over magnesium sulfate. The solvent was removed *in vacuo*. The oily residue crystallized from cyclohexane/petroleum ether, (b.p. 40–60°). Yield: 3.6 g (55%), m.p. 87–88°.

Anal. Calcd. for $C_{18}H_{20}ClNO_3$: C, 64.69; H, 6.05; N, 4.19; Cl, 10.63. Found: C, 64.59; H, 5.93; N, 4.27; Cl, 10.62.

*4-Fluoro-2′-[(N-methyl-N-ethoxycarbonylamino)-methyl]-benzhydrol (**13b**)*

This compound was prepared in the same way as **13***a*. Pure material (4 g) was obtained from 5.8 g of compound **3***b* (53%). The oil did not crystallize but showed the expected properties in the infrared (i.r.) (3330 cm^{-1}, 1675 cm^{-1}) and nuclear magnetic resonance (n.m.r.) spectrum, which were known from the chloro analogue.

Anal. Calcd. for $C_{18}H_{20}FNO_3$: C, 68.15; H, 6.32; N, 4.42; F, 6.00. Found: C, 68.51; H, 6.48; N, 4.44; F, 6.17.

*4-Chloro-2′-(dimethylaminomethyl)-benzhydrol (**14**)*

A mixture of 4-chloro-2′-(methylaminomethyl)-benzhydrol, (**3***c*) (12 g), 5 ml 40% aqueous formaldehyde solution and 40 ml 98% formic acid was heated to reflux for 15 min. After cooling, the mixture was poured over ice/concentrated ammonia and the reaction product extracted with three 100 ml portions of ether. The combined ether extracts were washed with water, dried over magnesium sulfate, and evaporated to dryness. The residue was transformed into the hydrochloride with ethereal hydrochloric acid and recrystallized from ethanol/ether. Yield: 11.5 g (80%), m.p. 203°.

Anal. Calcd. for $C_{16}H_{18}ClNO \cdot HCl$: C, 61.55; H, 6.09; N, 4.48. Found: C, 62.03; H, 6.20; N, 4.42.

*4-Chloro-2′-(methylaminomethyl)-benzhydrol Ethyl Ether (**15**)*

The solution of 4-chloro-2′-(methylaminomethyl)-benzhydrol hydrochloride (**3***c*) (6 g) in 200 ml of ethanol was saturated with hydrogen chloride at room temperature and then heated to reflux for 1 h. The solution was

kept at 0° for 12 h and the crystalline precipitate collected and recrystallized from water. Yield: 4.5 g (69%), m.p. 231°.

Anal. Calcd. for $C_{17}H_{20}ClNO \cdot HCl$: C, 62.65; H, 6.45; N, 4.29. Found: C, 62.80; H, 6.20; N, 4.42.

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