Some Derivatives of Certain Basically Substituted Phenyl-alkyl-carbinols

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During a search for new compounds with analgesic and spasmolytic properties we have prepared a number of derivatives of the following carbinols:

(See Table 1.)

Table 1.

Comp.	R ₁	R ₂	R ₃	R ₄	M.p base	° C HCl- salt	Empirical formula of HCl-salt	% Cl in HCl- salt calc. found	
1.	C ₆ H ₅	H	H	—N(CH ₃) ₂	161	204	C ₁₇ H ₂₂ ClNO	12.30	12.15
2.	C ₆ H ₅	CH ₃	H	—N(CH ₃) ₂	92	238	C ₁₈ H ₂₄ ClNO	11.60	11.50
3.	C ₆ H ₅	H	CH ₃	—N(CH ₃) ₂	123	202	C ₁₈ H ₂₄ ClNO	11.60	11.65
4.	C ₆ H ₅	CH ₃	H	—N(CH ₂) ₅	115	266	C ₂₁ H ₂₆ ClNO	10.29	10.21
5.	C ₆ H ₅	H	CH ₃	—N(CH ₂) ₅	76	213	C ₂₁ H ₂₆ ClNO	10.29	10.19
6.	C ₆ H ₁₁	CH ₃	H	—N(CH ₃) ₂	94	244	C ₁₈ H ₃₀ ClNO	11.42	11.45
7.	C ₆ H ₁₁	CH ₃	H	—N(CH ₂) ₅	112	267	C ₂₁ H ₃₄ ClNO	10.09	10.00

The carbinols were synthesized by the Grignard-Reaction, using phenyl magnesium bromide or cyclohexyl magnesium bromide and, in cases where R₃ was hydrogen, the corresponding phenylketones. These were obtained from acetophenone or propiophenone using the Mannich reaction with dimethylamine hydrochloride or piperidine hydrochloride. In cases where R₃ was a methyl group the carbinols were prepared by the Grignard-reaction from the corresponding aminoacid-ethylesters. These esters were obtained from allyl-

cyanide, which was condensed with the amine to the aminoacid nitrile which in turn was converted directly to the ester by hydrolysis in abs. ethanol saturated with hydrogen chloride.

None of the carbinols prepared, were found to exhibit any significant spasmolytic or analgesic effect in animal experiments.

Hydrochlorides of some esters of a number of these carbinols with acetic, propionic, butyric and benzoic acid, were prepared by treating an ethereal solution of the free carbinols with the acid chloride. The following esters were prepared:

(See Table 2.)

Table 2.

Comp	R ₁	R ₂	R ₃	Mp. of HCl-salt	Empirical for- mula of HCl-salt	% Cl in HCl salt calc. found.	
8.	C ₂ H ₅	H	H	183	C ₂₀ H ₂₆ ClNO ₂	10.20	10.12
9.	C ₂ H ₅	CH ₃	H	187	C ₂₁ H ₂₈ ClNO ₂	9.84	9.90
10.	C ₂ H ₅	H	CH ₃	158	C ₂₁ H ₂₈ ClNO ₂	9.84	9.79
11.	CH ₃	CH ₃	H	102	C ₂₀ H ₂₆ ClNO ₂	10.20	10.16
12.	C ₃ H ₇	CH ₃	H	80	C ₂₂ H ₃₀ ClNO ₂	9.47	9.41
13.	C ₆ H ₅	H	CH ₃	176	C ₂₅ H ₂₈ ClNO ₂	8.65	8.69

The free bases of any of these esters were immediately hydrolyzed in aqueous solution, and the hydrochlorides were, in aqueous solution, hydrolyzed to the carbinol and the acid in a few hours even at room temperature.

These new compounds, therefore, are of no interest from a practical point of view, although some of them, especially 9 and 10, show spasmolytic and analgetic properties (of very short duration).

In order to obtain more stable derivatives, attempts were made to prepare alkylethers of some of the carbinols, but without success. In sodium-alcoholate alcohol the free carbinols failed to react with alkylhalides.

By treating the carbinols with thionyl chloride in order to substitute the OH group with chlorine, water was in most cases removed and an unsaturated compound of the following formula was formed:

In a single case the hydrochloride of a chlorine-compound could be isolated: 1,1-Diphenyl-1-chloro-2-methyl-3-dimethyl-amino-propane.

Comp. 14.

This compound was extremely readily hydrolyzed to the carbinol, and like the esters the free base could not be isolated. By dissolving the hydrochloride in cold water both chlorine atoms could be estimated as ionised chlorine.

Treating the above hydrochloride with sodium propylate in abs. propanol gave no ether but liberation of formaldehyde and formation of 1,1-diphenyl propene-1 indicating destruction of the molecule.

By treating an ethereal solution of the carbinol 1,1-diphenyl-2-methyl-3-dimethylamino-propanol with bromoacetone, the hydrobromide of the following ether was formed:

Comp. 15.

As this compound was almost as unstable in aqueous solution as the esters, no other compounds of this type were prepared. The compound showed spasmodic properties of a high degree.

The olefins prepared by dehydration of the carbinols or by removing hydrogen chloride from the intermediately formed chlorine compounds were, as expected, quite stable in an aqueous solution of the hydrochloride salts. The following were prepared:

(See Table 3.)

Table 3.

Comp.	R ₁	R ₂	R ₃	R ₄	M.p. base	°C HCl- salt	Empirical formula of HCl-salt	% Cl in HCl- salt calc. found	
16.	C ₆ H ₅	CH ₃	H	—N(CH ₃) ₂	56	184	C ₁₈ H ₂₂ ClN	12.33	12.21
17.	C ₆ H ₅	H	CH ₃	—N(CH ₃) ₂	oil	161	C ₁₈ H ₂₂ ClN	12.33	12.30
18.	C ₆ H ₅	CH ₃	H	—N(CH ₂) ₅		222	C ₂₁ H ₂₆ ClN	10.88	10.73
19.	C ₆ H ₅	H	CH ₃	—N(CH ₂) ₅		88	C ₂₁ H ₂₆ ClN	10.88	10.68
20.	C ₆ H ₁₁	CH ₃	H	—N(CH ₃) ₂	oil	158	C ₁₈ H ₂₈ ClN	12.07	12.01
21.	C ₆ H ₁₁	CH ₃	H	—N(CH ₂) ₅		183	C ₂₁ H ₃₂ ClN	10.62	10.56

All the compounds showed spasmolytic properties and several of them of high degree.

EXPERIMENTAL

Preparation of the carbinols 1, 2, 4, 6 and 7

The general procedure employed here is suitably illustrated by the preparation of 1-cyclohexyl-1-phenyl-2-methyl-3-piperidino-propanol-1. (compound 7).

α -methyl- β -piperidino-propio-phenone was prepared as described for β -dimethylamino-propio-phenone¹: 80 g propiophenone, 100 g piperidine hydrochloride and 20 g para-formaldehyde in 100 ml of 96 % ethanol containing 1 ml conc. hydrochloric acid gave 67 g α -methyl- β -piperidino-propio-phenone bp. 30 mm: 174—180° C.

Calc. 6.06 % N

Found 6.10 % N

In the same way² the intermediate α -methyl- β -dimethylamino-propio-phenone used for the carbinols 4 and 7 was obtained in 75 per cent yield. bp₁₀ mm 160°—164° C. HCl-salt Mp. 147—149° C.

Calc. 7.33 % N

Found 7.36 % N

1-cyclohexyl-1-phenyl-2-methyl-3-piperidino-propanol-1. α -Methyl- β -piperidino-propio-phenone (50 g) in 100 ml dry ether was added drop by drop to a stirred ethereal solution of cyclohexyl magnesium bromide prepared from 7 g magnesium and 48 g cyclohexyl bromide in 150 cc dry ether. When the addition was completed, the mixture was stirred and heated under reflux for two hours. The mixture was then allowed to stand for two hours.

The mixture was poured onto cracked ice and acidified with concentrated hydrochloric acid. The hydrobromide of 1-cyclohexyl-1-phenyl-2-methyl-3-piperidino-propanol-1 separated and was isolated and washed with ether. White to slight yellow crystals Mp 264—268°. The free base was obtained as a white cryst. powder, Mp 110—112°, by treating the hydrobromide with 25 per cent ammonia. The hydrochloride was obtained by adding dry hydrogen chloride to a solution of the base in acetone-ether. White crystals Mp. 265—267° C.

Preparation of the carbinols 3 and 5

The procedure is illustrated by the preparation of 1,1-diphenyl-3-dimethylamino-butanol-1 (Comp. 3).

Ethyl 3-dimethylamino-butyrate was prepared according to Breckpot³ from 3-dimethylamino-butyronitrile, which was obtained from allylcyanide and dimethylamine. The corresponding 3-piperidino ester used in the synthesis of Comp. 5 was prepared in the same way⁴.

1,1-Diphenyl-3-dimethylamino-butanol-1. Ethyl 3-dimethylamino-butyrate (44.5 g) in 100 ml dry ether was added slowly under cooling and vigorous stirring to an ethereal solution of phenylmagnesium bromide prepared from 130 g bromobenzene in 300 ml dry ether and 20 g magnesium. After the addition was completed the mixture was allowed to stand for 12 hours. The mixture was then poured onto crushed ice and acidified with concentrated hydrochloric acid. The hydrobromide of the 1,1-diphenyl-3-dimethylamino-butanol separated as a white crystalline substance. It was isolated and washed with ether. M.p. 208° C. The free base was obtained as a slight yellow cryst. substance. M.p. 122–123° C, by treating the salt with aqueous ammonia, yield 45 g. By dissolving the base in ether-acetone and adding dry hydrogen chloride, the hydrochloride was obtained as white crystals M.p. 202°.

Preparation of the esters 8–13

The procedure is illustrated by the preparation of compound 9.

1,1-Diphenyl-2-methyl-3-dimethylamino-propanol-1 (10 g) was dissolved in 75 ml dry ether and freshly distilled propionyl chloride (5 g) was added. The mixture was allowed to stand for 24 hours. Carbinol hydrochloride (6.5 g) separated and was removed by filtering. To the filtrate was added dry hydrogen chloride in ether. The ester (4.2 g) was separated as a white crystalline substance. Mp. 170–175°. Recrystallisation from acetone-ether raised the Mp. to 187° C. In contrast to the hydrochloride of the carbinol, the hydrochloride of the ester is very soluble in acetone.

Preparation of compound 14

1,1-Diphenyl-1-chloro-2-methyl-3-dimethylamino-propane. 1,1-Diphenyl-2-methyl-3-dimethylamino-propanol-1, HCl (10 g) was suspended in 50 ml chloroform and 10 ml thionyl-chloride added. The mixture was heated under reflux for 1 hour when the excess of thionyl chloride and the chloroform were removed by distillation. Traces of thionyl chloride were removed by adding more chloroform and distilling in vacuum. The residue was dissolved in acetone and by subsequent addition of ether the hydrochloride of the chlorocompound was separated as a white crystalline substance. Mp. 125–131°. Recrystallisation from acetone-ether raised the Mp. to 131°. Yield 10.5 g.

Calc. 21.90 % Cl

Found 21.76 % Cl.

Preparation of compound 15

Hydrobromide of acetonyl-(1,1-diphenyl-2-methyl-3-dimethylamino-) propyl-ether.

1,1-Diphenyl-2-methyl-3-dimethylaminopropanol-1 (10 g) was dissolved in 75 ml dry ether and fresh distilled bromoacetone (8 g), was added. The mixture was allowed

to stand for 72 hours. The crystals which separated were recrystallised from acetone-ether. Yield 8 g. Mp. 107–110°.

Br calc. 19.71 % Br

found 19.65 %

Preparation of the olefines 16 – 21.

The procedure is illustrated by the preparation of compound 20. *1-Phenyl-1-cyclohexyl-2-methyl-3-dimethylaminopropene-1*.

The carbinol 1-phenyl-1-cyclohexyl-2-methyl-3-dimethylaminopropanol-1 (30 g) dissolved in 100 ml chloroform, was converted to the hydrochloride by adding dry hydrogen chloride. Thionyl chloride (30 g) was then added and the mixture heated under reflux for 3 hours. Thionyl chloride and chloroform were removed by distillation in vacuum, and the residue heated with 25 ml pyridine for 1 hour. After removing the pyridine by distillation in vacuum, the residue was dissolved in water and extracted with ether. The 1-phenyl-1-cyclohexyl-2-methyl-3-dimethylaminopropene-1 formed was separated from the aqueous solution as an oil by adding sodium hydroxide. The base was extracted with ether and traces of pyridine removed from the ethereal solution by shaking with water. The ethereal solution was then treated with activated carbon and dried with potassium carbonate. After filtering the hydrochloride of the compound was separated from the ether by adding dry hydrogen chloride. The hydrochloride was recrystallized from acetone ether. White needles M.p. 158° C. Yield 19 g.

SUMMARY

The preparation of seven α,α -diphenyl- or α -phenyl- α -cyclohexyl- γ -dimethylamino- or γ -piperidino propyl or butyl alcohols is described.

Six carboxylic esters of some of these carbinols and a number of the corresponding olefins are described.

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