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ANTISPASMODICS. *gamma*-AMINO ALCOHOLS AND AMINO ALKENES

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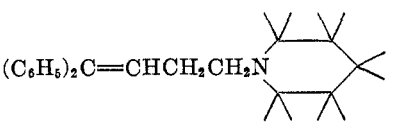
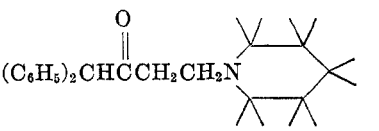
Received October 9, 1953

In a recent communication the elucidation of the structure of the base obtained by the Mannich reaction on *alpha, alpha*-diphenylacetone was reported (1). During the course of that investigation the known butene (I) was tested for its antispasmodic activity using excised rabbit ileum and found to be 5–10 times as effective as Trasentine. When this same drug was tested *in vivo* in the anes-



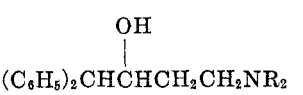
I



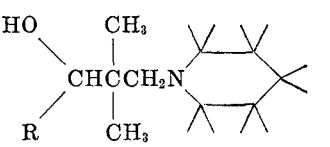
II

thetized dog, no demonstrable activity could be elicited.

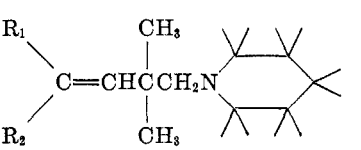
Wilson and Kyi (2) as well as others had observed the instability of the parent Mannich ketone (II) in aqueous solution and it was conceivable that the *in vivo* inefficacy of I was due to a similar degradation wherein *alpha, alpha*-diphenylbutadiene and piperidine would be formed. The present report describes two series of *gamma*-amino alcohols of types III and IV and the preparation of compounds, type V, which are incapable of degradation to substituted butadienes.



III



IV



V, A; $R_1 = R_2 = C_6H_5$
V, B; R_1R_2C = 9-Fluorenylidene
V, C; R_1R_2C = Cyclohexylidene
V, D; $R_1 = H$; $R_2 = C_6H_5$

The compounds of type III were prepared by the catalytic reduction of the requisite ketones previously described by Protiva and Jilek (3) and Wilson and Kyi (2). These amino alcohols bear a formal resemblance to the antispasmodics

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TABLE I

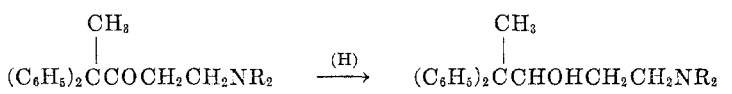
gamma-AMINO ALCOHOLS, TYPE III. $(C_6H_5)_2CHCHOHCH_2CH_2NR_2 \cdot HCl$

NR_2	Yield, %	M.P., °C.	Empirical Formula	Analyses					
				C		H		Cl	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
$N(CH_3)_2$	83	174–175[a]	$C_{18}H_{24}ClNO$	70.70	70.48	7.85	7.78		
$NHCH(CH_3)_2$	93	152–153[a]	$C_{19}H_{26}ClNO$	71.36	71.25	8.14	8.28	11.11	10.87
NC_4H_8	85	186–187[b]	$C_{20}H_{26}ClNO$	72.40	72.56	7.84	8.02		
NC_4H_8O	65	165–167[c]	$C_{20}H_{26}ClNO_2$	69.03	68.86	7.54	7.55		
NC_5H_{10}	91	164–165[c]	$C_{21}H_{28}ClNO$	72.94	73.19	8.10	8.12	10.29	10.39

[a] Recrystallized from propanol-2-isopropyl ether. [b] Recrystallized from ethylene chloride-isopropyl ether. [c] Recrystallized from methyl ethyl ketone.

reported by Denton, *et al.* (4) in a series of communications and are similar to some of the amino alcohols described by Schultz, Bicking, and Sprague (5). The physical characteristics of these compounds are contained in Table I.

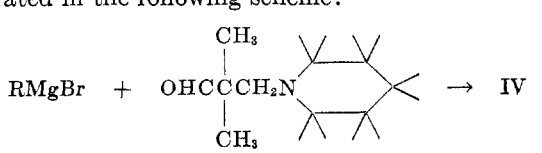
It is noteworthy to point out that several attempts were made to prepare the following amino alcohols VII from the respective ketone VI (6).



VI VII

Catalytic hydrogenation at low pressures or the Meerwein-Ponndorf aluminum isopropoxide reduction of VI were unsuccessful, starting material being invariably recovered. It is pertinent to mention that Zaugg, Freifelder, and Horrom (6) were unsuccessful in reducing the oxime of 3,3-diphenylbutanone-2 at ordinary pressures and resorted to Raney nickel at 75° and 1,000 pounds pressure to effect reduction. Reduction of VI with lithium aluminum hydride gave rise to a material which slowly degenerated upon crystallization of the hydrochloride salt. It is presumed that the carbinol formed initially and then gradually underwent rearrangement to a substituted stilbene derivative. Meerwein (7) has described the related easy conversion of 3,3-diphenylbutanol-2 to *alpha, alpha'*-dimethylstilbene in the presence of acid.

The synthesis of compounds of types IV and V was achieved by the reaction of a Grignard reagent with *alpha, alpha*-dimethyl-*beta*-(1-piperidyl)propionaldehyde (VIII) as illustrated in the following scheme:

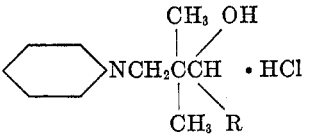


VIII

The compounds resulting from this reaction are tabulated in Table II. For the preparation of derivatives of type V those derivatives of type IV wherein

TABLE II

gamma-AMINO ALCOHOLS, TYPE IV.



R	Yield, %	M.P., °C.	Empirical Formula	Analyses			
				C		H	
				Calc'd	Found	Calc'd	Found
$CH_3CH_2CH_2CH_2$	40	120–121[a]	$C_{14}H_{30}ClNO$	63.73	63.78	11.46	11.70
C_6H_{11}	61	223–223.5[b]	$C_{16}H_{32}ClNO$	66.29	66.37	11.13	11.18
C_6H_5	62	225–226[b]	$C_{16}H_{26}ClNO$	67.70	67.78	9.23	9.10
$C_6H_5CH_2$	60	141–142[a]	$C_{17}H_{28}ClNO$	68.55	68.77	9.47	9.01
$(C_6H_5)_2CH$	35	95–96[c]	$C_{23}H_{31}NO$	81.90	82.15	9.20	9.30
9-Flourenyl	48	142–143[c,d]	$C_{23}H_{29}NO$	82.40	82.34	8.73	8.76

Recrystallized from: [a] propanol-2-isopropyl ether; [b] methanol-methyl ethyl ketone. [c] This material was isolated as the free base and recrystallized from aqueous methanol. [d] The hydrobromide salt melted at 244–246°. Calc'd for $C_{23}H_{30}BrNO$: C, 66.35; H, 7.21. Found: C, 66.94; H, 7.41.

R was equal to cyclohexyl or benzyl were subjected to a phosphorus oxychloride-pyridine dehydration. Derivatives of type V in which $R_1 = R_2 = C_6H_5$ or R_1R_2C = 9-fluorenyl were synthesized by the reaction of the requisite lithium compound with VIII and subsequent dehydration.

After the reaction of 9-fluorenyllithium, prepared in an exchange reaction with butyllithium, with VIII the reaction mixture was decomposed with 10 *N* hydrochloric acid. A white solid separated which was collected and shown to be the hydrobromide salt of the desired alcohol. The hydrogen bromide undoubtedly arose from the lithium bromide orginally formed during the preparation of butyllithium from butyl bromide.

Pharmacological activity. The antispasmodic activity of these compounds was determined by noting that concentration of drug in mcg./ml. of bath necessary to give a 50% decrease in amplitude of the spasms of rabbit ileum. The stimulus for making the strip spastic was either barium chloride or acetyl choline.

Those derivatives of IV in which R was *n*-butyl, cyclohexyl, or benzyl were inactive and V, C and D were likewise ineffective. Maximum activity was encountered with IV, R = diphenylmethyl, which was twice as effective as Trasentine against both stimuli, equal in activity to Artane against barium chloride, and twice as effective as Artane against acetyl choline. When this compound was dehydrated to V, A, a three-fold decrease in activity occurred.

EXPERIMENTAL[2]

Preparation of compounds in Table I. 1,1-Diphenyl-4-(1-piperidyl)butanol-2. Inasmuch as the hydrogenation experiments are similar, the following procedure is cited as an example. Into a 300-ml. hydrogenation bottle were placed 2.6 g. (0.0076 mole) of 1,1-diphenyl-

[2] All melting points are uncorrected. Analyses are by the Clark Microanalytical Laboratory, Urbana, Illinois.

4-(1-piperidyl)butanone-2, 100 ml. of methanol, and 0.1 g. of platinum oxide. This mixture was hydrogenated at an initial hydrogenation pressure of 15 lbs./in.^{2} in a Parr shaking apparatus. After 1 hr. the catalyst was separated and the filtrate was evaporated to dryness below 40°. Trituration of the resultant oil with methyl ethyl ketone gave a solid which was collected and dried to yield 2.4 g. (91%) m.p. 155–158°.

Preparation of compounds in Table II. 1-Phenyl-2,2-dimethyl-3-(1-piperidyl)propanol-1. The following synthesis illustrates the method of preparing the first four compounds in Table II. A 0.3-mole solution of phenylmagnesium bromide was prepared in a 300-ml. flask from 47.1 g. (0.3 mole) of bromobenzene, 8.2 g. (0.33 mole) of magnesium turnings, and 100 ml. of dry ether. To this solution at room temperature 16.9 g. (0.1 mole) of *alpha, alpha*-dimethyl-*beta*-(1-piperidyl)propionaldehyde (8) was added in ¼ hr. After the exothermic reaction had subsided, the mixture was heated an additional ½ hr. and decomposed by pouring into 500 g. of ice and water containing 50 g. of ammonium chloride. The aqueous solution was extracted with three 150-ml. portions of ether, and the ether extracts were combined and washed three times with 50-ml. portions of water. After drying over magnesium sulfate the ethereal solution was treated with dry hydrogen chloride. The solid, 17.6 g. (62%) was collected and dried at 60°; m.p. 206–210°. Recrystallization from methanol-methyl ethyl ketone raised the melting point to 225–226°.

4,4-Diphenyl-1-(1-pyrrolidyl)pentanone-3. This material was prepared essentially as described by Zaugg, *et al.* (8) for the synthesis of other dialkylamino derivatives. In place of the ethanol or isoamyl alcohol normally employed as solvents, Methyl Cellosolve[3] was used and the reaction time was 16 hrs. A 53.5% yield of Mannich base hydrochloride was obtained; m.p. 155–157°. A sample recrystallized twice from methyl ethyl ketone was submitted for analysis; m.p. 156–157°.

Anal. Calc'd for $C_{21}H_{26}ClNO$: C, 73.32; H, 7.62.

Found: C, 73.59; H, 7.80.

4,4-Diphenyl-1-(N-dialkylamino)butanone-2. The preparation of compounds of this type has been described (2, 3). In Table III below are listed those members of the series not previously synthesized.

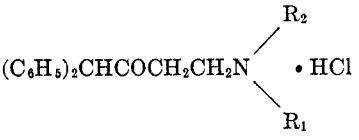
1-(9-Fluorenyl)-2,2-dimethyl-3-(1-piperidyl)propanol-1. Under an atmosphere of dry nitrogen butyllithium was prepared in 200 ml. of dry ether from 3.82 g. (0.55 mole) of lithium ribbon and 35.6 g. (0.26 mole) of *n*-butyl bromide. At the completion of this reaction some small chunks of lithium remained. Nevertheless 41.5 g. (0.25 mole) of fluorene was added over a period of 10 minutes. During the 2 hrs. in which the solution was heated under reflux it assumed a deep orange color. External heating was discontinued as 17.0 g. (0.10 mole) of *alpha, alpha*-dimethyl-*beta*-(1-piperidyl)propionaldehyde, dissolved in 50 ml. of dry ether, was added at a rate sufficient to maintain gentle refluxing. It was noted that the colored fluorenyllithium could be titrated with the aldehyde. In this manner only the quantity of aldehyde necessary to discharge the orange color was added. The reaction mixture was heated for an additional ½ hr. and then cooled in an ice-bath. Decomposition was achieved by adding 25 ml. of water and then 100 ml. of 6 *N* hydrochloric acid. A white solid separated which was collected, washed with water, and dried. This material, m.p. 244–246°, was not the hydrochloride salt. Elemental analysis showed it to be the hydrobromide which arose from the lithium bromide formed in the reaction mixture. The solid which weighed 20.0 g. (48% based on aldehyde employed) was converted to the free base; m.p. 140–142°. Recrystallization from aqueous methanol gave tiny white crystals; m.p. 142–143°.

1-(9-Fluorenylidene)-2,2-dimethyl-3-(1-piperidyl)propane. To a solution of 12.0 g. (0.028 mole) of 1-(9-fluorenyl)-2,2-dimethyl-3-(1-piperidyl)propanol-1 hydrobromide in 80 ml. of pyridine was added a cooled solution of 40 ml. of phosphorus oxychloride in 40 ml. of pyridine. The temperature during mixing was kept below 45°. The solution thus obtained was heated on a steam bath for 1 hr. and then decomposed by carefully pouring it into 1000 ml. of ice and water. The clear solution was neutralized by the addition of sodium carbonate. The oil which separated was allowed to stand overnight in an ice-chest. Crystallization

[3] Trade name for 2-methoxyethanol.

TABLE III

4,4-DIPHENYL-1-(N-DIALKYLAMINO)BUTANONE-2 COMPOUNDS



R_1	R_2	Yield, %	M.P., °C.	Empirical Formula	Analyses					
					C		H		Cl	
					Calc'd	Found	Calc'd	Found	Calc'd	Found
Pyrrolidino		60	170–171[a]	$C_{20}H_{24}ClNO$	72.84	72.76	7.28	7.16	10.77	10.59
H	$CH(CH_3)_2$	27	191–192[b]	$C_{19}H_{24}ClNO$	71.81	71.96	7.60	7.73	11.18	11.23
H	$C(CH_3)_3$	18	213–214[c]	$C_{20}H_{26}ClNO$	72.39	72.32	7.84	7.84	10.71	10.45

[a] This reaction was run for 2½ hrs. in amyl alcohol and the product was purified by crystallization from propanol-2. [b] The reaction was carried out in amyl alcohol for 3½ hrs. and the product was crystallized from methyl ethyl ketone. [c] Reaction run in Methyl Cellosolve for 18 hrs. Dilution of the reaction mixture with 3 volumes of methyl ethyl ketone precipitated the unreacted amine hydrochloride and subsequent workup of the filtrate by basifying and extracting yielded the product, which was recrystallized from propanol-2-isopropyl ether.

was slow unless seeds were available to induce formation. The solid was collected, washed with a copious quantity of water to remove any pyridine, and dried. This crude product weighed 8.3 g. (91%) and melted at 67–69°. Recrystallization from aqueous methanol gave white crystals; m.p. 70.5–71.5°.

Anal. Calc'd for $C_{23}H_{27}N$: C, 87.01; H, 8.55.
Found: C, 86.91; H, 8.79.

The *picrate*, prepared in the usual manner, was purified by crystallization from ethanol and formed short yellow needles; m.p. 187–189°.

Anal. Calc'd for $C_{29}H_{30}N_4O_7$: C, 64.25; H, 5.59.
Found: C, 63.60; H, 5.65.

1-(9-Fluorenyl)-2,2-dimethyl-3-(1-piperidyl)propane. Two grams (0.0063 mole) of 1-(9-fluorenylidene)-2,2-dimethyl-3-(1-piperidyl)propane dissolved in 25 ml. of ether was reduced in a Parr hydrogenation apparatus (30 lbs./in.² pressure, 0.1 g. of platinum oxide) for 3 hrs. The product, obtained by evaporating the ether on a steam-bath, set to a solid mass on cooling. The yield was essentially quantitative; m.p. 83–86°. White crystalline rods were obtained by crystallization from methanol; m.p. 83–85°.

Anal. Calc'd for $C_{23}H_{29}N$: C, 86.47; H, 9.15.
Found: C, 86.43; H, 9.19.

1,1-Diphenyl-3,3-dimethyl-4-(1-piperidyl)butanol-1. Essentially the procedure used to prepare 1-fluorenyl-2,2-dimethyl-3-(1-piperidyl)propanol-1 was followed. Diphenylmethyllithium was prepared by adding 42.0 g. (0.25 mole) of diphenylmethane to a butyllithium solution in the quantities previously cited. The deep red solution was heated under reflux for three hours and then the external source of heat was removed. A solution of 17.0 g. (0.10 mole) of *alpha, alpha*-dimethyl-*beta*-(1-piperidyl)propionaldehyde in 50 ml. of dry ether was added and the mixture was refluxed again for ½ hour. Decomposition with 25 ml. of water and 100 ml. of 6 *N* hydrochloric acid gave two clear phases. The aqueous layer was separated and the ethereal solution was washed with 100 ml. of water. Basification of the aqueous phase with potassium carbonate resulted in the separation of an oil which was extracted into 225 ml. (3 × 75 ml.) of ether. Evaporation of the ethereal solution to dryness

and trituration with cold methanol resulted in the formation of a white solid, 10.0 g.; m.p. 90–95°. Additional material was obtained when the filtrate was taken to dryness and the residue was distilled. The fractions which boiled up to 120°/1 mm. were discarded and the residue was dissolved in 70 ml. of methanol. White crystals separated which weighed 2.0 g.; m.p. 90–95°. The total yield, 12.0 g., represented 35% of theory based upon the amount of aldehyde employed. Recrystallization from methanol, then aqueous methanol, gave short white rods; m.p. 95–96°. The hydrochloride and hydrobromide were deliquescent solids.

Anal. Calc'd for $C_{23}H_{31}NO$: C, 81.90; H, 9.20.

Found: C, 82.15; H, 9.30.

1,1-Diphenyl-3,3-dimethyl-4-(1-piperidyl)butene-1 hydrobromide. Essentially the procedure employed for the preparation of 1-(9-fluorenylidene)-2,2-dimethyl-3-(1-piperidyl) propane was followed up until the isolation. The dehydrated product from 3.0 g. (0.089 mole) of 1,1-diphenyl-3,3-dimethyl-4-(1-piperidyl)butanol-2 was an oil which resisted all attempts to achieve crystallization. It was finally taken up into 100 ml. of ether, and the ether was washed six times with 20-ml. portions of water and then dried. To this was added an ethereal solution of dry hydrogen bromide. The white solid which separated was collected, washed with ether, and dried to yield 3.0 g. (84%); m.p. 175–178°. Recrystallization from methyl ethyl ketone resulted in the formation of white cubic crystals; m.p. 183–186°. The compound may also be crystallized from water containing a trace of hydrobromic acid but apparently a hydrate forms which melts and resolidifies at 124–140° then melts again at about 180°.

Anal. Calc'd for $C_{23}H_{30}BrN$: C, 68.98; H, 7.53.

Found: C, 69.20; H, 7.53.

3-Cyclohexylidene-2,2-dimethyl-1-(1-piperidyl)propane. This dehydration with phosphorus oxychloride and pyridine was similar to those already described. The oil obtained by extraction was dried in ether and treated with dry hydrogen chloride. Trituration of the resultant yellow oil with methyl ethyl ketone and subsequent recrystallization of the solid from the same solvent gave a 25% yield of white needles; m.p. 187–188°.

Anal. Calc'd for $C_{16}H_{30}ClN$: C, 70.68; H, 11.12; Cl, 13.04.

Found: C, 70.78; H, 10.82; Cl, 12.83.

3-Benzylidene-2,2-dimethyl-1-(1-piperidyl)propane. This material was prepared in 15% yield as described above and was recrystallized twice from methyl ethyl ketone-isopropyl ether; m.p. 186–187°.

Anal. Calc'd for $C_{17}H_{26}ClN$; C, 72.98; H, 9.30; Cl, 12.70.

Found: C, 73.20; H, 9.44; Cl, 12.76.

SUMMARY

Two series of *gamma*-amino alcohols have been described. One group was prepared by the reduction of Mannich bases derived from *alpha*, *alpha*-diphenylacetone and the second group by the addition of either a Grignard reagent or a lithium derivative to *alpha*, *alpha*-dimethyl-*beta*-(1-piperidyl)propionaldehyde. Several compounds of the latter group were dehydrated by phosphorus oxychloride and pyridine.

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