was continued for two to four hours. Where the product crystallized well from the cooled reaction mixture, it was collected on a filter and dried. More soluble products were precipitated by the addition of ether, acetone or isopropyl acetate.

Procedure B.—A mixture of molar proportions of amine hydrochloride and ketone, 1.1 moles of paraformaldehyde, and a slight excess of hydrogen chloride was refluxed in mixed amyl alcohols (Pentasol) for two to four hours. The product was isolated as in procedure A.

Procedure C.—This method is essentially that of Winstein and co-workers.[13] The reaction times were held to a minimum.

Procedure D.—One mole of formaldehyde (35% aqueous solution) was added dropwise to one mole of amine in dilute ethanol at 5–10°. The stirred mixture was allowed to warm to room temperature over a period of about one hour. One mole of the ketone was added. After one hour, the stirred reaction mixture was refluxed for one to four and one-half hours. Dilution with water caused precipitation of the amino ketone as a solid. It was collected, dried and converted to its hydrochloride.

6-Acetyl-1,4-benzodioxane.—To a flask equipped with stirrer, dropping funnel and condenser, were added 200 g. (1.5 moles) of aluminum chloride and 800 cc. of carbon disulfide. A mixture of 136 g. (1 mole) of 1,4-benzodioxane and 105 g. (1.34 moles) of acetyl chloride was added dropwise with stirring over a period of two hours. After the addition was completed, the reaction mixture was heated under reflux for four hours. The carbon disulfide was then removed by distillation, and the residue decomposed with ice and water. The solid which formed was collected on a filter and washed thoroughly with water. After one recrystallization from dilute alcohol, the light tan material weighed 152 g. (85.5% of the theory); m. p. 78–81°. Further recrystallization from alcohol gave the product in the form of colorless plates; m. p. 84–85°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.4; H, 5.62. Found: C, 67.5; H, 5.69.

(13) Winstein, Jacobs, Seymour and Linden, *J. Org. Chem.*, **11**, 218 (1946).

Acknowledgment.—For all microanalyses appearing in this article, we are indebted to O. E. Sundberg, M. E. Nielsen and I. H. Prokul. We wish to thank Dr. Barbara Roth for synthesizing compound XXXII.

Summary

1. Thirty-seven substituted β-aminoalkyl aryl and heterocyclic ketones, of which twenty-two are new compounds, have been prepared by means of the Mannich reaction.

2. Correlation of the chemical structures of the above ketones with their antispasmodic activities has shown the following to be generally true: (a) Substituted β-aminopropiophenones and propionaphthones are active; (b) the piperidyl group is the most effective while the morpholinyl group is the least effective amino group; (c) simple substituents in the para-positions of the aromatic rings of the propiophenones decrease the activity; (d) enhancement of activity results from the introduction of a phenyl group into the α-position of only some of these propiophenones.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Antispasmodics. II. Tertiary β-Amino Alcohols

BY J. J. DENTON, VIRGINIA A. LAWSON, W. B. NEIER AND R. J. TURNER

In the first paper of this series,[1] it was shown that several substituted β-amino ketones exhibited interesting antispasmodic activity. Since some of the structural modifications reported in that paper had an effect on the activity, it was considered that the transformation of these ketones to alcohols, principally tertiary alcohols, might possibly have a greater effect. The synthesis and study of a number of tertiary amino alcohols having generally the following structure were therefore undertaken:

$RR'C(OH)CH(R'')CH_2Am$
R is an aryl or heterocyclic group
R′ is an alkyl or phenyl group
R″ is hydrogen, a methyl, or phenyl group
Am is a tertiary amino group

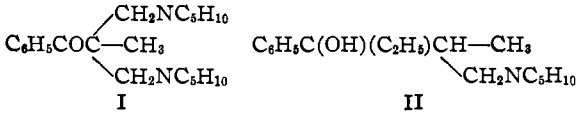
This paper deals principally with certain variations in R, recorded in Table A, and in R″, recorded in Table B.

We have prepared these tertiary alcohols by the addition of a Grignard reagent to some of the substituted β-amino ketones previously reported,[1] according to the reaction

$$RCOCH(R'')CH_2Am \xrightarrow{R'MgX} RR'C(OH)CH(R'')CH_2Am$$

During the course of this work, other investigators[2] have reported the preparation of compounds of the same general formula by the above method. In using this method we have obtained the expected tertiary alcohol from every ketone except one.

Treatment of β,β′-bis-(1-piperidyl)-pivalophenone (I) with an excess of ethylmagnesium bromide did not give the expected tertiary alcohol which would result from the simple addition of the Grignard reagent. Instead it gave 1-(1-piperidyl)-2-methyl-3-phenyl-3-pentanol (II), a tertiary alcohol lacking one of the piperidylmethyl groups originally present in the ketone (I).

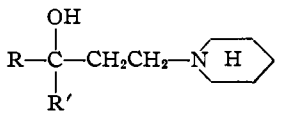


I II

(1) Denton, Turner, Neier, Lawson and Schedl, THIS JOURNAL, **71**, 2048 (1949).

(2) (a) Spaeth, Geissman and Jacobs, *J. Org. Chem.*, **11**, 399 (1946). (b) Ruddy and Buckley, Abstracts of Papers, 110th Meeting, A. C. S., Sept. 1946, p. 14K. (c) Becker, Ananenko, Glenwood and Miller, *Federation Proc.*, **5**, 163 (1946). (d) Kleiderer, Rice, Conquest and Williams, Report No. PB-981, Office of the Publication Board, Dept. of Commerce, Washington, 1945, p. 38.

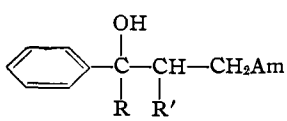
TABLE A



No.	Groups R	Groups R′	Formula	M. p., °C.[a]	Yield,[b] %	Procedure	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Activity
IA[4]	C_2H_5–	C_2H_5–	$C_{12}H_{25}NO\cdot HCl$	159.1–159.9	63.4		61.2	61.7	11.05	11.2	5.95	6.1	15.1	15.2	+
IIA	2-C_4H_3S–	C_2H_5–	$C_{14}H_{23}NOS\cdot HCl$	207–208.3	20	a					4.83	4.87	12.24	12.23	+
IIIA	*p*-BrC_6H_4–	C_2H_5–	$C_{16}H_{24}BrNO\cdot HCl$	243.5–244.1	13.4	a	52.97[c]	53.1	6.95	7.04	3.86	3.58	9.78	9.89	+++
IVA	*p*-BrC_6H_4–	*n*-C_4H_9–	$C_{18}H_{28}BrNO\cdot HCl$	242.2–242.6	35	a	55.82[d]	55.0	7.48	7.50	3.59	3.58	9.07	9.15	+++
VA	*p*-ClC_6H_4–	C_2H_5–	$C_{16}H_{24}ClNO\cdot HCl$	231.2–232	31.4	b	60.39	60.2	7.92	7.85	4.40	4.39	22.28	22.5	+++
VIA	*p*-$CH_3C_6H_4$–	C_2H_5–	$C_{17}H_{27}NO\cdot HCl$	172–174.5	16.5	a	68.55	68.8	9.38	9.27	4.70	4.82	11.91	12.0	+++
VIIA	*p*-$CH_3OC_6H_4$	C_2H_5–	$C_{17}H_{27}NO_2\cdot HCl$	172–174.5	18.4	b	65.06	65.4	8.99	8.89	4.46	4.51	11.3	11.3	+
VIIIA	*p*-$C_2H_5C_6H_4$–	*n*-C_4H_9–	$C_{20}H_{33}NO\cdot HCl$	229–229.2	20	b	70.66	70.6	10.08	10.02	4.12	4.22	10.43	10.40	++
IXA	1-$C_{10}H_7$–	C_2H_5–	$C_{20}H_{27}NO\cdot HCl$	150.0–154.0	49	a	71.94	71.6	8.45	8.47	4.20	4.39	10.62	10.8	++
XA	C_6H_5–	C_2H_5–	$C_{18}H_{25}NO\cdot HCl$	185.0–185.5	22.8	a	67.70	67.6	9.23	9.2	4.93	5.02	12.50	12.5	+++
			$C_{18}H_{25}NO$[e]	82.5–83.0			77.7	77.7	10.2	10.0	5.66	5.58			
	Trasentin														++

[a] All melting points are corrected. [b] Yields refer to pure hydrochlorides and are based on starting ketones. [c] Calcd. Br, 22.03. Found: Br, 21.9. [d] Calcd. Br, 20.45. Found: Br, 20.2. [e] Amine corresponding to preceding hydrochloride.

TABLE B



No.	Groups R	Groups R′	Am	Formula	M. p., °C.[a]	Yield,[b] %	Procedure	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Activity
IB	C_2H_5–	CH_3–	$C_5H_{10}N$–	$C_{17}H_{27}NO\cdot HCl$	216.5–218.3	26.5	a	68.53	68.5	9.47	9.4	4.70	4.83	11.91	12.0	+
IIB	H–	C_6H_5–	$C_5H_{10}N$–	$C_{20}H_{25}NO\cdot HCl$	264.5–265.5	90		72.38	72.4	7.90	7.84	4.22	4.17	10.68	10.6	+++
				$C_{20}H_{25}NO$[c]	92.3–93.4			81.31	81.4	8.53	8.59	4.74	4.86			
IIIB	C_2H_5–	C_6H_5–	$C_5H_{10}N$–	$C_{22}H_{29}NO\cdot HCl$	227–228.7	69.7	b	73.41	72.9	8.4	8.5	3.89	3.98	9.85	9.80	+
				$C_{22}H_{29}NO$[c]	133.8–135.2			81.68	81.6	9.04	9.04	4.33	4.37			
IVB	*n*-C_4H_9–	C_6H_5–	$C_5H_{10}N$–	$C_{24}H_{33}NO\cdot HCl$	208.5–210	32.8	b	74.30	74.4	8.83	8.56	3.61	3.70	9.14	9.08	–
				$C_{24}H_{33}NO$[c]	69.2–71.0			81.99	82.2	9.46	9.46	3.99	4.04			
VB	*iso*-C_5H_{11}–	C_6H_5–	$C_5H_{10}N$–	$C_{25}H_{35}NO\cdot HCl$	222–226.5	7.5	b	74.69	73.6	9.03	9.03	3.49	3.54	8.82	8.92	+
VIB	C_6H_5–	C_6H_5–	$C_5H_{10}N$–	$C_{26}H_{29}NO\cdot HCl$	204–205.5	27.2	b	76.54	76.2	7.41	7.49	3.34	3.43	8.69	8.88	++
				$C_{26}H_{29}NO$[c]	172.5–174			84.05	83.8	7.87	7.78	3.77	3.62			
VIIB	C_2H_5–	C_6H_5–	$(CH_3)_2N$–	$C_{19}H_{25}NO\cdot HCl$	230–232	46	b	71.34	71.6	8.18	8.17	4.38	4.26	11.09	11.3	+
				$C_{19}H_{25}NO$[c]	105.5–106.5			80.52	80.3	8.89	8.88	4.94	4.91			
VIIIB	C_2H_5–	C_6H_5–	OC_4H_8N–	$C_{21}H_{27}NO_2\cdot HCl$	231.8–232.5	39.8	b	69.64	69.3	7.80	7.65	3.87	4.04	9.80	9.64	+
				$C_{21}H_{27}NO_2$[c]	153.6–154.3			77.50	77.3	8.36	8.57	4.31	4.26			

[a] All melting points are corrected. [b] Yields refer to pure hydrochlorides and are based on starting ketones. [c] Amine corresponding to preceding hydrochloride.

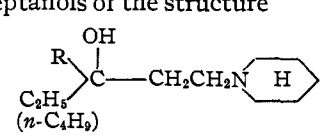
With the assumption that the cleavage of the piperidylmethyl group occurs before the addition of the Grignard reagent to the carbonyl group, this reaction demonstrates the cleavage of a highly substituted alkyl aryl ketone at the α-carbon–β-carbon bond by means of a Grignard reagent.

An analogous cleavage by phenylmagnesium bromide of the carbon–carbon bond in the α,β-position of α,β-dimorpholinobenzylacetophenones has recently been reported by Cromwell.[3] In the reported case and the present one the reaction resulting in cleavage predominated. The cases reported by Cromwell, however, differ from the present case first in that a tertiary amino group was present on the α-carbon, and secondly, in that no addition of the Grignard reagent to the carbonyl group of the cleaved product was observed.

(3) Cromwell, THIS JOURNAL, 69, 1857 (1947).

Pharmacological Activity

In Table A are listed eight piperidyl pentanols and two heptanols of the structure



One aliphatic pentanol, 1-(1-piperidyl)-3-ethyl-3-pentanol (IA), previously reported by Weizmann and Bergmann,[4] is included here for comparison. In this and the subsequent table, the antispasmodic activity has the same meaning as that given in the previous paper[1] of this series.

In Table A, the phenyl pentanols with a bromo, chloro, or methyl radical in the *p*-position (IIIA, VA and VIA) have the same activity rating as the unsubstituted phenylpentanol (XA), which is

(4) Weizmann and Bergmann, *J. Chem. Soc.*, 401 (1936).

different from what was observed in the corresponding propiophenones.[1] The methoxyphenylpentanol (VIIA) is much less active than any of the above four.

Perhaps the most significant fact is that all of the tertiary alcohols in Table A, except the thienyl compound (IIA), show greater antispasmodic activity than the ketones from which they were derived. Five of the ten tertiary alcohols listed have a higher activity rating and two are equal in rating to β-diethylaminoethyl diphenylacetate hydrochloride (Trasentin).

Table B lists tertiary alcohols (IIIB-VIIIB) obtained by the similar transformation of β-(1-piperidyl)-α-phenylpropiophenone, the corresponding dimethylamino, and morpholinyl compounds. In contrast to the tertiary alcohols in Table A, none of these showed greater antispasmodic activity than the ketones from which they were derived. Only the secondary alcohol (IIB) was more active than β-(1-piperidyl)-α-phenylpropiophenone, itself.

It is therefore indicated by this study that the transformation of β-amino propiophenones, having no α-phenyl group, to tertiary alcohols gives compounds having greater antispasmodic activity. The activity of these alcohols is not further enhanced by simple substituents in the *para*-position of the phenyl group.

Experimental

Procedure A.—One mole of the Grignard reagent was prepared in ethyl ether in the usual way and to it was added an ether solution of the appropriate ketone, the molar ratio of Grignard reagent to ketone varying between 3:1 and 2:1. After the addition of the ketone solution was completed, the mixture was heated under reflux for a period of one hour and then allowed to stand at room temperature overnight. The addition product was then decomposed with external cooling by the introduction of sufficient 5 *N* hydrochloric acid to render the reaction mixture acidic to congo red. The solid material which formed was collected and dried at 50°.

The product was purified by liberating the free base from an aqueous solution of its salt, extracting the base with ether, precipitating the hydrochloride from the dried ether solution, and recrystallizing the hydrochloride from alcohol or an alcohol–ether mixture.

Procedure B.—The Grignard reagent was prepared in the usual way except that dibutyl ether was used as the reaction medium and after the addition of the halide, the mixture was heated at 60° for one hour. The solution of the appropriate ketone in dibutyl ether was added to the Grignard reagent at about 40°, a temperature which was maintained for one hour after the addition was completed. The product was isolated and purified in a manner similar to that described in Procedure A.

1-(1-Piperidyl)-3-ethyl-3-pentanol Hydrochloride (IA).[5]—This compound was prepared essentially by the procedure of Weizmann and Bergmann,[4] except that the reaction was carried out in an open, rather than a closed, vessel. A mixture of 112 g. (0.72 mole) of 1-chloro-3-ethyl-3-pentanol and 136 g. (1.6 moles) of piperidine was heated on a steam-bath in a large test-tube for one-half hour. The piperidine hydrochloride formed was removed by filtration and washed with ether. The filtrate and washings were combined and fractionally distilled to give 88.3 g. (63.4%) of the amine, b. p. 81–86° at 3 mm. The amine was converted to its hydrochloride whose physical properties are recorded in Table A.

3-(1-Piperidyl)-1,2-diphenyl-1-propanol Hydrochloride (IIB).—To a glass-lined autoclave were added 49 g. (0.148 mole) of β-(1-piperidyl)-α-phenylpropiophenone hydrochloride, 0.5 g. of 10% palladium on charcoal, and 100 cc. of absolute ethanol. Hydrogenation was carried out at 93° until absorption ceased. The contents of the autoclave were treated with 1.5 l. of boiling absolute ethanol, the catalyst was removed by filtration, and the filtrate was concentrated to a volume of 1 liter. Cooling and dilution with an equal volume of ether caused crystallization of the propanol hydrochloride. It was purified by recrystallization from ethanol. Physical and analytical data concerning it are recorded in Table B.

Acknowledgments.—The authors greatly appreciate the coöperation in this work of Dr. R. W. Cunningham, Dr. B. K. Harned and their assistants of the Pharmacology Department of the Lederle Laboratories Division, who have determined the antispasmodic activity of these compounds. We are also grateful to Mr. O. E. Sundberg, Mrs. M. E. Nielsen, and Miss I. H. Prokul for the microanalyses.

Summary

1. Sixteen new tertiary amino alcohols have been prepared by the addition of Grignard reagents to substituted β-amino ketones.

2. Correlation of the chemical structures of the above tertiary alcohols with their antispasmodic activities shows the following to be generally true: (a) 1-(1-piperidyl)-3-aryl-3-alkanols are more active than the ketones from which they are derived, (b) introduction of simple substituents into the *p*-positions of the phenyl groups of the 1-(1-piperidyl)-3-phenyl-3-alkanols does not enhance the activity, (c) no enhancement in activity over the parent ketones results from converting β-amino-α-phenylpropiophenones to tertiary alcohols.

3. One anomalous reaction was noted in that 1-(1-piperidyl)-2-methyl-3-phenyl-3-pentanol resulted from the treatment of β,β′-bis-(1-piperidyl)-pivalophenone with ethylmagnesium bromide.

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(5) This compound was prepared by Dr. Barbara Roth.