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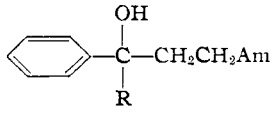
Antispasmodics. VII.[1] Additional Morpholinyl and Piperidyl Tertiary Alcohols.

BY J. J. DENTON, H. P. SCHEDL, VIRGINIA A. LAWSON AND W. B. NEIER

The antispasmodic activities shown by compounds which are members of the two homologous series having the structure

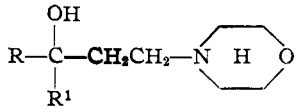


in which R represents various hydrocarbon radicals and Am is morpholinyl or piperidyl, have prompted us to extend these series[2] by studying particularly variations in the aromatic ring. prepared by the addition of a Grignard reagent to the corresponding *beta* amino ketone as previously described.[3]

Pharmacological Activity

Table I lists ten morpholinyl tertiary alcohols with their antispasmodic activity-ratings. The significance of the ratings is given in paper V of this series.[4] Compounds IA–IIIA are an extension of a homologous series already reported.[2] Two of these (IIA and IIIA) are more active than the parent ketone.[5] The octanol

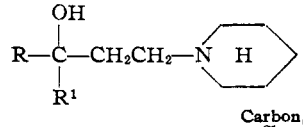
TABLE I



Number	R	R¹	Formula	M. p.,[a] °C.	Yield,[b] %	Procedure	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity
IA	C_6H_5-	CH_3-	$C_{14}H_{21}NO_2\cdot HCl$	191.4–192.0[c]	29.4	b	61.87	61.7	8.16	8.07	5.15	5.21	13.05	13.1	−
IIA	C_6H_5-	n-$C_5H_{11}-$	$C_{18}H_{29}NO_2\cdot HCl$	201.0–201.8[d]	5.9	a	65.93	66.1	9.22	9.21	4.27	4.43	10.81	11.0	++
IIIA	C_6H_5-	C_6H_5-	$C_{19}H_{23}NO_2\cdot HCl$	227.2–227.3 (d.)	15.0	a	68.35	68.2	7.25	7.10	4.20	4.23	10.62	10.8	+
			$C_{19}H_{23}NO_2$[e]	100.8–101.6			76.73	76.7	7.80	7.80	4.71	4.57			
IVA	p-$(CH_3)_2CHC_6H_4-$	C_2H_5-	$C_{18}H_{29}NO_2\cdot HCl$	242.5[f]	45.8	b	65.94	65.7	9.22	9.23	4.27	4.14	10.81	10.8	+
VA	p-$(CH_3)_2CHC_6H_4-$	n-C_4H_9-	$C_{20}H_{33}NO_2\cdot HCl$	240.0[g]	41.2	b	67.48	67.6	9.63	9.69	3.94	4.02	9.96	9.97	+
VIA	1-$C_{10}H_6Cl-$[h]	C_2H_5-	$C_{16}H_{24}ClNO_2\cdot HCl$	240.0–243.5 (d.)	26.7	a	61.62	61.4	6.81	6.57	3.78	3.85	19.15	19.0	−
			$C_{16}H_{24}ClNO_2$[e]	114.0–116.0			68.36	68.5	7.25	7.05	4.20	4.13	10.62	10.7	
VIIA	2-$C_{10}H_7-$	C_2H_5-	$C_{16}H_{23}NO_2\cdot HCl$	206.3–206.5 (d.)	40.2	a	67.94	68.0	7.80	7.57	4.17	4.23	10.56	10.6	−
VIIIA	1-$C_{10}H_6Cl-$[h]	n-C_4H_9-	$C_{21}H_{28}ClNO_2\cdot HCl$	217.0–218.0 (d.)	33.3	c	63.31	63.6	7.34	7.46	3.52	3.73	17.80	18.0	−
IXA	2-$C_{10}H_7-$	n-C_4H_9-	$C_{21}H_{29}NO_2\cdot HCl$	220.5–221.0 (d.)	39.3	a	69.31	69.0	8.31	8.43	3.85	3.87	9.74	9.83	++
XA	1-$C_{10}H_6Cl-$[h]	$C_6H_{11}-$	$C_{22}H_{30}ClNO_2\cdot HCl$	263.0–265.0 (d.)	8.4	c	65.09	64.7	7.36	7.49	3.30	3.44	16.71	16.9	−

[a] All melting points are corrected. [b] Yields refer to pure hydrochlorides and are based on starting ketones. [c] Sample immersed in a bath at 190°. [d] Sample immersed in a bath at 195°. [e] Amine corresponding to preceding hydrochloride. [f] Sample decomposes in approx. 10 sec. when immersed in a bath at 242.5°. [g] Sample decomposes in approx. 10 sec. when immersed in a bath at 240.0°. [h] 4-Chloro-1-naphthyl radical.

TABLE II



Number	R	R¹	Formula	M. p.,[a] °C.	Yield,[b] %	Procedure	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen % Calcd.	Nitrogen % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity
IB	C_6H_5-	C_5H_9-[c]	$C_{19}H_{29}NO\cdot HCl$	233.0–233.5 dec.	7.7	b	70.45	70.4	9.34	9.26	4.33	4.44	10.95	11.0	+++
IIB	1-$C_{10}H_6Cl-$[d]	C_2H_5-	$C_{20}H_{26}ClNO\cdot HCl$	251.0–252.0 dec.	5.2	c	65.29	65.2	7.39	7.50	3.80	3.82	19.25	19.4	+
IIIB	2-$C_{10}H_7-$	C_2H_5-	$C_{20}H_{27}NO\cdot HCl$	196.0–202.3 dec.	31.3	a	71.94	72.1	8.45	8.56	4.20	4.25	10.62	10.7	+++
IVB	1-$C_{10}H_6Cl-$[d]	n-C_4H_9-	$C_{22}H_{30}ClNO\cdot HCl$	254.0–255.0 dec.	23.8	c	66.66	66.9	7.88	8.20	3.53	3.66	17.89	17.9	−
VB	2-$C_{10}H_7-$	n-C_4H_9-	$C_{22}H_{31}NO\cdot HCl$	222.4–222.8	40.1	a	73.00	73.2	8.91	9.24	3.87	3.79	9.80	9.70	+++
VIB	1-$C_{10}H_6Cl-$[d]	$C_6H_{11}-$	$C_{24}H_{33}ClNO\cdot HCl$	368–372 dec.	4.7	c	68.24	68.0	7.87	8.12	3.32	3.39	16.79	16.7	−
VIIB	2-$C_{16}H_9-$[f]	n-C_4H_9-	$C_{26}H_{33}NO\cdot HCl$	207.0–207.2 dec.	42.3	c	75.06	74.8	8.57	8.69	3.50	3.66	8.86	9.03	−
			$C_{26}H_{33}NO$[e]	110.3–111.8			82.60	82.7	9.15	9.05	3.85	3.69			

[a] All melting points are corrected. [b] Yields refer to pure hydrochlorides and are based on starting ketones. [c] Cyclopentyl radical. [d] 4-Chloro-1-naphthyl radical. [e] Base corresponding to preceding hydrochloride. [f] 2-Fluorenyl radical.

These new tertiary amino alcohols have been

(1) For the preceding paper in this series see THIS JOURNAL, **72**, 3792 (1950).

(2) Denton, Schedl, Neier and Lawson, *ibid.*, **71**, 2054 (1949).

(3) Denton, Lawson, Neier and Turner, *ibid.*, **71**, 2050 (1949).

(4) Denton and Lawson, *ibid.*, **72**, 3279 (1950).

(5) Denton, Turner, Neier, Lawson and Schedl, *ibid.*, **71**, 2048 (1949).

(IIA) has one-tenth the activity of the methylheptanol.[2] This tenfold difference in activity has also been observed in the series containing the piperidyl group.[2] The data on compounds IVA and VA show what has already been observed with respect to *p*-alkyl substituents on the phenyl group.[3] As has already been observed in these amino alcohols with the phenyl group in the 3-position,[2] the naphthylheptanol (IXA) is more active than the corresponding pentanol (VIIA). The fact that the 4-chloro-1-naphthyl derivatives (VIA, VIIIA and XA) are less active than their parent ketone[5] must be attributed, at least in part, to their low solubility in the test medium.

Table II lists seven piperidyl tertiary alcohols. It is interesting that the cyclopentyl propanol (IB) is only one-tenth as active as the corresponding cyclohexyl propanol.[2] In this series the 2-naphthylpentanol (IIIB) and heptanol (VB) have the same activity, and are more active than the 1-naphthylpentanol.[3] The activities of compounds IIB, IIIB and VB when compared with the corresponding members of the morpholinyl series (VIA, VIIA and IXA) illustrate the superiority of the piperidyl group for conferring antispasmodic activity. The unexpected decrease in activity shown by the higher homologs (IVB and VIB) of compound IIB is probably due partially to their lower solubility in the test medium.

Experimental

Procedures a and b are identical with the corresponding procedures described in paper II of this series.[3]

Procedure c.—The Grignard reagent was prepared as in procedure b. The appropriate amino ketone hydrochloride was then added as a finely divided solid at 50–70°. The ratio of Grignard reagent to ketone varied between 3:1 and 4:1. The remainder of the procedure is identical with procedure 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. For their technical assistance in the synthesis of some of these compounds, we wish to thank Mr. Peter Drenchko, Miss Ellen G. Lee and Mr. Elmer K. Norton. The authors are indebted to Mr. O. E. Sundberg, Mrs. M. E. Nielsen and Miss I. H. Prokul for all microanalyses.

Summary

Seventeen new morpholinyl and piperidyl tertiary alcohols have been prepared by the addition of Grignard reagents to the corresponding β-aminoethyl aromatic ketones, and their antispasmodic activities have been reported.

Active amino alcohols show greater activity than the ketones from which they were derived.

Alcohols with complex aromatic substituents are, in general, less active than the corresponding alcohols with a simple phenyl substituent.

BOUND BROOK, NEW JERSEY

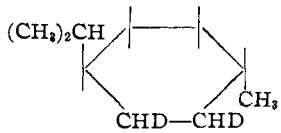
RECEIVED NOVEMBER 30, 1949

NOTES

Optical Activity in Compounds Containing Deuterium. II. 3-Deutero-*trans*-*p*-menthane

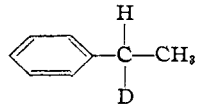
BY ELLIOT R. ALEXANDER

In an earlier communication[1] it was shown that the catalytic reduction of *trans*-2-*p*-menthene with deuterium gas gave an optically active 2,3-dideutero-*trans*-*p*-menthane (I). More recently it has been found[2] that the reduction of optically active



$[\alpha]^{25}D$ −0.09 ± 0.01°
(*l* = 2, no solvent)

I

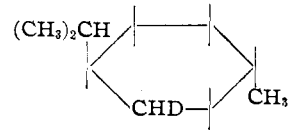


$[\alpha]^{25}D$ −0.30 ± 0.02°
(*l* = 2, no solvent)

II

(1) Alexander and Pinkus, THIS JOURNAL, **71**, 1786 (1949).
(2) Eliel, *ibid.*, **71**, 3970 (1949).

α-phenylethyl chloride with a mixture of lithium aluminum deuteride and lithium deuteride produced an optically active deuterohydrocarbon (II). These appear to be the only two compounds reported in which optical activity depends solely upon the replacement of hydrogen atoms by deuterium atoms. The preparation of an optically active 3-deutero-*trans*-*p*-menthane (III) by



$[\alpha]^{25}D$ −0.09 ± 0.02° (*l* = 2, no solvent)

III

the reaction of lithium aluminum deuteride with *l*-menthyl *p*-toluenesulfonate was particularly attractive since the same reaction with lithium