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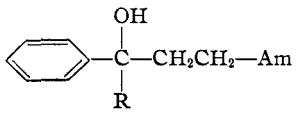
Antispasmodics. III. Study of the Amino Group in the Tertiary β-Amino Alcohols

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

It was shown in the preceding paper of this series[1] that the addition of an alkyl Grignard reagent to β-(1-piperidyl)-propiophenones, having no α-substituent, yielded tertiary alcohols generally with greater antispasmodic activity than the propiophenones[2] themselves. Both of these earlier reports had indicated further that the choice of the substituted amino group (dialkylamino, piperidyl, morpholinyl, etc.) had a considerable effect on the antispasmodic activity of these compounds.

It was to study this latter effect that we synthesized a group of compounds of the structure



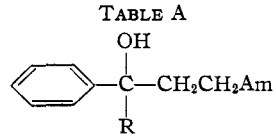
in which R is a lower alkyl group (ethyl), a branched-chain alkyl group (isoamyl), or a cycloalkyl group (cyclohexyl), and in which Am is a dimethylamino, diethylamino, piperidyl, morpholinyl, tetrahydroisoquinolyl or a 4-methylpiperazyl group.

These tertiary amino alcohols were synthesized by the addition of a Grignard reagent to the corresponding ketone, as previously described.[1] 3 - Dimethylamino - 1 - cyclohexyl - 1 - phenyl - 1 - propanol hydrochloride (compound III) has recently been reported by Ruddy and Buckley.[3] The same authors and others[4] have also studied 3 - (1 - piperidyl) - 1 - cyclohexyl - 1 - phenyl - 1 - propanol hydrochloride (IX). Table A, in which the column headings have the same meaning as those in the preceding report,[1] lists fifteen tertiary alcohols and one secondary alcohol which we have prepared.

Pharmacological Activity

Twelve of the fifteen tertiary amino alcohols listed in Table A show a greater antispasmodic rating than the ketones from which they were

TABLE A



No.	Groups R	Groups Am	Formula	M. p.,[a] °C.	Yield,[b] %	Procedure	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Activity
I	H-	$(CH_3)_2N$-	$C_{11}H_{17}NO\cdot HCl$	134.3-135.0	67.5		61.25	61.1	8.41	8.47	6.49	6.60	16.44	16.4	-
II	C_2H_5-	$(CH_3)_2N$-	$C_{13}H_{21}NO\cdot HCl$	125.2-125.8	26.2	b	64.05	63.8	9.10	9.0	5.75	5.80	14.55	14.8	+
IIA			$C_{13}H_{21}NO$	45.4- 46.2			73.32	75.0	10.22	10.4	6.76	6.75			
III[3]	C_6H_{11}-	$(CH_3)_2N$-	$C_{17}H_{27}NO\cdot HCl$	210.5-212.5[c]	23.2	b	68.55	68.6	9.48	9.48	4.70	4.70	11.90	11.9	++
IV	C_2H_5-	$(C_2H_5)_2N$-	$C_{16}H_{25}NO\cdot HCl$	167.0-167.5	13.9	a	66.26	66.1	9.64	9.7	5.15	5.59	13.04	13.1	++
V	iso-C_5H_{11}-	$(C_2H_5)_2N$-	$C_{18}H_{31}NO\cdot HCl$	206.7-207.0	6.0	a	68.87	69.2	10.28	10.4	4.46	4.44	11.29	11.3	++
VI	C_6H_{11}-	$(C_2H_5)_2N$-	$C_{19}H_{31}NO\cdot HCl$	186.9-187.4	13.1	a	70.01	70.2	9.90	10.0	4.30	4.40	10.87	10.8	++++
VII[4]	C_2H_5-	$C_5H_{10}N$-													+++
VIII	iso-C_5H_{11}-	$C_5H_{10}N$-	$C_{19}H_{31}NO\cdot HCl$	240.0-240.5	34.7	b	70.01	70.2	9.90	10.0	4.30	4.32	10.87	10.9	++++
VIIIA			$C_{19}H_{31}NO$	59.0- 59.5			78.83	78.8	10.79	10.7	4.84	4.91			
IX[3,4]	C_6H_{11}-	$C_5H_{10}N$-	$C_{20}H_{31}NO\cdot HCl$	258.5[d]	13.7	a	71.08	70.7	9.55	9.4	4.15	4.05	10.49	10.5	++++
IXA			$C_{20}H_{31}NO$	114.3-115.0			79.68	79.7	10.37	10.3	4.65	4.47			
X	C_2H_5-	OC_4H_8N-	$C_{18}H_{29}NO_2\cdot HCl$	179.3-179.7	10.0	a	63.02	63.2	8.48	8.4	4.90	4.95	12.41	12.5	+
XA			$C_{18}H_{29}NO_2$	57.8- 58.4			72.24	71.6	9.30	9.2	5.62	5.47			
XI	iso-C_5H_{11}-	OC_4H_8N-	$C_{19}H_{29}NO_2\cdot HCl$	218.0-219.5	8.5	a	65.93	65.5	9.23	9.09	4.27	4.42	10.81	10.9	+++
XII	C_6H_{11}-	OC_4H_8N-	$C_{19}H_{29}NO_2\cdot HCl$	225[e]	24.4	b	67.14	67.2	8.90	8.86	4.12	4.15	10.43	10.5	+++
XIIA			$C_{19}H_{29}NO_2$	116.3-117.0			75.12	75.3	9.63	9.61	4.62	4.62			
XIII	C_2H_5-	$C_9H_{10}N$-[g]	$C_{20}H_{29}NO\cdot HCl$	202.2-203.0	28.7	a	72.38	72.3	7.9	7.9	4.22	4.28	10.69	10.8	++
XIIIA			$C_{20}H_{29}NO$	92.2- 93.1			81.3	80.2	8.53	8.6	4.74	5.01			
XIV	iso-C_5H_{11}-	$C_9H_{10}N$-[g]	$C_{23}H_{31}NO\cdot HCl$	185.2-186.0	7.3	a	73.87	73.6	8.63	8.59	3.75	3.90	9.48	9.56	+
XV	C_6H_{11}-	$C_9H_{10}N$-[g]	$C_{24}H_{31}NO\cdot HCl$	219.6-220.4	8.3	a	74.67	74.9	8.36	8.37	3.63	3.66	9.19	9.06	-
XVA			$C_{24}H_{31}NO$	148.8-149.4			82.47	82.5	8.94	9.10	4.01	4.08			
XVI	C_2H_5-	$C_5H_{11}N_2$-[h]	$C_{16}H_{26}N_2O\cdot HCl\cdot {}^1/_2H_2O$[f]	216.8-217 d.	24.2	a	55.81	55.6	8.49	8.5	8.14	8.15	20.59	20.6	++

[a] All melting points are corrected. [b] Yields refer to pure hydrochlorides and are based on starting ketones. [c] Sample inserted in bath 5° below m. p. [d] With bath held at this temperature, inserted sample melts with decomposition in exactly ten seconds. [e] Sublimes above this temperature. [f] Calcd. % H_2O, 2.62. Found (by Karl Fischer method), 2.84. [g] 2-(1,2,3,4-Tetrahydroisoquinolyl) radical. [h] 1-(4-Methylpiperazyl) radical.

(1) Denton, Lawson, Neier and Turner, THIS JOURNAL, **71**, 2050 (1949).

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

(3) Ruddy and Buckley, Abstracts of Papers, 110th Meeting, A. C. S., Sept. 1946, p. 14K.

(4) Becker, Ananenko, Glenwood and Miller, *Federation Proc.*, **5**, 163 (1946).

derived. Only compound XV was less active than its parent ketone; the slight activity of compound XV appears to be due in part to its low solubility in the test medium.

The piperidyl group contributes outstandingly to the antispasmodic activity in all three series of tertiary alcohols: (1) the pentanols, where R in the general formula is ethyl (compounds II, IV, VII, X, XIII and XVI); (2) the methylheptanols, where R is isoamyl (compounds V, VII, XI and XIV); and (3) the cyclohexyl propanols, where R is cyclohexyl (compounds III, VI, IX, XII and XV). The morpholinyl alcohols (X, XI and XII) show a particularly interesting increase in activity over β-(4-morpholinyl)-propiophenone.

The antispasmodic activity of the one secondary alcohol (I) in Table A is less than its parent ketone.

Experimental

Procedures a and b, by which most of the compounds were prepared, are identical with those described in detail in paper II of this series.[1]

3-Dimethylamino-1-phenyl-1-propanol Hydrochloride (I).—Using the procedure of Mannich and Lammering,[5] who hydrogenated β-(1-piperidyl)-propiophenone hydrochloride, 3-dimethylamino-1-phenyl-1-propanol hydrochloride was obtained from the corresponding ketone. After removal of the catalyst from the hydrogenation mixture, the product was isolated by evaporation to dryness and purified by recrystallization from an alcohol–ether mixture. Data concerning this compound are recorded in Table A.

(5) Mannich and Lammering, *Ber.*, **55**, 3510 (1922).

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Summary

1. Fifteen tertiary amino alcohols have been prepared by adding cyclohexyl-, isoamyl- or ethylmagnesium halide to six different β-(substituted-amino)-propiophenones.

2. Twelve of the above alcohols have greater antispasmodic activity than the ketones from which they were derived. The morpholinyl alcohols show, in general, the greatest increase in activity over that of the parent ketone.

3. Outstanding in activity and promising as antispasmodic agents are two of the piperidyl alcohols, 3-(1-piperidyl)-1-cyclohexyl-1-phenyl-1-propanol and 1-(1-piperidyl)-6-methyl-3-phenyl-3-heptanol.

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Antispasmodics. IV. Morpholinyl and Piperidyl Tertiary Alcohols

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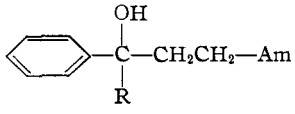
The interesting increase in antispasmodic activity of the morpholinyl alcohols over the corresponding ketone and the outstanding antispasmodic activity of the piperidyl alcohols, which were reported in our preceding paper,[1] interested us in the preparation and study of homologs of these compounds.

We therefore prepared, by the method previously described,[2] two homologous series of compounds of the structure



in which Am is (1) morpholinyl, compounds in Table A, and (2) piperidyl, compounds in Table B. References are cited in the tables for compounds previously reported in the literature.

Pharmacological Testing

Seven morpholinyl alcohols are listed in Table A, in which the rating of antispasmodic activity has the same meaning as given in a previous paper.[3] In every case, the activity of these morpholinyl alcohols is greater than that of the ketone, β-(4-morpholinyl)-propiophenone,[3] from which they are derived. The antispasmodic activity increased from the morpholinylpentanol (IA) to the methylpentanol (IIIA) and hexanol (IIA). The activity further increased to three plus in the methylhexanol (VA), heptanol (IVA) and methylheptanol (VIA) as well as the cyclohexylpropanol (VIIA). None of these morpholinyl compounds, however, showed the maximum activity-rating of the testing method, four plus.

In Table B are recorded seventeen piperidyl alcohols, nine of which on evaluation give the maximum activity-rating. In this homologous series, whose general formula is given above, the antispasmodic activity increases with increasing chain length from the secondary alcohol (compound IB), where R is hydrogen, through the butanol (IIB) and pentanol (IIIB) to the maximum rating in the methylpentanol (VB), where

(1) Denton, Neier and Lawson, THIS JOURNAL, **71**, 2053 (1949).
(2) Denton, Lawson, Neier and Turner, *ibid.*, **71**, 2050 (1949).
(3) Denton, Turner, Neier, Lawson and Schedl, *ibid.*, **71**, 2048 (1949).