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).

Acknowledgments.—The authors are indebted to Dr. R. W. Cunningham, Dr. B. K. Harned and their assistants of the Pharmacology Department of the Lederle Laboratories Division for the determination of the antispasmodic activity of these compounds. The microanalytical services of Mr. O. E. Sundberg, Mrs. M. E. Nielsen, and Miss I. H. Prokul are greatly appreciated.

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.

BOUND BROOK, NEW JERSEY RECEIVED DECEMBER 10, 1948

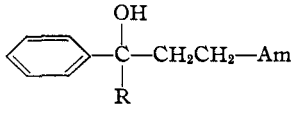
[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Antispasmodics. IV. Morpholinyl and Piperidyl Tertiary Alcohols

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

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.

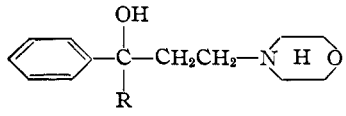
Pharmacological Testing

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).

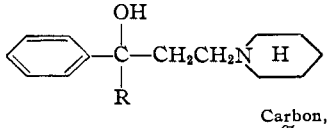
TABLE A



No.	R	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
IA[1]	C_2H_5-													+
IIA	n-C_3H_7-	$C_{16}H_{28}NO_2 \cdot HCl$	211.0–212.4	22.5	b	64.09	63.8	8.74	8.67	4.67	4.67	11.82	12.0	++
IIIA	iso-C_3H_7-	$C_{16}H_{28}NO_2 \cdot HCl$	203.5–204.8	10.5	a	64.09	64.2	8.74	8.93	4.67	4.78	11.82	11.9	++
IVA	n-C_4H_9-	$C_{17}H_{27}NO_2 \cdot HCl$	227.1–228.1	30.8	a	65.05	65.3	8.99	8.73	4.46	4.60	11.30	11.4	+++
		$C_{17}H_{27}NO_2$[c]	59.2–60.6			73.60	73.6	9.81	10.0	5.05	5.22			
VA	iso-C_4H_9-	$C_{17}H_{27}NO_2 \cdot HCl$	231.8–233.3	7.2	a	65.05	66.2	8.99	8.91	4.46	4.69	11.30	11.4	+++
		$C_{17}H_{27}NO_2$[c]	B. p. 151–159 (2 mm.)											
VIA[1]	iso-$C_5H_{11}-$													+++
VIIA[1]	$C_6H_{11}-$													+++

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

TABLE B



No.	R	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[4]	H-													++
IIB	CH_3-	$C_{14}H_{23}NO \cdot HCl$	200.3–200.9	14.6	b	66.76	67.1	8.97	8.9	5.19	5.11	13.14	13.3	++
		$C_{14}H_{23}NO$[c]	B. p. 137–142 (3 mm.)											
IIIB[2]	C_2H_5-													+++
IVB	n-C_3H_7-	$C_{17}H_{27}NO \cdot HCl$	202–203.5	35.6	a	68.55	68.7	9.48	9.4	4.70	4.67	11.90	12.0	++++
		$C_{17}H_{27}NO$[c]	92.2–94.0			78.11	77.9	10.41	10.2	5.36	5.51			
VB	iso-C_3H_7-	$C_{17}H_{27}NO \cdot HCl$	175[d]	26.0	a	68.55	68.4	9.48	9.6	4.70	4.80	11.90	12.0	++++
		$C_{17}H_{27}NO$[c]	72.7–75.1			78.11	77.4	10.41	10.4	5.36	5.20			
VIB	$CH_2{=}CH{-}CH_2-$	$C_{17}H_{25}NO \cdot HCl$	180.5–182.9	21.6	a	69.01	68.9	8.86	8.9	4.74	4.74	11.99	12.0	++
VIIB	n-C_4H_9-	$C_{18}H_{29}NO \cdot HCl$	223–224 d.	25.9	a	69.31	69.2	9.70	9.6	4.49	4.43	11.37	11.5	++++
		$C_{18}H_{29}NO$[c]	54.4–56.7			78.50	77.9	10.61	10.4	5.09	5.21			
VIIIB	iso-C_4H_9-	$C_{18}H_{29}NO \cdot HCl$	218.2–219.7	7.2	a	69.31	69.2	9.70	9.6	4.49	4.60	11.37	11.6	++++
		$C_{18}H_{29}NO$[c]	53.1–56.6											
IXB	s-C_4H_9-	$C_{18}H_{29}NO \cdot HCl$	210–212.5	7.7	a	69.31	69.2	9.70	9.85	4.49	4.48	11.37	11.3	++++
XB	t-C_4H_9-	$C_{18}H_{29}NO \cdot HCl$	228.5–230	2.1	a	69.31	69.4	9.70	9.70	4.49	4.36			++++
XIB	n-$C_5H_{11}-$	$C_{19}H_{31}NO \cdot HCl$	200–204.5	11.1	a	70.00	69.9	9.92	9.43	4.29	4.27	10.89	10.9	+++
		$C_{19}H_{31}NO$[c]	63.5–65.5			78.8	78.6	10.80	11.0	4.83	4.92			
XIIIB[2]	iso-$C_5H_{11}-$													++++
XIIIB	n-$C_7H_{15}-$	$C_{21}H_{35}NO \cdot HCl$	207–209.5	13.0	a	71.25	71.2	10.25	10.8	3.95	3.88	10.00	10.2	++
		$C_{21}H_{35}NO$[c]	63–65.5			79.51	79.7	11.12	11.3	4.42	4.26			
XIVB	n-$C_{12}H_{25}-$	$C_{26}H_{46}NO \cdot HCl$	192–193.5	22.8	a	73.6	73.7	10.94	10.9	3.30	3.34	8.37	8.40	-
XVB[2,5,6]	$C_6H_{11}-$													++++
XVIB[5,6,7]	C_6H_5-	$C_{20}H_{28}NO \cdot HCl$	233.8–234.4[e]	23.2	a	72.38	72.4	7.90	7.8	4.22	4.24	10.69	10.6	++++
		$C_{20}H_{28}NO$[c]	115.8–116.9			81.30	80.9	8.53	8.4	4.75	4.70			
XVIIB	$C_6H_5CH_2-$	$C_{21}H_{27}NO \cdot HCl$	239–240.5	35.8	a	72.91	72.7	8.16	8.2	4.05	4.10	10.25	10.4	+++

[a] All melting points are corrected. [b] Yields refer to pure hydrochlorides and are based on starting ketones. [c] Amine corresponding to preceding hydrochloride. [d] Melts in approx. 10 sec. when immersed in bath at 175°. [e] Melted in a sealed tube when immersed at 228° and heated at rate of 2° (min.).

R is isopropyl. This activity remains a maximum where R is any of the isomeric butyl groups (VIIB–XB) or an isoamyl group (XIIB); but it starts to decrease with increasing chain length in the octanol (XIB), where R is n-amyl, and continues to decrease through the decanol (XIIIB) and finally through the pentadecanol (XIVB). Alcohols in which R is allyl (VIB) or benzyl (XVIIB) are less active, while those in which R is phenyl (XVIB) or cyclohexyl (XVB) again exhibit the maximum activity-rating.

The outstanding antispasmodic activity of these piperidyl alcohols has led to the detailed pharmacological study of six of the most active compounds. This study will be reported[8] elsewhere.

Experimental

Procedures a and b, by which most of the com-

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

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

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

(7) Kleiderer, Rice, Conquest and Williams, Report No. PB-981, Office of the Publication Board, Dept. of Commerce, Washington, 1945, p. 39.

(8) Cunningham, Harned, *et al.*, to be published.

pounds were prepared, are identical with those described in detail in paper II[2] of this series.

Acknowledgments.—The authors express their gratitude to Dr. R. W. Cunningham, Dr. B. K. Harned and their assistants in the Pharmacology Department of the Lederle Laboratories Division for the pharmacological evaluation of these compounds. We wish also, to thank Mr. O. E. Sundberg, Mrs. M. E. Nielsen and Miss I. H. Prokul for carrying out all of the microanalyses reported.

Summary

1. Seven morpholinyl tertiary alcohols were prepared by the addition of various Grignard reagents to β-(4-morpholinyl)-propiophenone. All showed greater antispasmodic activity than the parent ketone, but none showed the maximum rating of the testing method.

2. Seventeen homologous piperidyl tertiary alcohols were prepared similarly from β-(1-piperidyl)-propiophenone. Nine of these showed the maximum antispasmodic activity-rating of the testing method.

3. Some, if not all, of these nine highly active piperidyl alcohols appear to warrant more extensive study as antispasmodic agents.

BOUND BROOK, N. J. RECEIVED DECEMBER 10, 1948

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Preparation of Gentisic Acid and its Fatty Alcohol Esters[1]

BY STEWARD G. MORRIS

It is well known that 3,4,5-trihydroxybenzoic acid (gallic acid) and its alkyl esters are effective antioxidants for fats and oils. Comparatively little work has been done on other hydroxybenzoic acids and their esters. For the purpose of extending our information on the antioxidant properties of this class of compounds, 2,5-dihydroxybenzoic acid (gentisic acid) and its normal octyl, dodecyl, tetradecyl, hexadecyl and octadecyl esters were synthesized. This paper is restricted to the preparation of these compounds.

Gentisic acid was early prepared from 5-iodosalicylic acid by fusion with potassium hydroxide.[2,3] Similarly it was prepared by fusing gentisicaldehyde with potassium hydroxide.[4] Senhofer and Sarlay[5] obtained gentisic acid by heating hydroquinone, potassium carbonate and water in a sealed tube at 130°. More recently Mauthner,[6] prepared gentisic acid in 31–36% yields by treating an alkaline solution of salicyclic acid with potassium persulfate in the presence of a small amount of ferrous sulfate.

In the work described here, hydroquinone was used as starting material in the preparation of gentisic acid. Hydroquinone diacetate was prepared in practically quantitative yields by the method of Chattaway.[7] Acetylhydroquinone was then made from the hydroquinone diacetate by the Fries isomerization reaction, according to a modification of the method of Rosenmund and Lohfert.[8] The acetylhydroquinone was benzylated.[9] The resulting 2,5-dibenzyloxyacetophenone was oxidized to 2,5-dibenzyloxybenzoic acid by means of the haloform reaction, and the product was debenzylated by catalytic hydrogenolysis, forming gentisic acid. The esters of gentisic acid were obtained by the reactions of the acid chloride of 2,5-dibenzyloxybenzoic acid with various alcohols, followed by debenzylations.

Experimental

Acetylhydroquinone.—Into a 3-liter, 3-neck experimental flask equipped for stirring of the contents and disposing of hydrogen chloride fumes was introduced 293 g. (2.2 moles) of anhydrous aluminum chloride and 850 cc. of *o*-dichlorobenzene. The mixture was heated to 130° in an oil-bath. A mixture of 55 g. (0.5 mole) of hydroquinone and 97 g. (0.5 mole) of hydroquinone diacetate[7] was added in small portions to the *o*-dichlorobenzene solution in one hour. The reaction mixture was then heated for three additional hours at 140–150°. The acetylhydroquinone obtained on hydrolysis of the reaction product in ice and hydrochloric acid was crystallized from 50% alcohol solution. The yield was 61 g. (40%); m. p., 204–205.5°[10]; previously reported,[8] 202°.

Dibenzyl Ether Acetylhydroquinone.—Seventy-three grams of acetylhydroquinone (0.48 mole) was dissolved in 250 cc. of acetophenone and benzylated by means of 130 g. of benzyl chloride and 142 g. of anhydrous potassium carbonate.[9] For this reaction it was necessary to alter the original purification procedure. After the steam distillation the residue was cooled and the water poured off. The residue was then extracted four times with 375-cc. portions of 80% alcohol solution heated to about 60°. The alcoholic extracts were centrifuged to separate some suspended globules of tarlike material. The clear alcoholic solutions when cooled to 2° yielded 82 g. of white crystalline dibenzyl ether acetylhydroquinone. The yield was 51%. When it was recrystallized from benzene–petro-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted. Presented at the Fall Meeting of the American Chemical Society, held at Washington, D. C., August 30-September 3, 1948.

(2) Miller, *Ann.*, **220**, 113 (1883).

(3) Rakowski and Leppert, *Ber.*, **8**, 788 (1875).

(4) Tiemann and Müller, *ibid.*, **14**, 1985 (1881).

(5) Senhofer and Sarlay, *Monatsh.*, **2**, 448 (1881).

(6) Mauthner, *J. prakt. Chem.*, **156**, 150 (1940).

(7) Chattaway, *J. Chem. Soc.*, 2495 (1931).

(8) Rosenmund and Lohfert, *Ber.*, **61**, 2601 (1928).

(9) Clinton and Geissman, THIS JOURNAL, **65**, 85 (1943).

(10) The 76-mm. immersion thermometer used for all melting point determinations was calibrated against a 76-mm. immersion thermometer which had been certified by the National Bureau of Standards.