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Preparation of N-Substituted 1-(*p*-Hydroxyphenyl)-2-aminoethanols[1]

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In an extensive investigation of highly active broncholytic compounds in the epinephrine series, Konzett[1a] reported that 1-(*p*-hydroxyphenyl)-2-isopropylaminoethanol hydrochloride possessed marked activity as a bronchodilator, and that it was more active than the corresponding methyl analog, 1-(*p*-hydroxyphenyl)-2-methylaminoethanol (Synephrine). This observation prompted us to prepare a number of other derivatives in this series for further pharmacological investigation. In this paper we are describing the synthesis and properties of these compounds, as the preparation of many of them has not been reported.

Most of the compounds in this series were prepared by the catalytic reduction of the corresponding ω-amino-*p*-hydroxyacetophenones with palladium on charcoal as the catalyst. Metallic sodium and alcohol was first used as the reducing agent for the preparation of the basic primary amine, 1-(*p*-hydroxyphenyl)-2-aminoethanol, as aluminum amalgam would not reduce the aminoketone.[2] Later Mannich and Thiele[3] used a catalytic reduction with palladium for the preparation of the same compound, and Legerlotz[4] reduced ω-methylamino-*p*-hydroxyacetophenone by the same procedure in the preparation of 1-(*p*-hydroxyphenyl)-2-methylaminoethanol. The properties of these compounds are summarized in Table I.

TABLE I

N-SUBSTITUTED DERIVATIVES OF 1-(*p*-HYDROXYPHENYL)-2-AMINOETHANOL, *p*-$HOC_6H_4CHOHCH_2NR'R''$

		Base			Nitrogen analyses, %[a]		Hydrochloride analyses, %[a]					Pharmacological data	
									Nitrogen		Chlorine		Effect on blood
R'	R''	Yield, %	M. p., °C.	Formula	Calcd.	Found	Yield, %	M. p., °C.	Calcd.	Found	Calcd.	Found	pressure[b]	LD_{50} mg./kg.[c]
H	H	..	.....	$C_8H_{11}O_2N$	..	..	99[d]	167–169[e]	7.38	7.31	18.70	18.35	++++	600
H	CH_3	89	182–183[e]	$C_9H_{13}O_2N$	8.38	8.50	91	184–185[f]	5.78	5.92	...	...	++	>1000
H	CH_2CH_3	71	141–142	$C_{10}H_{15}O_2N$	7.73	7.72	53	147–149	6.44	6.46	16.29	16.21	−−	550–600
H	$CH_2CH_2CH_3$	68	125–128	$C_{11}H_{17}O_2N$	7.18	7.02	78	147–148	6.05	6.18	15.30	15.14	−	300
H	$CH(CH_3)_2$	86	138–140	$C_{11}H_{17}O_2N$	7.18	7.26	89	155–157	6.05	6.14	15.30	15.28	−−−−	360–380
H	$CH_2CH_2CH_2CH_3$	83	123.5–125	$C_{12}H_{19}O_2N$	6.69	6.53	85	109–110	5.70	5.51	14.42	14.27	−	150
H	$CH_2CH_2(CH_3)_2$	87	157–158	$C_{12}H_{19}O_2N$	6.69	6.59	83	146–147	5.70	5.66	14.42	14.37	−	
H	$CH(CH_3)CH_2CH_3$	91	137–145[g]	$C_{12}H_{19}O_2N$	6.69	6.66						I[g]	−−	
												II	−−−−	
H	$C(CH_3)_3$	78	172–173.5	$C_{12}H_{19}O_2N$	6.69	6.82	46	159–161[e]	5.70	5.88	14.42	14.38	−−−	
CH_3	CH_3	..	.....	$C_{10}H_{15}O_2N$	..	..	75[d]	150–151	6.44	6.24	16.29	16.56	+	700

[a] We are indebted to Mary Jane Eastwood and to Elizabeth B. Macks for the analytical data on these compounds. [b] ++++ indicates a marked pressor activity, while −−−− indicates a marked depressor action. [c] The toxicity was determined by intraperitoneal injection in albino mice. [d] Yield from aminoketone. [e] Melts with decomposition. [f] Tartrate salt. [g] Mixture of isomers. I, m. p. 161–162°. *Anal.* Calcd.: N, 6.69. Found: N, 6.61. II, m. p. 132.5–133°. *Anal.* Calcd.: N, 6.69. Found: N, 6.62.

In the reduction of ω-*s*-butylamino-*p*-hydroxyacetophenone both racemic forms of 1-(*p*-hydroxyphenyl)-2-*s*-butylaminoethanol were produced. Fractional crystallization of the precipitated base from 90% methanol yielded the diastereoisomers. Hydrochloride salts of the two racemates were obtained as oils which resisted crystallization.

ω-Amino-*p*-hydroxyacetophenone could not be obtained from ω-chloro-*p*-hydroxyacetophenone by condensation with ammonia, according to Tutin, Caton and Hann,[2] although the experiment was conducted under a great variety of conditions. The compound was obtained by the acid hydrolysis of ω-phthalimido-*p*-acetoxyacetophenone, prepared by the condensation of potassium phthalimide with ω-chloro-*p*-acetoxyacetophenone,[2] and by the demethylation of ω-amino-*p*-methoxyacetophenone.[5] Catalytic reduction of α-isonitroso-*p*-benzyloxyacetophenone by Hartung's method[6] gave ω-amino-*p*-benzyloxyacetophenone,[7] although debenzylation of this compound has not been mentioned. We have found it convenient to prepare this compound by condensation of ω-iodo-*p*-benzoyloxyacetophenone with hexamethylenetetramine and hydrolysis of the addition product thus obtained with alcoholic hydrochloric acid according to a slight modification of the procedure described by Mannich and Hahn.[5]

The reaction of ω-chloro-*p*-hydroxyacetophenone with methylamine has been reported to be unsuccessful,[2] although Legerlotz[8] claimed a yield of 12% of ω-methylamino-*p*-hydroxyacetophenone when he used this procedure. The yield was appreciably increased when the hydroxyl group was

(1) Prepared for the 1945 meeting-in-print of the Division of Medicinal Chemistry, A. C. S.

(1a) Konzett, *Arch. exptl. Path. Pharmakol.*, **197**, 27 (1940).

(2) Tutin, Caton and Hann, *J. Chem. Soc.*, **95**, 2120 (1909).

(3) Mannich and Thiele, *Arch. Pharm.*, **253**, 193 (1915).

(4) Legerlotz, U. S. Patent 1,932,347 (October 24, 1933), *C. A.*, **28**, 485 (1934).

(5) Mannich and Hahn, *Ber.*, **44**, 1546 (1911).

(6) Hartung, THIS JOURNAL, **53**, 2248 (1931).

(7) Priestley and Moness, *J. Org. Chem.*, **5**, 355 (1940).

(8) Legerlotz, U. S. Patent 1,680,055 (August 7, 1928); *C. A.*, **22**, 3736 (1928). German Patent 518,636; *Friedländer*, **17**, 2518 (1933).

TABLE II

N-SUBSTITUTED DERIVATIVES OF ω-AMINO-*p*-HYDROXYACETOPHENONE HYDROCHLORIDE, *p*-HOC$_6$H$_4$COCH$_2$NR'R''·HCl

R'	R''	Yield, %	M. p., °C.[b]	Formula	Analyses, %[a] Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
H	H	64	241–245	$C_8H_9O_2N$·HCl	7.47	7.53	18.90	18.61
H	CH_3	50	241–243	$C_9H_{11}O_2N$·HCl	6.95	6.91	17.59	17.73
H	CH_2CH_3	51	228–231	$C_{10}H_{13}O_2N$·HCl	6.50	6.61	16.44	16.31
H	$CH_2CH_2CH_3$	59	236–238	$C_{11}H_{15}O_2N$·HCl	6.11	6.01	15.43	15.50
H	$CH(CH_3)_2$	64	250–252	$C_{11}H_{15}O_2N$·HCl	6.11	6.15	15.43	15.42
H	$CH_2CH_2CH_2CH_3$	44	228–229	$C_{12}H_{17}O_2N$·HCl	5.75	5.72	14.55	14.74
H	$CH_2CH(CH_3)_2$	43	228–230	$C_{12}H_{17}O_2N$·HCl	5.75	5.95	14.55	14.64
H	$CH(CH_3)CH_2CH_3$	64	243–245	$C_{12}H_{17}O_2N$·HCl	5.75	5.95	14.55	14.50
H	$C(CH_3)_3$	25	254–257	$C_{12}H_{17}O_2N$·HCl	5.75	5.95	14.55	14.78
CH_3	CH_3	47	233–235	$C_{10}H_{13}O_2N$·HCl	6.45	6.29	16.44	16.58

[a] We are indebted to Mary Jane Eastwood and Elizabeth B. Macks for the analytical data on these compounds. [b] All compounds softened and darkened between 20 and 40° below their melting points and all melted with decomposition.

benzoylated and the bromo derivative used. Priestley and Moness[7] have described a number of methods for the preparation of this compound and we obtained it in a yield of 50% following the reaction of ω-bromo-*p*-benzoyloxyacetophenone with aqueous methylamine in isopropanol. In the course of this reaction the benzoyl group was removed by hydrolysis. The tertiary amine, di-(*p*-hydroxyphenacyl)-methylamine, has been isolated in varying amounts from this reaction, depending upon the experimental conditions used.

The other substituted ω-amino-*p*-hydroxyacetophenones, see Table II, were prepared in an analogous manner, except in the case of the isopropyl, isobutyl, *s*-butyl, *t*-butyl and dimethyl derivatives where the benzoyl group did not hydrolyze off during the reaction and it was necessary to complete the hydrolysis with hydrochloric acid.

The tertiary amine, ω-dimethylamino-*p*-hydroxyacetophenone, has been prepared previously through the methoxy derivative by demethylation with phosphorus and hydriodic acid.[9] Condensation of ω-bromo-*p*-benzoyloxyacetophenone with dimethylamine gave the desired product in excellent yield.

We are indebted to Dr. A. M. Lands and coworkers in the Pharmacological Research Laboratories for a preliminary report of the pharmacological activity of these compounds as recorded in Table I. A more detailed report will be published elsewhere. In general, these compounds are active bronchodilators, with the isopropyl and butyl derivatives being among the most active of the series. As a vasopressor agent, the primary amine is the most active, being about one and one-half times more active than the corresponding methyl analog. The ethyl, isopropyl *s*- and *t*-butyl derivatives produce a transient pressor action which is immediately followed by a marked and prolonged depressor response. The isopropyl and *s*-butyl derivatives are the most active depressor agents. The *n*-propyl and *n*-butyl derivatives produce only a small transient depressor action of short duration. The toxicity of the alkyl derivatives increases with an increase in size of the alkyl group.

(9) Voswinckel, *Ber.*, **45**, 1004 (1912).

Experimental[10]

Most of the amines used in this work were supplied through the courtesy of Commercial Solvents Corporation and Sharples Chemicals, Inc.

ω-Amino-*p*-benzoyloxyacetophenone Hydrochloride (I).—Sodium iodide, 38 g. (0.25 mole), dissolved in 150 ml. of acetone, was added to a solution of 80 g. (0.25 mole) of ω-bromo-*p*-benzoyloxyacetophenone in 700 ml. of acetone. After standing for about four hours, the sodium bromide precipitate was filtered off and the filtrate evaporated to dryness. The residue was dissolved in 400 ml. of chloroform and the solution dried over anhydrous calcium chloride. To the dry solution was added 35 g. (0.25 mole) of hexamethylenetetramine dissolved in 400 ml. of chloroform. An addition compound began to separate within a few minutes and, after standing for two days, with occasional shaking, it was filtered. The white crystalline addition product was washed with chloroform and dried; m. p. 170–173°, dec.; yield 119.5 g. (95%).

A mixture of 92.5 g. (0.18 mole) of the addition compound, 100 ml. of concentrated hydrochloric acid, and 800 ml. of ethanol was refluxed for eight hours on a steam-bath to bring about decomposition to the primary aminoketone hydrochloride. The solution was cooled, filtered, and the white crystalline product washed with cold water to remove ammonium salts, and dried; m. p. 208–211°, dec.; yield 41 g. (77%).

Anal. Calcd. for $C_{15}H_{13}O_3N$·HCl: N, 4.80; Cl, 12.16. Found: N, 4.72; Cl, 12.30.

ω-Amino-*p*-hydroxyacetophenone Hydrochloride (II).—Forty grams (0.137 mole) of the benzoyloxy derivative (I) was refluxed for seven hours in 240 ml. of 20% hydrochloric acid solution. Benzoic acid was removed from the cooled solution by filtration and the filtrate evaporated to dryness on a steam-bath. The solid residue was washed with acetone, ether, and dried; yield of crude product, 22.5 g. (87%). Recrystallization from 15–20% hydrochloric acid solution gave white crystals; m. p. 241–245°, dec.; yield 20.5 g. (80%).

ω-Methylamino-*p*-hydroxyacetophenone Hydrochloride (III).—To a solution of 200 ml. (2.3 moles) of 40% aqueous methylamine in 300 ml. of isopropanol was added 200 g. (0.63 mole) of ω-bromo-*p*-benzoyloxyacetophenone over a period of three hours at 0–5°. After stirring for one hour the suspension was filtered and the ω-methylamino-*p*-hydroxyacetophenone obtained was washed with 150 ml. of cold 50% alcohol. The base was suspended in 300 ml.

(10) All melting points reported are uncorrected.

of water and converted to the hydrochloride by the addition of 30 ml. of concentrated hydrochloric acid. The acid solution was evaporated to dryness, acetone added and filtered. The cream-colored crystalline product was washed with acetone and recrystallized from 85% isopropanol; m. p. 241–243°, dec.; yield 63 g. (50%).

The alcoholic mother liquor was acidified with concentrated hydrochloric acid, cooled and filtered. The hydrochloride salt of di-(*p*-hydroxyphenacyl)-methylamine thus obtained was washed with water and dried; m. p. 245–252°, dec.; yield 31 g. (30%). Five grams of this material required 250 ml. of hot 75% methanol for solution and upon recrystallization melted at 261–263°, dec.

t-Butylamine, like methylamine, produced an insoluble aminoketone base while the bases from the other amines were soluble in the alcoholic reaction solution.

ω-Isopropylamino-*p*-hydroxyacetophenone Hydrochloride (IV).—ω-Bromo-*p*-benzoyloxyacetophenone, 800 g. (2.5 moles), was added to a well-stirred solution of 500 g. (8.5 moles) of isopropylamine in 1250 ml. of isopropanol over a period of one hour at 20–30°. After stirring for an additional hour the clear solution was acidified with 375 ml. of concentrated hydrochloric acid, and filtered. The solid product was refluxed for eight hours in a 15% hydrochloric acid solution to hydrolyze the benzoate ester. A yield of 331 g. of crude hydrolyzed product was obtained.

The solvent was removed from the alcoholic acid filtrate by evaporation and 500 ml. of acetone added to the warm sirupy residue with vigorous stirring. The resulting solution was cooled with ice water and filtered to separate the crystalline precipitate which formed. Recrystallization of the solid from water removed the isopropylamine salts and gave an additional 38 g. of hydrolyzed product. Total yield of crude material was 369 g. (64%). The combined materials were recrystallized from water and formed white crystals which melted at 250–252°, dec.; yield 345 g. (60%).

During the course of the condensation of the bromoketone with dimethyl, iso-butyl, *s*-butyl, and *t*-butylamines the hydrolysis of the benzoate ester was also only partially completed and further treatment with hydrochloric acid solution was necessary. In the case of the methyl, ethyl, *n*-propyl and *n*-butyl derivatives the benzoyl group was split off in the alkaline reaction solution during the condensation. When the isopropylamine condensation was run at reflux temperature for three hours, the hydrolyzed product was obtained but the yield dropped to 50%.

1-(*p*-Hydroxyphenyl)-2-isopropylaminoethanol Hydrochloride (V).—Twenty-three grams (0.1 mole) of the isopropylaminoketone (IV) was dissolved in 200 ml. of hot water, 2 g. of 10% palladium on Nuchar catalyst added, and the warm solution hydrogenated under 50 pounds pressure. The reduction was completed in forty-five minutes. After filtering off the catalyst, the solution was concentrated to one-half of the original volume and made alkaline with 25 ml. of concentrated ammonium hydroxide. The white crystalline base which separated was filtered off, washed with water and dried; m. p. 138–140°; yield 16.8 g. (86%).

One mole (195 g.) of 1-(*p*-hydroxyphenyl)-2-isopropylaminoethanol was dissolved in 1200 ml. of hot anhydrous ethanol, treated with Darco and filtered. Dry hydrogen chloride was passed over the warm filtrate with agitation until the solution was slightly acid. Anhydrous ether (750 ml.) was added to the warm filtrate until it became slightly cloudy. The white crystalline hydrochloride which separated from the cooled solution was filtered off, washed with a 50% anhydrous ethanol–ether solution and dried; m. p. 156–157°; yield 171 g. The filtrate was concentrated to a volume of 150 ml. and, while still warm, diluted with 75 ml. of anhydrous ether. The second crop of white crystals separated on cooling and was filtered off, washed with anhydrous ethanol–ether solution and dried; m. p. 155–157°; yield 34 g. The total yield was 205 g. (89%). Recrystallization from a mixture of anhydrous ethanol and ether gave a fine, white crystalline product; m. p. 158–159°.

Crystalline hydrochloride salts of the amino- and dimethylamino derivatives were isolated directly from the reduction solution by evaporation of the solvent. When the other derivatives were treated in the same manner, sirupy products resulted and it was found necessary to first isolate the amino alcohol bases from which the hydrochloride salts could be prepared in anhydrous media.

Summary

1. The reaction of ω-bromo-*p*-benzoyloxyacetophenone with various alkylamines proceeds smoothly in isopropanol. The *p*-benzoyl group is hydrolyzed off during the reaction, except in the case of the isopropyl, isobutyl, *s*-butyl, *t*-butyl and dimethyl derivatives where it is necessary to complete the hydrolysis with hydrochloric acid. A tertiary amine, from the disubstitution of the bromoketone on the primary amine, was isolated in only one case.

2. ω-Amino-*p*-hydroxyacetophenone was prepared by the condensation of ω-iodo-*p*-benzoyloxyacetophenone with hexamethylenetetramine and hydrolysis of the addition product thus obtained with alcoholic hydrochloric acid.

3. A series of N-substituted 1-(*p*-hydroxyphenyl)-2-aminoethanols has been prepared by the catalytic reduction of the corresponding ketones. The properties of these compounds are described. Both diastereoisomeric forms of 1-(*p*-hydroxyphenyl)-2-*s*-butylaminoethanol have been isolated by fractional crystallization.

4. All of the compounds possess broncholytic activity, with the isopropyl and butyl derivatives being the most active of the series. The primary amine and methyl derivative produce a pressor action on blood pressure whereas the other alkyl derivatives produce a depressor response, with the isopropyl and *s*-butyl derivatives being the most active. The toxicity of these compounds has been determined.

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