[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF FREDERICK STEARNS AND COMPANY, DIVISION OF STERLING DRUG, INC.]

Preparation of N-Substituted 1-(3′,4′-Dihydroxyphenyl)-2-aminoethanols[1]

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In a previous report[3] from these laboratories we have described the preparation of a series of N-substituted 1-(*p*-hydroxyphenyl)-2-aminoethanols. Our investigations were prompted by an observation of Konzett[4] that 1-(*p*-hydroxyphenyl)-2-isopropylaminoethanol was more active as a broncholidilator than the N-methyl analog (Synephrine). Konzett[4] also studied the broncholytic properties of several N-alkyl analogs of epinephrine and reported that 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol possessed ten times the bronchodilator activity of its N-methyl analog (epinephrine) against pilocarpine-induced bronchial spasm in dogs. The chemical synthesis of these N-alkyl epinephrine analogs (alkyl = ethyl, propyl, isopropyl, butyl and isobutyl) has not been reported. We have, therefore, extended our investigations to include the preparation of a series of N-substituted 1-(3′,4′-dihydroxyphenyl)-2-aminoethanols.

All of the amino alcohols in this series were obtained from the corresponding amino ketone hydrochlorides by catalytic hydrogenation with palladium-on-charcoal in aqueous solution. By careful removal of the solvent from the reduction solutions most of the amino alcohol hydrochlorides were isolated in crystalline form. In certain cases where the hydrochlorides resisted crystallization it was found necessary to precipitate the relatively unstable amino alcohol bases from the reduction solutions with ammonia. These bases, which were filtered if solid or extracted with butanol or ether if gummy, were converted to the acetate salts with glacial acetic acid in alcohol–ether solution. The properties of these amino alcohol salts are shown in Table I.

TABLE I

N-SUBSTITUTED DERIVATIVES OF 1-(3′,4′-DIHYDROXYPHENYL)-2-AMINOETHANOL 3,4-$(HO)_2C_6H_3CHOHCH_2NHR$ AS SALTS

R	M. p., °C., dec.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
CH_2CH_3	171–172	$C_{10}H_{16}O_3NCl$	5.99	5.88	15.17	15.02
$CH_2CH_2CH_3$	159–160	$C_{13}H_{21}O_5N^a$	5.17	5.14	...	...
$CH(CH_3)_2$	170–172	$C_{11}H_{18}O_3NCl$	5.66	5.56	14.31	14.56
$CH_2CH_2CH_2CH_3$	143.5–144.5	$C_{12}H_{20}O_3NCl$	5.35	5.24	13.54	13.57
$CH_2CH(CH_3)_2$	143.5–144.5	$C_{12}H_{20}O_3NCl$	5.35	5.24	13.54	13.32
$CH(CH_3)CH_2CH_3$	167–169	$C_{14}H_{23}O_5N^a$	4.91	4.78	...	...
$C(CH_3)_3$	179–180	$C_{14}H_{23}O_5N^a$	4.91	4.93	...	...
$CH_2CH_2CH_2CH_2CH_3$	123–124	$C_{13}H_{22}O_3NCl$	5.08	5.04	12.86	12.72
$CH(CH_3)CH(CH_3)_2$	142–144	$C_{15}H_{25}O_5N^a$	4.68	4.36	...	...
$CH(CH_2CH_3)_2$	141–143	$C_{15}H_{25}O_5N^a$	4.68	4.74	...	...
Cyclopentyl	180–181	$C_{13}H_{20}O_3NCl$	5.12	5.21	12.95	13.05
Cyclohexyl	174–176	$C_{14}H_{22}O_3NCl$	4.87	4.98	12.32	12.22

Acetate salt.

The amino ketones were prepared by condensing ω-chloro-3,4-dihydroxyacetophenone with various primary amines and were isolated as the hydrochloride salts. The reactions were usually carried out in ethanol or isopropanol. However it was found that ω-*t*-butylamino-3,4-dihydroxyacetophenone hydrochloride was isolated in higher yield when the condensation was run in dioxane instead of alcohol. The reaction temperatures were generally around 60–80° and the yields of amino ketone hydrochlorides varied between 15 and 55%. Properties of the aminoketone hydrochlorides are listed in Table II.

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. The N-isopropyl, N-*s*-butyl, and N-*t*-butyl analogs of epinephrine are the most active vasodepressor and bronchodilator members of this series. In general the most potent vasodepressor compounds were also the most active bronchodilators. The N-*n*-butyl derivative, however, is a very effective bronchodilator although its depressor activity is only 1/20 that of the N-isopropyl analog.

An extensive pharmacological study of 1-(3′,4′-

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(3) Corrigan, Langermann and Moore, THIS JOURNAL, **67**, 1894 (1945).

(4) Konzett, *Arch. Expil. Path. Pharmakol.*, **197**, 27 (1940).

TABLE II

N-SUBSTITUTED DERIVATIVES OF ω-AMINO-3,4-DIHYDROXYACETOPHENONE HYDROCHLORIDE, $3,4\text{-}(HO)_2C_6H_3COCH_2NHR\cdot HCl$

R	M. p., °C., dec.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
CH_2CH_3	240–242	$C_{10}H_{13}O_3N\cdot HCl$				
$CH_2CH_2CH_3$	234–236	$C_{11}H_{15}O_3N\cdot HCl$	5.70	5.69	14.43	14.40
$CH(CH_3)_2$	239–242	$C_{11}H_{15}O_3N\cdot HCl$	5.70	5.64	14.43	14.62
$CH_2CH_2CH_2CH_3$	206–208	$C_{12}H_{17}O_3N\cdot HCl$	5.39	5.11	13.65	13.15
$CH_2CH(CH_3)_2$	214–216	$C_{12}H_{17}O_3N\cdot HCl$	5.39	5.26	13.65	13.66
$CH(CH_3)CH_2CH_3$	226–227	$C_{12}H_{17}O_3N\cdot HCl$	5.39	5.57	13.65	13.77
$C(CH_3)_3$	233–235	$C_{12}H_{17}O_3N\cdot HCl$	5.39	5.19	13.65	13.49
$CH_2CH_2CH_2CH_2CH_3$	201–202	$C_{13}H_{19}O_3N\cdot HCl$	5.12	5.26	12.95	13.02
$CH(CH_3)CH(CH_3)_2$	231–233	$C_{13}H_{19}O_3N\cdot HCl$	5.12	5.04	12.95	12.76
$CH(CH_2CH_3)_2$	198–201	$C_{13}H_{19}O_3N\cdot NCl$	5.12	5.44	12.95	13.61
Cyclopentyl	213–214	$C_{13}H_{17}O_3N\cdot HCl$	5.17	5.15	13.09	12.86
Cyclohexyl	256–258	$C_{14}H_{19}O_3N\cdot HCl$	4.90	4.74	12.40	12.35

dihydroxyphenyl)-2-isopropylaminoethanol has shown it to be 1.5 to 2 times more active than epinephrine against histamine-induced asthma in guinea pigs and in addition its LD50 is approximately 450 mg./kg. by intraperitoneal administration in white mice as compared with 4 mg./kg. for epinephrine. This compound is a potent vasodepressor and also possesses marked antispasmodic properties.

Experimental[5]

Most of the amines in this work were supplied through the courtesy of Commercial Solvents Corporation and Sharples Chemicals, Inc. *t*-Butylamine was prepared by catalytic hydrogenation of 2,2-dimethylethylenimine.[6] Cyclopentylamine, 3-amylamine, and 2-methyl-isobutylamine were obtained from the appropriate ketones by catalytic hydrogenation in ammoniacal alcohol solution.

ω-Isopropylamino-3,4-dihydroxyacetophenone Hydrochloride (I).—A mixture of 37.5 g. (0.2 mole) of ω-chloro-3,4-dihydroxyacetophenone, 39 g. (0.66 mole) of isopropylamine, and 125 ml. of isopropanol was heated with stirring to 65–70° at which point the heat was removed to allow the reaction to proceed spontaneously. The amino ketone base which separated after completion of the reaction was converted to the hydrochloride salt by the addition of concentrated hydrochloric acid to the reaction solution. After cooling overnight the amino ketone hydrochloride was filtered, washed with acetone, and dried; m. p. 239–242°, dec., yield 26.5 g. (54%).

(5) All melting points are uncorrected.

(6) Campbell, Sommers and Campbell, THIS JOURNAL, 68, 140 (1946).

1-(3′,4′-Dihydroxyphenyl)-2-isopropylaminoethanol Hydrochloride (III).—Fifteen grams (0.06 mole) of (I) was dissolved in 150 ml. of hot water, 1 g. of 10% palladium-on-Nuchar catalyst added, and the warm solution hydrogenated under 50 pounds pressure. After filtering the catalyst, the water was carefully removed by distillation under reduced pressure. Acetone was distilled from the concentrate to remove residual water. The residue which solidified was recrystallized from alcohol–ether or 90% isopropyl alcohol to give a white crystalline product which melted at 170–172° dec., yield 11.5 g. (78%).

Summary

1. A number of ω-alkylamino-3,4-dihydroxyacetophenones have been prepared from ω-chloro-3,4-dihydroxyacetophenone and various primary amines in alcohol or dioxane.

2. A series of N-alkyl 1-(3′,4′-dihydroxyphenyl)-2-aminoethanols has been obtained by the catalytic hydrogenation of the corresponding ketones.

3. Most of these amino alcohols possess broncholytic and vasodepressor activity with the isopropyl, *t*-butyl and *s*-butyl derivatives being the most active on both counts. The *n*-butyl compound is one of the most active in the series as a bronchodilator although it is a relatively weak vasodepressor. One of these compounds, 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol is now in clinical use.

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