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Amino Alcohols. X. Ring Substituted Propadrins

BY WALTER H. HARTUNG, JAMES C. MUNCH AND FRANK S. CROSSLEY

It has been found that compounds having the skeletal formula AR—C(=N)—C—C possess optimum circulatory effect after either intravenous or oral administration.[1] However, the nature of the aryl group influences the qualitative as well as the quantitative effect produced. In continuing the examination of such compounds, additional analogs of propadrin[2] with three carbons in the side chain have been prepared and studied and in which the aromatic nucleus is *m*-methylphenyl, *p*-chlorophenyl, *p*-phenylphenyl (xenyl), α-naphthyl and β-naphthyl.

The method of preparation employed was that previously described for propadrin,[3] that is

$$ARCOCH_2CH_3 \xrightarrow[(HCl)]{RNO_2} ARCOC(CH_3)=NOH \xrightarrow[\text{reduction in presence of HCl}]{\text{Catalytic}} ARCHOHCHCH_3 \quad (NH_2(HCl))$$

m-Tolyl ethyl ketone and the α- and β-naphthyl ketones were prepared by means of the Grignard reaction, *i. e.*, by allowing ethylmagnesium bromide to react with the appropriate nitrile, according to the directions of Shriner and Turner.[4] The *p*-chloropropiophenone and *p*-phenylpropiophenone were prepared by means of the Friedel–Crafts reaction, *i. e.*, by allowing propionyl chloride to react with chlorobenzene and biphenyl, respectively. The experimental data for these ketones are summarized in Table I.

The conversion of the ketones into the corresponding α-oximino derivatives offered no difficulties and the procedure employed is that already described.[3]

TABLE I

KETONES

ArCOEt Ar =		B. p. or m. p. °C.	mm.	Yield, %	Derivative	M. p., °C.	Lit.
m-Methylphenyl	B	130–135	30–33	76.6	Semicarbazone	172	[a]
p-Chlorophenyl	B	115	3	81	..	.....	[b]
p-Phenylphenyl	M	102		90	Oxime[c]	162	[d]
α-Naphthyl	B	166–169	8	68	...	.....	[e]
β-Naphthyl	B	180–190	8–10	67	Oxime	133–133.5	[f]
	M	56			Semicarbazone	199	

[a] Wallach and Rentschler, *Ann.*, **360**, 61 (1908). [b] Collet, *Compt. rend.*, **126**, 1577 (1898). [c] *Anal.* Calcd. for $C_{16}H_{15}ON$: N, 6.22. Found: (Kjeldahl) N, 6.04, 6.22. [d] Not described; oxidation yielded acid, m. p. 222–224°; *p*-phenylbenzoic acid is described by Ciamician and Silber, *Ber.*, **28**, 1556 (1895), as melting at 224°. [e] Rousset, *Bull. soc. chim.*, [3] **15**, 62 (1896). [f] Rousset, *Bull. soc. chim.*, [3] **15**, 63 (1896); [3] **17**, 313 (1897).

The data relating to these are summarized in Table II.

TABLE II

ISONITROSO KETONES

ARCOCCH$_3$ ‖ NOH AR =	Yield, %	M. p., °C.	Formula	Nitrogen, % Calcd.	Found (Kjeldahl)
m-Methylphenyl	78.4	69.5–70.0	$C_{10}H_{11}O_2N$	7.91	7.79
p-Chlorophenyl[a]	83	122–123	$C_9H_8O_2NCl$	7.09	7.25
p-Phenylphenyl[b]	88.4	180	$C_{15}H_{13}O_2N$	5.63	5.70
α-Naphthyl	74	130	$C_{13}H_{11}O_2N$	6.57	6.77
β-Naphthyl	68.5	157	$C_{13}H_{11}O_2N$	6.57	6.57

[a] With hydroxylamine gives *p*-chlorophenyl methyl glyoxime, gray crystals, which darken at 208° and melt at 217°. [b] Glyoxime, m. p. 235°.

The reduction was accomplished by means of palladium on charcoal as catalyst, using as solvent absolute alcohol containing three equivalents of hydrogen chloride.[3,5] The compounds were isolated in the form of their hydrochlorides, from which the free base may be isolated by the usual methods of alkalinization. The data on the amino alcohols are collected in Table III.

Pharmacological Properties.—The amino alcohols were examined for toxicity and for the effect on the blood pressure on anesthetized dogs. The results are summarized briefly in Table IV,

(1) *Cf.* Hartung, *Chem. Rev.*, **9**, 389 (1931).

(2) For brevity compounds of the structure $C_6H_5CHOHCH(R)(NH_2)$ are called alkadrins from their relationship to ephedrine; the specific compounds are named after the number of carbon atoms in the side chain, thus $C_6H_5CHOHCH_2NH_2$ ethadrin, $C_6H_5CHOHCH(CH_3)(NH_2)$, propadrin, and so on through butadrin, pentadrin, etc.

(3) Hartung and Munch, THIS JOURNAL, **51**, 2262 (1929).

(4) Shriner and Turner, *ibid.*, **52**, 1267 (1930).

(5) Hartung, *ibid.*, **53**, 2248 (1931).

TABLE III

AMINO ALCOHOL HYDROCHLORIDES

ARCHOHCHCH$_3$ NH$_2$HCl AR =	M. p. (HCl), °C.	Soly. of salt 0.1 g. in water, ml.	Formula	Calcd., % N	Calcd., % Cl	Found, % (N Kjeldahl)	Cl(AgCl)
m-Naphthylphenyl	147	0.04	$C_{10}H_{15}ON\cdot HCl$	6.95	17.5	7.13	17.86
p-Chlorophenyl[a]	245	1.0	$C_9H_{13}ONCl\cdot HCl$	6.31	15.97	6.33	15.7[b]
p-Phenylphenyl[c]	228 (dec.)	6	$C_{15}H_{17}ON\cdot HCl$	5.31	13.45	5.18	13.26
α-Naphthyl[d]	267 (uncorr.)	1.6	$C_{13}H_{15}ON\cdot HCl$	5.89	14.92	5.71	14.96
β-Naphthyl	230–231	1.8	$C_{13}H_{15}ON\cdot HCl$	5.89	14.92	5.94	14.92

[a] The reduction of the corresponding oximino ketone to this amino alcohol proved to be extremely interesting. The first two thirds of the requisite hydrogen was taken up quite readily and then the rate dropped very markedly and at this time a heavy crystalline precipitate had formed. It is presumed that this was the amino ketone hydrochloride. As a rule, when this stage is reached in the catalytic reduction, water may be employed without any deleterious effect in further reducing to the amino alcohol. In order to facilitate solution of the product, water was added and the catalyst fortified by addition of more $PdCl_2$. The rate of hydrogen absorption increased rapidly and did not again drop off until a total of 4 equivalents had been taken up. The product (identified by its benzoylated derivative) proved to be propadrin. In order not to reduce off the aromatic chloride, it was found necessary to use large volumes of alcohol and to avoid the use of water.

[b] Only the ionizable chlorine is available for the formation of silver chloride.

[c] Formed by two-stage reduction. The amino ketone hydrochloride was isolated; formed a red melt at 253°; found N, 5.34%, Cl, 13.38%; calcd. for $C_{15}H_{15}ONHCl$, N 5.34, Cl, 13.55.

[d] Free base, m. p. 141–143° (uncorr.).

the activities being given in terms of the parent substance, propadrin.

TABLE IV

PHARMACOLOGICAL SUMMARY

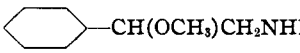
ARCHOHCHCH$_3$ NH$_2$HCl AR =	Relative pressor effect	Toxicity, M.L.D. mg./kg. guinea pig subcutaneously	Toxicity, M.L.D. mg./kg. rabbit intravenously
(propadrin)	1	600	75
CH$_2$	1/5	150	30–35
Cl	1/25	200	25
	trace	150	17.5
	1/6	100	15
	1/40	80	22.5

While a more detailed account of the pharmacodynamic properties of these compounds will be published elsewhere, the chemist is interested in determining the change in physiological action associated with a given definite modification in structure. Here are five additional simple structural variations in a given physiologically active parent substance.

The methyl group introduced into the meta-position of both propadrin and *p*-hydroxypropadrin makes the new compound decidedly more toxic. As with the *p*-methyl isomer, the toxicity increases and the activity tends to decrease.[3,6] Tainter reports *m*-methylpropadrin as having a pressor activity[7] ratio compared to epinephrine of 1:168, or 35% the activity of the unsubstituted parent substance, and a greatly diminished bronchodilator activity. These observations agree with the reports of Barger[8] that a *m*-methyl in tyramine decreases the activity.

Introduction of a chlorine into the para position of propadrin has quite the opposite effect from that which Burn[8] observed in the case of phenylethylamine, where the *p*-Cl substitution increases the activity several-fold.

The naphthyl analogs are of interest because here again previous reports indicated that greater activity might have been anticipated. Madinaveitia[9] found the sympathomimetic activity of



was increased about forty times if for the phenyl

(6) Hartung and Munch, THIS JOURNAL, **53**, 4149 (1931).

(7) Tainter, *J. Pharmacol.*, **51**, 371 (1934).

(8) Barger, "Organic Chemistry in Biology and Medicine," McGraw-Hill Book Co., Inc., New York, 1930, p. 87.

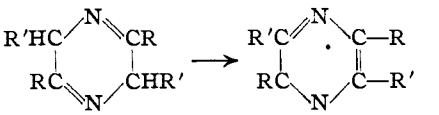
(9) Madinaveitia, *Bull. soc. chim.*, [4] **25**, 601 (1919); *Anal. soc. espan. fis. quim.*, **18**, 66 (1920); *Chem. Abs.*, **16**, 92 (1922).

an α-naphthyl nucleus was substituted. Possibly the apparent discrepancies between Madinaveitia's and our findings may be traced to the effects of the —OH as compared to the —OCH_3 group. In any event the large differences between the activity of the α- and β-naphthyl isomers is most striking.

Addenda.—After all the above data had been assembled there appeared the paper by Machlis and Blanchard[10] on 1-xenyl-2-aminopropanol. The hydrochloride is described by these authors as melting with decomposition at 235°, and on alkalinization "the precipitated colorless base rapidly underwent oxidation, assuming a yellow color which quickly passed through orange to a deep red." Our hydrochloride of the same amino alcohol melted with decomposition at 228°, but we were able to isolate the free base by the usual alkalinization procedures, *i. e.*, with sodium carbonate or sodium hydroxide, and the base shows no evidence of instability on prolonged exposure or even at the melting point, 148.5–149° (corr.).

Machlis and Blanchard did not get complete hydrogenation—89% of calculated hydrogen being used (*cf.* footnote (c) Table III)—and in the light of our experience with numerous compounds of this type[11] these investigators had appreciable amounts of the amino ketone hydrochloride in their product. Amino ketones of this type are unstable when liberated from their salts, undergoing spontaneous condensation to dihydropyrazines

$$2RCOCHR'NH_2 \longrightarrow$$



which are readily oxidized to the more stable pyrazine derivatives.[12] The color sequences described are quite in agreement with those observed by Gabriel and by us with various analogs.

(10) Machlis and Blanchard, THIS JOURNAL, **57**, 176 (1935).

(11) Hartung, *ibid.*, **53**, 2248 (1931).

Summary

1. The synthesis of five additional amino alcohols is described; they are members of a series whose general structure is ARCHOHCH(NH_2)-CH_3, in which AR is *m*-tolyl, *p*-chlorophenyl, *p*-phenylphenyl (xenyl), α-naphthyl and β-naphthyl.

2. All of these compounds, substitution products of the parent substance in which AR is phenyl, are more toxic and less active than the parent substance, AR = phenyl, from which they may be considered as being derived.

(12) Gabriel, *Ber.*, **41**, 1148 (1908).

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[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, TEACHERS COLLEGE, COLUMBIA UNIVERSITY]

Studies of Crystalline Vitamin B_1. VIII. Sulfite Cleavage. II. Chemistry of the Acidic Product

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In the third paper of this series[1] it was shown that crystalline vitamin B_1 is split on treatment with sulfite giving an acidic product, $C_6H_9N_3SO_3$ (I), in yields up to 97% of the theoretical. From its method of formation it may be inferred that this substance is a sulfonic acid and this view is confirmed by a study of its properties. The material chars slowly above 400° but does not melt up to 440°. It is almost insoluble in alcohol, very sparingly soluble in cold water, more freely in hot, but is easily soluble in dilute alkali or ammonia. It is also soluble unchanged in concentrated nitric or sulfuric acid. Recrystallization may be effected from hot water or by adding acetic acid to an ammoniacal solution; in either case characteristic small white needles are obtained. A solution of the substance either in ammonia or hydrochloric acid upon evaporation yields the original substance. The *p*H of a saturated aqueous solution is about 5.2. The sulfonic acid is not precipitated by phosphotungstic acid but is precipitated by silver nitrate at *p*H 8–9. In contrast to the vitamin it gives no color with diazotized sulfanilic acid[2] nor a nitroprusside reaction after heating with 20% alkali at 100°.

The action of hydrolytic agents was studied in some detail with a view to eliminating the sulfonic acid group. Heating with moist sodium hydroxide at 135° had little effect, 80% of the substance

(1) Paper III of this series, THIS JOURNAL, **57**, 536 (1935).

(2) Use was made of the technique of T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, **5**, 163 (1908).