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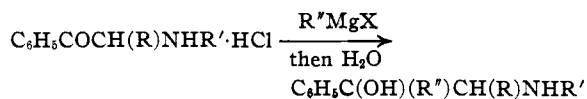
Physiologically Active Phenethylamines Containing a Tertiary Hydroxyl

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It has been found that the introduction of an alkyl group into the *beta* position of phenethylamines² or α -methylphenethylamines³ lowers the toxicity without appreciably affecting the physiological action. The extension of this study to include the effect of alkylating the carbon atom bearing the hydroxyl in amines of the type $C_6H_5CH(OH)CH(R)NHR$ (R is H or CH_3) seemed of interest.

Despite the great number of ephedrine derivatives that have been prepared, only one reference⁴ to the desired alkylephedrine, $C_6H_5C(OH)(R)CH(CH_3)NHCH_3$ (R is CH_3 or C_2H_5), was found. A report on the vasoconstricting action of these compounds was also included. Similarly, only the methyl derivatives of norephedrine, $C_6H_5C(OH)(CH_3)CH(CH_3)NH_2$,⁵ and of its isomer $C_6H_5C(OH)(CH_3)CH_2NHCH_3$ (I)^{6,7} have been described. Of the other possible series of amines, $C_6H_5C(OH)RCH_2NH_2$ (II), the methyl,^{4,8,9,10} ethyl,^{4,10} butyl,¹¹ and cyclohexyl¹¹ compounds have been prepared and some preliminary pharmacological data reported.^{4,11} More recently the 2,5-dimethoxy derivatives of I and II¹² have been synthesized.

In the present investigation representatives of three series of amines containing a tertiary hydroxyl in which the *beta* group is alkyl, alkenyl, or cycloalkyl have been prepared and some preliminary data on their toxicity and other pharmacological properties obtained.¹³ All these compounds were synthesized by the reaction of a



suitable Grignard reagent upon the aminoketone hydrochlorides. This method of preparing hydroxyamines has been used by other investigators.^{4,5,11,12,14} Although some of the compounds contained two asymmetric carbon atoms only one racemic modification was formed. This behavior also occurs in the reaction between amino ketones and aryl Grignard reagents¹⁵ and has been attributed to the effect of the adjacent carbon atom bearing the amino group.

The hydroxyamines were not isolated but were converted directly into their hydrochlorides and purified by crystallization. The yields were very good. The reaction of *t*-butylmagnesium chloride upon α -methylaminopropiophenone gave a mixture of amines whose hydrochlorides could not be separated readily. Apparently both reduction and addition had taken place.¹⁶

The toxicities¹³ of the amine hydrochlorides were determined on white mice by the method outlined earlier.¹⁷ The results are listed in the last three columns of Table I. For comparison purposes 2-amino-1-phenyl-1-propanol and ephedrine are included.

Preliminary data obtained from investigating the effect of these compounds on rabbits, dogs and guinea pigs indicate that in general their pressor activity is similar to that of ephedrine and phenylpropanolamine although the effect may be more transient. Tachyphylaxis was noted in all tests with these compounds. In accordance with the previous observations^{2,3} the presence of an alkyl group *beta* to the amino group greatly reduces the toxicity without apparently impairing the activity.

Three of the norephedrine derivatives, the *n*-butyl, *n*-hexyl, and cyclohexyl compounds, were examined for surface anesthesia on the rabbit's cornea.¹⁸ Some anesthesia was produced by the *n*-butyl and cyclohexyl compounds in 3% solution but this was accompanied by a marked irritation which was particularly pronounced in the *n*-butyl

- (1) Sharp and Dohme Research Associate, 1938-1940.
- (2) Weston, Ruddy and Suter, unpublished work.
- (3) Suter and Weston, *THIS JOURNAL*, **64**, 533 (1942).
- (4) Lévy and Sergent-Montsaratt, *Paris Médical*, **21**, 148 (1931).
- (5) Mills and Grigor, *J. Chem. Soc.*, 1568 (1934).
- (6) Tiffeneau, *Ann. chim. phys.*, [8] **10**, 145 (1907).
- (7) Fourneau, *J. pharm. chim.*, [6] **20**, 481 (1904).
- (8) Fourneau, *ibid.*, [7] **2**, 337 (1909).
- (9) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 436 (1915).
- (10) Tiffeneau and Cahnmann, *Bull. soc. chim.*, [5] **2**, 1876 (1935).
- (11) Kanō and Shinozuka, *J. Pharm. Soc. Japan*, **50**, 1152 (1930); *C. A.*, **25**, 1636 (1931).
- (12) Baltzy and Buck, *THIS JOURNAL*, **62**, 161 (1940).
- (13) We are grateful to Dr. Paul H. Mattis and Mr. Albert R. Latvin of Sharp and Dohme for permission to include a summary of their experiments on the toxicity and pressor activity of these compounds.

- (14) Tiffeneau, Oryekhov and Roger, *Bull. soc. chim.*, [4] **49**, 1757 (1931).
- (15) Tiffeneau, Lévy and Ditz, *ibid.*, [5] **2**, 1848 (1935).
- (16) Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).
- (17) Suter and Weston, *THIS JOURNAL*, **63**, 602 (1941).
- (18) We are grateful to Mr. Harry Robinson of Sharp and Dohme for a report of these tests.

TABLE I
 PROPERTIES OF AMINE HYDROCHLORIDES

Amine	Yield, %	M. p., °C. (cor.)	Solvent	Formula	Cl, %		Toxicity	
					Calcd.	Found ^h	LD ₅₀	LD ₁₀₀
C ₆ H ₅ C(OH)(C ₂ H ₅)CH ₂ NH ₂ ^a	73	180 -181	Dioxane	C ₁₀ H ₁₆ ONCl	17.59	17.66	400	630 900
C ₆ H ₅ C(OH)(C ₄ H ₉ - <i>n</i>)CH ₂ NH ₂ ^b	78	151 -152	Dioxane	C ₁₂ H ₂₀ ONCl	15.44	15.49	200	310 600
C ₆ H ₅ C(OH)(CH ₂)CH(NH ₂)CH ₃ ^c	63	239 -239.5 ^d	Abs. alc.	C ₁₀ H ₁₆ ONCl	17.59	17.69	600	850 1100
C ₆ H ₅ C(OH)(C ₂ H ₅)CH(NH ₂)CH ₃	93	220.5-222 ^d	Acetone-alc.	C ₁₁ H ₁₈ ONCl	16.44	16.47	200	350 450
C ₆ H ₅ C(OH)(C ₄ H ₉ - <i>n</i>)CH(NH ₂)CH ₃	85	213 -216 ^d	Bz-pet. ether	C ₁₃ H ₂₂ ONCl	14.55	14.53	200	315 450
C ₆ H ₅ C(OH)(C ₆ H ₁₃ - <i>n</i>)CH(NH ₂)CH ₃	81	193 -200 ^d	EtOAc-pet. ether	C ₁₅ H ₂₆ ONCl	13.05	12.94	300	375 450
C ₆ H ₅ C(OH)(C ₆ H ₁₁ -cyclo)CH(NH ₂)CH ₃	57	261 -263 ^{d,e}	Alc.-dioxane	C ₁₅ H ₂₄ ONCl	13.14	13.11	200	275 350
C ₆ H ₅ C(OH)(CH ₂)CH(NHCH ₃)CH ₃ ^f	75	234 -235	Abs. alc.	C ₁₁ H ₁₈ ONCl	16.44	16.44	900	1100 1400
C ₆ H ₅ C(OH)(C ₂ H ₅)CH(NHCH ₃)CH ₃ ^g	95	197.5-198.5 ^d	Abs. alc.-ether	C ₁₁ H ₂₀ ONCl	15.44	15.44	400	525 600
C ₆ H ₅ C(OH)(C ₄ H ₉ - <i>n</i>)CH(NHCH ₃)CH ₃	91	182.5-183.5 ^d	Chloroform	C ₁₃ H ₂₂ ONCl	14.55	14.25	200	310 400
C ₆ H ₅ C(OH)(C ₆ H ₁₃ - <i>n</i>)CH(NHCH ₃)CH ₃	88	149 -150	Acetone	C ₁₄ H ₂₄ ONCl	13.75	13.75	200	325 500
C ₆ H ₅ C(OH)(C ₂ H ₅)CH(NHCH ₃)CH ₃ ⁱ	90	166.5-167.8	Abs. alc.-ether	C ₁₃ H ₂₀ ONCl	14.67	14.88	300	550 700
C ₆ H ₅ CHOHCHNH ₂ CH ₃							100	490 900
C ₆ H ₅ CHOHCH(NHCH ₃)CH ₃							200	390 700

^a Previously prepared by reduction of oxime, m. p. 183.5° (cor.) ref. 10; ref. 4, m. p. 184-186°. ^b Ref. 11, m. p. 151-152°. ^c Ref. 5, m. p. 244°. ^d Melted with decomposition. ^e This material forms a dihydrate which retained water of crystallization even after two hours at 100° and 40 mm. After drying at 140° for nine hours the solvent was lost but was regained when exposed to the air for a day. *Anal.* Calcd. for C₁₁H₂₀ONCl·2H₂O: H₂O, 11.78. Found: H₂O, 12.46. ^f Ref. 4, m. p. 245-248°. ^g Ref. 4, m. p. 192°. ^h Since the agreement between our m. p. values and those given in the literature was not always entirely satisfactory, analyses for previously known compounds are included. The disagreement probably occurs because the "melting points" are decomposition temperatures and hence vary with the rate of heating. ⁱ The allylmagnesium bromide was prepared according to the procedure of Gilman and McGlumphy, *Bull. soc. chim.*, **43**, 1322 (1928).

and *n*-hexyl compounds and was evident even in 1% solutions. Because of this undesirable effect only preliminary tests were made.

Experimental

Aminoketone Hydrochlorides.—The ω -aminoacetophenone hydrochloride was prepared by hydrolysis of the product obtained from phenacyl bromide and hexamethylenetetramine.¹⁹ α -Aminopropiophenone hydrochloride was obtained by reduction of the corresponding isonitroso compound²⁰ with stannous chloride²¹ while the *N*-methyl derivative was obtained by the action of methylamine upon α -bromopropiophenone.²²

Reaction of Aminoketone Hydrochlorides with Grignard Reagents.—The preparation of β -ethylnorephedrine is described as a typical example. A Grignard reagent was prepared from 5.3 g. (0.24 mole) of magnesium and a slight excess of ethyl bromide so that no unused magnesium remained. To the ether solution was added at 0° with stirring 10 g. (0.054 mole) of α -aminopropiophenone hydrochloride. Stirring was continued for several hours and the mixture was allowed to stand overnight.²³ A two-layer

system formed. After hydrolysis with ice and dilute sulfuric acid the ether layer was removed and evaporated to dryness but left no residue. The aqueous layer was made alkaline, the amine extracted with ether, the ether layer dried over sodium sulfate and made acid with hydrogen chloride gas. The weight of air-dried material, m. p. 210-212° (dec.), was 10.8 g. or 93% of the theoretical amount. Crystallization from an acetone-alcohol mixture gave 8.8 g., m. p. 219-221° (dec.). Further crystallization raised the m. p. only slightly to 220.5-222° (dec.). Essential data for this and other similar compounds are listed in Table I. All melting points are corrected. The yields given are for the crude products.

Summary

1. Twelve β -hydroxyphenethylamine derivatives in which the hydroxyl group is tertiary have been prepared by the action of aliphatic Grignard reagents upon aminoalkyl phenyl ketone hydrochlorides. Seven of the amines are new compounds.

2. Toxicity data of these amines toward white mice indicate that they are less toxic than the corresponding hydroxy amines having no *beta* alkyl group.

3. A preliminary report on other pharmacological properties of these compounds has been made.

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(19) Slotta and Heller, *Ber.*, **63B**, 1027 (1930); Mannich and Hahn, *ibid.*, **44**, 1548 (1911).

(20) Hartung and Crossley, *Org. Syn.*, **16**, 44 (1936).

(21) Behr-Bregawski, *Ber.*, **30**, 1521 (1897).

(22) Hyde, Browning and Adams, *THIS JOURNAL*, **50**, 2287 (1928).

(23) This was unnecessary as there was little evidence of reaction after a few hours of stirring. In the case of the higher alkyl Grignards, however, it was sometimes necessary to reflux the mixture as unreacted solid remained after the addition.