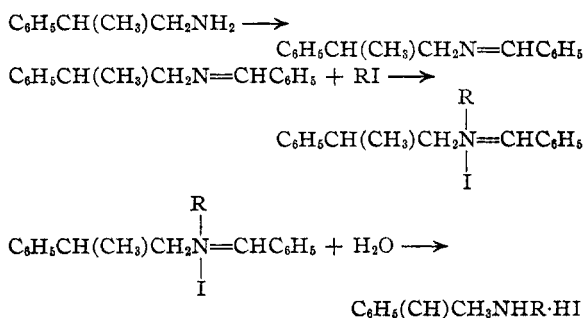


[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Physiologically Active Amines. III. Secondary and Tertiary β -Phenylpropylamines and β -PhenylisopropylaminesBY E. H. WOODRUFF, JOHN P. LAMBOOY¹ AND WILLIAM E. BURT²

It is known^{3,4} that the N-alkylation of analogs of phenethylamine has an effect on their physiological activity. The quantitative effect of this change in structure, as well as whether an increase or decrease of activity results, is variable, so that a prediction of expected properties is subject to doubt. In continuing the studies of amines it was desirable to determine the effect on the pressor and bronchodilator activity of the introduction of N-alkyl and N-aryl groups into the primary amines previously prepared in this Laboratory.^{5,6} The synthesis of the secondary and tertiary amines described here was accomplished by one or the other of two methods.

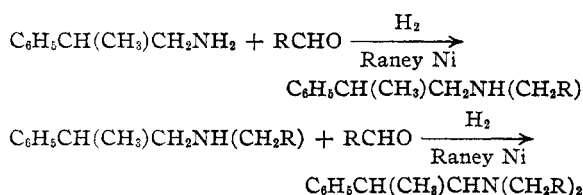
Method I.—



The hydrolysis of the quaternary salt formed by the reaction of a benzalmine and an alkyl halide is that of Decker and Becker.^{7,8,9} This method gave good results when R = CH₃ but variable and generally unsatisfactory results when used for the introduction of larger alkyl groups. The time required for the formation of the quaternary ammonium compound becomes progressively longer as the size of the alkyl group is increased. Decker and Becker¹⁰ state that when a certain temperature or duration of

heating is exceeded, by-products are obtained. This was evidently true where the hydrolysis of the ammonium compound failed to give products that could be isolated and identified and thereby limits the usefulness of the procedure.

Method II.—



This is the reduction of a mixture of an amine and an aliphatic aldehyde without isolation of the intermediate reaction product.¹¹⁻¹⁸ This direct reduction procedure has been termed "reductive alkylation."

The reduction of the isolated Schiff base¹⁹ is satisfactory when an aromatic aldehyde is used and the Schiff base readily isolated. When aliphatic aldehydes are used, Skita and Keil¹¹ and Emerson and Walters¹⁷ prefer reductive alkylation. While platinum oxide catalyst is quite satisfactory for the reduction of the isolated Schiff base,¹⁹ experiments by the authors as well as Emerson and Walters show it to be less satisfactory than Raney nickel when the reductive alkylation method is used. Skita, *et al.*,¹² on the other hand, found colloidal platinum superior to their nickel catalyst.

The procedure of Emerson and Walters, using Raney nickel and hydrogen, has been used for the reductive alkylation (II, R = H, CH₃, C₂H₅) of amines as indicated in the table of compounds. This catalyst was also successfully used to reduce the isolated benzal amine.

The only previous catalytic reductive alkylation experiments reported using formaldehyde (II, R = H) were with secondary amines.¹⁵ Contrary

(1) Kalamazoo College Fellow 1937-1938. A part of the data is from the thesis of John P. Lambooy for the degree of Master of Science from Kalamazoo College, June, 1938.

(2) Kalamazoo College Fellow 1938-1939. A part of the data is from the thesis of William E. Burt for the degree of Master of Science from Kalamazoo College, June, 1939.

(3) Chen and Schmidt, *Medicine*, **9**, 1 (1930).

(4) Hartung, *Chem. Rev.*, **9**, 390 (1931).

(5) Woodruff and Conger, *THIS JOURNAL*, **60**, 465 (1938).

(6) Woodruff and Pierson, *ibid.*, **60**, 1075 (1938).

(7) Decker and Becker, *Ann.*, **395**, 362 (1913).

(8) Buck, *THIS JOURNAL*, **54**, 3661 (1932).

(9) Späth and Bruck, *Ber.*, **70B**, 2450 (1937).

(10) Decker and Becker, *Ann.*, **395**, 328 (1913).

(11) Skita and Keil, *Ber.*, **61B**, 1452 (1928).

(12) Skita, Keil, Baesler and Boente, *ibid.*, **61B**, 1682 (1928).

(13) Skita, Keil and Boente, *ibid.*, **62B**, 1142 (1929).

(14) Skita and Keil, *Monatsh.*, **53-54**, 753 (1929).

(15) Skita, Keil, Havemann and Lawrosky, *Ber.*, **63B**, 34 (1930).

(16) Winans and Adkins, *THIS JOURNAL*, **54**, 306 (1932).

(17) Emerson and Walters, *ibid.*, **60**, 2023 (1938).

(18) Emerson and Robb, *ibid.*, **61**, 3145 (1939).

(19) Buck, *ibid.*, **53**, 2192 (1931).

^a All melting points taken on a thermometer standardized against a set of Bureau of Standards Anschütz thermometers. ^b Decker and Becker method. ^c Reductive alkylation. ^d Melting point. ^e Smith, *J. Chem. Soc.*, 2056 (1927), gives m. p. 87–88° for free amine and m. p. 189–190° for the hydrochloride. ^f Two forms of this hydrochloride were obtained. Simple crystallization was sufficient to make the change, though when the melting point would change could not be predicted. In fifteen consecutive crystallizations six crops were of the high melting form and nine were of the lower melting form. No further investigation is being made of this phenomenon.

to what might be expected from the work of Emerson and Walters it was not possible to isolate any secondary amine from the reaction product when formaldehyde was used as the alkylating agent. The products were identified as the N-dimethyl derivatives and were obtained in yields ranging from 51 to 85% of the theoretical. This result resembles that obtained when other than catalytic means of reduction are employed in the reductive alkylation of an amine with formaldehyde, such as the Eschweiler reaction,^{20,21,22,23} and gives a convenient method for the preparation of N-dimethylamines from the corresponding primary amine. The use of this method to convert 1-ephedrine to 1-methyl-ephedrine shows that the alcoholic hydroxyl is not disturbed in the reaction. Reductive alkylation with formaldehyde therefore offers a general one step method for the preparation of N-dimethylamines without affecting the aliphatic portion of the molecule.

With higher aldehydes (II, R = CH₃, C₂H₅) the monosubstitution products were isolated, the yield increasing as the alkyl groups became larger.^{17,18,24}

This change in type of product, *e. g.*, from N-dimethyl to a mixture of the higher N-alkyl and N-dialkyl amines, also resembles results obtained by the

(20) Decker and Becker, *Ber.*, **45**, 2404 (1912); *Ann.*, **395**, 342 (1913).

(21) Clarke, Gillespie and Weiss, *THIS JOURNAL*, **55**, 4571 (1933).

(22) Forsee and Pollard, *ibid.*, **57**, 1788 (1935).

(23) Baltzly and Buck, *ibid.*, **62**, 161 (1940).

(24) Unpublished data show the yield of β -3,4-dimethoxyphenylpropylethylamine was 36.8% and of β -3,4-dimethoxyphenylpropylpropylamine 64.1%.

TABLE I

Amine	B. p. of primary amine, °C., Mm.	B. p. of free amine, °C., Mm.	Yield, %	M. p. of hydrochloride, °C. ^a	Empirical formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
β -Phenylisopropylmethylamine ^b	170–171	78–80	6	135–136	C ₁₀ H ₁₅ ONCl	64.62	64.68	8.68	8.55	7.54	7.46		
β -o-Methoxyphenylisopropylmethylamine ^b	183	100–102	6	93	C ₁₁ H ₁₅ ONCl	61.24	61.29	8.41	8.19	6.49	6.62		
β -m-Methoxyphenylisopropylmethylamine ^b	192–194	135–137	18	50	C ₁₁ H ₁₅ ONCl	61.24	61.38	8.41	8.42	6.49	6.68	16.44	16.50
β -p-Methoxyphenylisopropylmethylamine ^b	191–193	117–119	8	29	C ₁₁ H ₁₅ ONCl	61.24	61.01	8.41	8.19	6.49	6.30		
β -Phenylpropylmethylamine ^b	174–176	96–98	18	80	C ₁₀ H ₁₃ NCl	64.62	64.52	8.68	8.84	7.54	7.49		
β -o-Methoxyphenylpropylmethylamine ^b	185–187	115–117	8	79	C ₁₁ H ₁₅ ONCl	61.24	61.25	8.41	8.17	6.49	6.33		
β -p-Methoxyphenylpropylmethylamine ^b	213	127–128	8	75.5	C ₁₁ H ₁₅ ONCl	61.24	61.42	8.41	8.45	6.49	6.45		
β -o-Methoxyphenylisopropylethylamine ^b	104	158–159	6	93	C ₁₂ H ₁₇ ONCl	62.73	62.94	8.77	8.76	6.14	5.96		
β -m-Methoxyphenylisopropylethylamine ^b	140	127	17	70	C ₁₂ H ₁₇ ONCl	62.73	62.62	8.77	8.72	6.14	6.31	15.42	15.28
β -p-Methoxyphenylisopropylethylamine ^b	137	127	9	48	C ₁₂ H ₁₇ ONCl	62.73	62.52	8.77	8.73	6.14	6.25	15.42	15.30
β -Phenylpropylethylamine ^c	127	30	94	159–160	C ₁₁ H ₁₅ NCl	66.10	66.43	9.08	9.27	7.01	7.15		
β -o-Methoxyphenylpropylethylamine ^c	137	9	48	156–157	C ₁₂ H ₁₇ ONCl	62.73	62.52	8.77	8.73	6.14	6.25	15.44	15.30
β -m-Methoxyphenylpropylethylamine ^c	137	9	48	156–157	C ₁₂ H ₁₇ ONCl	62.73	62.52	8.77	8.73	6.14	6.25	15.44	15.30
β -p-Methoxyphenylpropylethylamine ^c	100	12	67	159–161	C ₁₂ H ₁₇ ONCl	66.10	65.44	9.08	9.09	7.01	6.25	15.44	15.30
β -Phenylisopropylmethylamine ^c	125	10	80.0	157–158	C ₁₁ H ₁₅ ONCl	62.73	62.77	8.77	8.56	6.14	6.14	17.60	17.60
β -o-Methoxyphenylisopropylmethylamine ^c	132	10	85.5	134–135	C ₁₂ H ₁₇ ONCl	62.73	62.63	8.77	8.77	6.14	6.27	15.42	15.30
β -m-Methoxyphenylisopropylmethylamine ^c	137	13	51.3	161–162	C ₁₂ H ₁₇ ONCl	62.73	62.91	8.77	8.60	6.14	6.29	15.42	15.36
β -p-Methoxyphenylisopropylmethylamine ^c	130	12	63.5	175–176	C ₁₂ H ₁₇ ONCl	62.73	62.82	8.77	8.57	6.14	6.30	15.42	15.54
β -p-Methoxyphenylpropylmethylamine ^c	129	11	64.1	198–199	C ₁₁ H ₁₅ ONCl	62.73	62.56	8.77	8.97	6.14	6.31	15.42	15.28
α -(α -Dimethylamino)-benzyl alcohol ^f (methyl-ephedrine)	86.5–87.5 ^{d,e}		84	190–191 ^e									
β -Phenylisopropylbenzylamine	178	13	72	198–199	C ₁₄ H ₂₁ NCl	73.40	73.45	7.70	7.54	5.35	5.55	12.15	12.30
β -o-Methoxyphenylisopropylbenzylamine	194	9	64	130–131	C ₁₅ H ₂₁ ONCl	69.98	70.15	7.60	7.48	4.80	4.92	12.15	12.30
β -m-Methoxyphenylisopropylbenzylamine	196	10	55	143–144	C ₁₅ H ₂₁ ONCl	69.98	69.83	7.60	7.55	4.80	4.99	12.15	12.21
β -p-Methoxyphenylisopropylbenzylamine	197	10	85	146–147 ^f	C ₁₅ H ₂₁ ONCl	69.98	70.10	7.60	7.50	4.80	4.61	12.15	12.26
β -o-Methoxyphenylpropylbenzylamine				161–162								12.15	12.15
β -m-Methoxyphenylpropylbenzylamine	181		50	148–149	C ₁₄ H ₂₁ ONCl	69.98	69.83	7.60	7.58	4.80	5.03	12.15	11.97
β -p-Methoxyphenylpropylbenzylamine	209–212	13	78	154	C ₁₅ H ₂₁ ONCl	69.98	69.83	7.60	7.39	4.80	4.96		

reduction of aldehydes in the presence of ammonia.¹¹

Experimental difficulties with crystallization have retarded the reporting of more N-ethyl and N-propyl amines as well as the identification of the higher boiling N-diethyl and N-dipropyl amines.

Experimental

The preparation of the methoxy primary amines used in these syntheses has been described previously.^{5,6}

Alkylation by the Method of Decker and Becker.^{7,8,9}—

The Schiff bases used were prepared by refluxing for thirty minutes equimolecular quantities of the amine and benzaldehyde dissolved in 95% ethyl alcohol. The solvent was removed and the product distilled *in vacuo*. The Schiff bases were obtained in yields of 95% and were mostly yellow oils with a few low melting solids. They were used without further purification or analysis.

Equimolecular proportions of a benzal amine (Schiff base) and the appropriate alkyl iodide were introduced into a thoroughly dried Carius tube. After sealing, the tube was heated at 100° by steam for five to twenty-four hours, the longer time being used for the higher halides. The reaction was considered complete when the whole contents of the tube upon cooling was a red to orange viscous oil or a partially crystalline mass. A layer of mobile liquid above the viscous mass showed the reaction to be incomplete. After opening, the contents of the tube were washed out with an alcohol, methyl alcohol for the methylated product and ethyl alcohol for the higher alkylated product, to which had been added one-eighth of its volume of water. The mixture was refluxed for thirty minutes, after which it was poured into an equal volume of water and boiled until the odor of benzaldehyde had disappeared. The solution was made weakly acid with acetic acid and extracted three times with ether. After basification with 30% sodium hydroxide the amine was extracted with ether, the ethereal solution dried with anhydrous magnesium sulfate, and after removal of the solvent the residue was distilled *in vacuo*. The hydrochlorides were prepared from an anhydrous ether solution by the addition of gaseous hydrogen chloride and were recrystallized from ether-alcohol mixtures.

Reductive Alkylation.—One-tenth mole of amine, 0.3 mole of the desired aldehyde, and 1.0 g. of anhydrous sodium

acetate in 100 cc. of ethyl alcohol were reduced by 58 g. of Raney nickel and hydrogen (initial pressure 50 pounds (3 atm.)) in an Adams²⁵ reduction machine as described by Emerson and Walters.¹⁷ When hydrogenation was complete the catalyst was removed by filtration²⁶ and the alcoholic solution of the amine evaporated to dryness. The amine is extracted from the sodium acetate by ether, the ethereal solution dried with anhydrous magnesium sulfate and the residual oil fractionated. The amine hydrochlorides were prepared and purified as in Method I. Amines of the type prepared here are not sufficiently volatile with steam for this to be a practicable method to effect any separation.

Solution formaldehyde U. S. P. XI was used as the source of formaldehyde. Acetaldehyde and propionaldehyde were materials of usual purity.

Reduction of Schiff Bases with Raney Nickel.—0.05 mole of benzal amine, 30 g. of Raney nickel and 100 cc. of ethyl alcohol were shaken in the Adams²⁵ reduction machine under an initial hydrogen pressure of 50 pounds (3 atm.). The theoretical amount of hydrogen was absorbed in about two hours. The catalyst was removed by filtration, the solvent distilled off and the residue distilled *in vacuo*; yield, 55–85%. When less catalyst is used the reduction proceeds more slowly. These results parallel those obtained with platinum oxide¹⁹ as a catalyst. The hydrochlorides of the benzyl amines are less soluble in absolute alcohol than those of the N-alkyl amines.

The authors wish to thank Mr. C. H. Emerson for the microanalyses reported in this work.

Summary

For the purpose of pharmacological testing a group of N-alkyl, N-dimethyl, and N-benzyl-phenylpropyl and isopropylamines have been prepared.

The reductive dimethylation of primary amines by means of formaldehyde and Raney nickel has been described.

KALAMAZOO, MICH.

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(25) Adams and Voorhees, "Organic Syntheses," Coll. Vol. I, 1932, p. 53.

(26) If suction is used the catalyst should always be kept covered with alcohol as it ignites quickly if sucked dry.