

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN]

Phenethylamines. IV. Dimethoxy and Dihydroxyphenyl-*n*-propylamines (β -Methyl- β -phenethylamines)¹

By E. H. WOODRUFF

It was desired to have available for the purpose of pharmacological study a series of compounds possessing the phenethylamine skeleton in which all possible mono and disubstituted isomers were represented. This communication reports the preparation of all possible nuclear dimethoxy and dihydroxy- β -phenyl-*n*-propylamines. In conjunction with work already published² the first such complete series of isomers is available for pharmacological comparison, the results of which will appear elsewhere.

The general outline for the preparation of the amines described in the experimental section follows that previously used in this Laboratory.^{3,4} The appropriately substituted cinnamic acid was reduced to the hydrocinnamic acid, the amide prepared from the acid chloride and the amine then obtained from the amide by means of sodium hypobromite.

When possible it was found to be more convenient to prepare the β -methylcinnamic acids having an ortho methoxyl group by the hydrolysis and methylation of a hydroxy-4-methylcoumarin. This method gave uniformly the *trans* or high melting form of the cinnamic acid in contrast to the mixture of isomers obtained by the dehydration and saponification of a hydroxy ester.^{4,5} No satisfactory method for the preparation of 8-hydroxy-4-methylcoumarin was found so the 2,3-dimethoxy- β -methylcinnamic acid as well as those not containing an ortho methoxyl were obtained through the Reformatsky reaction on the appropriate ketone followed by dehydration and saponification.

The preparation of 2,6-dimethoxy- β -methylcinnamic acid from the 5-hydroxy-4-methylcoumarin gave an 80% yield of the *trans*-form melting at 185°. None of the low melting (148–150°) form previously reported⁷ as being obtained from this coumarin was found. However, when the

acid was prepared through the Reformatsky reaction after repeated crystallizations an acid melting at 143–144° was obtained. These two acids on further treatment gave identical products.

In an early attempt to prepare 3,5-dihydroxyacetophenone, the alkali fusion of the supposed acetophenone 3,5-disulfonyl chloride of Riesz and Frankfurter⁸ was tried. *m*-Hydroxybenzoic acid m. p. 201–202° and *m*-methoxybenzoic acid m. p. 102–108° from the methylation of the hydroxy acid were obtained. This confirms the statement of Suter and Weston⁹ that only one sulfonyl group had entered the ring.

The 2,3- and 3,5-dimethoxyacetophenones were prepared from the corresponding benzoyl chlorides and dimethylcadmium.¹⁰ This method is satisfactory for aromatic acid chlorides with dimethylcadmium to give methyl ketones but the yields are lower when used to prepare higher members of a series.

The reduction of the cinnamic acids by sodium amalgam as previously used⁴ was replaced early in this investigation by electrolytic reduction using a lead anode and a mercury cathode.¹¹ This method is as efficient as sodium amalgam in the reduction of cinnamic acids with the possible exception of the 2,6-dimethoxy derivative and is more convenient when large amounts of the amalgam must be prepared.

Experimental

Preparation of Coumarins.—7-Hydroxy-^{12,13} and 6-hydroxy¹⁴-4-methylcoumarins were prepared as described in the literature. For the preparation of 5-hydroxy-4-methylcoumarin the condensation of methyl β -resorcyate with acetoacetic ester by means of anhydrous aluminum chloride in nitrobenzene was carried out according to Sethna, Shah and Shah.⁷ After the removal of the nitrobenzene the product was boiled twice with 200-cc. portions of methyl alcohol, filtering hot and discarding the filtrate. The intermediate crude methyl 5-hydroxy-4-methylcoumarin-6-carboxylate melting at 175–182° was obtained

(1) A part of this material was presented at the St. Louis meeting of the American Chemical Society, April, 1941.

(2) Woodruff, Lambooy and Burt, *THIS JOURNAL*, **62**, 922 (1940).

(3) Woodruff and Conger, *ibid.*, **60**, 465 (1938).

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

(5) Lindenbaum, *Ber.*, **50**, 1272 (1917).

(6) Limaye and Kelkar, *Rasayanam* [I], **27**, 47 (1936), through *C. A.*, **31**, 2213 (1937).

(7) Sethna, Shah and Shah, *J. Chem. Soc.*, 231 (1938).

(8) Riesz and Frankfurter, *Monatsh.*, **50**, 68 (1928).

(9) Suter and Weston, *THIS JOURNAL*, **61**, 233 (1939).

(10) Gilman and Nelson, *Rec. trav. chim.*, **55**, 528 (1936).

(11) Ingersoll, "Organic Syntheses," Coll. Vol. I, 2nd ed., 1941, p. 311.

(12) Russell, Frye and Mauldin, *THIS JOURNAL*, **62**, 1443 (1940).

(13) Russell and Frye, "Organic Syntheses," Vol. **21**, 1941, p. 23.

(14) Borche, *Ber.*, **40**, 2731 (1907).

TABLE I
 ISOMERIC DIMETHOXY DERIVATIVES OF β -METHYLCINNAMIC ACID ($C_{12}H_{14}O_4$)

Isomer	B. p., °C.	Ethyl ester		Yield, %	M. p., °C.	Yield, ^a %	Analyses, %			
		Min.	Max.				Calcd.	Found	Calcd.	Found
2,3-	165-175	8		37	121 -122	84	64.83	64.74	6.35	6.22
2,6-	136-138 ^b	0.03		16 ^c	143 -144 ^d	83	64.83	64.51	6.35	6.51
3,4-	200-203	11		70	138 -140 ^e	67				
3,5-	197-203	11		75	123.5-124.5	88	64.83	64.79	6.35	6.28

^a From ester before crystallization. ^b *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.17; H, 7.20. Found: C, 67.11; H, 7.09. ^c Yield 48% allowing for recovered ketone. ^d From Reformatsky reaction. An 80% yield of acid melting at 185-185.5° was obtained by hydrolysis of 6-hydroxy-4-methylcoumarin. ^e M. p. 138-140°, ref. 34.

in 47% yield. The hydrolysis of the ester was accomplished by refluxing with 73% sulfuric acid instead of heating in a sealed vessel with a mixture of hydrochloric and acetic acids. The product so obtained was heated to 300° and after decarboxylation was distilled at 10 mm. The crude 5-hydroxy-4-methylcoumarin was obtained in 57.5% yield and melted when crystallized once from alcohol at 260°.

Preparation of Ketones.—2,3-Dimethoxybenzoic acid^{15,16} was prepared in 85% yield by the oxidation of 2,3-dimethoxybenzaldehyde¹⁷ with potassium permanganate.¹⁸ Oxalic acid was used to remove the manganese dioxide prior to the precipitation of the acid. The acid was converted to the chloride (94%)¹⁹ using a sixfold excess of thionyl chloride. Twice the calculated amount of thionyl chloride was consumed, the remainder being recovered. 3,5-Dimethoxybenzoic acid²⁰ was obtained by methylating 3,5-dihydroxybenzoic acid.²¹ The acid was converted to the acid chloride (90%) using phosphorus pentachloride and carbon tetrachloride.²² The 2,3- (71%) and 3,5- (84%) dimethoxyacetophenones^{23,24} were obtained from the acid chlorides by the procedure of Gilman and Nelson.¹⁹ The ketone so prepared was always contaminated with ester. This was removed by refluxing the crude product with alcoholic alkali. The yields given deduct for the recovered acid. 3,4-Dimethoxyacetophenone²⁵ was prepared by the reaction of veratrole with acetyl chloride and anhydrous aluminum chloride below +10°, using twice the quantity of solvent used in the previous preparation. After filtration from the insoluble complex (20% loss) the solvent may be reused without purification. 2,6-Dimethoxyacetophenone²⁶ was obtained by methylating 2,6-dihydroxyacetophenone.¹³

Preparation of Cinnamic Acids.—The cinnamic acids were prepared in two ways as previously mentioned. For a discussion of the Reformatsky reaction a recent review

(15) Perkin and Robinson, *J. Chem. Soc.*, 2383 (1914).

(16) Perkin, Robinson and Stoyke, *ibid.*, 197 (1925).

(17) Obtained through the courtesy of the Monsanto Chemical Company.

(18) Shriner and Kleiderer, "Organic Syntheses," Vol. X, 1930, p. 82.

(19) Mauthner, *J. prakt. Chem.*, 112, 60 (1926).

(20) Mauthner, *ibid.*, 87, 405 (1913).

(21) Weston and Suter, "Organic Syntheses," Vol. 21, 1941, p. 27. By the use of a countercurrent extraction column the yield of acid was 1983 g. from 6220 g. of barium salt or 82%.

(22) Fischer, Bergmann and Lipschutz, *Ber.*, 51, 55 (1918).

(23) (a) v. Krannichfeld, *ibid.*, 46, 4016 (1913); (b) Baker and Smith, *J. Chem. Soc.*, 347 (1936).

(24) Mauthner, *J. prakt. Chem.*, 107, 106 (1924).

(25) Koepfli and Perkin, *J. Chem. Soc.*, 2995 (1928).

(26) Sugawara, *ibid.*, 1483 (1934).

by Shriner²⁷ is recommended. In two instances the presence of *o*-methoxy groups caused a considerable lowering of the yield. This was so great in the case of the 2,6-dimethoxyacetophenone as to render this method unsuitable for the preparation of suitable quantities of the acid. The dehydration of the hydroxy esters was accomplished with a minimum of side reactions by heating to 250-300° at atmospheric pressure. The hydrolysis and methylation of a hydroxycoumarin is illustrated by the following example: 35.2 g. (0.2 mole) of 6-hydroxy-4-methylcoumarin was shaken with 25 cc. of dimethyl sulfate and 28 cc. of 33% potassium hydroxide solution. After the reaction had subsided the solution was cooled and again shaken with alkali and methyl sulfate. While hot, 50 cc. of 33% potassium hydroxide was added and the reaction refluxed one hour. The methylation treatment was repeated and after the addition of excess alkali the solution was refluxed to hydrolyze any methyl ester formed. The solution was diluted to one liter and boiled with decolorizing charcoal and filtered. When cold, hydrochloric acid was added, the precipitated acid collector on a Büchner funnel, washed with water and dried. Crystallization is best from a benzene-skelly-solve B mixture although alcohol-water may be used. The 2,5-dimethoxy- β -methylcinnamic acid (81%) so obtained melted at 119-120°. In a similar manner 2,4-dimethoxy- β -methylcinnamic acid (76% yield) melting at 148° was obtained.²⁸

Hydrocinnamic Acids.—The cinnamic acids were reduced electrolytically.¹¹ 2,6-Dimethoxy- β -methylhydrocinnamic acid was also prepared by the reduction of 5-hydroxy-4-methylcoumarin³⁰ followed by the hydrolysis and methylation of the dihydrocoumarin.

Seventeen and six-tenths grams (0.1 mole) of 5-hydroxy-4-methylcoumarin, 200 cc. of alcohol and 6 cc. of Raney nickel catalyst were reduced at 60° and 60 pounds hydrogen pressure in an Adams hydrogenator. After seven hours, the theoretical amount of hydrogen was absorbed. The catalyst was filtered and the solvent removed. The residue was crystallized from alcohol-water or benzene-skelly solve B.

Fourteen and six-tenths grams (82%) of 5-hydroxy-4-methyl-3,4-dihydrocoumarin b. p. 214° at 5 mm., m. p. 160° was obtained. *Anal.* Calcd. for $C_{10}H_{10}O_3$: C,

(27) "Organic Reactions," Roger Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 1.

(28) Baltzly and Buck, *THIS JOURNAL*, 62, 161 (1940), obtained an acid m. p. 113° from the Reformatsky reaction.

(29) v. Fehmann and Cohen, *Ber.*, 17, 2132 (1884).

(30) de Benneville and Connor, *THIS JOURNAL*, 62, 283 (1940), report the reduction of coumarin to dihydrocoumarin in ether using Raney nickel at 100°.

TABLE II
 ISOMERIC DIMETHOXY- β -METHYLHYDROCINNAMIC ACIDS (C₁₂H₁₆O₄)

Isomer	M. p., °C.	B. p. °C.	Mm.	Yield, %	Analyses, %			
					C		H	
					Calcd.	Found	Calcd.	Found
2,3-	77	181-184	0.15	85	64.27	64.43	7.24	7.33
2,4-	104 -105			82	64.27	64.28	7.24	7.10
2,5-	78 - 79 ^a	175-185	0.1	86				
2,6-	78.5- 79	190-197	3.0		64.27	64.38	7.24	7.33
3,4-	84 - 85 ^b			80				
3,5-	Liquid	184-188	0.05	85	64.27	64.05	7.24	7.09

^a M. p. 79°; ref. 5. ^b M. p. 84-85°; ref. 34.

 TABLE III
 ISOMERIC DIMETHOXY- β -METHYLHYDROCINNAMIDES C₁₇H₁₇ON

Isomer	M. p., °C.	Yield, ^a %	Analyses, %					
			Carbon		Hydrogen		Nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
2,3-	90 - 91	52	64.55	64.33	7.68	7.44	6.27	6.01
2,4-	133 -134	61	64.55	64.35	7.68	7.48		
2,5-	122 ^b	80						
2,6-	153 -155	88	64.55	64.40	7.68	7.60	6.27	6.09
3,4-	131	90	64.55	64.56	7.68	7.94		
3,5-	92.5- 93 ^c	60	64.55	64.40	7.68	7.50	6.27	6.09

^a Yield before crystallization. ^b M. p. 121°; ref. 5. ^c B. p. 210-235° at 0.15 mm. This amide is difficult to crystallize.

 TABLE IV
 ISOMERIC DIMETHOXY- β -PHENYL-*n*-PROPYLAMINO HYDROCHLORIDES (C₁₁H₁₅O₂NCl)

Isomer	B. p. °C. ^a	Mm.	Yield, %	M. p., °C.	Analyses, %							
					Carbon		Hydrogen		Nitrogen		Chlorine	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
2,3-	150-154	11	37	133.5-134	57.01	56.80	7.82	8.04	6.04	6.02	15.31	15.55
2,4-	158-160	14	15	146 -147	57.01	56.81	7.82	7.82				
2,5-	164-166 ^b	16	80	149 -150 ^b								
2,6-	155-158	5	36	143 -145	57.01	56.79	7.82	8.05	5.04	6.00	15.31	15.30
3,4-	163-166	15	62	205 -206	57.01	56.81	7.82	7.60				
3,5-	179-184	14	57	105 -107	57.01	56.79	7.82	8.07	6.04	6.18	15.31	15.11

^a The boiling point is for the free amine. ^b B. p. 114° at 1 mm., m. p. 149-150°; ref. 5.

 TABLE V
 ISOMERIC DIHYDROXY- β -PHENYL-*n*-PROPYLAMINE HYDROCHLORIDES (C₉H₁₄O₂NCl)

Isomer	M. p., °C.	Analyses, %									
		Carbon		Hydrogen		Nitrogen		Chlorine			
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
2,3-	191 -191.5	53.07	53.01	6.93	6.99	6.88	6.90	17.41	17.65		
2,4-	222 -223	53.07	53.11	6.93	7.08						
2,5-	167.5-169.5	53.07	53.01	6.93	7.15	6.88	6.98	17.41	17.50		
2,6-	93 - 95	53.07	52.99	6.93	7.14	6.88	6.72	17.41	17.26		
3,4-	180 -181	53.07	52.92	6.93	7.17						
3,5-	164 -166	53.07	52.99	6.93	7.20	6.88	6.98	17.41	17.14		

67.40; H, 5.66. Found: C, 67.10; H, 5.85. The hydrolysis to the hydrocinnamic acid was carried out as previously given. A yield of 91% was obtained. After two crystallizations from a dilute solution in skelly-solve B, crystals m. p. 78.5-79° were obtained identical with those obtained by the reduction of the cinnamic acid.

Dimethoxy- β -methylhydrocinnamides.—The amides were prepared as previously reported.³ They were crystallized from alcohol-water or benzene-skelly solve B.

Dimethoxyphenyl-*n*-propylamines.—The amines were prepared by the action of sodium hypobromite on the finely divided (to pass a 40-mesh screen) amide.³ The ease of solution of the amide appears to vary with the ring substituents. The presence of a *m*-methoxy group confers increased ease of solubility. The 2,4-dimethoxy amide was

the least soluble. The hydrochlorides were best prepared by adding a weighed amount (10% over the molecular quantity) of dry hydrogen chloride to absolute ethyl alcohol. The alcoholic hydrogen chloride was added to the amine and the hot solution is diluted with anhydrous ether until a faint cloudiness just fails to persist. On cooling, the amine hydrochloride precipitates in a crystalline condition. The direct addition of dry hydrogen chloride to an anhydrous ether solution of the amine often gave a gummy precipitate which later solidified. This was more difficult to purify. Recrystallization was carried out from an absolute alcohol-ether mixture.

Dihydroxyphenyl-*n*-propylamine Hydrochloride.—Demethylation was accomplished by heating in a sealed tube with concentrated hydrochloric acid for two hours at

160°. ^{3,4} The dihydroxyamine hydrochlorides are more hygroscopic and difficult to crystallize than the methoxy amines. The crystalline condition of the hydrochloride has much to do with its deliquescence. When alcohol-ether cannot be used for crystallization, alcohol-benzene, alcohol-toluene, or ethyl-acetate-alcohol may be used. The usefulness of the solvent varies with the amine hydrochloride even in such a closely related group of isomers as reported here.

The author wishes to thank Dr. Earl Pierson, Dr. John P. Lambooy and Dr. William E. Burt for their assistance while holders of Kalamazoo College Fellowships and Mr. Harold Emerson and Mr. William A. Struck for the micro analyses.

Summary

All of the nuclear dimethoxy- and dihydroxy- β -phenyl-*n*-propylamines and their hydrochlorides have been prepared. The properties are reported for the cinnamic acids, hydrocinnamic acids and hydrocinnamides used in the preparation of these amines as well as the syntheses of many of the intermediates used in their preparation. The hydrolysis and methylation of an hydroxy-4-methylcoumarin always gave the *trans* form of the resulting dimethoxy- β -methylcinnamic acid.

KALAMAZOO, MICHIGAN

RECEIVED AUGUST 1, 1942

[CONTRIBUTION FROM THE SANDERS LABORATORY OF CHEMISTRY, VASSAR COLLEGE]

The Reaction of *n*-Butylmagnesium Bromide with Some Aromatic Ketones^{1,2}

BY H. MARJORIE CRAWFORD, MARY ELIZABETH SAEGER³ AND FLORENCE E. WARNEKE⁴

Since *n*-butyl bromide can be prepared by students in good yield and reacts readily with magnesium to give a Grignard reagent, we had hoped to work out a series of student preparations by adding this Grignard reagent to a ketone and dehydrating the resulting tertiary alcohol to the corresponding unsaturated compound. This purpose was not achieved, but several new compounds were prepared in the course of the studies. Four ketones were selected for study: acetophenone, benzophenone, benzil and desoxybenzoin.

A. Acetophenone.—The reaction of acetophenone and *n*-butylmagnesium bromide gave good yields (72–80%) of the expected tertiary alcohol, 2-phenylhexanol-2 (I). This tertiary alcohol was very resistant to complete dehydration, but was finally transformed into the unsaturated hydrocarbon, 2-phenylhexene-2 (II), by heating with Lucas reagent. The position of the double bond was established by oxidation to acetophenone and *n*-butyric acid. The same results were obtained whether the oxidizing agent was potassium permanganate in sulfuric acid or chromium trioxide in acetic acid.

B. Benzophenone.—The reducing action of aliphatic Grignard reagents on benzophenone has

(1) Presented before the Organic Division of the American Chemical Society, Buffalo, September 7, 1942.

(2) Abstracted from the theses submitted by Mary Elizabeth Saeger and Florence E. Warneke in partial fulfillment of the requirements for the degree of Master of Arts at Vassar College.

(3) Present address, American Cyanamid Company, Stamford, Conn.

(4) Present address, U. S. Department of Agriculture, Chicago, Ill.

been studied by several workers.⁵ Schlenk and Bergmann⁶ obtained impure diphenyl-*n*-butylcarbinol by the reaction of phenylmagnesium bromide on ethyl *n*-valerate. It was mixed with the dehydration product and was easily converted into the unsaturated hydrocarbon. The two reactions which we carried out gave no tertiary alcohol and no unsaturated hydrocarbon. Benzohydrol (17 and 30%) was obtained. The remaining oils were distilled under reduced pressure and a yield of 5.6% of dibenzylhydril ether separated from the residue (above 270°, 42 mm.). Analyses of this compound agreed closely with the calculated values. Dibenzhydril ether had previously been reported by Kharasch and Weinhouse⁵ as resulting from the reaction of allylmagnesium bromide on benzophenone.

C. Benzil.—The reaction of *n*-butylmagnesium bromide on benzil gave small yields of solid products regardless of the variations in procedure. Both addition and reduction occurred. The reduction product, benzoin, was obtained in seven of the ten reactions in yields varying from 0.5 to 13.0%. The mono-addition product 1,2-diphenylhexanol-2-one-1 (II) was obtained in all ten reactions in yields varying from 0.5 to 5.6%. A solid which was possibly the di-addition product (V) was obtained twice in very small yields. Benzoic acid was obtained after the oily

(5) Blicke and Powers, *THIS JOURNAL*, **51**, 3378 (1929); Noller and Hilmer, *ibid.*, **54**, 2503 (1932); Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

(6) Schlenk and Bergmann, *Ann.*, **479**, 42 (1930).