pared by the action of sodium and amyl alcohol on sitostyl chloride.

Anal. Calcd. for $C_{29}H_{52}$: C, 86.9; H, 13.1. Found: C, 87.2; H, 13.0.

6-Hydroxystigmasterol.—The acetic anhydride filtrate from the preparation of the diacetate of 4-hydroxystigmasterol was evaporated to dryness *in vacuo*. The residue was dissolved in 200 cc. of ethyl alcohol, refluxed for one hour with 6 g. of potassium hydroxide, and the solution then acidified with acetic acid. On dilution with water a product separated and was filtered off, dissolved in ethyl alcohol and treated with Norite. Evaporation and cooling of the alcohol gave crystals which on recrystallization from ethyl acetate gave 6-hydroxystigmasterol in long needles melting at 237°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.2; H, 11.3. Found: C, 80.6; H, 11.2.

Summary

4-Hydroxy- and 6-hydroxystigmasterol have been prepared by the oxidation of stigmasterol with selenium dioxide in acetic acid–benzene solution. A similar oxidation of stigmasteryl acetate yielded 3-acetoxy-4-hydroxystigmasterol.

Hydrogenation of the diacetate of 4-hydroxystigmasterol yielded the diacetate of 4-hydroxystigmastanol which is identical with the diacetate of 4-hydroxysitostanol. Clemmensen reduction of the diacetate of 4-hydroxystigmastanol yields stigmastane which is identical with sitostane.

4-Hydroxystigmasterol when heated with alcoholic hydrochloric acid undergoes dehydration and rearrangement to form stigmastenone.

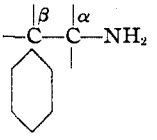
STATE COLLEGE, PENNA. RECEIVED FEBRUARY 25, 1938

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Physiologically Active Phenethylamines. II. Hydroxy- and Methoxy-β-methyl-β-phenethylamines (β-Phenyl-*n*-propylamines)

BY E. H. WOODRUFF AND EARL PIERSON[1,2]

The number of individual amines related structurally and pharmacologically to epinephrine and ephedrine that have been synthesized is large, numbering over four hundred at the present time. All possess the basic skeleton



which Barger and Dale[3] found to be necessary for sympathomimetic activity. The simplest compound possessing activity is that in which the valences of the carbon atoms in the side chain are satisfied with hydrogen. The substitution of alkyl groups in place of one of the hydrogen atoms on the α-carbon, in particular the methyl group, has been investigated extensively and a wide variety of compounds possessing this skeleton has been synthesized.[4]

The effect of alkyl groups on the β-carbon has received on the contrary no such strenuous attention. The only mention of this class of amines in the literature is confined to the simple β-methyl-β-phenethylamine.[5-7] Hartung and Munch report briefly on its properties in a study of the isomeric phenylpropylamines. In this work they state that it is orally active and possesses sympathomimetic activity. It is with the intention of more completely investigating the pharmacology of this hitherto overlooked group of amines that those characterized here have been synthesized. By direct comparison with the isomeric α-methyl homologs synthesized by one of us[4] the effect of moving the alkyl group from the α- to the β-carbon may be ascertained. As might be anticipated a comparison of the physical properties shows only a slight change with this change in structure. Pharmacological work now in progress indicates, however, a much more radical change in activity than might be expected. Toxicities of the β-methyl series are less than for the corresponding α-methylamine.

Experimental

The preparation of the β-methyl-β-phenethylamines follows the general outline for the preparation of the α-

(1) Kalamazoo College Fellow, 1936–1937.

(2) These data are from a thesis submitted by Earl Pierson as a part of the requirements for the degree of Master of Science from Kalamazoo College, June, 1937.

(3) Barger and Dale, *J. Physiol.*, **51**, 19 (1910).

(4) Woodruff and Conger, THIS JOURNAL, **60**, 465 (1938). References to extensive reviews are given in this article.

(5a) Hartung and Munch, *ibid.*, **53**, 1879 (1931).

(5b) Tainter, *Arch. Internat. Pharm. and Therap.*, **46**, 205 (1933).

(6) Freund and König, *Ber.*, **26**, 2875 (1893).

(7) Von Braun, Grabowski and Kirschbaum, *ibid.*, **46**, 1280 (1913).

TABLE OF COMPOUNDS

Compound	M. p., °C.	B. p. °C.	Mm.	% Yield	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl β-methylcinnamate		139–140	13[a]	70					
o-Methoxy		160	13[b]	65–70					
m-Methoxy		171	13	70–74	$C_{13}H_{16}O_3$	70.87	7.32	70.67	7.22
p-Methoxy		174–175	13[c]	70–75					
β-Methylcinnamic acid	97[d]			85–90					
o-Methoxy	76[e]	191	13	70–75					
m-Methoxy	100			80–85	$C_{11}H_{12}O_3$	68.71	6.29	68.81	6.32
p-Methoxy	154–155[f]			85–90					
β-Phenylbutyric acid		156–157	12[g]	80					
o-Methoxy	47	171	11	85–90	$C_{11}H_{14}O_3$	68.03	7.27	68.21	7.29
m-Methoxy		190	15	83–87	$C_{11}H_{14}O_3$	68.03	7.27	68.08	7.33
p-Methoxy	65	188–190	12	75–80	$C_{11}H_{14}O_3$	68.03	7.27	67.94	7.29
β-Phenylbutyramide	105[h]			80					
o-Methoxy	125–126			70	$C_{11}H_{15}O_2N$	68.35	7.83	68.50	7.79
m-Methoxy	71	215–218	14	82–88	$C_{11}H_{15}O_2N$	68.35	7.83	68.18	7.53
p-Methoxy	112			80	$C_{11}H_{15}O_2N$	68.35	7.83	68.15	7.67
β-Phenyl-β-methylethylamine·HCl[i]	146–147[j]	92	12[k,l]	57–60					
β-(o-Methoxyphenyl)	134–135	121–123	13[l]	55–60	$C_{10}H_{16}NCl$	59.53	8.00	59.68	7.90
β-(m-Methoxyphenyl)	124	130–132	14[l]	49–53	$C_{10}H_{16}NCl$	59.53	8.00	59.83	7.90
β-(p-Methoxyphenyl)	152–153	130–131	14[l]	60–65	$C_{10}H_{16}NCl$	59.53	8.00	59.35	7.88
β-(o-Hydroxyphenyl)	168–169				$C_9H_{14}NCl$	57.56	7.52	57.69	7.80
β-(m-Hydroxyphenyl)	126–127				$C_9H_{14}NCl$	57.56	7.52	57.27	7.49
β-(p-Hydroxyphenyl)	157–159				$C_9H_{14}NCl$	57.56	7.52	57.35	7.48

[a] B. p. 144.5–145.5° (14 mm.).[11] [b] B. p. 156–158° (10 mm.).[11] [c] B. p. 182–184° (14 mm.).[11] [d] M. p. 97°.[11] [e] This is a mixture of the two stereoisomers, Stoermer, Grimm and Laage, *Ber.*, **50**, 977 (1917). [f] M. p. 153°.[11] [g] B. p. 156–158° (13 mm.). Rupe, *Ann.*, **369**, 323 (1909). [h] M. p. 105°, Kohler and Reimer, *Am. Chem. J.*, **33**, 353 (1905). [i] Benzoate, m. p. 85°.[7] Found 85–86°. [j] M. p. 123–124°.[5] [k] B. p. 210° (760 mm.).[6] 104° (21 mm.).[7] [l] Boiling points are given for the free amine.

methyl series as used by Woodruff and Conger.[4] In this work the Reformatsky reaction has been used with uniform success in the preparation of the β-methylcinnamic acids. The various methoxyacetophenones used as starting material were prepared by us by combining or adapting methods appearing in the literature. Ortho- and para-hydroxyacetophenones were obtained by the Fries isomerization of phenyl acetate with anhydrous aluminum chloride at 160–170° without solvent. *m*-Hydroxyacetophenone was prepared from *m*-nitroacetophenone[8] by reduction with iron filings, water and hydrochloric acid, diazotization of the amine and hydrolysis with 20% sulfuric acid.[9] The use of stronger acid led to the formation of tar with no hydroxy ketone. All of the hydroxy ketones were methylated with dimethyl sulfate and potassium hydroxide following the procedure given by Freudenberg.[10]

Methoxy-β-methylcinnamic Acids.—These were prepared by the dehydration and hydrolysis of the ester formed by the condensation of ethyl bromoacetate with the appropriate acetophenone in anhydrous benzene following the proportions used by Lindenbaum,[11] using an 8% copper, 92% zinc alloy, as recommended by Nieuwland and Daly.[12]

The dehydration was accomplished by heating the benzene solution of the hydroxy ester with phosphorus oxychloride (Lindenbaum) or by twice distilling the ester.[13] In large amounts the ester, particularly the para-methoxy, are difficult to distil because of foaming and on hydrolysis the acid is difficult to crystallize.

β-Phenylbutyric Acids.—The reduction of the cinnamic acids was accomplished by the action of 4% sodium amalgam on an aqueous solution of the sodium salt. Sufficient amalgam was used to yield 4 H for each double bond. It was found not necessary to add acid to neutralize the alkali formed during the reduction. While the yields average about 10% lower than when a catalytic method[4] was used, the speed of the reduction and ease of handling larger amounts offset this loss.

In the case of *p*-methoxy-β-methylcinnamic acid it was found practical to reduce it directly, upon removal of the alcohol from the hydrolysis of the ester, without isolation and purification. The saturated acid so prepared was easily purified, and in the subsequent steps gave products of purity comparable to that obtained by reduction of the recrystallized acid.

β-Phenylbutyramides.—The amides were prepared in an identical manner with those previously reported.[4] They were crystallized from benzene.

β-Methyl-β-methoxyphenethylamines.—The amines were prepared by the Hoffman method using the same technique as reported in the previous paper. Sodium

(8) "Organic Syntheses," Vol. X, John Wiley and Sons, Inc., New York, N. Y., 1930, p. 74.
(9) Morgan and Pettit, *J. Chem. Soc.*, 420 (1934).
(10) Freudenberg, *Ber.*, **53**, 1424 (1920).
(11) Lindenbaum, *ibid.*, **50**, 1272 (1917).
(12) Nieuwland and Daly, THIS JOURNAL, **53**, 1842 (1931).
(13) Koepfli and Perkin, Jr., *J. Chem. Soc.*, 2995 (1928).

hypobromite was substituted for potassium hypobromite with improved yield. As in the α-methyl series solution could not be effected with sodium hypochlorite when tried on the *p*-methoxy amide. The methoxyamines are liquids having a faintly fishy ammoniacal odor which becomes more intense on standing.

β-Methyl-β-hydroxyphenethylamines.—The methoxyamines were demethylated and purified as described in the previous paper. No difficulty was encountered in the crystallization of their hydrochlorides from absolute alcohol–ether. The free bases have not as yet been isolated.

The authors wish to thank Mr. C. H. Emerson for the microanalyses given. The detailed pharmacological results will appear elsewhere.

Summary

The three monomethoxy and corresponding β-hydroxyphenyl β-methylethylamine hydrochlorides have been prepared in a pure state for the purpose of pharmacological testing.

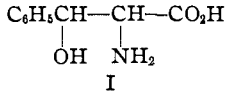
KALAMAZOO, MICH. RECEIVED FEBRUARY 23, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

β-Phenylnaphthalene[1]

BY HERBERT E. CARTER AND EDWARD J. VAN LOON

In connection with attempts to synthesize phenylserine (I) the corresponding methoxy acids (II) were subjected to treatment with hydrobro-



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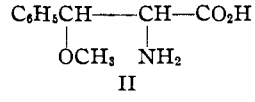
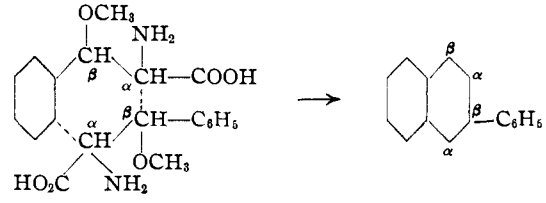


II

mic acid. It had been reported earlier by Schrauth and Geller[2] that this reaction gave a brominated hydrocinnamic acid and traces of cinnamic acid. However, we found the reaction to take an entirely different course. The two amino acids (II) behaved in the same manner when refluxed with hydrobromic acid. Each yielded a white crystalline hydrocarbon which was shown to be β-phenylnaphthalene by its analysis, melting point, and oxidation to β-phenylnaphthoquinone.

Elucidation of the mechanism of this reaction offers an interesting problem. The following facts must be explained satisfactorily: (1) The yield of β-phenylnaphthalene is 80 to 85% of the theoretical amount and the reaction is complete in one hour. Therefore, the intermediate steps must proceed smoothly and rapidly. (2) Carbon dioxide is evolved almost quantitatively during the reaction. Therefore, some intermediate must be decarboxylated readily. (3) As a corollary of (2) no phenylnaphthoic acids are isolated from the reaction product.

It is obvious on inspecting the formula of β-phenylnaphthalene that the naphthalene nucleus must arise from two molecules of the aminomethoxy acid with the elimination of two molecules each of methyl alcohol, ammonia, and carbon dioxide.



Furthermore, the α,β union of the two molecules suggests an aldol condensation of a carbonyl-containing intermediate.

The fact that phenylserine, when refluxed with hydrobromic acid, yielded β-phenylnaphthalene in exactly the same manner as the aminomethoxy acids indicated that demethylation was the first step in the reaction. A survey of the literature disclosed that phenylserine yields phenylacetaldehyde under the influence of moderately concentrated sulfuric acid[3] and that phenylacetaldehyde, when heated with strong mineral acids, gives β-phenylnaphthalene in poor yields.[4] More recently Bettzieche[5] reported that refluxing phenylserine with 10% sulfuric acid for twelve hours produced phenylacetaldehyde (identified by the oxime), β-phenylnaphthalene (characterized by its physical properties), and an acidic fraction giving a ferric chloride enol test which the author considered to be sufficient evidence for the presence of phenylpyruvic acid. Of course, phenylpyruvic acid was to be expected since Bettzieche and

(1) Part of the material contained in this paper was presented before the Division of Organic Chemistry at the Pittsburgh meeting of the American Chemical Society, September, 1936.

(2) Schrauth and Geller, *Ber.*, **55**, 2783 (1922).

(3) Erlenmeyer, *Ann.*, **307**, 82 (1899).

(4) Zincke and Breuer, *ibid.*, **226**, 24 (1884).

(5) Bettzieche, *Z. physiol. Chem.*, **150**, 177 (1925).