ketone (identified by conversion to the semicarbazone m. p. 159–160°)[1] and 10.4 g. of benzoic acid.

Summary

1. It has been shown that, in the presence of sodium triphenylmethyl, ethyl isobutyrate condenses with ethyl benzoate to form ethyl benzoyldimethylacetate.

2. Further observations are made on the acetoacetic ester or Claisen type of condensation.

DURHAM, N. C. RECEIVED DECEMBER 27, 1937

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Physiologically Active Phenethylamines. I. Hydroxy- and Methoxy-α-methyl-β-Phenethylamines (β-Phenylisopropylamines)

BY E. H. WOODRUFF AND THEODORE W. CONGER[1,2]

The rediscovery of ephedrine by K. K. Chen in 1923 revived interest in the synthesis and pharmacology of β-phenethylamine and related compounds as evidenced by the increased number of publications appearing on the subject since that time.

The fundamental principles regarding the chemical structure necessary for physiological activity, as well as the modifications in structure already investigated, are covered so thoroughly by extensive reviews in the literature[3–5] that any further discussion in connection with the work reported here is not considered necessary. Investigations covered in the reviews mentioned point to the presence of one or more hydroxyl groups in the benzene ring as one of the most potent modifiers of the magnitude of the physiological effects of compounds possessing the basic β-phenethylamine skeleton.

Practically all of the β-hydroxy-(methoxy)-phenethylamines have been prepared[6] and tested pharmacologically.[7]

In spite of the greater recent clinical interest in amines of the β-phenylpropyl series, this series has not been studied so completely. In this work the monohydroxy and methoxy amines of the latter series so far unknown have been prepared for the purpose of pharmacological study. Those previously prepared have been included for the purpose of comparison.

Experimental

The method used for the preparation of the α-methyl-β-phenethylamines is similar to that used by Buck[6] and Slotta and Heller[8] for the preparation of methoxyphenethylamines and involves the following reactions

$$\begin{array}{l}
\mathrm{(CH_3O)C_6H_4CHO} \longrightarrow \\
\quad \mathrm{(CH_3O)C_6H_4CH{=}C(CH_3)COOH} \longrightarrow \\
\quad \mathrm{(CH_3O)C_6H_4CH_2{-}CH(CH_3)COOH} \longrightarrow \\
\qquad \mathrm{(CH_3O)C_6H_4CH_2CH(CH_3)CONH_2} \longrightarrow \\
\qquad\qquad \mathrm{(CH_3O)C_6H_4CH_2CH(CH_3)NH_2} \longrightarrow \\
\qquad\qquad\qquad \mathrm{(HO)C_6H_4CH_2CH(CH_3)NH_2 \cdot HCl}
\end{array}$$

The older methods for the preparation of α-methylcinnamic acid were found to be inconvenient for the methoxy derivatives so a better method for their synthesis was sought. An excellent preparation for α-alkylcinnamic acids is that recently carried out by Bogert and Davidson[9] who oxidized with hypohalite methyl (α-alkyl styryl) ketones prepared by condensing benzaldehyde with a methyl alkyl ketone in the presence of dry hydrogen chloride gas. With modification this was found to give excellent yields of the methoxy-α-methylcinnamic acids. The other steps in the synthesis follow essentially experimental procedures already appearing in the literature.

Methoxy-α-methylcinnamic Acids.—The hypohalite oxidation of the methyl [(α-methyl) methoxystyryl] ketones to the corresponding cinnamic acid was carried out essentially as described by Bogert and Davidson, as was the preparation of the unsubstituted ketone. When condensing the methoxy aldehydes with methyl ethyl ketone it was necessary to cool the aldehyde–ketone mixture in an ice-salt bath during the addition of the hydrogen chloride gas and to allow the reaction to proceed in an electric refrigerator at 0–5° or in the freezing chamber at -10 to $-5°$ for twenty-four to forty-eight hours, instead of at room temperature. It was found further that a practical grade of methyl ethyl ketone could be used. In this case instead of recovering the unused ketone the reaction mixture was taken up in ether, neutralized with solid sodium carbonate and washed thoroughly with water before drying with anhydrous magnesium sulfate and distilling.

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[1] Kalamazoo College Fellow, 1935–1936.

[2] A part of the data is from the thesis of T. W. Conger submitted as partial requirement for the degree of Master of Science from Kalamazoo College, June, 1936.

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

[4] Hartung, *Chem. Rev.*, **9**, 389 (1931).

[5] Council on Pharmacy and Chemistry, *J. A. M. A.*, **109**, 2064 (1937).

[6] Buck, THIS JOURNAL, **54**, 3661 (1932).

[7] Hjort, *J. Pharmacol.*, **52**, 101 (1934).

[8] Slotta and Heller, *Ber.*, **63**, 3029 (1930).

[9] Bogert and Davidson, THIS JOURNAL, **54**, 334 (1932).

TABLE OF COMPOUNDS

Compound	M. p., °C.	B. p., °C.	B. p., Mm.	% yield	Empirical formula	Analyses Calcd. C	Analyses Calcd. H	Analyses Found C	Analyses Found H
Methyl (α-methyl styryl) ketone[a]	37–38	130–135	12	80–82					
o-Methoxy		162–163	12	77–81	$C_{12}H_{14}O_2$	75.75	7.42	75.76	7.55
m-Methoxy		120–122	0.05	58–61	$C_{12}H_{14}O_2$	75.75	7.42	75.62	7.68
p-Methoxy		173–174	12	80–84	$C_{12}H_{14}O_2$	75.75	7.42	75.63	7.29
α-Methylcinnamic acid	80–81[c]			91–93[b]					
o-Methoxy	105–106[d]			85[b]					
m-Methoxy	91–92[e]			81[b]					
p-Methoxy	155–157[f]			88[b]					
α-Methylhydrocinnamic acid		146–149	6[g]	95					
o-Methoxy	62–63[h]	132–136	0.04	95	$C_{11}H_{14}O_3$	68.00	7.27	68.13	7.30
m-Methoxy		142–144	0.02	93	$C_{11}H_{14}O_3$	68.00	7.27	67.71	7.13
p-Methoxy		132–134	0.005[i]	95	$C_{11}H_{14}O_3$	68.00	7.27	67.88	7.59
α-Methylhydrocinnamamide	107–108[j]			67					
o-Methoxy	114–115			81	$C_{11}H_{15}NO_2$	68.35	7.83	68.20	7.89
m-Methoxy	106–107			83	$C_{11}H_{15}NO_2$	68.35	7.83	68.27	7.90
p-Methoxy	126.5			72	$C_{11}H_{15}NO_2$	68.35	7.83	68.03	7.91
α-Methyl-β-phenethylamine hydrochloride	152[k]	102–104	22[l,m]	42[o]					
o-Methoxy	101–103	118–120	11[l]	38[o]	$C_{10}H_{16}ONCl$	59.53	8.00	59.49	8.19
m-Methoxy	112–113	124–126	11[l]	33[o]	$C_{10}H_{16}ONCl$	59.53	8.00	59.33	8.25
p-Methoxy	205–206[n]			68[o]					
o-Hydroxy	159				$C_9H_{14}ONCl$	57.56	7.52	57.27	7.59
m-Hydroxy[q]	138				$C_9H_{14}ONCl$	57.56	7.52	57.38	7.30
p-Hydroxy	170[p]								

[a] Ref. 9. [b] After recrystallization from alcohol–water or ligroin b. p. 60–90°. [c] M. p. 81–82°. Perkin, *J. Chem. Soc.*, **31,** 391 (1877). [d] M. p. 107°. Perkin, *ibid.*, **39,** 432 (1881). [e] M. p. 92–93.5°. Moureu, *Bull. soc. chim.*, [3] **15,** 1022 (1896). [f] M. p. 154°. Perkin, *J. Chem. Soc.*, **31,** 411 (1877). [g] B. p. 160–161 (17 mm.). Kipping and Clark, *ibid.*, **83,** 915 (1903). [h] M. p. 55–56. (ref. *c*). [i] M. p. 40°, b. p. 308 (760 mm.). v. Auwers and Auffenberg, *Ber.*, **52,** 112 (1919). [j] M. p. 109°. Edeleanu, *ibid.*, **20,** 618 (1887). [k] M. p. 144–147°. Hartung, THIS JOURNAL, **53,** 1878 (1931). [l] Boiling points given for free amine. [m] B. p. 203° (760 mm.). Edeleanu (ref. *j*). [n] M. p. 208–210°. Alles, THIS JOURNAL, **54,** 271 (1932). [o] Yields given for free amine. [p] M. p. 171–172°. (Ref. *n*). [q] Analysis for N: calcd. 7.43; found 7.41.

These changes were found to be of particular value in the case of the *m*-methoxy compound.

In one experiment with the *m*-methoxy ketone, hypohalite oxidation was performed on the washed but undistilled ketone, with an increase in the over-all yield of acid. This is due to the fact that methyl [(α-methyl) *m*-methoxystyryl] ketone can be distilled only with considerable loss due to polymerization.

Reduction of the α-Methylcinnamic Acids.—This was accomplished by means of hydrogen and Adams[10] catalyst using glacial acetic acid as a solvent. The time for reduction of 0.1 mole varied between one and sixteen hours.

Preparation of Amides.—The amides were prepared by treating the acid chloride with aqueous concentrated ammonium hydroxide in which approximately 5% by weight of solid sodium hydroxide had been dissolved. The acid chlorides were prepared by adding the acid to a slight excess of thionyl chloride and refluxing[10] (p. 142). When the acid was a solid it was dissolved in chloroform prior to addition to the thionyl chloride. The acid chlorides were not purified.

α-**Methyl-*β*-methoxyphenethylamines.**—The amines were prepared by dissolving 0.1 mole amide in a solution composed of 0.106 mole bromine dissolved in 4.0 moles of 10% potassium hydroxide solution cooled below 15°. The solution was shaken until no more amide went into solution, whereupon the cold solution was filtered and the filtrate heated under reflux at 70–80° for one and one-half hours. Sixteen grams of solid sodium hydroxide was added and the temperature kept at 80° for two hours. The amine which separated as a brown oil, upon cooling the solution, was extracted twice with ether. The ether solution was dried quickly with anhydrous magnesium sulfate, filtered, the magnesium sulfate washed with a little ether, and after removal of the solvent distilled *in vacuo*. The hydrochlorides were prepared by passing dry hydrogen chloride gas into an absolute ether solution of the amine. Recrystallization was from an absolute ethyl alcohol–ether mixture.

In a trial run using α-methyl-*p*-methoxycinnamamide with sodium hypochlorite a much larger amount of material failed to go into solution. Since it was thought desirable to have as much material in solution as possible the use of sodium hypochlorite was discontinued.

For drying ether solutions of amines, which contain a considerable quantity of dissolved water, anhydrous magnesium sulfate is quite rapid in its action and only a few minutes of contact with the solution (stirring is of help) is necessary to render the solution sufficiently dry for the removal of solvent and subsequent vacuum distillation.

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[10] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 452.

If a completely anhydrous solution is desired solid potassium hydroxide may be used after the preliminary drying with the anhydrous magnesium sulfate.

α-Methyl-β-hydroxyphenethylamines.— The amines were demethylated by heating the amine with 36% hydrochloric acid solution for two hours at 160° in a sealed tube. The solution was evaporated to dryness and the residue taken up in absolute alcohol and boiled with decolorizing charcoal. After filtration the alcoholic solution was concentrated and absolute ether added to cloudiness. The pure amine hydrochloride precipitated on cooling. The yield of the crude product, which was nearly pure, was the theoretical. Losses in crystallization were out of proportion with the amount of impurity present as shown by change in melting point. The α-methyl-β-*m*-hydroxyphenethylamine hydrochloride was particularly difficult to obtain in a crystalline condition. It finally was obtained by allowing a toluene–alcohol solution of the hydrochloride to stand at room temperature until crystals formed.

The authors are indebted to Mr. C. H. Emerson for the micro analyses given and to Mr. Earl Pierson for assistance in the demethylation of the methoxy amines. The pharmacological results will appear elsewhere.

Summary

1. The method of Bogert and Davidson for the preparation of α-alkyl cinnamic acids has been extended to their monomethoxy derivatives.

2. Four new and three previously known α-methyl-β-phenethylamines have been prepared for the purpose of pharmacological study.

KALAMAZOO, MICH. RECEIVED DECEMBER 20, 1937

[CONTRIBUTION FROM THE RESEARCH LABORATORY, UNITED STATES STEEL CORPORATION]

The Adsorption of Gases on Plane Surfaces of Mica

BY MARION H. ARMBRUSTER AND J. B. AUSTIN

As a preliminary to a general study of the adsorption of gases on plane surfaces of iron, it seemed advisable to check the reliability of the apparatus and to develop the technique of using it by making a few measurements of adsorption on mica, which has been investigated by Langmuir,[1] by Bawn[2] and by Zickermann.[3]

The adsorption of argon and of carbon monoxide on mica at −183° has therefore been determined with the following results. The data for carbon monoxide are in excellent agreement with those of Bawn but are not in accord with those reported by Langmuir, whereas the results for argon show better agreement with Langmuir's data than with Bawn's. At saturation the mica surface appears to be completely covered with carbon monoxide but is only 17% covered with argon. Two kinds of adsorption of carbon monoxide were observed. The first which occurs on approximately a quarter of the surface is a chemisorption, the second, which covers the rest of the surface is physical adsorption. It is concluded that adsorbed argon atoms and the chemisorbed carbon monoxide are held on active centers which are probably the points on the surface from which a potassium ion is removed on cleavage. The adsorbed carbon monoxide behaves as if it were a two-dimensional gas, and obeys a two-dimensional analog of the van der Waals equation.

Materials

Hydrogen for Calibration.—Three different samples were used: (1) hydrogen from a Bunsen flame, collected by diffusion through palladium; (2) tank hydrogen freed from traces of water and oxygen by passing it through sulfuric acid and calcium chloride, then over hot platinized asbestos and phosphorus pentoxide; (3) a commercial sample of spectroscopically pure hydrogen. All three samples gave the same results within the error of measurement.

Carbon monoxide was prepared by dropping formic acid into concentrated sulfuric acid. It was passed through a solution of potassium hydroxide to remove carbon dioxide and was dried over phosphorus pentoxide.

Argon.—A commercial sample of spectroscopically pure gas was used.

Mica.—Sheets of mica split from a specially selected piece of muscovite were cut into strips 9.0 × 1.7 cm., care being taken to avoid touching the surface with the fingers and to discard pieces with cracks. The geometrical area of the surface was 7200 sq. cm. and the sample weighed 34.0 g.

Apparatus

Adsorption was determined by observing the decrease in the amount of gas, as measured by the change in pressure, when a known volume of gas was admitted to a bulb of known volume containing the absorbing surface. The apparatus used, shown schematically in Fig. 1, was in principle the same as that used by Bawn[2] and need be described but briefly here. It consists of three parts: an adsorption system, A, comprising a bulb containing the

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(1) Langmuir, THIS JOURNAL, **40**, 1361 (1918).

(2) Bawn, *ibid.*, **54**, 72 (1932).

(3) Zickermann, *Z. Physik*, **88**, 43–54 (1934).