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ETHYLPHENETHYL-BARBITURIC ACID AND RELATED DERIVATIVES

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The great therapeutic importance of luminal (ethylphenyl-barbituric acid) suggested to the writer, some time since, the preparation of the next higher homolog, ethylbenzyl-barbituric acid, the manufacture of which would be much simpler and cheaper than that of luminal. To our surprise, the benzyl derivative was found to differ markedly from the phenyl derivative in its physiological action. Although a powerful hypnotic, it showed the objectionable feature of a tendency to produce a preliminary stage of tetany, which would, of course, preclude its use in the treatment of epilepsy. Shortly after the publication of this work[1] the observations were confirmed by Shonle and Moment.[2] In the aliphatic series, a number of illustrations might be cited to show similarity in properties of homologous compounds dependent upon the occurrence of an even or of an odd number of carbons in the chain. Also, examples are known of similarity in properties of isomers where substitution occurs on alternate carbons of the chain, giving two series with alpha, gamma and epsilon and with beta, delta and zeta substitution, respectively. In the dialkyl-barbituric acid series, a phenyl substitution on the beta carbon of the side chain might therefore be expected to show somewhat different properties from the lower homolog with substitution on the alpha carbon. By way of illustration, ethylphenethyl-barbituric acid might resemble more closely the ethylphenyl than the ethylbenzyl derivative. With increasing molecular weight, the solubility of the substance in water decreases with corresponding decrease in rate of absorption when administered orally, but with intravenous injection of the sodium salt, the difference in rate of absorption is less pronounced.

Considering the difference in physiological properties between ethylphenyl- and ethylbenzyl-barbituric acid, the substitution of phenyl on a beta carbon atom was undertaken for the purpose of comparing physiological action. Ethylphenethyl-barbituric acid was prepared by the usual method of condensation of the corresponding malonic ester with urea and incidentally, several related derivatives of no physiological importance were also prepared and identified.

Experimental Part

Phenethyl Bromide.—Grignard[3] prepared this substance by heating phenethyl-phenyl ether for four hours at 120° with a saturated solution

[1] Dox and Yoder, THIS JOURNAL, **44**, 1141 (1922).

[2] Shonle and Moment, *ibid.*, **45**, 243 (1923).

[3] Grignard, *Compt. rend.*, **138**, 1049 (1904).

of hydrobromic acid in acetic acid. He reports a boiling point of 92° at 11 mm., and 217–8° at 734 mm. The success experienced by the writer in the preparation of numerous other alkyl bromides directly from the corresponding alcohols by the hydrobromic-sulfuric acid method, led to the adoption of the same method in this preparation.

A mixture of 200 g. of phenethyl alcohol, 320 cc. of the hydrobromic-sulfuric acid mixture (equivalent to 170 g. of bromine) and 120 g. of sulfuric acid was used. On addition of the sulfuric acid, the mixture became homogeneous and the reaction did not begin immediately. After gentle warming for 15 minutes, a turbidity developed. The temperature was gradually raised and finally the mixture was refluxed for two and a half hours. In the presence of a few porous clay chips, the mixture boiled smoothly with very little loss of hydrobromic acid through the condenser. After cooling, the upper layer consisting of phenethyl bromide was separated, washed with water, then with 25 cc. of concd. sulfuric acid to remove unchanged alcohol and finally with sodium carbonate solution and with water. A troublesome emulsion was disposed of by the addition of a little benzene. Distillation in a vacuum gave 264 g. or 71% of a product boiling at 79–81° (4 mm.) and possessing an odor like that of benzyl chloride, but less irritating. The identity of the substance is established by the preparation of the following derivatives.

Ethyl Phenethyl-malonate.—A solution of sodium ethoxide was prepared from 14.4 g. of sodium and 250 cc. of absolute alcohol, and 100 g. of ethyl malonate was added to it. To this mixture was added 115.6 g. of phenethyl bromide during $^3/_4$ hour at a temperature of about 60°. Sodium bromide separated rapidly. The mixture was then refluxed for four hours until a test portion was neutral to litmus. The alcohol was distilled in a vacuum and the residue treated with water. A yellow oil was obtained which on fractionation gave styrene, ethyl malonate and 106.1 g. or 68% of ethylphenethylmalonate. The alcoholic distillate became turbid on dilution with water and contained considerable styrene. The latter was identified by its dibromo derivative melting at 73–74° and its polymerization to a transparent jelly. The ester is a colorless liquid, boiling at 142–143° at 2 mm. and 296–298° at 741 mm.; d_{25}, 1.0580. About 10 g. of a higher-boiling product remained in the flask.

Anal. Subs., 0.1865: H_2O, 0.1220; CO_2, 0.4642. Calc. for $C_{15}H_{20}O_4$: H, 7.59; C, 68.12. Found: H, 7.27; C, 67.88.

Phenethyl-malonic Acid.—Saponification of the ester described above was performed by four hours' refluxing of a homogeneous solution in 50% alcohol with a 50% excess of potassium hydroxide. After the alcohol had been evaporated and the residue dissolved in water, the addition of hydrochloric acid caused a separation of the acid in white needles. From 10 g. of the ester, 7.7 g. of the product was obtained. After recrystallization, the melting point was 132° with evolution of gas at about 145°. The substance is readily soluble in alcohol but only sparingly soluble in water.

Anal. Subs., 0.2, 0.2: H_2O, 0.0989, 0.1006; CO_2, 0.4610, 0.4598. Calc. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77. Found: C, 62.86, 62.70; H, 5.49, 5.59.

Phenethyl-malonic Ethyl Ester Amide.—Ten g. of the ester was dissolved in 200 cc. of alcoholic ammonia, the solution allowed to stand for one week at room temperature, then evaporated at 40° and the residue dried on a porous plate. The product was dissolved in alcohol and filtered from a small amount of insoluble residue. Concentration of the solution and cooling gave an abundance of fine, needle-shaped crystals. These were dissolved in benzene, filtered from an insoluble residue and the solution was evaporated to crystallization. Slender needles melting at 98° were obtained.

Anal. Subs., 0.2705, 0.3879: 11.05, 15.95 cc. of 0.1 *N* acid. Calc. for $C_{13}H_{17}O_3N$: N, 5.95. Found: 5.72, 5.76.

Phenethyl-malonamide.—The residue insoluble in benzene was recrystallized from alcohol and obtained in satiny needles; m. p., 232°. By far the greater part of the ester had been converted into the intermediate ester amide, only 0.24 g. of the pure diamide being obtained.

Anal. Subs., 0.2328: 22.15 cc. of 0.1 *N* acid. Calc. for $C_{11}H_{14}O_2N_2$: N, 13.59. Found: 13.32.

Ethyl Ethylphenethyl-malonate.—The best yield was obtained by introducing the phenethyl group first. When the successive alkylations were performed in the reverse order, the yield of the final product was small, owing to the formation of styrene. It appears that ethyl malonate holds one sodium more firmly bound than does the mono-alkylated ester, hence the advantage of using the less stable alkyl halide first. To a solution of 4.4 g. of sodium in 80 cc. of absolute alcohol, 21 g. of ethyl bromide and 50 g. of ethyl phenethyl-malonate was gradually added at a temperature of about 40°. The separation of sodium bromide began almost immediately. The mixture was refluxed for two hours, then the alcohol was distilled and the oil separated and treated in the usual way. The yield was 49.2 g. or 89% of a colorless, somewhat viscous oil, boiling at 148–150° at 2 mm. and 314–316° at 741 mm.; d_{25}, 1.0382. Practically no residue was obtained in the flask.

Anal. Subs., 0.1932: H_2O, 0.1405; CO_2, 0.4910. Calc. for $C_{17}H_{24}O_4$: H, 8.22; C, 69.86. Found: H, 8.08; C, 69.31.

Ethylphenethyl-malonic Acid.—The ester was saponified by refluxing 10 g. with 6 g. of potassium hydroxide in 40 cc. of 50% alcohol. The alcohol was evaporated on a steam-bath and the residue dissolved in water and acidified with hydrochloric acid. Very small, white crystals separated which had a bitter taste and melted at 125–126° with evolution of gas at about 160°. The substance dissolves in alcohol but is practically insoluble in water.

Anal. Subs., 0.2: H_2O, 0.1220; CO_2, 0.4828. Calc. for $C_{13}H_{16}O_4$: H, 6.77; C, 66.10. Found: H, 6.78; C, 65.84.

From the two esters described above, barbituric acids were prepared by the usual procedure of condensation with a slight excess of urea or a substituted urea in the presence of three molecular equivalents of sodium dissolved in absolute alcohol, and heating the mixture in an autoclave at 100–105° for six hours.

Barbituric acid	Formula	Yield %	M. p. °C.	N Calc. %	N Found %	
5-Phenethyl	$C_{12}H_{12}O_3N_2$	95	212–213	12.07	12.16	12.20
5-Phenethyl-1-phenyl	$C_{18}H_{16}O_3N_2$	75	164	9.09	9.16	9.21
5,5-Ethylphenethyl	$C_{14}H_{16}O_3N_2$	90	168	10.77	10.69	10.96
5,5-Ethylphenethyl-1-phenyl	$C_{20}H_{20}O_3N_2$	20	110	8.33	8.44	8.56
5,5-Ethylphenethyl-1-benzyl	$C_{21}H_{22}O_3N_2$	53	141–142	8.00	8.00	8.21

All of these were difficultly soluble in water, but readily soluble in alcohol and in dilute alkali.

Physiological Tests

Although phenethyl-barbituric acid is isomeric with luminal, it was physiologically inert, as was to be expected from the fact that the 5-carbon carries only one alkyl group. Ethylphenethyl-barbituric acid showed a powerful hypnotic effect when administered intraperitoneally, as the sodium salt, to mice or intravenously to dogs. A dose of 0.15

g. per kg. killed a dog almost instantaneously; 0.075 g. produced almost instant anesthesia, lasting about an hour, after which a rapid recovery occurred, while 0.0375 g. caused only a temporary muscular incoördination. It is interesting to note that the convulsive symptoms observed previously with ethylbenzyl-barbituric acid were absent. Administered orally, the substance is much less active, probably because of its insolubility and slow rate of absorption. One gram given orally to a 12.5-kg. dog produced only a slight drowsiness and muscular incoördination after about an hour, with complete recovery by the end of the second hour.

Summary

Ethylphenethyl-barbituric acid and several related derivatives and intermediate products are described.

The hypnotic action of this substance was demonstrated and appears to be of the same general type as that of numerous other dialkylbarbituric acids. If we regard luminal, ethylbenzyl-barbituric acid and ethylphenyl-barbituric acid as homologs, differing not merely in the number of carbons in the side chain but also in the location of the phenyl group, the evidence thus far is in support of the recurrence of physiological characteristics with substitution of a given group on alternate carbon atoms.

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THE ISOLATION FROM AUTOLYZED YEAST OF A CRYSTALLINE SUBSTANCE MELTING AT 223°, HAVING THE PROPERTIES OF A BIOS

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For convenience of presentation this report is classified under four divisions: (I) the method employed in isolating the product; (II) the characteristics of the product as shown by chemical and physical tests; (III) the evidence as to its "bios" nature; (IV) a discussion of its relation to vitamin B and the work of other investigators in the field.

I. The Method of Isolation for Autolyzed Yeast

a. Brewer's yeast[2] was allowed to autolyze under toluene until an autolyzate with a dry weight of 0.418 g. per cc. of filtered material was obtained. This filtrate had a Sörensen (P_H) value of 5.93; 3 kg. of yeast was used to obtain 500 cc. of autolyzate.

[1] Presented before the Biological Chemistry Division of the American Chemical Society at the Washington Meeting, April, 1924.

[2] The yeast for the purpose was generously donated by the Jacob Ruppert Co. of New York.