Summary

Arsphenamine forms additive compounds with methyl ketones in which the ketone is bound very firmly. Neither drying at room temperature or at 98°, nor reprecipitation from ketone-free methyl alcohol with ether removes the ketone. When an aqueous solution of arsphenamine and sodium arsenite is treated with hydrochloric and hypophosphorous acids, the yellow color gradually changes to red and a polyarsenide of arsphenamine is formed. The rate at which this reaction takes place depends upon the method used in preparing the arsphenamine and seems to be related to the physical properties of the latter. The quantity of 1 to 1 hydrochloric acid necessary to precipitate a dil. aqueous solution of arsphenamine is constant when one method of preparation is strictly followed, but slight variations in certain steps in the synthesis cause fluctuations in the amount of acid required. Therefore, this titration has been found useful in determining the closeness with which the routine method of preparation has been followed. The physical properties of arsphenamine are affected materially by the amount of hydrochloric acid used in converting the base into the hydrochloride; it is advantageous to use a slight excess over the two molecules needed to secure the dihydrochloride.

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5,5-DIARYLBARBITURIC ACIDS

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Considering the great importance of veronal (diethylbarbituric acid) and luminal (phenylethylbarbituric acid) as therapeutic agents, and the large number of homologs that have been prepared by substituting other alkyl groups, it is surprising that no attempts to prepare 5,5-diarylbarbituric acids are on record. Luminal, in which one of the ethyl groups of veronal has been replaced by phenyl, is said to be 2.5 times as powerful in its physiological action as veronal, and is widely used in the treatment of epilepsy. The introduction of a second phenyl group might be expected to increase the physiological activity still further, provided the resulting derivatives possessed certain essential physical properties. The isomeric 1,3-diphenylbarbituric acid has been prepared by Whiteley[1] from malonyl chloride and carbanilide. No statement is made regarding its physiological properties, but from analogy with other N-substituted barbituric acids, we should hardly expect this substance to be of medicinal value.

The substitution of one or more aryl groups on the 5-carbon atom of

[1] Whiteley, *J. Chem. Soc.*, **91**, 1330 (1907).

barbituric acid is much more difficult than the substitution of alkyl groups. Some of the more reactive alkyl halides, such as allyl bromide[2] and benzyl chloride,[3] react directly with barbituric acid or a mono-alkyl substituted barbituric acid. Other alkyls, as ethyl and its homologs, must be introduced in a previous step of the synthesis, as in the alkylation of an alkyl malonate before condensation with urea. An aryl halide, on the other hand, cannot be made to react with an alkyl malonate. The aryl group, in luminal, for example, is added in a still earlier step of the synthesis. The addition of a second aryl would naturally be attended by further complications.

The most satisfactory method for the preparation of 5,5-dialkylbarbituric acids is the condensation of an ester of the corresponding dialkylmalonic acid with urea.[4] An ester of a diarylmalonic acid might, therefore, be expected to condense with urea in the same manner. The simplest derivative of this type, methyl diphenylmalonate, was prepared by Staudinger, Göhring and Schöller,[5] from the acid chloride obtained by treatment of diphenylketene with oxalyl chloride. Obviously, this method is too costly to be of practical importance.

Several alkyl diarylmalonates have been prepared by Guyot and Esteva[6] by condensing aromatic hydrocarbons with alkyl oxomalonates in the presence of concd. sulfuric acid. In this reaction water is split out and 2 products are formed, an alkyl aryltartronate and an alkyl diarylmalonate, the amount of the latter depending upon the temperature and time of reaction. Guyot and Esteva describe the methyl and ethyl esters of ditolyl- and di-*o*-xylylmalonic acids. The lower homolog, diphenylmalonic ester, they evidently did not succeed in obtaining, although the methyl and ethyl esters of phenyltartronic acid are mentioned.

By the method of Guyot and Esteva the writers succeeded in preparing ethyl diphenylmalonate, but all attempts to condense this with urea were unsuccessful. The substance appears to lack the stability of the dialkylmalonic esters, and when treated with sodium ethylate and urea it readily loses a carboxyl group. No evidence of the formation of a diphenylbarbituric acid was obtained; the only products identified were diphenylacetamide and diphenylacetic acid. Likewise, ethyl di-*p*-tolylmalonate, prepared by the same method, gave only the corresponding acetamide and the substituted acid. However, the diphenylmalonic esters are apparently more stable when an hydroxyl is present on the benzene nucleus. Thus, from ethyl di-(*p*-hydroxyphenyl)malonate we obtained by the usual method, di-(*p*-hydroxyphenyl)barbituric acid.

[2] U. S. pat., 1,042,265, **1912.**

[3] Dox and Yoder, THIS JOURNAL, **44,** 1144 (1922).

[4] Fischer and Dilthey, *Ann.*, **335,** 334 (1904).

[5] Staudinger, Göhring and Schöller, *Ber.*, **47,** 43 (1914).

[6] Guyot and Esteva, *Compt. rend.*, **148,** 564 (1909).

This is the first diarylbarbituric acid containing 2 aromatic hydrocarbon radicals attached directly to the 5-carbon atom. It is isomeric with 5,5-diphenoxybarbituric acid in which the aryl groups are joined to the pyrimidine nucleus through oxygen.

Experimental Part

Ethyl Diphenylmalonate.—Ethyl oxomalonate was prepared by oxidation of ethyl malonate with nitrous anhydride.[7] Thirty g. of this product was dissolved in 90 g. of anhydrous benzene, and 60 g. of concd. sulfuric acid added. The sulfuric acid layer became purplish-blue and some heat was developed. The flask was then immersed in an oil-bath at 70° and the mixture mechanically stirred for 7 hours, after which it was poured on cracked ice and the sulfuric acid removed by agitation with several lots of water. The excess of benzene was removed by distillation, and the residue distilled in a vacuum. The main product consisted of 17.5 g. of a thick, yellow oil; b. p., 180–200° (9 mm.). After several days a few crystals appeared in this oil and when it was then stirred with a glass rod the entire mass solidified. It was purified by drying on a porous plate and recrystallizing from alcohol in which it is readily soluble. The product consisted of small white prisms; m. p., 58–59°.

Analyses. Subs., 0.1961: H_2O, 0.1110; CO_2, 0.5281. Calc. for $C_{19}H_{20}O_4$: H, 6.41; C, 73.08. Found: H, 6.29; C, 73.45.

From the mother liquor a small amount of a product melting at 27–28° was obtained. This corresponds to Guyot and Esteva's ethyl phenyltartronate.

Condensation of Ethyl Diphenylmalonate with Urea.—In our first experiment Fischer and Dilthey's veronal method was employed. A mixture consisting of 5.0 g. of ethyl diphenylmalonate, 1.5 g. of urea, and 1.5 g. of sodium dissolved in 25 cc. of absolute alcohol was heated in an autoclave at 106–108° for 7 hours. The product was neutralized with hydrochloric acid, filtered, diluted with water and evaporated; 2.5 g. of colorless crystals was thus obtained. Treatment with cold dil. alkali dissolved 1.0 g. and this was again recovered by acidifying the solution. The substance consisted of white needles; m. p., 145°. A qualitative test for nitrogen was negative. In making this test the characteristic orange odor of diphenylmethane was noted. This substance would result from simple loss of carbon dioxide from diphenylacetic acid. The neutralization constant of the acid was 222; calc. for $C_{14}H_{12}O_2$, 212. The substance was undoubtedly diphenylacetic acid.

The portion of the reaction product insoluble in dil. alkali was recrystallized from alcohol; m. p., 169–170°. The nitrogen content was 6.80%; calc. for $C_{14}H_{13}NO$, 6.63%. This identified the substance as diphenylacetamide.

Ethyl diphenylmalonate, in its instability toward sodium ethylate, is in striking contrast to the diethylmalonate which is saponified only with difficulty. In their preliminary paper, Guyot and Esteva[8] state that the free diarylmalonic acids could not be obtained, since treatment of the esters with alcoholic potash split out carbon dioxide and gave the corresponding diarylacetic acids. We attempted, therefore, the condensation with urea under less drastic treatment, using a lower temperature and 1 mole of sodium instead of 3. Nevertheless, the same products resulted, and in about the same proportions. No barbituric acid derivative could be isolated.

Condensation of Ethyl Di-*p*-tolylmalonate with Urea.—Ethyl di-*p*-tolylmalonate was prepared in a similar manner from ethyl oxomalonate, toluene and sulfuric acid; m. p., 91–92°; Guyot and Esteva report a melting point of 93.5°. When heated with

[7] Curtiss, *Am. Chem. J.*, **35**, 478 (1906).

[8] Guyot and Esteva, *Bull. soc. chim.*, [4] **3**, 803 (1908).

urea in the presence of sodium ethylate it gave two products which were readily separated by treatment with cold dil. alkali. The acid product contained no nitrogen and melted at 140–141°; the recorded melting point of di-*p*-tolylacetic acid is 144°.[9]

Di-*p*-tolylacetamide.—The alkali-insoluble product from the condensation described above was recrystallized from dil. alcohol and obtained in white needles melting at 190°. The substance is almost insoluble in water, but is readily soluble in alcohol.

Analyses. Subs., 0.2, 0.2: cc. of 0.1 *N* NH_3, 8.2, 8.2. Calc. for $C_{16}H_{17}NO$: N, 5.81. Found: 5.74, 5.74.

Again no barbituric acid derivative was obtained.

Ethyl Di(*p*-hydroxyphenyl)malonate.—Ten g. of phenol was dissolved in 10 g. of ethyl oxomalonate. A considerable lowering of temperature resulted. Dry hydrogen chloride was passed in, and the solution was finally immersed in a freezing mixture and saturated with the gas. A viscous oil was obtained, which crystallized after several days at 0°. The crystals were dried on a porous plate and recrystallized from a large volume of hot water. Flat lustrous needles were obtained; m. p., 133–134°. The substance was difficultly soluble in water, readily soluble in alcohol and in dil. aqueous alkali. It gave a blue color with ferric chloride.

Analyses. Subs., 0.2022, 0.2016: H_2O, 0.1026, 0.1024; CO_2, 0.4828, 0.4782. Calc. for $C_{21}H_{24}O_6$: H, 5.86; C, 66.24. Found: H, 5.69, 5.71; C, 65.12, 64.88.

5,5-Di(*p*-hydroxyphenyl)barbituric Acid.—The ester described above was autoclaved in the usual manner with urea and sodium ethylate. The reaction mixture was acidified, diluted with water and evaporated. The product separated first as an oil which soon solidified. Recrystallization from hot water gave small slender needles; m. p., 288–290°. The substance is moderately soluble in hot water, readily soluble in dil. alkali and in alcohol. From 7.5 g. of the ester 3.0 g. of the barbituric acid was obtained. This substance also gives the ferric chloride reaction.

Analyses. Subs., 0.2, 0.2: 12.4, 12.5, cc. of 0.1 *N* NH_3. Calc. for $C_{16}H_{12}N_2O_5$: N, 8.97. Found: 8.68, 8.75.

Ethyl Diphenoxymalonate.—Ten g. of sodium was dissolved in 200 cc. of absolute alcohol, the solution cooled in ice water and 40 g. of phenol added. To the cold sodium phenylate 75 g. of ethyl dibromomalonate was gradually added with stirring. The mixture was refluxed for 1 hour and then found to be neutral to litmus. The alcohol was distilled in a vacuum and the remaining oil washed with water and dried with calcium chloride. Distillation under diminished pressure gave 45 g. of an oil; b. p., 195–204° (6 mm.).

Analyses. Subs., 0.2518, 0.2502: H_2O, 0.1254, 0.1298; CO_2, 0.5996, 0.5962. Calc. for $C_{21}H_{24}O_6$; H, 5.86; C, 66.24. Found: H, 5.58, 5.81; C, 64.94, 64.98.

5,5-Diphenoxybarbituric Acid.—The ester described above was heated in an autoclave with urea and sodium ethylate. The barbituric acid was isolated by the usual procedure and recrystallized from a mixture of benzene and alcohol. From 11.5 g. of the ester we obtained 6.5 g. of the barbituric acid in very fine white needles melting at 192°. The substance is nearly insoluble in water, difficultly soluble in benzene and readily soluble in alcohol; it is intensely bitter. It is isomeric with the di(*p*-hydroxyphenyl)-barbituric acid described above.

Analyses. Subs., 0.2, 0.2: cc. of 0.1 *N* NH_3, 12.6, 12.5. Calc. for $C_{16}H_{12}N_2O_5$: N, 8.97. Found: 8.82, 8.75.

Ethyl Di-(4-hydroxy-3-methylphenyl)-malonate.—A solution of 14 g. of *o*-cresol in 12 g. of ethyl oxomalonate was saturated at 0° with dry hydrogen chloride. After 4

[9] Fritsch and Feldmann, *Ann.*, **306**, 81 (1899).

days the mass had solidified. The crystals were dried by suction and washed with water. Two recrystallizations from dil. alcohol gave 16 g. of short white prisms; m. p., 107–108°. From alcoholic solution water precipitated the substance as an oil which gradually solidified. A blue color is obtained with ferric chloride.

Analyses. Subs., 0.2504, 0.2514: H_2O, 0.1406, 0.1394; CO_2, 0.6158, 0.6220. Calc. for $C_{23}H_{28}O_6$: H, 6.49; C, 67.77. Found: H, 6.29, 6.22; C, 67.07, 67.47.

5,5-Di-(4-hydroxy-3-methylphenyl)-barbituric Acid.—Five g. of the ester obtained as described above, 2 g. of urea and 1.4 g. sodium dissolved in 25 cc. of absolute alcohol were heated in an autoclave for 7 hours at 107–109°. The usual treatment then gave an oil with a strong odor of cresol. The product was obtained in crystalline form by dissolving the oil in a small amount of absolute alcohol and adding petroleum ether. Recrystallization from dil. alcohol gave 1 g. of white prisms melting at 217–219°. The substance is insoluble in water, readily soluble in alcohol, odorless and tasteless, and in dil. alcoholic solution gives a blue color with ferric chloride.

Physiological Tests

The two isomers, di(*p*-hydroxyphenyl)barbituric acid and diphenoxybarbituric acid, were tested physiologically. A 3% solution, prepared by dissolving the substance in a minimum amount of dil. alkali, was injected intraperitoneally into white mice in the proportion of 0.02 cc. per g. of body weight. This corresponds to twice the effective dose of veronal. The mice were kept under observation for several hours, but no symptoms of somnolence were observed or even muscular incoördination. Veronal, when administered in the same way in doses $^1/_2$ as great, produces a profound state of coma within 15 minutes. We must conclude, therefore, that the two barbituric acid derivatives described above are physiologically inert, at least in moderate doses.

An examination of the structure of the synthetic hypnotics commonly used shows that practically all are aliphatic derivatives. Where an aromatic grouping is present, as in luminal and in phenylethyl-hydantoin, the aromatic group comprises a relatively small part of the molecule. On the other hand, aromatic derivatives for which hypnotic properties might be predicted, on the basis of their distribution coefficient and molecular stability, are generally inert. Acetophenone perhaps comes the nearest to being an aromatic hypnotic, but a further increase in the aromatic groupings, as in benzophenone and diphenylcarbinol, causes the hypnotic action to disappear. It is of interest to note that the 2 barbituric acids under discussion consist essentially of 2 benzene rings and 1 pyrimidine ring, that is, they are predominatingly aromatic. The hydantoins furnish a parallel case: phenylethyl-hydantoin, mainly aliphatic, is an hypnotic while diphenyl-hydantoin, mainly aromatic, is not. Further evidence is, of course, required to establish this point, but from the data at hand it would appear that a search for hypnotics among derivatives that are essentially aromatic is not very promising.

Summary

Ethyl diphenylmalonate and ethyl di-(*p*-tolyl)malonate when subjected to the usual treatment with urea and sodium ethylate for condensation into a barbituric acid undergo decomposition with loss of a carboxyl group. When, however, the phenyl groups carry an hydroxyl group, as in ethyl di(*p*-hydroxyphenyl)malonate and ethyl di-(3-methyl-4-hydroxyphenyl)-malonate the condensation to a 5,5-diarylbarbituric acid is readily effected. Neither 5,5-di(*p*-hydroxyphenyl)barbituric acid nor its isomer, 5,5-diphenoxybarbituric acid, shows noticeable hypnotic properties. Attention is called to the fact that these derivatives differ from the great majority of synthetic hypnotics in that they are predominantly aromatic.

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THE UREA DEARRANGEMENT. II

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Just as urea dearranges into ammonia and isocyanic acid, so substituted ureas, thio-urea and guanidine, and their substitution products dearrange in similar fashion. When urea is heated with aniline, the isocyanic acid which is formed combines with the aniline to form phenylurea. This substance dearranges in two modes to form on the one hand aniline and isocyanic acid, on the other phenylisocyanate and ammonia; the phenylisocyanate and aniline combine to produce *sym*-diphenylurea which can dearrange in only one fashion to regenerate the substances from which it was produced. In the first paper[1] of this series, experiments were described which elucidate the mechanism of these reactions. By heating the dry materials together at about 160° we were able to prepare a number of derivatives of various aromatic primary amines.

In continuing the study we now find that the reactions take place in boiling aqueous solution. If urea and aniline hydrochloride are boiled together in water solution under a reflux condenser, phenylurea is formed and remains in solution in the hot liquid. After the clear solution has boiled for some time, diphenylurea begins to precipitate. Diphenylurea may be filtered from the hot liquid, and monophenylurea may be obtained by cooling the filtrate. By suitable modifications of the process, by repeating the boiling and filtration, it is possible to obtain either or both of the products in excellent yield. We find also that phenylurea refluxed in water solution yields *sym*-diphenylurea just as it does when heated at 160° in the dry state. When its aqueous solution is distilled, aniline passes over.

[1] Davis and Underwood, THIS JOURNAL, **44**, 2595 (1922).