reduction, since the 159° melting β-acid yields allocinnamic acid,[1] whereas, according to its configuration, it should give the fum. acid; also, the ease with which it decomposes into phenyl acetylene, and a smaller velocity of elimination of HBr, are opposed to the stereostructures given above, and to the relation of the corresponding halogen acids in the crotonic series.

An attempt[2] to determine the affinity constants of the β-bromo acids was without success, but those of the corresponding chloro-acids are known.[3] The higher melting acid is the mal. derivative, but its affinity constant (28) is only slightly higher than that of the fum. acid (27.2). This relation shows that the increase in the affinity constant of acrylic acid (5.6) caused by cis-
6 6 7
Cl, less the decrease by trans-C_6H_5, is only slightly greater than the in-
6 7 6
crease due to cis-C_6H_5 plus that of trans-Cl, and the relation is reflected in the approximation of their melting points and solubilities in water. It is remarkable, that the β-chloro- and β-iodo-cinnamic acids, corresponding to 160° melting β-bromo derivative, yield in the same method of reduction cinnamic, instead of allocinnamic acid.[4] No other problem in the field of stereomeric configurations is so perplexing and enigmatical as that of the β-halogen cinnamic acids, and the recent experimental results have added to the difficulties awaiting a satisfactory solution.

In the next paper, the relations between these configurations of unsaturated acids and their other physical and chemical properties will be treated

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[Contribution from the Kent Chemical Laboratory of the University of Chicago.]

THE PREPARATION OF PHENYLETHYLBARBITURIC ACID.[5]

By Mary Rising and Julius Stieglitz.

Received March 19, 1918.

Phenylethylbarbituric acid is a member of the ureid group of hypnotic drugs, of which diethylbarbituric acid, introduced as "veronal" and now known as "barbital,"[6] is the best known and most important representative. Phenylethylbarbituric acid, "phenylbarbital,"[7] introduced as "luminal,"

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[1] Liebermann and Scholz, *Ber.*, **25**, 950 (1892).

[2] Michael and Bunge, *Ibid.*, **41**, 2913 (1908).

[3] Millikin, Dissertation, Leipsic (1890).

[4] Michael and Whitehorne, *Ber.*, **34**, 3659 (1901).

[5] The work reported on in this article will form part of the dissertation to be submitted to the University of Chicago by Miss Rising in part fulfillment of the requirements for the doctorate degree.

[6] The official name of this drug, adopted by the U. S. Federal Trade Commission in the issuance of licenses for its manufacture, is "barbital." The reasons for the adoption of new official names for the licensed drugs and for the recommendation that these names be generally used by chemists and physicians in this country are presented by one of the authors in the *J. Am. Med. Assoc.*, **70**, 536 (1918).

[7] "Phenyl-barbital" is the name for phenylethylbarbituric acid, which will be used in the issuance of licenses for its manufacture in this country.

is of specific value as a hypnotic and sedative in the treatment of epilepsy, and, therefore, is one of the group of essential synthetic remedies whose manufacture in this country has become a matter of importance in consequence of the war. In order to be in a position to advise and assist any would-be manufacturer with a minimum loss of time, the authors of this paper have studied the synthetic preparation of phenylethylbarbituric acid. Certain improvements in the method studied have suggested themselves and are reported for the benefit of any one preparing to supply this important synthetic.

The method of preparation of phenylethylbarbituric acid, which was investigated, is indicated in the following series of reactions:

(1) Ethyl oxalate is condensed with the ethyl ester of phenylacetic acid by means of sodium ethylate in order to form the sodium salt of the diethylester of oxalyl-phenylacetic acid.[3]

$$C_2H_5O_2C.CO_2C_2H_5 + H_2C(C_6H_5).CO_2C_2H_5 + NaOC_2H_5 \longrightarrow C_2H_5O_2C.C(ONa) : C(C_6H_5).CO_2C_2H_5 + C_2H_5OH. \quad (1)$$

W. Wislicenus,[1] who carried out this reaction, recommended as the condensing agent the use of pure sodium ethylate, which is prepared by the driving off of the excess of alcohol in a stream of inert gas (hydrogen) from a solution of sodium ethylate in ethyl alcohol.

In this stage of the synthesis two modifications have been found desirable. In the first place, one may do away with the laborious preparation of solid sodium ethylate and effect the combination in absolute ether solution by means of sodium wire and a few drops of absolute (ethyl or methyl) alcohol. A quantitative yield of the desired sodium salt is easily obtained. In the second place, the methyl esters may be substituted for the ethyl esters. Methyl oxalate is a solid and much more easily prepared than the ethyl ester, especially by the method finally adopted by us. The condensation of the methyl esters is, if anything, more smoothly effected than that of the ethyl esters.

(2) In the next stage of the synthesis, the dimethyl oxalylphenylacetic ester is converted by heat into the methyl ester of phenyl malonic acid by the loss of carbon monoxide, according to the method used by Wislicenus on the ethyl ester.

$$CH_3O_2C.CO.CH(C_6H_5)CO_2CH_3 \longrightarrow CO + C_6H_5CH(CO_2CH_3)_2. \quad (2)$$

Here too an advantage in the use of the methyl ester was observed in as much as methyl phenylmalonate is a solid which may be easily purified by recrystallization, whereas the ethyl ester is a liquid, which tends to decompose when distilled, even *in vacuo*.

(3) The ethylation of phenylmalonic methyl ester in alcoholic solution according to

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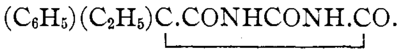
[1] *Ber.*, **27**, 1092 (1894); *Ann.*, **246**, 315 (1888).

$$C_6H_5CH(CO_2CH_3)_2 + NaOC_2H_5 + C_2H_5I \longrightarrow (C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + NaI + HOC_2H_5 \quad (3)$$

leads to not altogether satisfactory yields as a result of saponification and decomposition of the ester in a parallel reaction, exactly as observed by Wislicenus for the ethyl ester.[1] But again the new methyl ester had the advantage of being a solid, which may be purified by recrystallization. The sodium salt of phenylmalonic methyl ester is easily prepared in ether suspension by treatment of the ester dissolved in absolute ether with sodium wire and a little alcohol. Ethylation of this salt in sealed tubes at 100° has been studied in the hope of improving the yield by avoiding the loss due to the saponifying action of sodium ethylate in alcoholic solution. The results thus far obtained have not been as satisfactory as expected but the effort will be continued, especially in the direction of experiments to be carried out at higher temperatures. The use of an autoclave would be easily compensated for by a greater yield of the ethylated product.

(4) The condensation of ethylphenylmalonic dimethylester with urea is the last stage in the synthesis of phenyl barbituric acid.

$$(C_6H_5)(C_2H_5)C(COOCH_3)_2 + CO(NH_2)_2 \longrightarrow$$



$$(C_6H_5)(C_2H_5)C.CONHCONH.CO. \quad (4)$$

According to the patent specifications[2] the condensation is effected by sodium ethylate in alcoholic solution by the heating of the mixture under a reflux condenser. This produced phenylethylbarbituric acid but only in exceedingly small quantity. A far better result was obtained by the method of condensation that Fischer[3] used in the preparation of diethylbarbituric acid, with the modification that sodium methylate in methyl alcohol was substituted for sodium ethylate in ethyl alcohol solution.

Further work on the improvement of the yields in the later stages of the synthesis of phenylethylbarbituric acid is in progress and other methods of accomplishing the synthesis especially with the aid of the Grignard reaction, are to be investigated.

Experimental Part.

1. **Phenylacetic Methyl Ester,** $C_6H_5CH_2CO_2CH_3$.—Phenylacetic methyl ester was prepared in general according to the directions of Wislicenus[4] for the preparation of the ethyl ester. To 200 g. of absolute methyl alcohol are added 100 g. of benzyl cyanide and 20 g. of water. The flask containing this mixture is placed under reflux, and dry hydrogen chloride gas passed into it at a rather rapid rate. The solution becomes hot, and after the gas is passed in for half an hour or so, a heavy white precipitate

[1] *Ber.*, **28**, 815 (1895).

[2] U. S. Pat. 1,025,872 (1912).

[3] *Ann.*, **335**, 338 (1904).

[4] *Ibid.*, **296**, 361 (1896).

of ammonium chloride settles out with a rather violent reaction. The treatment with hydrogen chloride is continued to saturation, first without cooling, and then the mixture is cooled and saturated in the cold. The flask and contents are left standing for twenty-four hours, and are then heated for one hour on the water bath. The mixture is cooled, and 300 g. of ether and finally just sufficient water are added to it to dissolve the ammonium chloride when shaken in a separatory funnel. The ether solution is separated and washed with 10 cc. portions of sodium carbonate until the washings are alkaline. All the wash waters are combined, including that containing the ammonium chloride, and shaken with a little ether. This ether layer is separated, and all the ether solutions are combined, filtered, and dried over granulated calcium chloride. The oil remaining after the evaporation of the ether is fractionated. The yield of oil of boiling point[1] 212–216° (uncorr.) was 110 g., or 85.9% of the theoretical yield.

In this process, care was taken to wash the ether solution of the oil with only small amounts of sodium carbonate, in order to avoid hydrolysis of the ester by alkali. The alkali was then separated quickly and completely from the ether solution of the ester.

The course of the reaction may be summarized as follows:

Main reaction: $C_6H_5.CH_2.CN + CH_3OH + HCl \longrightarrow$

$$C_6H_5CH_2C(:NH_2Cl)OCH_3 \quad (5)$$

$$C_6H_5.CH_2C(:NH_2Cl)OCH_3 + H_2O \longrightarrow NH_4Cl + C_6H_5.CH_2.CO_2CH_3 \quad (6)$$

By reactions: $C_6H_5.CH_2.CO_2CH_3 + HOH \longrightarrow$

$$C_6H_5.CH_2CO_2H + CH_3OH \quad (7)$$

and, to some extent: $C_6H_5CH_2C(:NH_2Cl)(OCH_3) \longrightarrow$

$$C_6H_5CH_2CONH_2 + CH_3Cl \quad (8)$$

2. **Methyl Oxalate,** $(COOCH_3)_2$.—Vanino's[2] method for the preparation of methyl oxalate was modified and the following far simpler method used with better results. In Vanino's method the sodium carbonate used rapidly saponifies the ester, lowering the yield.

To 378 cc. of absolute methyl alcohol are added 300 g. of dehydrated oxalic acid. The dehydration is accomplished sufficiently by the heating of the hydrated acid in shallow vessels in a steam oven overnight. The solution of oxalic acid in methyl alcohol is placed under reflux, and hydrogen chloride gas is passed into it in a strong stream. The mixture quickly becomes hot; it is then cooled in an ice bath to prevent decomposition of the ester. White crystals of methyl oxalate separate out slowly after hydrogen chloride has been passed in for some time and a solid mass of

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[1] Radziozewski, *Ber.*, 2, 208 (1869), gives the b. p. 220° for the ester prepared from phenylacetic acid in the usual way.

[2] *Präparative Chemie*, 2, 110 (1914).

crystals eventually forms in the flask. The flask and contents are left standing for twenty-four hours, and the crystals are then brought on a funnel, and kept over suction for some hours to remove the hydrogen chloride. By drying the crystals further *in vacuo* for several days over sodium hydroxide or lime, the last traces of hydrogen chloride are removed. The melting point of the crystals was found to be 53.5°. The yield was 333 g., or 84% of the theoretical yield. This yield includes 28 g. recovered from the mother liquor when cooled to —15°.

Anschütz and Pictet's method,[1] used in the preparation of tartaric acid esters, and said to give quantitative yields for oxalic acid esters, was also tried. It gave very poor results and proved much more laborious than the above method.

3. Sodium Oxalylphenylacetic Methyl Ester, $CH_3O_2C.C(ONa):-C(C_6H_5)CO_2CH_3$.—Wislicenus[2] obtained an 85% yield of the sodium salt of oxalylphenylacetic ethyl ester by the condensation of ethyl oxalate with phenylacetic ethyl ester, using alcohol-free sodium ethylate prepared in a stream of hydrogen as the condensing agent. We applied the Nef method of preparation of acetoacetic ester to this condensation, using sodium wire in an ether solution of the two esters, and adding a few drops of absolute methyl alcohol to start the reaction. Our yield ranged from 85 to 92% of the theoretical.

To 80 g. of sodium dried ether are added 4 g. of sodium wire and 20 g. of methyl oxalate. The oxalate dissolves only partially. There are then added 25 g. of phenylacetic methyl ester, and about ten drops of absolute methyl alcohol, and the mixture is placed at once under reflux. Soon after the alcohol is added, yellow crystals begin to form upon the sodium wire, and a flocculent precipitate appears in the ether solution. The sodium dissolves very slowly, with the evolution of hydrogen, and a mass of yellow precipitate gathers in the bottom of the flask, the liquid above it turning to a dark red. Two days are allowed for the completion of the reaction, and the mixture is then heated for one hour on the water bath. It sometimes happened that gentle heating on an electric oven was necessary to start the reaction, and then the precipitate came down rapidly. After the contents of the flask are cooled, the yellow precipitate of sodium oxalylphenylacetic methyl ester is brought upon a filter, washed with dry ether, and dried *in vacuo*. The yield varies from 37 to 40 g.

As the salt is very easily decomposed the product of the reaction must be kept dry. Our product was yellow, and perhaps not absolutely pure but attempts to purify it by solution of the salt in alcohol and precipitation with ether, as recommended by Wislicenus for the corresponding salt of

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[1] *Ber.*, **13**, 1178 (1880).

[2] *Ibid.*, **27**, 1092 (1894).

the ethyl ester, failed, as the substance turned quickly to a soft, jelly-like mass.

A sodium determination showed that the salt is rather pure.

Subst. 0.7881; Na_2SO_4, 0.1919.
$C_{12}H_{11}O_5Na$. Calc. Na: 8.92%. Found: 8.77%.

The reaction is

$$(COOCH_3)_2 + C_6H_5CH_2CO_2CH_3 + NaOCH_3 \longrightarrow CH_3O_2C.C(ONa):C(C_6H_5)CO_2CH_3 + 2CH_3OH. \quad (9)$$

4. **Oxalylphenylacetic Methyl Ester,** $CH_3O_2C.CO.CH(C_6H_5)CO_2CH_3$.—The sodium salt of oxalylphenylacetic methyl ester is treated with cold dilute sulfuric acid in excess, whereby an oil is formed. The oil is separated from the acid by extraction with ether, and the ether extract dried over calcium chloride.

After the evaporation of the ether, the ester is decomposed with the loss of carbon monoxide by being treated *in vacuo* in the manner described by Wislicenus[1] for the ethyl ester. The ester when warmed at 90° C. and 10 mm. shows evidence of decomposition, with evolution of a gas, and change of color of the oil from bright red to dark brown. The manometer shows a decided increase in pressure, and the bubbles of gas forming at the outlet of the pump may be ignited and burn with the blue flame characteristic of carbon monoxide. When the loss of carbon monoxide is complete, the pressure falls rapidly to the original 10 mm. The reaction is expressed in Equation 2 above.

5. **Phenylmalonic Methyl Ester,** $(CH_3OOC)_2CHC_6H_5$.—The distillation *in vacuo* is continued as described in (4), until the thermometer rises to 130°. The small fraction of impure ester passing over below this point is collected separately. At 120° crystals of phenylmalonic methyl ester form at the tip of the water condenser and in the receiving vessel, and at this time the distillation is interrupted, and the liquid in the flask transferred to an Anschütz distilling flask. The distillation is then resumed, after the pressure is again brought to 10 mm., and the main fraction of the oil distilling between 147° and 159° is collected. This entire distillate crystallizes readily.

The purification of the ester is accomplished by recrystallization from ligroin of low boiling point (40–50°) from which rosets of white crystals separate, when the solvent is allowed to evaporate spontaneously. The melting point of pure crystals was found to be 50°. The ester was identified by analysis.[2]

Subs. 0.1555; CO_2, 0.3628; H_2O, 0.0813.
Calc. for $C_{11}H_{12}O_4$: C, 63.46%; H, 5.82%. Found: C, 63.64%; H, 5.85%.

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[1] *Ber.*, **27**, 1091 (1894).

[2] We are indebted to Mr. R. Q. Brewster for this combustion and for the others reported on in this paper.

The crude yield from 78 g. of the sodium salt of oxalylphenylacetic ester was 42.2 g., or 67% of the theoretical yield.

6. Phenylethylmalonic Methyl Ester, $(CH_3OOC)_2C(C_2H_5)(C_6H_5)$.—Wislicenus[1] describes the alkylation of phenylmalonic ethyl ester with methyl iodide in the presence of sodium methylate. He reports a yield of the pure ester, an oil, which was 60% of the theoretical. Our experience with the ethylation of the methyl ester by the method of Wislicenus (described in detail for malonic esters by Conrad and Limpach),[2] was discouraging with regard to yields, which were very low.

Sodium methylate is prepared from 30 g. of absolute methyl alcohol and 3 g. of sodium. To this solution, 30 g. of phenylmalonic methyl ester are added, and the flask containing the mixture is placed under reflux. After solution of the ester, which occurs readily, 30 g. of ethyl iodide are added in small portions through the condenser tube. There is no apparent reaction, and it is necessary to heat the mixture for three or four days over a water bath in order to bring about the ethylation. That the reaction does not go to completion is shown by the fact that the mixture in the flask remains alkaline. It was, therefore, necessary to neutralize it before proceeding further with the preparation of the ester.

At this point the directions of Conrad and Limpach were modified, with good results. The residue left in the flask after being heated for several days is made neutral, or slightly acid, with dilute sulfuric acid, and enough water is added to dissolve the sodium iodide formed in the reaction, and to cause the ethylated ester to separate in an oily layer at the bottom of the flask. This oil is separated from the water above it, and dried over calcium chloride. The aqueous layer contains a small amount of the oil, and is extracted twice with ether, and the ether solution is dried over calcium chloride. After the evaporation of the ether, the remaining oil, which is dark red in color, is added to the main portion, and distilled *in vacuo*.

From 80 to 90°, at 10 mm., there is obtained a dark red oil and some purple iodine fumes are formed. This change is complete below 100°, and a pale yellow liquid remains in the distilling flask. From 100 to 135°, a fraction of impure ethylated ester is obtained, and from 135 to 155°, the main fraction of the oil distils.

The fraction of the higher boiling point crystallizes when cooled, and remains solid at room temperature. The fraction of the lower boiling point crystallizes slowly on cooling, but softens somewhat at room temperature. The yield of the two fractions before purification was 26 g. or 76% of the theoretical, and the crystals showed a melting point of 33°.

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[1] *Ber.*, **28**, 815 (1895).

[2] *Ann.*, **204**, 129 (1880).

By recrystallization from ligroin of low boiling point, crystals were obtained with a melting point of 37°. The crystals obtained by spontaneous evaporation of the solvent were large, colorless, and transparent.

The ethylated ester was identified by analysis:

Subs. 0.1544; CO_2, 0.3750; H_2O, 0.0954.
Calc. for $C_{13}H_{16}O_4$: C, 66.17; H, 6.83. Found: C, 66.24; H, 6.91.

The reaction is expressed in Equation 3 above.

7. **Phenylethylbarbituric Acid,** $(C_6H_5)(C_2H_5)\underline{C.CONHCONHCO}$.—The condensation of the phenylethylmalonic methyl ester with urea to form phenylethylbarbituric acid was first attempted by the method described in the patents. The ester and urea are heated under reflux for six hours, with sodium alcoholate as the condensing agent. By the use of this method, we obtained only a very small amount of phenylethylbarbituric acid, and the yield was too low to warrant the use of the method for practical purposes.

The method of Fischer[1] for the preparation of diethylbarbituric acid, was followed next, with much better success and when carried out on a large scale, this method would undoubtedly give a higher yield than was obtained by us in working with small amounts of material.

Sodium methylate is prepared from 14.2 g. of absolute methyl alcohol and 0.9 g. of sodium. To it are added 2.5 g. of phenylethylmalonic methyl ester and 1.1 g. of urea. This mixture is heated in a sealed tube at 105–108°, for six hours. When the tube has cooled, the white precipitate (chiefly of sodium carbonate) is removed and the filtrate is again heated in a sealed tube for six hours at 105–108°. Any further precipitate of sodium carbonate which has formed during the second heating is removed as before. The filtrate, which is alkaline, is neutralized with acetic acid, and the alcohol evaporated *in vacuo*. When the last of the alcohol is gone, the residue in the distilling flask has an oily appearance, and when a few cubic centimeters of water are added, a cloudy emulsion of the oil and water forms. This emulsion is now extracted with ether, and the ether allowed to evaporate spontaneously. The residue is a mass of crystals in a thick oil, and is a mixture of phenylethylbarbituric acid and unchanged ester. It is extracted with ligroin of low boiling point, which dissolves the ester. The remaining white mass is purified by recrystallization from boiling water, and after two recrystallizations, the product shows a melting point of 174°. The crystals are pure white, and lustrous. The yield was close to a gram or about 40% of the theoretical. The reaction is given in Equation 4 above.

CHICAGO, ILL.

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[1] *Ann.*, **335**, 338 (1904).