being used as the solvent; 0.656 g. of acetonyl pyrrole in 100 cc. of the solvent at the boiling point gave an equivalent boiling point elevation of 0.052°, corresponding to a molecular weight of 403. The molecular weight calculated for $C_{28}H_{36}N_4$ is 428. It thus seems very probable that $C_{28}H_{36}N_4$ is the structural molecule. These molecules, since their centers are in the general positions, do not necessarily have an element of symmetry.

The formula $C_{28}H_{36}N_4$ depends upon the analysis of Dennstedt and Zimmerman.[1] It is possible that the hydrogen content of the molecule is not correctly given. Such a possibility does not influence the correctness of the above conclusions concerning the molecular symmetry and the number of molecules associated with the unit of structure.

Summary

Laue and spectrum photographs have been obtained and analyzed from crystals of acetonyl pyrrole. The unit of structure containing four $C_{28}H_{36}N_4$ molecules has the dimensions $a_0 = b_0 = 10.09$ Å., $c_0 = 23.85$ Å. The space group is $4C$-2 or $4C$-4, the molecules being in the general positions and thus not necessarily having an element of symmetry. The molecular weight is twice that corresponding to the previously assigned formula. A determination of the molecular weight by a differential vapor pressure method gave a value in agreement with the formula $C_{28}H_{36}N_4$.

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[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

PHENYLETHYLMALONIC METHYL ESTER. A NEW METHOD OF SYNTHESIS

BY MARY M. RISING AND TSOH-WU ZEE[1]

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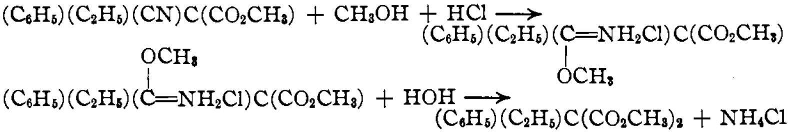
There appeared recently a paper[2] in which there was described a method of preparation of phenylethylmalonic methyl ester, $(C_6H_5)(C_2H_5)C(CO_2CH_3)_2$, by a procedure summarized as follows.

$$(C_6H_5)CH_2(CN) + NH_2Na + C_2H_5I \longrightarrow (C_6H_5)(C_2H_5)CH(CN) + NaI + NH_3\uparrow \quad (1)$$

$$2(C_6H_5)(C_2H_5)CH(CN) + 2Na \longrightarrow 2(C_6H_5)(C_2H_5)\ C{=}C{=}NNa + H_2\uparrow \quad (2)$$

$$(C_6H_5)(C_2H_5)C{=}C{=}NNa \rightleftarrows (C_6H_5)(C_2H_5)(CN)CNa \quad (3)$$

$$(C_6H_5)(C_2H_5)(CN)CNa + ClCO_2CH_3 \longrightarrow (C_6H_5)(C_2H_5)(CN)C(CO_2CH_3) + NaCl \quad (4)$$



$$(C_6H_5)(C_2H_5)(CN)C(CO_2CH_3) + CH_3OH + HCl \longrightarrow (C_6H_5)(C_2H_5)(\underset{\displaystyle OCH_3}{\underset{|}{C}}{=}NH_2Cl)C(CO_2CH_3) \quad (5)$$

$$(C_6H_5)(C_2H_5)(\overset{\displaystyle OCH_3}{\overset{|}{C}}{=}NH_2Cl)C(CO_2CH_3) + HOH \longrightarrow (C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + NH_4Cl \quad (6)$$

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[1] This paper describes work done by Tsoh-Wu Zee in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Chicago, 1926.

[2] Rising and Zee, THIS JOURNAL, 49, 541 (1927).

The ester is an intermediate product in the synthesis of the hypnotic phenylethylbarbituric acid, or pheno-barbital, $\mathrm{(C_6H_5)(C_2H_5)\text{-}\underline{CCONHCONHCO}}$, a valuable therapeutic agent in the treatment of epilepsy, and is therefore a compound of considerable importance. It was first prepared in this Laboratory in 1918 in the course of the synthesis of pheno-barbital,[3] undertaken as a war measure. Condensation of phenylethylmalonic methyl ester with urea produced phenylethylbarbituric acid.

$$\mathrm{(C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + (NH_2)_2CO \longrightarrow (C_6H_5)(C_2H_5)\underline{CCONHCONHCO} + 2CH_3OH} \quad (7)$$

Other methods of production of phenylethylmalonic methyl ester have been sought more recently in the hope of improving the yield of ester obtained in the earlier synthesis (76% of crude material). As the plan of preparation developed during the war constitutes the basis for the commercial production of pheno-barbital, the importance of obtaining good yields is apparent. The first of the recent methods[2] is particularly interesting and valuable for its discovery of a series of sodium salts of aromatic nitriles;[4] it is not as satisfactory from the point of view of yield as is the plan outlined in the present paper.

Another method of synthesis of phenylethylmalonic methyl ester is now to be reported in which the yield of ester is the best so far obtained by any process. This plan makes use of the following reactions.

$$\mathrm{(C_6H_5)CH_2(CN) + NH_2Na + C_2H_5I \longrightarrow (C_6H_5)(C_2H_5)CH(CN) + NaI + NH_3\uparrow} \quad (8)$$

$$\mathrm{(C_6H_5)(C_2H_5)CH(CN) + CH_3OH + HCl \longrightarrow (C_6H_5)(C_2H_5)CHC({=}NH_2Cl)(OCH_3)} \quad (9)$$

$$\mathrm{(C_6H_5)(C_2H_5)CHC({=}NH_2Cl)(OCH_3) + HOH \longrightarrow (C_6H_5)(C_2H_5)CH(CO_2CH_3) + NH_4Cl} \quad (10)$$

$$\mathrm{2(C_6H_5)(C_2H_5)CH(CO_2CH_3) + 2Na \longrightarrow 2(C_6H_5)(C_2H_5)C{=}C(OCH_3)(ONa) + H_2\uparrow} \quad (11)$$

$$\mathrm{(C_6H_5)(C_2H_5)C{=}C(OCH_3)(ONa) \leftrightarrows (C_6H_5)(C_2H_5)C(CO_2CH_3)Na} \quad (12)$$

$$\mathrm{(C_6H_5)(C_2H_5)C(CO_2CH_3)Na + ClCO_2CH_3 \longrightarrow (C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + NaCl} \quad (13)$$

The total yield of phenylethylmalonic methyl ester obtained by this method, calculated from the amount of phenylacetonitrile used, was 43.1%, as compared with 27.4% by the first method of Zee and 41.0% in the war-time synthesis.

Of particular interest in the series of reactions just enumerated is that represented by Equation 11. α-Sodium-α-phenylbutyric methyl ester is produced by treatment of α-phenylbutyric methyl ester with sodium in dry ether. The sodium salt is a white, amorphous substance of interesting

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[3] Rising and Stieglitz, This Journal, **40**, 725 (1918).

[4] A paper entitled "Sodium Salts of Aromatic Nitriles," by Rising and Zee will be published shortly in This Journal.

behavior. It takes part in substitution reactions, the group entering the molecule becoming attached to the carbon atom carrying the phenyl group. For example, when treated with chloroformic ester the carbmethoxy group, —$COOCH_3$, replaces the sodium atom, and the salt is converted into phenylethylmalonic methyl ester, as shown in reaction 13. This behavior indicates that the salt is a carbide of structure $(C_6H_5)(C_2H_5)C(CO_2CH_3)Na$. The carbide is undoubtedly a tautomer of an enol salt of structure $(C_6H_5)(C_2H_5)C{=}C(OCH_3)(ONa)$, and the latter is analogous to enol sodium acetoacetic ester, $CH_3COCH{=}C(OC_2H_5)(ONa)$. It is probable that enol α-sodium α-phenylbutyric methyl ester is formed by the reaction of α-phenylbutyric methyl ester with sodium, and that under the conditions used for the conversion of the salt into phenylethylmalonic ester, tautomerization of the enol salt to the more reactive carbide occurs, this being the reactive molecule in substitutions. A detailed formulation of these changes follows.

$$[(C_6H_5)(C_2H_5)C^-(CO_2CH_3)]H \leftrightarrows [(C_6H_5)(C_2H_5)C{=}C(OCH_3)O^-]H \qquad (14)$$

Keto α-phenylbutyric methyl ester Enol α-phenylbutyric methyl ester

$$2[(C_6H_5)(C_2H_5)C{=}C(OCH_3)O^-]H + 2Na \longrightarrow 2[(C_6H_5)(C_2H_5){=}C(OCH_3)O^-]Na + H_2\uparrow \qquad (15)$$

The negative enol ion of the salt tautomerizes to the carbide ion

$$[(C_6H_5)(C_2H_5){=}C(OCH_3)O^-]Na \leftrightarrows [(C_6H_5)(C_2H_5)C^-(CO_2CH_3)]Na \qquad (16)$$

$$[(C_6H_5)(C_2H_5)C^-(CO_2CH_3)]Na + ClCO_2CH_3 \longrightarrow (C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + NaCl \qquad (17)$$

α-Sodium α-phenylbutyric methyl ester is decomposed by water and all acids into α-phenylbutyric methyl ester. The reaction may occur as follows.

$$[(C_6H_5)(C_2H_5)C{=}C(OCH_3)O^-]Na + H_2SO_4 \longrightarrow [(C_6H_5)(C_2H_5)C{=}C(OCH_3)O^-]H + NaHSO_4 \qquad (18)$$

$$[(C_6H_5)(C_2H_5)C{=}C(OCH_3)O^-]H \rightleftarrows [(C_6H_5)(C_2H_5)C^-(CO_2CH_3)_2]H \qquad (19)$$

Experimental Part

1. α-Phenylbutyronitrile, $(C_6H_5)(C_2H_5)CH(CN)$.—α-Phenylbutyronitrile was prepared according to the method of Bodroux and Taboury.[5] Experience has taught us that the most satisfactory results, both in yield and purity of product, are obtained only when certain precautions are observed: the purest phenylacetonitrile and sodamide (Kahlbaum's) were used; all apparatus and reagents were thoroughly dried; several fractionations of the product of the reaction were made *in vacuo*. These details are fully discussed in a previous paper.[2] Under the conditions described therein yields as high as 87.4% were obtained of pure α-phenylbutyronitrile of boiling point 114–115° (uncorr.) at 16 mm. Equations 8–13, expressing this reaction and those to be described subsequently, are to be found in the introduction.

2. α-Phenylbutric Methylimino Ester Hydrochloride, $(C_6H_5)(C_2H_5)CHC(:NH_2Cl)(OCH_3)$.—In general the procedure developed by Stieglitz and Carr[6] for the

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[5] Bodroux and Taboury, *Bull. soc. chim.*, [7] **4,** 666 (1910).

[6] Carr, unpublished Doctor's Dissertation, University of Chicago, 1910.

preparation of imino ester hydrochlorides was followed. α-Phenylbutyronitrile was converted into its methyl imino ester hydrochloride by treatment of the nitrile with absolute methyl alcohol and hydrogen chloride in dry ether. It is of the utmost importance that all apparatus and reagents used should be thoroughly dry. The reaction vessel was fitted with a two-holed stopper holding an inlet and an outlet tube, the latter protected from moisture by means of a large calcium chloride tube. Nitrile (1 mole) and absolute methyl alcohol ($1^1/_4$ moles) were introduced into this vessel through a pipet inserted into the outlet tube. Two volumes of ether were siphoned into the vessel through the outlet tube from the container in which it was kept in quantity over bright sodium. Hydrogen chloride, dried by being led first through concentrated sulfuric acid and then over phosphorus pentoxide, was brought into the reaction mixture in a rapid stream until the solution was saturated, the temperature of the mixture being kept at −5° to −10° during the passage of the gas. When saturation was complete the flow of gas was interrupted, the inlet tube of the reaction vessel was tightly plugged, and the reaction mixture was allowed to stand for two hours at −10°. At the end of this time the stopper was removed from the reaction vessel; the vessel was brought into a vacuum desiccator which was charged with soda lime and phosphorus pentoxide and the desiccator placed in a refrigerator overnight without evacuation. The next day the desiccator was brought over a suction pump for an hour to remove the excess of methyl alcohol, as well as ether. The reaction vessel was then removed from the desiccator, 200 cc. of dry ether was introduced into the vessel and it was quickly closed by means of a piece of rubber dam tied tightly over the opening, a stirring rod being inserted in the rubber. When the contents of the tube were stirred, white, granular crystals formed. These were washed with a mixture of dry ether and dry benzene (1:1), the wash solution being siphoned into and out of the reaction vessel. The crystals were then placed in a desiccator over soda lime and phosphorus pentoxide. They showed a melting point of 92°, and decomposed slightly on standing. Their purity was shown by analysis.

Anal. Subs., 0.1200, 0.1244: 5.64, 5.82 cc. of 0.1 *N* $AgNO_3$; factor, 0.9923. Calcd. for $C_{11}H_{16}NOCl$: Cl, 16.60. Found: 16.53, 16.45.

The yield of hydrochloride from 26.5 g. of nitrile was 30 g., or 76.9%.

3. **α-Phenylbutyric Methyl Ester,** $(C_6H_5)(C_2H_5)CH(CO_2CH_3)$.—α-Phenylbutyric methyl ester was obtained by the hydrolysis of α-phenylbutyric methyl imino ester hydrochloride. For this purpose the hydrochloride (20 g.) was dissolved in 100 cc. of water at 40°, whereupon the solution clouded due to the formation of α-phenylbutyric methyl ester. The temperature of 40° was maintained for ten minutes and the solution was then cooled and extracted with ether, the ether layer being decanted from the water, which was again warmed, cooled and extracted with ether. The ether extracts were combined, dried over fused calcium chloride, and the ether was removed by distillation. The oil which remained was distilled, boiling at 225–226° (uncorr.). When allowed to stand for a time in a desiccator this oil solidified and the white, transparent needles which formed melted at 77–78°. Neure,[7] who first prepared the ester, states that it is an oil of boiling point 228°; our product was evidently purer than his. The ester was identified by its hydrolysis products, α-phenylbutyric acid of melting point 43°, and methyl alcohol, and by analysis.

Anal. Subs., 0.1161: CO_2, 0.3161; H_2O, 0.0845. Calcd. for $C_{11}H_{14}O_2$: C, 74.11; H, 7.92. Found: C, 74.24; H, 8.09.

The yield of ester obtained by hydrolysis of the hydrochloride (20 g.) was 15 g. or 90.3%.

4. **α-Sodium-α-phenylbutyric Methyl Ester,** $(C_6H_5)(C_2H_5)C{:}C(OCH_3)(ONa)$.—

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[7] Neure, *Ann.*, **250**, 155 (1889).

α-Sodium-α-phenylbutyric methyl ester was prepared by the treatment of α-phenylbutyric methyl ester with sodium in dry ether. The apparatus and reagents used were carefully dried. The sodium was used in the form of minute globules, prepared by a method outlined in a previous paper.[2] Sodium (1.5 g.) was prepared for use in this way in a flask fitted with a stopper carrying a dropping funnel and a reflux condenser holding at the top a calcium chloride tube. Sodium-dried ether (100 cc.) was then siphoned into the flask through the dropping funnel and 12.8 g. of α-phenylbutyric methyl ester (10% in excess of the calculated amount) dissolved in ether was dropped rather slowly into the flask. Shortly a pure white, amorphous precipitate formed, hydrogen was evolved and the ether boiled. The flask and contents were shaken frequently. The sodium was practically all consumed in two hours. The reaction mixture was allowed to stand overnight and was then refluxed for an hour over a water-bath. By this time large quantities of the white precipitate had formed. The supernatant solution was decanted from it and the precipitate was washed several times by decantation with dry ether, care being used to protect it from moisture and carbon dioxide. The salt was then brought onto a Büchner funnel and washed briefly with dry ether, while suction was applied, then removed quickly to a vacuum desiccator. Analysis for sodium showed the salt to be pure.

Anal. Subs., 0.1080, 0.0846: Na_2SO_4, 0.0375, 0.0294. Calcd. for $C_{11}H_{13}O_2Na$: Na, 11.49. Found: 11.23, 11.24.

The yield of the salt from 1.5 g. of sodium and 12.8 g. of α-phenylbutyric methyl ester was 11 g., or 86.9%, calculated in terms of the sodium used. To obtain the salt in pure form it was found necessary to use an excess (about 10%) of α-phenylbutyric methyl ester, so that the last traces of sodium would react, contamination of the salt with particles of the metal being thus avoided. The excess of ester used was readily recovered from the ether filtrate.

α-Sodium-α-phenylbutyric methyl ester is decomposed by water and all acids into α-phenylbutyric methyl ester. Treatment of the salt with cold 50% sulfuric acid produces this ester in 85% yield.

5. **Phenylethylmalonic Methyl Ester,** $(C_6H_5)(C_2H_5)C(CO_2CH_3)_2$.—Phenylethylmalonic methyl ester was prepared by the treatment of α-sodium-α-phenylbutyric methyl ester with chloroformic ester in ether. All apparatus and reagents were thoroughly dried before use. α-Sodium-α-phenylbutyric methyl ester (10 g.) was suspended in 100 cc. of dry ether. The reaction flask was then closed with a stopper carrying a dropping funnel and a reflux condenser protected at the top by a calcium chloride tube. Chloroformic methyl ester (1.5 g.) was dropped slowly into the flask, whereupon a vigorous reaction occurred, the ether boiled, and a granular precipitate of sodium chloride appeared. When all the chloroformic ester had been added the reaction mixture was heated for an hour over the water-bath and then allowed to stand overnight. The next day small portions of water were added to dissolve the sodium chloride. The ether layer was decanted, the water solution remaining was extracted several times with ether, and these ether extracts were combined with the main ether solution, the whole being dried over granulated calcium chloride. The ether was removed by distillation and the oil remaining crystallized upon cooling into thick, white plates which showed a melting point of 39–40°, the melting point of phenylethylmalonic methyl ester.[8] A mixture of equal quantities of this product and phenylethylmalonic ester of known purity also melted at 39–40°. The yield of ester from 10 g. of the sodium salt was 10 g., or 84.7%.

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[8] Ref. 3, p. 730; Rising and Zee (ref. 2) obtained the ester in slightly purer form, melting at 39–40°.

Summary

1. A new method of synthesis of phenylethylmalonic methyl ester, an intermediate in the production of pheno-barbital, is described.

2. The yields at all stages of the process are good and the method is the most satisfactory of all those known at present.

3. The isolation of the salt, α-sodium-α-phenylbutyric methyl ester, an intermediate product in this synthesis, is discussed. The behavior of the salt indicates that it exists in tautomeric forms, of structures $[(C_6H_5)(C_2H_5)C{=}C(OCH_3)O^-]Na^+$ and $[(C_6H_5)(C_2H_5)C^-(CO_2CH_3)]Na^+$.

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

A NEW MICRO PHOSPHORUS DETERMINATION

BY ADALBERT ELEK

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Various methods for the micro determination of phosphorus in organic substances have been described. In most cases, however, the methods used lack either simplicity or accuracy.

The procedure as described by Lieb,[1] though accurate, is inconvenient inasmuch as it involves washing the combustion tube and boiling the boat in dilute nitric acid. The method described by Lieb and Wintersteiner[2] and by Josephson and Sjörberg[3] was found to yield low results for at least one substance, namely, for thymus nucleic acid.

The new method described in this paper eliminates the undesirable features of the methods cited.

Experimental Part

A sample of 3–6 mg. is weighed by difference into a silver crucible of approximately 18 mm. lower diameter, 33 mm. upper diameter and 40 mm. in height. About 0.2 g. of potassium nitrate and 1 g. of potassium hydroxide are then added and the mixture is fused by heating the upper part of the crucible over a small flame with a slow, rotating motion to prevent spattering. In the course of about two to three minutes the fusion is complete, as shown by the clearness of the melt. The crucible is covered and allowed to cool on a copper block. The cooling requires about four minutes. A slight pressure on the walls of the crucible loosens the cake, which is then easily transferred into a large Pyrex test-tube of about 30 mm. diameter and 200 mm. in length. The crucible is then washed 2–3 times with a small quantity of water and the washings are transferred to the test-tube. Enough nitric acid (prepared according to Lieb)[1] is then added to make the volume up to 15 cc. The solution is placed in a boiling water-bath for about ten to fifteen minutes. In some cases the solution is slightly turbid, but on warming in

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[1] Pregl, "Die quantitative organische Mikroanalyse," 2nd ed., Springer (Berlin), **1923**, p. 151.

[2] Lieb and Wintersteiner, *Mikrochemie*, **2**, 78 (1924).

[3] Josephson and Sjörberg, *Svensk Kemisk Tidskrift*, **36**, 267 (1924).