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

A NEW METHOD OF PREPARATION OF PHENYLETHYLMALONIC METHYL ESTER

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Phenylethylmalonic methyl ester, $\mathrm{C_6H_5.C(C_2H_5)(CO_2CH_3)_2}$, is an important intermediate product in the synthesis of the hypnotic phenylethylbarbituric acid, or pheno-barbital, $\mathrm{(C_6H_5)(C_2H_5)\underline{C.CO.NH.CO.NH.CO}}$. The preparation of this hypnotic, important for its use in the treatment of epilepsy, was undertaken in this Laboratory in 1918 as a war measure.[2] The procedure followed at that time is summarized in the following series of equations.

$$\mathrm{C_6H_5.CH_2.CN + CH_3OH + HCl + H_2O \longrightarrow C_6H_5.CH_2.CO_2CH_3 + NH_4Cl} \tag{1}$$

$$\mathrm{C_6H_5.CH_2.CO_2CH_3 + (CO_2CH_3)_2 + CH_3ONa \longrightarrow CH_3O_2C.C(ONa){:}C(C_6H_5)(CO_2CH_3) + 2CH_3OH} \tag{2}$$

$$\mathrm{CH_3O_2C.C(ONa){:}C(C_6H_5)(CO_2CH_3) + H_2SO_4 \longrightarrow CH_3O_2C.CO.CH(C_6H_5)(CO_2CH_3) + NaHSO_4} \tag{3}$$

$$\mathrm{CH_3O_2C.CO.CH(C_6H_5)(CO_2CH_3) \xrightarrow{90^\circ} CO + C_6H_5.CH(CO_2CH_3)_2} \tag{4}$$

$$\mathrm{C_6H_5.CH(CO_2CH_3)_2 + CH_3ONa + C_2H_5I \longrightarrow C_6H_5.C(C_2H_5)(CO_2CH_3)_2 + CH_3OH + NaI} \tag{5}$$

$$\mathrm{C_6H_5.C(C_2H_5)(CO_2CH_3)_2 + (NH_2)_2CO \longrightarrow (C_6H_5)(C_2H_5)\underline{C.CO.NH.CO.NH.CO}} \tag{6}$$

The preparation of phenylethylmalonic methyl ester by means of the ethylation of phenylmalonic methyl ester, as expressed in Equation 5, was accomplished satisfactorily, except that the yield obtained (76% of crude material) was not as high as was desired. Since the plan outlined constitutes the basis for the commercial production of pheno-barbital, the importance of obtaining good yields in each intermediate step of the process is apparent.

The desirability of obtaining phenylethylmalonic methyl ester in better yield led to the study of a number of other methods for its preparation. Of these, the one expressed in the equations which follow has proved particularly successful and interesting.

$$\mathrm{C_6H_5.CH_2.CN + NH_2Na + C_2H_5I \longrightarrow C_6H_5.CH(C_2H_5)(CN) + NaI + NH_3\uparrow} \tag{7}$$

$$\mathrm{2\ C_6H_5.CH(C_2H_5)(CN) + 2Na \longrightarrow C_6H_5.CNa(C_2H_5)(CN) + H_2\uparrow} \tag{8}$$

$$\mathrm{C_6H_5.CNa(C_2H_5)(CN) + Cl.CO_2CH_3 \longrightarrow C_6H_5.C(CO_2CH_3)(C_2H_5)(CN) + NaCl} \tag{9}$$

$$\mathrm{C_6H_5.C(CO_2CH_3)(C_2H_5)(CN) + CH_3OH + HCl \longrightarrow C_6H_5.C(CO_2CH_3)(C_2H_5)C({:}NH_2Cl)(OCH_3)} \tag{10}$$

$$\mathrm{C_6H_5.C(CO_2CH_3)(C_2H_5)C({:}NH_2Cl)(OCH_3) + HOH \longrightarrow C_6H_5.C(C_2H_5)(CO_2CH_3)_2 + NH_4Cl} \tag{11}$$

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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 Stieglitz, This Journal, **40**, 725 (1918).

In the course of the preparative work just outlined, some significant observations were made. The treatment of α-phenylbutyronitrile with sodium in dry ether led to the formation of a sodium derivative, α-phenyl-α-sodiumbutyronitrile (Equation 8). A study of the properties of this salt showed it to be exceedingly sensitive to traces of moisture and of carbon dioxide, as was expected. When treated with acid, the salt forms hydrocyanic acid and some other product, the identity of which has not yet been determined. We are continuing the study of this decomposition. The reaction of the sodium salt with acid suggests the structure $C_6H_5.C(C_2H_5):C:N.Na$ for the more stable form of the salt. A tautomeric carbide, $C_6H_5.CNa(C_2H_5)(CN)$, presumably takes part in reactions in which such groups as alkyl and $—CO_2R$ are introduced into the molecule. The preparation and behavior of similar salts is to be studied.

The behavior of α-phenylbutyronitrile shown in Equations 8–9 indicates that the hydrogen atom carried by the tertiary carbon atom of the molecule may be readily replaced. The tertiary nitrile, α-phenyl-α-cyanobutyric methyl ester, formed from the sodium salt of α-phenylbutyronitrile and chloroformic methyl ester (Equation 9), shows the usual absorption reactions of nitriles (Equations 10–11) in spite of the close proximity of a carbon atom carrying three radicals. Apparently, there is a minimum of steric interference with the substitution reactions of the secondary nitrile, α-phenylbutyronitrile, and with the usual absorption reactions of the nitrile group in the case of the tertiary nitrile.

In the light of the results so far obtained by us, it seems altogether likely that chloroformic methyl ester will prove a useful agent for introducing the group $—CO_2R$ into molecules which are closely related to α-phenylbutyronitrile. We are therefore continuing work along lines similar to those which have been discussed. The preparation of α-phenyl-α-sodiumbutyric methyl ester, $C_6H_5.CNa(C_2H_5)(CO_2CH_3)$ (or the tautomeric enol salt), is now under way from sodium and α-phenylbutyric methyl ester, which was first prepared by Singleterry[3] from α-phenylbutyric methylimido ester hydrochloride. The pure sodium salt, when obtained, will be treated with chloroformic methyl ester to form the product phenylethylmalonic methyl ester. Such a method of obtaining phenylethylmalonic methyl ester, if successful, would be materially simpler than any known at present.

Experimental Part

1. **α-Phenylbutyronitrile,** $C_6H_5.CH(C_2H_5)(CN)$.—α-Phenylbutyronitrile was prepared according to the method of Bodroux and Taboury.[4] The most satisfactory results were obtained in both yield and purity of the product when extreme precautions were taken to have all reagents and

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[3] Singleterry, *Master's Dissertation*, University of Chicago, **1926**.

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

apparatus used in the preparation thoroughly dry. The purity of the product of the reaction was further insured by the use of benzyl cyanide of known purity. The sodium amide was finely powdered before use, care being taken to protect it from moisture while it was being broken up in a mortar. The crude product of the ethylation is a mixture of unchanged benzyl cyanide, α-phenylbutyronitrile and α-phenyl-α-ethylbutyronitrile in proportions which vary particularly with the speed with which benzyl cyanide is dropped into dry ether in the presence of sodium amide to convert it into a sodium salt. When the nitrile is introduced rather slowly it seems to react with the sodium amide more completely to form a monosodium salt, thus insuring the greatest possible yield of the mono-alkylated benzyl cyanide. The fraction boiling at 114–115° (uncorr.) at 16 mm. was found by analysis to be pure α-phenylbutyronitrile.

Anal. Subs., 0.9543: 13.68 cc. of 0.5 *N* HCl. Calcd. for $C_{10}H_{11}N$: N, 9.65. Found: 9.63.

The yield obtained was 65 g. of pure α-phenylbutyronitrile from 60 g. of benzyl cyanide, or 87.4%. Equations 7–11, expressing this reaction and those to be described subsequently, are to be found in the introduction.

2. **α-Phenyl-α-sodiumbutyronitrile,** $C_6H_5.CNa(C_2H_5)(CN)$ or $C_6H_5(C_2H_5)$-$C:C:NNa$.[5]—α-Phenyl-α-sodiumbutyronitrile was prepared by the treatment of α-phenylbutyronitrile with sodium in dry ether. The sodium was brought into a form convenient for use in the following way. Five g. of bright sodium in freshly cut pieces was placed in a dry flask and covered with 30 cc. of dry xylene. The flask was placed under a reflux condenser, the top of which was fitted with a calcium chloride tube. The flask was then warmed gently until the sodium melted, at about 96°, after which the metal floated upon the surface of the xylene. The flask was then removed from the condenser, corked, and while still hot was shaken vigorously until the sodium was divided into small globules. When the contents of the flask were cold, the xylene was decanted and the sodium quickly washed several times with dry ether.

The flask containing the sodium was then fitted with a stopper carrying a dry dropping funnel and a dry reflux condenser which held at the top a calcium chloride tube. One hundred cc. of dry ether was introduced into the flask through the dropping funnel, and 35 g. of α-phenylbutyronitrile (1% in excess of the amount calculated for 5 g. of sodium) was dropped rather slowly into the ether. Shortly a yellow amorphous precipitate collected upon the sodium and upon the bottom of the flask. At the same time hydrogen was evolved. The ether boiled for a time and slowly became dark red. The reaction mixture was allowed to stand for two days, the flask being shaken frequently. At the end of this time the flask was heated over a water-bath for one hour. When the contents of the flask had cooled, the heavy precipitate of sodium salt was quickly brought upon a filter and washed thoroughly with cold, dry ether, care being used to protect it from moisture and carbon dioxide. The salt was then placed in a vacuum desiccator to remove traces of ether. Analyses for sodium showed the salt to be pure.

Anal. Subs., 0.2577, 0.1336: Na_2SO_4, 0.1098, 0.0567. Calcd. for $C_{10}H_{10}NNa$: Na, 13.76. Found: 13.80, 13.75.

The yield of the salt from 5 g. of sodium and 35 g. of α-phenylbutyronitrile was

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[5] See the introduction.

29 g., or 79.8%, calculated in terms of the sodium used. To obtain the salt in pure form it was found necessary to use a slight excess of α-phenylbutyronitrile so that the last traces of sodium would be used up in the reaction, contamination of the salt with particles of sodium being thus avoided. The behavior of the salt towards moisture and acids has been discussed in the introduction.

3. **α-Phenyl-α-cyanobutyric Methyl Ester,** $C_6H_5.C(C_2H_5)(CN)(CO_2CH_3)$.—α-Phenyl-α-cyanobutyric methyl ester was prepared by the treatment of α-phenyl-α-sodiumbutyronitrile with chloroformic ester in dry ether. To this end 100 cc. of dry ether was placed in a dry flask and 10 g. of α-phenyl-α-sodiumbutyronitrile was suspended in the ether. The flask was then closed with a stopper carrying a dry dropping funnel and a reflux condenser which was protected at the top by means of a calcium chloride tube. Chloroformic methyl ester (6 g.) was dropped slowly into the flask, whereupon a vigorous reaction occurred, with evolution of considerable heat. The mixture was allowed to stand overnight, during which time the yellow sodium salt gradually disappeared and sodium chloride was precipitated. When the yellow salt was entirely transformed the flask and contents were heated on the water-bath for an hour. A little water was added to the contents of the flask to dissolve the sodium chloride, and the ether layer was then decanted. The water solution remaining was extracted several times with ether, the ether washings were combined with the main ether extract and the whole was dried over fused calcium chloride. When the ether was removed by distillation a red oil remained, most of which boiled at 180–192° (uncorr.), at 17 mm. The product of distillation, pale yellow in color, was shown by analysis to be pure α-phenyl-α-cyanobutyric methyl ester.

Anal. Subs., 0.1977, 0.0857: N_2 (over 50% KOH), 12.70 (22.5°, 744.7 mm.), 5.50 cc. (25°, 753.8 mm.). Calcd. for $C_{12}H_{13}O_2N$: N, 6.90. Found: 7.12, 7.11.

The yield obtained from 10 g. of α-phenyl-α-sodiumbutyronitrile was 8 g. of the cyano ester, or 66%.

4. **Phenylethylmalonic Monomethyl Ester Methylimido Ester Hydrochloride,** $C_6H_5.C(C_2H_5)(CO_2CH_3)C{=}NH_2Cl.OCH_3$.—For the conversion of α-phenyl-α-cyanobutyric methyl ester into its imido ester hydrochloride, molecular quantities of α-phenyl-α-cyanobutyric methyl ester and absolute methyl alcohol were placed in a dry vessel with two volumes of dry ether, and a rapid stream of dry hydrogen chloride was passed into the mixture. In general, the procedure developed by Stieglitz and Carr[6] for the preparation of imido ester hydrochlorides was followed. The reaction vessel was fitted with a two-hole stopper holding an inlet and an outlet tube. The latter was protected from moisture by means of a large calcium chloride tube. All apparatus and reagents used were dried with the utmost care. The alcohol and cyano ester were introduced into the reaction vessel through a pipet inserted into the outlet tube. The ether was siphoned directly into the vessel from the container in which it is kept in quantity over bright sodium. The hydrogen chloride was dried by being led first through concentrated sulfuric acid and then over phosphorus pentoxide. Before the gas was brought into the reaction mixture, the latter was cooled to —5° to —10° and was kept at that temperature while being saturated with the gas. When saturation was complete, white needle crystals of the imido ester hydrochloride were forming in the reaction mixture. The passage of the hydrogen chloride was interrupted and the inlet tube of the reaction tube tightly plugged. The mixture was kept at —5° for two hours, during which time more crystals formed. The vessel was then transferred to a vacuum desiccator charged with phosphorus pentoxide and soda lime and the desiccator was kept at about 40° overnight. The next day it was placed over a water pump and the ether was drawn off slowly during half an hour. The reaction vessel was then removed from

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

the desiccator and closed by means of a piece of rubber dam tied tightly over the opening, a stirring rod being inserted in the center of the rubber. The contents of the vessel was viscous, and the crystals formed previously had settled to the bottom. Upon being stirred, the viscous mass became crystalline. The crystals were washed rapidly with a cold mixture of dry ether and benzene, the wash solution being siphoned into and out of the reaction vessel. The crystals were placed in a vacuum desiccator over phosphorus pentoxide and soda lime. They showed a melting point of 102° and were somewhat sticky. Analysis for chlorine was made when the crystals had remained for some time in a vacuum over soda lime. The analysis showed the substance to be practically pure imido ester hydrochloride.

Anal. Subs., 0.2385, 0.1505: 93.65, 59.60 cc. of 0.01 *N* $AgNO_3$. Calcd. for $C_{13}H_{18}NO_3Cl$: Cl, 13.05. Found: 13.31, 13.42.

The yield of hydrochloride from 5 g. of cyano ester was 5.5 g., or 82%.

5. **Phenylethylmalonic Methyl Ester,** $C_6H_5.C(C_2H_5)(CO_2CH_3)_2$.—The hydrolysis of phenylethylmalonic monomethyl ester methylimido ester hydrochloride led to the formation of phenylethylmalonic methyl ester. For this purpose, 5 g. of the imido ester hydrochloride was dissolved in 50 cc. of water at 40°. The solution clouded at once due to the formation of the oily dimethyl ester. The temperature of 40° was maintained for ten minutes, and the solution was then cooled and extracted with ether and the ether layer decanted. The water residue was again warmed to 40°, cooled and extracted with ether. The combined ether extracts were dried over fused calcium chloride and the ether removed by distillation. The remaining oil crystallized into white needles having the odor of phenylethylmalonic methyl ester, and showed after recrystallization from low-boiling ligroin a melting point of 39.5° (uncorr.). This melting point is slightly higher than that reported previously by Rising and Stieglitz[2] for the same compound. The crystals obtained when a ligroin solution of the ester was allowed to evaporate spontaneously in a desiccator were thick, transparent plates.

Anal. Subs., 0.1395: CO_2, 0.3383; H_2O, 0.0868. Calcd. for $C_{13}H_{16}O_4$: C, 66.07; H, 6.83. Found: C, 66.13; H, 6.96.

The yield of ester from 5 g. of the hydrochloride was 3.5 g., or 81.4%.

Summary

1. A new method for the preparation of phenylethylmalonic methyl ester, an intermediate product in the synthesis of the hypnotic phenobarbital, is described.

2. The yields at all stages of the process were good, and these could undoubtedly be increased if the reactions were carried out on a larger scale. The method seems, therefore, to be a promising one for commercial adaptation.

3. In the course of the reactions studied an interesting sodium salt, α-phenyl-α-sodiumbutyronitrile, was prepared, the behavior of which suggests the structure $C_6H_5.C(C_2H_5){=}C{=}NNa$.

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