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THE SYNTHESIS OF ETHYL-(1-METHYLBUTYL)- AND ETHYLISOAMYL-MALONURIC ACIDS[1]

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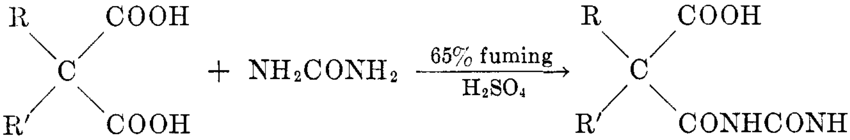
In connection with some studies on the metabolic fate of ethyl-(1-methylbutyl)barbituric acid (Pentobarbital) and ethylisoamylbarbituric acid (Amytal), it was necessary to prepare the corresponding malonuric acids for isotope dilution experiments. The only dialkylmalonuric acids with unsubstituted nitrogen atoms encountered in a literature survey were the diethyl and the di-*n*-propyl derivatives. Fischer and Dilthey (1) prepared these compounds by the reaction of the appropriate dialkylmalonic acids with urea in 70% fuming sulfuric acid. Diethylmalonuric acid was also synthesized by Einhorn (2) through the addition of diethylmalonyl chloride to a cold solution of urea in pyridine.

A modification of the procedure of Fischer and Dilthey proved to be satisfactory for the preparation of ethyl-(1-methylbutyl)malonuric acid. The product was obtained in 50% yield and consisted of only one of the two possible diastereoisomers. The identity of the malonuric acid was established by decarboxylation; a quantitative yield of the acetyl urea was obtained. The methyl ester and the methylammonium salts were prepared as further derivatives of the acid. Treatment of the methyl ester with alkali converted it to the corresponding barbituric acid.



The Fischer method was not as satisfactory for the synthesis of ethylisoamylmalonuric acid. It was possible on occasion to obtain the pure compound, but in low yield; at other times under the same conditions no malonuric acid could be isolated. A search for better experimental conditions was unsuccessful.

Fischer and Dilthey (1) found that their procedure could not be used for the synthesis of dimethylmalonuric acid. In fuming sulfuric acid, dimethylmalonic acid and urea react to form dimethylbarbituric acid. In the preparation of diethyl-, ethyl-(1-methylbutyl)-, and ethylisoamyl-malonuric acids in fuming sulfuric acid, no trace of the barbituric acids was encountered. In order to decide whether barbituric acids were formed from the malonic acids and urea and subsequently hydrolyzed to the malonuric acids during the isolation procedures, diethyl- and ethylisoamyl-barbituric acids were treated with fuming sulfuric acid. The only isolable products were the unchanged barbituric acids.

No success was achieved in attempts to prepare ethyl-(1-methylbutyl)- and ethylisoamyl-malonuric acids by the method of Einhorn (2). The reaction of the

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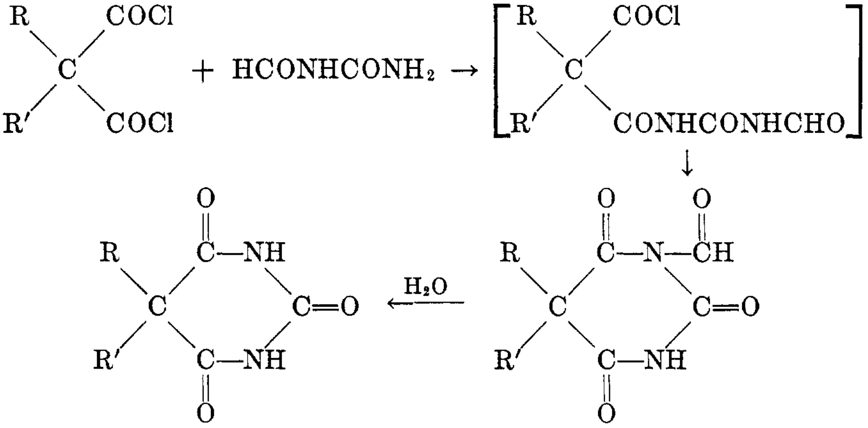
malonyl chlorides with cold suspensions of urea in pyridine yielded only brown oils from which no crystalline compounds could be isolated. When the reaction mixtures were heated, the barbituric acids were obtained.

It was of interest to see whether the formation of the barbituric acid could be blocked by causing a malonyl chloride to react with an acyl urea instead of urea. Formylurea was considered attractive for this purpose because of the possibility that the formyl group could be removed later by oxidation or hydrolysis. Treatment of this compound with ethylisoamylmalonyl chloride yielded a product containing the barbituric acid ring. Under anhydrous conditions it was possible to isolate a chloride-free substance which was probably the formylbarbituric acid. It resisted purification but yielded pure ethylisoamylbarbituric acid when treated with water.



EXPERIMENTAL[2]

Ethyl-(1-methylbutyl)malonic acid. Dialkylmalonic esters are very resistant to hydrolysis. A mixture of 100 g. of ethyl-(1-methylbutyl)malonic ester,[3] 150 g. of potassium hydroxide, 140 ml. of water, and 80 ml. of ethanol was stirred and heated under reflux for fifteen hours. Water was added to dissolve crystals which separated upon cooling. The solution was extracted with ether to remove unchanged ester, made acid to Congo Red, and again extracted with ether. The ether solution was washed with a little water and dried with sodium sulfate. Evaporation of the solvent gave an oil which would not crystallize on long standing. Trituration of the oil with ligroin yielded 54 g. of a white crystalline solid, m.p. 107–109°. After recrystallization from water it melted at 118–119°.

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.37; H, 8.97; M. W., 202.
Found: C, 59.37; H, 8.86; M. W., 202.

The molecular weight was determined by titration of the acid as a monobasic acid with sodium hydroxide using a *p*H meter with a glass electrode.

Ethyl-(1-methylbutyl)malonuric acid. The procedure was similar to that used by Fischer and Dilthey (1) for diethylmalonuric acid. Four grams of ethyl-(1-methylbutyl)malonic acid and 2 g. of urea were ground together in a mortar and the mixture added in small portions with constant stirring over a period of 20–30 minutes to 5 ml. of 65% fuming sulfuric acid cooled to −10 to −15°. The thick brown mixture was kept in the ice-salt bath

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[2] All melting points were taken with a Fisher-Johns apparatus.

[3] This compound was kindly supplied by Dr. D. L. Tabern of the Abbott Laboratories.

until all the ice had melted (if it was removed from the bath too soon, it decomposed spontaneously). It was then heated to 60–70° for ten minutes; during this period there was considerable evolution of gas. After cooling, the mixture was poured into 60 ml. of ice-water. A thick, brown oil separated. The mixture was extracted with ether; almost all of the color remained in the water phase. The ether was washed with a small amount of water and then extracted with 10% sodium carbonate solution. Neutralization of the alkaline extract yielded 2.6 g. of a white crystalline solid, m.p. 137–139° with evolution of carbon dioxide. The compound was purified by dissolving it in chloroform and precipitating with ligroin; m.p. 144–145° with evolution of carbon dioxide. The melting point depended very much on the rate of heating; rapid heating of an analytical sample gave much higher values (144–145°) than slow heating (127–128°).

Anal. Calc'd for $C_{11}H_{20}N_2O_4$: N, 11.47. Found: N, 11.54.

Evaporation of the ether extract gave 0.7 g. of a white crystalline solid, m.p. 77–88°. It was dissolved in ether and precipitated with ligroin to yield 0.3 g. of a compound melting at 91–92°; the melting point of a mixture with ethyl-(1-methylbutyl)acetamide[3] was 91–93°. From the filtrates a product melting at 60–75° was obtained; presumably this substance contained ethyl-(1-methylbutyl)acetylurea (*cf.* 1), but this compound could not be isolated from the mixture.

The preparation of the malonuric acid was repeated with consistent results. In one experiment carried out on a five-times larger scale the yield was 46%.

Decarboxylation of ethyl-(1-methylbutyl)malonuric acid. The malonuric acid (300 mg.) was heated in an oil-bath to 165°. After ten minutes the evolution of gas ceased. Upon cooling, the product crystallized. It was purified by precipitation from alcohol with water, m.p. 135–136°. It was shown to be ethyl-(1-methylbutyl)acetylurea by the melting point of a mixture with an authentic sample.[3] The yield was quantitative.

Methylammonium ethyl-(1-methylbutyl)malonurate. The malonuric acid (500 mg.) was dissolved in ether and treated with an ether solution of methylamine. The flask was scratched with a glass rod to start precipitation of the salt. Yield, 356 mg.; m.p. 133–136°.

Anal. Calc'd for $C_{12}H_{25}N_3O_4$: N, 15.27. Found: N, 15.37.

Methyl ethyl-(1-methylbutyl)malonurate. To a solution of diazomethane in ether was added 2 g. of the malonuric acid. As soon as the evolution of nitrogen ceased, the ether was evaporated in a stream of air to yield a faintly yellow solid. The ester was recrystallized from ligroin and from aqueous methanol; m.p. 109.5–110.5°.

Anal. Calc'd for $C_{12}H_{22}N_2O_4$: N, 10.85. Found: N, 10.85.

Equimolecular amounts of the ester and sodium hydroxide in aqueous alcoholic solution were heated under reflux for one day. The product consisted of ethyl-(1-methylbutyl)-barbituric acid and a small amount of unchanged ester. Other malonuric esters are reported to react in the same manner (3).

Ethylisoamylmalonic acid. The hydrolysis of ethylisoamylmalonic ester[4] was effected under the same conditions as those used for ethyl-(1-methylbutyl)malonic ester. Evaporation of the ether extract gave a 92% yield of the crystalline acid, m.p. 116–118°. After recrystallization from water it melted at 118–119°. Tiffeneau (4) reported m.p. 116–118°; a patent reference (5) gives 120–121°.

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.37; H, 8.97; M. W. 202.
Found: C, 59.35; H, 8.63; M. W. 202.

Ethylisoamylmalonuric acid. A study of conditions for the synthesis of this compound did not indicate a change from those used for ethyl-(1-methylbutyl)malonuric acid. In the most successful experiment a yield of 19% of crude acid melting at 135–137° (with evolution of carbon dioxide) was obtained. When the strength of the fuming sulfuric acid was decreased, the only product was some unchanged malonic acid. In no experiment could the corresponding acetylurea or acetamide be isolated as a by-product. The crude

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[4] This compound was kindly supplied by Dr. E. C. Kleiderer of the Lilly Research Laboratories.

malonuric acid was purified by dissolving it in chloroform and adding an equal volume of ligroin. The pure acid melted at 149–150° with evolution of carbon dioxide; the melting point did not appear to depend on the rate of heating.

Anal. Calc'd for $C_{11}H_{20}N_2O_4$: N, 11.47. Found: N, 11.50.

Decarboxylation of ethylisoamylmalonuric acid. The reaction was effected with a procedure identical with that for ethyl-(1-methylbutyl)malonuric acid. The product was identified as ethylisoamylacetylurea by the melting point of a mixture with an authentic sample.[4]

Methyl ethylisoamylmalonurate. This compound was prepared by the treatment of the malonuric acid with diazomethane; m.p. 74–75°.

Anal. Calc'd for $C_{12}H_{22}N_2O_4$: C, 55.79; H, 8.58.
Found: C, 55.82; H, 8.50.

Ethyl-(1-methylbutyl)- and ethylisoamyl-malonyl chlorides. These compounds were prepared by heating the malonic acids and a four-fold excess of thionyl chloride under reflux for two hours. Following the removal of excess thionyl chloride at atmospheric pressure, the malonyl chlorides were distilled *in vacuo*. No attempt was made to obtain analytically pure compounds.

Ethyl-(1-methylbutyl)malonamide.[5] This compound was obtained by adding a solution of the malonyl chloride in ether to an anhydrous, saturated solution of ammonia in ether at 4°. After two recrystallizations from water the product melted at 147–148°.

Anal. Calc'd for $C_{10}H_{20}N_2O_2$: N, 13.99. Found: N, 13.88.

Treatment of malonyl chlorides with urea in pyridine. Four grams of either ethylisoamyl- or ethyl-(1-methylbutyl)- malonyl chloride was added slowly with stirring to a mixture[6] of 1 g. of urea and 4 g. of dry pyridine at 0°. After two hours the mixture was acidified with hydrochloric acid and diluted with water. The product was a brown oil. When the procedure was conducted at room temperature, the product was also an oil. Heating the reaction mixtures under reflux gave the barbituric acids in good yield.

Formylurea. The procedure of Scheitz, *et al.* (6) was found to give yields of only 10% or less and called for anhydrous formic acid. A method was devised in which commercial formic acid could be used. In a flask attached to a reflux condenser *via* a moisture trap were placed 6 g. of urea, 10.5 g. of technical formic acid (88%), 25 ml. of benzene, and 2 drops of sulfuric acid. The mixture was heated in a water-bath for six hours; during this period 4 ml. of water was collected in the trap. The solution was allowed to stand overnight at room temperature. The white solid which separated was dried in a vacuum desiccator. After one recrystallization from 200 ml. of absolute alcohol the product melted at 166–167°. The yield was 2.8 g. (32% based on urea). Further recrystallization from alcohol raised the melting point to 168–169°; Scheitz reported the same values. Evaporation of the alcoholic filtrates yielded a mixture of urea and formylurea which could not be separated easily.

Anal. Calc'd for $C_2H_4N_2O_2$: N, 31.8. Found: N, 32.0.

In the procedure reported above a 100% excess of formic acid was employed. When only the theoretical amount of formic acid was used the yield was 16%.

Reaction of ethylisoamylmalonyl chloride with formylurea. (a) *In boiling dioxane.* To a suspension of 1.0 g. of formylurea in 25 ml. of purified dioxane (7) was added 3.6 g. of the acid chloride dissolved in 5 ml of dioxane. The solution was heated under reflux for four hours and then allowed to stand at room temperature overnight. Since no solid separated, the dioxane was evaporated to yield an orange, oily solid which was triturated with ligroin and filtered. Yield, 1.9 g.; m.p. 122–135°. The substance contained nitrogen but no chlorine. It was soluble in alcohols and acetone, only slightly soluble in chloroform, ether, and benzene and insoluble in ligroin. However, it was not possible to bring it to analytical

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[5] This compound was prepared by Mr. E. F. Gurnee.

[6] Einhorn stated that he used a solution of 0.6 g. of urea in 2 g. of pyridine. It was found that at room temperature about 30 g. of pyridine was required to dissolve 0.6 g. of urea.

purity. Triturating with water or dissolving in sodium carbonate and acidifying yielded pure ethylisoamylbarbituric acid.

(b) *In dioxane at 60°.* A mixture of 4.3 g. of the acid chloride, 1.6 g. of formylurea, and 75 ml. of purified dioxane was stirred at room temperature for one day. Since none of the solid formylurea appeared to dissolve, the mixture was heated to 60° and stirred at this temperature for another day. All of the formylurea dissolved, and there was no precipitation on cooling. Water (2 ml.) was added and the solution stirred for two hours. Then 5 ml. of 40% sodium hydroxide was added; a white solid separated. The solvent was removed *in vacuo* and sufficient water added to dissolve the residue. The alkaline solution (*p*H 10) was extracted with ether to give 0.4 g. of oil which was not investigated further. It was then brought to *p*H 7.5. A white solid (1.1 g.) precipitated; it was identified as ethylisoamylbarbituric acid. Extraction of the filtrate yielded an additional 0.2 g. of the barbituric acid. The solution was then acidified (*p*H 3) and again extracted with ether; evaporation of the ether yielded 0.3 g. of ethylisoamylmalonic acid.

(c) *In benzene.* The conditions used by Stoughton (8) for the preparation of diacyl ureas were not satisfactory for the reaction of the malonyl chloride with formylurea or acetylurea. The acyl ureas would not dissolve and were recovered unchanged.

SUMMARY

Ethyl-(1-methylbutyl)- and ethylisoamyl-malonuric acids were synthesized by the reaction of the corresponding malonic acids with urea in fuming sulfuric acid. Attempts to prepare these compounds by other methods, both old and new, were unsuccessful.

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