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THE SYNTHESIS OF DIMETHOXYPHTHALIMIDINE-ACETIC ACID

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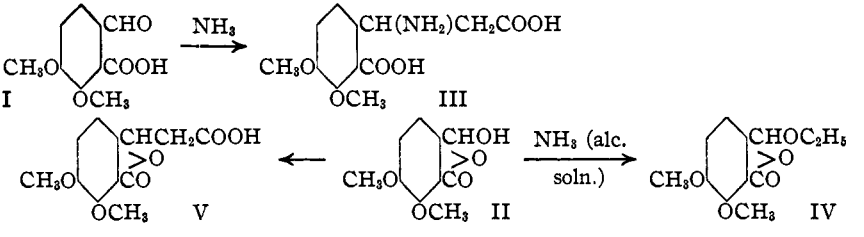
Some time ago[1] we announced a general method for the preparation of aryl-β-amino fatty acids by the condensation of aromatic aldehydes with malonic acid according to the equation

$$RCHO + NH_3 + CH_2(COOH)_2 = RCH(NH_2)CH_2COOH + CO_2 + H_2O$$

The mechanism of this reaction was explained in the paper with E. A. Postovskaja[1d] as a condensation reaction between aldehyde-ammonia and malonic acid

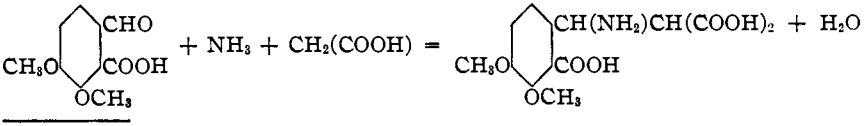
$$RCH(OH)NH_2 + CH_2(COOH)_2 = RCH(NH_2)CH_2COOH + CO_2 + H_2O$$

It was very interesting for many reasons to extend this reaction to an aldehyde carbonic acid. We have chosen for this purpose the most accessible substance of this type, opianic acid. This substance can react in two forms, as a true aldehyde, I, or in its ψ-form as an alcohol, II

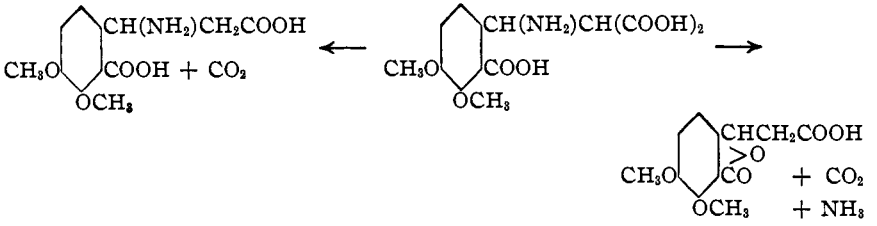


Only the first form could give 3′,4′-dimethoxyphenyl-1′-β-alanine-2′-carbonic acid, III; the second form would give the ψ-ethyl ester of opianic acid, IV, and meconine-acetic acid, V.

Experiment showed that the condensation with opianic acid gave a mixture of the corresponding amino acid and meconine-acetic acid; the formation of the ψ-ethyl ester was not established. It is possible that this condensation takes place in the same course, as we have shown with benzaldehyde and piperonal[1e]

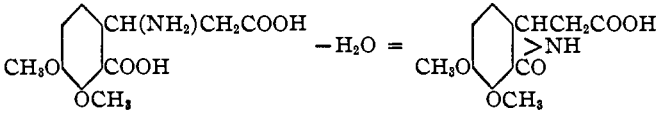


[1] (a) W. M. Rodionow and E. Th. Malevinskaja, *Ber.*, **59**, 2952 (1926); (b) W. M. Rodionow and A. M. Fedorova, *ibid.*, **60**, 804 (1927); (c) *Arch. Pharm.*, **266**, 116–121 (1928); (d) W. M. Rodionow and E. A. Postovskaja, THIS JOURNAL, **51**, 841 (1929); (e) W. M. Rodionow, *ibid.*, **51**, 847 (1929).



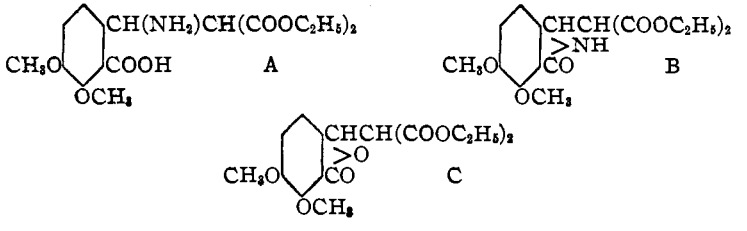
Until now we have not succeeded in isolating the tricarbonic acid and have obtained only the β-aryl-amino acid and meconine-acetic acid. The method of preparation of these substances is a very simple process. Equimolecular proportions of opianic and malonic acids and a slight excess of alcoholic ammonia solution are heated for two to three hours, then dissolved in soda solution, filtered off from small quantities of resinous matter and acidified. The precipitated mixture of both acids is separated with ether (see Experimental Part). The purified dimethoxyphenylalaninecarbonic acid melts over the range of 134–137° uncorr. Further crystallization from alcohol slowly changed the melting point; it became higher and nitrogen determinations gave larger percentages of nitrogen.

It seemed very probable that this acid would give a phthalimide derivative easily (with ring formation and loss of water) in accordance with the equation



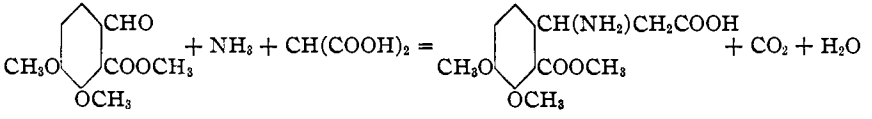
This supposition was proved experimentally. On heating the amino acid above its melting point for one to two hours, evolution of water takes place and the phthalimidine derivative is formed nearly quantitatively. When recrystallized from alcohol this substance melts at 174–175° and gives without difficulty a methyl ester and a nitrosamine derivative.

In our former investigation[1b] we showed that by replacing malonic acid by its ester, one could obtain the ester of β-aryl-β-amino-isosuccinic acid. It was expected that in the case of opianic acid either the derivative with the open chain, opianylmalonic ester (A) or the corresponding phthalimidine derivative (B) would be obtained. Both esters might be accompanied by the meconine-malonic ester (C).



Our attempts to prepare these substances showed that only the meconine-malonic ester, not yet described, was obtained. It is a new confirmation of our former investigations, that the formation of esters of the β-aryl-β-amino-isosuccinic acid does not go with such good yield as the preparation of β-phenylalanine derivatives.

In order to avoid the ring formation we tried to condense the true esters (α-esters) of opianic acid with malonic acid in accordance with the equation



We have found, however, that methyl alcohol is split off and dimethoxy-phthalimidine-acetic acid is formed exclusively.

Experimental Part

β-3′,4′-Dimethoxy-2′-carboxyphenyl-1′-β-aminopropionic Acid, $(CH_3O)_2C_6H_2(COOH)CH(NH_2)CH_2(COOH)$.—A mixture of 20 g. of opianic acid, 40 cc. of 10% alcoholic ammonia solution and 10 g. of malonic acid is heated for two hours on a boiling water-bath with a condenser set for distillation. The condensation product is dissolved in 10% soda solution, filtered from small quantities of tarry matter and acidified with hydrochloric acid. A heavy oil begins to separate from the solution and solidifies very slowly, but it is not advisable to allow it to crystallize as it is much more difficult to purify the solid substance. The acidified mixture of oil and water is immediately shaken with a large quantity of ether, whereby only the meconine-acetic acid goes into solution in the ether layer and gives, after recovery and recrystallization from water, 7.8 g. of substance melting at 165–167°. The yield is about 32.7% of the theoretical amount.

From the water solution the amino acid crystallizes after standing. Complete separation requires from ten to twelve hours, but the time is diminished considerably if mechanical stirring is used. The yield is 13.2 g. (about 55% of the theoretical). The filtrate gives after evaporation 3 g. of heavy oil, a mixture of opianic, meconine-acetic and β-amino acids.

The pure dimethoxyphenylalanine-carbonic acid crystallizes in thin plates from alcohol, is soluble in water and insoluble in ether. It melts at 132–134° with loss of water.

Anal. Calcd. for $C_{12}H_{15}O_6N$: N, 5.21. Found: N, 5.23, 5.28.

3,4-Dimethoxyphthalimidine-acetic Acid.—Three grams of dimethoxyphenylalanine-carbonic acid is heated for two hours on an oil-bath at 140–150°. The substance remaining is recrystallized from alcohol and then melts at 174–175°.

Anal. Calcd. for $C_{12}H_{13}O_5N$: N, 5.57. Found: N, 5.5, 5.6.

Methyl Dimethoxyphthalimidine-acetate, $(CH_3O)_2\overline{C_6H_2CONHCH}COOCH_3$.—Two grams of dimethoxyphthalimidine-carbonic acid is dissolved in methyl alcohol and a current of dry hydrogen chloride is passed into the solution. This requires about two hours. After saturation the mixture is heated for two hours on the water-bath. When the temperature has dropped to 20–25°, the solution is poured into water and the substance which separates is filtered off and dried. The yield is 1.65 g. (about 80% of the theoretical). On recrystallizing from alcohol the ester gives lustrous prisms melting at 141–143°. The substance is easily soluble in alcohol and ether and is insoluble in water.

Anal. Calcd. for $C_{13}H_{15}O_5N$: N, 5.28. Found: N, 5.30.

Preparation of the Nitrosamine of Dimethoxyphthalimidine-carbonic Acid.—Two grams of dimethoxyphthalimidine-carbonic acid is dissolved in 40 cc. of water and mixed with 15 cc. of concd. hydrochloric acid. The solution is cooled with ice and treated little by little with 7 cc. of 10% sodium nitrite solution. After stirring for some time, the precipitated nitrosamine derivative is filtered by suction and crystallized from water. The yield is 1.9 g. (about 90% of the theoretical). The pure product melts at 167° with decomposition; it may be titrated with sodium hydroxide. Neutralization of 0.2 g. of the substance required 7.14 cc. of 0.1 *N* sodium hydroxide.

3,4-Dimethoxyphthalimidine-acetic acid from the α-Methyl Ester of Opianic Acid.—Two and one-half grams of α-ester and 1.2 g. of malonic acid are mixed with 5 cc. of 10% ammonia solution and heated for two hours on a boiling water-bath. The condensation product is dissolved in 10% soda solution and filtered. The filtrate is acidified with hydrochloric acid. The precipitate after crystallization from alcohol melts at 172–174°. The yield is 1.7 g. (about 60% of the theoretical). The melting point of this substance mixed with the dimethoxyphthalimidine-acetic acid of other preparations did not show any depression.

Diethyl Meconine-malonate, $(CH_3O)_2\overline{C_6H_2COOCHCH(COOC_2H_5)_2}$.—A mixture of 20 g. of opianic acid, 15.3 g. of malonic ester and 25 cc. of 14% alcoholic ammonia solution is heated as usual for five hours. The condensation product, a heavy oil, is dissolved in ether and separated from a part of the oil which is not soluble in ether. The ethereal solution is treated with an alcoholic solution of hydrogen chloride and filtered again. The ether solution is then evaporated on the water-bath to a small volume. On cooling the diethyl meconine-malonate separates in large white prisms. The yield of unpurified substance is 26.5 g. (about 75% of the theoretical.) The product is very easily soluble in ether or alcohol and insoluble in water. The diethyl meconine-malonate melts at 74–75° after recrystallization from alcohol.

Anal. Subs., 0.1300: CO_2, 0.2756; H_2O, 0.0673. Calcd. for $C_{17}H_{20}O_8$: C, 57.95; H, 5.68. Found: C, 57.82; H, 5.75.

Summary

The reaction between opianic acid and malonic acid in the presence of alcoholic ammonia solution has been investigated and it was found that the primary condensation product, the β-phenylalanine derivative, forms dimethoxyphthalimidine-acetic acid very easily on heating, and that the condensation of opianic acid with malonic ester does not give an amino derivative but results in the corresponding meconine-malonic ester. The preparation and properties of these compounds are described.

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