Summary

The mechanism of formation of β-aryl-β-amino acids is explained; a general method of preparation of the diethyl esters of β-aryl-β-amino-α-alkyl-ethane-α,α-dicarbonic acids and also of the preparation of β-aryl-β-amino-α-alkylpropionic acids is worked out and many examples of this class of compound are described.

MOSCOW, RUSSIA

[CONTRIBUTION FROM THE TECHNICAL COLLEGE, MOSCOW]

SYNTHESIS OF BETA-ARYL-BETA-AMINO-ETHANE-ALPHA, ALPHA-DICARBONIC ACIDS THE MECHANISM OF KNOEVENAGEL'S SYNTHESIS OF CINNAMIC ACIDS

BY W. M. RODIONOW

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For some time the writer and his collaborators[1] have studied Knoevenagel's synthesis of cinnamic acids[2] and have found that this reaction, in the presence of alcoholic ammonia solution as a catalytic agent, takes a more complicated path than is generally assumed. We have proved that in this reaction besides cinnamic acid derivatives β-aryl-β-aminopropionic acids also are formed in accordance with the following equation

$$RCH\begin{matrix}NH_2\\OH\end{matrix} + CH_2(COOH)_2 = RCH(NH_2)CH_2COOH + CO_2 + H_2O$$

In our paper with E. A. Postovskaja[3] we gave a satisfactory explanation of the mechanism of this reaction and could show that the formation of aryl-β-aminopropionic acids is a condensation reaction between aldehyde-ammonia and malonic acid and not an addition reaction of ammonia to the double bond of the corresponding cinnamic acid.

In our fundamental experiments we have first taken as condensing agent only alcoholic ammonia solution but later, with Mrs. Malevinskaja and Miss V. B. Zenkovich,[4] we replaced the ammonia with monomethylamine and monoethylamine and thus prepared with fair yields β-aryl-β-alkylaminopropionic acids

$$RCHO + NH_2R' + CH_2(COOH)_2 = RCHNHR'CH_2COOH + H_2O + CO_2$$

R′ may be either methyl or ethyl.

We also tried to prepare β-aryl-β-dialkylaminopropionic acids and found that in this case the cinnamic acid derivatives are formed nearly

[1] W. M. Rodionow and E. Th. Malevinskaja, *Ber.*, **59**, 2952 (1926); W. M. Rodionow and A. M. Fedorova, *ibid.*, **60**, 804 (1927); *Arch. Pharm.*, **266**, 126–311 (1928).

[2] Knoevenagel, *Ber.*, **31**, 2596 (1898).

[3] W. M. Rodionow and E. A. Postovskaja, THIS JOURNAL, **51**, 841 (1929).

[4] The unpublished thesis of Miss V. B. Zenkovich from the Laboratory for Alcaloid-Chemistry of the 2. State University of Moscow.

exclusively, accompanied by very small amounts of dialkylaminopropionic acids. We extended our preparations to other amines, especially to piperidine, which is, according to the investigations of many authors, the best catalytic agent for the synthesis of cinnamic acid, and we can state that in this case only cinnamic acids are formed and no traces of β-aryl-β-piperidylpropionic acids can be isolated.

This failure to prepare the piperidyl derivatives has induced us to modify the conditions of our condensations and we carried out this reaction at room temperature. Indications toward such modification had already been given in the very interesting paper of Mannich and Ganz.[5] These authors found that β-aminodicarbonic acids are formed when monosubstituted malonic acids, ammonia, or better still, methylamine or dimethylamine and formaldehyde are mixed together and allowed to stand at ordinary temperature or in ice. After ten to twenty hours a solid mass of crystals separates from the mixture and the corresponding aminodicarbonic acids are formed.

With Miss Holmogorzeva[6] we have worked out a method of preparation of such aryl-β-piperidylethane dicarbonic acids. It is very simple and consists in mixing piperidine and malonic acid at ordinary temperature in an alcoholic solution of the aromatic aldehyde. In the case of benzaldehyde the following reaction takes place

$$C_6H_5CHO + C_5H_{11}N + CH_2(COOH)_2 = C_6H_5CH(NC_5H_{10})CH(COOH)_2 + H_2O$$

and β-phenyl-β-piperidylethane-α,α-dicarbonic acid is formed (details in Experimental Part).

The replacement of benzaldehyde with piperonal gives with a good yield β-piperonyl-β-piperidylethanedicarbonic acid. The attempts to obtain β-aryl-β-amino-ethanedicarbonic acids were also crowned with success when an equimolecular mixture of benzaldehyde, malonic acid and a small excess of alcoholic ammonia solution was allowed to stand for some time. After five to ten minutes a reaction occurred with evolution of heat and on cooling the phenylamino-ethanedicarbonic acid separated as a white crystalline mass.

All compounds thus obtained are stable at ordinary temperature and may even be crystallized from alcohol and water, but on heating (above the melting or decomposition point) these substances undergo a decomposition with evolution of carbon dioxide and sometimes of ammonia.

It was proved further without difficulty that the heating of β-aryl-β-piperidylethanedicarbonic acids gives exclusively the corresponding cinnamic acid, but aryl-β-amino-ethanedicarbonic acids furnish a mixture of cinnamic acid and aryl-β-alanine.

[5] Mannich and Ganz, *Ber.*, **55**, 3487 (1922).

[6] The unpublished thesis of Miss J. A. Holmogorzeva from the Laboratory for Alcaloid-Chemistry of the 2. State University of Moscow.

Further attempts were made in order to obtain β-alkylated β-aryl-β-amino-ethanedicarbonic acids. Two experiments, carried out by Miss Zenkovich, with alcoholic ethylamine solution proved that such condensations are possible, also with a fair yield, and two compounds of this type, β-piperonyl-β-ethylamino-ethanedicarbonic acid and β-phenyl-β-ethylamino-ethanedicarbonic acid are described in the Experimental Part.

It has already been mentioned that these condensations give an excellent yield (80–90% and more of the theoretical amount); but as the formation of β-aryl-aminopropionic acid is always accompanied by cinnamic acid and the maximum yield of either component seldom reaches 50%, it may be assumed that Knoevenagel's synthesis of cinnamic acid is a secondary process: first the formation of arylamino-ethanedicarbonic acid takes place and, second, this compound being unstable on heating, decomposes with evolution of carbon dioxide and ammonia and forms cinnamic acid.

The condensation of malonic acid with amine and aromatic aldehyde occurs then at room temperature or, better, on slight cooling, in the following way

$$RCHO + NH_3 + CH_2(COOH)_2 = RCHNH_2CH(COOH)_2 + H_2O$$

This compound may be isolated with an excellent yield; generally this process is not stopped at this point but the product is warmed further and the arylamino-ethanedicarbonic acid produced decomposes in two directions

$$RCH(NH_2)CH(COOH)_2 = RCH(NH_2)CH_2COOH + CO_2 \quad (1)$$
$$RCH(NH_2)CH(COOH)_2 = RCH{=}CHCOOH + CO_2 + NH_3 \quad (2)$$

The same products also may be obtained either by heating the isolated arylamino-ethanedicarbonic acid above its melting point or by dissolving it in hot water and acidifying with strong mineral acid.

The proportion of the mixture of both acids may be changed by many means: temperature, concentration of mineral acid, the nature of it and many other circumstances have a great influence on the course of this reaction and on the yield of each component.

It is interesting to note that β-aryl-β-amino-ethanedicarbonic acids readily undergo decomposition on heating and on boiling with mineral acids. The aryl-β-aminopropionic acids are more stable but in many cases the warming of their hydrochlorides with sodium acetate also causes elimination of the ammonia molecule and a corresponding cinnamic acid is formed with a fair yield. Another observation which was made is that the condensation with veratric aldehyde does not at ordinary temperatures give the dimethoxyphenylamino-ethanedicarbonic acid. Many attempts in this direction resulted only in the isolation of uninviting, resinous, tarry compounds from which with great difficulty

were recovered the dimethoxycinnamic acids (probably a mixture of *cis* and *trans* isomerides).

Nearly all condensations with piperonal occur with a poorer yield than the same ones with benzaldehyde.

On summarizing all observations described in this paper and in our former investigations, the conclusion may be drawn that not only β-aryl-β-amino-ethanedicarbonic acids but also β-aryl-β-aminomonocarbonic acids are not so stable as the well-known α-amino acids. The existence of methoxy groups and also of methylene-dioxy groups in the benzene ring makes these compounds much more unstable, as was proved by unsuccessful attempts to obtain the dimethoxyphenylamino-ethanedicarbonic acid and smaller yields in many condensations with piperonal.

This work, as a whole, raises an interesting question from the biochemical standpoint. It is not impossible that the protein molecule contains not only α-amino acids but in certain, though indeed very small amounts, also β-amino acids; our methods for their isolation are too crude and the acid hydrolysis at comparatively high temperature decomposes β-amino compounds and leaves unchanged only the more stable α-amino acids.

The same decomposition can take place in living nature, where several enzymes can undertake the role of heat and transform β-amino acids and especially methoxylated compounds into cinnamic acid derivatives, and in this manner may be explained the fact that in many plant oils and drugs are found such acids as ferulic, isoferulic, coffeinic and many other styrolene derivatives.

Experimental Part

This part of the work was carried out by Miss V. B. Zenkovich and Miss J. A. Holmogorzeva; their shares are indicated with their initials (Z. or H.) at each preparation. For many of the analyses and constant assistance I am much indebted to Miss A. M. Fedorova (F.), to whom I also express my thanks in this place.

β-Piperonyl-β-ethylaminopropionic Acid (Z.), $CH_2O_2C_6H_3CH(NHC_2H_5)CH_2CO-OH$.—A mixture of 22 g. of piperonal, 70 cc. of 11% alcoholic ethylamine solution and 18 g. of malonic acid was heated on a boiling water-bath with the condenser set for distillation. The alcohol was distilled off and the yellowish residue dissolved in hot water and acidified with an excess of acetic acid. On cooling, the piperonylacrylic acid separated nearly quantitatively and was filtered off; 19.6 g. (70% of the theoretical). The filtrate was evaporated to dryness and crystallized from alcohol. The piperonyl-ethylaminopropionic acid is insoluble in ether, sparingly soluble in alcohol and easily soluble in water, from which it crystallizes in fine, white needles.

The nitrosamine of this acid, $CH_2O_2C_6H_3CH(NNOC_2H_5)CH_2COOH$, may be prepared easily by treating the hydrochloride of the acid with sodium nitrite solution. It crystallizes very well from water and forms long, fine needles which melt at 136–138°.

Hydrochloride of β-Piperonyl-β-dimethylaminopropionic Acid (Z.), $CH_2O_2C_6H_3CH-$

$[N(CH_3)_2HCl]CH_2COOH$.—Twenty g. of piperonal, 40 cc. of 18% alcoholic dimethylamine solution and 16 g. of malonic acid were heated on a strongly boiling water-bath. After an hour 10 cc. of dimethylamine solution of the same strength was added and the whole warmed until the evolution of carbon dioxide ceased (nine to ten hours). The residue was dissolved in hot water, acidified with hydrochloric acid and the piperonylacrylic acid filtered off and dried; yield 14 g. (about 95% of the theoretical). The filtrate was evaporated to dryness, washed with chloroform and crystallized from alcohol. The acid has no melting point but seems to be chemically pure, as proved by its analysis.

All attempts to prepare in a similar manner the diethylamine compound were unsuccessful and only piperonylacrylic acid was obtained, in nearly quantitative yield.

β-Phenyl-β-amino-ethane-α,α-dicarbonic Acid (F.), $C_6H_5CH(NH_2)CH(COOH)_2$.—Twenty g. of benzaldehyde, 55 cc. of 6% alcoholic ammonia solution and 20 g. of malonic acid are mixed. The reaction occurs instantaneously; in order to prevent the raising of temperature the mixture is allowed to stand for twelve hours in ice water and then the solid is filtered off and washed with ether. The acid is sparingly soluble in cold water and alcohol and insoluble in ether. It crystallizes from alcohol in long lustrous needles.

On heating at 150° the acid decomposes with evolution of carbonic acid and ammonia and gives exclusively cinnamic acid; but on heating with hydrochloric acid 5 g. of the acid gave 2.50 g. of the hydrochloride of β-phenylalanine (*ca.* 50% of theoretical amount) and 1.65 g. of cinnamic acid (*ca.* 40%). The loss of the last compound is only to be explained with its volatility.

β-Phenyl-β-piperidylethane-α,α-dicarbonic Acid (F. and H.), $C_6H_5CH(NC_5H_{10})CH(COOH)_2$.—Four and nine-tenths g. of malonic acid was dissolved in 20 cc. of alcohol, 5 g. of benzene added and then 4 g. of piperidine. The reaction occurs with great evolution of heat and a white, crystalline mass begins to separate almost immediately. The mixture was allowed to stand for twelve hours and then the solid was filtered off and crystallized from alcohol. The acid is easily soluble in hot water, sparingly soluble in cold water and alcohol and insoluble in ether. It crystallizes from alcohol in lustrous plates and from water in long needles. It is interesting to observe that only one carboxylic group of this acid is neutralized by alkali. Calcd. for one carboxyl group of 0.1 g. of acid: 3.6 cc. of 0.1 *N* sodium hydroxide. Found: 3.5.

Five grams of the acid was heated with water and hydrochloric acid; on cooling, 2.2 g. of cinnamic acid (m. p. 132–134°) separated (84.6% of the theoretical). From the filtrate were recovered the whole amount of piperidine and small amounts of cinnamic acid; no traces of β-phenyl-β-piperidylpropionic acid were found.

β-Piperonyl-β-piperidylethane-α,α-dicarbonic Acid (H.), $CH_2O_2C_6H_3CH(NC_5H_{10})CH(COOH)_2$.—Four and three-tenths g. of piperonal, 3 g. of malonic acid and 2.3 g. of piperidine were dissolved in 15 cc. of absolute alcohol and allowed to stand for twenty-four hours. The compound which separated off was crystallized from alcohol, giving lustrous plates. The acid is easily soluble in water, sparingly soluble in alcohol and insoluble in ether. Only one carboxyl group reacts with sodium hydroxide.

β-Phenyl-β-ethylamino-ethane-α,α-dicarbonic Acid (Z.), $C_6H_5CH(NHC_2H_5)CH(COOH)_2$.—Four and one-half g. of benzaldehyde, 13 cc. of 15% alcoholic ethylamine solution and 4.5 g. of malonic acid are mixed; reaction occurs instantaneously, the temperature rises to 50° and after a few minutes the aminodicarbonic acid begins to separate and is filtered off. After standing for some hours a small amount more of the compound may be recovered from the filtrate. The acid may be crystallized from hot alcohol. Lack of time made impossible the repurification and re-analysis of the substance.

TABLE I

ANALYTICAL AND OTHER DATA OF THE ACIDS

β-( )-β-( )-amino-propionic acids	Yield, g.	Yield, %	M. p., °C.	Formula	Analysis, N, % Calcd.	Analysis, N, % Found
Piperonyl, ethyl	9.4	26	198–200	$C_{12}H_{15}O_4N$	5.90	5.60
Piperonyl, dimethyl-[a]	1	2–3	.....	$C_{12}H_{16}O_4NCl$[a]	5.12	5.32
β-( )-β-( )-ethane-α,α-dicarbonic acids						
Phenyl, amino	30.0	76	148	$C_{10}H_{11}O_4N$	6.69	6.98
Phenyl, piperidyl	11.8	91	163–164[b]	$C_{15}H_{19}O_4N$	5.05	5.07
Piperonyl, piperidyl	8	87	150–152[b]	$C_{15}H_{19}O_6N$	4.36	4.42
Phenyl, ethylamino	6	68.8	163–164[b]	$C_{12}H_{15}O_4N$	5.9	6.54
Piperonyl, ethylamino	5.8	58.2	155–157[b]	$C_{13}H_{15}O_6N$	4.98	4.94

[a] Hydrochloride. Calcd.: Cl, 12.95. Found: 13.09.

[b] With decomposition.

β-Piperonyl-β-ethylamino-ethane-α,α-dicarbonic Acid (Z.), $CH_2O_2C_6H_3CH(NHC_2H_5)CH(COOH)_2$.—Five and three-tenths g. of piperonal, 3.85 g. of malonic acid and 12 cc. of 15% alcoholic ethylamine solution were mixed and treated as in the previous experiment. The acid is easily soluble in hot water, less so in alcohol and insoluble in ether; it crystallizes from alcohol in little rods.

Summary

A new explanation of the mechanism of Knoevenagel's synthesis of cinnamic acids is proposed, a method of preparation of aryl-β-amino-ethanedicarbonic acids and their N-substituted derivatives is described and the specific preparation of some compounds of this type and the properties of these compounds are given.

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[CONTRIBUTION FROM THE FAYERWEATHER CHEMICAL LABORATORY OF AMHERST COLLEGE]

REACTION OF CHLORO-ACETIC ACIDS WITH ZINC

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In previous contributions from this Laboratory[1,2] the reaction of trichloro-acetic acid with copper has been discussed and it has been shown that it affords an excellent method for the preparation of dichloro-acetic acid. The reaction is exothermic and the acid was used in benzene solution. During these investigations it was noted that the reaction of trichloro-acetic acid with zinc is also very vigorous, and the present authors, therefore, have studied this reaction. The work has been interrupted by change of residence of the junior author, so it seems advisable to make a brief statement of results so far obtained.

When zinc dust is added to a solution of trichloro-acetic acid in benzene,

[1] Doughty and Freeman, THIS JOURNAL, **44**, 636 (1922).

[2] Doughty and Black, *ibid.*, **47**, 1091 (1925).