3. A quantitative relationship has been derived for the change of the rate of hydrolysis with temperature.

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[CONTRIBUTION FROM THE 2. STATE UNIVERSITY, MOSCOW]

THE MECHANISM OF FORMATION OF BETA-ARYL-BETA-AMINO FATTY ACIDS BY THE CONDENSATION OF AROMATIC ALDEHYDES WITH MALONIC ACID AND ITS DERIVATIVES[1]

BY W. M. RODIONOW AND E. A. POSTOVSKAJA

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In our former investigations[2] we have found that the mechanism of Knoevenagel's synthesis of cinnamic acids[3] in the presence of ammonia is much more complicated than Knoevenagel himself and other authors assumed. We have discovered that besides cinnamic acid derivatives the corresponding amino acid is formed with a good yield, in accordance with the following equation

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

By replacing malonic acid by its esters, A. M. Fedorova[2b] obtained the esters of β-aryl-β-amino-isosuccinic acid

$$RCHO + NH_3 + CH_2(COOC_2H_5)_2 = RCH(NH_2)CH(COOC_2H_5)_2 + H_2O$$

After saponification with hydrochloric acid these derivatives give, quantitatively, the corresponding amino acids.

Two possibilities may be worthy of consideration in order to interpret the mechanism of this reaction

I (a) $RCHO + NH_3 = RCH(OH)NH_2$

(b) $RCH(OH)NH_2 + CH_2(COOH)_2 = RCH(NH_2)CH(COOH)_2 + H_2O$

(c) $RCHNH_2CH(COOH)_2 = RCH(NH_2)CH_2COOH + CO_2$

II (a) $RCHO + CH_2(COOH)_2 = RCH{=}CHCOOH + CO_2 + H_2O$

(The final result of Knoevenagel's reaction)

(b) $RCH{=}CHCOOH + NH_3 = RCHNH_2CH_2COOH$

In favor of the second explanation and against the first may be cited the interesting investigations of Körner and Menozzi,[4] Engel[5] and of

[1] This paper is an abstract of a thesis presented by E. A. Postovskaja in partial fulfilment of the requirements for the degree of Diplom-chemist of the 2. State University of Moscow.

[2] (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**, 116–311 (1928).

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

[4] Körner and Menozzi, *Ber.*, **21**, ref. 86 (1886); *ibid.*, **22**, ref. 735 (1889); *ibid.*, **27**, ref. 121 (1894).

[5] Engel, *Compt. rend.*, **104**, 1805 (1887); **106**, 1677 (1888).

many other authors, who have found that a certain yield of β-amino acids may be prepared by treatment of esters of unsaturated acids with ammonia.

The execution of this reaction is very difficult; it is necessary to warm both components many hours, often many days, under pressure in sealed tubes or in an autoclave. The yields are most unsatisfactory, only Engel having asserted that he obtained excellent yields in his preparations.

The formation of arylamino fatty acids in our case, especially with non-substituted malonic acid, goes very easily at moderate temperature not exceeding 90°, and generally under ordinary pressure. All the conditions of this reaction make the first explanation more probable and it seems that the first consideration is more nearly correct and corresponds better to all the facts.

In order to confirm this supposition, we have made our aldehyde condensations with mono-substituted malonic esters of the general formula $R'CH(COOC_2H_5)_2$, where R′ represents any aliphatic or fatty aromatic radical.

Substances of this type cannot give condensations with loss of water and formation of unsaturated acids capable of additional reactions with ammonia. It may also be mentioned that according to the researches of Claisen[6] the mono-substituted malonic acids in general do not condense with aldehydes.

We have carried out our condensations with methyl-, ethyl- and benzyl-malonic esters. Benzaldehyde and piperonal were employed as second components.

It has already been mentioned that this condensation takes place under ordinary pressure, but with substituted malonic esters the yield increases generally, when the reaction is carried out in sealed tubes; but for this increase it is of much greater importance to have the correct temperature and particularly the correct time of heating.

In most cases the portion of the materials used which does not enter into the reaction remains unchanged; sometimes this condensation is contaminated with the formation of such by-products as diamides of the general formula $RCH(CONH_2)_2$, but we could never find any unsaturated compounds, which affirms the correctness of the first explanation of the mechanism of this interesting reaction.

We have extended our investigations to free methyl-, ethyl- and benzyl-malonic acids and obtained the corresponding amino acids. It is evident that in this case the reaction takes more complicated paths, and as final substances the amino-*mono*-carbonic acids are formed according to the following equation

$$RCHO + R'CH(COOH)_2 + NH_3 = RCH(NH_2)CH(R')COOH + H_2O + CO_2$$

[6] Claisen and Crimson, *Ann.*, **218**, 144 (1883).

The β-aryl-β-amino-α-alkylpropionic acid obtained is identical with the acid that can by prepared by saponification of the corresponding ester, $RCHNH_2C(R')(COOC_2H_5)_2$; R and R′ must naturally be identical in ester and in acid.

The identity of both acids affirms again the correctness of our supposition. This is very important to note, since the use of free mono-substituted malonic acids makes possible many kinds of reaction and besides β-amino acids there also may be formed unsaturated substances, the constitutions of which have not yet been elucidated completely.

The formation of unsaturated acids may be explained in the following manner

$$\text{I} \quad RCHO + CH_3CH(COOH)_2 = RCH{=}CHCH_2COOH + CO_2 + H_2O$$

$$\text{II (a)} \quad RCHO + CH_3CH(COOH)_2 = RCH(OH)CH(CH_3)(COOH)_2$$

$$\text{(b)} \quad RCH(OH)CH(CH_3)(COOH)_2 = RCH{=}C(CH_3)COOH + H_2O + CO_2$$

When a more complicated mono-substituted malonic acid is employed, that is, ethylmalonic acid, a third isomeride may be expected, as the possibility of an aldehyde condensation with the methyl group or with the methylene group of the ethyl radical is not excluded

$$RCHO + H_2C\underset{\displaystyle CH_3}{\underset{|}{C}}H(COOH)_2 = RCH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_2COOH + CO_2 + H_2O$$

If the formation of amino acids may be ascribed to the addition of ammonia to the double linkage of unsaturated acids, we should expect in this case, in accordance with the investigations of Koerner, Menozzi, Engel and others, to obtain α-amino acids but our investigations show that this supposition is not justified.

The preparation of β-amino esters is a very simple operation. Equimolecular proportions of aromatic aldehyde, mono-substituted malonic esters and a little excess of alcoholic ammonia solution are heated on a water- or oil-bath until the alcohol is evaporated; the dry mixture is heated for three to four hours and then dissolved in ether and shaken with sodium bisulfite solution to remove any residue of unreacted aldehyde; the etheric solution is washed with water, dried with sodium sulfate and then treated with dry hydrogen chloride. The hydrochloride of the β-amino-ester separates as a heavy oil that solidifies not too rapidly and crystallizes from alcohol usually in snow-white needles. It is very easy to fix the end-point of the reaction with mono-substituted malonic acids. The mixture is heated until the development of carbon dioxide ceases. The dry residue is dissolved with addition of sodium carbonate in warm water (*ca.* 60°) and treated with ether in order to remove the unreacted aldehyde; the water solution is acidified with hydrochloric acid and the precipitated unsaturated acid is filtered off by suction and washed with water; the filtrate is shaken with ether to free it from unsaturated and fatty acids

and then evaporated on the water-bath; it is finally dried in a desiccator over sulfuric acid *in vacuo*.

The resulting mixture, containing chlorohydrate of β-amino acid, common salt and ammonium chloride, is dissolved in absolute alcohol, filtered by suction from inorganic salts and evaporated on the water-bath. The chlorohydrate of the amino acid nevertheless usually is contaminated with small quantities of inorganic salts and must be twice recrystallized from absolute alcohol. The product is now pure and gives correct analytical results.

Experimental Part

Diethyl β-Phenyl-β-amino-α-methyl-ethane-α,α-dicarbonate Hydrochloride, $C_6H_5CH(NH_2HCl)C(CH_3)(COOC_2H_5)_2$.—In a little, round-bottomed flask fitted with a direct condenser are placed 5 g. of methylmalonic ester, 3 g. of benzaldehyde and 1 g. of alcoholic ammonia solution (12 g. of ammonia in 100 g. of dry alcohol). After evaporating off the alcohol, the mixture is heated on a water-bath for five hours and then dissolved in 100 cc. of dry ether. Dry hydrogen chloride is then passed into the solution. The hydrochloride separates as a heavy oil. The flask is then tightly stoppered and allowed to stand until the oil sets to a mass of crystals, which usually requires one or two days. Double crystallization from hot, dry alcohol gives colorless needles, m. p. 158°; yield, 1.5 g. (about 16%).

A much better yield is obtained with modified conditions, as follows: 10 g. of methylmalonic ester, 6 g. of benzaldehyde and 15 cc. of alcoholic ammonia solution (10 g. of ammonia in 100 g. of alcohol) were heated in a sealed tube on a strongly boiling water-bath for seven hours. The mixture was then placed in a round-bottomed flask, the alcohol distilled off, the residue dissolved in dry ether, filtered from 0.6 g. of methylmalonyldiamide (m. p. 203°) and the hydrochloride of the amino ester precipitated from the filtrate with hydrogen chloride. The product was crystallized from alcohol and dried in a desiccator. 2.8 g. of benzaldehyde and 4.6 g. of methylmalonic acid were recovered from the ethereal solution after filtering off the amino ester. The yield of the ester, calculated on the benzaldehyde actually combined, then increases to 96.6%.

Hydrochloride of Diethyl β-Piperonyl-β-amino-α-methyl-ethane-α,α-dicarboxylate, $CH_2O_2C_6H_3CH(NH_2HCl)C(CH_3)(COOC_2H_5)_2$.—Five g. of diethyl methylmalonate, 4.3 g. of piperonal and 20 cc. of 7% alcoholic ammonia solution were placed in a sealed tube and heated at 150° for five hours on an oil-bath. The mixture was evaporated to dryness, dissolved in dry ether and treated exactly as in the preceding preparation. The oil which separates solidifies very slowly and after several crystallizations the pure substance forms large plain needles. The ethereal solution from which the amino ester has been removed contains only unchanged piperonal and diethyl methylmalonate.

Hydrochloride of Diethyl β-Phenyl-β-amino-α-ethyl-ethane-α,α-dicarboxylate, $C_6H_5CH(NH_2HCl)C(C_2H_5)(COOC_2H_5)_2$.—Five g. of diethyl ethylmalonate, 2.8 g. of benzaldehyde and 1 g. of 12% alcoholic ammonia solution were heated in a sealed tube for five hours on a water-bath The alcohol was then evaporated, leaving in the flask a heavy oil. The oil was dissolved in 100 cc. of ether and filtered from 0.5 g. of an unknown substance, insoluble in ether, which was probably the diamide of ethylmalonic acid (m. p. 199°). The filtrate was treated with dry hydrogen chloride and an oil separated which solidified to fine, white needles. It was crystallized twice from alcohol. The best way of purifying the hydrochloride is by solution in alcohol and precipitation with dry ether. The ethereal alcoholic solution contains unchanged benzaldehyde

(1 g.), diethyl ethylmalonate (1.8 g.) and in small and varying quantities an unidentified substance melting at 74°.

Hydrochloride of Diethyl β-Piperonyl-β-amino-α-ethyl-ethane-α,α-dicarboxylate, $CH_2O_2C_6H_3CH(NH_2HCl)C(C_2H_5)(COOC_2H_5)_2$.—Ten g. of diethyl ethylmalonate, 8 g. of piperonal and 20 cc. of 10% alcoholic ammonia solution were heated at 130–140° in a sealed tube for ten hours, with subsequent treatment as in the previous experiment. The very small yield of amino ester is explainable by the stability of the condensation product of piperonal with ammonia. The ester is insoluble in ether and may be isolated very easily.

Hydrochloride of β-Phenyl-β-amino-α-methylpropionic Acid, $C_6H_5CH(NH_2HCl)$-$CH(CH_3)COOH$.—Five g. of methylmalonic acid, 4.5 g. of benzaldehyde and 15 cc. of 10% alcoholic ammonia solution were heated on a water-bath until the evolution of carbon dioxide had ceased. The residue was dissolved in 20 g. of 15% soda solution at 60°. The undissolved oil was extracted with ether (0.2 g.). The alkaline solution was acidified with hydrochloric acid and again extracted with ether. This extract contains an unsaturated, nitrogen-free acid. After crystallization from alcohol it melted at 173° with decomposition. The water solution after treatment with ether was evaporated to dryness. The resulting hydrochloride of phenylaminomethylpropionic acid is contaminated with inorganic salts and must be crystallized from absolute alcohol.

Hydrochloride of β-Piperonyl-β-amino-α-methylpropionic Acid, $CH_2O_2C_6H_3CH$-$(NH_2HCl)CH(CH_3)COOH$.—Three and one-half g. of methylmalonic acid, 4.5 g. of piperonal and 15 cc. of 10% alcoholic ammonia solution were heated for six days on a water-bath until the evolution of carbon dioxide ceased. The residue was dissolved in 15 cc. of 15% soda solution and further treated as in the previous preparation. The first ethereal extract gave 0.9 g. of oil. The yield of unsaturated acid melting at 201–202° was only 0.8 g., about 13% of the theoretical. It is either $CH_2O_2C_6H_3CH{=}CH$-CH_2COOH or $CH_2O_2C_6H_3CH{=}C(CH_3)COOH$. A molecular weight determination on the unsaturated acid gave 202.4; calcd. for $C_{10}H_9O_4$, 206.

Hydrochloride of β-Phenyl-β-amino-α-ethylpropionic Acid, $C_6H_5CH(NH_2HCl)$-$CH(C_2H_5)COOH$.—Nine g. of ethylmalonic acid, 7.2 g. of benzaldehyde and 30 cc. of 10% alcoholic ammonia solution were heated for five hours on a water-bath and then for three hours at 145°. The mixture was dissolved in 30 cc. of 15% soda solution and

TABLE I

ANALYTICAL AND OTHER DATA OF ACID HYDROCHLORIDES

Diethyl β-( )-β-amino-α-( )-ethanedicarboxylates	Yield, g.	Yield, %	M. p., °C.	Formula	Analyses Calcd. Cl, %	Calcd. N, %	Found Cl, %	Found N, %
Phenyl, methyl	9.2	51.7	158	$C_{15}H_{22}O_4NCl$	11.20	4.43	11.17	4.51
Piperonyl, methyl	3.9	38.2	125–127	$C_{16}H_{22}O_6NCl$	9.86	3.89	9.72	4.13
Phenyl, ethyl	1.5	17.0	166	$C_{16}H_{24}O_4NCl$	10.76	4.25	10.64	4.43
Piperonyl, ethyl	1.2	6.0	157	$C_{17}H_{24}O_6NCl$	9.49	..	9.43	..
Propionic acids								
Phenyl, methyl	5.5	60.4	225	$C_{10}H_{14}O_2NCl$	16.45	6.5	16.32	6.55
Piperonyl, methyl	5	76.95	...	$C_{11}H_{14}O_4NCl$	13.28	5.39	13.26	5.21
Phenyl, ethyl	3.7	23.7	249	$C_{11}H_{16}O_2NCl$	15.45	6.1	15.39	6.29
Piperonyl, ethyl	2.5	13.4	215[a]	$C_{12}H_{16}O_4NCl$	12.92	5.12	12.76	4.94
Phenyl, benzyl	5.2	34.6	222	$C_{16}H_{18}O_2NCl$	12.17	4.80	12.05	4.96
Piperonyl, benzyl	3.5	20.3[b]	203–205[a]	$C_{17}H_{18}O_4NCl$	10.54	4.17	10.53	4.07

[a] With decomposition.

[b] 42.3 calculated on the basis of piperonal actually combined.

treated with ether. The ethereal solution gave 2.6 g. of oil (principally contaminated benzaldehyde). After acidifying with hydrochloric acid, the water solution gave 4 g. of unsaturated acid (36% of the theoretical) with a melting point of 107°. The hydrochloride of the amino acid was crystallized from alcohol. A molecular weight determination on the unsaturated acid gave 177.9; calcd. for $C_{11}H_{12}O_2$, 176.

Hydrochloride of β-Piperonyl-β-amino-α-ethylpropionic Acid.—Nine g. of ethylmalonic acid, 10.2 g. of piperonal and 30 cc. of 10% alcoholic ammonia solution were heated for ten hours on a water-bath and then for eight hours at 145°, considerable tar being formed. Treatment with soda solution gave an oil insoluble in water, soda and ether. The water solution after acidification gave 4.3 g. (about 31% of the theoretical) of an unsaturated acid melting at 135° and, after evaporation, the amino acid, which may be crystallized from absolute alcohol. The molecular weight of the unsaturated acid was determined as 216; calcd. for $C_{12}H_{12}O_4$, 220.

Hydrochloride of β-Phenyl-β-amino-α-benzylpropionic Acid, $C_6H_5CH(NH_2HCl)$-$CH(CH_2C_6H_5)COOH$.—Ten g. of benzylmalonic acid, 5.4 g. of benzaldehyde and 20 cc. of 10% alcoholic ammonia solution were heated for one hour on a water-bath with a condenser and then for three hours at 145°. The mixture was dissolved in soda solution and treated with ether. On evaporating the ethereal solution an oil separated (2.8 g.).[7] The water solution was acidified with hydrochloric acid and gave 6.5 g. (53% of the theoretical) of an unsaturated acid, probably $C_6H_5CH{=}C(C_6H_5)CH_2COOH$, crystallizing from alcohol in snow-white needles with a melting point of 160°. After removing this substance, the water solution was shaken several times with ether, from which 0.5 g. of hydrocinnamic acid was isolated, m. p. 40° uncrystallized and 47° after crystallization. A mixed melting point with a known sample gave no depression. The solution was finally evaporated to dryness and the residue crystallized from alcohol. A molecular weight determination of the unsaturated acid gave 234.1; calcd. for $C_{16}H_{14}O_2$, 238.

Another Method of Preparation.—Five g. of benzylmalonic acid, 4 g. of benzhydramide and 20 cc. of alcohol were heated for eight hours on a water-bath and then at 120–125° for six hours. The treatment of the mixture was carried out exactly as in the foregoing experiment and gave 1.6 g. of oil, 2.9 g. of unsaturated acid (m. p. 160–161°), 0.3 g. of hydrocinnamic acid and 3.9 g. of the hydrochloride of β-phenyl-β-amino-α-benzylpropionic acid (about 52% of the theoretical amount).

Hydrochloride of β-Piperonyl-β-amino-α-benzylpropionic Acid, $CH_2O_2C_6H_3CH$-$(NH_2HCl)CH(CH_2C_6H_5)COOH$.—Ten g. of benzylmalonic acid, 7.7 g. of piperonal and 30 cc. of 10% alcoholic ammonia solution were heated for twelve to thirteen hours on a water-bath. The mixture was dissolved in soda solution and filtered from 2.8 g. of crystalline material insoluble in cold soda solution (probably the diphenylaminopropane derivative). In order to remove the unchanged piperonal, the water solution was treated with benzene. The benzene solution was concentrated on a boiling water-bath to a thin sirup; crystallization usually began as soon as the sirup cooled, 4 g. of piperonal being separated in this way. The water solution was then acidified with hydrochloric acid and 2.8 g. of unsaturated acid melting at 205° separated. This yield was about 20% of the theoretical calculated for $CH_2O{=}C_6H_5CH{=}C(C_6H_5)CH_2COOH$. The acid solution was extracted with ether and gave 2.3 g. of unchanged benzylmalonic acid. Finally, the water solution was evaporated on the water-bath and the residual hydrochloride was crystallized from alcohol. A molecular weight determination of the unsaturated acid gave 284.9; calcd. for $C_{17}H_{14}O_4$, 282.

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[7] The investigation of this substance has not been finished but it seems to be α,γ-diphenyl-α-aminopropane, $C_6H_5CH(NH_2)CH_2CH_2C_6H_5$.

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

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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.