[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY]

Syntheses of β-Amino Acids and Their *N*-Alkyl Derivatives

ALBERT ZILKHA, E. S. RACHMAN, AND JOSEPH RIVLIN

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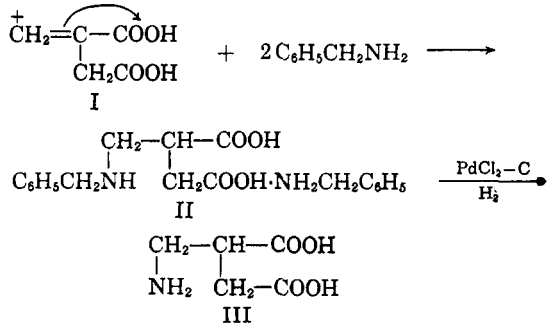
N-Benzylaminomethylsuccinic acid had been prepared by the addition of excess of benzylamine to itaconic acid in aqueous solution. *N*-Alkyl-β-alanines had been prepared by the addition of amines to acrylic acid. The reaction of primary aliphatic amines with methacrylic acid gave in some cases *N*-alkyl-β-aminoisobutyric acids and in other cases polymerization products. Aminomethylsuccinic acid, β-alanine, and β-aminoisobutyric acid were obtained by reduction of the corresponding *N*-benzyl derivatives.

The reaction of amines (especially aromatic) with itaconic acid had been extensively studied; *N*-aryl- or alkyl-4-carboxy-2-pyrrolidone derivatives are obtained.[1,2,3,4] The formation of these derivatives was assumed to occur through the *N*-alkyl derivative of aminomethyl succinic acid first formed, which then cyclized to the pyrrolidone derivative.[4] However, no such derivative had been isolated.

We have studied the reaction of benzylamine with itaconic acid in a view of obtaining *N*-benzylaminomethyl succinic acid; the *N*-benzyl group can act as a protecting group for the syntheses of peptides of the aminoacid.

We investigated the addition of benzylamine to itaconic acid in various solvents. On heating one mole of benzylamine with an equivalent of itaconic acid in pyridine in an oil bath at 110–120°, *N*-benzyl-4-carboxy-2-pyrrolidone[1] was obtained in good yield. With two moles of benzylamine under otherwise similar conditions, the benzylamine salt of this pyrrolidone was obtained, treatment of which with alkali in the cold and acidification gave the pyrrolidone. Working in dimethylformamide solution at 110–120°, the reaction of one mole of benzylamine with one mole of itaconic acid gave the pyrrolidone derivative in lower yield. In the reaction of two moles of benzylamine with itaconic acid at room temperature the double benzylamine salt of itaconic acid precipitated immediately. This dissolved on heating in dimethylformamide and gave in low yield a product which was not identified.

N-Benzyl-4-carboxy-2-pyrrolidone was obtained on heating equimolar quantities of benzylamine and itaconic acid in aqueous solution.[1] In view of the fact that the pyrrolidone is considered to occur through the *N*-benzylaminomethylsuccinic acid by reaction of the secondary amino group with the γ-carboxyl group, we decided to carry out the reaction with two moles of benzylamine in order to avoid cyclization, by salt formation with the γ-carboxyl group. (It seems probable that the β-carboxyl group, due to its zwitterion formation with the *N*-alkylamino group, is not inclined to salt formation with the excess amine.) The benzylamine salt of *N*-benzyl-DL-aminomethylsuccinic acid (II) (Chart) was thus obtained in good yield. From this *N*-benzyl-DL-aminomethylsuccinic acid was obtained on treatment with alkali in the cold and acidification. It differed from the corresponding pyrrolidone in being insoluble in hot acetone, slightly soluble in ethanol and more soluble in hot water. On recrystallization from water or water-ethanol it melted at 148–149° as compared with 144° for the latter.[1] It gave a positive reaction with ninhydrin on paper chromatograms and was reduced in acetic acid solution in the presence of palladium chloride on charcoal (30%); the pyrrolidone, being an *N*-benzylamide, did not give these reactions.



The addition reaction of benzylamine with itaconic acid proceeds probably by the following route (Chart). The electronegative carboxyl groups, polarize the double bond as shown in I, and the nucleophilic amine attaches to the positive carbon atom by the unshared electron pair of the nitrogen and *N*-alkylaminomethylsuccinic acid (II) is formed. From this by hydrogenolysis the new β-aminoacid, DL-aminomethylsuccinic acid (DL-α-carboxymethyl-β-alanine), (III) was obtained, which melted at 180–181°. This differs from both

(1) P. L. Paytash, E. Sparrow, and J. C. Gathe, *J. Am. Chem. Soc.*, **72**, 1415 (1950).
(2) P. L. Paytash, M. J. Thompson, and M. E. Fykes, *J. Am. Chem. Soc.*, **74**, 4549 (1952).
(3) P. L. Paytash, M. J. Thompson, and E. B. Clarke, *J. Am. Chem. Soc.*, **76**, 3500 (1954).
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DL-α-methyl[5] and β-methyl[6] aspartic acids which melt at 232–234° and 274°, respectively. This proves the correctness of the above scheme and also proves that no isomerization to citraconic acid had occurred during the reaction as addition of amine to citraconic acid should have given derivatives of the methyl-aspartic acids.

DL-Aminomethylsuccinic acid is soluble in water, insoluble in absolute ethanol and crystallizes from water-ethanol. Its solution in water is acidic. It gives a positive ninhydrin test and a negative test with copper carbonate[7] as is compatible with β-aminoacids. Ascending paper chromatography using aqueous phenol (80%) gave R_f value of 0.4 which is higher than that of aspartic acid (0.19) or glutamic acid (0.31), and the color of the spot was more brown.

In continuation of previous work[8] on the preparation of N-alkyl-β-aminobutyric acids, we prepared N-alkyl-β-alanines by the addition of amines to acrylic acid in pyridine solution at 110–120°, according to the following scheme:

$$CH_2{=}CH{-}COOH + RNH_2 \longrightarrow \underset{\displaystyle NHR}{\overset{\displaystyle |}{CH_2CH_2{-}COOH}}$$

These derivatives were previously prepared by the action of amines on β-propiolactone, the substances being sometimes contaminated with amides of hydracrylic acid obtained as side products.[9] β-Alanine was obtained in high yield by catalytic hydrogenolysis of the N-benzyl derivative.

It was interesting to prepare β-aminoisobutyric acids by the addition of amines to methacrylic acid. The importance of these derivatives can be seen from recent researches[10] in the field of the metabolic breakdown of pyrimidines to which β-aminoisobutyric acid is connected. L-β-Aminoisobutyric acid was isolated for the first time[11] from human urine. It was found to accumulate in the urine of certain people and its presence was thought to be a matter of genetic peculiarities. Later research[10] has shown that introducing thymine to rats caused the appearance of β-aminoisobutyric acid in their urine, while uracil caused the appearance of β-alanine. From this it may be supposed that the formation of these β-amino acids in the body is connected with the metabolic degradation of nucleic acids.

No syntheses of N-alkyl-β-aminoisobutyric acids have been reported. Some esters of these compounds were prepared by the reaction of amines and methyl methacrylate.[12]

The reaction of amines with methacrylic acid in various solvents gave various results depending on the amine and the reaction solvent. The reaction of benzylamine, isobutylamine, and hexylamine with methacrylic acid in pyridine under conditions similar to that with acrylic acid gave the N-alkyl-β-aminoisobutyric acids. The compounds are soluble in water, ethanol, and insoluble in acetone. They gave negative reaction with copper carbonate when this was added to their boiling aqueous solution, as is compatible with N-alkyls of β-aminoacids.[8] Their reactions with aqueous potassium permanganate and ninhydrin were negative indicating the absence of double bonds and of amine salts.

The reaction of benzylamine with methacrylic acid in water gave only polymerization products which were high melting, soluble in water, and insoluble in acetone and ethyl acetate. These polymers seemed to be amine salts of polymethacrylic acid. They gave a positive ninhydrin reaction and negative reaction for unsaturation with permanganate. Their total nitrogen content was about the same as the Van Slyke amino nitrogen. The nitrogen analyses show that not all carboxyl groups of the polymethacrylic acid were involved in salt-formation with the amine.

Polymeric products were also obtained with n-butylamine, n-propylamine, and methacrylic acid on carrying the reaction either in pyridine or in water. With cyclohexylamine in water a polymer was obtained.

The reaction of benzylamine with methacrylic acid in water in the presence of hydroquinone also led to the formation of polymeric products, which seems to indicate that the polymerization is not by free radicals. There also exists the possibility of anionic polymerization initiated by the addition of the amine to methacrylic acid giving a carbanion as an intermediate which can initiate polymerization.

$$RNH_2 + CH_2{=}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}{-}COOH \longrightarrow \underset{\displaystyle RHN^{2+}}{\overset{\displaystyle |}{CH_2}}{-}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{\bar{C}}}{-}COOH$$

Provided that the velocity of abstracting a proton from the reaction medium by the carbanion is relatively slow, polymerization can occur by addition of the carbanion to monomer. However, this mechanism is far from being definite as anionic polymerization in aqueous medium which is a good proton donor seems to be rather improbable.

DL-β-Aminoisobutyric acid was prepared by catalytic hydrogenolysis of the N-benzyl derivative.

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(6) H. D. Dakin, *J. Biol. Chem.*, **141**, 945 (1941).

(7) Y. Liwschitz, Y. Edlitz-Pfeffermann, and Y. Lapidoth, *J. Am. Chem. Soc.*, **78**, 3069 (1956).

(8) A. Zilkha and J. Rivlin, *J. Org. Chem.*, **23**, 94 (1958).

(9) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. T. Fiedorek, *J. Am. Chem. Soc.*, **73**, 3168 (1951).

(10) J. S. Fruton and S. Simmonds, *General Biochemistry*, 3rd Ed., Wiley and Sons, New York, 1958, p. 858.

(11) H. R. Crumpler, C. E. Dent, H. Harris, and R. G. Westall, *Nature*, **167**, 307 (1951).

(12) A. Vystricil and S. Hudecek, *Chem. listy*, **44**, 262 (1950).

The present synthesis is simpler than the methods used in previous preparations—*e.g.*, from α-chloropropionic acid which involved more complicated steps;[13] or from α-methyl-β-propiolactone and ammonia (patent)[14] for which no details or physical properties were given.

Passing phosgene into a suspension of *N*-benzyl-DL-β-aminoisobutyric acid in dioxane at 60° gave the mixed anhydride of *N*-benzyl-DL-β-aminoisobutyric acid with chloroformic acid.[15] This interacted with ammonia with evolution of carbon dioxide to give the amide. In this way amides and peptides of DL-β-aminoisobutyric acid could be synthesized, the *N*-benzyl protecting group being easily removed by catalytic hydrogenation.

EXPERIMENTAL

Micro combustion analyses were carried out by Drs. Weiler and Strauss. Melting points were determined in a Fisher-Johns apparatus. The ascending method of paper chromatography (80% phenol) was used.

N-Benzyl-4-carboxy-2-pyrrolidone. (*A*). To a solution of 6.5 g. (0.05 mole) itaconic acid in 20 ml. pyridine was added 5.4 g. (0.05 mole) of benzylamine. The solution was heated in an oil bath at 110–120° for 3 hr. The solvent was removed *in vacuo* and water was added to the residue and evaporated. The crystalline residue was filtered and washed with water; yield 8.7 g. (80%). The pyrrolidone[1] was crystallized from water; m.p. 144°. It gave negative permanganate and ninhydrin reactions.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.7; H, 5.9; N, 6.4. Found: C, 65.8; H, 6.0; N, 6.4.

(*B*). To a solution of 3.25 g. (0.025 mole) itaconic acid in 10 ml. dimethylformamide was added 2.7 g. (0.025 mole) benzylamine. The solution was heated as above for 3 hr. On evaporating the solution *in vacuo*, 2.4 g. (40%) of pyrrolidone was obtained. The substance was identical with that prepared according to method (A).

Benzylamine salt of N-benzyl-4-carboxy-2-pyrrolidone. Itaconic acid (3.25 g., 0.025 mole) was heated as above in pyridine with benzylamine (5.4 g., 0.05 mole). The solvent was removed *in vacuo* and the solid residue was washed with acetone and filtered; yield 6.1 g. (75%); m.p. 111° on recrystallization from ethanol–ethyl acetate. It gave negative permanganate and positive ninhydrin reactions. It is soluble in water (neutral reaction), less in ethanol and insoluble in ether and acetone. *N*-benzyl-4-carboxy-2-pyrrolidone was obtained on dissolving the substance in sodium hydroxide (10%), extracting the benzylamine liberated with ether and acidification.

Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 70.0; H, 6.7; N, 8.6; N (Van Slyke), 4.3. Found: C, 69.7; H, 6.8; N, 8.7; N (Van Slyke), 4.3.

Double benzylamine salt of itaconic acid. To a solution of 1 g. (0.08 mole) of itaconic acid in 4 ml. of dimethylformamide was added 1.7 g. (0.016 mole) of benzylamine. The double benzylamine salt precipitated immediately; yield, 2.4 g. (90%); m.p. 138° on recrystallization from ethanol-acetone. It is soluble in water (neutral reaction), alcohol, and insoluble in cold acetone. It gave positive ninhydrin and permanganate reactions.

Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.2; H, 7.0; N, 8.1. Found: C, 66.1; H, 7.0; N, 8.1.

On heating the double benzylamine salt in dimethylformamide for 2–3 hr. at 110–120°, evaporating the solvent *in vacuo*, and adding ethyl acetate to the residue, 0.25 g. of a substance melting at 160° was obtained. This was soluble in water (acid reaction) and insoluble in ethanol and acetone. It gave negative ninhydrin and permanganate reactions.

Benzylamine salt of N-benzyl-DL-aminomethyl succinic acid. To a solution of 3.25 g. (0.025 mole) of itaconic acid in 10 ml. of water was added 5.4 g. (0.05 mole) of benzylamine, and the solution refluxed on a boiling water bath for 1 hr. On standing for several hours in the ice-box, the substance crystallized; or the solution could be evaporated *in vacuo* and the residue washed with acetone and filtered; yield 6.9 g. (80%). The substance gave weakly positive permanganate reaction. On recrystallization from water-acetone or water-ethanol the substance melted at 139–140°. It gave positive ninhydrin and negative permanganate reactions; R_f value 0.87.

Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.2; H, 7.0; N, 8.1; N (Van Slyke), 4.1. Found: C, 66.1; H, 7.0; N, 8.1; N (Van Slyke), 4.1.

N-Benzyl-DL-aminomethyl succinic acid. The benzylamine salt of *N*-benzyl-DL-aminomethyl succinic acid (7 g.) was dissolved in sodium hydroxide (20 ml., 3*N*). The solution was extracted twice with ether to remove benzylamine and then acidified to *p*H 3–4 with concd. hydrochloric acid. The solution was cooled in ice and filtered; yield, 4 g. (85%); m.p. 149° on recrystallization from water-ethanol. R_f value 0.83.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.8; H, 6.4; N, 5.9. Found: C, 60.7; H, 6.6; N, 5.7.

DL-Aminomethylsuccinic acid. Benzylamine salt of *N*-benzyl-DL-aminomethylsuccinic acid (5 g.) was dissolved in acetic acid (80 ml.) and 30% palladium chloride on charcoal (0.4 g.) was added. The hydrogenolysis was carried out in a Parr low pressure hydrogenation apparatus for 16 hr. at 50–60°. After separation of the catalyst the solvent was removed *in vacuo*, the residue was dissolved in water-ethanol and evaporated once more *in vacuo* to remove the last traces of acetic acid. The solid residue was filtered and washed with acetone. On recrystallization from 75% ethanol, 2.5 g. (70%) was obtained; m.p. 180–181°. The substance is insoluble in acetone and absolute ethanol and soluble in water (acid reaction).

Anal. Calcd. for $C_5H_9NO_4 + H_2O$: C, 36.4; H, 6.6; N, 8.5; N (Van Slyke), 8.5. Found: C, 36.9; H, 6.6; N, 8.3; N (Van Slyke), 8.6.

n-Butylamine salt of polymethacrylic acid. (*A*) (in pyridine). To a solution of 4.3 g. (0.05 mole) methacrylic acid in 15 ml. pyridine was added 7.3 g. (0.1 mole) *n*-butylamine. The solution was heated in an oil bath at 110–120° for 2 hr. and evaporated to dryness *in vacuo*. The viscous residue was triturated with hot ethyl acetate and filtered; yield 6 g. The substance was further purified by trituration with ethanol; m.p. 265°. The substance is soluble in water (neutral reaction) and slightly soluble in ethanol, ethyl acetate, and acetone. It gave positive ninhydrin and negative permanganate reactions. Analysis shows that not all the carboxyl groups of the polymer participated in salt formation with the *n*-butylamine; one mole of *n*-butylamine is attached to every three moles of methacrylic acid. Furthermore, the small difference between the total nitrogen and the amino nitrogen may be possibly due to the presence of a terminal alkylamino group from anionic initiation of polymerization by butylamine.

Anal. Calcd. for $[(C_4H_6O_2)_3 + C_4H_{11}N]_n$: C, 58.0; H, 8.8; N, 4.3; N (Van Slyke), 4.3. Found: C, 58.0; H, 9.0; N, 4.7; N (Van Slyke), 4.4.

(*B*) (in water). Methacrylic acid (4.3 g., 0.05 mole) was dissolved in water (10 ml.) and *n*-butylamine (3.7 g., 0.05 mole) added. The solution was heated for 2 hr. on a water bath and evaporated *in vacuo* and the residue recrystallized from water-acetone. The sticky polymer obtained was dried in a vacuum desiccator over phosphorus pentoxide. It is

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TABLE I

PREPARATION OF N-ALKYL DERIVATIVES OF β-ALANINE

N-Alkyl Substituent	M.P.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Isobutyl	160	69	$C_7H_{15}NO_2$	57.9	57.9	10.4	10.6	9.7	9.4
Cyclohexyl	181[a]	67	$C_9H_{17}NO_2$	63.2	62.9	9.9	9.9	8.3	8.0
2-Hydroxyethyl	147[b,d]	60	$C_5H_{11}NO_3$	45.1	45.1	8.4	8.7	10.5	10.3
2-Hydroxy-n-propyl	194[d]	88	$C_6H_{13}NO_3$	49.0	48.5	8.8	8.9	9.5	9.2
Benzyl	196[c]	65	$C_{10}H_{13}NO_2$	67.0	66.7	7.3	7.5	7.8	7.6

[a] M.p. previously reported,[9] 170–171°. [b] M.p. previously reported,[9] 143–145°. [c] M.p. previously reported,[9] 182–183°. [d] Recrystallized from absolute ethanol.

TABLE II

PREPARATION OF N-ALKYL DERIVATIVES OF DL-β-AMINOISOBUTYRIC ACID[a]

N-Alkyl Substituent	M.P.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Benzyl	159	70[b]	$C_{11}H_{15}NO_2$	68.4	68.2	7.8	7.7	7.3	7.2
Isobutyl	186	80	$C_8H_{17}NO_2$	60.4	60.5	10.7	10.7	8.8	8.5
n-Hexyl	129	20	$C_{10}H_{21}NO_2$	64.2	64.1	11.2	11.3	7.5	7.5

[a] Substances were recrystallized from ethanol-acetone. [b] Using 2 equivalents of benzylamine gave 80% yield.

soluble in water and insoluble in acetone. It melted around 265°. It gave positive ninhydrin and negative permanganate reactions. Nitrogen analysis showed that the polymer had one butylamine salt for every two molecules of methacrylic acid. The greater capacity of the polymethacrylic acid for salt formation in water than in pyridine may be due to the greater polarity of the solvent or to a different steric structure of the polymer obtained. Models of polymethacrylic acid show that there is a considerable steric hindrance for the introduction of bulky amine groups to the polymer molecules. That is why no polymer having an amine salt with every carboxyl group had been obtained.

Anal. Calcd. for $[(C_4H_6O_2)_2 + C_4H_{11}N]_n$: N, 5.7; N (Van Slyke), 5.7. Found: N, 5.8; N (Van Slyke), 5.7.

Benzylamine salt of polymethacrylic acid. This was prepared as above by heating methacrylic acid (4.3 g., 0.05 mole) and benzylamine (5.4 g., 0.05 mole) in water (20 ml.). It was purified by trituration with acetone and recrystallization from ethanol-acetone; yield 6 g., m.p. about 250°. The polymer was soluble in water (neutral reaction), less soluble in ethanol and insoluble in acetone. It gave positive ninhydrin and negative permanganate reactions. Nitrogen analysis showed that similar to butylamine, the polymer had one amine in salt formation for every two molecules of methacrylic acid.

Anal. Calcd. for $[(C_4H_6O_2)_2 + C_7H_9N]_n$: N, 5.0; N (Van Slyke), 5.0. Found: N, 4.8; N (Van Slyke), 4.7.

Cyclohexylamine salt of polymethacrylic acid. The reaction of methacrylic acid (2.15 g., 0.025 mole) with cyclohexylamine (2.5 g., 0.025 mole) in water (10 ml.) was carried out as above. The polymer was purified by trituration with acetone and recrystallized from water-acetone; yield 4 g.; m.p. about 250°. The substance gave a positive ninhydrin reaction, and contrary to the other polymers, a positive reaction with permanganate. The total nitrogen contained (6.3%) was much different from the amino nitrogen (2.2%), so that we cannot have a simple salt of the amine with monomeric methacrylic acid.

n-Propylamine salt of polymethacrylic acid. This polymer was prepared in pyridine as in the case of n-butylamine salt. The properties of the polymer were similar to that of the n-butylamine salt. The polymer melted at about 270°. Analysis showed it to have one mole amine salt for every three methacrylic acid molecules.

Anal. Calcd. for $[(C_4H_6O_2)_2 + C_3H_9N]_n$: C, 56.7; H, 8.5; N, 4.4; N (Van Slyke), 4.4. Found: C, 56.4; H, 9.0; N, 4.7; N (Van Slyke), 4.6.

N-Alkyl-β-alanines. To a solution of 3.6 g. (0.05 mole) of acrylic acid in 20 ml. of pyridine was added 0.05 mole of amine. The solution was heated in an oil bath at 110–120° for 2–3 hr. On cooling the N-alkyl-β-alanine crystallized. Otherwise, the pyridine was evaporated to dryness *in vacuo*, water added, and the solution evaporated once more to dryness. The residue was heated with acetone to effect crystallization, cooled, and filtered. The substances are soluble in water and may be recrystallized from ethanol-acetone or ethanol-ethylacetate. The pure products give negative ninhydrin and permanganate reactions.

The N-alkyl-β-alanines thus prepared are listed in Table I.

N-Alkyl-β-aminoisobutyric acids. The reaction of methacrylic acid with amines was carried out as in the case of acrylic acid. The N-alkyl-DL-β-aminoisobutyric acids are soluble in water, less in ethanol and insoluble in acetone. They are listed in Table II.

DL-β-Aminoisobutyric acid. N-benzyl-DL-β-aminoisobutyric acid (7 g.) was dissolved in 80 ml. glacial acetic acid and 0.6 g. of 30% palladium chloride on charcoal was added. The hydrogenolysis was carried out in a Parr low pressure apparatus for 15 hr. at 50–60°. After separation of the catalyst the solvent was removed *in vacuo* and the residue was dissolved in water and evaporated once more *in vacuo* to complete dryness to remove the last traces of acetic acid. The remaining oily residue solidified on addition of acetone, cooling in an ice salt bath, and scratching. The substance was filtered and washed with acetone; yield 3 g. (80%); m.p. 181° on recrystallization from water–absolute ethanol; R_f value 0.8.

Anal. Calcd. for $C_4H_9NO_2$: C, 46.6; H, 8.7; N, 13.6; N (Van Slyke), 13.6. Found: C, 46.6; H, 8.8; N, 13.3; N (Van Slyke), 13.3.

β-Alanine. N-Benzyl-β-alanine (1.7 g.) was dissolved in 40 ml. acetic acid and 0.1 g. catalyst added. The hydrogenolysis and recovery of β-alanine was carried out as above. The yield was approximately quantitative. The substance melted at 200° on recrystallization from water–absolute ethanol, and was checked for purity by mixed melting point determination with an authentic sample and by its R_f value.

DL-β-*Benzylaminoisobutyramide.* *N*-Benzyl-DL-β-aminoisobutyric acid (4 g.), which had been dried before in a vacuum desiccator over phosphorus pentoxide, was suspended in 100 ml. dry dioxane in a 3-necked flask equipped with a gas leading tube, reflux condenser connected to a calcium chloride tube, and a mechanical stirrer. Phosgene was bubbled in with stirring for 60 min. and the temperature maintained at 60°. Excess phosgene and solvent were removed *in vacuo* at 40°. The residue was dissolved in 50 ml. dry dioxane and dry ammonia gas passed in with stirring and cooling for 20 min. After leaving overnight, the solution was filtered from ammonium chloride and evaporated to dryness *in vacuo*. The substance refused to crystallize from ethyl acetate–petroleum ether. Cooling in a Dry Ice–acetone bath caused complete crystallization but on heating to room temperature the substance became sticky. The *N*-benzyl-DL-β-aminoisobutyramide was obtained on vacuum distillation at 165°/0.3 mm. On leaving overnight in a vacuum dessicator over phosphorus pentoxide the substance crystallized, m.p. 58°; yield 2.8 g. (70%). It is soluble in ethanol, acetone, chloroform, less in water (basic reaction) and ether.

Anal. Calcd. for $C_{11}H_{16}N_2O$: N, 14.6. Found: N, 14.3.

Reaction of alcoholic picric acid with the amide gave the picrate derivative, m.p. 168° on recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{19}N_5O_8$: N, 17.0. Found: N, 17.2.

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TEXAS TECHNOLOGICAL COLLEGE]

The "Thermal" Rearrangement of Hydrazo Compounds. IV. The Intramolecularity of the Rearrangement[1]

H. J. SHINE, FUI-TSENG HUANG,[2] AND R. L. SNELL[3]

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The products of the rearrangement of 2,2′-hydrazonaphthalene, 1,2′-hydrazonaphthalene and 1-phenyl-2-β-naphthylhydrazine have been isolated. The 2,2′-hydrazonaphthalene was caused to rearrange in the absence of solvent at 90° and 150°, and in cyclohexane at 95°. The only products isolable and in excellent recovery were 2,2′-diamino-1,1′-binaphthyl and 3,4:5,6-dibenzocarbazole. The 1,2′-hydrazonaphthalene was caused to rearrange in cyclohexane at 95°. The only products isolable and in very poor recovery were 1,2′-diamino-1′,2-dinaphthyl and 1,2:5,6-dibenzocarbazole. The 1-phenyl-2-β-naphthylhydrazine was caused to rearrange in 95% ethanol at 90°. The only products isolable and in fairly good recovery were 1-(2-aminophenyl)-2-naphthylamine and 7-benzo[*c*]carbazole. For the last two hydrazo compounds authentic samples of products of intramolecular rearrangement were prepared by acid-catalyzed rearrangement. The results show that the thermal rearrangement is intramolecular.

In recent years reports have appeared[4–8] on the benzidine rearrangement that occurs when certain hydrazo compounds are heated. Only one reference has been made to the molecularity of this rearrangement. Vecera, Gasparic, and Petranek[6] found no evidence of intermolecular rearrangement in the case of 4-methylhydrazobenzene, and concluded, therefore, that the thermal rearrangement, like the well known acid catalyzed rearrangement, is intramolecular. We have also been occupied with this question. However, since hydrazobenzenes undergo intermolecular dismutation almost completely when heated, we have turned our attention to hydrazo compounds in which this does not occur. It is perhaps, a reasonable assumption that the rearrangement is intramolecular, if a hydrazo compound undergoes thermal rearrangement without evidence of dismutation. This is the case with 2,2′-hydrazonaphthalene, a detailed analysis of which has been given[8] and on which further information is now supplied.

Rearrangement of 2,2′-hydrazonaphthalene has been carried out in the absence of a solvent at 90°, which is below the melting point of the hydrazo compound; at 150°, which is above the melting point of the hydrazo compound; and in cyclohexane solution at 95°. The only products of these rearrangements were 2,2′-diamino-1,1′-binaphthyl and 3,4:5,6-dibenzocarbazole. The rather insoluble and easily isolable 2,2′-azonaphthalene was found in only one of these cases and in very small quantity, 0.9%, resulting, we believe, from air oxidation of the unrearranged hydrazonaphthalene. These results are similar to those obtained earlier with polar solvents.[8]

Vecera's work[6] concerned the rearrangement of 1,1′-hydrazonaphthalene and some hydrazobenzenes in the absence of solvent. In that research the products were not isolated but were identified semiquantitatively by dye-developing a paper chromatogram. The present and earlier results from 2,2′-hydrazonaphthalene show quite clearly that dismutation to azonaphthalene and naphthylamine does not occur. This indicates, therefore, that the rearrangement may be intramolecular, since, during

(1) Taken in part from the Ph.D. degree thesis of R. L. Snell, Texas Technological College, 1959.

(2) Robert A. Welch Foundation Fellow, 1958–60.

(3) Robert A. Welch Foundation Fellow, 1955–58.

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