[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

5-CARBOXYVALEROHYDROXAMIC ACID, 5-CARBOXYVALERYL AZIDE, 3-CARBOXYPROPIONOHYDROXAMIC ACID, *o*-CARBOXYBENZOHYDROXAMIC ACID, AND POLYAMIDES PREPARED FROM THEM BY REARRANGEMENT

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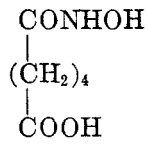
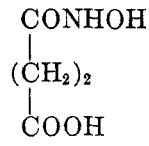
Recent studies (1, 2) have shown that the rearrangement of carboxyacetohydroxamic acid (N-hydroxymalonamic acid) and homologs, $RCH(COOH)CONHOH$, wherein R = H, C_2H_5, C_4H_9, $C_6H_5CH_2$ gives rise to polypeptides of the type $(—NH—CHR—CO—)_n$. In these malonic derivatives the COOH and CONHOH groups were attached to the same carbon. The present work extends this study to comparable derivatives of adipic, succinic, and phthalic acids (I, II, III, respectively). 5-Carboxyvalerohydroxamic acid (I) was obtained by reaction of



I



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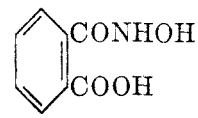


III

ethyl hydrogen adipate and hydroxylamine, 3-carboxypropionohydroxamic acid (II) from succinic anhydride or ethyl hydrogen succinate, and *o*-carboxybenzohydroxamic acid (III) from phthalic anhydride. II and III have been made before.

Treatment of II with acetic anhydride results in the formation (3) of acetylsuccinylhydroxylamine of cyclic structure, and benzoylation of sodium succinohydroxamate at elevated temperature yields (4) benzoylsuccinylhydroxylamine of comparable cyclic structure. It is of interest, therefore, to record that open-chain derivatives of both I and II, $HOOC(CH_2)_nCONHOC_6H_5$, were formed by benzoylation at 0–5°.

Similarly III, which yields a cyclic acetyl derivative (5), yielded the acyclic benzoyl derivative on applying the Schotten-Baumann method at low temperature.

Rearrangements in water were carried out by treating the acyclic benzoyl derivatives of the hydroxamic acids with an equimolar amount of alkali and heating the solutions, but better results were generally achieved when the intermediate salts were isolated. Rearrangements were performed in water and in toluene in all examples.

Sodium 5-carboxyvalero(benzoylhydroxamate), $HOOC(CH_2)_4CONa—OOCC_6H_5$. When this salt was heated in toluene, a polymeric amide, $[—NH(CH_2)_4CO—]_n$, was formed together with a small quantity of 2-piperidone. The polymer was

soluble in acidic and alkaline solutions. It melted at about 240°. Polymeric amides of comparable structure, but prepared by heating ω-amino acids, were observed (27) to exhibit an alternating effect in melting point as carbons in the monomer were increased. Thus, for polyamides from ω-amino acids of 6 to 11 carbons they reported melting points of 205, 225, 178, 197, 176, and 180° respectively. Our C_5 analog, with its m.p. of 240°, obviously fits into this general relationship.

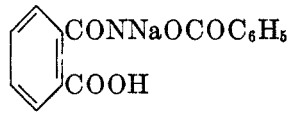
When the rearrangement was carried out in water, some 2-piperidone was obtained also, but the major product, m.p. 188°, was N,N′-ureadivaleric acid, $CO[NH(CH_2)_4COOH]_2$. This compound underwent pyrolysis into 2-piperidone and hydrolysis into 5-aminovaleric acid. For a time its identity was in doubt and some of the carboxypiperidones were tested as possibilities. The 3-carboxy compound was eliminated from consideration by synthesis; although it underwent ready decarboxylation to 2-piperidone, it melted at 120°. That the known (6) 6-carboxy compound could not have been the 180°-product (in spite of its close m.p. of 177–178°) was evident, since it is known to hydrolyze to 2-aminoadipic acid, not 5-aminovaleric.

The urea acid was synthesized, thus clinching its identity. To do this, 5-aminovaleric acid and ethyl 5-isocyanatovalerate were prepared and placed in reaction in alkaline solution. This product was the same as that appearing in the rearrangement.

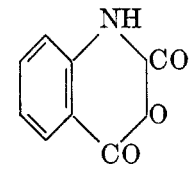
To explain these results, it seems that the hydroxamic salt decomposes first to 5-isocyanatovaleric acid. In toluene solution this cannot hydrolyze; hence it undergoes (13) self reaction: $RNCO + HOOCR' \rightarrow (RNHCOO—COR') \rightarrow RNHCOR' + CO_2$. Since R is $HOOC(CH_2)_4—$ and since R′ is $—(CH_2)_4NCO$, the amide, RNHCOR′, reacts further in this manner to build a polymer. In contrast, the isocyanate which comes in the aqueous experiment is hydrolyzed in part to amine. Then isocyanate and amine unite to form the urea: $RNCO + RNH_2 \rightarrow RNHCONHR$.

Sodium 3-carboxypropiono(benzoylhydroxamate). From the rearrangement of this salt by heating in toluene, it was possible to isolate a polyamide of the structure $[(—NHCH_2CH_2CO)—]_n$ (7). The physical properties of this material (solubility and gelatinous form) are similar to those of the polyglycine prepared from sodium carboxyaceto(benzoylhydroxamate) (1). Hydrolysis of a sample of the poly-β-alanine followed by benzoylation gave 3-benzamidopropionic acid and a trace of the dibenzoyl derivative of ethylenediamine. The presence of the latter has no satisfactory explanation at present. A considerable quantity of β-alanine, isolated as 3-benzamidopropionic acid, was obtained also after aqueous rearrangement of sodium carboxyaceto(benzoylhydroxamate) (8) and hydrolysis of the oily product.

Sodium o-carboxybenzo(benzoylhydroxamate) (IV). This salt gave rise to two products on rearrangement in hot water, namely, isatoic anhydride (V), which was stable even in hot water, and N-anthranoylanthranilic acid, which has been reported as a product from isatoic anhydride in the presence of limited amounts of alkali (9, 10).



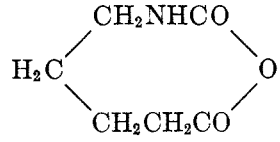
IV



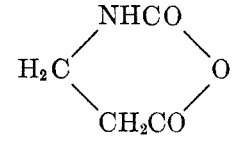
V

Isatoic anhydride is more stable in refluxing toluene, and rearrangement of IV under these conditions yielded only V (m.p. 236–238° dec.), identified by acidic and alkaline hydrolysis to anthranilic acid. In one non-reproducible experiment a less crystalline substance melting at 270–272° was obtained. This melting point was higher than could be obtained on samples of V recrystallized from various solvents (see reference 26). This material could also be hydrolyzed to anthranilic acid and was perhaps polyanthranilic acid resulting from "polymerization" of V initiated by an impurity not present in other experiments (compare 10a).

One may speculate on the immediate precursor of the polyamides (11), whether it is the isocyanato acid or a cyclic acid anhydride. Bayer (12) suggested that the azasuccinic anhydride of Leuchs possibly pyrolyzed into isocyanatoacetic acid, which then underwent self-reaction to give a polypeptide and carbon dioxide. As a matter of fact, isocyanates and carboxylic acids have been known (13) to react to give unstable mixed anhydrides, RCO—O—CONHR. More often (14, 15) these anticipated anhydrides decompose into amides, RCONHR, and carbon dioxide. Hurd and Buess (1) assumed a sequence opposite from that of Bayer, namely, that the isocyanato acid, RCH(NCO)COOH, isomerized to the azasuccinic anhydride and it, in turn, decomposed to the polypeptide. In support of the latter viewpoint, Curtius and Sieber (16) isolated azasuccinic anhydrides by decomposing 2-carboxyalkanoyl azides in ether. In this "Curtius rearrangement" the presumption that an isocyanate is an intermediate is very strong. Isocyanates also are generally accepted as intermediate products of the Lossen rearrangement; hence the presumption is equally strong that the isatoic anhydride formed from IV came by way of an isocyanate. If I and II were to produce similar acid anhydrides as intermediates in the formation of polyamides, these would be 2-azapimelic anhydride (VI) and 2-azaglutaric anhydride (VII), respectively.



VI



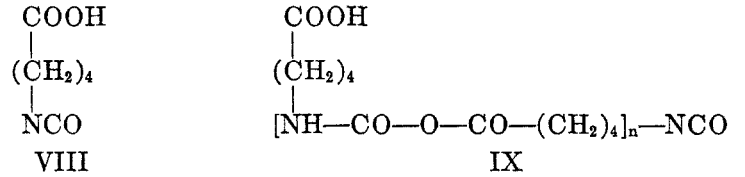
VII

A few other examples of the rearrangement of half azides of dicarboxylic acids are on record. One such is the half azide of succinic acid which gave a poor yield of β-alanine (17a). A better yield was realized later on by the use of ethyl succinimidoacetate (18). The rearrangement of 2-carboxy-3-nitrobenzoyl azide has been shown by Curtius and Semper (10) to give isatoic anhydride. In the

absence of similar work on 5-carboxyvaleryl azide, its rearrangement was studied.

Reaction of sodium ethyl adipate with hydrazine gave rise to the sodium salt of 5-carboxyvalerohydrazide. Diazotization by the method of Curtius and Sieber (16) and subsequent rearrangement of the intermediate azide in hot carbon tetrachloride yielded a semisolid, discussed below, and a small amount of crystalline 1,2-bis(5-carboxyvaleryl)hydrazine, $HOOC(CH_2)_4CONHNHCO(CH_2)_4COOH$. Curtius (17b) observed a similar formation of diacylhydrazines following diazotization of the corresponding succinic and oxalic derivatives.

The semi-solid product fused between 70–75° and could not be recrystallized. On keeping it for ten days it became more oily. Analysis conformed to the empirical formula $C_6H_9NO_3$. This could be the isocyanato acid (VIII), or its tautomer 2-azapimelic anhydride (VI), or a linear polymer (IX) formed by addition of the carboxy group to the isocyanate group.



VIII IX

The substance was insoluble in most organic solvents, including acetic anhydride at 100°, but it dissolved readily in hot water, 5 *N* hydrochloric acid, 2 *N* sodium hydroxide solution, hot acetic acid, and ethanol by reacting with these solvents. With water it gave α-piperidone and some polymeric product with simultaneous evolution of carbon dioxide. The polymer dissolved in cold dilute hydrochloric acid or in hot water from which it precipitated partially on cooling, thus resembling the polypeptides obtained from the Lossen rearrangement of 5-carboxyvalero(benzoylhydroxamic) acid in toluene. Neither 5-aminovaleric acid nor N,N′-ureadivaleric acid could be found. If hot 5 *N* hydrochloric acid was used, carbon dioxide was evolved as before and 5-aminovaleric acid hydrochloride was isolable from the solution. Vacuum-distillation of the substance gave a good yield of α-piperidone, characterized as its hydrochloride. On treatment with aniline in benzene or acetic acid, the substance changed into carbon dioxide and a water-soluble plastic gum. When the substance was heated with morpholine at 100° a water-soluble gum was obtained which dissolved partly in hot 2-propanol, from which an amorphous powder separated on cooling.

These properties suggest that the product from the Curtius rearrangement is the polymeric anhydride (IX). Structure VIII is ruled out, since no N,N′-ureadivaleric acid or 5-aminovaleric acid was obtained on treating with water. Although all other reactions could be explained on structures VI and VIII, the general insolubility points to the polymeric structure IX.

Two facts require an explanation. First is the formation of α-piperidone under non-pyrolytic conditions. Second is the formation of polyamide. To explain these facts, one may assume that a terminal isocyanate group of such a polymeric anhydride as IX is hydrolyzed to an amino group, $HOOC(CH_2)_4$-[NH—CO—O—CO—$(CH_2)_4]_n$—NH_2. Intramolecular reaction of this amine group with the

neighboring anhydride group would yield α-piperidone. A new terminal amine group would appear (by way of a carbamic acid group) to repeat the process. An intermolecular reaction between the amine and anhydride groupings would yield an amide structure. There is no way of knowing at present whether the polyamide is formed in this way or by direct detachment of carbon dioxide from IX.

Although it is impossible to isolate such intermediates as these from the Lossen rearrangements, it is conceivable that a similar type of reaction actually occurs.

EXPERIMENTAL

Melting points reported herein are uncorrected.

The disodium salts of I, II, and III. Sodium ethyl adipate, sodium ethyl succinate, and sodium ethyl phthalate were prepared by neutralizing the acid esters with an alcoholic sodium ethoxide solution.

Quantities of 0.1 mole of these salts were mixed at either 5° or 20° with 0.14 mole of alcoholic hydroxylamine solution (made from the hydrochloride and sodium ethoxide) and 0.1 mole of alcoholic sodium ethoxide solution. The homogeneous mixture was stirred for 30 minutes with the phthalic derivative and up to four hours with the adipic derivative. During this time the mixture was allowed to warm to room temperature. The separated hygroscopic salts were collected, washed with ether, dried, and analyzed. Yields were 91–97%. The salts, on acidification, all gave intense red-violet colors with ferric chloride solution.

Analyses. Salts from I, II, and III; respectively, $C_6H_9NNa_2O_4$, $C_4H_5NNa_2O_4$, $C_8H_5NNa_2O_4$.

Calc'd: Na, 22.4, 26.0, 20.4.
Found: Na, 22.2, 25.2, 19.7.

The phthalic and succinic derivatives also were made directly from phthalic or succinic anhydrides, alcoholic hydroxylamine, and two equivalents of alcoholic sodium ethoxide solution.

5-Carboxyvalerohydroxamic acid. The free acid was prepared by shaking the disodium salt (5.0 g.) in ethyl acetate (50 ml.) with dilute, ice-cold hydrochloric acid (2 *N*; 25 ml.) until two clear layers resulted. The aqueous phase was twice extracted with 50-ml. portions of ethyl acetate and the combined ester fractions were evaporated in a dry-air stream at 25°. The residue was triturated with benzene and the insoluble acid (0.7 g.) crystallized from ethyl acetate. The tiny needles melted at 109–110° (decomp.) in a sealed capillary when plunged in a preheated bath at 100° and then heated further. The acid is very soluble in water and gives an intense reddish-purple color with ferric chloride.

Anal. Calc'd for $C_6H_{11}NO_4$: N, 8.7. Found: N, 8.4.

Benzoyl derivatives of I, II, and III. Solutions of 5–8 g. of the disodium salts in 40 ml. of water were stirred at about 5° with a little saponin, benzoyl chloride, and a comparable molar amount of solid sodium acetate (or dilute sodium hydroxide solution). The last two reagents were added gradually until a 10–20% excess had been taken. After 30 minutes, benzene (25 ml.), petroleum hexane (25 ml.), and concentrated hydrochloric acid (10 ml.) were added to the stirred mixture. The separated solid was collected and washed with water until free of hydrochloric acid. This washing is important. Then it was rinsed with benzene-ligroin and crystallized either from ethyl acetate alone or from 1:1 mixtures of this ester with either benzene or ethanol. Yields were 55–67%. The samples melted with decomposition. That for the adipic derivatives melted at 144–145°, the succinic at 142–143° and the phthalic at 159–160°. These crystals were needle shaped.

Analyses of benzoyl derivatives.

From I: Calc'd for $C_{13}H_{15}NO_5$: C, 58.9; H, 5.7; N, 5.3.
Found: C, 59.2; H, 5.3; N, 5.5.

From II: Calc'd for $C_{11}H_{11}NO_5$: C, 55.7; H, 4.7; Neut. equiv. (dibasic), 118.6.
Found: C, 55.8; H, 4.6; Neut. equiv. (phenolphthalein) 119.

From III: Calc'd for $C_{15}H_{11}NO_5$: C, 63.2; H, 3.9; N, 4.9.
Found: C, 63.6; H, 4.0; N, 4.9.

Monosodium salts of benzoyl derivatives. An ethanolic solution of 5-carboxyvalero(benzoylhydroxamic) acid (3.1 g. in 20 ml.) was treated with an equivalent quantity of sodium ethoxide solution at 0°. Dry ether (25 ml.) and ligroin (75 ml., b.p. 35–60°) were added and the precipitate of sodium 5-carboxyvalero(benzoylhydroxamate) was collected. Yield, 3.0 g. or 90%. It was dried over sulfuric acid.

Anal. Calc'd for $C_{13}H_{14}NNaO_5$: Na, 8.0. Found: Na, 7.7.

Sodium 3-carboxypropiono(benzoylhydroxamate) and sodium *o*-carboxybenzo(benzoylhydroxamate) were prepared similarly in yields of 92 and 85%.

Anal. Calc'd for $C_{11}H_{10}NNaO_5$ and $C_{15}H_{10}NNaO_5$: Na, 8.9 and 7.5.
Found: Na, 9.2 and 7.9, respectively.

Rearrangement of sodium 5-carboxyvalero(benzoylhydroxamate) in toluene. A suspension of the salt (5.74 g.) in toluene (50 ml.) was boiled for three hours. Carbon dioxide was evolved as tested by barium hydroxide solution. The mixture was filtered hot and the residue was washed with hot benzene. The 4.8 g. of solid dissolved completely in 15 ml. of water. Acidification of the aqueous solution with acetic acid (5 ml.) caused precipitation of a mixture of benzoic acid and poly-(5-aminovaleric acid) which was collected and extracted with hot benzene (20 ml.). The weight of the insoluble polyamide was 0.56 g. [28% based on $-(C_5H_9NO)_n-$]. It was totally soluble in 5 *N* hydrochloric acid and 2 *N* sodium hydroxide solution and did not give a ninhydrin test. It was partly soluble in boiling ethanol (20 ml.) and the insoluble portion (fraction A, filtered while hot) weighed 0.34 g. From the alcoholic filtrate there was deposited, on cooling, the amorphous polymer, m.p. 225° (decomp.). This solid was dried for two hours at 110° under 20 mm. and analyzed.

Anal. Calc'd for $(C_5H_9NO)_n$: N, 14.1. Found: N, 14.2.

All but 50 mg. (fraction B) of fraction A dissolved in hot 2-ethoxy-1-ethanol, from which it partly crystallized on cooling. The mixture was filtered and the solid was washed with ethanol, boiled with toluene, and dried for four hours at 170° and 1 mm. The melting point of the sample was 240° (decomp.).

Anal. Calc'd for $(C_5H_9NO)_n$: C, 60.6; H, 9.2; N, 14.1.
Found: C, 59.0; H, 9.0; N, 14.3.

Fraction B was taken up in anhydrous formic acid and precipitated therefrom by adding dry ether. It was boiled with toluene prior to drying as described above. On being heated in a capillary, the material charred at 240° and melted with decomposition at 245°.

Anal. Found: C, 57.8; H, 8.9; N, 14.1.

The original, combined toluene-benzene filtrate was evaporated to dryness and treated with ethanolic hydrogen chloride and dry ether to give a crystalline precipitate of 2-piperidone hydrochloride (0.10 g.). Recrystallization from a mixture of 2-propanol and dry ether yielded a sample which melted at 175°, undepressed on admixture with an authentic specimen of m.p. 182–183°.

The dilute acetic acid solution was worked up as follows. The solution was acidified with hydrochloric acid, evaporated to dryness in a dry-air stream on a steam-bath, and finally dried *in vacuo*. The gummy residue was separated from sodium chloride by extraction with 2-propanol containing some anhydrous hydrogen chloride, which solution was concentrated and treated with ether. The gum which settled out was dissolved in 2-propanol and reprecipitated with anhydrous ether, a procedure which was repeated thrice. The semi-solid material thus obtained was dried at 20 mm. and 100° for four hours. The glass so obtained weighed 0.57 g. [29% yield based on $-(C_5H_9NO)_n-$]. After this heat treatment there was 0.3 g. of material (fraction I) which was insoluble in hot water and 0.27 g. of a water-soluble fraction S. Fraction I gave no test for chloride ions (acidified silver nitrate) and was now only partly soluble in 2-propanol. The 2-propanol-soluble material was precipitated from this solvent by the addition of dry ether and was dried at 100° under 1 mm. for four hours. When heated in a sealed capillary, this material softened at 190° and melted at 205° with decomposition (Found: N, 12.0).

Fraction S was freed of chloride ion by shaking it with silver carbonate (1.3 g.) for

one hour. The solution was filtered and the filtrate saturated with hydrogen sulfide, treated with Norit, and filtered. This treatment was repeated twice more and finally the silver-free solution was evaporated to dryness. The residue was taken up in 2-propanol and the poly-(5-aminovaleric acid) precipitated from it by means of dry ether. The solid was dried at 100° for four hours under 1 mm. pressure. This sample softened at 160° and melted at 170° with decomposition (Found: N, 12.5).

In another experiment 4.0 g. of sodium 5-carboxyvalero(benzoylhydroxamate) was rearranged as above yielding 0.38 g. (29%) of water-insoluble polyamide and 0.61 g. (44%) obtained from the aqueous filtrate. The 0.38-g. portion was heated with hydrochloric acid (10 *N*, 5 ml.) at 150° in a sealed tube for 12 hours. The contents of the tube were diluted with water, treated with Norit, and evaporated to dryness. Crystallization of the residue from 2-propanol and anhydrous ether afforded a sample of the deliquescent 5-aminovaleric acid hydrochloride (0.30 g. or 51%), m.p. 75–80°. The melting point of the product was raised to 92–93° by a second crystallization (19).

Rearrangement in water, Experiment 1. An aqueous solution of 4.0 g. of sodium 5-carboxyvalero(benzoylhydroxamate) in 10 ml. of water was heated at 100° for 30 minutes. Carbon dioxide was evolved. The solution was cooled, made alkaline with sodium hydroxide pellets, and extracted with chloroform (50 ml. in all). After evaporation of the chloroform, the residue was treated with ethanolic hydrogen chloride and dry ether yielding 2-piperidone hydrochloride (0.26 g., 14%), m.p. 180° (20). In a similar experiment, the 2-piperidone was isolated by fractional distillation of the chloroform layer. From 5.6 g. of the salt there was obtained 0.53 g. (27%) of 2-piperidone, b.p. 143° at 18 mm. The base was converted to its hydrochloride by treatment with ethanolic hydrogen chloride, precipitation with dry ether, and recrystallization from 2-propanol; m.p. 183–184°.

Acidification of the alkaline solution with concentrated hydrochloric acid at 0° resulted in the precipitation of a mixture of benzoic acid and ureadivaleric acid. The former was removed by washing with ether. The residue was then washed with water; yield, 0.51 g., 28%. After recrystallization from 2-propanol and desiccation, the compound was obtained as flat needles, m.p. 188° (dec.).

Anal. Calc'd for $C_{11}H_{20}N_2O_5$: C, 50.8; H, 7.75; N, 10.8.
Found: C, 51.0; H, 7.78; N, 10.9.

Experiment 2. The 5-carboxyvalero(benzoylhydroxamic) acid (5.30 g.) was dissolved by 0.8 g. of sodium hydroxide in 20 ml. of water and this solution was heated on a steam-bath for one hour. The mixture was then acidified with 50 ml. of concentrated hydrochloric acid and heated under reflux for two hours. When cool, benzoic acid was extracted from the mixture with ether and the aqueous phase was evaporated. The residue was desiccated and the organic residue was separated from sodium chloride by extraction with 2-propanol. Since the addition of ether caused no precipitation, all solvents were removed and the semi-solid residue was refluxed with hydrochloric acid (10 *N*; 25 ml.) for three hours. The solution was diluted, treated with carbon, and evaporated. Crystallization of the residue from 2-propanol containing a little dry ether afforded 5-aminovaleric acid hydrochloride (m.p. 86–88°, 1.27 g., 41%) which was recrystallized from 2-propanol and obtained as needles, m.p. 94–95°.

After addition of more anhydrous ether to the filtrate from which the amino acid hydrochloride crystallized, 0.35 g. of ureadivaleric acid separated. After recrystallization from water or 2-propanol, this melted at 188° (dec.).

For positive identification, 5-aminovaleric acid hydrochloride (0.32 g.) was dissolved in 1 *N* sodium hydroxide (10 ml.) and treated with benzoyl chloride (0.5 ml.) at 5° for one-half hour. The solution was then extracted with ether, acidified, and re-extracted with ether. The solvent was removed from the second extract and the residue, after being dried *in vacuo*, was extracted with ligroin (b.p. 86–100°) and crystallized from benzene, yielding colorless needles of 5-benzamidovaleric acid (21) (0.25 g., 54%), m.p. 93–94°.

Ethyl 5-aminovalerate hydrochloride. A mixture of 5.0 g. of 5-aminovaleric acid hydrochloride, 35 ml. of absolute ethanol, and 15 ml. of benzene was refluxed through a Dean-Stark apparatus (22) while a steady stream of hydrogen chloride was passed in. Every

half-hour for two hours, 10 ml. of distillate was removed and replaced with 10 ml. of dry benzene. The mixture was left at room temperature for 15 hours and then diluted with ether (100 ml.) and petroleum hexane (50 ml.), whereupon 5.0 g. (85%) of lustrous flakes of the ester hydrochloride separated. These were recrystallized from ethanolic hydrogen chloride and ether; m.p. 116°.

Anal. Calc'd for $C_7H_{16}ClNO_2$: N, 7.7. Found: N, 7.55.

Ethyl 5-isocyanatovalerate. Ethyl 5-aminovalerate hydrochloride (6.3 g.) was treated in boiling toluene with a stream of phosgene gas for one hour. Distillation of the products yielded 4.15 g. (70%) of the desired isocyanate at 115–117° (14 mm.).

Anal. Calc'd for $C_8H_{13}NO_3$: N, 8.2. Found: N, 8.5.

N,N'-Ureadivaleric acid. A mixture of 0.34 g. of ethyl 5-isocyanatovalerate, 0.34 g. of 5-aminovaleric acid hydrochloride, and 0.3 g. of sodium hydroxide in 4 ml. of water was warmed on a steam-bath for 30 minutes, then was cooled and acidified to Congo Red with concentrated hydrochloric acid. This caused the separation of 0.4 g. of ureadivaleric acid, m.p. 187°. Its m.p. was raised to 189° after crystallization from 2-propanol. This m.p. was not depressed on admixture of a sample of m.p. 188° formed above from the Lossen rearrangement.

Pyrolysis. The acid (0.28 g.) was held in a 10-ml. distillation flask in a preheated bath at 195–200° for 15 minutes. The flask was cooled and the contents distilled at 11 mm. to give crude 2-piperidone (0.22 g. or 76%), b.p. 135–140°. The latter was converted to its hydrochloride which was recrystallized first from a mixture of 2-propanol and ether (m.p. 178°), then from a little 2-propanol to bring the m.p. to 182–184°. This melting point was undepressed by mixing with an authentic specimen.

Ethyl N,N'-ureadivalerate, $CO(NHCH_2CH_2CH_2CH_2COOC_2H_5)_2$. A mixture of 0.65 g. of ethyl 5-isocyanatovalerate and 1 g. of water was boiled for a few minutes. On cooling, the oil solidified to a mass of silky needles; yield, 0.62 g. (100%); m.p. 94–95°. Crystallization from ethyl acetate or from a large volume of water brought the m.p. to 96–97°.

Anal. Calc'd for $C_{15}H_{28}N_2O_5$: N, 8.9. Found: N, 8.7.

Ethyl 5-(N'-phenylureido)valerate, $C_6H_5NHCONH(CH_2)_4COOC_2H_5$. A mixture of 0.85 g. of ethyl 5-isocyanatovalerate, 0.5 g. of aniline, and 25 ml. of dry ether was refluxed for two hours. The solvent was removed and the residue was taken up in benzene. Addition of petroleum hexane precipitated the product as an oil, which crystallized; yield, 1.22 g. or 100%. It was recrystallized from a mixture of ethyl acetate and petroleum hexane forming feathery needles, m.p. 87°.

Anal. Calc'd for $C_{14}H_{20}N_2O_3$: N, 10.6. Found: N, 10.7.

2-Piperidone-3-carboxylic acid. Ethyl 3-carbethoxy-2-piperidone, b.p. 160–170° (0.2 mm.) was prepared from ethyl 2-cyanoethylmalonate by the reductive cyclization procedure outlined by Albertson and Fillman (23). After distillation it solidified; m.p. 70–71° [Koelsch (24) reports 78–79°]. It was used directly in the next step. To the ester (1.71 g.) was added an ethanolic potassium hydroxide solution (0.56 g. in 10 ml.) and the resulting solution was kept at 25° for 11 hours. The salt which separated (1.52 g., 83%) was filtered off and washed with absolute ethanol and ether. An aqueous solution of the salt (1.5 g. in 1.5 ml. of water) was acidified at 0° to Congo Red with concentrated hydrochloric acid. The 2-piperidone-3-carboxylic acid (0.75 g., 60%) which separated was washed with a small amount of ice-water. It was crystallized from 2-propanol in the form of colorless prisms, m.p. 120°, with decomposition (sealed capillary, preheated bath temperature, 115°).

Anal. Calc'd for $C_6H_9NO_3$: C, 50.34; H, 6.3; N, 9.8.

Found: C, 50.19; 50.63; H, 6.0, 5.9; N, 9.7.

Rearrangement of sodium 3-carboxypropiono(benzoylhydroxamate). In toluene, Experiment 1. A suspension of 5.2 g. of the salt in 50 ml. of toluene was refluxed for three hours. The mixture was cooled and dry hydrogen chloride was passed through it for 30 minutes. The solid part was collected and washed with benzene. To remove some of the sodium chloride from the polyamide, the solid was suspended first in 2-propanol, then in anhydrous formic acid. The solution was filtered and evaporated, sodium chloride being fil-

tered off intermittently. Some sodium chloride persisted. The residue was dried at 100° under 20 mm. for six hours. This left a gum, in which some sodium chloride crystals were imbedded. It was soluble in water, pyridine, and concentrated hydrochloric acid and was insoluble in methanol, 2-propanol, Cellosolve, and chloroform. The gum had no melting point.

A 0.7-g. sample of the gum was treated in a sealed tube with 5 ml. of concentrated hydrochloric acid for five hours at 150°. The mixture was then diluted with water, treated with Norit, and evaporated. The residue was taken up in 10 ml. of normal sodium hydroxide solution and heated with 1.5 ml. of benzoyl chloride for an hour at 25°. It was then extracted with ether, acidified, and re-extracted with ether. Evaporation of the ether solution left a residue which was crystallized from benzene-ligroin; yield, 0.11 g., m.p. 110°. Repeated crystallization from benzene raised the m.p. to 116–117°. This was undepressed on admixture with an authentic specimen of 3-benzamidopropionic acid, m.p. 117–118°.

During benzoylation, 0.04 g. of material precipitated in the alkaline solution. This solid was insoluble in ether. It was collected, recrystallized from aqueous acetic acid, washed with benzene and water, and was recrystallized twice from ethanol. Its m.p. of 243° was undepressed on admixture with an authentic specimen of N,N′-ethylenedibenzamide, m.p. 243° (lit., 249°).

Experiment 2. A suspension of 2.5 g. of the salt in 20 ml. of toluene was heated on a steam-bath for two hours. The toluene-insoluble portion was extracted with two 50-ml. portions of boiling, absolute ethyl alcohol. There remained 0.47 g. of crude poly-β-alanine (m.p. 180°). A test for ash was positive. The sample was, therefore, dissolved in 4 ml. of water and the solution adjusted to approximately *p*H 5 by adding acetic acid. The polypeptide was then precipitated with ten volumes of absolute ethyl alcohol. Yield, 132 mg. This purification was repeated prior to analysis, yielding poly-β-alanine. This sample decomposed above 200° but did not melt at 300°. The analytical sample was dried at 150° for four hours.

Anal. Calc'd for $(C_3H_5NO)_x$: C, 50.7; H, 7.1; N, 19.7.

Found: C, 50.0; H, 7.2; N, 19.0

In water. A solution of 4.00 g. of sodium 3-carboxypropiono(benzoylhydroxamate) in 15 ml. of water was heated on a steam-bath for 30 minutes. Carbon dioxide was evolved. The solution was cooled and acidified with 4 ml. of concentrated hydrochloric acid. Benzoic acid (1.37 g., 72%, m.p. 116–118°) was removed and the filtrate was evaporated at 40–50°. The residue was dried *in vacuo* over sulfuric acid to an oily product which was refluxed with dry ethanolic hydrogen chloride. After precipitation with anhydrous ether, a semi-solid gum was obtained which was very soluble in chloroform, alcohol, and water and sparingly soluble in ether and benzene, but no crystalline hydrochloride could be obtained. The solvents, therefore, were evaporated. The residue was taken up in 10 ml. of concentrated hydrochloric acid and the solution was refluxed for one hour and then evaporated and dried *in vacuo* over sulfuric acid. Yield of crude β-alanine hydrochloride, m.p. 75–85°, 0.84 g., 44%.

For identification the sample was dissolved in 5 ml. of water and treated at 0° with 1.2 g. of sodium hydroxide in 5 ml. of water and 1.5 g. of benzoyl chloride. The 3-benzamidopropionic acid was worked up as described above for 5-benzamidovaleric acid, then was washed with benzene and recrystallized from water. Yield: 0.39 g., m.p. 112–114°. On recrystallization the melting point was raised to 117–118°. The melting point was not depressed on admixture with authentic 3-benzamidopropionic acid (25). Some N,N′-ethylenedibenzamide (0.09 g., m.p. and mixture m.p. 240–242°) was also isolated as above.

Rearrangement of sodium o-carboxybenzo(benzoylhydroxamate). In toluene. A suspension of 1.00 g. of this salt in 25 ml. of dry toluene was protected from moisture and placed on a steam-bath for one hour. Traces of carbon dioxide were observed in the exit gases with aqueous barium hydroxide. The cooled suspension was filtered. The residue was triturated with water, filtered, and washed with dilute hydrochloric acid and then with water. Benzoic acid was isolated from the first aqueous filtrate after acidification. After being crystallized from absolute ethyl alcohol, the sample of isatoic anhydride (26), m.p. 236–238° (dec.), weighed 0.32 g. (60%).

When dissolved in cold, dilute alkali, it exhibited the blue fluorescence typical of isatoic anhydride. Hydrolysis by an excess of either dilute potassium hydroxide or hydrochloric acid at atmospheric pressure yielded anthranilic acid, m.p. and mixture m.p. 143–144°.

In water. To 2.85 g. of *o*-carboxybenzo(benzoylhydroxamic) acid was added 15.0 ml. of 0.750 *N* sodium hydroxide solution. On gentle warming a clear solution was obtained but on further heating a precipitate was formed. This product was separated and recrystallized from ethanol, yielding isatoic anhydride (0.52 g., 32% yield), m.p. 237–238° by rapid heating.

Anal. Calc'd for $C_8H_5NO_3$: N, 8.6. Found: N, 8.5.

When the filtrate was acidified to Congo Red, 1.12 g. of crude benzoic acid, m.p. 115–118°, precipitated. The filtrate obtained after its separation was carefully neutralized (basic to Congo Red, acidic to litmus) and 0.56 g. of the amphoteric N-anthranoylanthranilic acid (m.p. 203–204°, 44% yield) was obtained after filtration and recrystallization from water (9).

5-Carboxyvalerohydrazide. A mixture of sodium ethyl adipate (19.6 g.) and hydrazine hydrate (85%, 10 g.) was warmed on the steam-bath for one hour, then was desiccated to dryness over sulfuric acid. The solid sodium salt was triturated with ethanol and ether, and collected; weight, 19.9 g., m.p. around 150° (dec.).

Anal. Calc'd for $C_6H_{11}N_2NaO_3$: N, 15.4; Na, 12.6.
Found: N, 15.4; Na, 12.3.

A suspension of the salt (1.82 g.) in ethanol (20 ml.) was neutralized with cold ethanolic sulfuric acid (0.5 g. in 10 ml.) and allowed to stand with occasional stirring for 30 minutes. Sodium sulfate was removed, the ethanolic filtrate was evaporated in an air stream, and the residue was rubbed with ethyl acetate and benzene to give 5-carboxyvalerohydrazide (0.4 g., 25% yield) which crystallized from ethyl acetate in colorless prisms, m.p. 92–93°.

Anal. Calc'd for $C_6H_{12}N_2O_3$: N, 17.5. Found: N, 17.9.

p-Methoxybenzylidene derivative. This compound was prepared by shaking an aqueous solution of the salt (3.6 g. in 15 ml.), just acidified with dilute hydrochloric acid, with anisaldehyde (3.0 g.). Crystals (5.16 g. or 93%) separated, m.p. 132°. Recrystallization from either ethyl acetate or ethanol produced felted needles, m.p. 142°.

Anal. Calc'd for $C_{14}H_{18}N_2O_4$: N, 10.1. Found: N, 9.9.

5-Carboxyvaleryl azide and its rearrangement. A solution of sodium 5-carboxyvalerohydrazide (3.64 g.) and sodium nitrite (1.4 g.) in water (16 ml.) was covered with alcohol-free ether (25 ml.) and stirred at 0° while dilute hydrochloric acid (18.5%, 8 ml.) was added slowly during 15 minutes. The temperature was kept below 10°. The aqueous phase was extracted several times with ether, and the combined ether fractions were washed with water and dried (sodium sulfate) at 0 to 5° for about two hours. The aqueous layer and the ether layer were processed separately.

The aqueous layer (45 ml.), after 24 hours at 25°, deposited 0.05 g. of beautiful plates, whose m.p. of 221° was not raised by recrystallization from water. This was 1,2-bis(5-carboxyvaleryl)hydrazine.

Anal. Calc'd for $C_{12}H_{20}N_2O_6$: C, 50.0; H, 7.0; N, 9.7.
Found: C, 50.4; H, 7.3; N, 10.1.

The ether solution was filtered into carbon tetrachloride (25 ml.) and the ether was slowly distilled off. The residual liquid was kept on a steam-bath for one hour. A vigorous evolution of nitrogen ensued and at first a gum separated which partly solidified. The solution was chilled and filtered to give an unstable, amorphous solid (1.81 g. or 63% based on $C_6H_9NO_3$) which was desiccated and used as soon as possible. The melting point range was about 70–75°. It was insoluble in the usual organic solvents including acetic anhydride at 100°. It reacted, however, with hot acetic acid or hot alcohol.

Anal. Calc'd for $C_6H_9NO_3$: C, 50.4; H, 6.3; N, 9.8.
Found: C, 50.5; H, 6.9; N, 9.8.

Evaporation of the carbon tetrachloride gave a gum, which was extracted with ether. Distillation of the ethereal solution gave a little α-piperidone which was converted to the hydrochloride (0.11 g.) and crystallized from 2-propanol; m.p. 183°. The ether-insoluble fraction was only a few milligrams.

Reaction with water. About 0.3 g. of the solid was boiled for several minutes with 3 ml. of water. Carbon dioxide was evolved (barium hydroxide solution). Evaporation of the clear solution *in vacuo* left an oil. Ethanolic hydrogen chloride and dry ether converted the latter to a precipitate of α-piperidone hydrochloride. After crystallization from 2-propanol, its m.p. and mixture m.p. was 180–182°.

Reaction with acid. Similarly when the substance (0.28 g.) was treated with 5 *N* hydrochloric acid (3 ml.), carbon dioxide was evolved. Evaporation, then two crystallizations from 2-propanol and a little dry ether yielded 5-aminovaleric acid hydrochloride (0.26 g. or 85%). It melted at 90° and was undepressed with authentic material. The material was further characterized by its benzoyl derivative which was first crystallized from benzene (m.p. 88°), then from water; m.p. 93–94°, undepressed with an authentic sample.

Pyrolysis of compound. The compound of m.p. 70–75° (0.34 g.) was distilled slowly *in vacuo* to give a pale yellow oil (0.19 g. or 81%), b.p. 155–160° at 30 mm. This was α-piperidone. Its hydrochloride (0.21 g.) prepared as above was crystallized from 2-propanol; m.p. 182–184°.

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SUMMARY

Previously described methods for acetylation or benzoylation of 3-carboxypropionohydroxamic or *o*-carboxybenzohydroxamic acids or their salts have yielded only cyclic derivatives. Conditions for obtaining the acyclic benzoyl derivatives are now described. Lossen rearrangement of the succinic acid derivative and also of the benzoyl derivative of 5-carboxyvalerohydroxamic acid affords polyamides or urea derivatives depending on the reaction medium. *o*-Carboxybenzo(benzoylhydroxamic) acid gave rise to isatoic anhydride and N-anthranoylanthranilic acid. 5-Carboxyvalerohydrazide was prepared and converted to the azide. Decomposition of the latter yielded α-piperidone and an amorphous product which behaved like a polymeric acid anhydride. The steps underlying these processes are discussed.

EVANSTON, ILLINOIS

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