flux for eight hours. After cooling, 30 ml. of water was added and the precipitated solid collected by filtration, washed thoroughly with water and dried; yield 0.57 g. (quantitative). Recrystallization first from 95% ethanol and then from 75% aqueous dimethylformamide gave long yellow needles, m.p. 258–259° (dec.).

Anal. Calcd. for $C_{20}H_{18}N_8O$: C, 67.0; H, 5.1; N, 23.4. Found: C, 67.3; H, 5.3; N, 23.2.

2-Amino-4-benzylamino-6,7-diphenylpteridine.—A mixture of 0.50 g. of 2,4-diamino-6,7-diphenylpteridine and 10 ml. of freshly distilled benzylamine was heated under reflux for eight hours. Addition of 50 ml. of 50% ethanol and cooling gave 0.44 g. (68%) of yellow crystals which were recrystallized from 40% aqueous dimethylformamide; m.p. 237–238°.

Anal. Calcd. for $C_{25}H_{20}N_6$: C, 74.2; H, 5.0; N, 20.8. Found: C, 74.5; H, 5.3; N, 21.1.

Acid Hydrolysis of 2-Amino-4-alkylaminopteridines.—A solution of 0.10 g. of the 2-amino-4-alkylaminopteridine in 4 ml. of 6 *N* hydrochloric acid was heated under reflux for one-half hour. The reaction mixture was evaporated to dryness, the residue dissolved in 10 ml. of 2 *N* sodium hydroxide and poured into 10 ml. of 3 *N* acetic acid. The product was identified as the corresponding 2-amino-4-hydroxypteridine by melting point and ultraviolet absorption spectrum.[2,10]

4-Ethanolamino-2-methylamino-6,7-dimethylpteridine (XIV).—A mixture of 0.30 g. of 2,4-bis-(methylamino)-6,7-dimethylpteridine and 10 ml. of freshly distilled ethanolamine was heated under reflux for 36 hours, at the end of which time the slow evolution of methylamine had ceased. Water was added to the cooled reaction mixture and the aqueous solution subjected to continuous ether extraction for four hours. Evaporation of the ether extract gave a yellow solid which was dissolved in methanol, treated with Norit and filtered. The product crystallized out in yellow needles upon the addition of an equal volume of benzene; yield 0.218 g. (64%). The compound was recrystallized from acetone for analysis; m.p. 214–215°.

Anal. Calcd. for $C_{11}H_{16}N_6O$: C, 53.2; H, 6.5; N, 33.9. Found: C, 53.5; H, 6.6; N, 33.9.

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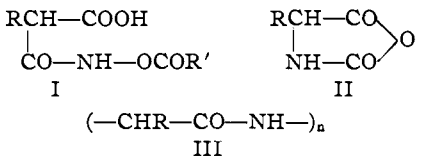
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Polypeptides Formed by the Lossen Rearrangement

BY CHARLES D. HURD AND LUDWIG BAUER

Two alkylcarboxyacetohydroxamic acids, HOOC–CHR–CONHOH, have been synthesized and studied to determine their behavior in the Lossen rearrangement. The radical R represents benzyl and ethyl. Polypeptides related to phenylalanine and α-aminobutyric acid were obtained. These polypeptides were insoluble in water but solubility was found in some organic solvents. All of the polypeptide fractions were hydrolyzable to the amino acids if sufficiently forced.

This work extends the findings of Hurd and Buess[1] on the rearrangement of α-carboxy hydroxamic acid derivatives into glycine and norleucine type polypeptides. An azasuccinic anhydride (II) was regarded as an intermediate between the hydroxamic derivative (I) and the polypeptide (III).



The present study takes up polypeptides, similarly prepared, which are composed of phenylalanine and α-aminobutyric acid units (R in III representing benzyl and ethyl, respectively).

A recent article by Hanby, Waley and Watson[2] mentions an attempt to synthesize 3-benzylazasuccinic anhydride by the Lossen rearrangement of α - carboxy - β - phenylpropiono - (benzoylhydroxamic) acid (I, R = benzyl). They gave no indication of their reaction conditions, but their article created the impression that the Lossen rearrangement failed to proceed. Since we have been studying this compound among others and have found that it does rearrange smoothly, we submit this report at the present time.

Tracey's summary[3] presents concisely the chemical and physical aspects of the Leuchs polymerization of azasuccinic anhydrides into polypeptides. Studies appearing since this summary are those of Hanby,[2] Coleman,[4] and by Wessely, Riedl and Tuppy.[5] That azasuccinic anhydrides were isolable on rearranging 2-carboxyalkanoyl azides in ether was demonstrated by Curtius and Sieber.[6] These anhydrides could be polymerized to polypeptides by conventional procedures. In contrast to this formation of polypeptides by both the Curtius and Lossen rearrangements, it is of interest to note that they are not formed by the Hofmann rearrangement. Instead, malonamic acids[7] give rise to amino acids. Similarly the Schmidt reaction on malonic acid[8] and on benzylmalonic acid gives glycine (29%) and DL-phenylalanine (16%) directly.

Preparation of the benzoylated α-carboxy hydroxamic acids followed the general procedure of Hurd and Buess.[1] Rearrangement of the sodium salts of these acids proceeds smoothly either in water solution or benzene suspension. With either approach polypeptide formation was observed accompanied by evolution of carbon dioxide and formation of sodium benzoate. The polypeptides did not melt sharply and were remarkably insoluble in water or boiling hydrochloric acid. They gave the ninhydrin test by adsorption.

Poly-DL-phenylalanine prepared in water was totally soluble in hot anhydrous formic acid, pyridine, formodimethylamide, *m*-cresol, and could be precipitated on adding water to the cold solution. If, however, this polymer was prepared in benzene, it was totally soluble only in *m*-cresol or pyridine. Whether or not this difference in solubility in formic acid and cresol gives an indication of the

(1) Hurd and Buess, THIS JOURNAL, **73**, 2409 (1951).
(2) Hanby, Waley and Watson, *J. Chem Soc.*, 3010 (1950).
(3) Tracey, *Annual Reports of the Chemical Society*, **46**, 225 (1949).
(4) Coleman, *J. Chem. Soc.*, 3222 (1950), and preceding papers.
(5) Wessely, Riedl and Tuppy, *Monatsh.*, **81**, 861 (1950).
(6) Curtius and Sieber, *Ber.*, **55**, 1543 (1922).
(7) Huang, Lin and Li, *J. Chinese Chem. Soc.*, **15**, 31 (1947), and preceding papers.
(8) Adamson, *J. Chem. Soc.*, 1564 (1939); Briggs, *et al.*, *ibid.*, 61 (1942).

structural configuration (folded or extended form) as pointed out recently by Bamford, Hanby and Happey[9] remains a speculative question. Poly-DL-α-aminobutyric acid, however, is soluble in anhydrous formic acid whether the polymer is prepared in water or in benzene.

The polypeptides were partly soluble in ethanol. Poly-DL-phenylalanine also was partly soluble in benzene. Attempts to isolate any water-soluble polypeptides formed during the rearrangement met with little success.

When the rearrangement of α-carboxy-β-phenylpropiono-(benzoylhydroxamic) acid (II, R = $C_6H_5CH_2$–) was conducted in water in the presence of DL-phenylalanine, the polypeptide so formed was much more soluble in ethanol. Indeed, a little of it could even be recrystallized from hot water. Possibly this greater solubility is related to a shorter chain length in the polymer.

When the rearrangement was carried out in ethanol, practically no precipitation of polypeptide occurred. Hydrolysis of the reaction mixture with hot hydrochloric acid in an open vessel yielded phenylalanine. Heating in sealed tubes was required, however, to effect hydrolysis of the more insoluble polypeptides.

No rearrangement of I or its sodium salt was observed when the reaction was performed in the presence of hot ammonium hydroxide solution. Instead, ammonolysis occurred, yielding benzamide and the hydroxamic acid

$$C_6H_5CH_2CH\begin{matrix}\diagup CONHOH \\ \diagdown COONH_4\end{matrix}.$$

Rearrangement to α-amino-β-phenylpropionamide would have been plausible in view of Curtius and Sieber's[6] observation that the corresponding anilide was formed on treatment of C-benzylazasuccinic anhydride with aniline.

Experimental

Sodium Ethyl Benzylmalonate.—Ethyl benzylmalonate (25.0 g.) was treated with sodium hydroxide (4.0 g.) in ethanol (200 ml.) at 20° for 21 hours, then at 80° for half an hour. The hot solution was filtered (2.6 g. insoluble) and concentrated *in vacuo*. Colorless felted needles separated on cooling. Eventually, 19.3 g. (79%) of the salt was obtained. Recrystallization from ethanol afforded fine needles, m.p. 157° (dec.) when plunged into a preheated bath at 150°. The salt was not hygroscopic.

Anal. Calcd. for $C_{12}H_{13}O_4Na$: Na, 9.4. Found: Na, 9.3.

Disodium α-Carboxy-β-phenylpropionohydroxamate.—An ethanolic solution of hydroxylamine was prepared by adding a cold sodium ethoxide solution (2.3 g. of sodium in 50 ml. of ethanol) to a warm ethanolic hydroxylammonium chloride solution (7.0 g. in 75 ml. of ethanol) and filtering off the precipitated sodium chloride. This filtrate was added to a solution of sodium ethyl benzylmalonate (19.3 g.) in ethanol (150 ml.) and the mixture was treated slowly at 0° with sodium ethoxide solution (2.3 g. of sodium). The disodium salt was collected after four hours at room temperature; yield when dry, 19.6 g. or 77% based on ethyl benzylmalonate. The salt gave a brownish-violet color with ferric chloride solution. It dissolved in hot methanol, but was insoluble in hot ethanol.

Anal. Calcd. for $C_{10}H_9NO_4Na_2$: Na, 18.2; N, 5.5. Found: Na, 17.6, 17.7; N, 5.1, 5.2.

α-Carboxy-β-phenylpropionohydroxamic Acid.—Careful acidification of an ice-cold aqueous solution of the disodium salt afforded the hydroxamic acid which crystallized from a mixture of ethyl acetate and petroleum pentane in colorless platelets, m.p. 146° (dec.), when a sealed tube was plunged in the preheated bath at 140°; m.p. in literature,[2] 150° (dec.); red-violet color with ferric chloride solution.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7. Found: C, 57.8; H, 5.0; N, 6.8.

Ammonium Salt.—α-Carboxy-β-phenylpropionohydroxamic acid readily dissolved in concentrated ammonium hydroxide solution. Addition of dry dioxane precipitated the salt. It was recrystallized from the same solvents in colorless platelets as the monohydrate, m.p. 178° (effervescence) in a sealed tube, preheated bath (temperature being 170°). It was dried at 110° for two hours, preceding the analysis.

Anal. Calcd. for $C_{10}H_{14}N_2O_4.H_2O$: N, 11.5. Found: N, 11.1, 11.2.

Potassium Salt.—A mixture of ethyl benzylmalonate (25.0 g.) and cold methanolic potassium hydroxide solution (5.6 g. in 50 ml.) was let stand for 12 hours, then was warmed on the steam-bath for 20 minutes, filtered and concentrated *in vacuo*. The residual gum was dissolved in methanol (25 ml.) and added to an ethanolic solution (75 ml.) of hydroxylamine (equivalent to 3.3 g.). The solution was treated with potassium ethoxide solution (3.9 g. potassium in 75 ml. of ethanol). The solution was concentrated *in vacuo*. Addition of ether precipitated 12.3 g. of the salt. Further concentration gave another crop of 10.5 g., making a total of 22.8 g. (92%). The salt was recrystallized from methanol (Dry Ice and acetone) and dried at 100° for one hour.

Anal. Calcd. for $C_{10}H_{10}NO_4K$: K, 15.8; N, 5.7. Found: K, 16.0; N, 5.6, 5.7.

Potassium Sodium α-Carboxy-β-phenylpropionohydroxamate.—Ethyl benzylmalonate (25.0 g.) was hydrolyzed as described above, and to the solution of potassium ethyl benzylmalonate in methanol (25 ml.) was added a methanolic solution of hydroxylamine (from 7 g. of hydroxylammonium chloride) followed by a solution of sodium methoxide (2.3 g. of sodium in 25 ml. of methanol). The product was filtered off after one hour, dried *in vacuo* and weighed 24 g. When heated, it turned brown at 250° but melted above 300°. This salt was used without further purification in the next experiment.

α-Carboxy-β-phenylpropiono-(benzoylhydroxamic) Acid.—Disodium α-carboxy-β-phenylpropionohydroxamate (5.1 g., 0.02 mole) was dissolved in water (50 ml.) and stirred vigorously with benzoyl chloride (2.8 ml., 20% excess) around 0 to 5° in the presence of a little saponin. A gum separated. The solution was kept slightly alkaline by the addition of 10% sodium hydroxide solution as required (universal indicator). After 15 minutes another 1.0 ml. of benzoyl chloride was added and the mixture stirred 15 minutes longer. After 30 minutes ethyl acetate (75 ml.) was added and the solution acidified in the cold with concentrated hydrochloric acid. The two layers were separated. The aqueous layer was extracted with ethyl acetate (100 ml. in all). The combined ester fraction was evaporated under diminished pressure and the residue triturated with benzene. There was obtained α-carboxy-β-phenylpropiono-(benzoylhydroxamic) acid (3.5 g. or 55% yield). It melted at 137° (dec. with frothing) when the sealed tube was plunged in a preheated bath at 130°. Recrystallization from chloroform mixed with petroleum pentane or benzene gave colorless cube-like crystals with the same melting point. Hanby[2] reports m.p. 145–146° (dec.).

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.2; H, 4.8; N, 4.5. Found: C, 65.5; H, 4.8; N, 4.7.

Benzoylation of the potassium sodium salt (8.1 g.) as described above gave 3.8 g. (40%) of this acid.

Sodium α-Carboxy-β-phenylpropiono-(benzoylhydroxamate).—To 25 ml. of an ice-cold ethanolic solution of 8.33 g. of α-carboxy-β-phenylpropiono-(benzoylhydroxamic) acid was added an equivalent portion of sodium ethoxide solution (0.615 g. of sodium). The salt separated as a gelatinous precipitate, but became more granular and easier to filter after addition of dry ether (10 ml.) and petroleum pentane (50 ml.). The salt was filtered and dried *in vacuo* over phosphoric anhydride, yield 8.9 g. (91%).

Anal. Calcd. for $C_{17}H_{14}NO_5Na$: Na, 6.9. Found: Na, 7.3.

Rearrangement of Sodium α-Carboxy-β-phenylpropiono-(benzoylhydroxamate) in Hot Water.—A solution of 3.2 g.

(9) Bamford, Hanby and Happey, *Nature*, **166**, 829 (1950); Hanby, Waley and Watson, *J. Chem. Soc.*, 3239 (1950).

of the sodium salt in water (50 ml.) was heated on the steam-bath for two hours. Carbon dioxide was evolved and the insoluble polypeptide separated. The mixture was cooled and filtered, the polypeptide washed with cold water, dried first at 60° then *in vacuo* over phosphoric anhydride. The yield of 1.02 g. represents a 74% yield of a polypeptide $[-CH(C_7H_7)CONH-]_x$. A suspension of it in ethanol (1.02 g. in 25 ml.), when boiled for 15 minutes and filtered hot, afforded an insoluble fraction (0.41 g.). This product was practically insoluble in boiling benzene. When heated with an aqueous solution of ninhydrin, the polypeptide turned blue. The material turned brown around 210° and decomposed extensively in the range 240–250°.

This insoluble fraction was insoluble also in chloroform but it was soluble in boiling formamide (solution turning somewhat yellow), *m*-cresol, pyridine, formo-(dimethylamide) and hot anhydrous formic acid. On cooling, the polypeptide did not crystallize from formic acid. For analysis it was precipitated from formic acid solution by water and dried at 130° and 3 mm. for 4 hours.

Anal. Calcd. for $(C_9H_9NO)_x$: C, 73.5; H, 6.1; N, 9.5. Found: C, 70.9; H, 6.2; N, 9.4.

The ethanolic filtrate was evaporated in an air stream and the residue recrystallized from aqueous ethanol twice and then dried at 100° (3 mm.) for 4 hours. The product commenced to decompose around 135° and melted approximately at 155°. It was soluble not only in ethanol but also in 1-butanol, formic acid, sparingly soluble in benzene, and insoluble in boiling hydrochloric acid. It also gave a ninhydrin test by adsorption.

Anal. Calcd. for $(C_9H_9NO)_x$: C, 73.5; H, 6.1; N, 9.5. Found: C, 73.1; H, 6.2; N, 9.3.

Rearrangement in Hot Water in the Presence of DL-Phenylalanine.—A solution of sodium α-carboxy-β-phenylpropiono-(benzoylhydroxamate) (1.5 g.) and DL-phenylalanine (0.80 g.) in water (25 ml.) was heated at 100° for two hours, and was filtered hot from some gummy precipitate which solidified on cooling. The insoluble polypeptide gave a strong ninhydrin test by adsorption and, when heated, turned brown at 180°, m.p. 240° (dec.). The yield was 0.28 g. When some of this polypeptide (0.17 g.) was boiled with ethanol (15 ml.) for 30 minutes, only 0.025 g. did not dissolve. On cooling, 0.03 g. of the polypeptide crystallized from ethanol.

The hot aqueous filtrate precipitated some polypeptide (0.08 g.) which turned brown and started to decompose around 180° and melted around 250°. This product crystallized from water and was dried. The yield from this experiment was 0.36 g. (54%).

Anal. Calcd. for $(C_9H_9NO)_n$: C, 73.4; H, 6.16; N, 9.52. If assumed as a pentapeptide, $C_{45}H_{47}N_5O_6$: C, 69.2; H, 6.45; N, 8.95. Found: C, 68.0; H, 6.3; N, 8.1.

Action of Ammonia on α-Carboxy-β-phenylpropiono-(benzoylhydroxamic) Acid.—A solution of 3.1 g. of the acid in 25 ml. of concentrated ammonium hydroxide was heated on the steam-bath for 30 minutes and then extracted with three 40-ml. portions of boiling chloroform. Evaporation of the solvent left a crystalline residue (1.1 g. or 90%) of crude benzamide, m.p. 120°; m.p. and mixed m.p., 127°, after recrystallization from water.

The ammoniacal aqueous phase was boiled with sodium hydroxide to expel ammonia, acidified with hydrochloric acid, and evaporated to dryness. Extraction with ether gave benzylmalonic acid, m.p. 119–120° after recrystallization. This m.p. was depressed by benzoic acid. No amino acid could be isolated.

Action of Ammonia on Sodium α-Carboxy-β-phenylpropiono-(benzoylhydroxamate).—The sodium salt (3.4 g.) when treated as above also gave benzamide (0.83 g.), m.p. 125–126°. Careful acidification of the alkaline solution yielded α-carboxy-β-phenylpropionohydroxamic acid, m.p. 146° (dec.).

Rearrangement of Sodium α-Carboxy-β-phenylpropiono-(benzoylhydroxamate) in Cold Water.—A filtered aqueous solution of sodium α-carboxy-β-phenylpropiono-(benzoylhydroxamate) (1.35 g. in 25 ml.) was set aside at room temperature for nearly five days. Several hours after commencement of the experiment, the polypeptide separated in the form of a gel occluding most of the solvent. The gelatinous precipitate was collected, dried at 60° then *in vacuo* over phosphoric anhydride and weighed 0.45 g. (76% yield). The polypeptide sintered and darkened around 160°, and melted approximately at 200° with extensive decomposition. The aqueous filtrate gave a strong ninhydrin test but did not precipitate any polypeptide when heated. When some of the polypeptide (0.20 g.) was boiled with ethanol, four-fifths of it dissolved leaving the ethanol-insoluble polypeptide (0.04 g.) which now melted approximately at 290° with decomposition, but it began to turn brown at 190°.

A sample from the same batch of sodium salt (1.39 g.), when rearranged in hot water (25 ml.) for two hours, yielded 0.52 g. (83%) of the polypeptide.

Rearrangement of Sodium α-Carboxy-β-phenylpropiono-(benzoylhydroxamate) in Dry Benzene.—A suspension of 3.35 g. of sodium α-carboxy-β-phenylpropiono-(benzoylhydroxamate) in 50 ml. of pure benzene, dried over sodium, was refluxed for three hours. The mixture was cooled, filtered and washed with cold benzene. The colorless material on the filter was digested with warm water and refiltered. The insoluble part weighed 1.00 g. (68%, based on $[-CH(C_7H_7)CONH-]_x$). Evaporation of the colorless benzene filtrate gave a glass (0.31 g. or 21%) which was insoluble in hot ethanol, or boiling concentrated hydrochloric acid. It turned brown around 240°, black at 290° and melted above 300°.

Anal. (for benzene-soluble substance). Calcd. for $(C_9H_9NO)_x$: C, 73.5; H, 6.1; N, 9.5. Found: C, 71.8; H, 6.1; N, 9.5.

The benzene-insoluble material (0.60 g.) was boiled with ethanol (25 ml.) for 15 minutes and filtered hot. There remained 0.46 g. of insoluble polypeptide. This material turned brown around 260°, black around 320°, and melted around 330° with extensive decomposition. The polypeptide gave a faint ninhydrin test by adsorption and was totally soluble in hot *m*-cresol or pyridine, sparingly soluble (only 10%) in hot formamide and insoluble in hot formic acid or formodimethylamide.

Anal. Found: C, 70.3, 70.9; H, 5.7, 5.4; N, 9.5, 10.4.

Rearrangement of Sodium α-Carboxy-β-phenylpropiono-(benzoylhydroxamate) in Ethanol.—α-Carboxy-β-phenylpropiono-(benzoylhydroxamic) acid (3.13 g.) was dissolved in dry ethanol (50 ml.) and treated with sodium ethoxide solution (0.23 g. of sodium). The gelatinous sodium salt commenced to precipitate. The mixture was refluxed for two hours, cooled to 0°, and acidified with concentrated hydrochloric acid (15 ml.). Sodium chloride so formed was removed and washed with hydrochloric acid (10 ml.).

The filtrate was then heated at 100° with more hydrochloric acid (50 ml.) for 18 hours, cooled and filtered from some brown insoluble material (0.14 g.), and concentrated to small bulk in a stream of dry air to yield DL-phenylalanine hydrochloride (0.71 g.), m.p. 228° (dec.). Further evaporation gave an additional crop (0.38 g.) of similar purity and then a second crop (0.22 g.), m.p. 224–226°. The total yield (1.31 g.) was 65%.

Rearrangement in Aqueous Ethanol.—A solution of α-carboxy-β-phenylpropiono-(benzoylhydroxamic) acid (1.04 g.) in ethanol (10 ml.) was treated with sodium ethoxide solution (0.15 g. of sodium) and then diluted with water (35 ml.). The solution was kept on the steam-bath for two hours. After most of the ethanol had evaporated, a crystalline precipitate appeared which was filtered (0.031 g.), m.p. 289–290°. Recrystallization from dilute acetic acid gave platelets, m.p. 290–291°. Dibenzyldiketopiperazine described by Erlenmeyer and Lipp[10] melted at 290–291°.

Hydrolysis of the Polypeptides (a) from Water Rearrangement.—The polypeptide (0.70 g.) prepared in the reaction in a water solution was heated with concentrated hydrochloric acid (10 ml.) in a sealed tube at 150° for 12 hours. When cool, the mixture was dissolved in warm water, treated with decolorizing carbon and concentrated in a stream of dry air on the steam-bath till a crust of crystals formed. The solution was cooled to 0°. The DL-phenylalanine hydrochloride was collected on a filter, washed with a little ice-cold hydrochloric acid, then dry ether, oven dried at 100°, then desiccated *in vacuo* over potassium hydroxide. The filtrates were processed similarly for additional yield. In this way 0.78 g. of DL-phenylalanine hydrochloride (81% based on polypeptide) was obtained as colorless crystalline salt, m.p. 228° (dec.), bath tempera-

(10) Erlenmeyer and Lipp, *Ann.*, **219**, 206 (1883); Fischer, *Ber.*, **34**, 451 (1901).

ture 220°. The m.p. recorded by Curtius and Sieber is 235° (dec.). Treatment of an aqueous solution of the salt with ammonium hydroxide afforded DL-phenylalanine, m.p. 273° (dec.) (lit.[11] m.p. is 271–273°).

(b) From Benzene Rearrangement.—The benzene-insoluble polypeptide (0.70 g.) was heated with hydrochloric acid (10 ml.) as described above, affording DL-phenylalanine hydrochloride (0.82 g. or 85%), m.p. 228° (dec.).

The *p*-toluenesulfonyl derivative of DL-phenylalanine was prepared by the procedure of McChesney and Swann[12] and was recrystallized once from aqueous ethanol, then twice from benzene, forming clusters of soft colorless needles, m.p. 133° (lit. 135°).

Disodium α-Carboxybutyrohydroxamate.—Ethyl ethylmalonate (18.8 g.) was added to a cold ethanolic sodium hydroxide solution (4.0 g. in 200 ml.) and set aside at 5° for 11 hours. The reaction mixture was then placed for half an hour on the steam-bath, filtered hot from insoluble material (3.9 g.) and concentrated to small bulk *in vacuo*. Since the sodium salt could not be isolated easily, it was mixed with an ethanolic solution of hydroxylamine (from 10.5 g. of hydroxylammonium chloride). This was followed by the slow addition of sodium ethoxide solution (2.3 g. of sodium in 50 ml. of ethanol) at 20°. The salt commenced to separate and was totally precipitated by the addition of dry ether (50 ml.) and ligroin (b.p. 30–60°, 200 ml.). It was collected after eight hours, washed with ligroin and dried *in vacuo;* yield 15.8 g. (83% based on ethyl ethylmalonate). The salt was slightly deliquescent and gave brownish-violet color with ferric chloride. For analysis it was boiled with ethanol, filtered hot and dried at 100°.

Anal. Calcd. for $C_5H_7NO_4Na_2$: Na, 24.1. Found: Na, 23.8.

Potassium Sodium α-Carboxybutyrohydroxamate.—Ethyl ethylmalonate (18.8 g.) was hydrolyzed with ethanolic potassium hydroxide solution (5.6 g. in 125 ml.) as described above. Potassium ethyl ethylmalonate was not isolated but was treated at room temperature as above, first with ethanolic hydroxylamine solution and then with sodium ethoxide solution. The mixed salt (19.7) was isolated and used without further purification for benzoylation experiments.

α-Carboxybutyrohydroxamic Acid.—A suspension of 1 g. of the disodium salt in ethyl acetate was shaken with 5 *N* hydrochloric acid (minimum quantity) till solution was effected. The organic layer was separated. The aqueous phase was extracted with ethyl acetate; the combined ester layers were dried (sodium sulfate), and the solvent removed at 25° in a current of dry air leaving a residue of 0.1 g. of the crude acid. This was crystallized from ethyl acetate: colorless rhombs, m.p. 123–124° (effervescence) when a sealed tube was plunged into a preheated bath at 120°. The acid gave a red-violet color with ferric chloride solution.

Anal. Calcd. for $C_5H_9NO_4$: C, 40.7; H, 6.2; N, 9.5. Found: C, 41.1; H, 6.3; N, 9.8.

Ammonium Salt.—Addition of dioxane to a solution of α-carboxybutyrohydroxamic acid in ammonium hydroxide solution afforded beautiful colorless rhombs, m.p. 168° (frothing), preheated bath temperature 160°.

Anal. Calcd. for $C_5H_{12}N_2O_4$: N, 17.1. Found: N, 17.2.

α-Carboxybutyro-(benzoylhydroxamic) Acid.—A solution of disodium α-carboxybutyrohydroxamate (3.82 g., 0.02 mole) in cold water (40 ml.) was benzoylated at 5° as described above in the preparation of α-carboxy-β-phenylpropiono-(benzoylhydroxamic) acid, affording α-carboxybutyro-(benzoylhydroxamic) acid. After crystallization from a mixture of ethyl acetate and petroleum hexane it weighed 2.91 g. (58%). For analysis the material was recrystallized from ethyl acetate and was obtained in clusters of colorless prisms, m.p. 144° (with effervescence) with preheated bath at 138°.

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.4; H, 5.2; N, 5.6. Found: C, 58.0; H, 5.0; N, 5.8.

Benzoylation of the potassium sodium salt (4.15 g., 0.02 mole) gave the same derivative (3.28 g. or 66%).

Sodium α-Carboxybutyro-(benzoylhydroxamate).—A mixture of α-carboxybutyro-(benzoylhydroxamic) acid (4.64 g.), ethanol (15 ml.) and sodium ethoxide solution (0.46 g. in 10 ml. of ethanol) remained homogeneous at room temperature. Precipitation was achieved on addition of dry ether (25 ml.) and petroleum pentane (100 ml.); yield 4.77 g. after drying *in vacuo*.

Anal. Calcd. for $C_{12}H_{12}NO_5Na$: Na, 8.4. Found: Na, 7.9, 8.0.

Rearrangement of Sodium α-Carboxybutyro-(benzoylhydroxamate) in Hot Water.—An aqueous solution of the salt (2.73 g. in 30 ml.) was heated on the steam-bath for two hours and gave on cooling 0.59 g. of the polypeptide (70% yield based on $[-CH(C_2H_5)CONH-]_x$). When boiled for one hour with ethanol, and filtered hot, 0.36 g. of the polypeptide remained insoluble. This sample was suspended in boiling toluene for 15 minutes but no appreciable loss in weight was observed (0.02 g.). The polypeptide was then dried for four hours at 160° (0.2 mm.).

Anal. Calcd. for $(C_4H_7NO)_x$: C, 56.45; H, 8.3; N, 16.45. Found: C, 54.8; H, 8.0; N, 15.9.

The polypeptide was then dissolved in hot formic acid, cooled and precipitated with two volumes of water, boiled again with toluene and then dried at 160° (0.5 mm.) for four hours.

Anal. Found: C, 55.3; H, 7.7; N, 15.4.

Rearrangement of Sodium α-Carboxybutyro-(benzoylhydroxamate) in Benzene.—A suspension of the salt (1.38 g.) in dry benzene (15 ml.) was heated for two hours, cooled and filtered. The mixture of sodium benzoate and polypeptide was warmed with water (15 ml.) and refiltered to separate the polypeptide (0.38 g. or 88%). About 0.33 g. of this product remained undissolved on boiling with ethanol (25 ml.) for one hour. This material was boiled with toluene (25 ml.) for 15 minutes but lost no weight. It was soluble in hot formic acid. The polypeptide was dried at 160° (0.2 mm.) for four hours for analysis.

Anal. Found: C, 55.9; H, 8.45; N, 15.7.

Both types of polypeptides gave ninhydrin colors by adsorption.

When heated, the sample browned at 240–250°; it turned black around 300° but did not melt to give a meniscus by 360°.

Rearrangement in Ethanol.—To a solution of α-carboxybutyro-(benzoylhydroxamic) acid (5.0 g.) in dry ethanol (100 ml.) was added sodium ethoxide solution (0.46 g. of sodium). Sodium benzoate separated during 3 hours of refluxing, and it occluded most of the solvent. Concentrated hydrochloric acid (50 ml.) was then added, and the reaction mixture was heated overnight on the steam-bath and finally concentrated in a dry air stream to a small bulk. The yellow solution was treated with carbon, evaporated and dried. The gum so obtained was triturated with ethanolic hydrogen chloride and dry ether and filtered after some time. The crystals were washed thoroughly with dry ether and dioxane till colorless; m.p. 170°. The yield of crude α-aminobutyric acid hydrochloride was 1.0 g. (37%). Further recrystallizations from ethanolic hydrogen chloride and dry ether raised the melting point to 179–180°, undepressed on admixture of an authentic specimen of similar melting point. The mother liquors were heated overnight with ethanolic hydrogen chloride. Treatment with dry ether and dry dioxane caused precipitation of ethyl α-aminobutyrate hydrochloride (0.06 g.). It was crystallized from the same solvents; m.p. and mixed m.p. 137–138°, undepressed on admixture with an authentic specimen.

Hydrolysis of Poly-DL-α-aminobutyric Acid.—This polypeptide (0.85 g.) was heated in a sealed tube with hydrochloric acid (10 *N*, 5 ml.) at 140° for 10 hours. On cooling, the contents of the tube were treated with Norit, then evaporated at 100° and finally dried over phosphoric anhydride for 3 days at 20 mm. and then for four hours under 0.5 mm. pressure. Recrystallization from ethanol (containing some dry hydrogen chloride) and dry ether afforded colorless needles (0.855 g., 61%) of α-aminobutyric acid hydrochloride, m.p. 175–177°. Similarly after heating the mother liquor with alcoholic hydrogen chloride as above, colorless needles of ethyl α-aminobutyrate hydrochloride (0.265 g., 16%) were isolated, m.p. 137–138°.

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The Arylmethylation of Benzene Derivatives

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The acid-catalyzed condensation of paraformaldehyde with a number of substituted benzenes to produce substituted diphenylmethanes has been studied. Conditions have been found under which good yields (up to 86%) of the diphenylmethanes are obtained. It has also been shown that further condensation to form substituted dihydroanthracenes is possible.

The acid-catalyzed condensation of a number of aromatic compounds with formaldehyde or formaldehyde derivatives is known to yield diarylmethanes under the proper conditions. This reaction is similar to the process of chloromethylation studied in a previous publication,[1] the benzyl type of carbonium ion being a possible intermediate in both processes. The similarity of the two reactions is borne out by the frequent appearance of diarylmethanes as by-products in chloromethylations.

The arylmethylation reaction is known chiefly for such reactive benzene derivatives as the phenols and arylamines. A smaller number of the less reactive compounds have been studied, examples being benzene,[2] toluene,[3] benzyl chloride,[3] diphenyl,[3] iodobenzene,[4] naphthalene[5] and mesitylene.[6] In most of this early work the yields were not reported. The preparative value of the reaction appeared in later studies on the reaction of benzene with formalin to give 70–76% yields of diphenylmethane.[7]

In these examples the formaldehyde was used in a variety of forms such as formalin, paraformaldehyde, methylal, trioxymethylene and methylene diacetate. Sulfuric acid, often with a diluent, was used as the catalyst.

The present studies were made to determine further applications and limitations of the reaction when used with non-phenolic and non-aminated derivatives of benzene. A variety of polyalkylbenzenes, a polyhalobenzene, and a polyalkyldiphenylmethane were condensed with paraformaldehyde in the presence of sulfuric acid. The aromatic compounds were chosen having such a configuration as would permit the formation of only a single isomer in the product. A diluent for the acid was found to be necessary in order to prevent excessive sulfonation of the compounds. For this purpose 95% ethanol was usually employed since previous work[7a,8] indicates the presence of alcohols to be advantageous. The results appear in Table I.

In addition to the above syntheses, unsuccessful attempts were made to condense *p*-toluic acid with paraformaldehyde. Reaction other than esterification occurred only at high concentrations of sulfuric acid and resulted chiefly in sulfonation.

These results show that many benzene derivatives whose substituents are *o*- and *p*- directing (even though they may be deactivating) can be converted to the diarylmethanes in good yield. The reaction is free from rearrangements and extensive tar formation, and the products are readily purified. Except for bis-(2,4,6-trimethylphenyl)-methane, none of these diarylmethanes had been previously prepared in yields exceeding 15% of theory based on the benzene derivative. Bis-(2,4,6-trimethylphenyl)-methane had been prepared in 50% over-all yield from bromomesitylene by means of a four-step synthesis, involving the preparation of dimesityl ketone.[9] Bis-(2,4,6-triisopropylphenyl) - methane and bis - (2,4 - dichlorophenyl)-methane are new compounds.

An interesting extension of the method is seen in the further condensation of bis-(1,2,3,4-tetramethylphenyl)-methane with paraformaldehyde to give 1,2,3,4,5,6,7,8-octamethyl-9,10-dihydroanthracene. The over-all yield based on 1,2,3,4-tetramethylbenzene was 52%. The compound had been previously prepared in three steps from 2,3-dimethylhexadiene-2,4 by means of a Diels–Alder condensation, resulting in an over-all yield of 25%.[10] Selenium dehydrogenation of the product gave 1,2,3,4,5,6,7,8-octamethylanthracene as described by these workers. The formation of anthracenes as by-products in condensations using formaldehyde has also been noted.[11]

The slow reaction and low yield obtained in preparing bis-(triisopropylphenyl)-methane is indicative of the great steric hindrance present in 1,3,5-triisopropylbenzene. The latter is electronically analogous to 1,3,5-trimethylbenzene, a compound which gave good yields. The inertness of *p*-toluic acid shows that meta-directing groups have a strong suppressive action with respect to arylmethylation.

The side reactions observed in these preparations were sulfonation and polymer formation. Both reactions were minimized by the use whenever possible of low acid concentration, low reaction

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