[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF PRINCETON UNIVERSITY.]

NEW HYDROXAMIC ACIDS DERIVED FROM CYCLOPROPANE CARBOXYLIC ACID, ISOBUTYRIC ACID AND DIBENZYL-ACETIC ACID. A COMPARATIVE STUDY OF THE BECKMANN REARRANGEMENT OF THEIR DERIVATIVES.[1]

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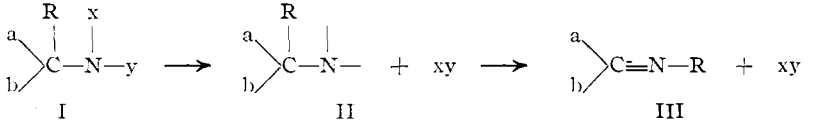
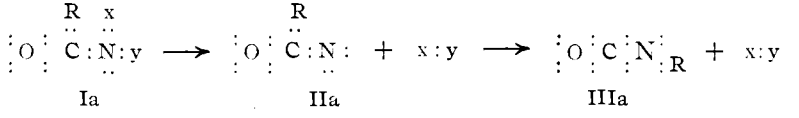
I. Introduction.

Although many different classes of organic compounds show rearrangements of the Beckmann[2] type, there is one fundamental transformation which stands out as essential to all such reactions; some radical, R, attached to a carbon atom in the original compound, is found in combination with a nitrogen atom after the rearrangement has occurred. If oximes are excluded, a general formula may be employed to represent the classes of compounds which show such changes.



The symbols a and b stand for R_2, O=, HN=, and for similar groups; while x and y may be replaced by H or a metal atom together with some other radical such as Cl, Br, OH, OCOR. In the azides, N_2= takes the place of x and y.

For several years, plain structural formulas of this kind have been replaced by electronic formulas[3] in which positive and negative signs serve to represent bonds between atoms. In an article[4] recently published in THIS JOURNAL, the rearrangement of a hydroxamic acid derivative was represented by symbols more in harmony with recent views concerning the structure of the atom and the nature of "bonds" in organic compounds. Thus:



[1] This article is based upon a thesis submitted by Alfred W. Scott to the Faculty of the Graduate School of Princeton University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] In this article, the term Beckmann rearrangement is used in its broadest sense and includes rearrangements of the Hofmann, of the Curtius and of the Lossen types.

[3] Jones, *Am. Chem. J.*, **48**, 25 (1921); **50**, 441 (1913); THIS JOURNAL, **36**, 1268 (1914). Stieglitz, *ibid.*, **36**, 288 (1914).

[4] Jones and Hurd, THIS JOURNAL, **43**, 2424 (1921).

It has been assumed for some time that, during the reaction, the radical R separates from the carbon atom and "wanders" to the univalent nitrogen atom (IIa) not because of "any complicated mechanism" such as ring formation, a bivalent carbon radical, or the like,[5] but, rather, under the influence of electrical constraint brought about by the necessity for redistribution of electrons[3] to form the more stable system represented by the isocyanate stage (IIIa) in the reaction.

If this be the case, then, while the positive radical R is shifting its position from the carbon atom to the nitrogen atom, it must exist momentarily as a *free radical.* An hypothesis which follows logically as a consequence of this conclusion was advanced in the article mentioned above;[4] *viz.*, that an intimate relation must exist between the ease of rearrangement of the univalent nitrogen derivative (IIa) and the ability of the radical R to exist as a *free radical* (*e. g.*, triphenylmethyl, tri-biphenylmethyl, etc.).

Furthermore, this assumption suggests definite experiments which are now being tried in this laboratory. If certain azides, $RCON_3$, are caused to undergo rearrangement in a solution which contains a group such as triphenylmethyl, it seems probable that *this free radical* may compete with the radical R for possession of the nitrogen position and, consequently, that *two isocyanates may be formed* instead of one.

$$O{=}C(R){-}N_3 + R' \longrightarrow O{=}C(R){-}N{=} + N_2 + R' \begin{cases} \longrightarrow O{=}C{=}N{-}R + R^1 + N_2 \\ \longrightarrow O{=}C{=}N{-}R^1 + R + N_2 \end{cases}$$

Thus, with benzoyl azide, $C_6H_5CON_3$, and triphenylmethyl, both phenyl isocyanate and triphenylmethyl isocyanate would be expected. The results of these experiments will be published later.

The compounds described in this paper were prepared and studied for the purpose of determining the influence which certain hydrocarbon radicals would exert in producing variations in the ease of rearrangement of several related hydroxamic acid derivatives.

For this purpose, the following series of hydroxamic acids was prepared. With the exception of (d), the parent substances were new compounds.

(a) $(H_3C)_2CHC(O)NHOH$

*Iso*butyr-hydroxamic Acid

(b) $(H_2C)_2CHC(O)NHOH$

Cyclopropane-carboxyl-hydroxamic Acid

(c) $(C_6H_5CH_2)_2CHC(O)NHOH$

Dibenzylacet-hydroxamic Acid

(d) $C_6H_5CH_2CH_2C(O)NHOH$

Benzylacet-hydroxamic Acid

[5] Stieglitz (Hesse), *Am. Chem. J.*, **29**, 57 (1903). Nef, *Ann.*, **298**, 308 (1897); **318** (1901). Jones, Ref. 3.

Compound (d) was studied by Thiele and Pickard[6] and the behavior of some of its derivatives described. This acid was included in the series in order to be able by comparison to determine more definitely the effect of the second benzyl group in Compound (c).

The preparation of tribenzylacetic acid was undertaken in order to note the effect of three benzyl groups. For this purpose, tribenzylmethyl chloride was synthesized. However, since this chloride failed to react to give a Grignard reagent, we have not synthesized tribenzylacetic acid; so the study of tribenzylacet-hydroxamic acid and its derivatives was discontinued for the present.

The reactions of the potassium, sodium, and silver salts of the acetyl esters and of the benzoyl esters of the parent substances were used for comparison. Dry salts of this kind usually have a fairly definite temperature at which they puff or explode to form an isocyanate and an acetate or benzoate. However, the length of time the salts have been kept after their preparation frequently alters perceptibly the temperature at which this change occurs.

In order to avail ourselves of a somewhat more reliable source of information concerning the ease of rearrangement of these salts, the effect of heat upon clear aqueous solutions of the potassium and the sodium salts was also studied. Under these circumstances, the isocyanate first produced is usually converted into the corresponding *sym.*di-substituted urea

$$2\ O{=}C{=}N{=}R + H_2O \longrightarrow O{=}C{=}(NHR)_2 + CO_2.$$

II. Comparison and Interpretation of Results.

The following table shows the temperatures at which sudden decomposition of the dry salts occurred.

TABLE I
DECOMPOSITION TEMPERATURES

Parent hydroxamic acids	Benzoyl Ester			Acetyl Ester		
	K Salt	Na Salt	Ag Salt	K Salt	Na Salt	Ag Salt
$(CH_3)_2CHCONHOH$ (a)	Spontaneous	75°	Above 200°	Spontaneous	——	——
$(C_3H_5)CONHOH$ (b)	103°	143°	Above 200°	155°	——	——
$(C_6H_5CH_2)_2CHCONHOH$ (c)	Not isolated	Not isolated	143°	Not isolated	Not isolated	145°

These substances may be regarded as derivatives of acet-hydroxamic acid. On the other hand, Compounds (b) and (c) bear a structural relation to *iso*butyr-hydroxamic acid (a).

[6] Thiele and Pickard, *Ann.*, **309**, 197 (1921).

In the interpretation of this table, we shall make the assumption that extreme ease of rearrangement explains the failure to isolate some of the salts of (c). No doubt, the failure to obtain these salts may be attributed, in part, to their solubility in alcohol-ether in which they were prepared. From a general survey of the table, it appears that, in every case, the derivatives of (c) were found to undergo rearrangement with the greatest ease; that the compounds of (b) required the highest temperature to effect their rearrangement; and that the salts of (a) occupy an intermediate position. It is interesting to note, that, in the case of the salts of each hydroxamic acid ester (dihydroxamic acid) the ease of rearrangement was as follows: K > Na > Ag.

Two salts, both derivatives of (a), exhibited properties worthy of special mention. A pure sample of the potassium salt of the benzoyl ester of *iso*butyr-hydroxamic acid was made and placed in a desiccator. The desiccator was evacuated, and in less than 20 minutes the salt decomposed spontaneously with such violence as to scatter potassium benzoate throughout the entire container.

The potassium salt of the acetyl ester of (a) exhibited the same phenomenon, although, in this instance, it was necessary for the salt to stand in an evacuated desiccator from 5 to 6 hours before the change occurred. Two similar cases have been described previously; *viz.*, the potassium salt of the benzoyl ester of phenylacet-hydroxamic acid[7] and the sodium salt of the benzoyl ester of dichloro-acet-hydroxamic acid.[8]

In studying the second method of comparison of the different salts given in Table I, it was found that the temperature required to produce a precipitate in an aqueous solution of the potassium salt, also caused a precipitate with an aqueous solution of the sodium salt of the same hydroxamic acid ester. Therefore, the table given in Table II was condensed in order that the behavior of these compounds could be seen at a glance.

Rearrangement was determined by measuring the temperature at which clear aqueous solutions (approximately equivalent) of the salts of alkali metals began to give a precipitate. The components of the precipitate were determined. In the case of the cyclopropane series, about 75% of the corresponding hydroxamic ester was found to be regenerated. The presence of this proportion of the ester showed that, to a large extent, simply hydrolysis of the salt had taken place, and that rearrangement to give the isocyanate and then the urea was distinctly a secondary reaction. In the *iso*butyric acid series, similar products of hydrolysis were also detected; here, however, the urea was the primary product and the regenerated ester occurred in almost negligible amounts. A more detailed

[7] Jones, *Am. Chem. J.*, **48**, 8 (1912).

[8] Jones and Sneed, THIS JOURNAL, **39**, 670 (1917).

description of the treatment to which these salts were subjected will be found in the experimental part. The temperatures recorded in the table are those of the bath employed in heating the vessel which contained the different solutions.

TABLE II

Parent Hydroxamic Acids		Aqueous Solutions of the Potassium or Sodium Salts of the Benzoyl Esters
		° C.
$(CH_3)_2CHCONHOH$	(a)	50 chiefly rearrangement
$(C_3H_5)CHCONHOH$	(b)	90 mainly hydrolysis
$(C_6H_5CH_2)_2CHCONHOH$	(c)	20 rearrangement
$(C_6H_5CH_2)CH_2CONHOH$	(d)	80 rearrangement

It may be seen that, insofar as the ease of arrangement is concerned, the results of this table agree fairly well with those of Table I. Since the acyl group was always the same (*viz.*, benzoyl) and, from Table II, we see that the metal atom caused no appreciable difference in reactivity, we are forced to the conclusion that the variations in behavior of these compounds must be attributed to the influence of the hydrocarbon radicals of the acyl groups from which the hydroxamic acids were originally formed. Therefore, in terms of these radicals the ease of rearrangement may be expressed by the following sequence: dibenzylmethyl > *iso*propyl > benzylmethyl > cyclopropyl.

Without further consideration, it can be seen that, among these hydroxamic acid derivatives, those which contain the trimethylene ring are the most stable. On the other hand, the derivatives of *iso*butyr-hydroxamic acid show a remarkable tendency to rearrange. This is especially noteworthy, because of the intimate structural relationship which exists between the hydroxamic acids derived from *iso*butyric acid, and the corresponding derivatives of cyclopropane-monocarboxylic acid.

It may be noted also that derivatives of acet-hydroxamic acid[9] and of propionhydroxamic acid[10] undergo rearrangement with greater difficulty than the corresponding derivatives of *iso*butyr-hydroxamic acid.

The wide differences observed in the behavior of derivatives of benzylacetic acid and of dibenzylacetic acid seems, at first, to lead to the assumption that the introduction of the second benzyl radical increases, in a marked degree, the ease with which corresponding derivatives undergo

[9] Jones, *Am. Chem. J.*, **29**, 1 (1898).

[10] The benzoyl ester of propionhydroxamic acid was prepared by Jones and Neuffer, THIS JOURNAL, **39**, 664 (1917). It was observed that the solid potassium salt of this ester decomposed at 120–124°, the sodium salt, at 86° and the silver salt, above 150°.

rearrangement. However, the fact that derivatives of acethydroxamic acid[9] and of propionhydroxamic acid[10] (methylacet-hydroxamic acid) are not so sensitive to rearrangement as similiar derivatives of *iso*butyr-hydroxamic acid (dimethylacet-hydroxamic acid) seems to force upon us the conclusion that at least a part of the effect produced by the introduction of the second benzyl radical must be attributed to the formation of an *iso*- or branched chain.

The relations existing between chemical constitution and melting points are presented in the following table.

Parent Hydroxamic Acids			Benzoyl Ester	Acetyl Ester
		°C.	°C.	°C.
$(CH_3)_2CHCONHOH$	(a)	116	148	87
$(C_3H_5)CHCONHOH$	(b)	112	150	108
$(C_6H_5CH_2)_2CHHONHOH$	(c)	146	147	126

It is interesting to note that the difference between the melting points of dibenzylacet-hydroxamic acid and of its benzoyl ester is only one degree. A regularity is observed throughout the series, *viz.*, the melting points of the free hydroxamic acids lie between those of the higher-melting benzoyl derivatives and of the lower-melting acetyl derivatives.

III. Consideration of Some Details.

The behavior of cyclopropane-monocarboxyl-hydroxamic acid and its derivatives was of particular interest, since no other hydroxamic acids related to cyclic hydrocarbons other than benzene and its homologs, or hydrocarbons with condensed benzene nuclei, have ever been described.

In the preparation of this hydroxamic acid, the method employed by Perkin[11] for the preparation of the necessary ethyl cyclopropane-monocarboxylate was found to give the best results. However, by modifying Perkin's procedure in several details, we have been able to obtain yields 50% better than those secured by him.

It was observed that the formation of dibenzylacet-hydroxamic acid by the interaction of ethyl dibenzylacetate and free hydroxylamine proceeded very slowly, even when the reaction mixture was kept between 60° and 70°. The presence of an extra mol of sodium methylate failed to increase the speed of the reaction to any great extent.

It was found that this hydroxamic acid could be prepared readily and in quantity by the action of free hydroxylamine on the acid chloride dissolved in benzene. The preparation of hydroxamic acids from acid chlorides is a well known method.[12] If water, generally employed, is used as the reaction medium, a mixture of the mono- and the dihydroxamic acids always results. The method suggested above for obtaining mono-

[11] Perkin, *J. Chem. Soc.*, **75**, 921 (1899).

[12] Lossen, *Ann.*, **161**, 347 (1872); **175**, 285 (1875).

hydroxamic acids gives yields almost quantitative, with no traces of the di- acids; it has been studied previously in this laboratory.[4]

Experimental Part.

1. Hydroxamic Acids Related to Cyclopropane Carboxylic Acid.

The Preparation of Ethyl Cyclopropane-1:1-Cyanocarboxylate.—Perkin[13] described the preparation of cyclopropane-monocarboxylic acid in which an alcoholic solution of sodium ethyl malonate and ethylene dibromide was digested under pressure. All attempts to prepare the acid by this method gave very small yields. Later Perkin[14] stated that when ethyl cyano-acetate was substituted for ethyl malonate and the mixture was digested at ordinary pressure, he was able to obtain a 50% yield of ethyl cyclopropane-1:1-cyanocarboxylate. We found the latter method preferable.

The changes made in Perkin's synthesis consisted first, in the use of an automatic stirrer; and second, in the elimination of the washing to which Perkin submitted the product of reaction to remove colored materials. We find that practically all the color is eliminated by the steam distillation which follows.

To 400 cc. of absolute alcohol in a flask provided with an automatic stirrer and reflux condenser, 27.4 g. of sodium was added in small portions. After all of the sodium had disappeared and the solution had cooled to room temperature, 100 g. of ethyl cyano-acetate was introduced; this caused the sodium salt to separate. Then 100 g. of ethylene dibromide was introduced and the mixture was heated to boiling on a water-bath. The reaction mixture was stirred continuously during the entire operation. After the product had become neutral to litmus, all of the alcohol was distilled and sufficient water was added to dissolve the sodium bromide which had separated. The mixture was extracted with ether several times, the ether was evaporated, and the residual oil was submitted to steam distillation. This distillate was saturated with ammonium sulfate and extracted with ether 5 or 6 times. After the ether had been dried over calcium chloride, it was distilled and the oil was submitted to fractional distillation. The distillate which boiled between 212° and 216°, weighed 64.4 g. Yield, 76%.

The Preparation of 1:1-Cyclopropane-dicarboxylic Acid was carried out according to the method described by Perkin. A portion of the acid, recrystallized from ether, gave a melting point of 134°.

The Preparation of Cyclopropane-monocarboxylic Acid.—In the preparation of cyclopropane-monocarboxylic acid by dry distillation of this dibasic acid, it was found that, by using a lower temperature than that called for by Perkin and by distilling the monobasic acid under diminished pressure as it formed, a better yield was secured.

When 36.4 g. of the dibasic acid was distilled slowly under diminished pressure and the distillate was fractionated, 11.6 g. of material was obtained. It boiled between 182° and 195°. On refractionation, nearly all of this substance distilled between 184° and 186°. This was practically pure cyclopropane-monocarboxylic acid. A small amount of this compound can be recovered by redistillation of the lower as well as the higher boiling fractions.

Attempts to prepare the ethyl ester by saturation of an alcoholic solution of this acid with dry hydrogen chloride gave a product which contained chlorine. This substance was ethyl chlorobutyrate produced by the splitting of the trimethylene ring.[15] In order to obtain the ester of cyclopropane-monocarboxylic acid, the method of Per-

[13] Perkin, *J. Chem. Soc.*, **47**, 807 (1885).

[14] Ref. 11, p. 925.

[15] Boone and Perkin, *J. Chem. Soc.*, **67**, 118 (1895); *Ber.*, **35**, 2104 (1902). Kijner *J. Russ. Chem. Soc.*, **41**, 659 (1909). Tanatar, *Z. physik. Chem.*, **41**, 735 (1902). Kotz, *J. prakt. Chem.*, [11] **68**, 153 (1903). Barthe, *Bull. soc. chim.*, [111] **35**, 40 (1906).

kin[13] was followed. This required the silver salt. Since the silver salt is extremely soluble in water which contains small amounts of acid, of ammonia, or even of ammonium salts, a method for the preparation of the pure, solid ammonium salt was devised, so that a concentrated solution of it could be used to prepare the silver salt.

AMMONIUM SALT.—A stream of dry ammonia gas was passed through a solution of the free acid in anhydrous ether, kept cold throughout the operation by means of an ice-salt bath. After a short time, the ammonium salt began to separate as a voluminous white solid. It was collected and dried in a desiccator containing calcium oxide mixed with ammonium chloride. The dry salt melted at 115°. For analysis the ammonium salt was digested with aqueous sodium hydroxide and the ammonia was distilled into 0.1 *N* acid. The excess of acid was titrated with a solution of a standard base.

Analysis. Subs., 0.2149: 2.12 cc. of 1 *N* acid. Calc. for $C_4H_9O_2N$: N, 13.87. Found: 13.82.

The salt was extremely soluble in water and in alcohol containing very small amounts of water. It could be kept for several months in a desiccator containing a mixture of calcium oxide and ammonium chloride.

SILVER SALT.—To 25 g. of the ammonium salt dissolved in a very small amount of water, the calculated amount of a concentrated solution of silver nitrate was added slowly, while the solution was stirred vigorously. The silver salt was collected and washed with cold water. Since this salt retained moisture very tenaciously, it was dried for some time at 110°, and then analyzed. The analysis confirmed the formula $C_4H_5O_2Ag$, found by Perkin.

The dry salt was heated slowly in a test-tube immersed in a bath of sulfuric acid. At about 120°, it assumed a pale yellow color and, finally, a deep brown shade when the bath had reached 170°.

The Preparation of Ethyl Cyclopropane-monocarboxylate was carried out by refluxing a suspension of the silver salt in ether with ethyl iodide according to the method described by Perkin.

A. **Cyclopropane-carboxyl-hydroxamic acid,** $\begin{matrix} H_2C \\ | \\ H_2C \end{matrix}\!\!>\!CHC(O)NHOH$.—A solution of 0.96 g. of sodium in methanol was added to a solution of 2.9 g. of hydroxylammonium chloride in 25 cc. of methanol. After this mixture had been cooled and filtered to remove sodium chloride, 4.2 g. of ethyl cyclopropane-monocarboxylate was poured into it. Finally, 0.84 g. of sodium in methanol was introduced and the mixture was allowed to stand over night in a warm place. After half an hour, a drop of the solution gave a deep purple color when acidified and treated with ferric chloride. The next morning dry carbon dioxide was passed into the solution thoroughly cooled, and the sodium carbonate which formed was removed by filtration. After evaporation of the alcohol, a viscous semi-solid mass resulted.

This mass was dissolved in water and treated with a solution of copper acetate. A grass-green copper salt of the hydroxamic acid was precipitated; it was collected, washed thoroughly with water and dried over sulfuric acid. When the dry copper salt had been pulverized carefully, it was suspended in methanol and a stream of dry hydrogen sulfide was passed through the suspension. The solution was filtered from copper sulfide and the methanol evaporated.

The product was a yellowish crystalline material possessing an odor characteristic of impure hydroxamic acids prepared from their copper salts by this method. Upon recrystallization of it from warm ethyl acetate, pure cyclopropane-monocarboxylic hydroxamic acid was obtained; it melted at 124° with decomposition. When ligroin is

added to the ethyl acetate solution, some of the yellow impurity is precipitated together with a part of the hydroxamic acid.

Analyses. Subs., 0.2145: 26.03 cc. of N (22.3°, 754. mm.). Calc. for $C_4H_7O_2N$: N, 13.86. Found: 13.92.

Subs., 0.21: H_2O, 0.1345; CO_2, 0.364. Calc. for $C_4H_7O_2N$: C, 47.5; H, 6.99. Found: C, 47.27; H, 7.16.

The hydroxamic acid was soluble in water, in methanol, in ethyl alcohol, and in hot ethyl acetate. It was only slightly soluble in ether and was insoluble in ligroin.

B. Benzoyl Ester of Cyclopropane-Carboxyl-hydroxamic Acid, $C_3H_5C(O)NHO \cdot COC_6H_5$.—When an aqueous solution of the sodium salt of (**A**) was shaken with benzoyl chloride, the benzoyl ester mixed with benzoyl chloride and benzoic acid separated as a white mass. The product was collected and pressed on a porous plate and, when dry, was extracted repeatedly with boiling ligroin and recrystallized from hot ethyl alcohol to which water was added until a slight turbidity occurred. As the solution cooled, pure benzoyl ester separated in the form of white needles which were collected, washed with dilute alcohol and dried. It melted at 150°.

Analyses. Subs., 0.4931; 30.4 cc. of N (24.7°, 741 mm.). Calc. for $C_{11}H_{11}O_3N$: N, 6.83. Found: 6.9.

Subs., 0.1543: H_2O, 0.0772; CO_2, 0.3643. Calc. for $C_{11}H_{11}O_3N$: C, 64.36; H, 5.41. Found: C, 64.38; H, 5.59.

It is soluble in ether and in ethyl alcohol, but only slightly soluble in ligroin and is insoluble in water.

POTASSIUM SALT OF (**B**).—A solution of 0.4 g. of the benzoyl ester in absolute alcohol was cooled by means of an ice-salt bath, and treated with the calculated amount of potassium ethylate. The potassium salt, a white solid, was collected, washed with anhydrous ether and dried *in vacuo* over sulfuric acid. Anhydrous ether added to the filtrate precipitated more of the potassium salt. The dry salt puffed when it was heated to 103°. An isocyanate odor was detected and potassium benzoate was formed.

Analysis. Subs., 0.172: K_2SO_4, 0.0599. Calc. for $C_{11}H_{10}O_3NK$: K, 16.07. Found: 15.64.

A clear aqueous solution of 1.2 g. of the potassium salt, when heated to 90°, gave a white solid product. This was collected and washed with water. A portion of the filtrate was made slightly acid and, upon the addition of a solution of ferric chloride, an intense purple coloration was produced, which showed that a part of the benzoyl ester, formed by hydrolysis of the salt, had been hydrolyzed still further to yield some monohydroxamic acid. When the filtrate was acidified, carbon dioxide was evolved and 0.3 g. of benzoic acid was precipitated.

The solid product was extracted with a solution of sodium hydroxide, and from this solution 0.1 g. of the benzoyl ester was recovered. That portion of the solid which was insoluble in alkalies resembled the expected symmetrical di-cyclopropyl urea. It was insoluble in water, but very soluble in alcohol and in ether. However, the quantity obtained was too small to permit of complete purification and analysis. The partially purified solid melted between 172° and 178°.

When the dry potassium salt was heated until decomposition ensued, it gave a low-boiling oil, evidently cyclopropyl isocyanate. This oil was distilled and the vapor was passed into a small amount of aniline. The excess of aniline was removed by extraction with acid and the solid residue was crystallized from hot ether and ligroin. It melted at 151°, and its properties corresponded with those of phenyl-cyclopropyl urea, $C_6H_5NHCONH(C_3H_5)$, described by Kijner.[16]

[16] Kijner, *J. Russ. Chem.*, **47**, 304–317 (1905).

SODIUM SALT OF (B).—A solution of 0.5 g. of the benzoyl ester in cold absolute alcohol was treated with the calculated amount of sodium ethylate. The addition of more than 6 volumes of anhydrous ether was required to precipitate the sodium salt. This was collected and dried *in vacuo* over sulfuric acid. The dry salt puffed at 143°; a deposit of sodium benzoate remained in the test-tube and an isocyanate odor was noticed. An aqueous solution of the sodium salt behaved in a manner similar to that of the potassium salt described above.

SILVER SALT OF (B).—A solution of silver nitrate was added to a clear aqueous solution of the potassium salt. The white silver salt was collected, washed with water, then with alcohol, and finally with ether.

Analysis. Subs., 0.2468: Ag, 0.0843. Calc. for $C_{11}H_{10}O_3NAg$: Ag, 34.57. Found: 34.16.

When the dry salt was heated above 200°, it decomposed and gave a strong isocyanate odor.

C. **Acetyl Ester of Cyclopropane-monocarboxyl-hydroxamic acid,** $(C_3H_5)CONHO\cdot COCH_3$.—A slight excess of acetic anhydride was added to 1 g. of cyclopropane-monocarboxyl-hydroxamic acid. When the mixture was warmed gently, it became a clear liquid which solidified almost immediately. As the temperature was raised slightly, the product became liquid once more. This solution was stirred until a test portion failed to give a purple coloration with ferric chloride. The excess of acetic anhydride and of acetic acid was removed by placing the product in a vacuum desiccator over solid potassium hydroxide.

The ester, recrystallized from warm ether, formed very fine white needles so closely matted together that the product retained the shape of the filter paper upon which it was collected. Dried *in vacuo* over sulfuric acid, it melted at 108°.

Analysis. Subs., 0.2783: 24.2 cc. of N (23°, 748 mm.). Calc. for $C_6H_9O_3N$: N, 9.78. Found: 9.87.

It was soluble in water, in alcohol, in acetone, in ethyl acetate, and in hot ether, but only slightly soluble in cold ether, and insoluble in ligroin.

POTASSIUM SALT OF (C).—A cold solution of 0.5 g. of the acetyl ester in absolute alcohol was treated with the calculated amount of potassium ethylate; upon the addition of anhydrous ether, the potassium salt was obtained as a white precipitate. This was separated, washed with ether, and dried *in vacuo* over sulfuric acid. The dry salt puffed when immersed in a bath previously heated to 155°.

Analysis. Subs., 0.0891: K_2SO_4, 0.0423. Calc. for $C_6H_8O_3NK$: K, 21.58. Found: 21.32.

2. Hydroxamic Acids Related to Dibenzylacetic Acid.

The Preparation of Dibenzylacetyl Chloride, $(C_6H_5CH_2)_2CHCOCl$.—Ethyl dibenzyl-aceto-acetate was prepared according to the method of Merz and Weith[17] and also that of F. Sesermann.[18] Both methods gave good results. This compound was made to undergo the "acid splitting," as described by Deikmann and Kron,[19] *viz.*, by refluxing it with sodium ethylate. The ethyl dibenzylacetate, thus produced, was saponified with alcoholic potash. One crystallization of the product from hot ligroin gave dibenzylacetic acid which melted at 89°. Its properties corresponded with the known properties of dibenzylacetic acid.

When 10 g. of dibenzylacetic acid was treated with an excess of thionyl chloride

[17] Merz and Weith, *Ber.*, **10**, 759 (1877).

[18] Sesermann, *ibid.*, **6**, 1086 (1873).

[19] Deikmann and Kron, *ibid.*, **41**, 1266 (1908).

and the mixture was warmed, sulfur dioxide and hydrogen chloride were evolved and the reaction mixture became liquid. After this material had been refluxed for a short time the excess of thionyl chloride was distilled and the residual oil was submitted to fractional distillation under diminished pressure. When the last traces of thionyl chloride had been removed, the thermometer rose rapidly to 203°, and the entire product distilled between 203° and 205° under 17 mm. It was a yellow oil soluble in benzene and insoluble in water. It was hydrolyzed slowly in moist air.

D. Dibenzylacet-hydroxamic Acid, $(C_6H_5CH_2)_2CHCONHOH$. METHOD I.—A methanol solution containing 5.25 g. of hydroxylammonium chloride was treated with 1.7 g. of sodium in methanol. Sodium chloride was removed and the filtrate was treated with 20 g. of ethyl dibenzylacetate. These materials were thoroughly mixed and a solution of 1.5 g. of sodium in methanol was poured in. After several hours at room temperature, the mixture gave no test with ferric chloride for a hydroxamic acid. At the end of 18 hours, only a slight coloration was produced when ferric chloride was added to an acidified test portion of the reaction mixture. So the solution was warm several hours to 60° or 70° and the methanol allowed to evaporate.

This gave a white solid which was dissolved in a cold solution of sodium hydroxide and extracted with ether to remove any unchanged ester. When the solution was acidified, a solid white substance separated. This was collected, washed with water and pressed on a porous plate. The dry solid was extracted repeatedly with hot ligroin to remove any dibenzylacetic acid, and the undissolved dibenzylacet-hydroxamic acid was recrystallized from hot benzene. It melted at 146°. The yield was very small.

Analysis. Subs., 0.2718: 13.16 cc. of N (18°, 745.3 mm.). Calc. for $C_{16}G_{17}O_2N$: N, 5.49. Found: 5.57.

It was soluble in hot benzene, in alcohol, in alkalies and in ethyl acetate, but only slightly soluble in cold benzene and in ether, and insoluble in water or in ligroin. An alcoholic solution, made faintly acid with acetic acid, gave a grass-green copper salt when an alcoholic solution of copper acetate was added. An alcoholic solution of the hydroxamic acid reduced a solution of silver nitrate slowly.

METHOD II.—The following method gave dibenzylacet-hydroxamic acid practically quantitatively. To a solution of 10 g. of dibenzylacetyl chloride in dry benzene, slightly more than the calculated amount of free hydroxylamine was added. When the mixture was agitated, it became warm rapidly, so that it was necessary to cool the flask with tap water. Hydroxylammonium chloride and some of the hydroxamic acid separated as a white precipitate, while the excess of free hydroxylamine formed a gum which adhered to the side of the containing vessel. When the solution was heated to boiling, filtered while hot, and then cooled, pure dibenzylacet-hydroxamic acid separated. Its properties corresponded in every way with those described above.

E. Benzoyl Ester of Dibenzylacet-hydroxamic Acid, $(C_6H_5CH_2)_2CHCONHO-COC_6H_5$.—When an aqueous solution of 10 g. of dibenzylacet-hydroxamic acid with the calculated amount of alkali was cooled and shaken with benzoyl chloride, this ester separated as a white solid. This material collected and pressed on a porous plate The dry product, extracted with hot ligroin several times to remove unused benzoyl chloride and benzoic acid, was crystallized from hot alcohol by addition of hot water until the solution became faintly turbid. As this mixture cooled, pure benzoyl ester of dibenzylacet-hydroxamic acid separated in the form of white needles which were collected, washed with cold, very dilute alcohol and dried. It melted at 147°.

Analysis. Subs., 0.3068: 10.2 cc. of N (20°, 746 mm.). Calc. for $C_{23}H_{21}O_3N$: N, 3.90. Found: 3.80.

The ester was soluble in alcohol; it was only slightly soluble in ether and was insoluble in water.

POTASSIUM SALT OF (**E**).—Five-tenths g. of the benzoyl ester was dissolved in cold absolute alcohol and treated with the calculated amount of potassium ethylate, upon the addition of over 10 volumes of anhydrous ether, only a very small amount of the solid salt was precipitated. This was collected and dried *in vacuo* over sulfuric acid. When the salt was heated on a spatula, it decomposed to give a vapor with an isocyanate odor, and potassium benzoate. When the salt was treated with cold water, an insoluble part always remained. This was washed with alkali and water. After it was crystallized from dil. alcohol, its properties corresponded with those of the synthesized *sym.*bi-dibenzylmethyl urea described below. When the potassium salt was dissolved in water at room temperature, a turbidity appeared immediately, and the corresponding disubstituted urea began to separate at once. Application of heat increased the speed of this reaction.

An attempt was made to prepare the sodium salt of (**E**) by the method used above in the preparation of the potassium salt No precipitate was produced, even when several hundred cubic centimeters of anhydrous ether was added. An aqueous extraction of this alcohol-ether solution of the sodium salt soon gave the urea.

SILVER SALT OF (**E**).—A solution of 1 g. of the benzoyl ester in absolute alcohol was cooled to $-10°$, and treated with slightly less than the calculated amount of potassium ethylate. Then an alcoholic solution containing slightly less than the calculated amount of silver nitrate was added to this cold solution. Only a small amount of a very light, fluffy precipitate resulted. However, upon the addition of anhydrous ether, the silver salt was obtained in quantity. This was collected, washed with absolute alcohol and with water, then again with absolute alcohol and finally with anhydrous ether. This silver salt, dried *in vacuo* over sulfuric acid, puffed at 143°, to give an oil which distilled into the cooler portions of the tube, while silver benzoate was left as solid. Evidently, this oil was dibenzylmethyl isocyanate, for upon treating it with warm water the corresponding urea was produced.

Analysis. Subs., 0.1860: Ag, 0.0428. Calc. for $C_{23}H_{20}O_3NAg$: Ag, 23.14: Found: 23.01.

F. Acetyl Ester of Dibenzylacet-hydroxamic Acid, $(C_6H_5CH_2).CHCON(H)\text{-}OCOCH_3$.—Five-tenths g. of pure dibenzylacet-hydroxamic acid and a slight excess of acetic anhydride were heated on a water-bath until a test portion failed to give a violet coloration with ferric chloride. As the product became cool, it solidified. It was kept over soda-lime in a vacuum desiccator until all traces of acetic acid and acetic anhydride had disappeared, and then recrystallized from hot benzene. It melted at 126°.

Analysis. Subs., 0.4194: 18.4 cc. of N (19°, 741 mm.). Calc. for $C_{16}H_{12}O_3N$: N, 4.71. Found: 5.00.

The ester was soluble in hot benzene, in alcohol, in ethyl acetate and in acetone. It was only slightly soluble in ether and was insoluble in water and in ligroin. When a hot, saturated solution of the ester in absolute alcohol was cooled slowly, large, clear, square plates were obtained.

An attempt to prepare the potassium salt by dissolving 1.2 g. of (**F**) in cold absolute alcohol and adding to it the calculated amount of potassium ethylate failed to give any precipitate, even when more than 200 cc. of anhydrous ether was introduced. Traces of moisture absorbed during manipulation evidently effected rearrangement of some of the salt, for on evaporation of a part of the alcohol-ether solution *in vacuo* over sulfuric acid some *sym.*bi-dibenzylmethyl urea was obtained. In the preparation of the sodium salt, difficulties similar to those described in the preparation of the potassium salt were encountered.

SILVER SALT OF (**F**).—Five-tenths g. of the acetyl ester was dissolved in ab-

solute alcohol. To this solution, cooled to $-12°$, slightly less than the calculated amount of an alcoholic solution of silver nitrate was added. When the walls of the containing vessel were scratched with a stirring rod, a white silver salt was precipitated. This was collected, washed with absolute alcohol, then with water, again with absolute alcohol, and finally with anhydrous ether.

The dry salt, heated slowly, turned brown at 125°, and suddenly black at 145°. When it was heated on a spatula, an isocyanate odor was detected. On exposure to light it turned purple. It was insoluble in water, in alcohol and in ether, but was soluble in ammonium hydroxide. A suspension of the salt in cold water containing the calculated amount of potassium bromide was shaken thoroughly and filtered from the silver bromide formed. When this solution was warmed, it gave a precipitate of *sym.* bi-dibenzylmethyl urea.

In order to prepare a sample of this urea for comparison, dibenzyl ketone made by the dry distillation of the calcium salt of phenylacetic acid, as described by Apitzsch,[20] was converted into the oxime, from which dibenzylmethyl amine was prepared according to the method described by Noyes.[21] The urea was synthesized from this amine as follows.

G. Sym.-bi-dibenzylmethyl Urea, $((C_6H_5CH_2)_2CHNH)_2CO$.—Phosgene was passed into a dry ether solution of the amine. Bi-dibenzylmethyl urea and dibenzyl-carbamine hydrochloride were precipitated as a white solid which was collected and extracted several times with boiling water in order to dissolve the amine hydrochloride. The crude urea, left after extraction, was recrystallized from hot alcohol and hot water. The pure urea separated in the form of small white needles which melted at 159°.

Analysis. Subs., 0.1407: 7.26 cc. of N (18°, 748 mm.). Calc. for $C_{31}H_{32}ON_2$: N, 6.25. Found: 6.25.

It was soluble in ethyl acetate, in acetone, in alcohol, and in benzene, but was insoluble in water, in ether and in ligroin. A melting point was taken of a mixture of the urea synthesized above and of that formed as a product of the rearrangement of the different salts of the esters of dibenzylacet-hydroxamic acid. This melting point of the mixture was 159°.

3. Experiments with Tribenzylmethyl Chloride.

Tribenzyl carbinol was made from ethyl phenylacetate by the Grignard reaction according to Klages and Heilmann.[22] A considerable quantity of dibenzyl was obtained as a by-product.

H. Tribenzylmethyl Chloride, $(C_6H_5CH_2)_3CCl$.—To 10 g. of the carbinol, 15 cc. of acetyl chloride was added and the mixture was refluxed for hours. A short time after the refluxing was commenced the undissolved carbinol passed into solution. When the solution was allowed to cool very slowly, rosets of colorless needles of tribenzylmethyl chloride separated. These needles were collected and washed thoroughly with anhydrous ether to remove acetyl chloride, acetic acid, and any unchanged carbinol. After the chloride had been dried over calcium chloride, it melted at about 173° with decomposition.

Analysis. Subs.,[23] 1601: 4.15 cc. of 0.12094 *N* NaSCN. Calc. for $C_{22}H_{21}Cl$: Cl, 11.06. Found: 11.16.

[20] Apitzsch, *Ber.*, **36**, 1428 (1904).

[21] Noyes, *Am. Chem. J.*, **14**, 226 (1892).

[22] Klages and Heilmann, *Ber.*, **37**, 1456 (1904).

[23] An analysis of this chloride was made by heating a sample of it with 10 g. of Na_2O_2 in a Parr sulfur bomb. The usual Volhard method was employed to determine the chlorine.

It was soluble in hot benzene and in hot acetone. It was only very slightly soluble in ligroin, in cold benzene and in cold acetone. It was insoluble in water, in alcohol, and in ether.

Because of the ease of decomposition, the preparation of the chloride through the action of phosphorus trichloride or pentachloride on the carbinol was unsuccessful. The chloride could be recrystallized from acetyl chloride, but recrystallization from anhydrous benzene always lowered the melting point. It was very slowly decomposed by boiling water or by a boiling 10% solution of potassium hydroxide.

When the chloride was heated slightly above its melting point until the evolution of hydrogen chloride ceased, an oil formed which would not solidify when it was cooled in an ice-salt bath. This oil was soluble in ether, and an anhydrous ether solution of it decolorized bromine fairly rapidly. This seemed to indicate that the oil contained a compound of an unsaturated olefin nature, most likely dibenzyl-cinnamene, $C_6H_5CH = C(CH_2C_6H_5)_2$. This product was not investigated further.

Behavior of the Chloride toward Magnesium (Grignard Reaction).—An anhydrous ether solution of tribenzylmethyl chloride mixed with magnesium was refluxed for 8 hours. No evidence of a reaction could be detected, even when iodine was added. Methyl iodide also failed to start the reaction.

Because of the insolubility of the chloride in ether, anhydrous benzene was employed as the reaction medium. Iodine, methyl iodide, and aniline were used as "primers," and the solution was refluxed for 3 days without effect. When this benzene solution was cooled, needles of the chloride separated. These crystals melted at about 165°, instead of 173°, the melting point of the pure chloride.

4. Hydroxamic Acids Related to Isobutyric Acids.

I. **Isobutyr-hydroxamic Acid or Dimethylacet-hydroxamic Acid,** $(CH_3)_2CHC(O)$-NHOH.—Isobutyr-hydroxamic acid was made by two methods.

METHOD I.—A solution of 4.9 g. of sodium in methanol was poured into a methanol solution of 7.85 g. of hydroxylammonium chloride and the mixture cooled to −12°. The sodium chloride was removed and 11.5 g. of methyl *iso*butyrate was added to the filtrate. After these substances were thoroughly mixed, 4.8 g. of sodium in methanol was introduced and the solution allowed to stand at room temperature overnight. When a test portion of the reaction mixture, removed immediately after the last addition of sodium methylate, was acidified it gave a pronounced color with ferric chloride. After 12 hours, a stream of dry carbon dioxide was passed through the solution to precipitate sodium carbonate. The product, thoroughly cooled in an ice-salt bath, was filtered from the sodium carbonate and the methanol was evaporated.

The solid, which consisted of sodium chloride and of *iso*butyr-hydroxamic acid, was dissolved in water made faintly acid with acetic acid. Upon the addition of an aqueous solution of copper acetate, a grass-green copper salt of the hydroxamic acid was precipitated. This salt was collected, washed with water, then with alcohol and finally with ether. After it had been dried thoroughly and pulverized, it was suspended in methanol and a stream of dry hydrogen sulfide was passed through the mixture. When the copper sulfide had been removed by filtration, and the ether evaporated, *iso*butyr-hydroxamic acid was obtained. Crystallized from ethyl acetate and ligroin, or from benzene, it melted at 116°.

Analysis. Subs., 0.0857: 10.35 cc. of N (21°, 743 mm.). Calc. for $C_4H_6O_2N$: N, 13.60. Found: 13.73.

It was soluble in ether, in alcohol, in water, in acetone, in hot ethyl acetate, and in hot benzene. It was insoluble in ligroin.

METHOD II.—*Iso*butyric acid was refluxed a short time with thionyl chloride and the excess of this reagent was distilled. *Iso*butyryl chloride was obtained by fractionat-

ing the resulting oil. An anhydrous benzene solution of the acid chloride, kept thoroughly cooled by immersion in an ice-bath, was agitated vigorously with a slight excess of free hydroxylamine. When the reaction was complete, the solution was heated and filtered while hot. As the filtrate cooled, *iso*butyr-hydroxamic acid separated. It was recrystallized from ethyl acetate and ligroin. For the preparation of this particular hydroxamic acid, Method I was found to be preferable.

J. Benzoyl Ester of Isobutyr-hydroxamic Acid, $(CH_3)_2CHCONHOCOC_6H_5$.—This ester was prepared in two ways.

METHOD I.—*Iso*butyr-hydroxamic acid was treated with benzoyl chloride according to the Schotten-Baumann method. The precipitate was removed and pressed on a porous plate. When this crude material was extracted several times with hot ligroin and crystallized from a mixture of hot alcohol and hot water, the benzoyl ester of *iso*butyr-hydroxamic acid separated in the form of white needles; m. p. 148°.

METHOD II.—*Iso*butyr-hydroxamic acid was warmed on a water-bath with a slight excess of benzoic anhydride, until a test portion of the reaction mixture failed to give a violet color when treated with a solution of ferric chloride. The product solidified when cold. This mass was broken up, extracted several times with hot ligroin, and recrystallized from a mixture of hot alcohol and hot water. It formed white needles which melted at 148°.

Analysis. Subs., 0.2301: 14.01 cc. of N (24.3°, 744 mm.). Calc. for $C_{11}H_{13}O_3N$: N, 6.77. Found: 6.85.

The benzoyl ester was soluble in alcohol, in ethyl acetate, and in hot benzene. It was slightly soluble in ether, and was insoluble in water and in ligroin.

POTASSIUM SALT OF (J).—A solution of 0.5 g. of the benzoyl ester of *iso*butyr-hydroxamic acid in absolute alcohol was immersed in an ice-salt bath, and 0.094 g. of sodium dissolved in absolute alcohol was added. Anhydrous ether caused a white precipitate to form which was collected, washed with anhydrous ether and dried over sulfuric acid. When the dry salt was heated slowly to 200°, no decomposition occurred; but when a portion in a test-tube was quickly thrust into a bath at 150° it puffed; an isocyanate odor was noticed and a deposit of potassium benzoate remained in the tube.

The salt obtained above was thought to be impure, so it was prepared a second time. In the second preparation, slightly less than the calculated amount of potassium ethylate was used and the salt was washed more thoroughly with anhydrous ether. It was placed over sulfuric acid in a desiccator immediately and the desiccator evacuated. In about 20 minutes, the salt decomposed spontaneously with such violence as to scatter potassium benzoate throughout the desiccator. When the desiccator was opened, it was found to be filled with the vapor of the isocyanate.

An aqueous solution of the potassium salt was warmed to 50° for some time. The light, oily layer which separated possessed a strong isocyanate odor. This solution, allowed to stand for several hours at room temperature, finally deposited a mass of fine white needles. These were collected, washed with alkali to remove any unchanged ester and any traces of *iso*butyr-hydroxamic acid produced by hydrolysis. Its properties were like those of the symmetrical di-*iso*propyl urea described by Hofmann.[24]

SODIUM SALT OF (J).—To 0.5 g. of the benzoyl ester dissolved in absolute alcohol and cooled to −10°, 0.055 g. of sodium dissolved in absolute alcohol was introduced. Upon the addition of anhydrous ether, the white sodium salt was precipitated. This was collected, washed with ether and dried over sulfuric acid. At 75° it puffed, gave an isocyanate odor and left sodium benzoate in the tube. An aqueous solution of the sodium salt behaved in a manner analogous to that of the potassium salt described above.

[24] Hofmann, *Ber.*, **15**, 756 (1882).

SILVER SALT OF (J).—An aqueous solution of the potassium or sodium salt was treated with an aqueous solution of silver nitrate. The white silver salt was collected, washed with water, then with a little alcohol, and finally with ether. When the dry silver salt was heated slowly in a test-tube, it turned brown at 180°. When the bath has reached 200° the sample was removed and passed through a free flame, whereupon it puffed vigorously; an isocyanate odor was noticed and silver benzoate remained in the tube. The silver salt prepared from the potassium salt gave the following analytical results.

Analysis. Subs., 0.0460: Ag, 0.0158. Calc. for $C_{11}H_{12}O_3NAg$: Ag, 34.35. Found: 34.35.

K. Acetyl Ester of Isobutyr-hydroxamic Acid, $(CH_3)_2CHCONHOCOCH_3$.—A mixture of 1 g. of the hydroxamic acid and 1 cc. of acetic anhydride was warmed on a water-bath until a test portion failed to give a ferric chloride reaction. As the mixture became cool, the product solidified. The mass was broken up and placed in a vacuum desiccator over sodium hydroxide, where it remained until all the acetic anhydride had been removed. After it was recrystallized from hot benzene and ligroin, it melted at 87°.

Analysis. Subs., 0.2004: 17.45 cc. of N (21°, 748 mm.). Calc. for $C_6H_{11}O_3N$: N, 9.65. Found: 9.95.

The acetyl ester was soluble in water, in hot ether, in hot benzene and in alcohol, but was insoluble in ligroin.

POTASSIUM SALT OF (**K**).—Upon the addition of ether to a cold absolute alcoholic solution of the acetyl ester of *iso*butyr-hydroxamic acid to which the calculated amount of potassium ethylate had been added, a white precipitate of the potassium salt was obtained. This was filtered, washed with anhydrous ether and dried. The potassium salt was very deliquescent; it absorbed sufficient moisture from the air to effect its solution in a very short time. A sample of the dry salt which had stood over sulfuric acid for 30 minutes, puffed when heated to 53°, and gave an isocyanate odor. After it had remained in the desiccator for several hours, it decomposed spontaneously as it was being removed from the desiccator.

When an aqueous solution of silver nitrate was added to a cold aqueous solution of the potassium salt, the silver nitrate was reduced and a mirror was formed upon the walls of the container. This reduction was caused by *iso*butyr-hydroxamic acid formed by hydrolysis. The presence of the hydroxamic acid was verified by a test with ferric chloride and by the formation of its copper salt.

Summary.

1. The preparation and properties of the following new hydroxamic acids, together with their benzoyl and acetyl esters, are described.—(1) cyclopropane-carboxyl-hydroxamic acid; (2) *iso*butyr-hydroxamic acid; (3) dibenzylacet-hydroxamic acid.

The sodium, potassium and silver salts of many of these esters were made, and the conditions under which these salts rearrange were determined and compared.

2. The conclusions arrived at in this paper are, that the radicals present in the acyl groups from which these hydroxamic acids were derived influence the ease with which their derivatives suffer the Beckmann rearrangement in the following order: dibenzylmethyl > *iso*propyl > benzylmethyl > cyclopropyl.

3. During the investigation, it became necessary to improve the methods employed in the preparation of cyclopropane-monocarboxylic acid and its ammonium salt, and also, to synthesize the following new compounds: bi-dibenzylmethyl urea and tribenzylmethyl chloride. The failure of tribenzylmethyl chloride to react with magnesium to form a Grignard compound is discussed.

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A NEW QUANTITATIVE METHOD FOR THE DETERMINATION OF IRON IN THE BLOOD.

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A new method for the determination of small amounts of iron in the blood which has been worked out in this laboratory offers possibilities for use in pathological laboratories and clinical diagnosis.

Principle.—A known amount of blood after laking in water is treated with conc. hydrochloric acid and a very small amount of potassium chlorate. By this method the proteins are precipitated and the iron rendered soluble. After heating in boiling water, the material is filtered and filtrate made up to a known volume. An aliquot portion of the filtrate is then compared colorimetrically with a standard iron solution.

Method.—To 4 cc. of distilled water contained in a test-tube 0.5 cc. of blood sample is added. After laking, 1 cc. of conc. hydrochloric acid and a very small amount of potassium chlorate (about 0.01 g.) are added. The test-tube and contents are then placed in boiling water and heated for about 15 minutes, until the liquid becomes white or light yellow and the proteins are entirely precipitated and have become white. The material is then allowed to cool and the residue to settle. The latter is then filtered and washed with water until 15 cc. of filtrate is obtained. After thoroughly shaking, 1.5 cc. of the filtrate is placed in one side of the test-tube colorimeter. To the other side of the colorimeter 0.25 cc. of the standard iron solution is added. To both tubes is added enough 0.1 N potassium permanganate solution to oxidize all the iron completely and until a permanent pink color remains. Then 5 cc. of 5 N ammonium thiocyanate solution is added and the standard diluted to 25 cc. with distilled water. The sample is then diluted until the two colors match. Should a brown residue form after the addition of ammonium thiocyanate solution, several drops of a 10% solution of hydrochloric acid are added to dissolve the precipitate.