mm. It was not possible to crystallize this oil from methanol, even after attempted purification of an *n*-pentane solution on an activated alumina column. The infrared spectrum of this oil dissolved in chloroform, however, was consistent with that to be expected of the impure dimer of 2-phenyl-1,3-butadiene. A broad absorption maximum in the region of 900 cm.$^{-1}$ ($CR_1R_2{=}CH_2$) seems to indicate that dimerization was not complete.

URBANA, ILL.

[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH DIVISION, DIRECTORATE OF RESEARCH, USA CHEMICAL WARFARE LABORATORIES]

Synthesis of Some Hydroxamic Acids. Reactivity with Isopropyl Methylphosphonofluoridate (GB)

G. F. ENDRES[1] AND JOSEPH EPSTEIN[2]

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Eight hydroxamic acids, of which five are new compounds, were synthesized and tested for reactivity with the nerve gas GB, isopropyl methylphosphonofluoridate. The compounds were designed to sterically increase the reactivity of hydroxamic acids with GB. The reactivity however, was found to be not appreciably different from that predicted from well-established relationships of *p*Ka and reaction rate with other hydroxamic acids.

Several papers[3-5] have appeared since the publication of Hackley *et al.*[6] reporting on various aspects of the reaction between hydroxamic acids and the nerve gas GB (isopropyl methylphosphonofluoridate). In connection with our program to find nonprotein substances which react more rapidly with GB in aqueous solution at neutral *p*H than the compounds studied in the previous publications, we have synthesized and tested several hydroxamic acids. Table I contains data on the dissociation constants, rate constants for their reaction with GB and the moles of hydrogen ion released per mole of GB at infinite time for hexanehydroxamic acid, gluconohydroxamic acid, three long-chain hydroxamic acids derived from sebacic acid and three carboxyhydroxamic acids. The results of our kinetic studies indicate that none of the compounds is significantly more or less active than would be predicted from the relationship of the reactivity with the basic strength of the hydroxamic acid anion reported in previous publications[4,5] (*e.g.* see Fig. 1) and hence offer no clues as to the means of increasing the reactivity between hydroxamic acids and GB.

The hydroxamic acids reported herein represent an unsuccessful attempt to increase the reactivity of these materials by steric effects. Some success has been achieved by pursuing this line of approach with the hydroxylated benzenes,[7,8] and ortho substituted hydroxybenzyl amines.[9]

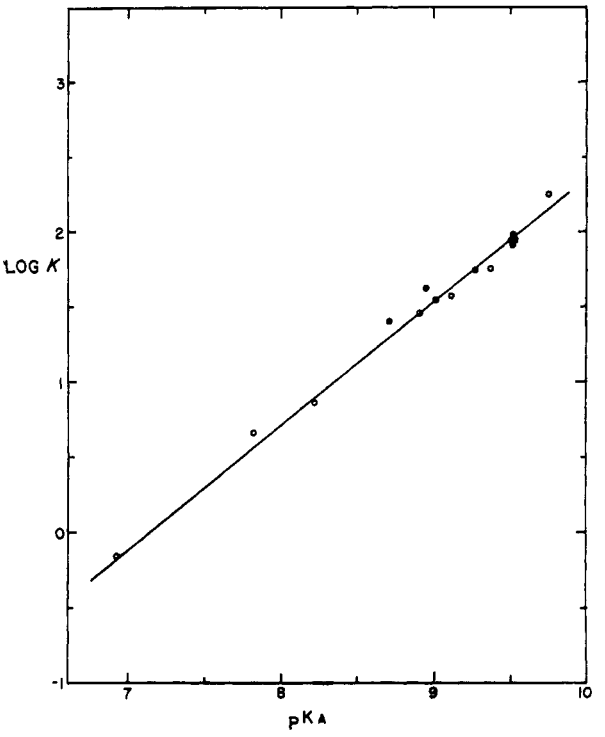

Fig. 1. Relationship between log k (second order rate constant 1 mole^{-1} sec.$^{-1}$) and *p*Ka of various hydroxamic acids. ● Data of present publication. ○, Data of Swidler *et al.* (see ref. no. 7 of ref. 4)

In the design of the hydroxamic acids sterically capable of polyfunctional attack, it was assumed that (*a*) the reaction is mediated through a simultaneous nucleophilic and electrophilic attack of the hydroxamic acid anion on the phosphorus and

(1) Present address, General Electric, Schenectady, N. Y.
(2) To whom requests for reprints should be addressed.
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(4) M. A. Stolberg and W. A. Mosher, *J. Am. Chem. Soc.*, **79**, 2618 (1957).
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(7) B. J. Jandorf, T. Wagner-Jauregg, J. J. O'Neill and M. Stolberg, *J. Am. Chem. Soc.*, **74**, 1521 (1952).
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(9) To be published.

TABLE I

DISSOCIATION CONSTANTS, RATE CONSTANTS OF GB REACTION[a] AND MOLES OF ACID PRODUCED PER MOLE OF GB REACTING FOR EIGHT HYDROXAMIC ACIDS

Compd. No.	Hydroxamic Acid	*p*Ka	No. of Runs	Pseudo First Order Rate Constant k_{obs} (min.$^{-1}$)	Bimolecular[b] Rate Constant k (L. mole^{-1} sec.$^{-1}$)	Moles [H$^+$] Released per Mole GB
I	$CH_3(CH_2)_4CONHOH$	9.48	4	0.0658 ± 0.0003	84.3	2.2 ± 0.2
II	$H_2NCO(CH_2)_8CONHOH$	9.49	2	0.067 ± 0.003	87.7	2.26 ± 0.00
III	$CH_3NHCO(CH_2)_8CONHOH$	9.47	2	0.073 ± 0.002	91.6	2.35 ± 0.08
IV	$HO(CH_2)_9CONHOH$	9.26	4	0.0735 ± 0.002	57.1	2.2 ± 0.2
V	$HOCH_2(CHOH)_4CONHOH$	8.94[c]	1	0.113	43.1	2.3
VI	HOOCCONHOH	8.69[d]	1	0.113	25.2	2.7
VII	$HOOC(CH_2)_2CONHOH$[e]	9.50[d]	2	0.0378	83.2[g]	1.48 ± 0.08
VIII	HOOCCH=CHCONHOH[f]	9.15[d]	1	0.0259	21.7[g]	1.7

[a] Rates determined at 30.0°, *p*H of reaction mixture = 7.6, [Hydroxamic Acid] = $1 \times 10^{-3}M$; [GB] = $1 \times 10^{-4}M$. [b] Calculated from equation $k = k_{obs}/[\text{Hydroxamic Acid Ion}] = k_{obs}\frac{[H^+ + K_A]}{[K_A]} \cdot \frac{1}{[HA]}$. [c] Ref. 13. [d] *p*Ka of the hydroxamic acid function. [e] Purity 69.7% by titration. [f] Purity 72.5% by titration. [g] Corrected for purity.

phosphoryl oxygen atoms[3,4,10] and (*b*) the attack is upon the side of the GB molecule opposite to the phosphorus-fluorine bond.

Compounds II, III, and IV, which contain a second electrophilic group at the opposite end of the molecule, are sterically able to attack the fluorine as well as the phosphorus (and perhaps the phosphoryl oxygen atoms[10]) by wrapping themselves around the GB molecule. Compound V contains a number of groups capable of hydrogen bonding at different distances from the hydroxamic acid function. Compounds VI, VII, and VIII contain negatively charged sites (carboxylate ions) at different distances from the hydroxamic acid anion. It is believed that the enzyme cholinesterase contains two negatively charged groups, one of which attacks the carbonyl function in esters, the other confers on the enzyme greater binding power for the substrate. The extreme reactivity with GB at the site containing the two negatively charged groups[11,12] suggested that compounds VI, VII, and VIII might be effective.

EXPERIMENTAL

I. *Kinetic studies and dissociation constant measurements.* The *p*Ka's of the carboxyhydroxamic acids (Compounds VI, VII, and VIII) were determined by titration of 0.025*M* (0.05*N*) solutions with 0.5*N* NaOH. The solutions were 0.1*M* in KNO_3 and their initial volume was 25.0 ml. Oxalomonohydroxamic acid (VI) appeared to be 100% pure by titration; succino and maleic hydroxamic acids (VII and VIII) were 69.7% and 72.5% pure, respectively.

For the other hydroxamic acids listed in Table I, the *p*Ka's were determined by the buffer method.[3] Solutions were made up 0.1*M* in potassium nitrate and approximately 0.01*M* (stoichiometric) in hydroxamic acid, exactly half-neutralized with 0.01*N* sodium hydroxide. Equilibrium water was used, and the *p*H's were read as quickly as possible. The value given for gluconohydroxamic acid is a literature value determined by titration.[13] In our hands, this compound was hydrolyzed too rapidly in alkaline solution for a determination by the buffer method.

The rate measurements were carried out using a Beckman automatic titrimeter, the solutions contained in a jacketed beaker of 250 ml. capacity through which water at 30.0° was circulated. The *p*H was maintained at 7.6, checked by an auxiliary *p*H meter and electrodes. All solutions were 0.1*M* in potassium nitrate, $1.00 \times 10^{-3}M$ in hydroxamic acid and approximately $1 \times 10^{-4}M$ in GB (known accurately).

The uptake of 0.01*N* sodium hydroxide was corrected for absorption of carbon dioxide (*ca.* 0.01 ml./min.) and the data treated according to the method of Guggenheim.[14] First order constants were calculated from the slopes of the straight lines obtained by plotting $\log(V' - V)$ against time. The bimolecular rate constant, k, was calculated from the equation

$$k_{obs} = k\left[\frac{K_A}{H^+ + K_A}\right] \cdot [KA]$$

where K_A is the acid dissociation constant of the hydroxamic acid, [H$^+$] is the hydrogen ion concentration of the reaction and [HA] is the concentration of the hydroxamic acid. For a discussion on the kinetics of the reaction between GB and hydroxamic acid and the validity of these calculations see ref. (3).

The volume of base taken up at infinite time, used to determine the moles of hydrogen ion released per mole GB, was calculated from the intercept of the Guggenheim plot.

II. *Preparation of the hydroxamic acids.* (New compounds are marked with an asterisk.) A. *Sebacic acid derivatives.* Compounds of the structure $X(CH_2)_8CONHOH$, where X = H_2NCO—CH_3NHCO— and $HOCH_2$—, were synthesized by the action of hydroxylamine on the ethyl esters of the corresponding carboxylic acids, and attempts were made to prepare the compound where X = $H_2NCONHCO$— in the same manner. These four esters were prepared from sebacic acid as follows:

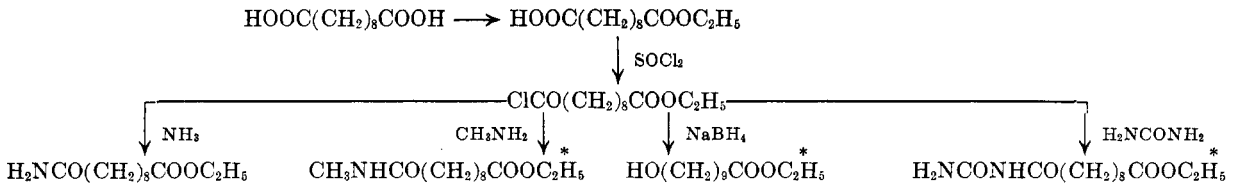
(10) The recent work of Green *et al.*, ref. 5, casts doubt upon the bifunctional mechanism of attack by the hydroxamic acid anion. The choice of hydroxamic acids used herein, however, is not dependent upon the mono- or bifunctionality of the hydroxamic acid anion attack.

(11) I. B. Wilson, *The Physical Chemistry of Enzymes*, A General Discussion of The Faraday Society, 1955, p. 120.

(12) B. J. Jandorf, H. O. Michel, N. K. Schaffer, R. Egan, and W. H. Summerson, *The Physical Chemistry of Enzymes*, A General Discussion of The Faraday Society, 1955, p. 135.

(13) F. Mathis, *Compt. rend.*, **231**, 357 (1950).

(14) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).



Ethyl hydrogen sebacate was prepared by the esterification of sebacic acid with ethanol in the presence of concentrated hydrochloric acid, diethyl sebacate, and di-*n*-butyl ether, following the directions of *Organic Syntheses*.[15]

9-Carboethoxypelargonyl chloride. Ethyl hydrogen sebacate (16.8 g., 0.0730 mole) was treated with thionyl chloride (8 ml., 0.11 mole) in a 50 ml. round bottom flask fitted with reflux condenser and drying tube. After about 1.5 hr. at room temperature, the flask was immersed in a water bath, the temperature of which was slowly raised to 40°, where it was maintained until the total reaction time was about 3 hr. After standing overnight at room temperature, the excess thionyl chloride was stripped off, at the water pump, and the product distilled at reduced pressure (oil pump). B.p. 137°/2.5 mm.–139°/2.7 mm., yield 17.4 g. (96%).

Ethyl sebacamate was prepared by a procedure similar to that given for the methyl ester in *Organic Syntheses*.[16] 21.6 g. (0.087 mole) of 9-carboethoxypelargonyl chloride was added slowly from a dropping funnel to 220 ml. of conc. aqueous ammonia cooled in an ice bath. The reaction mixture was mechanically stirred, and the temperature was not allowed to rise above 8°. The product separated immediately as a white solid, and was filtered off and washed with ice cold water. After drying in a vacuum desiccator, it weighed 19.8 g. (99.6% yield) and melted at 68–69°. Literature m.p. 68.5–69°.[17]

*Ethyl N-methylsebacamate.** 11.0 g. (0.044 mole) of 9-carboethoxypelargonyl chloride was added slowly from a dropping funnel to a mechanically stirred aqueous solution of 0.4 mole of methylamine, the temperature being kept below 8° with an ice bath. (The methylamine solution had been prepared by adding, slowly with cooling, 41 ml. of 10*N* sodium hydroxide solution to 30 g. of methylamine hydrochloride dissolved in 49 ml. of water.) The white precipitated product was filtered off, washed with ice cold water, and dried in the vacuum desiccator. The yield of crude product (m.p. 53–55°) was 10.7 g. (99.6%). Two recrystallizations from benzene–petroleum ether (32–63°) mixture gave a product melting at 55.5–56° (bundles of tiny silvery needles).

Anal. Calcd. for $C_{13}H_{25}NO_3$: C, 64.2; H, 10.4; N, 5.8. Found: C, 64.3; H, 10.0; N, 5.5.

*Ethyl 10-hydroxycaprate** was synthesized by the reduction of 9-carboethoxypelargonyl chloride by sodium borohydride in dioxane suspension after the general procedure of Chaiken and Brown.[18] This synthesis provides a further illustration of the selectivity of sodium borohydride as a reducing agent.

The apparatus consisted of a 300 ml. three-neck round-bottom flask with a reflux condenser and drying tube, mechanical stirrer with vapor-tight seal, and dropping funnel. To 7.6 g. (0.2 mole) of sodium borohydride stirred in 68 ml. dioxane (purified and dried over sodium ribbon) was added dropwise 9.9 g. (0.040 mole) of the ester chloride. The dropping funnel was washed with 5 ml. dioxane, and this was added to the reaction mixture, which was stirred for 0.5 hr. at room temperature, and then for 2 hr. on a steam bath. After being allowed to cool, the mixture was chilled in ice and treated dropwise with 25 ml. water. A vigorous reaction, accompanied by foaming, took place. The mixture was then warmed to room temperature over about 0.5 hr., stirred for 1.5 hr. longer, and filtered under suction. The residue was washed with 25 ml. dioxane, which was combined with the filtrate. This was treated with 125 ml. water, which induced phase separation, and extracted with three portions of ether (30, 15, and 15 ml.). After the ether was evaporated on the steam bath, dioxane was stripped off and the product distilled under reduced pressure through a 9-cm. Vigreux column. The yield of colorless oil boiling at 153–154.5°/4 mm. was 3.1 g. (36%). The compound solidifies on standing in the refrigerator. Redistillation through the same column afforded an analytical sample, $n_D^{24.3}$ 1.4465.

Anal. Calcd. for $C_{12}H_{24}O_3$: C, 66.6; H, 11.2. Found: C, 66.5; H, 11.3.

The product can be saponified to an acid of m.p. 71–73°. The literature m.p. of 10-hydroxycapric acid is 75–76° (corr.).[19]

*9-Carboethoxypelargonyl urea.** This compound was prepared according to the general procedure for monoacylureas given by Stoughton.[20] In a 100-ml. three-neck flask equipped with reflux condenser, sealed mechanical stirrer and dropping funnel, 4.8 g. (0.08 mole) of urea and two small drops of conc. sulfuric acid were dissolved in 12 ml. of benzene. While the solution was being stirred and refluxed on the steam bath, 17.4 g. (0.070 mole) of 9-carboethoxypelargonyl chloride was added dropwise over a period of 15 min. After heating on the steam bath for 0.5 hr. longer, the reaction mixture was a thick slurry. After 1 hr., 13 ml. of benzene was added, and after 3 hr. total reaction time the mixture was cooled to room temperature, 25 ml. petroleum ether (32–63°) was added and the insoluble product was filtered off. The reaction flask was rinsed with petroleum ether. The white solid was then transferred to a beaker, and treated with an excess of 5% aqueous sodium bicarbonate. It was collected once more on a filter, packed into a cake, and washed with distilled water. After being dried in the vacuum desiccator, the product weighed 13.7 g. (72% yield) and melted at 150–152°. An analytical sample recrystallized twice from 95% ethanol melted at 149.5–150.5°.

Anal. Calcd. for $C_{13}H_{24}N_2O_4$: C, 57.3; H, 8.9; N, 10.3. Found: C, 57.8; H, 9.2; N, 10.6.

The esters ethyl sebacamate, ethyl *N*-methylsebacamate, and ethyl 10-hydroxycaprate were converted to the corresponding hydroxamic acids by the method of Hurd and Botteron.[21] 9-Carboethoxypelargonyl urea yielded a mixture of products by this procedure, from which the pure hydroxamic acid could not be separated. The general procedure may be illustrated by the synthesis of *9-carboxamidopelargonohydroxamic acid* (*N*-hydroxysebacamide).* 1.10 g. (0.048 g. atom) of sodium metal was dissolved in 24 ml. absolute ethanol in a round-bottom flask fitted with reflux condenser and drying tube. An ethanolic solution of hydroxylamine was made up by dissolving 1.74 g. (*ca.* 0.024 mole) hydroxylamine hydrochloride (Coleman and Bell, Reagent, minimum assay 96%) in 36 ml. absolute ethanol, and treating this solution dropwise with about one half of the sodium

(15) S. Swann, Jr., R. Oehler and R. J. Buswell, *Org. Syntheses*, **Coll. Vol. II**, 276 (1943).

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(18) S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).

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(20) R. W. Stoughton, *J. Org. Chem.*, **2**, 514 (1938).

(21) C. D. Hurd and D. G. Botteron, *J. Org. Chem.*, 11 207 (1946).

ethoxide solution. The flask was cooled in ice during the neutralization, which was carried on until a drop of the mixture was alkaline to phenolphthalein. The precipitated sodium chloride was then filtered off using suction, and the filter washed with a small amount of absolute ethanol. The hydroxylamine solution was added to a solution of 5.0 g. (0.022 mole) ethyl sebacamate in 10 ml. of absolute ethanol, followed by the remainder of the sodium ethoxide solution. Reaction commenced at once with a rise in temperature, and the solution was cooled in ice for about 0.5 hr., at the end of which time a white precipitate had separated. After standing at room temperature for 1.5 hr. longer, the mixture was again cooled in ice and the sodium salt of the hydroxamic acid was filtered off. The flask and precipitate were washed with a small amount of ice cold absolute ethanol. After drying in the vacuum desiccator, the salt weighed 3.8 g. (73% yield). 3.3 g. of this material was dissolved in about 40 ml. distilled water and acidified by addition of glacial acetic acid. The solution was cooled in ice, and the precipitated free acid filtered off and washed with ice cold water. The dried product weighed 2.5 g. (83% yield from the salt; 61% of the ester) and melted at 120–123.5°.

The yield of the sodium salt could be increased to 92.5% by treating ethyl sebacamate with hydroxylamine in solution in the absence of sodium ethoxide for 2 hr. in an ice bath, adding the sodium ethoxide solution and permitting to stand at room temperature for 1 hr. longer, and finally adding an equal volume of absolute ether to render the salt less soluble. The yield of free acid from the salt was not altered when the *p*H was lowered to 7.1 with the aid of a *p*H meter.

A sample of the hydroxamic acid suitable for analysis and kinetic studies was obtained by two recrystallizations from water. If the water solutions are only moderately concentrated so that crystallization takes place after some cooling, a white crystalline material is obtained which melts at 127–127.5° and gives an intense red-violet coloration with ferric chloride in solution.

Anal. Calcd. for $C_{10}H_{20}N_2O_3$: C, 55.5; H, 9.3; N, 13.0. Found: C, 55.7; H, 9.3; N, 13.2.

If the acid is crystallized from hot concentrated aqueous solution, a material melting at 140.5–141.5° may be obtained which is evidently a different crystalline modification of the hydroxamic acid. This material gives the same test with ferric chloride, and may be converted to the lower-melting form by recrystallization from dilute aqueous solution, or solutions in absolute ethanol, ethanol-ether or ethanol-benzene. Sodium in dilute aqueous alkali and neutralization with acetic acid also leads to the lower-melting form.

Anal. Found: C, 55.5; H, 9.3; N, 13.0.

*9-(N-Methylcarboxamido)pelargonohydroxamic acid.** (*N*-Hydroxy-*N'*-methylsebacamide) was prepared from ethyl *N*-methylsebacamate by a procedure similar to that used for the amide above, with the exception that the hydroxylamine solution was made up by treating a suspension of the hydrochloride in ethanol rather than a solution with sodium ethoxide. This is an alternative procedure described by Hurd and Botteron.[21] From 9.3 g. (0.038 mole) of the ester was obtained 7.3 g. of a sodium salt, which on acidification with acetic acid produced 5.0 g. of an impure product melting at 93–103°. Recrystallization from absolute ethanol and then from water produced 2.8 g. (32% yield from the ester) of material melting at 123–124.5° and giving a red-violet color with ferric chloride. Further recrystallization from ethanol gave an analytical sample of melting point 125–126.5°.

Anal. Calcd. for $C_{11}H_{22}N_2O_3$: C, 57.4; H, 9.6; N, 12.2. Found: C, 58.1, 57.8; H, 9.8, 9.8; N, 12.0.

The low purity of the precipitated acid and low yield of product are believed due to incomplete liberation of hydroxylamine from its hydrochloride in suspension. Hydroxylamine would then be present in less than an equivalent amount to the ester in the reaction mixture, permitting the ester to be partially saponified by hydroxide ion, a contaminant of the sodium ethoxide solution. This would produce *N*-methylsebacamic acid, the probable impurity.

*10-Hydroxycaprohydroxamic acid** was prepared by the same procedure as the *N*-methylcarboxamido compound, and in this instance also considerable difficulty was encountered with impurities. 7.8 g. (0.042 mole) of ethyl 10-hydroxycaprate produced 6.0 g. of sodium salt, and upon acidification of this with an excess of glacial acetic acid there was obtained 4.7 g. of mixed acids melting over a wide range. After recrystallization from water failed to produce pure material, the remaining 3.2 g. of product were dissolved in 30 ml. of 5% aqueous sodium hydroxide and filtered. The filtrate was then treated dropwise with glacial acetic acid until the *p*H was lowered to 7.5. After chilling in the refrigerator, the white precipitated product was filtered off and dried. The material weighed 2.7 g. and melted over a wide range. Recrystallization from water yielded 2.1 g. (25%) of crystalline product melting at 100–101°, which gave a strong positive test with ferric chloride. A further recrystallization from water afforded an analytical sample.

Anal. Calcd. for $C_{10}H_{21}NO_3$: C, 59.1; H, 10.4; N, 6.9. Found: C, 59.8; H, 10.4; N, 6.8.

The *p*H of the filtrate of the precipitation solution was lowered to 2.1 by the addition of 10% hydrochloric acid, the mixture cooled, and the white precipitate filtered off and dried. There was obtained 0.48 g. of a compound melting at 72–74°, evidently 10-hydroxycapric acid (lit. m.p. 75–76° corr.)[19] resulting from saponification of the ester.

B. *Hexanehydroxamic acid* was synthesized from ethyl caproate by the general procedure given above, except that the solution of the ester and hydroxylamine was permitted to stand at room temperature for 4 hr. before addition of the sodium ethoxide, and an equal volume of absolute ether was added. Only a small amount of solid had separated after standing in the refrigerator for several days, but concentration of the solution and further addition of absolute ether produced several crops of the salt, the total weight of which was 9.8 g. This was dissolved in the minimum amount of water (*ca.* 40 ml.) and the *p*H was adjusted to 7.4 by the addition of glacial acetic acid. After chilling in ice, the white solid precipitate was filtered off, washed with a little ice cold water, and dried. Recrystallization from benzene produced 4.2 g. (47% yield) of mica-like plates melting at 61.5–63.5° and giving an intense red-violet coloration with ferric chloride. The melting point reported in the literature is 63.5–64°.[22]

C. *D-Gluconohydroxamic acid* was prepared from delta-gluconolactone as directed by Mathis,[23] with the substitution of ethanol for methanol as the reaction solvent. The weight of material melting at 136.5–138.5° (dec.) was 22.5 g. (95% yield). The literature melting point is 138–140° (dec.).[23] For kinetic studies, the material was recrystallized twice from water-ethanol. It was found that under the conditions of the kinetic runs D-gluconohydroxamic acid takes up alkali at an appreciable rate, probably due to hydrolysis of the hydroxamic acid function. The data were accordingly corrected for this.

D. *Carboxy derivatives. N-hydroxysuccinamic acid.* A sample of this compound was prepared by the action of hydroxylamine on succinic anhydride in ethanol solution,[24] and recrystallized once from methyl ethyl ketone. This material melted at 101–106°, while the literature value is 105–106° (sample prepared by the action of benzyloxyamine on succinic anhydride, followed by catalytic hydrogenation of the product[25]). An attempt to further purify the compound by recrystallization from methyl ethyl ketone was

(22) Y. Inoue and H. Yukawa, *J. Agr Chem. Soc. Japan*, **16**, 504 (1940); *Chem. Abstr.*, **35**, 731[1] (1941).

(23) F. Mathis, *Compt. rend.*, **229**, 226 (1949).

(24) G. Errera, *Gaz. Chim. ital.*, **25II**, 25 (1895).

(25) D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 631 (1955).

unsuccessful. Titration revealed that the sample was only 69.7% pure, and probably contaminated by succinic acid.

*N-Hydroxymaleamic acid** was synthesized in a similar manner from maleic anhydride. There was obtained a 48.5% yield of tan triangular plates, melting at 121–128° (dec.). Ferric chloride in aqueous solution produced an intense reddish purple color. According to titration data, this material is 72.5% pure, but attempts to improve it by recrystallization were unsuccessful.

Anal. Calcd. for $C_4H_5NO_4$: C, 36.7; H, 3.8; N, 10.7. Found: C, 35.1; H, 3.8; N, 10.2.

*N-Hydroxyoxalamic acid** (oxalomonohydroxamic acid). Although this compound has not been prepared previously, the sodium, copper, barium, and lead salts have been reported.[26] The copper salt, however, was probably the mixed copper–sodium salt $(NaOOCCONHO)_2Cu$, since upon treatment with hydrogen sulfide it produced the monosodium salt NaOOCCONHOH.

The potassium salt KOOCCONHOH was prepared by the action of hydroxylamine in ethanol on potassium ethyl oxalate. This compound is unchanged on heating to 250°, but decomposes suddenly when held near a flame. Aqueous ferric chloride yields a deep red-brown colored complex, and aqueous cupric acetate a bright green precipitate, probably $(KOOCCONHO)_2Cu$.

The free hydroxamic acid is believed to have been isolated in low yield as follows. The *p*H of a solution of the potassium salt was lowered to 0.19 by the addition of dilute hydrochloric acid, at which point 90% of the carboxyl groups should be in the undissociated form, assuming that the *p*K of the carboxyl group of oxalomonohydroxamic acid is the same as the first *p*K of oxalic acid (1.19). Addition of cupric chloride to this solution yielded a cupric salt, probably $(HOOCCONHO)_2Cu$, which liberated the hydroxamic acid on treatment with hydrogen sulfide.

14.3 g. (0.1 mole) of the potassium salt was dissolved in 150 ml. of water, and the *p*H lowered to 0.19 by the dropwise addition of 3*N* hydrochloric acid with vigorous stirring. At this point there was added dropwise a solution of 25.6 g. (0.15 mole) of cupric chloride dihydrate in 50 ml. of water, which had been adjusted to *p*H 0.15 with concentrated hydrochloric acid. The light green precipitate of copper salt began to separate, and the mixture was allowed to stand in the refrigerator overnight. The copper salt was then filtered off under suction, washed with water and then methanol, and dried on the filter, weight 7.57 g. This was suspended in 150 ml. of methanol and hydrogen sulfide was passed in with occasional shaking. When it was judged that all of the copper salt had reacted, the copper sulfide was filtered off and washed with methanol. The combined filtrate and washings were evaporated under reduced pressure to produce a moist white solid, which was redissolved in 25 ml. absolute ethanol, filtered, and treated with several volumes of petroleum ether (34.5–55°). Since only a very small amount of material had appeared after standing for 3 days in the refrigerator, the solvents were evaporated once more to yield an oil, which on trituration with petroleum ether produced a solid. After filtration, washing with petroleum ether and drying, there was obtained 0.22 g. (2% yield) of a white product melting with vigorous decomposition at 130.5–134° to a white solid residue, which in turn melted at about 195° (dec.). The color produced with aqueous ferric chloride seemed to depend on the concentrations used and the *p*H, ranging from intense violet to red-brown. Although a satisfactory elemental analysis was not obtained, the titration curve was in good agreement with theory. Neutral equivalents: monobasic, 106 (calcd., 105); dibasic, 53.6 (calcd., 52.5).

Anal. Calcd. for $C_2H_3NO_4$: C, 22.9; H, 2.9; N, 13.3. Found: C, 20.3; H, 2.4; N, 12.1.

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ARMY CHEMICAL CENTER, MD.

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[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, INDIANA]

The Reaction of Maleic Hydrazide with Formaldehyde and Alcohols in Acidic Medium[1,2]

HENRY FEUER AND RONALD HARMETZ

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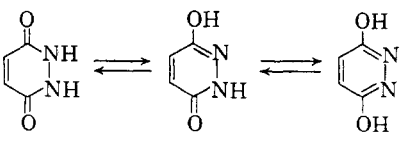
Maleic hydrazide reacts in the presence of acid with formaldehyde and ethanol or methanol to give 2-ethoxymethyl-6-hydroxy-3(2H)-pyridazinone and 2-methoxymethyl-6-hydroxy-3(2H)-pyridazinone respectively. A structure determination is presented which unambiguously proves that these products are *N*-substituted maleic hydrazide derivatives.

Maleic hydrazide (I) has been reported to undergo a number of reactions with substitution on oxygen or nitrogen. Feuer and Rubinstein[3] recently reported that acylation and benzenesulfonylation of compound I resulted in the exclusive



I

formation of 3-(1H-6-pyridazinonyl) acetate (II) and 3-(1H-6-pyridazinonyl) benzenesulfonate (III) respectively. The present authors established[4] that compound I underwent the Michael type reaction

(1) Paper VI in the series, "The Chemistry of Cyclic Hydrazides."

(2) (a) From the Ph.D. thesis of Ronald Harmetz; (b) presented before the Division of Organic Chemistry at the New York City Meeting of the American Chemical Society, September, 1957.

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