257. *The Oxidation of Hydroxamic Acids: a Synthesis of Amides.*

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The oxidation of hydroxamic acids by periodate and other oxidising agents in the presence of primary aliphatic amines gives variable yields of amides by a process of oxidative acylation.

THE periodate oxidation of hydroxamic acids, R·CO·NR′·OH (I), gives the parent carboxylic acid and (when R′ = alkyl) an alkylnitroso-dimer.[1,2] The formation of *O*-benzoylbenzhydroxamic acid during periodate[3] and bromine[4] oxidation of benzhydroxamic acid suggests that an oxidative acylation is involved. Related acylations have been observed in the oxidation of aralkylhydroxamic acids with mercuric oxide.[5]

The oxidation of hydroxamic acids in the presence of amines has been studied. Besides periodate, the reagents *N*-bromosuccinimide, iodine, and potassium ferricyanide, all of which have been applied to a somewhat analogous oxidation of acid hydrazides,[6] were found to yield amides.

TABLE 1.

Oxidations with periodate.

Hydroxamic acid	Amine	pH	Yield (%)	M. p. *
Benzhydroxamic	Ethylamine	6—8	37	70° (60—71°)
	Ethyl glycinate	6—8	25	59—60° (60°)
	Cyclohexylamine	6—7	55 †	150—151° (147°)
	Benzylamine	6	63 †	106—107° (105—106°)
	Benzylamine	9	9 †	106—107° (105—106°)
Phenylacethydroxamic ‡ ...	Benzylamine	7	60 †	119—121° (122°)
	Diethylamine	7	0	
Hippurhydroxamic	Ethyl glycinate	6·9	10	117—118° (117°) §
	p-Nitrobenzyl glycinate	6·9	43	112° (impure)
	Cyclohexylamine	6·5	45	164—165° (162°)
N-Methylhippurhydroxamic	Cyclohexylamine	6·5	22 †	164—165° (162°) §

* Literature values (in parentheses) from Beilstein's Handbuch or from Heilbron and Bunbury's Dictionary of Organic Compounds. † Yield of crude material. ‡ Rupe and Fiedler, *J. prakt. Chem.*, 1911, [2], **84**, 815. § Schwyzer, Iselin, and Feurer, *Helv. Chim. Acta*, 1955, **38**, 83.

The conditions and yields in the periodate oxidations are summarised in Table 1. Optimum yields of amide (45—60%) were obtained when the hydroxamic acid solution was added slowly to that of sodium periodate and amine at pH 6—7, and particularly when the amide was precipitated during the reaction. In acid solution (pH 3) no amides were formed, presumably owing to complete protonation of the amine. At pH 8—10 yields were also occasionally lower. In all experiments it was difficult to free the product from a yellow impurity which was not removed by thiosulphate.

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[1] Emery and Neilands, *J. Amer. Chem. Soc.*, 1960, **82**, 4903.
[2] Clark, Sklarz, and Todd, *J.*, 1959, 2123.
[3] Emery and Neilands, *J. Org. Chem.*, 1962, **27**, 1075.
[4] de Paolini, *Gazzetta*, 1932, **62**, 1053.
[5] Exner, *Chem. listy*, 1956, **50**, 779.
[6] Wolman, Gallop, Patchornik, and Berger, *J. Amer. Chem. Soc.*, 1962, **84**, 1889.

TABLE 2.

Periodate oxidation of hippurhydroxamic acid; effect of pH on yields of amides.

Amine	Cyclohexylamine				Ethyl glycinate	
pH	9	6·5	4	3·1	8·6	6·9
Yield (%)	43	45	6·3	0	0	10

TABLE 3.

Oxidations with *N*-bromosuccinimide (NBS) and iodine.

Hydroxamic acid	Amine	Reagent	Crude material Yield	Crude material M. p.
Benzhydroxamic	Benzylamine	NBS	70	105—106°
	Benzylamine	I_2	58	
Phenylacethydroxamic	Morpholine	NBS	0	
	Diethylamine	I_2	0	
Hippurhydroxamic	Cyclohexylamine	NBS	73	164—165°
	Cyclohexylamine	I_2	50	
	p-Nitrobenzyl glycinate	NBS	41	
N-Methylhippurhydroxamic	Cyclohexylamine	NBS	Hydroxamic acid unchanged	

Oxidations with *N*-bromosuccinimide and iodine in dimethylformamide are summarised in Table 3. The amides were precipitated, sometimes analytically pure, by dilution with water and aqueous thiosulphate, respectively. Slight differences in procedure are noted in the Experimental section.

Similar yields were also obtained in oxidations with alkaline potassium ferricyanide.

Diethylamine and morpholine were not acylated in any of the above procedures. In an experiment with periodate, aniline was itself oxidised.[7]

It is of interest that *N*-methylhippurhydroxamic acid (m. p. 170—172°) was oxidised by periodate (cf. ref. 1) but not by *N*-bromosuccinimide. The first step in the oxidation of simple hydroxamic acids (I; R′ = H) by this reagent is therefore bromination on the amide nitrogen. The rapid conversion of NH·OH into N=O by periodate seems to be a general reaction [1,8,9] the extension of which to hydroxamic acids (I; R′ = H) leads to the hypothetical intermediate R·CO·NO; this we have assumed to be the acylating entity in the periodate oxidation described here.

Experimental

N-*Methylhippurhydroxamic Acid.*—*N*-Methylhydroxylamine hydrochloride [10] (3·4 g., 0·041 mole), in methanol was added to methanolic potassium hydroxide (6 g., 0·011 mole). Ethyl hippurate (4 g., 0·019 mole) was added to the filtered solution and the mixture kept at room temperature for 48 hr. After removal of the methanol under reduced pressure at room temperature, the residue was taken up in water and neutralised with glacial acetic acid (4 ml.), whereupon N-*methylhippurhydroxamic acid* crystallised out. Recrystallised from aqueous ethanol, it (3·2 g., 80%) had m. p. 170—172° (Found: C, 58·0; H, 5·8; N, 13·7. $C_{10}H_{12}N_2O_3$ requires C, 57·7; H, 5·8; N, 13·5%).

Oxidation with Periodate.—Estimation. From stock aqueous solutions of hippurhydroxamic acid [11] (0·0966 g. in 100 ml.) and sodium periodate (0·2126 g. in 100 ml.), aliquots (10 ml.) were mixed and quickly diluted to 100 ml. Aliquots (10 ml.) of the reaction mixtures were titrated within 2 min. (and at intervals subsequently) with 0·001039N-sodium arsenite in the usual way. A blank containing only periodate was used for comparison. A periodate uptake of 1·27 moles/mole of substrate was found after 2 min., and was constant during 1 hr.

Preparative oxidations. Buffer solutions were prepared by mixing appropriate volumes of 0·2N-sodium acetate and 0·2N-acetic acid, or of N-sodium dihydrogen and N-dipotassium hydrogen phosphate. pH was measured with a Cambridge portable pH-meter.

The following procedures with hippurhydroxamic acid are typical.

[7] Tanabe, *J. Pharm. Soc. Japan*, 1958, **78**, 410.

[8] Tanabe, *J. Pharm. Soc. Japan*, 1956, **76**, 1023.

[9] Snow, *J.*, 1954, 2588; Neilands and Azari, *Acta Chem. Scand.*, 1963, **17**, 190.

[10] Beckmann, *Annalen*, 1909, **365**, 204.

[11] Green, Sainsbury, Saville, and Stansfield, *J.*, 1958, 1583.

Ethyl benzoylglycylglycinate. Hippurhydroxamic acid [11] (0·59 g., 3 mmoles), in phosphate buffer adjusted to pH 6·9, was added dropwise and with stirring to a cold buffered solution of ethyl glycinate hydrochloride (0·56 g., 4 mmoles). The mixture became slightly yellow, and after *ca.* 1 hr. it was extracted with chloroform. After extraction with sodium arsenite and water, a yellow oil was obtained which crystallised. It was treated with charcoal in benzene and recrystallised from water, giving needles (0·15 g., 20%), m. p. 117—118°.

N-*Cyclohexylhippuramide.* Cyclohexylamine (0·9 ml., 7 mmoles) was added to sodium periodate (0·64 g., 3 mmoles) in acetate buffer (sodium acetate–acetic acid, 85 : 15, v/v), and the pH adjusted to 6·7 by the addition of glacial acetic acid (0·25 ml.). Hippurhydroxamic acid (0·58 g., 3 mmoles), in the original buffer solution, was added dropwise, with cooling and stirring. The pH remained constant at *ca.* 6·5. The amide was precipitated during the reaction and was collected after a total reaction time of 1½ hr. It was recrystallised repeatedly from aqueous ethanol but remained slightly yellow (0·36 g., 45%), m. p. 164—165°.

The experiment was repeated at pH 4 and 3·1 (NaOAc–HOAc, 75 : 25 and 50 : 50, v/v, respectively).

p-*Nitrobenzyl benzoylglycylglycinate.* Hippurhydroxamic acid (0·95 g., 5 mmoles), in the phosphate buffer adjusted to pH 7, was added as above to the buffered mixture of sodium periodate (1·12 g., 5 mmoles) and *p*-nitrobenzyl glycinate hydrobromide [12] (1·51 g., 5 mmoles). The coloured reaction product was collected and recrystallised six times from aqueous ethanol, giving the amide still impure (0·78 g., 43%), m. p. 112°.

In experiments in which an excess of sodium thiosulphate was added before oxidation, the yellow colour persisted.

Oxidations with N-*Bromosuccinimide.*—N-*Benzylbenzamide.* Recrystallised *N*-bromosuccinimide (1·28 g., 7 mmoles) in dry dimethylformamide was added dropwise during 1 hr. to a cold stirred mixture of benzhydroxamic acid [13] (0·68 g., 5 mmoles) and benzylamine (1·2 ml., 12 mmoles) in the same solvent. After a further 30 min. (negative ferric chloride test), the mixture was diluted with water, and the precipitated amide air-dried (0·74 g., 70%), m. p. 105—106° (Found: C, 78·4; H, 6·1; N, 6·3. Calc. for $C_{14}H_{13}NO$: C, 79·5; H, 6·2; N, 6·6%).

N-*Cyclohexylhippuramide.* *N*-Bromosuccimide (0·72 g., 4 mmoles) in dimethylformamide was added to a mixture of hippurhydroxamic acid (0·58 g., 3 mmoles) and excess of cyclohexylamine. After work-up as above, the amide was precipitated (0·57 g., 73%), m. p. 164—165° (Found: C, 69·5; H, 7·5; N, 12·0. Calc. for $C_{15}H_{20}N_2O_2$: C, 69·2; H, 7·7; N, 10·8%).

p-*Nitrobenzyl benzoylglycylglycinate.* *N*-Bromosuccinimide (1·09 g., 6·1 mmoles) was added to a mixture of hippurhydroxamic acid (0·92 g., 4·7 mmoles), *p*-nitrobenzyl glycinate hydrobromide [12] (1·45 g., 5 mmoles), and triethylamine (1 ml., 10 mmoles), all in dimethylformamide. After 20 min., water was added, and the precipitated amide was dried (0·72 g., 41%). Repeated crystallisation from aqueous ethanol gave the *dipeptide ester*, m. p. 115—116° (Found: C, 57·9; H, 4·7; N, 11·1. $C_{18}H_{17}N_3O_6$ requires C, 58·2; H, 4·7; N, 11·3%).

Oxidation with Iodine.—N-*Benzylbenzamide.* Solutions of iodine (2·54 g., 10 mmoles) and benzhydroxamic acid (0·69 g., 5 mmoles) in dimethylformamide were added dropwise and simultaneously to an ice-cold stirred solution of benzylamine (1 ml., 10 mmoles). After 1 hr., aqueous thiosulphate was added until the iodine was destroyed, and the amide was then completely precipitated with more water, collected, and air-dried (0·61 g., 58%); it had m. p. 106—107° (from aqueous ethanol).

Oxidation with Ferricyanide.—N-*Cyclohexylhippuramide.* Aqueous hippurhydroxamic acid (0·58 g., 3 mmoles) was added dropwise to a cold stirred solution of potassium ferricyanide (3·95 g., 12 mmoles) and cyclohexylamine (1·2 ml., 12 mmoles) in aqueous potassium carbonate. After 1 hr., the mixture was filtered, and the solid washed and dried (0·49 g., 63%); it had m. p. 165—166° (from aqueous ethanol).

N-*Benzylbenzamide.* Prepared by an entirely parallel procedure, the amide (58%) had m. p. 106—107° (from aqueous ethanol).

We thank Professor D. H. R. Barton for his interest and advice.

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[*Received, September 6th,* 1963.]

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[12] Schwarz and Arakawa, *J. Amer. Chem. Soc.*, 1959, **81**, 5691.
[13] *Org. Synth.*, Coll. Vol. II, 1943, p. 67.