[CONTRIBUTION FROM THE CHEMOTHERAPY BRANCH, BIOCHEMICAL RESEARCH DIVISION, CHEMICAL WARFARE LABORATORIES]

N-Hydroxy Aryl Carbamates. A Class of Hydroxamic Acids Which Form Stable Phosphorylated and Sulfated Derivatives[1]

G. M. STEINBERG AND JAMES BOLGER[2]

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N-hydroxy aryl carbamates react readily with phosphorylating and sulfating agents. Unlike the products of reaction with the closely related hydroxamic acids, which are highly unstable and subject to immediate Lossen rearrangement, these compounds are easily prepared, reasonably high melting solids which may be useful for the characterization of phosphorylating and sulfating agents. A comparison is made between the properties of hydroxamic acids and N-hydroxy carbamates and an explanation advanced for the resistance of the latter to the Lossen rearrangement.

Hydroxamic acids undergo the Lossen rearrangement with particular ease under the influence of phosphorylating and sulfating agents. It has been postulated that the reaction proceeds by initial phosphorylation (or sulfation) followed by very rapid rearrangement of the phosphorylated product[3]; however, it has not been possible to isolate the postulated intermediates, *e.g.* RC(=O)-NHOP(=O)(OR)$_2$, presumably because of their extreme instability. This is in contrast to the appreciable stability of acylated hydroxamic acids, *e.g.* RC(=O)NHOC(=O)R′, which have been isolated and characterized,[4] yet which can be rearranged under alkaline conditions.

It has been noted[5] that the tendency of phosphorylated hydroxamic acids to rearrange is far greater than would be predicted from the inverse relationship observed by Hauser and co-workers[4] between pK_a of the acylating acid and the rate of rearrangement of the corresponding O-acylated hydroxamic acid. Hence, it was of considerable interest to investigate the reaction of N-hydroxy aryl carbamates (ROC(=O)NHOH) with phosphorylating (and sulfating) agents inasmuch as the RO— group does not generally participate in molecular rearrangements. The products of reaction were found to be quite stable.

The N-hydroxy aryl carbamates appear in most other ways to be typical hydroxamic acids. They give characteristic wine-colored, water-soluble complexes with ferric ion and light green, difficultly filterable, water-insoluble complexes with cupric salts. After phosphorylation (or sulfation) the product no longer gives these characteristic tests,[6] thus indicating the original presence of the grouping —C(=O)NHOH, and its conversion upon phosphorylation to —C(=O)NHOP(=O)(OR)$_2$.[7] The N-hydroxy aryl carbamates exhibit the remarkably rapid rates of reaction with Sarin (isopropyl methylphosphonofluoridate) and DFP (diisopropyl phosphorofluoridate) which have been previously reported for a large number of hydroxamic acids,[3a] Table I. The pK_a values of the hydroxy carbamates

TABLE I

RATE OF REACTION OF SEVERAL HYDROXAMIC ACIDS WITH SARIN[a]

Substance	$t_{\frac{1}{2}}$[b]	pK_a[c]
Sarin only	300	—
Sorbo hydroxamic acid[d]	1.0	9.2
Benzo hydroxamic acid	2.0	8.8
Tropo hydroxamic acid[d]	2.0	—
N-Hydroxy phenyl carbamate	1.4	10.0[e]
N-Hydroxy *p*-cresyl carbamate	2.3	10.3[e]

[a] 5 *μ-moles* of Sarin [isopropyl methylphosphonofluoridate, $CH_3P(=O)(O—iPr)F$], and 25 *μ-moles* of hydroxamic acid or hydroxy carbamate in 2.2 ml. of a carbonate-bicarbonate buffer, *p*H 7.6, 30°C.; rate of acid production determined manometrically.[8] [b] $t_{\frac{1}{2}}$ = half-time of pseudo first order reaction in minutes. [c] Determined as *p*H of half-neutralized solution. See ref. 5. [d] Previously unreported compounds. Prepared by conventional methods by R. C. Tweit. Sorbo hydroxamic acid (from sorbyl chloride,[9] m.p. 131–133° (dec.) (acetone-pet ether). Calc'd: C, 56.7; H, 7.13; N, 11.02. Found: C, 57.0; H, 7.1; N, 11.00. Tropo hydroxamic acid (from ethyl tropate) m.p. 171–172° (ethanol-H_2O). Calc'd: C, 59.7; H, 6.12; N, 7.73. Found: C, 59.6; H, 6.25; N, 7.8. [e] These compounds hydrolyze rapidly at *p*H 10. True values may be slightly higher, by perhaps 0.1–0.3 *p*K units.

(1) Presented before the Meeting-in-miniature of the Maryland Section of the American Chemical Society, November, 1955.

(2) Present address: Riker Laboratories, Los Angeles, California.

(3) (a) Hackley, Plapinger, Stolberg, and Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 3651 (1955); (b) Stolberg, Tweit, Steinberg, and Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 765 (1955); (c) Hurd and Bauer, *J. Am. Chem. Soc.*, **76**, 2791 (1954).

(4) Hauser and Renfrow, *J. Am. Chem. Soc.*, **59**, 2308 (1937); Bright and Hauser, *J. Am. Chem. Soc.*, **61**, 618 (1939).

(5) Swidler and Steinberg, *The Kinetics of Reaction of Sarin with Benzohydroxamic Acid*, submitted for publication.

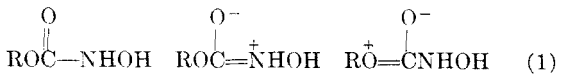
(6) Metal chelates of similar properties are formed by hydroxamic acids and oximino ethers in which the oximino hydroxyl group is unsubstituted. Oximino O-substituted products no longer form complex ions having the same characteristic properties. Houben-Weyl, *Methoden der Org. Chem.*, 4th Ed., George Thieme Verlag, Stuttgart, 1952, Vol. 8, p. 685. Yale, *Chem. Revs.*, **33**, 249 (1943).

(7) Acylation of N-hydroxy aryl carbamates takes place in the oxygen atom of the hydroxylamine group. Oesper and Cook, *J. Am. Chem. Soc.*, **47**, 422 (1925).

(8) Wagner-Jauregg and Hackley, *J. Am. Chem. Soc.*, **75**, 2125 (1953).

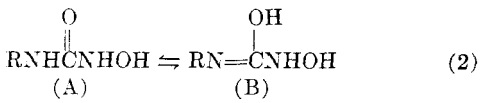
(9) Jones, *Am. Chem. J.*, **20**, 39 (1898).

are slightly higher than those of the corresponding hydroxamic acids, RC(=O)NHOH. The differences in properties of the N-hydroxy aryl carbamates and hydroxamic acids can be explained in terms of the contribution of the cross-conjugated resonance structure 1C.[10] Its contribution would tend to increase pK_a and provide partial double bond character to the RO-C bond with resultant resistance to



(1)

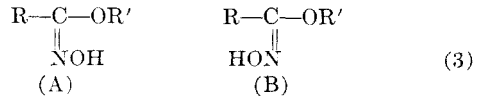
rearrangement. This explanation is in accord with the observations of Hurd and Spence[11] that N-alkyl (or aryl)-N′-hydroxy ureas (RNHCONHOH) resisted rearrangement, while N,N-disubstituted compounds ($R_2NCONHOH$) rearranged normally. They attributed the non-rearrangement of the monosubstituted hydroxy ureas to the double bond character of the group which would normally migrate due to formation of the tautomeric form 2B.



(2)

The capacity for rearrangement observed in the N,N-disubstituted-N′-hydroxy ureas suggests that in compounds of this type there is little contribution from the cross-conjugated resonance form corresponding to 1C, presumably because of steric factors. Support for this view has been presented recently in independent studies by Edward and Meacock[12] and Grob and Fisher[13] in which there were compared the UV spectra of unsaturated amides with varying degrees of substitution on the amide N atom. Both groups concluded that the hypsochromic shift in UV spectra observed with N,N-disubstituted saturated amides (compared to mono- and un-substituted amides), which shift they failed to find in the unsaturated compounds, was due to steric inhibition of normal amide resonance. This corresponds to inhibition of a resonance form equivalent to 1C.

The stability of phosphorylated N-hydroxy carbamates is in accord with the resistance of one of the two stereoisomeric forms of oximino ethers, 3A and 3B, to participate in the closely related Beckmann rearrangement. One form, presumably 3A, rearranges upon treatment with phosphorus pentachloride to yield RNHCOOR′. The other form phosphorylates without rearrangement.[14] It is well known that acylation increases the strength of hydroxamic acids. Thus, Ph-C(=O)NHOC(=O)NH-Ph with a pK_a of 6.4,[15] is 2.4 pK units more strongly acidic than benzohydroxamic acid. In a similar fashion, phosphorylation increases the acidity of N-hydroxy carbamates. Both Ph-O(C=O)NHOP(=O)(O-iPr)$_2$ and Ph-O(C=O)NHOP(=O)(CH_3)-(O-iPr) have pK_a values of 6.2, corresponding to an increase in acid strength of 4 pK units.



(3)

There is a general need for identification reagents for organophosphorus compounds. This is especially true for those compounds of importance as insecticides and medicinals. The N-hydroxy aryl carbamates react readily and are useful for the identification of some of the more reactive compounds used in these areas, including the phosphoro- and phosphono-halidates and the pyrophosphates (See Table II). However, under the conditions of this study no reaction was observed with the more stable types, such as Paraoxon (diethyl p-nitrophenyl phosphate) or OMPA (octamethylpyrophosphoramide).

Reactions were carried out in both aqueous and pyridine solution; the latter solvent giving better yields with those compounds which hydrolyse readily in water. In aqueous solution, it was found most convenient to run the reaction at constant pH, with a Beckman Autotitrator. However, the reaction could also be conducted by manually adding alkali to maintain the reaction mixture alkaline to Neutral Red. A pH of about 8 is generally optimum. At lower pH, reaction is appreciably slowed, while higher pH values lead to increased hydrolysis of both the hydroxy carbamates and the phosphoryl and sulphonyl reagents.

Although quite stable when compared to the corresponding phosphorylated hydroxamic acids, salts of the phosphorylated N-hydroxy aryl carbamates can be thermally decomposed. Thus, the pure dry potassium salt of Ph-OC(=O)NHOP(=O)(CH_3)-(O-iPr) decomposed vigorously at 50° with much charring and strong odor of phenol. In refluxing dioxane, decomposition occurred relatively slowly and was incomplete after 8 hours. Under these conditions, 30–40 mole-percent of CO_2 was evolved (determined as $BaCO_3$) and 10–15 mole-percent of phenol produced (isolated and determined as the tribromo derivative).

EXPERIMENTAL[16]

N-Hydroxy phenyl carbamate was prepared by reaction of phenyl chlorocarbonate with hydroxylamine hydrochloride

(10) Branch and Calvin, *Theory of Organic Chem.*, Prentice-Hall, Inc., New York, 1941, pp. 235–240.

(11) Hurd and Spence, *J. Am. Chem. Soc.*, **49**, 266 (1927).

(12) Edward and Meacock, *Chemistry & Industry*, No. 19, 536 (1955).

(13) Grob and Fischer, *Chemistry & Industry*, No. 34, 1063 (1955); *Helv. Chim. Acta*, **38**, 1794 (1955).

(14) Wheland, *Advanced Organic Chemistry*, 2nd Ed., John Wiley and Sons, Inc., New York, 1949, p. 347.

(15) Determined by S. Seltzer.

(16) Melting points are uncorrected.

TABLE II

HYDROXY CARBAMATE DERIVATIVES

Reactant	Procedure[a]	Yield	M.P., °C	Recrystallized from	Analysis: Theory C	H	N	P	Found C	H	N	P
(A) N-HYDROXY PHENYL CARBAMATE: $C_6H_5OCONHOH$												
Sarin (isopropyl methylphosphonofluoridate)	A	70	137–139	CH_2Cl_2-lig. (60–80°)	48.3	5.86	5.13	11.36	48.4	6.0	5.1	11.2
DFP (diisopropyl phosphorofluoridate	A	51	122–124	$CHCl_3$-lig. (60–80°)	49.2	6.31	4.42	9.78	49.2	6.2	4.2	9.8
DClP (diisopropyl phosphorochloridate)	A	14	122–124[b]	$CHCl_3$-lig. (60–80°)								
DClP	B	57.5	122–124[b]	$CHCl_3$-lig. (60–80°)								
TIPP (tetraisopropyl pyrophosphate)	A	23	122–124[b]	$CHCl_3$-lig. (60–80°)								
TEPP (tetraethyl pyrophosphate)	A	8	65–66	$CHCl_3$-pet. ether (30–60°)	...	..	4.85	10.79	..	...	5.0	10.8
p-Toluenesulphonyl chloride	A	49	110–111		54.7	4.26	4.56	10.43[c]	54.8	4.2	4.5	10.4[c]
(B) N-HYDROXY *p*-CRESYL CARBAMATE: *p*-$CH_3C_6H_4OCONHOH$												
Sarin	A	64	145–146	$CHCl_3$-lig. (60–80°)	50.12	6.31	4.88	10.78	49.6	6.1	4.7	10.8

[a] See Experimental Section. [b] No melting point depression with DFP reaction product. [c] Value for sulfur.

and potassium carbonate in moist ether;[17] yield, 71.5%; m.p. 105–107° (reported 102.5°).

N-Hydroxy p-cresyl carbamate was prepared as above from *p*-cresyl chlorocarbonate; yield, 51%, m.p. 98–99° (reported 99°).[17]

Preparation of hydroxy carbamate derivatives. Typical reactions are presented below. Yields, physical and analytical data are given in Table II.

Procedure A. N-Hydroxy phenyl carbamate, 1.0 g. (0.0065 mole) was dissolved in 50 ml. of water and the solution was adjusted to *p*H 8. Diisopropyl phosphorochloride (DClP), 0.9 g. (0.0045 mole), was added and the solution was maintained at *p*H 8 by addition of 0.2 *N* sodium hydroxide solution by the Beckman Autotitrator. Upon completion of reaction (no further production of acid), the solution was acidified to *p*H 3. The white solid (0.2 g.) which precipitated was dried and recrystallized.

With more soluble substances, the product was extracted from the acid solution with chloroform, and this solution was dried over magnesium sulfate, then concentrated to a small volume and crystallized by addition of ligroin (b.p. 60–80°).

Procedure B. To a stirred solution of N-hydroxy phenyl carbamate, 3.0 g. (0.0196 mole) in 15 ml. of dry pyridine at 0°, there was slowly added 3.3 g. (0.0165 mole) DClP. The reaction mixture was allowed to warm to room temperature. Next morning, the mixture was poured onto ice and acidified with concentrated hydrochloric acid to *p*H 4. The solid which precipitated was collected, dissolved in chloroform and worked up as above.

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ARMY CHEMICAL CENTER, MARYLAND

(17) Oesper and Broker, *J. Am. Chem. Soc.*, **47**, 2607 (1925).