The Oxidation of Hydroxamic Acids

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The oxidation of alkyl or benzyl *N*-hydroxycarbamate produced mainly the corresponding *O*-alkoxycarbonyl or *O*-benzoxycarbonyl *N*-hydroxycarbamates and small amounts of the corresponding trisubstituted hydroxylamines. The oxidation of sodium benzhydroxamate with iodine gave *O*-benzoyl benzhydroxamate; hydroxyurea and *N*-hydroxy-*N'*-phenylurea were similarly converted into *N*-carbamoyloxyurea and *N*-hydroxy-*N'*-phenyl-*N*-phenylcarbamoylurea, respectively. Oxidation of ethyl, n-propyl, and benzyl *N*-hydroxycarbamates or hydroxyurea or *N*-hydroxy-*N*-phenylurea with iodine in aqueous ammonium carbonate gave the corresponding carbamates, urea, or phenylurea. With silver oxide in ether, alkyl *N*-hydroxycarbamates and their *O*-alkoxycarbonyl derivatives yielded *N*-silver-*N*-alkoxycarbonyloxycarbamates; simultaneous oxidation of ethyl and benzyl *N*-hydroxycarbamates gave *NO*-di- and *NNO*-tri-substituted hydroxylamines in which the substituents were ethoxycarbonyl, benzyloxycarbonyl, or, possibly, ethyl and benzyl groups.

N-HYDROXYURETHANE (I; R = Et), on oxidation, gave mainly the urethane (II; R = Et) and small amounts of (III; R = Et), together with a compound (IV) chromatographically identical with the product of the reaction of (II) with ethyl iodide and which was probably the *N*-ethyl derivative of (II). Iodine, silver oxide, mercuric oxide, manganese dioxide, lead tetra-acetate, silver nitrate, and cupric sulphate formed relatively

$$\underset{(I)}{RO{\cdot}CO{\cdot}NH{\cdot}OH} \quad \underset{(II)}{RO{\cdot}CO{\cdot}NH{\cdot}O{\cdot}CO_2R} \quad \underset{(III)}{RO{\cdot}CO{\cdot}N(CO_2R){\cdot}O{\cdot}CO_2R}$$

decreasing amounts of (II). Methyl *N*-hydroxycarbamate (I; R = Me) similarly gave the corresponding derivatives (II), (III), and (IV) (R = Me). Oxidation with potassium dichromate or hydrogen peroxide decomposed the hydroxycarbamates (I; R = Me or Et) and no (I)—(IV) could be detected in the reaction mixture after 1 hour.

The oxidation of *N*-hydroxyurethane by silver oxide in ether yielded the light-sensitive crystalline silver derivative of (II), (V) $EtO{\cdot}CO{\cdot}NAg{\cdot}O{\cdot}CO_2R$. The compound showed no salt-like properties, since it was soluble in non-polar organic solvents and insoluble in water. It gave compound (II; R = Et) and other products when it was (a) dissolved in benzene or carbon tetrachloride or suspended in water and exposed to light, (b) dissolved in ether and treated with dry hydrogen chloride, (c) suspended in aqueous sodium chloride, or (d) heated. With methyl iodide or bromine in methylene chloride, it gave the *N*-methyl or *N*-bromo-derivative of compound (II; R = Et). Further proof of the identity of the compound was obtained by its synthesis from compound (II) and silver oxide in ether. These results indicate that the silver is covalently bound to nitrogen. Other *N*-hydroxycarbamates gave similar silver derivatives with R = Me, Pr^n, and Bu^n.

The oxidation of benzyl *N*-hydroxycarbamate by iodine provided a convenient route to the synthesis of the dibenzyloxycarbonyl derivative (II; R = $PhCH_2$) which was obtained as an impure oil by the usual synthetic methods. Benzhydroxamic acid, hydroxyurea, and *N*-hydroxy-*N'*-phenylurea similarly gave *O*-benzoyl benzhydroxamate, carbamoyloxyurea, and phenylcarbamoyl-*N*-hydroxy-*N'*-phenylurea. If compounds containing the grouping CO·N(OR) give coloured ferric complexes only when R is hydrogen, the following structures may be assigned to the carbamoyl and phenylcarbamoyl derivatives which follow: *N*-carbamoyloxyurea ($NH_2{\cdot}CO{\cdot}NH{\cdot}O{\cdot}CO{\cdot}NH_2$, gave no colour with ferric chloride), *N*-hydroxy-*N*-phenylcarbamoylurea [$NH_2{\cdot}CO{\cdot}N(OH){\cdot}CO{\cdot}NHPh$, wine-red coloration], *N*-hydroxy-*N'*-phenyl-*N*-phenylcarbamoylurea [$(PhNH{\cdot}CO)_2{\cdot}N{\cdot}OH$, wine-red coloration], *N*-phenylcarbamoyloxyurethane ($EtO{\cdot}CO{\cdot}NH{\cdot}O{\cdot}CO{\cdot}NHPh$, no colour), and *N*-hydroxy-*NN'*-diphenylurea [$PhN(OH){\cdot}CO{\cdot}NHPh$, purple coloration].

While heterolytic mechanisms might be involved in these reactions, bond homolysis to produce free-radical intermediates seems more probable, for the following reasons. (a) The polarity of the solvent did not affect the course of the reactions, as the same products were formed in ether, benzene, chloroform, or water as solvent. (b) The oxidation of several types of hydroxamic acid, *e.g.*, *N*-acyl-, *N*-alkoxycarbonyl-, *N*-carbamoyl-, and *N*-hydroxycarbamoylhydroxylamines with iodine in neutral or alkaline media, followed by acidification of the reaction mixtures, produced nitrous acid, which was determined by known methods.[1] This reaction provided a sensitive procedure for the colorimetric determination of hydroxamic acids (to be reported elsewhere). The iodine oxidation of hydroxylamine to nitrous acid, by contrast, occurs in acid media.[2] The alkyl and aryl hydroxylamines did not liberate nitrous acid under the conditions employed, probably because of the high energy required for carbon–nitrogen bond homolysis. This agrees with the known reactions of these compounds, including oxidations, reductions, rearrangements, cyclisations, and condensations which occur without carbon–nitrogen bond fission.[3] The formation of nitrous acid may be used as an alternative to the ferric chloride test normally employed to distinguish between these classes of hydroxylamine derivative. (c) When a mixture of ethyl and benzyl *N*-hydroxycarbamates was oxidised by silver oxide in ether followed by treatment of the ethereal solution with dry hydrogen chloride, (i) ethyl ethoxycarbonyloxy-, (ii) ethyl benzyloxycarbonyloxy-, (iii) benzyl ethoxycarbonyloxy-, and

[1] A. C. Bratton and E. K. Marshall, *J. Biol. Chem.*, 1939, **128**, 537.
[2] F. Feigl and V. Demant, *Mikrochim. Acta*, 1937, **1**, 132.
[3] E. Bamberger, *Annalen*, 1921, **424**, 233, 297; *ibid.*, 1925, **441**, 207.

(iv) benzyl benzyloxycarbonyloxy-carbamates together with at least six other reducing substances, which were probably the *N*-ethyl, *N*-benzyl, *N*-ethoxycarbonyl, or *N*-benzyloxycarbonyl derivatives of compounds (i)—(iv), were formed. Such diversity of products is usual in free-radical reactions and may be expected if ethoxycarbonyl, benzyloxycarbonyl, ethyl, and benzyl radicals were formed. Substitution of the hydrogen atoms of the hydroxyamido-group in (I) by the ethoxycarbonyl or benzyloxycarbonyl radicals gave compounds of type (II) or (III), and of the hydrogen atom of (II) by the ethyl or benzyl radical gave compounds of type (IV). On the basis of the amounts of silver derivatives and carbon dioxide formed during the oxidation of *N*-hydroxycarbamates with silver oxide, it appears that the alkoxycarbonyl radical reacted with unchanged (I) about 10—15 times faster than by the following route: $RO{\cdot}CO \longrightarrow R{\cdot} + CO_2$. The formation of carbamoyloxyurea or *N*-hydroxy-*N'*-phenyl-*N*-phenylcarbamoylurea from the oxidation of hydroxyurea or *N*-hydroxy-*N'*-phenylurea possibly occurred by reaction of the carbamoyl or phenylcarbamoyl radical with the parent compound. Further evidence for the formation of alkoxycarbonyl, benzyloxycarbonyl, carbamoyl, and phenylcarbamoyl radicals was provided by the fact that oxidation of the parent compounds in the presence of a competitive radical acceptor, *e.g.*, ammonia, gave the corresponding carbamates or ureas, *i.e.*, reduction products were obtained by an oxidative process. This was not due to ammonolysis of the parent hydroxamic acids, as they were recovered unchanged or as ammonium salts when the oxidising agent was not present.

The oxidations might proceed by the following reaction scheme:

$$A{-}CO{-}NHOH\ (VI) + B \longrightarrow A{-}CO{-}NHO{\cdot}\ (VII) + BH{\cdot}$$

$$(VII) \longrightarrow A{-}CO{\cdot}\ (VIII) + NOH{\cdot}$$

$$(VI) + (VIII) \xrightarrow{-H{\cdot}} A{-}CO{-}NH{-}O{-}CO{-}A\ (IX)\ [\text{or } A{-}CO{-}N(OH){-}CO{-}A, \text{ when A is PhNH}]$$

$$(VIII) + NH_3 \longrightarrow A{-}CO{-}NH_2\ (X) + H{\cdot}$$

In these reactions, A is $PhCH_2$, $PhCH_2{\cdot}O$, AlkO, H_2N, or PhNH, and B is a one-electron-abstracting oxidant, *e.g.*, iodine. When A is $PhCH_2{\cdot}O$ or AlkO(RO), the following reactions also occur:

$$(VIII) \longrightarrow R{\cdot} + CO_2$$

$$R{\cdot} + (IX) \longrightarrow (IV) + H{\cdot}$$

$$(VIII) + (IX) \longrightarrow (III) + H{\cdot}$$

$$(IX) + \tfrac{1}{2}Ag_2O \longrightarrow (V) + \tfrac{1}{2}H_2O$$

Free radicals of type (VII) have been detected by e.s.r. spectroscopy.[4]

The formation of the nitroxyl radical was indicated by the fact that one mole of the compound oxidised immediately consumed one gram-atom of iodine. The oxidation of *N*-arylhydroxamic acids by lead tetra-acetate gave nitroso-aryls (Ar·NO),[5] which are *N*-aryl derivatives of nitroxyl ($HNO \rightleftharpoons NOH$).

The fact that hydroxamic acids, including the carcinogenic [6] and antiviral agents,[7] the *N*-hydroxycarbamates, and the cancer chemotherapeutic agent, *N*-hydroxyurea,[8] produce nitroxyl and nitrite and act as alkylating, alkoxycarbonylating, acylating, and carbamoylating agents on oxidation may be significant in the diverse biological activities of these compounds. Thus, urethane is oxidised by mammals to *N*-hydroxyurethane which can alkylate and alkoxycarbonylate cysteine derivatives *in vivo*.[9] The oxidation of *N*-hydroxycarbamates and hydroxyurea in the presence of ammonium carbonate produced carbamates and urea, so the biological reduction [9-11] of these compounds may occur by an oxidative mechanism.

EXPERIMENTAL

Light petroleum had b. p. 80—100° unless otherwise stated.

Thin-layer Chromatography.—Glass plates were coated with films of silica gel G (Merck) of 0·25 mm. thickness, and the chromatograms were developed in (A) acetone–light petroleum (b. p. 40—60°) (3 : 7), (B) chloroform containing 0·5% (v/v) of acetic acid, (C) butan-1-ol–acetic acid–water (10 : 1 : 1), (D) propan-1-ol–ethanol (7 : 3), and (E) butan-1-ol–acetic acid (19 : 1). For the detection of compounds, the following reagents were used: (i) ammoniacal aq. 2% (w/v) silver nitrate, (ii) 1% (w/v) ferric chloride in aq. 50% ethanol, and (iii) 1% (w/v) sodium amminoprusside in water containing 0·1% magnesium chloride hexahydrate. The *N*-hydroxycarbamates (I) gave purple and red colours, respectively, with (ii) and (iii), and reduced (i) within 5 min.; the alkoxycarbonyloxycarbamates (II) gave purple to blue colours with (iii) and reduced (i) after about 40 min.; and the *NO*-disubstituted *N*-hydroxycarbamates (III) and (IV) gave faint purple to blue colours with (iii) and reduced (i) after several hours.

Preparation of Alkyl N-*Hydroxycarbamates and their* O-*Substituted Derivatives.*—These were prepared from the corresponding alkyl chloroformates and hydroxylamine hydrochloride as previously described.[12]

Benzyl N-*Hydroxycarbamate.*—Benzyl chloroformate (68 g.) was added dropwise to a stirred solution of hydroxylamine hydrochloride (31 g.) and sodium hydroxide (36 g.) in water (500 ml.) at 0°. After 3 hr., the pH of the mixture was adjusted to 2 with 6N-hydrochloric acid and the precipitated solid recrystallised from benzene–light petroleum, to yield colourless plates (10 g.) of *benzyl* N-*hydroxycarbamate*, m. p. 71° (Found: C, 57·6; H, 5·4; N, 8·4. $C_8H_9NO_3$ requires C, 57·5; H, 5·4; N, 8·4%). The filtrate was extracted with ether (2 × 200 ml.), the combined extracts

[4] C. J. W. Gutch and W. A. Waters, *J. Chem. Soc.*, 1965, 751.
[5] H. E. Baumgarten, A. Staklis, and E. M. Miller, *J. Org. Chem.*, 1965, **30**, 1203.
[6] I. Berenblum, D. Ben-Ishai, N. Haran-Ghera, A. Lapidot, E. Simon, and N. Trainin, *Biochem. Pharmacol.*, 1959, **2**, 169.
[7] C. P. de Sousa, E. Boyland, and R. Nery, *Nature*, 1965, **206**, 688.
[8] B. Stearns, K. A. Losee, and J. Bernstein, *J. Medicin. Chem.*, 1963, **6**, 201.
[9] E. Boyland and R. Nery, *Biochem. J.*, 1965, **94**, 198.
[10] S. S. Mirvish, *Biochim. Biophys. Acta*, 1964, **93**, 673.
[11] R. H. Adamson, J. D. Davidson, S. L. Ague, and S. M. Hess, *Proc. Amer. Assn. Cancer Res.*, 1965, **6**, 1.
[12] E. Boyland and R. Nery, *Analyst*, 1964, **89**, 520.

were washed with water (50 ml.), and dried (Na_2SO_4), the solvent was removed *in vacuo*, and the residues recrystallised similarly, to yield a further crop (35 g.), m. p. and mixed m. p. 71°.

Benzyl N-*Ethoxycarbonyloxycarbamate*.—Ethyl chloroformate (10 g.) was added dropwise to a stirred solution of benzyl *N*-hydroxycarbamate (10 g.) in pyridine (30 ml.) at 0°. After 2 hr., the mixture was diluted with ice–water (200 ml.), extracted with ether (3 × 50 ml.), and the combined extracts were washed with water (50 ml.), 2N-hydrochloric acid (3 × 30 ml.), and water (2 × 50 ml.), dried (Na_2SO_4), and distilled. *Benzyl ethoxycarbonyloxycarbamate* was obtained as a colourless oil (9·0 g.), b. p. 162—164°/0·03 mm., which solidified on cooling and crystallised from benzene–light petroleum as colourless prisms, m. p. 65—66° (Found: C, 54·8; H, 5·6; N, 5·9%; *M*, 246. $C_{11}H_{13}NO_5$ requires C, 55·2; H, 5·5; N, 5·9%; *M*, 239). Catalytic hydrogenation in methanol–acetic acid with palladised charcoal gave benzyl carbamate, m. p. and mixed m. p. 89°, intead of the expected *O*-ethoxycarbonylhydroxylamine.

Ethyl Benzyloxycarbonyloxycarbamate.—This *compound* was obtained as a colourless oil, b. p. 152—154° at 0·05 mm., from the reaction of *N*-hydroxyurethane (5·2 g.) with benzyl chloroformate (8·5 g.) in water (150 ml.) containing sodium carbonate (5·0 g.) (Found: C, 55·6; H, 5·6; N, 5·7. $C_{11}H_{13}NO_5$ requires C, 55·2; H, 5·5; N, 5·9%).

N-*Hydroxy*-NN′-*diphenylurea*.—Phenyl isocyanate (5·0 g.) was added dropwise to a stirred solution of phenylhydroxylamine (5·0 g.) in benzene (60 ml.) at 10°, and the precipitated solid recrystallised from benzene, to give the title compound (9·5 g.) as colourless needles, m. p. 135° (decomp.) (lit.,[13] 126°) (Found: C, 68·3; H, 5·2; N, 12·3. Calc. for $C_{13}H_{12}N_2O_2$: C, 68·4; H, 5·3; N, 12·3%). The compound gave a blue colour with reagent (ii).

N-*Hydroxy*-N-*phenylcarbamoylurea*.—Phenyl isocyanate (1·2 g.) was added to a solution of hydroxyurea (0·76 g.) in dimethylformamide (5 ml.) at 0°. After 30 min., the mixture was diluted with ice–water (50 ml.) and the precipitated solid recrystallised from ethanol–water (1 : 10), to yield the *product* as colourless plates (0·56 g.), m. p. 156° (decomp.) (Found: C, 49·4; H, 4·7; N, 21·7. $C_8H_9N_3O_3$ requires C, 49·2; H, 4·65; N, 21·5%). It gave a wine-red colour with reagent (ii).

Preparation of NO-*Disubstituted Hydroxylamines by the Iodine Oxidation of the Corresponding Mono*-N-*substituted Analogues*.—A solution of *N*-hydroxyurethane (5·2 g.) in water (100 ml.) containing sodium hydrogen carbonate (8·0 g.) was treated with a solution of iodine (7·0 g.) in ethanol (100 ml.) at 0°. After 20 min., a 1% (w/v) aqueous solution (0·2 ml.) of sodium starch glycollate was added, the mixture titrated with 2M-sodium thiosulphate to a colourless endpoint, evaporated *in vacuo* to half bulk, extracted with ether (2 × 100 ml.), the combined extracts were washed with water (25 ml.), dried (Na_2SO_4), and distilled *in vacuo*, to give ethoxycarbonyloxyurethane (1·8 g.); its chromatographic properties, colour reactions, and infrared spectrum were identical with those of an authentic specimen, b. p. 96—98°/0·7 mm., n_D^{22} 1·4258, d_4^{22} 1·170. Benzyl *N*-hydroxycarbamate (1·0398 g., 6·01 mmole) similarly consumed 3·1 mmole of iodine and gave *benzyl benzyloxycarbonyloxycarbamate* (II; R = $PhCH_2$) (0·56 g.) as colourless plates (from benzene–light petroleum), m. p. 69° (Found: C, 63·7; H, 5·1; N, 4·2. $C_{16}H_{15}NO_5$ requires C, 63·8; H, 5·0; N, 4·65%).

Attempts to prepare this compound from the reaction of benzyl chloroformate and hydroxylamine hydrochloride in aqueous sodium hydroxide gave the compound as an oil contaminated with benzyl *N*-hydroxycarbamate, a component having R_F 0·82 and 0·80 in solvents (A) and (B), respectively, which probably was benzyl *NO*-benzyloxycarbonyl-*N*-hydroxycarbamate, and toluene (by odour); attempted purification of this oil by distillation at 0·05 mm. gave a mixture, boiling range 134—150°, with extensive decomposition.

Similar oxidation of benzhydroxamic acid (0·5 g.) with iodine (0·4 g.) gave *O*-benzoyl benzhydroxamate (0·23 g.) as colourless needles (from aq. ethanol), m. p. 168° (lit.,[14] m. p. 153, 156—158, 158—159, 161, and 165°) (Found: C, 69·6; H, 4·9; N, 5·9. Calc. for $C_{14}H_{11}NO_3$: C, 69·7; H, 4·6; N, 5·8%). A solution of *N*-hydroxyurea (1·9 g.) and sodium hydrogen carbonate (5·0 g.) in water (50 ml.) was treated with iodine (3·2 g.) in ethanol (20 ml.). The mixture was evaporated *in vacuo*, the residue extracted with ethanol (2 × 50 ml.), the combined ethanolic extracts were treated with ether until the precipitation of inorganic salts ceased, filtered, and the filtrate was evaporated *in vacuo*. The residue was recrystallised from ethanol, to yield colourless needles of hydroxyurea (0·24 g.), m. p. and mixed m. p. 140° (decomp.), and colourless prisms of *N*-carbamoyloxyurea (0·43 g.), m. p. and mixed m. p. 134° (decomp.) [lit.,[4] 134° (decomp.)] (Found: C, 20·2; H, 4·3; N, 35·6. Calc. for $C_2H_5N_3O_3$: C, 20·2; H, 4·2; N, 35·3%). *N*-Carbamoyloxyurea gave no colour with reagent (ii), and reduced (i) after 10—20 min. The solid (0·1 g.) was dissolved in 2N-hydrochloric acid (1 ml.) or 2M-sodium hydrogen carbonate (1 ml.), and the solutions were neutralised with 2M-sodium hydrogen carbonate or 2N-hydrochloric acid after 16 hr. at 23° and examined by chromatography. Both contained hydroxyurea, which had R_F 0·59 and 0·47 in solvents (D) and (E), respectively, reduced reagent (i) immediately, and gave bluish-purple and brick-red colours with reagents (ii) and (iii), respectively.

Oxidation of N-*Hydroxycarbamates and Hydroxyureas with Iodine in the Presence of Ammonium Carbonate*.—A stirred solution of benzyl *N*-hydroxycarbamate (1·7 g.) and ammonium carbonate (3·0 g.) in 50% aqueous ethanol (50 ml.) was treated dropwise with a solution of iodine (1·3 g.) in ethanol (20 ml.). The mixture was concentrated *in vacuo*, to yield colourless plates (from aqueous ethanol) of benzyl carbamate (0·35 g.), m. p. and mixed m. p. 87°. The filtrate was extracted with ether (2 × 20 ml.), the combined extracts were washed with water (10 ml.), dried (Na_2SO_4), evaporated, and the residue was recrystallised from benzene–light petroleum, to yield benzyl carbamate (0·12 g.), m. p. and mixed m. p. 87°, and colourless plates of benzyl *N*-benzyloxycarbonyloxycarbamate (0·21 g.), m. p. and mixed m. p. 69°. Ethyl (1·1 g.), n-propyl (1·2 g.), or n-butyl (1·3 g.) *N*-hydroxycarbamate was similarly oxidised, the resulting mixture extracted with ether (3 × 30 ml.), the combined extracts were dried (Na_2SO_4), evaporated *in vacuo*, and the residue was examined by chromatography in solvents (A) and (B), to reveal the presence of the corresponding carbamate and compounds of type (II). When the experiments were repeated in the absence of iodine, only the starting materials were detected by chromatography. Solutions of ethyl, n-propyl,

[13] J. F. Durand and R. Naves, *Compt. rend.*, 1925, **180**, 522.
[14] "Beilstein's Handbuch der Organischen Chemie," Springer, Berlin, 4th edn., 1926, vol. IX, p. 303.

or n-butyl *N*-hydroxycarbamate (0·5 g.) in ether (5 ml.), at 0°, were treated with dry ammonia to yield the corresponding ammonium salts, m. p. 48, 52, and 54°, respectively, as colourless plates. On standing in air or in an evacuated desiccator over phosphorus pentoxide, the ammonium salts were converted into ammonia and the parent *N*-hydroxycarbamates within 5—10 min.

Hydroxyurea (0·76 g.) and ammonium carbonate (2·0 g.) in water (25 ml.) were treated with 10% (w/v) iodine in ethanol until the iodine colour just persisted. The mixture was filtered, the filtrate evaporated, and the residue examined by chromatography, to reveal urea as the major product (R_F 0·56 and 0·42 in solvents D and E, respectively). The residue was extracted with ethanol (20 ml.), the extract treated with ether until the precipitation of inorganic salts ceased, filtered, evaporated *in vacuo*, and the residue recrystallised from ethanol, to yield colourless prisms of urea (0·18 g.), m. p. and mixed m. p. 132°. *N*-Hydroxy-*N'*-phenylurea (1·5 g.) similarly gave colourless needles of N-hydroxy-*N'*-phenyl-*N*-phenylcarbamoylurea (0·23 g.), m. p. and mixed m. p. 180°, and phenylurea (0·16 g.) as colourless plates, m. p. and mixed p. 147°.

Oxidations with Silver Oxide in Ether.—A solution of *N*-hydroxyurethane (20 g.) in dry, peroxide-free ether (250 ml.) was stirred at 0° in the dark with silver oxide (50 g.) and anhydrous sodium sulphate (5 g.) for 2·5 hr. The mixture was filtered, the silver residues were washed with benzene (100 ml.), and the combined filtrate and washings evaporated *in vacuo*. The residual solid was dissolved in the minimum volume of benzene, treated with light petroleum until milky and stored at −10° in the dark. This gave *N-silver N-ethoxycarbonyloxyurethane* (22 g., 81%) as buff needles, m. p. 140° with decomposition to a black residue (Found: C, 25·6; H, 3·5; Ag, 36·9; N, 4·7. $C_6H_{10}AgNO_5$ requires C, 25·4; H, 3·6; Ag, 38·0; N, 4·9%). n-Propyl *N*-hydroxycarbamate (12 g.) similarly gave *n-propyl N-silver-propoxycarbonyloxycarbamate* (13 g., 83%) as colourless needles (from benzene–light petroleum), m. p. 131° (decomp.) (Found: C, 30·5; H, 4·4; N, 4·4. $C_8H_{14}AgNO_5$ requires C, 30·8; H, 4·5; N, 5·5). n-Butyl *N*-hydroxycarbamate (6 g.) similarly gave *n-butyl N-silver-n-butoxycarbonyloxycarbamate* (6·6 g., 85%) as fine colourless needles (from light petroleum, b. p. 40—60°), m. p. 92° (decomp.) (Found: C, 35·4; H, 5·2; N, 4·5. $C_{10}H_{18}AgNO_5$ requires C, 35·3; H, 5·3; N, 4·1%). The analogous silver derivatives obtained from methyl *N*-hydroxycarbamate and benzhydroxamic acid decomposed in benzene solution and were not obtained as pure specimens. Chromatography examination (see Table) showed that the decomposition products were mainly methyl *N*-methoxycarbonyloxycarbamate (II; R = Me) and *O*-benzoyl benzhydroxamate, respectively.

R_F Values of alkyl *N*-hydroxycarbamates and some of their derivatives

Formula	R_F Values with solvent (A)	(B)	(C)
MeO·CO·NH·OH	0·18	0·08	—
MeO·CO·NH·O·CO_2Me	0·46	0·45	—
MeO·CO·NMe·O·CO_2Me	0·50	0·52	—
EtO·CO·NH·OH	0·23	0·15	0·74
EtO·CO·NH·O·CO_2Et	0·50	0·50	0·79
EtO·CO·N(CO_2Et)·O·CO_2Et	0·61	0·69	—
EtO·CO·NH·O·CO_2·CH_2Ph	0·59	0·58	0·88
PhCH_2·O·CO·NH·OH	0·27	0·20	0·84
PhCH_2·O·CO·NH·O·CO_2Et	0·59	0·60	0·88
PhCH_2·O·CO·NH·O·CO_2·CH_2Ph	0·65	0·65	0·92

The silver derivatives were heat- and light-sensitive. They were soluble in benzene, chloroform, or ether, and insoluble in water or light petroleum. When their aqueous suspensions were shaken in daylight or warmed in the dark, a silver mirror was deposited. Their methanolic or ethanolic solutions quickly became coloured (red to brown). In aqueous N-potassium hydroxide they gave mainly the corresponding *N*-hydroxycarbamates (I) and the *O*-alkoxycarbonyl derivatives (II); in N-hydrochloric acid, they gave mainly (II); in both, other unidentified decomposition products were formed on prolonged standing.

Production of Carbon Dioxide during the Oxidation of N-Hydroxycarbamates with Silver Oxide.—*N*-Hydroxyurethane (10 g.) was dissolved in benzene (100 ml.) and stirred with silver oxide (15 g.) at 5—10° while the evolved gases were passed through two solutions of 5% (w/v) aqueous barium hydroxide in a stream of carbon dioxide-free nitrogen. After 2·5 hr. the amount of carbon dioxide evolved was determined gravimetrically as barium carbonate. Methyl, ethyl, n-propyl, and n-butyl *N*-hydroxycarbamates gave 0·04, 0·03, 0·04, and 0·05 mole of carbon dioxide per mole of *N*-hydroxycarbamate.

Reactions of the Silver Derivative (V; R = Et).—(a) *With bromine.* The silver derivative (8·0 g.) was dissolved in methylene chloride (30 ml.) at 0° and treated with 4% (v/v) bromine in the same solvent until the bromine colour persisted (bromine consumed, 4·8 g.; 107% of theory). The precipitated silver bromide (5·1 g., 98%) was filtered off, washed with methylene chloride (30 ml.), and the combined filtrate and washings were washed with water (10 ml.), dried (Na_2SO_4), and distilled, to give *ethyl N-bromo-N-ethoxycarbonyloxycarbamate* (4·5 g.) as an orange oil, b. p. 93—95°/0·8 mm. (Found: C, 28·5; H, 4·2; Br, 30·4; N, 5·5. $C_6H_{10}BrNO_5$ requires C, 28·1; H, 3·9; Br, 31·2; N, 5·5%). This compound (0·5 g.) was dissolved in ethanol (5 ml.) and treated with aniline (0·2 g.) in ethanol (5 ml.). After 10 min., the mixture was concentrated *in vacuo* to about 2 ml., to give 2,4,6-tribromoaniline (0·32 g.) as colourless needles, m. p. and mixed m. p. 122°. The filtrate contained mainly *N*-ethoxycarbonyloxyurethane (by chromatography, see Table). When a solution of the *N*-bromo-derivative (0·256 g.) in ethanol (10 ml.) was treated with potassium iodide (1·0 g.) in water (10 ml.), iodine (0·124 g., 98% of theory, by thiosulphate titration) was liberated.

(b) *With methyl iodide.* A solution of the silver derivative (5·0 g.) in benzene (30 ml.) was treated with methyl iodide (3·0 g.) in benzene (20 ml.). After 30 min., the precipitated silver iodide was filtered off, washed with benzene (10 ml.), and the combined benzene solutions were distilled, to give *N-methyl-N-ethoxycarbonyloxyurethane* (1·2 g.) as a colourless oil, b. p. 60—61°/0·5 mm. (Found: C, 43·6; H, 7·0; N, 7·2. $C_7H_{13}NO_5$ requires C, 44·0; H, 6·8; N, 7·3%).

Simultaneous Oxidation of Ethyl and Benzyl N-hydroxycarbamates.—A solution of ethyl (0·42 g.) and benzyl (0·69 g.) *N*-hydroxycarbamates in ether (100 ml.) was shaken with silver oxide (1 g.) in the dark at 0° for 4 hr. The mixture was filtered, the residue washed with benzene (50 ml.), the combined filtrate and washings were treated with dry hydrogen chloride at 0°, the precipitated silver chloride was filtered off and washed with ether (20 ml.), the filtrate and washings were combined, and the solvent was removed *in vacuo*. Examination of the residual oil

by chromatography in solvents (A), (B), and (C) (see Table) revealed the presence of (i) ethyl ethoxycarbonyloxy-, (ii) ethyl benzyloxycarbonyloxy-, (iii) benzyl ethoxycarbonyloxy-, and (iv) benzyl benzyloxycarbonyloxycarbamates together with six other products which reduced ammoniacal silver nitrate after several hours and showed the following R_F values in solvent (B): 0·70, 0·78, 0·84, 0·89, 0·95, and 0·98. Compounds (ii) and (iii) could not be separated on chromatograms since they appeared as one spot in several solvent systems including (A), (B), and (C); their presence was shown as follows: the spot was scraped off the plate, eluted with benzene, the benzene evaporated *in vacuo*, the residue heated to 70° for 30 min. in 2N-hydrochloric acid–ethanol (1 : 1), the solvent evaporated *in vacuo*, and the residue chromatographed in solvents (A), (B), and (C), to reveal ethyl and benzyl *N*-hydroxycarbamates, which were also produced from the similar hydrolysis of authentic (ii) and (iii).

Oxidation of Methyl and Ethyl N-*Hydroxycarbamates by Various Agents.*—1% (w/v) Aqueous solutions (1 ml.) of ethyl *N*-hydroxycarbamate were treated at 20° with 5% (w/v) aqueous solutions or suspensions (1 ml.) of (*a*) iodine, (*b*) silver oxide, (*c*) red mercuric oxide, (*d*) manganese dioxide, (*e*) lead tetra-acetate, (*f*) silver nitrate, (*g*) cupric sulphate, (*h*) hydrogen peroxide, and (*i*) potassium dichromate. Mixture (*a*)—(*d*) were shaken. The solutions were examined by chromatography after 1 and 16 hr. in solvents (A)—(C). Solutions (*h*) and (*i*) showed complete disappearance of *N*-hydroxyurethane after 1 hr.; all the others contained ethoxycarbonyloxyurethane as the main product, a compound with R_F 0·76 in solvent (A) which reduced reagent (i) after 2—3 hr. and appeared identical with the product obtained from the reaction of compounds (II) or (V) (R = Et) with ethyl iodide, and *NO*-diethoxycarbonyl-*N*-hydroxyurethane. The amounts of oxidation products formed were not determined; qualitatively, the relative amounts of ethoxycarbonyloxyurethane produced are listed in descending order in the series (*a*)—(*g*). Oxidations of methyl *N*-hydroxycarbamate gave analogous results.

The Production of Nitrite by the Oxidation of N-*Hydroxycarbamates and Related Compounds with Iodine.*—Aqueous solutions (0·2M; 10 ml.) of the following compounds in 10% (w/v) aqueous sodium carbonate (20 ml.) were treated with 2N-iodine in ethanol (4 ml.) while the evolved gases were carried in a stream of nitrogen into a solution of sulphanilamide (0·1 g.) and *N*-(1-naphthyl)ethylenediamine hydrochloride (5 mg.) in 2N-hydrochloric acid (10 ml.): (*a*) *N*-hydroxyurethane, (*b*) benzyl *N*-hydroxycarbamate, (*c*) benzhydroxamic acid, (*d*) hydroxyurea, (*e*) sodium nitrite, (*f*) *N*-methylhydroxylamine, and (*g*) *N*-phenylhydroxylamine. Faint or no colours were produced in the sulphanilamide reagent, indicating that no nitric oxide was formed. Upon acidification with 2N-hydrochloric acid, the mixtures containing (*a*)—(*e*) liberated nitric oxide which produced an intense colour in the sulphanilamide reagent; (*f*) and (*g*) gave no colours. The nitrous acid produced on acidification of solutions (*a*), (*c*), and (*d*), determined by the Bratton and Marshall [1] procedure, was 0·72, 0·60, and 0·74 mole of nitrous acid per mole of compound oxidised.

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