The Synthesis and Some Reactions of *N*-Hydroxycarbamates

By E. Boyland and R. Nery

Hydroxylamine and alkyl chloroformates reacted in alkaline media to form *N*-, *NO*-di-, and *NNO*-tri-alkoxycarbonylhydroxylamines, successively. *N*-Methylhydroxylamine similarly gave *N*- and *NO*-di-alkoxycarbonyl-*N*-methylhydroxylamines, and *O*-methylhydroxylamine produced *N*- and *NN*-di-alkoxycarbonyl-*O*-methylhydroxylamines. *N*-Phenylhydroxylamine, with 1 equivalent of ethyl chloroformate, gave *N*-hydroxy-*N*-phenylurethane. Hydroxylamine hydrochloride and ethyl chloroformate yielded a product which changed into hydroxyurethane. Alkyl *N*-hydroxycarbamates and hydroxyurea gave *O*-xanthydryl derivatives. The *N*-hydroxycarbamates with aqueous dipotassium tetracyanonickelate(II) formed dipotassium tricyanonitrosylnickelate(II). No evidence of a Lossen-type rearrangement during the acid and alkaline hydrolysis of these hydroxylamino-derivatives was seen. The possible mechanisms of hydrolysis are discussed.

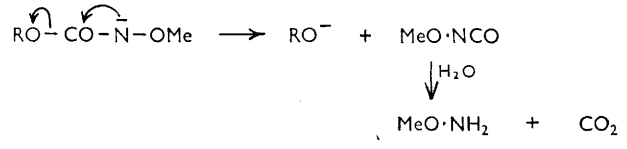
THE *N*-hydroxycarbamates show diverse biological activities including the induction of chromosomal aberrations in the root tips of *Vicia faba* [1] and in Chinese hamster cells,[2] and the inhibition of thymidine incorporation into DNA of HeLa monolayers [3] and of multiplication of the Shope fibroma virus.[4] The corresponding carbamates are inactive in these systems. The synthesis and some reactions of a number of *N*-hydroxycarbamates and their derivatives are now described.

Acylation and alkoxycarbonylation reactions involving nucleophilic reaction with hydroxylamine occurred on the nitrogen atom. Further reaction with the mono-*N*-substituted hydroxylamines occurred with the hydroxyl group if the *N*-substituent was electron-withdrawing and at nitrogen if it was electron-releasing. Thus, hydroxylamine reacted with 1, 2, or 3 equivalents of alkyl chloroformate in alkali to yield the corresponding *N*-mono-, *NO*-di-, or *NNO*-tri-alkoxycarbonylhydroxylamines, respectively. The alkyl group in the chloroformate could be varied or the alkyl chloroformate replaced by an acid chloride or anhydride at any stage in the sequence without affecting the order of substitution. Alkoxycarbonylation of mono-alkylhydroxylamines gave the *N*-alkoxycarbonyl derivatives. Apparently, unlike the hydroxamic acids (RCO·NH·OH), the tautomeric hydroximic acids [RO·C(OH)=N·OH] were not formed, since infrared spectra of the product did not show the characteristic ν(C=N) absorptions (R. Lumley Jones, personal communication).

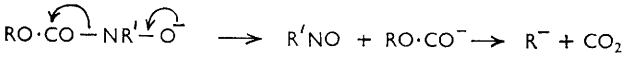
Further evidence that the alkyl *N*-hydroxycarbamates are nucleophilic reagents which undergo further substitution at the oxygen of the hydroxyamido-group was provided by the fact that they gave *O*-xanthydryl derivatives in media known [5] to contain xanthydryl carbonium ions. Alkyl halides react with *N*-hydroxyurethane in alkali to yield *O*-alkyl derivatives.[6]

Nucleophilic attack by hydroxylamine hydrochloride on ethyl chloroformate presumably gave the unstable *O*-ethoxycarbonylhydroxylamine hydrochloride, NH_2·O·CO_2Et,HCl. This compound or its free base readily rearranged in aqueous solution into its isomer, HO·NH·CO_2Et. A similar reaction between *N*-methylhydroxylamine hydrochloride and an *N*-carboxyanhydride has been reported.[7] *O*-Acylhydroxylamines also rearranged spontaneously,[8] but *N*-acetyl-*N*-hydroxyurethane gave the *O*-acetyl isomer.[9]

The alkaline or the acidic hydrolysis of the *N*-hydroxycarbamates and their *N*- or *O*-methyl derivatives gave hydroxylamine and *N*- or *O*-methylhydroxylamine, respectively. Presumably, the acidic hydrolysis was of the S_N2 type, involving nucleophilic attack by water on the carbonyl carbon of the *N*-protonated *N*-hydroxycarbamate. The alkaline hydrolysis of the *O*-methyl derivatives probably involved an unstable alkoxyl isocyanate.



Removal of hydrogen-ions from β-iodoalkylurethanes gave *N*-ethoxycarbonylaziridines.[10] The reaction of urethane with hydroxylamine in alkali to give *N*-hydroxyurea [11] may also involve prior cyanate formation. The *N*-alkyl-*N*-hydroxycarbamates cannot form isocyanates but may yield a nitroso-alkyl and a strongly reducing alkoxycarbonyl or alkyl anion.



Thus, benzyl *N*-phenyl- and the alkyl *N*-methyl-*N*-hydroxycarbamates reduced ammoniacal silver nitrate immediately, but the *O*-methyl analogues only did so after several hours. Benzyl *N*-hydroxy-*N*-phenylcarbamate and *N*-phenylacethydroxamic acid yielded nitrosobenzene in aqueous ethanolic potassium hydr-

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[2] A. Bendich, E. Borenfreund, G. C. Korngold, and M. Krim, *Fed. Proc.*, 1963, **22**, 582.
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[4] C. P. deSousa, E. Boyland, and R. Nery, *Nature*, 1965, **206**, 688.
[5] A. G. Davies, R. V. Foster, and R. Nery, *J. Chem. Soc.*, 1954, 2204.
[6] A. O. Ilvespaa and A. Marxer, *Chimia* (*Switz.*), 1964, **18**, 1.
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[8] W. P. Jencks, *J. Amer. Chem. Soc.*, 1958, **80**, 4581, 4585; L. A. Carpino, C. A. Giza, and B. A. Carpino, *ibid.*, 1959, **81**, 955.
[9] E. Boyland and R. Nery, *Biochem. J.*, 1965, **94**, 198.
[10] A. Hassner and C. Heathcock, *J. Org. Chem.*, 1964, **29**, 3640.
[11] R. Deghenghi, *Org. Synth.*, 1960, **40**, 60.

oxide. The fact that the *N*-phenyl- and *N*-alkyl-*N*-hydroxycarbamates also gave the corresponding *N*-phenyl- or *N*-alkyl-hydroxylamines in alkali indicated that the normal $B_{AC}2$ reaction also occurred.

The mechanism of the alkaline hydrolysis of the *N*-hydroxycarbamates (RO·CO·NH·OH) may be complex, involving proton abstraction from (a) nitrogen or (b) oxygen and subsequent reactions of the resulting anions formed, in addition to (c) nucleophilic attack by hydroxyl ion on the carbonyl carbon. Mechanisms (a) and (c) but not (b) would yield hydroxylamine. The liberated hydroxylamine, when heated with dipotassium tetracyanonickelate(II), formed the purple tricyanonitrosylnickelate(II) complex $[Ni(CN)_3NO]^{2-}$. The related hydroxamic acids (R·CO·NH·OH) and hydroxyurea also gave this reaction, but in no case was the stoicheiometric amount of hydroxylamine liberated.

If the Lossen-type rearrangement given by hydroxamic acids occurred, the *N*-hydroxycarbamates should yield alkoxyl isocyanates ($RO{\cdot}CO{\cdot}\bar{N}{\cdot}OH \longrightarrow RO{\cdot}NCO + OH^-$) which, on hydrolysis, would give the corresponding *O*-alkylhydroxylamines. Solutions of methyl, ethyl, or benzyl *N*-hydroxycarbamate in boiling aqueous ethanolic potassium hydroxide contained hydroxylamine, ammonia, potassium carbonate, and the corresponding alcohol (hydrolysis products), but no *O*-alkylhydroxylamines (the expected products if rearrangement had occurred). *N*-Hydroxyurea and its *N'*-phenyl derivative did not undergo this rearrangement;[12] the expected hydrazines were not formed, and both yielded the corresponding *O*-carbamoyl derivatives by bimolecular eliminations.

The order of hydrolysis by acid or alkali of the alkoxycarbonyl or acetyl groups in the trisubstituted hydroxylamines is the same as that observed for the replacement of the hydrogen atoms of hydroxylamine by these groups in alkaline media. Thus, the graded acid or alkaline hydrolysis of *NO*-diethoxycarbonyl-*N*-hydroxyurethane (compound **13**, Table 2) gave, successively, *O*-ethoxycarbonyl-*N*-hydroxyurethane (compound **12**, Table 2), *N*-hydroxyurethane, and hydroxylamine. Similar hydrolysis of n-butyl *NO*-diacetyl-*N*-hydroxycarbamate (compound **16**, Table 2) showed that the *N*-acetyl group was more acid- and alkali-labile than the *N*-n-butoxycarbonyl group, since the main products were n-butyl *O*-acetyl- (compound **15**, Table 2) and n-butyl *N*-hydroxy-carbamates; a small amount of acethydroxamic acid was formed during the alkaline hydrolysis, and none during the acid hydrolysis.

EXPERIMENTAL

Chromatography.—Glass plates were coated with films of silica gel G (Merck) of 0·25 mm. thickness, and the chromatograms were developed with (A) methanol–benzene (7 : 13), (B) acetone–light petroleum (b. p. 40—60°) (3 : 7), and (C) chloroform–acetic acid (99 : 1). Compounds on chromatograms were detected by (i) a solution of sodium pentacyanoammineferrate (II) monohydrate (0·5 g.), sodium hydrogen carbonate (1 g.), magnesium chloride hexahydrate (0·05 g.), and aniline (0·02 g.) in water (20 ml.), (ii) *p*-dimethylaminocinnamaldehyde (2 g. in 100 ml. of 6N-hydrochloric acid and 100 ml. of ethanol), (iii) 1% (w/v) ferric chloride in aqueous 50% ethanol, and (iv) ammoniacal aqueous 2% silver nitrate. Compounds **1**, **2**, **5**, **6**, **8**, **14**, **18**, and **19** (see Table 2) reduced reagent (iv) almost immediately; the others required from 20 min. to several hours.

Alkyl Chloroformates.—The appropriate alcohol was added dropwise to a gently agitated solution of phosgene (15% w/v) in benzene at 0°, so that the final solution contained a 50—100% excess of phosgene. After 16 hr. at 23°, the excess phosgene and hydrogen chloride were removed in a stream of dry nitrogen. The benzene solution was washed with cold N-sodium hydrogen carbonate, and with water, dried ($CaCl_2$), and distilled. Yields were 75—90%. The following were obtained as colourless, lachrymatory liquids: *n-pentyl chloroformate*, b. p. 48—50°/15 mm. (Found: C, 47·9; H, 7·8; Cl, 22·9. $C_6H_{11}ClO_2$ requires C, 47·9; H, 7·4; Cl, 23·5%); *n-hexyl chloroformate*, b. p. 68—69°/15 mm. (Found: C, 51·3; H, 8·3; Cl, 20·8. $C_7H_{13}ClO_2$ requires C, 51·1; H, 8·0; Cl, 21·5%); *tetramethylene 4-di(chloroformate)*, b. p. 128—130°/15 mm. (Found: C, 33·9, H, 3·9; Cl, 32·4. $C_6H_8Cl_2O_4$ requires C, 33·5; H, 3·8; Cl, 33·0%).

General Preparation of Alkyl N-Hydroxycarbamates and their Acyl, Alkoxycarbonyl, and N- and O-Methyl Derivatives (see Table 1).—These were prepared by the general methods described by Boyland and Nery.[13] Derivatives of *N*- and *O*-methylhydroxylamines were prepared by similar methods, except that the appropriate methylhydroxylamine replaced hydroxylamine. Methyl *N*-hydroxycarbamates were also prepared as follows. A 2% (w/v) ethanolic solution of the alkyl *N*-hydroxycarbamate containing 1·2 equiv. of dissolved potassium hydroxide and 1·5 equiv. of methyl iodide was heated under reflux for 2—4 hr., cooled to 0°, filtered, the solvent evaporated, and the residue extracted with ether (3 × 100 ml.). The combined ethereal extracts were washed with water (2 × 20 ml.), and dried (Na_2SO_4), the solvent was evaporated and the residual oil distilled *in vacuo*. The *O*-alkoxycarbonyl- and *NO*-di(alkoxycarbonyl)-*N*-hydroxycarbamates were prepared from hydroxylamine and 2·2 or 3·3 molar equiv., respectively, of the appropriate alkyl chloroformate, or from 1·1 molar equiv. of the appropriate alkyl chloroformate and 1 molar equiv. of the alkyl *N*-hydroxy- or the alkyl *O*-alkoxycarbonyl-*N*-hydroxycarbamate, respectively. Reaction mixtures containing derivatives of methyl and ethyl *N*-hydroxycarbamates were extracted continuously with ether for 16 hr. where necessary; others were extracted with 2—4 volumes of ether, depending upon the partition coefficients of the required product. The ethereal extracts were washed with cold water, dried (Na_2SO_4), and distilled. The products were colourless oils, some of which crystallised on keeping at 4° (see Table 1). Yields were 80—100%.

Xanthydryl Derivatives.—Xanthydrol (0·4 g., 0·002 mole) and the appropriate alkyl *N*-hydroxycarbamate (0·002 mole) were dissolved in the minimum volume of acetic acid, and the solution was cooled to 0° and treated with concentrated sulphuric acid (0·1 ml.). After 1 hr. the

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[13] E. Boyland and R. Nery, *Analyst*, 1964, **89**, 520.

TABLE 1

Hydroxycarbamates and some of their derivatives ($RO{\cdot}CO{\cdot}NR'{\cdot}OR''$)

R	R′	R″	M. p. or b. p./mm.	n_D^{20}	d_4^{20}	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Me	H	CO_2Me	86—88°/0·6	1·4310	1·661	32·6	5·0	9·5	32·2	4·7	9·4
Me	Me	H	45—46/0·6	1·4296	1·179	34·3	7·0	13·3	34·3	6·7	13·3
Et	COMe	CO_2Et	85—86/0·6	1·4300	1·184	44·1	6·3	6·6	43·8	6·0	6·4
,,	,,	COMe	72—74/0·6	1·4334	1·155	44·7	5·8	7·3	44·4	5·9	7·4
,,	Me	H	42/0·6	1·4200	1·092	40·7	7·7	11·7	40·3	7·6	11·8
,,	H	Me	46—48/0·6	1·4209	1·089	40·5	7·5	11·8	,,	,,	,,
,,	Me	COMe	50—52/0·6	1·4196	1·100	45·0	7·0	8·3	44·7	6·9	8·7
,,	,,	CO_2Et	60—61/0·5	1·4230	1·121	43·8	7·0	7·4	44·0	6·9	7·3
Pr^n	COMe	CO_2Pr^n	98—100/0·6	1·4339	1·105	48·7	6·6	5·8	48·6	6·9	5·7
,,	CO_2Pr^n	,,	126—130/0·6	1·4325	1·113	49·7	7·4	5·0	49·5	7·3	4·8
,,	H	Me	48—49/0·6	1·4282	1·059	45·3	8·4	10·5	45·1	8·3	10·5
,,	Me	H	46—47/0·6	1·4330	1·079	44·8	8·3	10·7	,,	,,	,,
Bu^n	H	COMe	94—96/0·5	1·4439	1·093	48·1	7·5	8·4	48·0	7·5	8·0
,,	COMe	,,	92—94/0·5	1·4382	1·100	49·8	7·0	6·9	49·8	7·3	7·4
,,	CO_2Bu^n	CO_2Bu^n	136—139/0·5	1·4372	1·070	53·9	8·4	4·7	54·0	8·2	4·2
,,	H	Me	59—60/0·6	1·4310	1·030	49·2	8·9	9·7	49·0	8·9	9·5
,,	Me	H	64—66/0·5	1·4395	1·008	49·2	9·2	9·4	,,	,,	,,
,,	CO_2Bu^n	Me	97—99/0·5	1·4370	1·087	53·2	8·7	6·2	53·4	8·6	5·7
,,	Me	CO_2Bu^n	98—99/0·5	1·4315	1·037	53·4	8·5	5·6	,,	,,	,,
,,	Me	COMe	62—64/0·5	1·4280	1·033	51·0	8·1	7·2	50·8	8·0	7·4
iso-C_4H_9	H	H	41 (*a*)	—	—	45·0	8·6	10·2	45·1	8·3	10·5
n-C_5H_{11}	H	H	115—118/0·04 (*b*)	—	—	49·3	9·1	9·6	49·0	8·9	9·5
n-C_6H_{13}	H	H	42 (*a*)	—	—	51·9	9·3	8·6	52·1	9·4	8·7
$PhCH_2$	Ph	H	84 (*c*)	—	—	69·1	5·4	5·7	69·1	5·4	5·8
$HO{\cdot}NH{\cdot}CO{\cdot}O{\cdot}[CH_2]_4$	H	H	151 (*e*)	—	—	34·9	5·7	13·2	34·6	5·8	13·5
			Xanthydryl derivatives								
Me	H	$C_{13}H_9O$ (*f*)	184 (*d*)	—	—	66·8	4·8	5·0	66·4	4·8	5·2
Et	H	,,	183 (*d*)	—	—	67·1	5·3	5·4	67·4	5·3	4·9
Pr^n	H	,,	136 (*d*)	—	—	67·9	6·1	4·6	68·2	5·7	4·7
Bu^n	H	,,	102 (*d*)	—	—	70·4	6·1	4·4	70·0	6·1	4·5
Compound											
$NH_2{\cdot}CO{\cdot}NH{\cdot}O{\cdot}C_{13}H_9O$ (*f*)			142 (*d*)	—	—	66·1	4·8	10·4	65·6	4·7	10·9

(*a*) Colourless plates from light petroleum. (*b*) Low-melting solid. (*c*) Buff needles from benzene–light petroleum. (*d*) Colourless needles melting with decomposition. (*e*) Colourless prisms from water, melting with decomposition (Found: *M*, 212. Reqd., *M*, 208). (*f*) $C_{13}H_9O$ = xanthydryl.

TABLE 2

R_F Values and colour reactions of hydroxylamine and some of its derivatives

Formula	R_F in solvent (A)	(B)	(C)	Colour * with reagent (i)	(ii)	(iii)
1. $NH_2{\cdot}OH,HCl$	0·30	0	0	Purple	Red (faint)	None
2. $MeNH{\cdot}OH,HCl$	0·37	0	0	Pink	,,	,,
3. $MeO{\cdot}NH_2,HCl$	0·42	0	0	Grey	,,	,,
4. $Ph_2O{\cdot}NH_2,HCl$	0·49	0	0	Mauve	,,	,,
5. $EtO{\cdot}CO{\cdot}O{\cdot}NH_2,HCl$ (?)	0·45	0·13	0	Red (slow)	Red	,,
6. $EtO{\cdot}CO{\cdot}NH{\cdot}OH$	0·56	0·23	0·14	Red	Red	Blue-purple
7. $EtO{\cdot}CO{\cdot}O{\cdot}NH{\cdot}CO_2{\cdot}CH_2Ph$	0·72	0·59	0·45	Red-brown	Red (slow)	None
8. $MeCO{\cdot}NH{\cdot}OH$	0·35	0·05	0·02	Red (faint)	Red	Purple
9. $EtO{\cdot}CO{\cdot}NH{\cdot}OAc$	0·83	0·65	0·62	Purple	Red (slow)	None
10. $EtO{\cdot}CO{\cdot}N(Ac){\cdot}OAc$	0·98	0·84	0·81	Purple (slow)	,,	,,
11. $EtO{\cdot}CO{\cdot}N(Ac){\cdot}O{\cdot}CO_2Et$	0·94	0·75	0·80	Purple (slow)	,,	,,
12. $EtO{\cdot}CO{\cdot}NH{\cdot}O{\cdot}CO_2Et$	0·80	0·50	0·30	Purple	,,	,,
13. $EtO{\cdot}CO{\cdot}N(CO_2Et){\cdot}O{\cdot}CO_2Et$	0·96	0·61	0·56	Purple (slow)	,,	,,
14. $Bu^nO{\cdot}CO{\cdot}NH{\cdot}OH$	0·50	0·41	0·17	Red	Red	Purple
15. $Bu^nO{\cdot}CO{\cdot}NH{\cdot}OAc$	0·67	0·59	0·56	Purple	Red (slow)	None
16. $Bu^nO{\cdot}CO{\cdot}N(Ac){\cdot}OAc$	0·80	0·73	0·84	Purple (slow)	,,	,,
17. PhNO	0·89	0·90	0·87	Mauve	,,	,,
18. $PhN(OH)Ac$	0·60	0·40	0·28	Mauve (slow)	,,	Purple
19. $PhN(OH){\cdot}CO_2{\cdot}CH_2Ph$	0·75	0·63	0·34	,,	,,	,,

* On a green background.

solutions were diluted with ice–water (30 ml.) and the precipitated solids were recrystallised from ethanol or aqueous ethanol to constant melting points. All gave colourless needles which melted with decomposition. Yields were 70—80%. Like the *O*-methyl derivatives of the *N*-hydroxycarbamates, they failed to give colours with reagent (iii), and reduced (iv) slowly.

Benzyl N-Hydroxy-N-phenylcarbamate.—Benzyl chloroformate (10 g.) was added dropwise during 30 min. to a stirred solution of phenylhydroxylamine (15·3 g.) in ether (150 ml.) at 0°. After 16 hr., the precipitated phenylhydroxylamine hydrochloride was filtered off and washed with ether (50 ml.), the filtrate and washings were combined and washed with water (3 × 25 ml.), and dried (Na_2SO_4), and the solvent was evaporated *in vacuo*, and the residue recrystallised from benzene–light petroleum, to give colourless needles of phenylhydroxylamine (3·6 g.), m. p. and mixed m. p. 82°, and the required *carbamate* as clusters of buff needles (6·8 g.).

O-Ethoxycarbonylhydroxylamine.—Ethyl chloroformate (6·2 g.) was added dropwise to a stirred solution of hydroxylamine hydrochloride (3·5 g.) in water (50 ml.) at 23°. After 20 hr. the mixture was evaporated *in vacuo* and the residual solid recrystallised from ethanol–benzene, to yield hydroxylamine hydrochloride (1·2 g.), m. p. and mixed m. p. 165°. Evaporation of the mother-liquors *in vacuo* gave a solid (1·52 g.) which, on chromatographic examination (see Table 2), appeared to be *O*-ethoxycarbonylhydroxylamine hydrochloride, which reduced reagent (iv), gave a red colour with (ii), and faint initial colours, which intensified on standing, with (i) and (iii). Attempts at recrystallisation from ethanol, aqueous ethanol, or ethanol–benzene gave precipitates contaminated with increasing amounts (on repeated crystallisations) of hydroxylamine hydrochloride, ammonium chloride, and *N*-hydroxyurethane. A similar product (1·1 g.) was obtained from the reaction of *O*-ethoxycarbonylacetoxime (8 g.) in ethanol (20 ml.) with dry hydrogen chloride. The solid hydrochloride (0·1 g.) in pyridine (0·2 ml.) or N-sodium hydrogen carbonate (1 ml.) gave *N*-hydroxyurethane; with benzyl chloroformate (0·1 ml.) both solutions gave benzyl *O*-ethoxycarbonyl-*N*-hydroxycarbamate (compound 7, Table 2). A solution of the solid hydrochloride (0·2 g.) and *p*-nitrobenzaldehyde (0·12 g.) in 80% aqueous acetic acid (4·5 ml.) was heated at 60° for 2 min. and evaporated *in vacuo* after 2 hr., to yield pale yellow needles (from aqueous ethanol) of *p*-nitrobenzaldehyde *anti*-oxime (0·15 g.), m. p. and mixed m. p. 128° (Found: C, 50·5; H, 4·0; N, 16·7. Calc. for $C_7H_6N_2O_3$: C, 50·5; H, 3·6; N, 16·8%). Attempts to prepare the title compound by the catalytic hydrogenation of *N*-benzyloxycarbonyl-*O*-ethoxycarbonylhydroxylamine (6 g.) in methanol (80 ml.) containing acetic acid (0·5 ml.) and 5% palladised charcoal (1 g.) gave mainly benzyl carbamate (1·6 g.) as plates (from aqueous ethanol), m. p. and mixed m. p. 87°.

Hydrolysis of N-Hydroxycarbamates.—(a) *In hot alkali.* A solution of *N*-hydroxyurethane (8·2 g.) in 80% aqueous ethanol (150 ml.) containing dissolved potassium hydroxide (5·6 g.) was heated under reflux for 4 hr. and distilled into 10N-hydrochloric acid (5 ml.). The distillate was evaporated *in vacuo* and the residue recrystallised from aqueous ethanol, to yield colourless needles of ammonium chloride (0·42 g.), no m. p. below 350°, and hydroxylamine hydrochloride (0·84 g.), m. p. and mixed m. p. 165°. The residue from the distillation was dissolved in water (20 ml.) and treated with saturated aqueous barium hydroxide, to give barium carbonate (14·2 g.). Methyl *N*-hydroxycarbamate (4·5 g.) similarly gave ammonium chloride (0·24 g.), hydroxylamine hydrochloride (0·36 g.), and barium carbonate (9·5 g.); benzyl *N*-hydroxycarbamate (5 g.) gave benzyl alcohol (2·8 g.), b. p. 98°/12 mm., as a colourless oil which was identified as its phenylurethane, m. p. and mixed m. p. 75°. Ethyl *N*- or *O*-methyl-*N*-hydroxycarbamate (6 g.) similarly gave *N*- (0·4 g., m. p. and mixed m. p. 89°) or *O*-methylhydroxylamine hydrochloride (0·51 g., m. p. and mixed m. p. 149°), respectively. Benzyl *N*-hydroxy-*N*-phenylcarbamate (0·6 g.) or *N*-phenylacethydroxamic acid (0·4 g.) in 80% aqueous ethanol (10 ml.) containing dissolved potassium hydroxide (0·2 g.), after 30 min. at 60° or 16 hr. at 0°, gave nitrosobenzene and phenylhydroxylamine, which were detected by chromatography.

(b) *In hot acid.* A solution of *N*-hydroxyurethane (5 g.) in 4N-hydrochloric acid (50 ml.) was heated at 75° for 5 hr. while the evolved gases were led into a saturated aqueous solution (50 ml.) of barium hydroxide. The mixture was evaporated *in vacuo*, to yield colourless needles of hydroxylamine hydrochloride (from ethanol) (2·5 g.), m. p. and mixed m. p. 165°. Barium carbonate (8·6 g.) was obtained from the barium hydroxide solution. *N*- or *O*-Methyl-*N*-hydroxyurethane (0·2 g.) similarly gave *N*- (0·41 g., m. p. and mixed m. p. 89°) or *O*-methylhydroxylamine hydrochloride (0·49 g., m. p. and mixed m. p. 149°), respectively. Chromatography of the acidic or alkaline hydrolysates of the *N*-hydroxycarbamates failed to reveal the presence of the corresponding *O*-alkylhydroxylamines which would have arisen if rearrangement of the Lossen type had occurred (see Table 2).

(c) *In cold acid or alkali; order of hydrolysis of substituents.* Molar solutions of (i) *NO*-diethoxycarbonyl- (compound 13, Table 2), (ii) *NO*-diacetyl- (compound 10, Table 2), and (iii) *N*-acetyl-*O*-ethoxycarbonyl-*N*-hydroxyurethanes (compound 11, Table 2), and (iv) n-butyl *NO*-diacetyl-*N*-hydroxycarbamate (compound 16, Table 2) in 80% aqueous ethanolic 2N-potassium hydroxide or 2N-hydrochloric acid were kept at 25°. Samples were removed after 1, 2, 3, and 16 hr., neutralised with 2N-hydrochloric acid or 2N-potassium hydroxide, and examined by chromatography in solvents (A), (B), and (C). Solutions (i) and (iii) slowly formed *O*-ethoxycarbonyl-*N*-hydroxyurethane (compound 12, Table 2), solution (ii) formed *O*-acetyl-N-hydroxyurethane (compound 9), and solution (iv) n-butyl *O*-acetyl-*N*-hydroxycarbamate (compound 15) after 1 hr. Solutions (i), (ii), and (iii) also contained *N*-hydroxyurethane, and solution (iv) n-butyl *N*-hydroxycarbamate in increasing amounts after 2 and 3 hr. After 16 hr., the main products were the corresponding *N*-hydroxycarbamates and hydroxylamine. Acethydroxamic acid was found in small amounts in the alkaline hydrolysates of solutions (ii), (iii), and (iv), but not in the acid hydrolysates.

The Production of Nitroxyl during the Alkaline Hydrolysis of Alkyl N-Hydroxycarbamates and Related Compounds.—0·1M-Aqueous solutions (0·5 ml.) of the following compounds (in duplicate) were treated with aqueous solutions of potassium tetracyanonickelate(II) (0·25M; 2 ml.), potassium hydroxide (20N; 1 ml.), and water (2 ml.): (a) methyl, (b) ethyl, and (c) benzyl *N*-hydroxycarbamate, (d) *O*-ethoxycarbonyl-*N*-hydroxyurethane, (e) benzhydroxamic acid, and (f) hydroxyurea. The reagent blank contained 0·5 ml. of water in place of the test solution. The solutions were

heated in stoppered tubes at 100° for 3 hr., cooled to room temperature, and the absorption at 510 mμ in a 1-cm. cell was measured against the reagent blank. The values obtained were compared with those on a standard extinction–concentration curve similarly obtained from hydroxylamine hydrochloride which was given the arbitrary value of 50% conversion into nitroxyl as reported by Nast and Foppl [14] according to the reaction: $2NH_2{\cdot}OH \longrightarrow NOH + NH_3 + H_2O$. The values obtained were: (a) 28, 30; (b) 42, 45; (c) 38, 40; (d) 27, 29; (e) 16, 20; and (f) 34, 38%.

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