N-Acyl-*O*-alkylhydroxylamines VI.* Preparation of some *N*-acyl-*O*-alkylhydroxylamines and their reactions with isocyanates**

R. P SHARMA, A. SOOD, D. TANDON, and B. N. MISRA

Department of Chemistry, Himachal Pradesh University, Summer Hill, Shimla - 171005, India

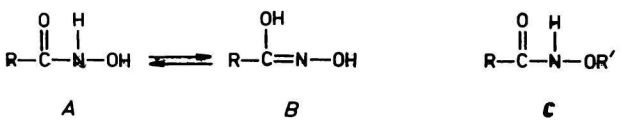
Received 26 october 1984

Accepted for publication 19 July 1985

Reactions of a wide variety of *N*-acyl-*O*-alkylhydroxylamines with phenyl and α-naphthyl isocyanates, respectively, have been investigated with a view to synthesizing compounds expected to show biological activities. *N*-Acyl-*O*-alkylhydroxylamines were prepared by the alkylation of potassium and barium salt of hydroxamic acids under weakly basic conditions. The structure elucidation of compounds arising from the reaction of *N*-acyl-*O*-alkylhydroxylamine and isocyanates is performed by chemical and spectroscopic method.

Изучена широкая шкала реакций *N*-ацил-*O*-алкилгидроксиламинов с фенил- и α-нафтилизоцианатами. Внимание было уделено возможности приготовления соединений с ожидаемой биологической активностью. *N*-Ацил-*O*-алкилгидроксиламины были получены посредством алкилирования калиевых и бариевых солей гидроксамовых кислот в слабо щелочной среде. Установление строения соединений, возникающих при взаимодействии *N*-ацил-*O*-алкилгидроксиламина с изоцианатами проведено с использованием химического и спектроскопического методов.

Hydroxamic acids and their esters have attracted attention of chemists because of their expected biological activity. Alkylation of hydroxamic acids has been extensively investigated [1], and depending upon the reaction conditions various mono- and dialkylated products have been prepared. *Exner* and *Bauer* [2] in a recent review have summarized their findings on alkylation reaction of hydroxamic acid (Scheme 1).



A *B* *C*

Scheme 1

* For Part *V* see *Indian J. Chem. 23B*, 728 (1984).

** Part of the work was carried out at the Slovak Technical University, Bratislava, under the Indo-Czechoslovak Cultural Exchange Programme, 1983.

It has been reported by a number of workers [3, 4] that use of molar equivalent of alkyl halide and hydroxamic acid in the presence of base affords monoalkylated products in major amount. In [5] we have observed that alkylation of a number of potassium salts of hydroxamic acids under basic conditions affords monoalkylated products in a yield of 60—65 % and in every case a small amount of dialkylated product (often as a semi-solid mass) was isolated. Hydroxamic acid (Scheme 1) can exist in two tautomeric forms (*A* and *B*) and possesses three potential sites such as hydroxylamine oxygen, carbonyl oxygen, and nitrogen where alkylation can occur. Dialkylation of potassium benzohydroxamate has been reported to give products arising from alkylation on hydroxylamine oxygen and carbonyl oxygen [6, 7]. Only during alkylation of potassium salt of benzohydroxamic acids with butyl bromide dialkylation was reported to occur on hydroxylamine oxygen and nitrogen [8]. In all our studies, dialkylation in basic medium occurred on hydroxylamine oxygen and carbonyl oxygen [5].

The present study is concerned with the reaction of monoalkylated hydroxamates with isocyanates and therefore alkylation conditions have been so chosen as to give monoalkylated products in major amount. While a large number of monoalkylated products have been synthesized [1] by alkylation of potassium salt of hydroxamic acid in basic medium, some monoalkylated products were not amenable by this method and an alternative method involving alkylation of barium salt of hydroxamic acid was found suitable.

^{1}H NMR data and mass spectroscopic data on monoalkylated products (*C*) have not been reported in literature. In the present communication we report on synthesis of known and some new *N*-acyl-*O*-alkylhydroxylamines (*C*) which have been characterized by ^{1}H NMR, IR, and mass spectroscopic methods. The structures of the products resulting from the reaction of *N*-acyl-*O*--alkylhydroxylamines and isocyanates have been elucidated by IR and ^{1}H NMR spectroscopy. Reactions of isocyanates with alcohols and amines have been extensively investigated [9, 10]. Amides and ureas have been reported to react with isocyanate to give acylurea and biuret, respectively [11, 12]. Comparatively little work has been reported on the reactions of isocyanates with *N*-acyl-*O*--alkylhydroxylamines. *Cooley* and *Jacobs* [13] have recently investigated the reactions of few *N*-acyl-*O*-alkylhydroxylamines with isocyanates and observed that carbamoyl group is preferentially attached to nitrogen of the hydroxamic acid ester. Recently reactions of benzyloxyamine with phenyl isocyanate have been studied [13].

Experimental

All melting points are uncorrected. The petroleum ether used throughout this work had boiling range of 60—80°C. The purity of compounds was checked by TLC using benzene—

ethyl acetate (volume ratio = 9 1) as solvent. IR spectra were recorded in Perkin—Elmer Infrared Cord. Model 337 spectrometer using KBr pellet. ^{1}H NMR spectra were recorded with a Jeol 100 instrument, in deuterated chloroform using TMS as an internal standard, chemical shifts are expressed in δ/ppm. Mass spectra of some *N*-acyl-*O*-alkylhydroxylamines were recorded with MS 9025, using emission of 100 μA at 95 °C.

N-Acyl-O-alkylhydroxylamine (C)

Method A

A solution of 10.47 g (0.05 mol) of potassium salt of 4-chlorobenzohydroxamic acid, 0.06 mol of cyclohexyl bromide, and 2.5 g of anhydrous sodium carbonate in 50 cm^3 of methanol and 20 cm^3 of water was refluxed for four days. Upon removal of solvent by distillation under reduced pressure a residue was obtained which was acidified with 12 M-HCl. The crude product was extracted four times with 20 cm^3 portion of chloroform. The combined chloroform extracts were washed with 10 % sodium hydrogen carbonate solution. The product was extracted from chloroform by 50 cm^3 portions of 6 M sodium hydroxide solution. The combined sodium hydroxide extracts were acidified with 12 M hydrochloric acid. The aqueous solution was extracted four times with 50 cm^3 portion of chloroform. The chloroform was removed by distillation and the residue slowly solidified on cooling. The residue was crystallized from petroleum ether and *N*-(*p*-chlorobenzoyl)-*O*-cyclohexylhydroxylamine (*V*) was obtained; IR, $\tilde{\nu}$/cm^{-1}: 3180 (N—H), 1640 (C=O); ^{1}H NMR, δ/ppm: 1.29 to 1.92 (m, 11H, C_6H_{11}), 7.24—7.32 (d, 2H, Ar—H), and 6.92 to 6.94 (d, 2H, Ar—H); mass spectrum, *m/z* (I_r/%): 253 (62), 172 (5.10), 171 (13.3), 156 (42), 139 (100), 111 (40), 75 (35).

Method B

A solution of 25 g (0.05 mol) of barium salt of 3-nitrobenzohydroxamic acid, 11 cm^3 (9.12 mol) of n-propyl bromide, and 5 g of anhydrous sodium carbonate in 10 cm^3 of methyl alcohol and 40 cm^3 of water was refluxed for four days. Upon removal of solvent by distillation under reduced pressure a residue was obtained which was acidified with 12 M-HCl. The crude product was extracted four times with 10 cm^3 portions of chloroform and combined sodium hydroxide extracts were acidified with 12 M-HCl. The aqueous solution was extracted four times with 50 cm^3 portions of chloroform. The chloroform was removed by distillation and the residue slowly solidified on cooling. The residue was crystallized from petroleum ether and *N*-(3-nitrobenzoyl)-*O*-propylhydroxylamine was obtained; m.p. = 84 °C, yield = 45 %; IR, $\tilde{\nu}$/cm^{-1}: 3180 (N—H), 1640 (>C=O), 1590 (—NO_2); ^{1}H NMR, δ/ppm: 0.95 (t, 3H, CH_3), 1.70 (m, 2H, CH_2), 4.0 (t, 2H, OCH_2), 7.6 to 8.6 (m, 4H, Ar—H).

For $C_{12}H_{12}N_2O_4$ w_i(calc.): 53.57 % C, 5.35 % H, 12.50 % N; w_i(found): 53.70 % C, 5.50 % H, 12.30 % N.

Upon distillation of chloroform solution a highly viscous liquid was obtained which was identified as *O*,*N*-dialkylated product in 8 % yield. The infrared spectrum of dialkylated compound showed a band at $\tilde{\nu}$ = 1590 cm^{-1} (C=N) and no band was obtained in the carbonyl and N—H regions.

Other hydroxamates prepared by method *A* and *B* are reported in Table 1.

Reaction of N-(3-nitrobenzoyl)-O-propylhydroxylamine with phenyl isocyanate (XIV)

To 1.344 g (0.006 mol) of *N*-(3-nitrobenzoyl)-*O*-n-propylhydroxylamine in 10 cm^3 of toluene 0.006 mol of phenyl isocyanate was added. The mixture was heated until the solution began to boil spontaneously. The flask was then fitted with calcium chloride drying tube and set aside until the odour of phenyl isocyanate had disappeared. The semi-solid mass was recrystallized twice from petroleum ether. IR, $\tilde{\nu}/cm^{-1}$: 3200 (N—H), 1680 (C=O).

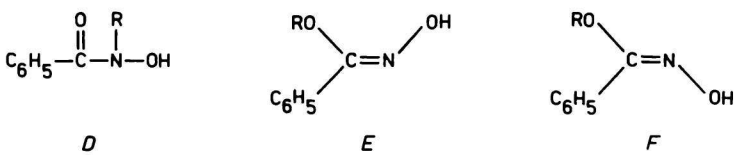
Reaction of N-(3-nitrobenzoyl)-O-butylhydroxylamine with α-naphthyl isocyanate (XXI)

To *N*-(3-nitrobenzoyl)-*O*-butylhydroxylamine (0.05 mol) in a flask 0.8 g (0.005 mol) of α-naphthyl isocyanate was added. The reaction mixture was heated slightly on water bath. The mixture which was liquid on the water bath solidified on cooling. The product was recrystallized from petroleum ether. IR, $\tilde{\nu}/cm^{-1}$: 3200 (N—H), 1680 (C=O).

Other hydroxamates were reacted with phenyl isocyanate and α-naphthyl isocyanate by the method described above and the results are given in Table 3.

Results and discussion

Benzohydroxamic acid (*A*, R = C_6H_5) offers three sites for alkylation, *e.g.* the hydroxylamine oxygen, the nitrogen, and carbonyl oxygen. The four possible monoalkylated products are alkylbenzohydroxamate (*C*, R = C_6H_5), *N*-alkyl-benzohydroxamic acid (*D*), *Z*-isomer and *E*-isomer of alkylbenzohydroximate (*E* and *F*) (Scheme 2).



D *E* *F*

Scheme 2

We have observed that in the presence of weak base alkylation of potassium salt of hydroxamic acid preferentially affords monoalkylated products. Alkylation of potassium salt of 3-nitrobenzohydroxamic acid did not proceed smoothly and therefore alkylation of 3-nitrobenzohydroxamic acid was carried out by alkylation of its barium salt to form monoalkylated product in major amount. Since ^{1}H NMR and mass spectral data on monoalkylated products (*C*) are not reported in the literature, it is considered worthwhile to present mass and ^{1}H NMR spectroscopic data of known as well as unknown monoalkylated products (Table 1).

Table 1

Characterization of *N*-acyl-*O*-alkylhydroxylamines (*C*)

Compound	R′	Formula	w_i(calc.)/% / w_i(found)/%			Yield/%	M.p./°C	Method
			C	H	N			
R = 3-$NO_2C_6H_4$								
I	$CH_2CH=CH_2$	$C_{10}H_{10}N_2O_4$	54.05 53.85	4.50 4.01	12.61 12.29	50	94—95	*B*
II	$CH_2CH_2CH_2CH_3$	$C_{11}H_{14}N_2O_4$	55.46 54.98	5.88 5.49	11.76 11.61	50	89—90	*B*
III	CH_2CH_3	$C_9H_{10}N_2O_4$	51.42 51.12	4.76 4.61	13.33 13.21	44	120—121	*B*
R = 4-ClC_6H_4								
IV	$CH_2CH_2CH_2CH_3$	$C_{11}H_{14}NO_2Cl$	58.14 57.85	6.17 5.80	6.17 6.01	79	95—96	*A*
V	C_6H_{11}	$C_{13}H_{16}NO_2Cl$	61.66 61.12	6.32 6.14	5.53 5.09	30	125—126	*A*
VI	$CH(CH_3)_2$	$C_{10}H_{12}NO_2Cl$	56.33 55.98	5.63 5.01	6.57 6.28	68	99—100	*A*
VII	$CH_2CH=CH_2$	$C_{10}H_{10}NO_2Cl$	56.87 55.72	4.74 4.61	6.63 6.45	58	95—96	*A*
VIII	$(CH_3)C=CH(CH_3)$ (*trans*)	$C_{11}H_{12}NO_2Cl$	58.66 58.25	5.33 5.01	6.22 5.98	20	149—150	*A*

Table 1 (Continued)

Compound	R′	Formula	w_i(cal.)/% w_i(found)/%			Yield/%	M.p./°C	Method
			C	H	N			
R = 4-$NO_2C_6H_4$								
IX	$CH_2CH{=}CH_2$	$C_{10}H_{10}N_2O_4$	54.05 53.78	4.50 4.01	12.61 12.08	52	117—118	*A*
X	C_6H_{11}	$C_{13}H_{16}N_2O_4$	59.09 58.85	6.06 5.78	10.60 10.25	10	156—157	*A*
XI	$CH_2CH_2CH_3$	$C_{10}H_{12}N_2O_4$	53.57 53.41	5.35 5.01	12.50 12.15	40	161—162	*A*
XII	$(CH_3)C{=}CH(CH_3)$ (*trans*)	$C_{11}H_{12}N_2O_4$	55.93 55.59	5.08 4.88	11.87 11.78	22	151—152	*A*
R = C_6H_5								
XIII	C_6H_{11}	$C_{13}H_{17}NO_2$	71.23 70.98	7.76 7.61	6.39 6.18	20	131—132	*A*

Table 2

Mass and ^{1}H NMR spectral data of some monoalkylated hydroxamates

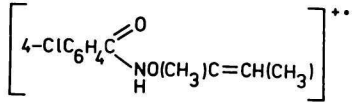
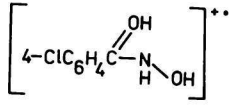
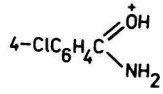
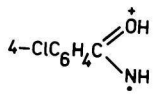
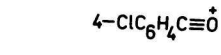
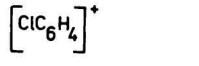
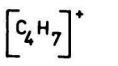
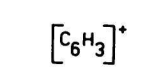
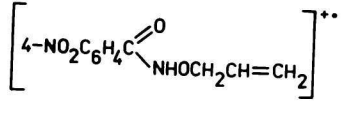
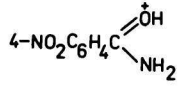
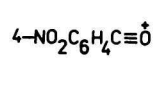
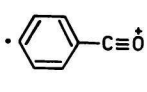
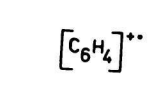
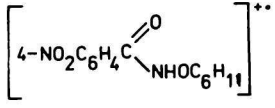
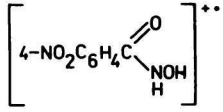
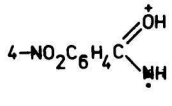
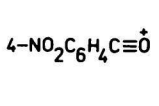
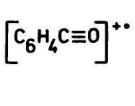
VIII	*m/z*	225	171	156	155
	I_r	2.3	27.9	4.6	9.3
	Structure of fragments				
	m/z	139	111	55	75
	I_r	97	30	100	30
	Structure of fragments				
	^{1}H NMR, δ/ppm: 1.68 (d, 3H, CH_3), 4.6 (d, 3H, CH_3), 5.4 (m, 1H, =CH), 6.8 (d, 2H, Ar—H), 7.2 (d, 2H, Ar—H)				
IX	*m/z*	222	167	150	104	76
	I_r	8.5	33	100	29	33
	Structure of fragments					
	^{1}H NMR, δ/ppm: 4.08 (d, 2H, OCH_2), 4.80—5.08 (m, 2H, $=CH_2$), 5.32 (quintet, 1H, =CH), 7.6—7.8 (d, 4H, Ar—H)					

Table 2 (Continued)

X	*m/z*	264	182	166	150	104
	I_r	6.5	14.2	28	100	14
Structure of fragments						

^{1}H NMR, δ/ppm: 1.29—1.92 (m, 1H, C_6H_{11}), 3.96 (s, 1H, NH), 7.6—7.68 (m, 4H, Ar—H)

Table 3

Characterization of carbamoyl derivative of hydroxamate (*G*)

Compound	R′	R″	Formula	^{1}H NMR, δ/ppm	w_i(calc.)/% w_i(found)/%			Yield/%	M.p./°C
					C	H	N		
R = 3-$NO_2C_6H_4$									
XIV	$CH_2CH_2CH_3$	Ph	$C_{17}H_{17}N_3O_5$	0.6 (t, 3H, CH_3), 3.05 (t, 2H, OCH_2), 5.6—7 (m, 9H, Ar—H), 1.1 (sextet, 2H, $CH_2CH_2CH_3$)	59.47 59.11	4.95 4.81	12.24 11.95	68	64
XV	$CH_2CH{=}CH_2$	Ph	$C_{17}H_{15}N_3O_5$		59.82 59.69	4.39 4.12	12.31 12.15	56	77—78
XVI	$CH_2CH_2CH_2CH_3$	Ph	$C_{18}H_{19}N_3O_5$	0.60 (t, 3H, CH_3), 1.05 (m, 4H, —CH_2CH_2—), 3.05 (t, 2H, —OCH_2), 6.0—6.8 (m, 9H, Ar—H), 8.25 (s, 1H, N—H)	60.50 59.10	5.32 5.21	11.76 11.63	65	68—69
XVII	CH_2CH_3	Ph	$C_{16}H_{15}N_3O_5$	0.85 (t, 3H, CH_3), 3.1 (q, 2H, OCH_2), 6.0—7.0 (m, 9H, Ar—H), 8.20 (s, 1H, N—H)	58.35 58.11	4.55 4.28	12.76 12.51	45	82—83
XVIII	$CH_2C_6H_5$	Ph	$C_{21}H_{17}N_3O_5$	4.8 (s, 2H, $CH_2C_6H_5$), 7.3—7.85 (m, 16H, Ar—H)	64.45 63.95	4.34 4.12	10.74 10.35	50	42—43

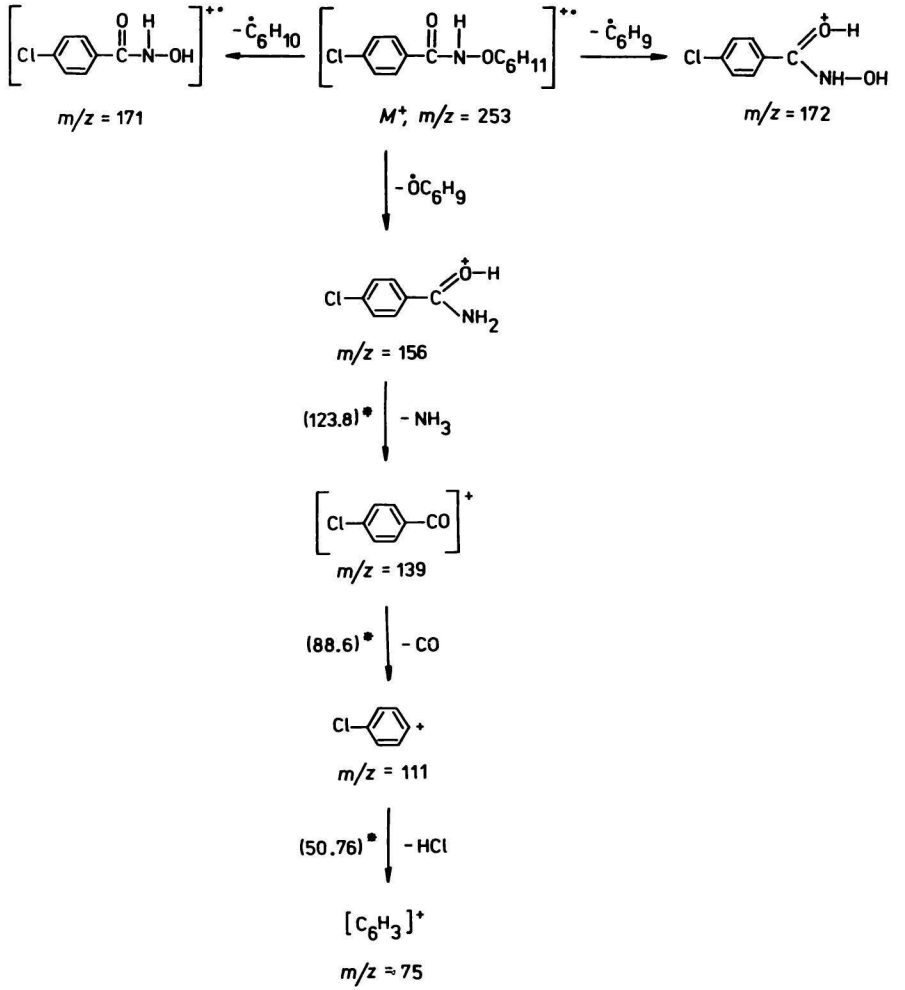
Table 3 (Continued)

Compound	R′	R″	Formula	^{1}H NMR, δ/ppm	w_i(calc.)/% w_i(found)/% C	H	N	Yield/%	M.p./°C
XIX	$CH_2CH_2CH_3$	α-Naphth	$C_{21}H_{19}N_3O_5$	0.85 (t, 3H, CH_3), 3.1 (q, 2H, OCH_2), 6.0—7.0 (m, 9H, Ar—H), 8.20 (s, 1H, NH)	64.12 64.01	4.83 4.50	10.68 10.40	45	48—49
XX	$CH_2CH{=}CH_2$	α-Naphth	$C_{21}H_{17}N_3O_5$	4.08 (d, 2H, OCH_2), 4.8 (quintet, 1H, −CH=), 6.0—6.9 (m, 11H, Ar—H), 7.9 (s, 1H, N—H)	64.45 64.12	4.34 4.21	10.74 10.55	60	53—54
XXI	$CH_2CH_2CH_2CH_3$	α-Naphth	$C_{22}H_{21}N_3O_5$	0.61 (t, 3H, CH_3), 1.18 (m, 4H, $CH_2\underline{CH_2CH_2}$—CH_3), 3.18 (t, 2H, OCH_2), 6.15—6.75 (m, 4H, Ar—H), 6.0—6.15 (m, 7H, $C_{10}H_7$—H)	64.86 64.59	5.16 4.96	10.31 10.12	40	97—98
XXII	CH_2CH_3	α-Naphth	$C_{20}H_{17}N_3O_5$		63.32 62.89	4.48 4.17	11.08 10.55	29	285
XXIII	$CH_2C_6H_5$	α-Naphth	$C_{25}H_{19}N_3O_5$		68.02 67.92	4.30 4.01	9.52 9.15	60	68
XXIV	$CH(CH_3)_2$	α-Naphth	$C_{21}H_{19}N_3O_5$		64.12 63.75	4.83 4.56	10.68 10.55	35	60—61
R = 4-$NO_2C_6H_4$									
XXV	C_6H_{11}	Ph	$C_{20}H_{21}N_3O_5$		62.66 62.35	5.48 5.23	10.96 10.80	60	100
XXVI	$CH_2C_6H_5$	Ph	$C_{20}H_{17}N_2O_5$		64.45 64.20	4.34 4.30	10.74 10.50	35	114

Table 3 (Continued)

Compound	R′	R″	Formula	^{1}H NMR, δ/ppm	w_i(calc.)/% / w_i(found)/%			Yield/%	M.p./°C
					C	H	N		
XXVII	$CH_2CH_2CH_2CH_3$	Ph	$C_{18}H_{19}N_3O_5$		60.50 60.40	5.32 5.30	11.76 11.40	40	95
XXVIII	$CH_2CH{=}CH_2$	Ph	$C_{17}H_{15}N_3O_5$	4.12 (t, 2H, OCH_2), 4.72—4.82 (m, 2H, =CH), 5.32 (quintet, 1H, =CH−), 6.60—7.76 (m, 9H, Ar—H)	59.82 59.50	4.39 4.02	12.31 12.20	56	77—78
R = 4-ClC_6H_4									
XXIX	C_6H_{11}	Ph	$C_{20}H_{21}N_2O_3Cl$		64.51 64.40	5.64 5.30	7.52 7.40	65	99
XXX	$CH_2CH{=}CH_2$	Ph	$C_{17}H_{15}N_2O_3Cl$		61.81 61.70	4.54 4.40	8.48 8.38	40	52
XXXI	$CH_2C_6H_5$	α-Naphth	$C_{25}H_{19}N_2O_3Cl$		69.76 69.40	4.42 4.42	6.51 6.90	30	70—71
XXXII	$CH_2CH_2CH_2CH_3$	α-Naphth	$C_{22}H_{21}N_2O_3Cl$		66.67 66.40	5.30 5.20	7.07 7.02	65	60—61

The fragmentation pattern in mass spectrum of *N*-(4-chlorobenzoyl)-*O*--cyclohexylhydroxylamine (*V*) as typical example is given in Scheme 3. Mass spectral data of other monoalkylated hydroxamates are presented in Table 2.

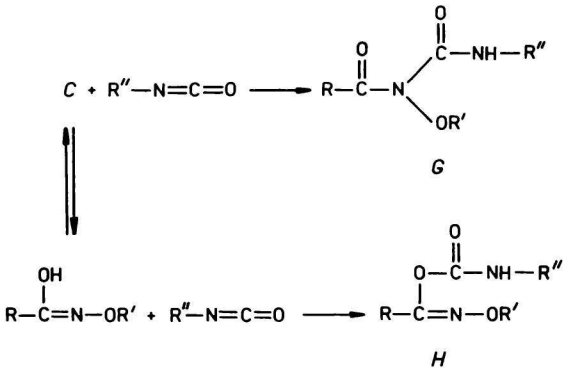


* The value refers to metastable ions.

Scheme 3

^{1}H NMR data on some alkylhydroxamates (*VIII*— *X*) are presented in Table 2. Both ^{1}H NMR and mass spectral evidence indicates that *N*-acyl-*O*-alkyl-hydroxylamines have the structure *C*. After having synthesized hydroxamates (*C*) we investigated their reactions with phenyl isocyanate and α-naphthyl iso-

cyanate under varying conditions. In some cases toluene was used as solvent to give a better yield. Two possible structures *G* and *H* (Scheme 4) can be written for



Scheme 4

the obtained products. Since most of the reactions were carried out by addition of solid *N*-acyl-*O*-alkylhydroxylamine to the liquid isocyanates the possibility of formation of products *H via* tautomer is quite low. The ^{1}H NMR data (Table 3) confirm the structure *G* and in none of the products, C=N absorption in the IR spectra was observed, thus eliminating the possibility of formation of compound having structure *H*. Instead all the products (Table 3) showed in IR spectrum absorptions at $\tilde{\nu} = 1685\ \mathrm{cm}^{-1}$ (C=O) and $\tilde{\nu} = 3100-3200\ \mathrm{cm}^{-1}$ (N—H).

Acknowledgements. Two of the authors (R. P. Sharma and A. Sood) are grateful to May and Baker Ltd., London and D. Tandon is grateful to University Grants Commission, New Delhi, for the award of Junior Research Fellowships. Sincere gratitude is expressed to Dr. M. Sahai of Weizmann Institute of Science, Israel, for the ^{1}H NMR measurements of some compounds. We are grateful to Dr. T. Jakubík of the Laboratory of Mass Spectrometry, Slovak Technical University, Bratislava, for mass spectral measurements.

References

1. Johnson, J. E., Springfield, J. R., Hwang, J. S., Hayes, L., Cunningham, W. C., and McClaugherty, D. L., *J. Org. Chem. 36*, 284 (1971).
2. Bauer, L. and Exner, O., *Angew. Chem., Int. Ed. Engl. 13*, 376 (1974).
3. Smith, P. A. S., *The Chemistry of Open-Chain Organic Nitrogen Compound*, Vol. *II*, p. 68—98. W. A. Benjamin, New York, 1966.
4. Cooley, J. H., Bills, W. D., and Throckmorton, J. R., *J. Org. Chem. 25*, 1734 (1960).
5. Singha, A. S., *Ph.D. Thesis*. Himachal Pradesh University, Shimla, 1983.
6. *Beilsteins Handbuch der Organischen Chemie*, Vol. *IX*, pp. 309—313. Springer-Verlag, Berlin, 1926.

7. Yale, H. L., *Chem. Rev. 33*, 209 (1944).
8. Fuller, A. T. and King, H., *J. Chem. Soc. 1947*, 963.
9. Arnold, R. G., Nelson, J. E., and Verbanc, J. J., *Chem. Rev. 57*, 47 (1957).
10. Baker, J. W. and Bailey, D. N., *J. Chem. Soc. 1957*, 4649, 4652, 4663.
11. Khun, *Ber. 17*, 28880 (1884).
12. Lakra and Dains, *J. Amer. Chem. Soc. 51*, 2220 (1929).
13. Cooley, J. H. and Jacobs, P. T., *J. Org. Chem. 40*, 552 (1975).