SYNTHESIS AND CHARACTERIZATION OF MIXED ANHYDRIDES OF O-BENZYLBENZOHYDROXIMIC ACID*

Namita SHARMA and Bhupendra Nath MISRA

Department of Chemistry, Himachal Pradesh University, Summer Hill, 171 005 Shimla, India

Received May 16, 1988
Accepted March 7, 1989

Mixed anhydrides of O-benzylbenzohydroximic acid have been prepared by acylation and sulfonylation of O-benzylbenzohydroxamic acid using a variety of acyl and sulfonyl halides in the presence of trimethylamine and pyridine in dioxane and benzene. Structure elucidation of the resulting products was performed by chemical and spectroscopic methods. All evidences indicate that the products have the mixed anhydride structure with (*Z*)-configuration. Corresponding (*E*)-isomer and the isomeric N-acylated or sulfonylated products, if formed, could not be isolated. Several mixed anhydrides showed antiparasitic activity.

Acylation of hydroxylamine by ester to give hydroxamic acid is a well known reaction.[1] Monoalkylation[2-5] of a number of hydroxamic acids has been successfully carried out to give N-acyl-O-alkylhydroxylamines. The protonation, alkylation and acylation sites of amides have been the subject of intense investigation.[6-8] In general, since O → N acyl migrations are known to be rapid,[9] it is difficult to decide whether the N-acylated product isolated from the acylation of amide is formed kinetically or through preliminary O-acylation. Unfortunately, O-acylimidates (i. e. isoimides) are generally too unstable to be isolated and therefore, in the present work acylation and sulfonylation of O-benzylbenzohydroxamate is studied, since the resulting (*Z*)-O-acyl derivatives are expected to be enough stable.

Acylation of N-acyl-O-alkylhydroxylamines has not been extensively investigated. Cooley et al.[10] and Misra et al.[11,14] studied the reaction of *p*-toluenesulfonyl chloride with sodium salt of a large number of N-acyl-O-alkylhydroxylamines in benzene and isolated O-tosylated compounds as the only products. Ward et al.[3] reported the reactions of acetyl chloride with potassium and silver salts of several N-acyl-O-alkylhydroxylamines and observed the formation of both O- and N-acetylated products, depending upon the structure of O-alkylhydroxamic acid and the nature of the metal ion. It was not mentioned whether the N-acetylated compounds isolated by them were the products of rearrangement of initially formed

* The paper was presented in part in the VIIth Conference of Indian Council of Chemists held in Gwalior, India, December 28—30, 1987.

O-acetylated products. McCarthy and Hegarty[12] investigated the reactions of acetyl chloride with the ambident anions derived from O-alkylbenzohydroxamic acids and reported the formation of O-acetylated products. Challis et al.[13] studied the acetylation of a number of O-benzylarylcarbohydroxamates by acetic anhydride and pyridine in organic solvents and reported that the reaction proceeds by the primary formation of (Z)-acetic O-benzylhydroximic anhydride.

In the reaction of benzoyl chloride with silver salt of N-acyl-O-acylhydroxylamines, Johnson et al.[2] observed the formation of (Z)-isomer of the O-benzoylated product. Literature survey reveals that except acetyl chloride and *p*-toluenesulfonyl chloride, no other acyl or sulfonyl halides have been used for studying the acylation of N-acyl--O-alkylhydroxylamines. In the present article, we report studies on the reaction of O-benzylbenzohydroxamic acid with a variety of acylating agents which include: benzoyl chloride, *p*-nitrobenzoyl chloride, anisoyl chloride, ethyl chloroformate, methanesulfonyl chloride, benzenesulfonyl chloride and *p*-acetaminobenzenesulfonyl chloride in dioxane in the presence of trimethylamine and in benzene in the presence of pyridine. Attempts have been made to determine the structure of the resulting products. A plausible mechanism for the exclusive formation of (Z)-isomer of the mixed anhydride has been suggested.

EXPERIMENTAL

All the melting points were determined in open capillaries and are uncorrected. The progress of all the reactions was monitored by TLC on plates coated with silica gel-G using benzene ethyl-acetate, benzene–petroleum ether as eluants. Spots were developed in an iodine Chamber. IR spectra were recorded on 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 were recorded with MS 9025 machine, using emission of 100 μA at 95°C. Biological activity of several compounds was determined in the laboratory of Organon Research Centre, Calcutta. Ultraviolet spectra were measured on Beckman DU-6 spectrophotometer. Potassium benzohydroxamate was prepared by the modified method of Misra et al.[14]

Preparation of N-Benzoyl-O-benzylhydroxylamine

A solution of 87·5 g (0·5 mol) of potassium benzohydroxamate, 76·9 g (0·6 mol) of benzyl chloride, 25 g of anhydrous Na_2CO_3 in 500 ml of methanol was refluxed for 96 hours. The progress of the reaction was monitored by $FeCl_3$ test and the reaction was complete when no further deepening of red colour of the solution was observed upon addition of freshly prepared 1% $FeCl_3$ solution in water. Upon removal of solvent by distillation, the residue obtained was acidified with 12M-HCl. The crude product was extracted four times with 100 ml portions of chloroform and the chloroform extract was washed with 10% sodium bicarbonate solution. N-Benzoyl-O-benzylhydroxylamine was extracted from the chloroform solution by 50 ml-portions of 10% sodium hydroxide solution. The combined sodium hydroxide extracts were acidified with 12M hydrochloric acid and the aqueous solution was extracted four times with 50 ml-por-

tions of chloroform. The chloroform was removed by distillation and the residue which slowly solidified upon cooling to room temperature was recrystallised from ethanol. The yield was 55% (m.p. 103–104°C). The infrared spectrum showed bands at 1 650 cm^{-1} (C=O) and at 3 300 cm^{-1} (NH). UV spectrum: λ_{max} in ethanol at 267·5 nm. For $C_{14}H_{13}NO_2$ (227·3) calculated: 74·00% C, 5·72% H, 6·12% N; found: 73·75% C, 5·67% H, 6·23% N.

Acylation of N-Benzoyl-O-benzylhydroxylamine with Benzoyl Chloride Using Trimethylamine as Base (method *A*)

N-Benzoyl-O-benzylhydroxylamine, 5·67 g (0·025 mol) in 25–50 ml of *p*-dioxane was treated with 3·5 ml (0·025 mol) of benzoyl chloride. The reaction mixture was stirred for four hours at room temperature. To the reaction mixture was added 5–7 ml of trimethylamine (0·09–0·1 mol) and the reaction mixture was refluxed for 4 hours. After the completion of the reaction, the reaction mixture was poured in 250 ml of distilled water. A solid residue was obtained which was crystallised from benzene and ethanol. The yield was 45% (m.p. 75–76°C). For $C_{21}H_{17}NO_3$ (331·4) calculated: 76·13% C, 5·14% H, 4·23% N; found: 76·01% C, 5·03% H, 4·14% N. The IR spectrum showed bands at 1 745 cm^{-1} (ester), 1 575 cm^{-1} (C=N), 745 cm^{-1} (aromatic). NMR spectrum (δ, ppm): 5·19 s, 2 H (OCH_2), 7·23–8·33 m, 15 H (arom. H).

Acylation of N-Benzoyl-O-benzylhydroxylamine with Benzoyl Chloride Using Pyridine as Base (method *B*)

N-Benzoyl-O-benzylhydroxylamine (0·01 mol) in 25–50 ml of benzene was treated with 1·40 ml (0·01 mol) of benzoyl chloride, followed by addition of 7–10 ml of pyridine (0·08–0·12 mol). The reaction mixture was stirred at room temperature for 24 hours. After the completion of the reaction, the reaction mixture was poured into ice bath. The organic layer (benzene) was extracted successively with saturated $NaHCO_3$ solution (2 × 50 ml), 10% HCl (2 × 50 ml) and water (2 × 50 ml) and dried over anhydrous Na_2SO_4. Upon removal of solvent under reduced pressure, a crude product was obtained as a viscous oil which was taken up in 50 ml of ether. Ether solution was washed with 1% NaOH solution followed by washing with 1% HCl and distilled water. After drying the ether solution over anhydrous Na_2SO_4, it was concentrated to half its volume and kept in the refrigerator when the product appeared as white crystals. The product was recrystallised from ehter–petroleum ether and the purity was checked by TLC using benzene and petroleum ether (3 : 7) as eluents. The yield was 60%, (m.p. 75–76°C). For $C_{21}H_{17}NO_3$ (331·37) calculated: 76·13% C, 5·14% H. 4·23% N; found: 75·89% C, 5·07% H, 4·19% N. The IR spectrum showed bands at 1 745 cm^{-1} (ester), 1 575 cm^{-1} (C=N), and at 745 cm^{-1} (aromatic). NMR spectrum (δ, ppm): 5·19 s, 2 H (OCH_2), 7·23–8·33 m, 15 H (arom. H).

Preparation of other mixed anhydrides of O-benzylbenzohydroxamic acid using *p*-nitrobenzoyl chloride, benzenesulfonyl chloride, methanesulfonyl chloride, *p*-acetaminobenzenesulfonyl chloride, ethyl chloroformate and anisoyl chloride was carried out by the method *B* and the results are presented in Table I.

Attempted rearrangement of p-nitrobenzoyl-N-benzyloxybenzimino ether (compound *IIIb* Table I). The title compound (0·200 g) in about 50 ml dioxane was refluxed for 8 hours. Then, the solvent was distilled off, the residue obtained was recrystallised from ether. Examination of the product by TLC and IR analysis showed that no rearrangement had occurred.

TABLE I

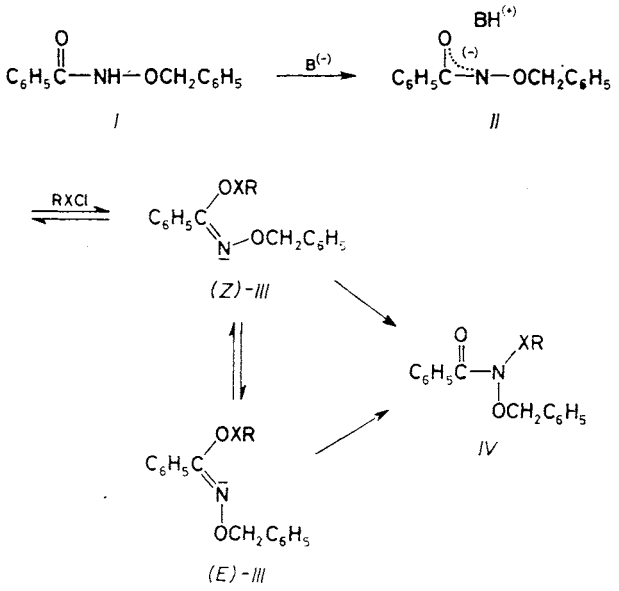
Physical data of mixed anhydrides *III* ($C_6H_5C(-O-X-R)=N-OCH_2C_6H_5$)

Compound	X—R	Formula (M.w.)	Calculated/Found % C	% H	% N	% S	Procedure[a] yield, %	m.p., °C
IIIa	COC_6H_5	$C_{21}H_{17}NO_3$ (331·4)	76·13 75·98	5·14 5·07	4·23 4·19	— —	*A*[b] 45	75—76[c]
IIIb[d]	$OCC_6H_4NO_2$-*p*	$C_{21}H_{16}N_2O_5$ (376·4)	67·02 67·08	4·25 4·11	7·44 7·38	— —	*B* 60	131—132
IIIc	$OCC_6H_4OCH_3$-*p*	$C_{22}H_{19}NO_4$ (361·4)	73·13 73·11	5·26 5·18	3·87 3·82	— —	*B* 60	62—63
IIId	$COOC_2H_5$	$C_{17}H_{17}NO_4$ (299·3)	68·22 68·32	5·69 5·56	4·68 4·42	— —	*B* 60	105—106
IIIe[d]	$SO_2C_6H_5$	$C_{20}H_{17}NSO_4$ (367·4)	65·39 65·42	4·63 4·56	3·81 3·72	8·71 8·66	*B* 62	68—69
IIIf	SO_2CH_3	$C_{15}H_{15}NSO_4$ (305·3)	59·01 58·96	4·92 4·86	4·59 4·61	10·47 10·36	*B* 53	110—111·5
IIIg	$SO_2C_6H_4NHCOCH_3$-*p*	$C_{22}H_{20}N_2SO_5$ (427·5)	62·26 62·32	4·72 4·63	6·57 6·48	7·54 7·43	*B* 60	120—121

[a] See Experimental. Pyridine was used in general as base when procedure *B* was applied to the synthesis. [b] Using trimethylamine as the base. The product of identical properties in 60% yield was obtained when using procedure *B*. [c] Reported m.p. (ref.[3]) 74·5—75°C. [d] Compound showed anthelmintic activity.

RESULTS AND DISCUSSION

Acylation of O-benzylbenzohydroxamic acid (*I*) in the presence of base can give rise to three products e.g., isoimides (*Z*)-*III* and (*E*)-*III* and imides *IV* via the ambident anion *II* (Scheme 1).



In formulae *III*–*IV*: *a*, R = C_6H_5; X = CO
b, R = *p*-$O_2NC_6H_4$; X = CO
c, R = *p*-$H_3COC_6H_4$; X = CO
d, R = OC_2H_5; X = CO
e, R = C_6H_5; X = SO_2
f, R = CH_3; X = SO_2
g, R = *p*-$H_3CONHC_6H_4$; X = SO_2

SCHEME 1

Acylation of O-benzylbenzohydroxamic acid in dioxane was carried out in the presence of trimethylamine and in benzene in the presence of pyridine at room temperature. In the presence of pyridine, the yield of the product was higher (Table I). The acylation was monitored by TLC and the reaction was stopped when the spot due to hydroxamate disappeared. The spectral properties of the products were consistent with the O-acylated and O-sulfonylated structure (*E*)- or (*Z*)-*III*. It is observed from Table II that all the O-acylated products in the IR spectra showed strong absorptions in the regions of 1 730–1 745 cm^{-1} assigned to the ester car-

bonyl. Vinyl acetate[15] and O-acylureas[16] also show absorptions in this region. Further, all the acylated products showed in the IR spectra bands in the region of 1 810–1 950 cm^{-1} attributed to —C(=O)—O—C(=N)— function. The IR spectra of the sulfonylated products (Table II) showed strong absorptions in the region 1 365–1 370 cm^{-1} (SO_2) and in the region 1 155–1 160 cm^{-1} assigned to OSO_2 group. All the acylated and sulfonylated products showed absorptions in the region 1 575–1 645 cm^{-1} assigned to C=N function. Hydroxamic ester chlorides[17] also showed absorption in this region. The presence of C=N function in the products indicates that the acylated compounds have the mixed anhydride structure (*Z*)-*III* or (*E*)-*III*. Proton NMR spectral data of the products (Table III) support the struc-

TABLE II

IR data of mixed anhydrides *III* (KBr pellet)

Compound[a]	Band maxima in cm^{-1} (assignment)
IIIa	1 745 (ν(C=O)), 1 575 (ν(C=N)), 745 (δ(=C—H)
IIIb	1 745 (ν(C=O)), 1 605 (ν(C=N)), 750 (δ(=C—H)), 1 950 (ν(CO—O—CO)), 1 350 (ν(ONO))
IIIc	1 730 (ν(C=O)), 1 575 (ν(C=N)), 750 (δ(=C—H)), 1 160 (ν(C—O—C))
IIId	1 770 (ν(C=O)), 1 575 (ν(C=N)), 1 950, 1 890 and 1 810 (ν(CO—C—CO))
IIIe	1 365 (ν(SO_2)), 1 160 (ν(O—SO_2)), 1 640 (ν(C=N)), 735 (δ(=C—H))
IIIf	1 370 (ν(SO_2)), 1 155 (ν(O—SO_2)), 1 640 (ν(C=N)), 745 (δ(=C—H))
IIIg	1 370 (ν(SO_2)), 1 155 (ν(O—SO_2)), 1 645 (ν(C=N)), 745 (δ(=C—H)), 3 240 (ν(N—H)), 1 950, 1 890 and 1 810 (ν(CO—O—CO))

[a] For structure see Table I.

TABLE III

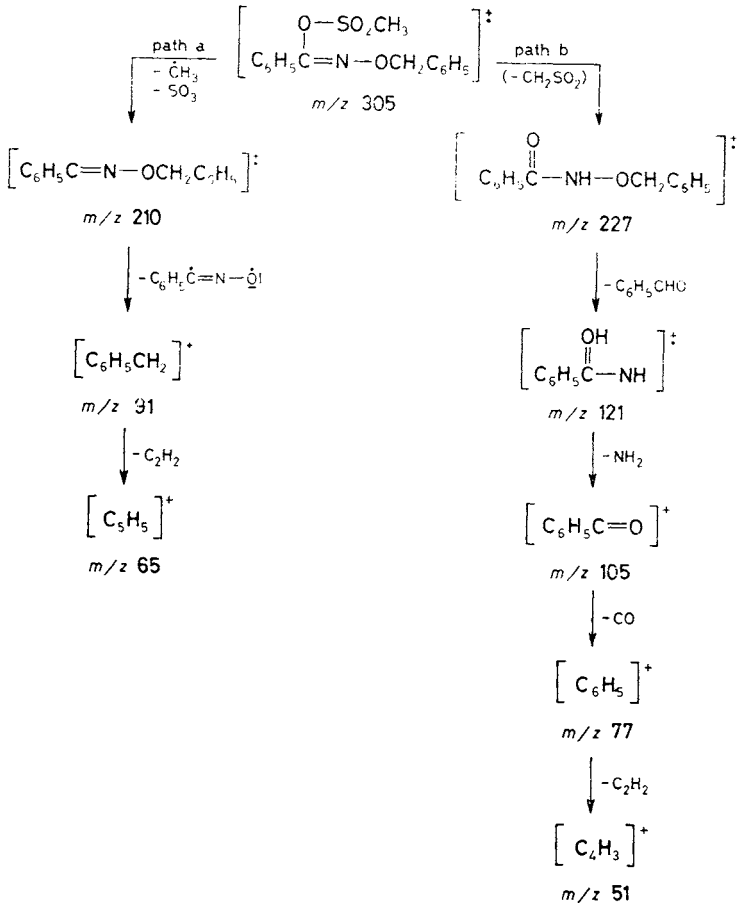
^{1}H NMR spectral data of mixed anhydrides *III*

Compound[a]	Chemical shifts δ (ppm)
IIIa	5·19 s, 2 H (OCH_2), 7·23–8·33 m, 15 H (arom. H)
IIIb	5·19 s, 2 H (OCH_2), 7·16–8·49 m, 14 H (arom. H)
IIIc	5·03 s, 2 H (OCH_2), 6·66–7·23 m, 14 H (arom. H), 3·72 s, 3 H (OCH_3)
IIIf	5·12 s, 2 H (OCH_2), 7·00–8·33 m, 15 H (arom. H)
IIIg	5·13 s, 2 H (OCH_2), 7·13–8·13 m, 14 H (arom. H)

[a] For structure see Table I.

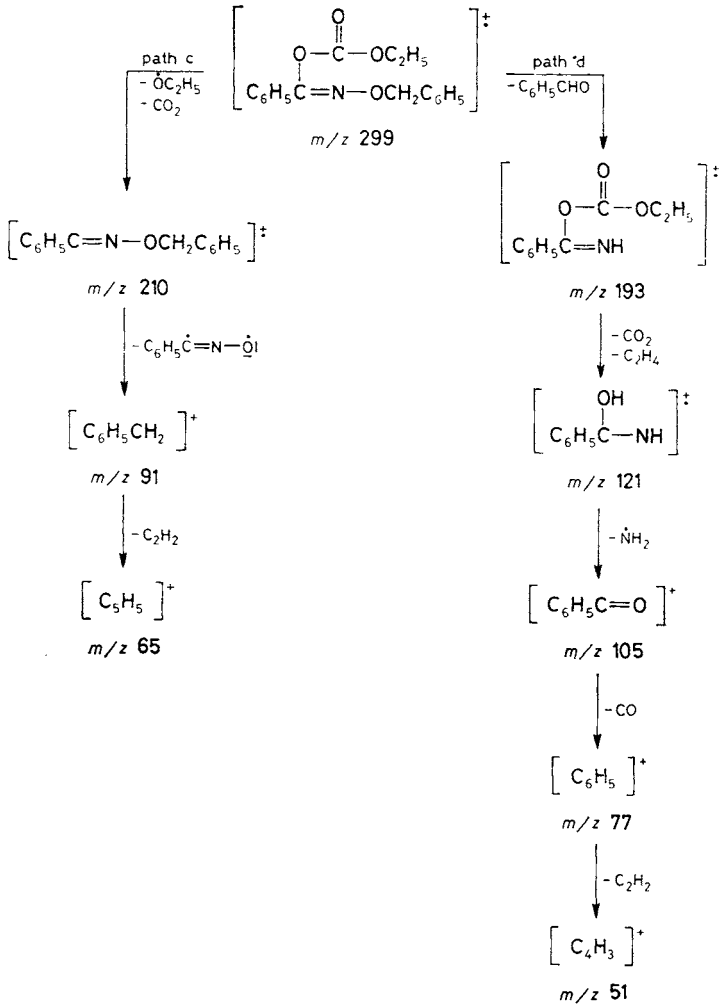
tures (*Z*)-*III*. All the acylated and sulfonylated products in NMR spectra showed singlet at δ 5·03–5·19 for the methylene protons (=N—OCH_2). Such a downfield chemical shift of methylene protons was also observed by Challis et al.[13] in a series of acetic O-benzyl-benzohydroximic anhydrides. The methylene protons in the isomeric N-acetylated compounds[13] showed up field absorption in the region δ 4·83–4·92. Infrared and ^{1}H NMR spectroscopic analysis indicates that the acylated and sulfonylated products are represented by the hydroximic anhydride structure (*Z*)-*III* in which acyl and sulfonyl groups are attached to oxygen.

Mass spectroscopic analysis of methane sulfonyl-N-benzyloxy benzimino ether and ethoxycarbonyl-N-benzyloxy benzimino ether (compounds *IIIf* and *IIId*, Table I) as two representative products is described in Scheme 2 and Scheme 3,



SCHEME 2

respectively. The fragmentation pattern of both the compounds appears straightforward. However, appearance of the fragment with m/z 210 by path a in Scheme 2 and path c in Scheme 3 needs to be explained. It appears that this fragment arises by the loss of SO_3 and CH_3 radical (Scheme 2) nad by the loss of CO_2 and OC_2H_5 radical in Scheme 3 from the respective molecular ions. The greater stability of the benzyl cation provides the driving force for the elimination of the species A which is resonance stabilized to give the canonical structure for nitrosophenylcarbene B.



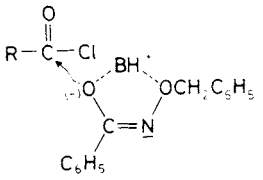
SCHEME 3

A B

Benzyl cation is known to eliminate acetylene to give the species $C_5H_5^+$ with m/z 65. Alternatively, the molecular ion from methane sulfonyl-N-benzyloxy benzimino ether (m/z 305, Scheme 2) may lose CH_2SO_2 by path b to give radical cation of benzyl benzohydroxamate (m/z 227) which then loses a molecula of C_6H_5CHO to give the fragment m/z 121. This fragment is also present in the fragmentation pattern of ethoxycarbonyl-N-benzyloxy benzimino ether by path d in Scheme 3. In this case, however, the molecular ion m/z 299 first eliminates a molecule of benzaldehyde to give the fragment m/z 121. The mass spectroscopic analysis conclusively establishes the mixed anhydride structure (*E*)-*III* or (*Z*)-*III* for the acylated product.

O-Acylated and O-sulfonylated products however, can exist as (*Z*)- or (*E*)-isomers *III*. Rapid thermally induced rearrangement of the O-acylisoimides to the N-acyl compound through 1,3-acyl migration is well documented[18]. When the oxime derivative *III* was heated in dioxane for 8 hours, no change was found by IR and TLC analysis. The rearrangement of isoimides to N-acyl compounds by 1,3-acyl migration requires that the lone pair of electrons on the imino nitrogen be *cis* to the acyl group.[12,13]

There is considerable evidence that in the absence of catalyst[13], (*E*) → (*Z*)- isomerization does not occur and therefore absence of rearrangement of *II* upon prolonged heating indicates that the acyl group is *trans* to the lone pair of electrons on nitrogen as in *III*. A possible explanation for the exclusive formation of (*Z*)--isomer rather than (*E*)-isomer *III* during acylation is due to the existence of ion pair C, where BH^+ represents Me_3NH^+ or PyH^+. The formation of the five membered ion pair C forces the hydroximate anion to adopt the configuration observed in the product.



C

The products *IIIb* and *IIIe* (Table I) showed considerable antiparasitic activity towards *Entamoeba histolytica* in in vitro tests. Details of the biological activity measurements carried out by Organon Research Centre, Calcutta, were not made available.

The authors are grateful to Dr Iva Sroková of the University of Bratislava for providing mass spectral analysis of several compounds. The authors are also grateful to Dr S. K. Chaudhary of Organon Research Centre, Calcutta for screening a number of compounds for biological activity.

REFERENCES

1. Smith P. A. S.: *The Chemistry of Open-Chain Organic Nitrogen Compounds*, Vol. II, pp. 68–98. W. A. Benjamin, New York 1966.
2. Johnson J. E., Springfield J. R., Hwang J. S., Hayes J. L., Cunnigham W. C., McClaugherty D. L.: J. Org. Chem. *36*, 284 (1971).
3. Hearn M. J. W., Ward A. D.: Aust. J. Chem. *22*, 1731 (1969).
4. Chehate M., Bocabeille F., Thuillier G., Rumpf P.: C. R. Acad. Sci. *268*, 445 (1969).
5. McHale M., Green J., Mamalis P.: J. Chem. Soc. *1960*, 229 and 225.
6. Williams A.: J. Am. Chem. Soc. *97*, 6278 (1975).
7. Liler M.: Chem. Commun. *1971*, 115.
8. Challis B. C.: *The Chemistry of the Amide Group*. Wiley–Interscience, New York 1968.
9. McCarty C. G. in: *The Chemistry of the Carbon–Nitrogen Double Bond* (S. Patai, Ed.), Chap. 9. Wiley–Interscience, New York 1970.
10. Cooley J. H., Misra B. N., Throckmorton J. R., Bills W. D.: J. Med. Chem. *11*, 196 (1968).
11. Misra B. N.: Indian J. Chem. *11*, 546 (1973).
12. McCarthy D. G., Hegarty A. F.: J. Chem. Soc., Perkin Trans. 2, *1977*, 1085.
13. Challis B. C., Challis J. A., McDermott I. R.: J. Chem. Soc., Perkin Trans. 2, *1979*, 634.
14. Misra B. N., Pande C. S., Mahajan R. K., Jassal J. K., Mehta I. K.: Indian J. Chem., B *15* 49 (1977).
15. Williams D. H., Fleming I. in: *Spectroscopic Methods in Organic Chemistry*, p. 61. McGraw-Hill, London 1966.
16. McCormack M. T.: *Thesis*. National University of Ireland, Dublin 1976.
17. Misra B. N., Singha A. S., Chauhan G. S., Sharma R. P.: Indian J. Chem., B *23* 728 (1984).
18. Curtin D. Y., Miller L. I.: J. Am. Chem. Soc. *89*, 637 (1967).

Translation revised by J. Hetflejš.