PREPARATION, CHARACTERIZATION AND STEREOCHEMISTRY OF MIXED ANHYDRIDES OF O-ALKYLBENZOHYDROXIMIC ACID

Sunita LAKHANPAL, G. C. RAO and Bhupendra Nath MISRA

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

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A number of stable isoimides have been prepared by acylation and sulfonylation of O-benzylbenzohydroxamic acid and O-butylbenzohydroxamic acid by anisoyl chloride, benzoyl chloride phenoxyacetyl chloride, *p*-toluenesulfonyl chloride, benzenesulfonyl chloride and *p*-nitrobenzenesulfonyl chloride in the presence of pyridine. Spectral investigations indicate that the products have the mixed anhydride structure with (*Z*)-configuration. Corresponding (*E*)-isomers and isomeric N-acetylated products if formed, could not be isolated. An attempt has been made to study 1,3-rearrangement of the mixed anhydrides by thermal method.

Isoimides usually are unstable compounds although their involvement as intermediates in many reactions including carbodiimide mediated condensations has been proposed[1]. Isoimides have also been proposed as models in active CO_2 transfer by the coenzyme biotin[2]. O-Acylisoimides were isolated and used with limited succes as acyl transfer agents in peptide synthesis[3]. Curtin and Miller[4] were succesful in isolating N-(2,4-dinitrophenyl)benzimidoyl benzoates and the stability of these compounds was attributed to the reduced nucleophilicity of imino nitrogen due to the presence of electron withdrawing nitro groups in benzene ring attached to the imino nitrogen. O-Alkylhydroxamic acids can act as substrates for the preparation of isoimides since the resulting isoimides are expected to be stabilized owing to the reduced nucleophilicity of imino nitrogen attached to the electronegative oxygen atom. Cooley and Misra[5] were the first to isolate *p*-toluenesulfonyl N-benzyloxybenzimidate from the reaction of sodium salt of O-benzylbenzohydroxamic acids with *p*-toluenesulfonyl chloride in benzene. Later on Ward et al.[6] investigated acylation of a number of hydroxamic acids and obtained both O- and N-acetylated products depending upon the structure of hydoxamic acids and the metal ion present in the ambident anion. Hegarty and coworkers[7] claimed to have isolated (*Z*)-isomers of O-acetylated products. Misra et al.[8] investigated the reactions of a number of

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O,N-diacylhydroxylamines with benzenesulfonyl chloride in pyridine and obtained O-benzenesulfonylated compound as major products. Recently Misra et al.[9] have isolated a number of O-acylated and O-sulfonylated products from acylation and sulfonylation of O-benzylbenzohydroxamic acid. As an extension of earlier work, we report in the present article acylation and sulfonylation of O-benzyl and O-butylbenzohydroxamic acids in pyridine using a variety of acylating agents which include: anisoyl, benzoyl, phenoxyacetyl and *p*-toluenesulfonyl chloride. The structure of the resulting mixed anhydrides has been determinated and an attempt has been made to study 1,3[O→N] acyl migration by thermal method.

EXPERIMENTAL

All melting points were determined in open capillaries and are uncorrected. The progress of all reactions was monitored by TLC on silica gel-G using benzene–ethyl acetate; benzene–petroleum ether as eluants. Spots were developed by iodine vapors. IR spectra were recorded in KBr on a Perkin Elmer 337 spectrophotometer ($\tilde{\nu}_{max}$ in cm^{-1}), ^1H NMR spectra in $CDCl_3$ on a FT-100 NMR (Jeol) instrument, using TMS as an internal standard (chemical shifts in δ (ppm)).

TABLE I
Analytical data on mixed anhydrides *IV*

Compound	Formula M.w.	M.p. °C	Yield %	Calculated/Found			
				% C	% H	% N	% S
IVa	$C_{22}H_{19}NO_4$	106	60	76·52	5·50	4·05	—
	261·4			76·41	5·42	4·01	
IVb	$C_{20}H_{16}N_2O_6S$	136	62	60·30	4·02	3·52	8·04
	384·3			60·21	3·94	4·41	8·01
IVc	$C_{18}H_{21}NO_4S$		52	62·24	6·05	4·03	9·22
	247·4			62·08	5·98	3·97	9·13
IVd	$C_{17}H_{19}NO_4S$	114	58	61·26	5·70	4·20	9·60
	333·3			61·18	5·61	4·11	9·48
IVe	$C_{19}H_{21}NO_4$	186—190	61	69·72	6·42	4·28	—
	327·4			69·62	6·38	4·25	
IVf	$C_{18}H_{19}NO_3$	25	68	72·72	6·39	4·71	—
	297·3			72·60	6·28	4·63	
IVg	$C_{19}H_{21}NO_4$	60—65	71	73·31	6·75	4·50	—
	327·4			73·20	6·62	4·39	

Pottasium benzohydroxamate was prepared by the modified method of Jeanrenaud[10]. O-Benzylbenzohydroxamic acid was prepared by following the method of Cooley et al.[11]. The yield of the product after recrystallization from ethanol was 52%, m.p. 103–104°C. Infrared spectrum: 1 650 (CO), 3 300 (NH).

TABLE II

IR data of mixed anhydrides *IV*

Compound	cm^{-1}
IVa	1 740 [ν(C=O)], 1 575 [ν(C=N)], 747 [δ(=C—H), aromatic]
IVb	1 370 [$\nu(SO_2)$], 1 644 [ν(C=N)], 1 155 [ν(O—SO_2)], 1 560 [$\nu(NO_2)$], 835 [δ(=C—H), aromatic]
IVc	1 370 [$\nu(SO_2)$], 1 644 [ν(C=N)], 1 158 [ν(O—SO_2)], 795 [δ(=C—H), aromatic]
IVd	1 370 ($\nu(SO_2)$], 1 640 [ν(C=N)], 1 160 [ν(O—SO_2)], 760 [δ(=C—H), aromatic]
IVe	
IVf	1 738 [ν(C=O)], 1 581 [ν(C=N)], 745 [δ(=C—H), aromatic]
IVg	1 740 [ν(C=O)], 1 599 (ν(C=N)], 747 [δ(=C—H), aromatic]

TABLE III

^{1}H NMR chemical shifts of mixed anhydrides *IV*

Compound	δ, ppm
IVb	5·1 s, 2 H (OCH_2); 7·35–7·68 m, 15 H (ArH)
IVc	0·9 t, 3 H (CH_3), 1·5 m, 4 H (CH_2CH_2); 2·45 t, 3 H ($ArCH_3$); 4·1 t, 2 H (OCH_2); 7·2–8·05 m, 9 H (ArH)
IVd	0·9 t, 3 H (CH_3); 1·4 m, 4 H (CH_2CH_2); 4·2 t, 2 H (OCH_2), 7·2–8·3 m, 10 H (ArH)
IVe	0·91 t, 3 H (CH_3); 1·5 m, 4 H (CH_2CH_2); 4·0 t, 2 H (OCH_2); 4·5 s, 3 H (OCH_3); 7·35–7·95 m, 9 H (ArH)
IVf	0·91 t, 3 H (CH_3); 1·42 m, 4 H (CH_2CH_2); 4·0 t, 2 H (OCH_2); 7·36–7·91 m, 10 H (ArH)
IVg	0·98 t, 3 H (CH_3); 1·49 m, 4 H (CH_2CH_2); 4·1 t, 2 H (OCH_2); 5·3 s, 2 H ($COCH_2$); 7·1–8·0 m, 9 H (ArH)

O-*Butylbenzohydroxaminic acid* was prepared similarly. The product was obtained as a viscous liquid having boiling point 182°C in a yield of 65%. ^{1}H NMR spectrum: 0·9 t, 3 H (CH_3); 1·45 m, 4 H (2 × CH_2); 3·9 t, 2 H (OCH_2); 7·42–7·9 m, 5 H (ArH); 8·9 s, 1 H (NH). For $C_{11}H_{15}NO_2$ (193·2) calculated: 68·37% C, 7·82% H, 7·25% N; found: 68·1% C, 8·6% H, 7·6% N.

Preparation of *p*-Nitrobenzenesulfonic O-Benzylbenzohydroximic Anhydride

O-Benzylhydroxamic acid (2·27 g, 0·01 mol) in 20–25 ml of pyridine was treated with (1·98 g, 0·01 mol) of *p*-nitrobenzenesulfonyl chloride. The reaction mixture was stirred for 24 h. The reaction was monitored by TLC using benzene–petroleum ether (3 : 7) as eluants. After the completion of the reaction, the excess pyridine was removed and the residue was washed with water and then extracted with chloroform (3 × 30 ml). The chloroform layer was extracted successively with saturated $NaHCO_3$ solution (2 × 50 ml) 10% HCl and water (2 × 50 ml), dried over anhydrous Na_2SO_4 and concentrated to half of its volume. In refrigerator the product separated as white crystals. After crystallization from ether–petroleum ether the yield was 62%, m.p. 136°C. For $C_{20}H_{16}N_2O_6S$ (412·4) calculated: 58·25% C, 3·88% H, 6·79% N, 23·28% O, 7·76% S; found: 58·05% C, 3·82% H, 6·71% N, 22·9% O, 7·72% S. Infrared spectrum: 1 370 (SO_2), 1 155 (OSO_2), 1 644 (C=N), 835 (aromatic), 1 560 (NO_2). ^{1}H NMR spectrum: 5·1 s, 2 H (OCH_2); 7·35–7·68 m, 14 H (ArH).

By following the above method mixed anhydrides of O-butylbenzohydroximic acid were also prepared by using *p*-toluenesulfonyl chloride, benzenesulfonyl chloride, anisoyl chloride, benzoyl chloride and phenoxyacetylchloride as acylating agents.

Physical and spectroscopic data of the mixed anhydrides are presented in Tables I, II and III.

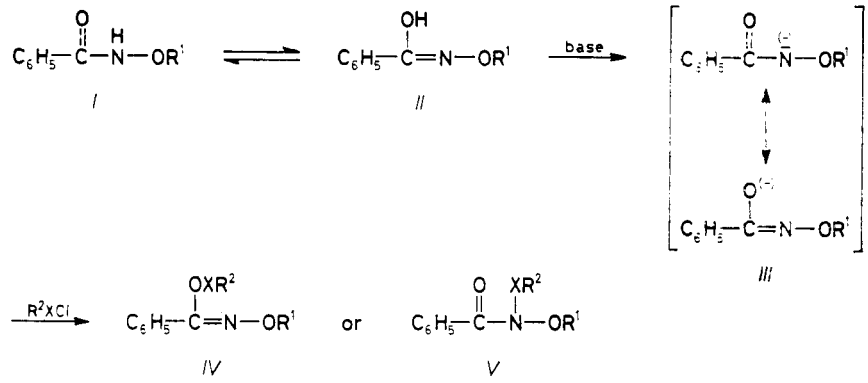
Attempted Thermal 1,3-Rearrangement of *p*-Nitrobenzenesulfonic O-Benzylbenzohydroximic Anhydride

The title compound (0·200 g) in about 50 ml dioxane was refluxed for 8 h. The solvent was distilled off and the residue was recrystallized from ether. TLC showed that no rearrangement had occurred. The IR spectrum of the product was identical with that of the starting material.

RESULTS AND DISCUSSION

O-Alkylhydroxamic acids in solution can exist as a mixture of oxo and imino tautomeric forms *I* and *II*. Treatment with acylating agents in pyridine may give rise to both O- and N-acylated products *IV* and/or *V*, via the ambident anion *III* (Scheme 1).

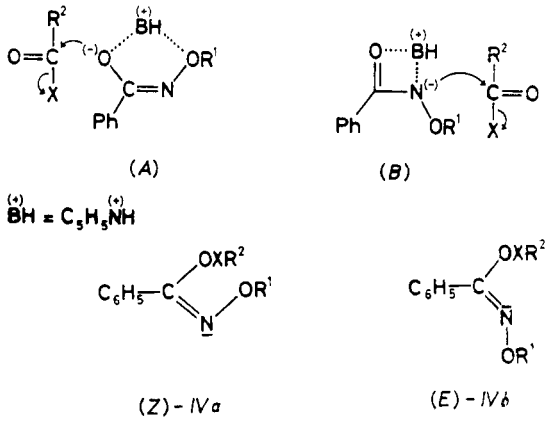
All the O-acylated products in IR spectra showed strong absorption in the region 1 740–1 752 cm^{-1} assigned to ester carbonyl function. Vinyl acetate[12] and O-acylurea[13] also show absorption in the same region. The infrared spectra of sulfonylated products (Table II) showed strong absorption in the region 1 152–1 160 cm^{-1} assigned to OSO_2 group. Moreover all O-acylated and sulfonylated products showed absorption bands in the region 1 599–1 614 cm^{-1} attributed to C=N function. IR spectroscopic data indicate that the products presumably have the mixed anhydride structure *IV*. The mixed anhydride *IV*, however, can exist as (*Z*)- or (*E*)-isomers (*IVa* or *IVb*).



IV, V	R^1	R^2	X
a	$CH_2C_6H_5$	$C_6H_5OCH_2$	CO
b	$CH_2C_6H_5$	*p*-$NO_2C_6H_4$	SO_2
c	C_4H_9	*p*-$CH_3C_6H_4$	SO_2
d	C_4H_9	C_6H_5	SO_2
e	C_4H_9	*p*-$CH_3OC_6H_4$	CO
f	C_4H_9	C_6H_5	CO
g	C_4H_9	$C_6H_5OCH_2$	CO

SCHEME 1

The (*Z*)-isomer *IVa* having lone electron pair *trans* to the acyloxy group is expected to be more stable than the corresponding (*E*)-isomer *IVb*. In order to gain more information on the configuration of C=N double bond attemts were made to



effect thermal rearrangement of the mixed anhydrides. On heating *p*-nitrobenzenesulfonic O-benzylbenzohydroximic anhydride in dioxane for 8 h, no change in TLC or IR spectrum was observed. The failure of mixed anhydrides rapidly rearrange to imides upon heating suggested that the mixed anhydrides in the present investigation were formed in (*Z*)-configuration. The correct assignment of the configuration of the mixed anhydrides, however, remains to be investigated further.

The exclusive formation of O-acylated products in preference to the N-acylated product can be explained by assuming that acylation perhaps proceeds through the formation a five membered ion pair (*A*). Formation of N-acylated products on the contrary would have required the involvement of a relatively less stable ion pair (*B*).

It is concluded that in the presence of base acylation and sulfonylation of O-alkylbenzohydroxamic acid gives rise to kinetically controlled O-acylated products whose constitution has been established. More work is needed to establish the stereochemistry of the mixed anhydrides and the study is in progress.

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