Photochemical Studies of a New Group of Isoimides

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Several stable isoimides have been prepared by acylation of *O*-benzyl-4-nitro-, *O*-(1-propyl)-, *O*-(1-propyl)-4-nitro-, *O*-benzyl-4-chloro-, and *O*-allyl-4-chlorobenzohydroxamic acids in pyridine which acted both as a solvent and a weak base. As acyl halides were used methanesulfonyl, 4-toluenesulfonyl, 4-methylbenzoyl, and 4-nitrobenzoyl chlorides. The resulting mixed anhydrides were characterized by chemical and spectroscopic methods. Thermal as well as photochemical rearrangement of the mixed anhydrides has been attempted. Structure elucidation of the rearranged products was performed by spectroscopic methods.

Acylation of hydroxylamine by ester to give hydroxamic acids is a well-known reaction [1]. Alkylation of hydroxamic acids has been extensively investigated [2—5] and formation of both monoalkylated and dialkylated products has been reported. By controlling the reaction conditions as well as the ratio of potassium or barium salts of hydroxamic acid to alkylating agent, it is possible to selectively prepare monoalkylated products in major amount. Comparatively little studies have been reported on acylation of *O*-alkylhydroxamic acids. *Misra et al.* [6] were the first to attempt sulfonylation of a number of *O*-alkylhydroxamic acids and reported on the formation of 4-toluenesulfonyl-*N*-benzyloxybenzimidate from the reaction of 4-toluenesulfonyl chloride with sodium salt of *O*-benzylbenzohydroxamic acid in benzene. They established the structure of the imino ether compound by spectral analysis. Reaction of acetyl chloride with potassium and silver salts of several *N*-acyl-*O*-alkylhydroxylamines was studied by *Ward* and coworker [3]. They observed the formation of both *O*- and *N*-acylated products, depending upon the structure of *O*-alkylhydroxamic acids, and the nature of the metal ion. It was not mentioned whether the *N*-acylated products isolated by them were the products of rearrangement of the initially formed *O*-acylated products. *McCarthy* and *Hegarty* [7] investigated the reaction of acetyl chloride with the ambident anions derived from some *O*-alkylbenzohydroxamic acids and reported on the exclusive formation of *O*-acetylated products. Later on *Challis et al.* [8] studied acylation of a number of *O*-benzylbenzohydroxamic acids by acetic anhydride and pyridine in organic solvents in the presence of bromide ion and reported that the reaction proceeds by the primary formation of (*Z*)-acetic *O*-benzylbenzohydroximic anhydride. Prompted by the findings of *Challis et al.* [8], *Misra et al.* [9, 10] investigated acylation and sulfonylation of a number of *O*-alkyl- and *O*-acylhydroxamic acids and reported the formation of *O*-acylated and sulfonylated products in major amounts. Isoimides, in general, are unstable compounds. However, their intermediacy in many reactions has been reported [11]. Isoimides have been proposed as models in active CO_2 transfer by the coenzyme biotin [12]. *O*-Acylisoimides were isolated and used with limited success as acyl transfer agents in peptide synthesis [13]. *Curtin* and *Miller* [14] were successful in isolating *N*-(2,4-dinitrophenyl)benzimidoyl benzoates and the stability of the compound 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 atom. Mixed anhydrides prepared by *Misra et al.* [15] were found to be thermally stable and it was concluded that the mixed anhydrides were formed in *Z* configuration. *Z* isomers may be thermally stable but they should undergo isomerization to *E* isomers upon photolysis and the *E* isomers may be rearranged easily to *N*-acylated products by O—N acyl 1,3-migration. In order to examine this hypothesis, in the present work several mixed anhydrides were photolyzed and the resulting products have been characterized by spectral methods.

EXPERIMENTAL

All melting points were determined in open capillaries and are uncorrected. The progress of all reactions was monitored by thin-layer chromatography (TLC) on silica gel G using benzene—ethyl acetate

Table 1. Physical and Spectral Data of *O*-Alkylbenzohydroxamic Acids

Compound	Yield/% M.p./°C	IR $\tilde{\nu}$/cm^{-1}	^{1}H NMR δ
Ia	54 174—175	1650 (CO), 3300 (NH), 1360, 1570 (NO_2)	5.12 (s, 2H, $H_{benzilic}$), 7.30 (m, 9H, H_{arom})
Ib	56 58	1655 (CO), 3400 (NH)	1.03 (t, 3H, CH_3), 1.75 (q, 2H, CH_2) 4.12 (t, 2H, OCH_2), 7.24 (m, H, H_{arom})
Ic	59 80—81	1658 (CO), 3250 (NH), 1395, 1575 (NO_2)	1.03 (t, 3H, CH_3), 1.80 (q, 2H, CH_2) 4.05 (t, 2H, OCH_2), 7.17 (m, H, H_{arom})
Id	62 122	1660 (CO), 3300 (NH), 735 (C—Cl)	5.20 (s, 2H, $H_{benzilic}$), 7.32 (m, 9H, H_{arom})
Ie	60 90—92	1640 (CO), 3200 (NH), 690 (C—Cl)	4.45 (s, 2H, OCH_2), 5.2—5.3 (d, 2H, $=CH_2$) 7.3—7.7 (m, 4H, H_{arom})

(φ_r = 8 : 2) as an eluant. Spots were developed by iodine vapours. IR spectra were recorded in KBr on a Perkin—Elmer 337 spectrophotometer ($\tilde{\nu}_{max}$/cm^{-1}). ^{1}H NMR spectra were taken in $CDCl_3$ on a FT-100 NMR (Jeol) instrument using TMS as an internal standard (chemical shifts δ). UV spectra were recorded in Beckman DU-6 spectrophotometer in acetone-free methanol.

Potassium salt of benzohydroxamic acid was prepared by the modified method of *Jeanrenaud* [16]. *O*-Benzyl-4-nitro- (*Ia*), *O*-(1-propyl)- (*Ib*), *O*-(1-propyl)--4-nitro- (*Ic*), *O*-benzyl-4-chloro- (*Id*), and *O*-allyl-4-chlorobenzohydroxamic (*Ie*) acids were prepared by following the method of *Cooley et al.* [17]. The physical and spectral data of the above compounds are presented in Table 1.

4-Y-Benzoic or 4-Toluenesulfonic, *O*-(Alkyl or Benzyl)-4-X-benzohydroximic Anhydride *IVa—IVf*

To a solution of *O*-(1-propyl)benzohydroxamic acid (1.76 g; 0.01 mol) in 20—25 cm^3 of pyridine, methanesulfonyl chloride (1.14 g; 0.01 mol) was added. The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction, excess of pyridine was distilled off and the residue was washed with water (3 × 50 cm^3) portions of chloroform. The chloroform layer was extracted successively with saturated sodium bicarbonate solution (2 × 50 cm^3), 10 % HCl solution (2 × 50 cm^3), and water (2 × 50 cm^3) and was dried over anhydrous sodium sulfate. Dried chloroform layer was concentrated to the half of its volume and kept in a refrigerator when the product appeared as crystals. The product *IVa* was recrystallized from ether—petroleum ether, in a yield of 70 %, m.p. = 139—140 °C. For $C_{11}H_{15}NO_4S$ w_i(calc.): 51.34 % C, 5.87 % H, 5.44 % N, 12.46 % S; w_i(found): 51.20 % C, 5.32 % H, 5.32 % N, 12.41 % S. IR spectrum, $\tilde{\nu}$/cm^{-1}: 1645 ν(C=N), 1308 ν(SO_2), 1150 ν(OSO_2). UV spectrum (acetone), λ_{max}/nm (log ε): 300 (3.09). ^{1}H NMR spectrum ($CDCl_3$), δ: 1.08 (t, 3H, CH_3), 1.40 (s, 3H, SO_2CH_3), 1.73—1.77 (m, 2H, CH_2), 3.47 (t, 2H, OCH_2), 7.46 (m, 5H, H_{arom}).

4-Nitrobenzoic *O*-(1-propyl)-4-nitro- (*IVb*), 4-methylbenzoic *O*-(1-propyl)-4-nitro- (*IVc*), 4-toluenesulfonic *O*-benzyl-4-nitro- (*IVd*), 4-toluenesulfonic *O*-benzyl-4-chloro- (*IVe*), and 4-nitrobenzoic *O*-allyl-4-chlorobenzohydroximic (*IVf*) anhydrides were prepared by the above method using 4-nitrobenzoyl, toluyl, and 4-toluenesulfonyl chlorides as acylating agents.

Table 2. Physical Data of the Mixed Anhydrides *IV*

Compound	Formula M_r	M.p. °C	Yield %	w_i(calc.)/% w_i(found)/% C	H	N	S
IVa	$C_{11}H_{15}NO_4S$ 257.3	140	70	51.34 51.20	5.87 5.32	5.44 5.32	12.46 12.41
IVb	$C_{17}H_{16}NO_5$ 314.3	135	65	64.96 64.89	5.13 5.07	4.45 4.37	– –
IVc	$C_{18}H_{18}N_2O_5$ 342.3	150	50	63.15 63.01	5.29 5.10	8.18 8.09	– –
IVd	$C_{21}H_{18}N_2O_6S$ 426.4	160	80	59.14 59.12	4.25 4.16	6.56 6.43	7.51 7.43
IVe	$C_{21}H_{18}NO_4SCl$ 429.7	172—173	79	58.69 58.40	4.22 4.13	6.51 6.45	7.46 7.39
IVf	$C_{17}H_{13}N_2O_5Cl$ 360.5	78—79	52	56.63 56.52	3.63 3.59	7.76 7.60	– –

Table 3. IR Spectral Data of Mixed Anhydrides *IV*

Compound	$\tilde{\nu}$/cm^{-1}						
	ν(CO)	ν(C=N)	ν(SO_2)	ν(OSO_2)	ν(NO_2)		γ(C—H)
IVa	–	1645	1308	1150	–	–	800
IVb	1695	1640	–	–	1375	1570	850
IVc	1690	1610	–	–	1375	1575	850
IVd	–	1645	1303	1155	1365	1575	850
IVe	–	1645	1305	1155	–	–	845
IVf	1720	1604	–	–	1370	1565	847

Table 4. ^{1}H NMR Spectral Data of the Mixed Anhydrides *IV*

Compound	Chemical shift δ
IVa	1.08 (t, 3H, CH_3), 1.40 (s, 3H, SO_2CH_3), 1.73—1.77 (m, 2H, CH_2), 3.97 (t, 2H, OCH_2), 7.46 (m, H_{arom})
IVb	0.99 (t, 3H, CH_3), 1.68 (m, 2H, CH_2), 3.98 (t, 2H, OCH_2), 7.47 (m, H_{arom})
IVc	1.0 (t, 3H, CH_3), 1.64 (m, 2H, CH_2), 4.01—4.05 (t, 2H, OCH_2), 7.27 (m, H_{arom})
IVd	1.6 (s, 3H, CH_3), 5.05 (s, $CH_2C_6H_5$), 7.42 (m, H_{arom})
IVe	1.67 (s, 3H, CH_3), 5.01 (s, $CH_2C_6H_5$), 7.40 (m, H_{arom})
IVf	4.45 (d, 2H, $=CH_2$), 3.45 (d, 2H, OCH_2), 6.0—6.2 (m, 1H, =CH), 7.2—7.65 (m, H_{arom})

Table 5. UV Spectral Data of the Isoimides and Photochemically Rearranged Products

Compound	λ_{max}/nm (log ε)	
	Isoimide	Photochemically rearranged products
IVa	300 (3.08)	210 (3.04)
IVd	362 (3.16)	307 (3.02)
IVe	402 (3.22)	307 (3.00)
IVf	304 (3.08)	200 (2.99)

Physical and spectral data of the resulting mixed anhydrides are presented in Tables 2—5.

Attempted Thermal 1,3-Rearrangement of 4-Nitrobenzoic *O*-Allyl-4-chlorobenzohydroximic Anhydride (*IVf*)

The title compound (200 mg) in about 50 cm^3 of dioxane was refluxed for 12 h. The solvent was distilled off and the residue was recrystallized from petroleum—ether. TLC showed that no rearrangement had occurred. The R_f value and the IR spectrum of the product were identical to those of the starting material.

Photochemical O—N Acyl 1,3-Migration in Isoimides

The photochemical rearrangement was carried out by photolysis of 4-toluenesulfonic *O*-benzyl-4-chlorobenzohydroximic anhydride (*IVe*) (200 mg) dissolved in 50 cm^3 of acetone-free methanol using a mercury lamp (λ = 254 nm) for 72 h. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed by distillation and the crude product isolated was recrystallized from chloroform in a yield of 80 %. UV spectrum (acetone), λ_{max}/nm (log ε): 307 (3.0). Photochemical rearrangement of other isoimides was carried out by the above method and UV spectral data of the rearranged products are given in Table 5.

RESULTS AND DISCUSSION

O-Alkylhydroxamic acid *I* in solution tautomerizes to *O*-alkylhydroximic acid *II*. *O*-Alkylhydroxamic acid in appropriate solvent in the presence of pyridine as a base forms the ambident anion *III* which reacts with acyl halides to give *O*-acylated or *N*-acylated products *IV* or *V*.

In aprotic solvent, the negative charge of the ambident anion is located on the more electronegative oxygen atom. Upon treatment of this anion with acyl halide, the acyl group becomes preferentially attached to the more electronegative oxygen atom to give products having mixed anhydride structure *IV*. *N*-Acylated products, if at all formed, could not be isolated. Preferential *O*-acylation can be explained by invoking the theories of *Kornblum et al.* [18] concerning orientation of alkyl group on the ambident anion.

All the *O*-acylated products in IR spectra showed strong absorption in the region $\tilde{\nu}$ = 1690—1695 cm^{-1} assigned to the ester carbonyl function. Vinyl acetate [19] and *O*-acylurea [20] also show absorption in this region. The IR spectra of sulfonylated products (Table 3) showed absorption at $\tilde{\nu}$ = 1155—1308 cm^{-1} assigned to the OSO_2 group. Further, all the acylated and sulfonylated products showed absorption band in the region $\tilde{\nu}$ = 1610—1645 cm^{-1} attributed to the C=N function. IR spectroscopic data indicate that the products presumably have the mixed anhydride

structure *IV*. Similar arguments were given earlier by *Lakhanpal Sunita et al.* [15] for elucidating the structure of mixed anhydrides prepared by acylation of other *O*-alkylhydroxamic acids. The mixed anhydride *IV*, however, can exist as *Z* or *E* isomer.

In order to decide whether *Z* or *E* isomer is formed, several mixed anhydrides were subjected to facile O—N acyl 1,3-migration by thermal and photochemical methods. No change in the TLC and IR was observed upon refluxing mixed anhydride (200 mg) dissolved in dioxane for 12 h and this indicated that the mixed anhydride presumably was formed in the more stable *Z* configuration.

The mixed anhydrides (*IVa, IVd—IVf*) were photolyzed in acetone-free methanol using a mercury lamp λ = 254 nm for 72 h. The progress of the photochemical reaction was monitored by TLC and the products were isolated after the completion of the reaction. The R_f values of the photolyzed compounds were found to be different from those of the original mixed anhydrides. Further, all the products showed λ_{max} value in UV spectra different from those of the mixed anhydrides. λ_{max} values for the photolyzed products (Table 5) were less than those of the original mixed anhydrides. This indicates that photolysis of mixed anhydride leads to isomerization from the more stable *Z* isomer to less stable *E* isomer which then may undergo facile O—N acyl 1,3-migration in the following manner (Scheme 1).

The mixed anhydrides *IV* owing to the extended conjugation are expected to absorb at longer wavelength (λ_{max}).

Upon photolysis, mixed anhydrides undergo facile O—N acyl 1,3-migration to give products having imide structure *V*. In these compounds, conjugation is cut short and therefore compounds *V* are expected to absorb at shorter wavelength. Table 5 shows that all the mixed anhydrides upon photolysis give products which absorb at shorter wavelength in the UV region. It may be concluded that acylation of *O*-alkylhydroxamic acids affords mixed anhydrides having *Z* configuration. The *Z* isomers are thermally stable but upon photolysis undergo facile O—N acyl 1,3-migration *via E* isomers. Complete structure elucidation of rearranged products, however, remains to be established.

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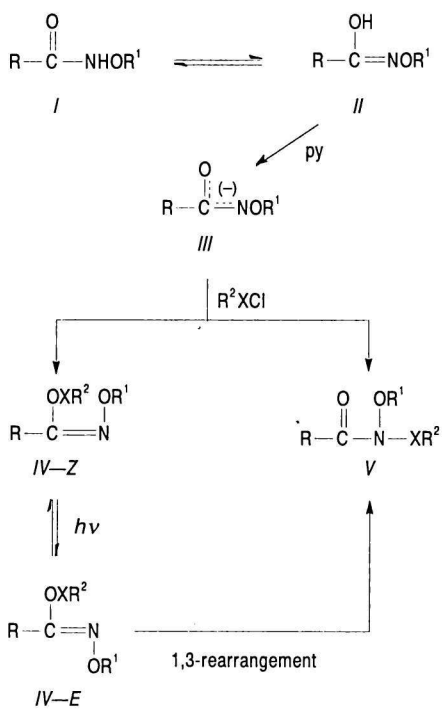

IV	R	R^1	R^2	X
a	C_6H_5	C_3H_7	CH_3	SO_2
b	4-$NO_2C_6H_4$	C_3H_7	4-$NO_2C_6H_4$	CO
c	4-$NO_2C_6H_4$	C_3H_7	4-$CH_3C_6H_4$	CO
d	4-$NO_2C_6H_4$	$CH_2C_6H_5$	4-$CH_3C_6H_4$	SO_2
e	4-ClC_6H_4	$CH_2C_6H_4$	4-$CH_3C_6H_4$	SO_2
f	4-ClC_6H_4	$CH_2CH{=}CH_2$	4-$NO_2C_6H_4$	CO

Scheme 1

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One-Pot Base-Catalyzed Condensation Reactions of Activated Nitriles and 2-Hydroxy-1-naphthalenecarbaldehyde with Different Ketones

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Several new naphtho[1′,2′:5,6]pyrano[2,3,4-*de*](pyrido[2,3-*d*]pyrimidine), naphtho[1′,2′:5,6]-pyrano[2,3-*d*]pyrimidine, and naphtho[2,1-*b*]pyran derivatives were prepared by a one-pot condensation reaction of malononitrile and 2-hydroxy-1-naphthalenecarbaldehyde (*I*) in the presence of different kinds of ketones and ammonium acetate. The effect of solvents and different basic catalysts on the reaction of *I* with cyanoacetamide or ethyl cyanoacetate in the presence of different ketones was also investigated.

Previous reports have shown that pyran derivatives possess pronounced biological properties [1]. On the other hand, substituted pyridines showed acaricidal, insecticidal, and herbicidal activities [2]. Moreover, pyrimidines are important analgesic and anti-inflammatory [3, 4] agents. So, compounds having a combination of naphthopyran with pyridine and/or pyrimidine moieties can be expected to possess marked biological properties. It has been reported that malononitrile condenses with cresotaldehyde (3-methyl- or 4-methyl-2-hydroxybenzaldehyde) in the presence of ammonium acetate to give the substituted benzopyran-3-carbonitrile derivatives [5]. When methyl ethyl ketone is added to the reaction mixture, the substituted nicotinonitrile derivatives are formed.

Thus, in an extension to our previous work [6—8] for synthesis of novel heterocyclic fused-ring systems of potential activity, we report herein on the synthesis of some new heterocycles that incorporate both naphthopyran, pyridine and/or pyrimidine moieties *via* one-pot base-catalyzed condensation of 2-hydroxy-1-naphthalenecarbaldehyde (*I*) with activated nitriles and different ketones. The produced compounds might have extended and/or improved biological activities.

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EXPERIMENTAL

Melting points are not corrected. The IR spectra (KBr) of the prepared compounds were measured on a Pye—Unicam SP 2000 spectrophotometer. EIMS (70 EV) were recorded on GC—MS apparatus, QP-1000 EX (Schimadzye, Japan).

Derivatives *II—XV*

Characterization data for the prepared compounds are given in Table 1.

Method A — Reaction of Activated Nitriles with 2-Hydroxy-1-naphthalenecarbaldehyde (I)

A mixture of compound *I* (0.03 mol), activated nitrile (0.03 mol), and ammonium acetate (0.05 mol) or triethylamine (2—3 drops) in ethanol or glacial ace-