The Synthesis and Properties of 4-Acetoxy-2,3-dihydro-3-oxo-4*H*-naphth[1,2-*b*] [1,4]oxazine, an Analog of Known Carcinogenic Hydroxamic Acids

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A synthesis of 4-acetoxy-2,3-dihydro-3-oxo-4*H*-naphth[1,2-*b*][1,4]oxazine (**4***a*) from 2-nitroso-1-naphthol is described. This compound (**4***a*) is substituted by various nucleophiles at position 5, with loss of the *N*-acetoxy group; in contrast, it did not react at physiological p*H* with the biological nucleophile methionine. On heating, **4***a* rearranges to the 2- and 5-acetoxy isomers.

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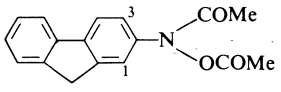
On décrit une synthèse de l'acétoxy-4 dihydro-2,3 oxo-3 [4*H*]-naphth [1,2-*b*] oxazine-1,4 (**4***a*) à partir du nitroso-2 naphthol-1. Le composé (**4***a*) subit des réactions de substitution par divers nucléophiles en position 5 avec perte du groupe *N*-acétoxy; toutefois il ne réagit pas au p*H* physiologique avec la méthionine agissant comme nucléophile biologique. Par chauffage, **4***a* se réarrange dans ses isomères acétoxy-2 ou -5. [Traduit par le journal]

N-Acetoxy-2-acetylaminofluorene (**1**) is a known carcinogenic compound which reacts *in vitro* with tissue nucleophiles such as methionine, at physiological p*H*. Attack by methionine occurs at positions 1 and 3 yielding 2-acetylamino-1-methylthiofluorene (**2**) and the corresponding 3-methylthio isomer (1, 2). *N*-Hydroxy-



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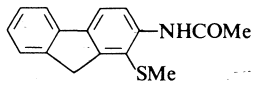

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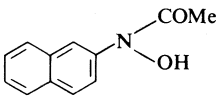

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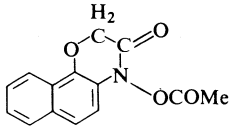
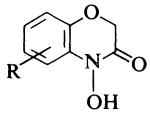


4*a*



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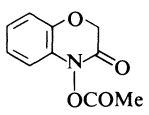

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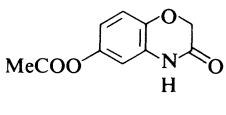

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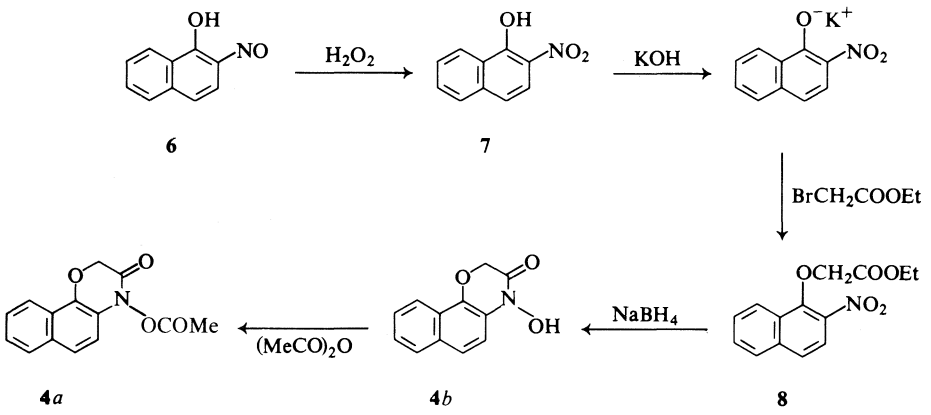
2-acetylaminonaphthalene (**3**) and compounds with related structures are also carcinogenic (3). So far, only acyclic hydroxamic acid derivatives such as **1** and **3** have been evaluated for their carcinogenic properties and their ability to react under mild conditions with tissue nucleophiles. We wished to determine whether cyclic hydroxamic acids possessed similar properties and selected 4-acetoxy-2,3-dihydro-3-oxo-4*H*-naphth[1,2-*b*][1,4]oxazine (**4***a*) as a suitable compound for investigation in view of its structural similarities to both compounds **1** and **3**, and its resemblence to 2*H*-1,4-benzoxazine hydroxamic acids (**5**) whose syntheses and properties have been previously investigated by us (4). Compound **4***a* possesses an *N*-acetoxy grouping and, since acetate is a good leaving group, **4***a* would be expected to be very reactive to nucleophilic reagents. As in compounds **1** and **3**, the position *para* to the N atom is blocked and, thus, nucleophilic attack might be expected at the *ortho* position.

The synthesis of **4***a* was achieved using 2-nitroso-1-naphthol (**6**) as starting material according to Scheme 1. Oxidation of **6** with hydrogen peroxide in acetic acid, according to a general procedure (5), gave 2-nitro-1-naphthol (**7**) which was converted to its potassium salt, then alkylated with ethyl bromoacetate to give ethyl (2-nitro-1-naphthoxy)acetate (**8**). The i.r. and p.m.r. spectra of this compound were consistent with its structure. Catalyzed sodium borohydride reduction (6) of **8** gave a product, $C_{12}H_9NO_3$, which was deduced to be the hydroxamic acid, 2,3-dihydro-4-hydroxy-3-oxo-

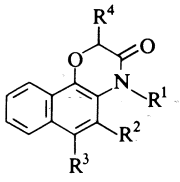


SCHEME 1

4*H*-naphth[1,2-*b*][1,4]oxazine (**4***b*) for the following reasons. It gave a purple color when treated with aqueous ferric chloride and was soluble in dilute sodium hydroxide solution, then reprecipitated on adding dilute hydrochloric acid. It also gave an i.r. spectrum (ν_{max} C=O 1645 and 1698 cm^{-1}) in support of structure **4***b* (7) as well as the expected p.m.r. spectrum which included a D-exchangeable OH signal at δ 10.90 (8, 9). Acetylation of **4***b* to **4***a* proved more difficult than envisaged but **4***a* was eventually obtained by acetylation of **4***b* with acetic anhydride in pyridine. This acetate was also characterized by its elemental analysis and its p.m.r. and i.r. spectra. One carbonyl stretching band was located at 1802 cm^{-1} which is characteristic of the *N*-acetoxy carbonyl group (7, 10).

Initial attempts to prepare **4***a* by reaction of **4***b* with acetyl chloride in benzene or with acetic anhydride in acetic acid were unsuccessful. The reaction product, obtained in 74% yield when **4***b* was treated with acetyl chloride was 5-chloro-2,3-dihydro-3-oxo-4*H*-naphth[1,2-*b*][1,4]oxazine (**4***c*). The same product was also obtained when a solution of **4***a* in benzene was saturated with anhydrous hydrogen chloride. When **4***b* was refluxed with acetic anhydride in acetic acid, 5-acetoxy-2,3-dihydro-3-oxo-4*H*-naphth[1,2-*b*][1,4]oxazine (**4***d*) was obtained in excellent yield. Refluxing a solution of **4***a* in acetic acid also gave **4***d*.

The formation of **4***c* when **4***b* was treated with acetyl chloride can be explained by the initial formation of **4***a* which then further reacted with the nucleophile, Cl^-, generated in the reaction medium. Similarly, when **4***b* was treated with acetic anhydride in acetic acid, the initially formed **4***a* reacted with acetate ions present in the reaction medium. Compound **4***a* was also found to react with dilute aqueous sulfuric acid to give 2,3-dihydro-5-hydroxy-3-oxo-4*H*-naphth-[1,2-*b*][1,4]oxazine (**4***e*), and with sulfuric acid in methanol to give 2,3-dihydro-5-methoxy-3-oxo-4*H*-naphth[1,2-*b*][1,4]oxazine (**4***f*).



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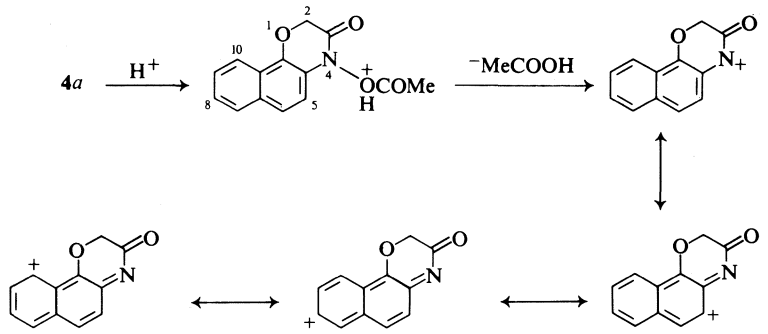
	R^1	R^2	R^3	R^4
a	OCOMe	H	H	H
b	OH	H	H	H
c	H	Cl	H	H
d	H	OCOMe	H	H
e	H	OH	H	H
f	H	OMe	H	H
g	H	H	OCOMe	H
h	H	H	H	OCOMe
k	H	SMe	H	H
m	H	H	H	H

The structural assignments for the products obtained by treating **4***a* with the nucleophiles just described were made mainly as a result of mechanistic considerations, and with supporting p.m.r. data. It is theoretically possible to obtain 5-, 8-, or 10-substituted lactams from **4***a* since three carbonium ion intermediates can be envisaged (Scheme 2) on the expulsion of the

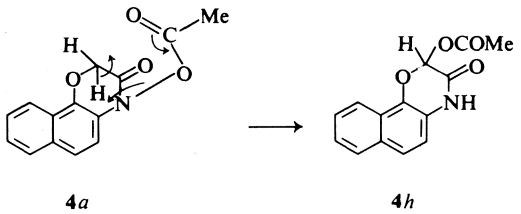


SCHEME 2

acetate group. The p.m.r. spectra of compounds **4***c–f* were quite distinctive. They all exhibited absorptions corresponding to —CH_2CO— and —N*H*—, as well as aromatic signals, each of which was comprised of an intense 1-proton singlet and a 4-proton complex multiplet. Since inter-ring coupling is negligible in naphthalene (11), an intense 1-proton singlet in the aromatic region signified that one of the naphthalene rings had a lone uncoupled proton and thus excluded the possibility that the nucleophiles had attacked the C-8 or C-10 positions.

In the case of the reaction of **4***a* with acetic acid, the possibility was considered that substitution could occur at the C-6 position (→ **4***g*) in light of our recent work (4) on the analogous benzoxazine, 4-acetoxy-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine (**9**), which, on refluxing in acetic acid gave the 6-acetoxy isomer (**10**). However, hydrolysis of the acetate **4***d* gave a phenolic lactam which was identical (i.r., p.m.r., m.p.) with the phenol **4***e* obtained from the reaction of **4***a* with dilute sulfuric acid.

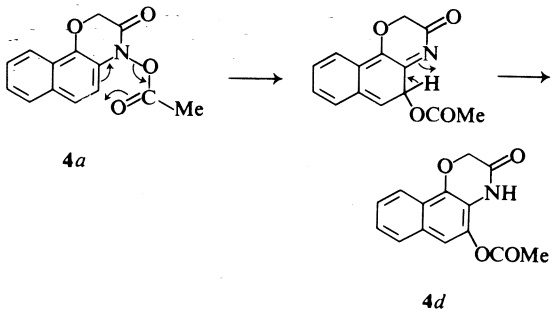
When acetate **4***a* was refluxed in toluene, a mixture of isomeric acetates A and B was obtained. The isolated yields corresponded to a 3.4:1 ratio of A to B but the actual composition as determined by p.m.r. spectroscopy was 52:48. The structure **4***h* (Scheme 3) is assigned to A on



4*a* **4***h*

SCHEME 3

the basis of its p.m.r. spectrum which showed unequivocally that the substituent nucleophile was located on the oxazine ring and not on the naphthalene portion of the molecule. Thus, **4***h* exhibited a 1-proton singlet at δ 6.84 corresponding to the H atom located at C-2, and a 6-proton multiplet at δ 7.28–8.12, indicative of there being six naphthalene protons in the molecule. In contrast, the p.m.r. spectrum of B exhibited a 2-proton singlet at δ 4.82 (O—CH_2—CO), a 1-proton singlet at δ 7.07 (C_6—*H*) and a 4-proton multiplet at δ 7.34–8.12 (remaining aromatic protons), which indicated identity with **4***d*. A mechanism explaining the formation of **4***d* from **4***a* is suggested (Scheme 4).



4*a* **4***d*

SCHEME 4

An examination of Dreiding models of **4***a* confirmed that the molecule can adopt conformations in which the ester carbonyl oxygen atom is in close proximity to C-2 or C-5. This thermal process, **4***a* → **4***d*, is analogous to the well-known Cope rearrangement. It is interesting that a cyclic carbinolamide analog of the antileukemic natural product, maytansine, shows nucleophilic addition reactions resembling those shown by **4***a* (12).

When a solution of **4***a* in ethanol–acetone was added to a solution of methionine in phosphate buffer (p*H* 7.8) at 40° under nitrogen, *i.e.*, conditions under which we have confirmed that **1** is converted to **2**, no methylthio compound (**4***k*) could be detected in the reaction mixture. Only a small amount of **4***m* was isolated and its structure confirmed by comparison with authentic material. Failure of **4***a* to react with methionine was thought to be due to the very low solubility of **4***a* in the solvent employed, so the reaction was repeated in 50% aqueous dimethylformamide. Again no **4***k* was obtained. In both instances, the reaction mixture turned dark purple, presumably indicative of undesired decomposition of **4***a*.

Experimental

Melting points (capillary tube) are uncorrected. Infrared spectra were recorded as Nujol mulls using a Beckman IR-10 spectrophotometer and p.m.r. spectra were obtained using a Varian A-60D spectrometer with DMSO-d_6 as solvent and TMS as the internal standard. Mass spectra were measured on an A.E.I. MS-12 mass spectrometer at an ionizing potential of 70 eV using the direct probe technique. Elemental analyses were performed by Mr. W. Dylke of our faculty.

2-Nitro-1-naphthol (7)

A stirred solution of 2-nitroso-1-naphthol (10 g), 30% hydrogen peroxide (150 ml), and concentrated nitric acid (10 ml, d 1.42) in glacial acetic acid (450 ml) was heated slowly (15 min) to 70° and for a further 15 min at this temperature. The mixture was poured onto ice (750 g) and the title compound (7.91 g), m.p. 126–128° separated (lit. (13) m.p. 128–129°). The product was used without purification in the synthesis of **8**.

Ethyl (2-Nitro-1-naphthoxy)acetate (8)

2-Nitro-1-naphthol (18.9 g) was added with vigorous stirring to a solution of potassium hydroxide (10 g) in absolute ethanol (100 ml). A thick red paste formed. Stirring was contined for a further 0.5 h, then the suspension was filtered and then washed with a mixture of ethanol and ether (1:1 v/v). The red potassium salt was suspended in acetone (75 ml) and dimethylformamide (75 ml) and ethyl bromoacetate (16.7 g) were added, and the resulting mixture was heated under reflux for 18 h. The mixture was filtered to remove potassium bromide and the filtrate flash-evaporated to a viscous brown oil. This was dissolved in chloroform (100 ml) and the chloroform solution was washed several times with water, then dried (K_2CO_3). Evaporation gave a yellow oil which solidified when triturated with cold ethanol. Recrystallization from ethanol gave the title compound (16.9 g) as yellow needles, m.p. 46–47°; i.r. ν_{max} 1750 cm^{-1} (C=O); p.m.r. δ 1.33 (t, 3H, J = 7 Hz, CH_3), 4.32 (q, 2H, J = 7 Hz, CH_2CH_3), 4.82 (s, 2H, —OCH_2CO), 7.58–8.67 (m, 6H, aromatic protons); mass spectrum *m/e* (% relative abundance) 275 (53) (M^+); 229 (44) (M − NO_2); 201 (100).

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.08; H, 4.76; N, 5.08. Found: C, 61. 31; H, 4.82, N, 5.24.

2,3-Dihydro-4-hydroxy-3-oxo-4H-naphth[1,2-b][1,4] oxazine (4b)

A solution of ethyl (2-nitro-1-naphthoxy)acetate (2.75 g) in dioxane (60 ml) was added dropwise over 15 min to a magnetically stirred suspension of 10% Pd–C (0.15 g) in water–dioxane (40:30, 50 ml) containing sodium borohydride (1.50 g). The mixture was stirred for a further 0.5 h and filtered through Celite. The solid remaining was washed with 10% Na_2CO_3 (20 ml) then water (50 ml) and these washings were added to the original filtrate. The combined solution was cooled in an ice bath and concentrated H_2SO_4 was added dropwise with stirring until the solution was acidic. The resulting white precipitate was collected, washed (H_2O) and dried *in vacuo* and yielded **4***b* (1.91 g), m.p. 199° after recrystallization (dioxane); i.r. ν_{max} 1645 and 1698 (C=O), 3100 (OH) cm^{-1}; p.m.r. δ 4.98 (s, 2H, CH_2), 7.40–8.12 (m, 6H, aromatic protons), 10.98 (s, 1H, D-exchangeable, N—OH); mass spectrum *m/e* (% relative abundance) 215 (33) (M^+); 199 (100).

Anal. Calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.50. Found: C, 67.08; H, 4.27; N, 6.29.

4-Acetoxy-2,3-dihydro-3-oxo-4H-naphth[1,2-b][1,4]-oxazine (4a)

A solution of the hydroxamic acid (**4***b*, 0.81 g) and acetic anhydride (2.5 ml) in pyridine (7.5 ml) was shaken at room temperature for 5 min then cooled in an ice bath. Cold water was added dropwise and the title compound (0.85 g) crystallized from solution. Recrystallization (pyridine–H_2O) gave cream-colored needles, m.p. 77–78°; i.r. ν_{max} 1700 (lactam C=O), 1802 (N—O—acetate C=O); p.m.r. δ 2.52 (s, 3H, CH_3); 5.18 (s, 2H, CH_2), 7.40–8.23 (m, 6H, aromatic protons); mass spectrum *m/e* (% relative abundance) 257 (39) (M^+); 215 (100) (M − CH_2=C=O)$^+$; 43 (79) [CH_3CO^+].

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.44. Found: C, 65.16; H, 4.42; N, 5.48.

5-Chloro-2,3-dihydro-3-oxo-4H-naphth[1,2-b][1,4]-oxazine (4c)

(*a*) A suspension of the hydroxamic acid (**4***b*, 0.47 g) in benzene (50 ml) containing acetyl chloride (5 ml) was refluxed under conditions which excluded the access of moisture. After 15 min a clear solution was obtained, then a colorless solid began to precipitate. After refluxing for an additional 45 min the mixture was cooled and filtered. The solid was washed with benzene and crystallized from chloroform–hexane to give the title compound (0.29 g), m.p. 270–272°; i.r. ν_{max} 1685 (C=O), 3165 (NH) cm^{-1}; p.m.r. δ 4.81 (s, 2H, CH_2), 7.32 (s, 1H, C_6-H), 7.49–8.16 (m, 4H, remaining aromatic protons), 10.90 (broad s, 1H, D-exchangeable, NH); mass spectrum *m/e* (% relative abundance) 233 (100), 235 (32) (M^+); 205 (19), 207 (9) (M − CO)$^+$; 192 (22), 194(7) [M − CH=C=O]$^+$.

Anal. Calcd. for $C_{12}H_{18}ClNO_2$: C, 61.68; H, 3.45; N, 6.00. Found: C, 61.86; H, 3.58; N, 5.98.

(*b*) A suspension of **4***a* (0.43 g) in benzene (25 ml) saturated with anhydrous HCl was stirred for 12 h. The resulting solid was crystallized from chloroform–hexane to give the title compound (0.36 g), m.p. 270–272°, whose i.r., p.m.r., and mass spectra were identical to those described immediately above.

*5-Acetoxy-2,3-dihydro-3-oxo-4H-naphth[1,2-b][1,4]-oxazine (**4***d*)

(*a*) A solution of the hydroxamic acid (**4***b*, 1.05 g) in glacial acetic acid (40 ml) and acetic anhydride (20 ml) was heated under reflux for 0.5 h, then poured into ice. The pale pink precipitate which formed was washed (H_2O), dried over KOH, and crystallized (ethyl acetate) to give the title compound as colorless needles (1.07 g), m.p. 235–236°; i.r. ν_{max} 1688 (lactam C=O), 1765 (ester C=O) and 3175 (NH) cm^{-1}; p.m.r. δ 2.44 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 7.07 (s, 1H, C_6-H), 7.34–8.12 (m, 4H, remaining aromatic protons), 10.90 (broad s, 1H, D-exchangeable, NH); mass spectrum *m/e* (% relative abundance) 257 (23) (M^+); 215 (100) ($M - CH_2{=}C{=}O)^+$; 43 (26) [CH_3CO^+].

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.44. Found: C, 65.26; H, 4.27; N, 5.44.

(*b*) When a solution of the acetate (**4***a*, 0.39 g) in glacial acetic acid (30 ml) was heated under reflux for 1 h, then poured into ice and treated further as described immediately above, the title compound (**4***d*, 0.34 g), m.p. 235–237° was obtained. Its i.r., p.m.r., and mass spectra were identical to those of the product obtained in reaction *a*.

*2,3-Dihydro-5-hydroxy-3-oxo-4H-naphth[1,2-b][1,4]-oxazine (**4***e*)

(*a*) The acetate (**4***a*, 0.80 g) was heated under reflux in 5% H_2SO_4 (150 ml) for 2 h. After standing overnight at room temperature, the reaction mixture was filtered and the solid which remained was washed (H_2O) and dried *in vacuo* to a pale brown solid (0.51 g), m.p. 272–282°. A solution of this product in 20% NaOH was declorized (charcoal) and the filtrate was acidified (HCl) to give the title compound (0.42 g), m.p. 293–294°; i.r. ν_{max} 1678 (C=O), 3160 (NH) cm^{-1}; p.m.r. δ 4.75 (s, 2H, CH_2), 6.83 (s, 1H, C_6—H), 7.30–8.32 (m, 4H, remaining aromatic protons), 10.14 (broad s, 1H, D-exchangeable, OH), 10.86 (broad s, 1H, D-exchangeable, NH); mass spectrum *m/e* (% relative abundance) 215 (100) (M^+); 187 (23) ($M - CO)^+$; 186 (11) ($M - HCO)^+$; 174 (14) ($M - CH{=}C{=}O)^+$.

Anal. Calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.50. Found: C, 67.04; H, 4.40; N, 6.64.

(*b*) Acetate **4***d* (0.48 g) was heated under reflux in 20% NaOH (10 ml) for 1 h. The reaction mixture was cooled and acidified (30% H_2SO_4) to give the title compound (**4***e*, 0.35 g), m.p. 292°, identical (i.r., p.m.r., mass spectrum) with the product obtained by procedure *a*.

(*c*) Acetate **4***d* (0.55 g) was heated under reflux in 5% H_2SO_4 (50 ml) for 2 h. The cooled solution was filtered to give **4***e* (0.44 g), m.p. 292°, identical (i.r. and p.m.r.) with the product obtained by procedure *a*.

*2,3-Dihydro-5-methoxy-3-oxo-4H-naphth[1,2-b][1,4]-oxazine (**4** f)*

A solution of the acetate (**4***a*, 0.82 g) in methanol (150 ml) and concentrated H_2SO_4 (1.0 ml) was heated under reflux for 4 h. The reaction mixture was concentrated until precipitation occurred. After cooling, the precipitate was collected, washed (H_2O), and dried *in vacuo* to give the title compound (0.63 g), m.p. 235–236° (from ethanol); i.r. ν_{max} 1692 (C=O), 3200 (NH) cm^{-1}; p.m.r. δ 3.98 (s, 3H, OCH_3), 4.76 (s, 2H, CH_2), 6.72 (s, 1H, C_6—H), 7.30–8.07 (m, 4H, remaining aromatic protons), 10.74 (broad s, 1H, D-exchangeable, NH); mass spectrum *m/e* (% relative abundance) 229 (100) (M^+); 214 (26) ($M - CH_3)^+$; 201 (7) ($M - CO)^+$.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.83; N, 6.11. Found: C, 67.93; H, 4.92; N, 5.80.

*2,3-Dihydro-3-oxo-4H-naphth[1,2-b][1,4]oxazine (**4***m*)

To a suspension of ethyl (2-nitro-1-naphthoxy)acetate (1.6 g) in concentrated HCl (15 ml) and ethanol (10 ml) was added $SnCl_2{\cdot}2H_2O$ (4.5 g) in ethanol (15 ml). The mixture was stirred for 10 h, during which time a clear yellow solution first formed, from which a colorless solid precipitated. The suspension was diluted with water (40 ml), filtered, and the precipitate was recrystallized (aqueous ethanol) to give the colorless title compound (0.76 g), m.p. 238–240°; i.r. ν_{max} 1722 (C=O), 3175 (NH) cm^{-1}; p.m.r. δ 4.86 (s, 2H, CH_2), 7.25–8.18 (m, 6H, aromatic protons), 11.02 (broad s, 1H, D-exchangeable, NH); mass spectrum *m/e* (% relative abundance) 199 (100) (M^+); 171 (28) ($M - CO)^+$; 170 (32) ($M - HCO)^+$, 158 (29) ($M - CH{=}C{=}O)^+$.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.02. Found: C, 72.30; H, 4.49; N, 7.11.

*Thermal Rearrangements of 4-Acetoxy-2,3-dihydro-3-oxo-4H-naphth[1,2-b][1,4]oxazine (**4***a*)

A solution of **4***a* (0.76 g) in toluene (100 ml) was heated under reflux for 3 h, then filtered. The filtrate was flash-evaporated and gave a solid, m.p. 188–204°. Fractional crystallization from chloroform first gave 2-acetoxy-2,3-dihydro-3-oxo-4*H*-naphth[1,2-*b*][1,4]oxazine (**4***h*, 0.37 g), as a colorless solid, m.p. 222°; i.r. ν_{max} 1698 (lactam C=O), 1770 (ester C=O), 3175 (NH) cm^{-1}; p.m.r. δ 2.06 (s, 3H, $COCH_3$), 6.84 (s, 1H, OC*H*(OAc)CO), 7.28–8.12 (m, 6H, aromatic protons), 11.57 (broad s, 1H, D-exchangeable, NH); mass spectrum *m/e* (% relative abundance) 257 (42) (M^+); 215 (48) ($M - CH_2{=}C{=}O)^+$; 186 (100) (*m/e* 215 − HCO)$^+$.

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.44. Found: C, 65.54; H, 4.57; N, 5.48.

The chloroform filtrate was evaporated, and the residue was crystallized from ethyl acetate to yield 5-acetoxy-2,3-dihydro-3-oxo-4*H*-naphth[1,2-*b*][1,4]oxazine (**4***d*, 0.11 g), identical (i.r., p.m.r., m.p.) with the sample of **4***d* prepared as described earlier.

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