# Selective Acetylation of Substituted (*E*)-4(1*H*)-Hydroxyimino-2,3-dihydro-1,8-naphthyridine



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We report a selective acetylation of compounds **2** in 1-, 4- or 1,4-position. The treatment of **2** with acetic anhydride gave the compounds **3** and with acetyl chloride the compounds **4**. The 1-acetyl derivatives were obtained starting from **5** *via* the oxime derivatives **6, 7** and **8**. Tests on phytoiatric antimycotic activity and on reactivation of phosphylated acetylcholinesterase and inhibition of acetylcholinesterase were performed.

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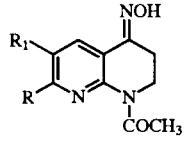
It has been reported that several oximes, having aromatic or heterocyclic rings, exhibited an interesting activity against fungal plant pathogens of different taxonomic classes [1-3] or abilities to reactivate acetylcholinesterase inhibited by organophosphates [4,5].

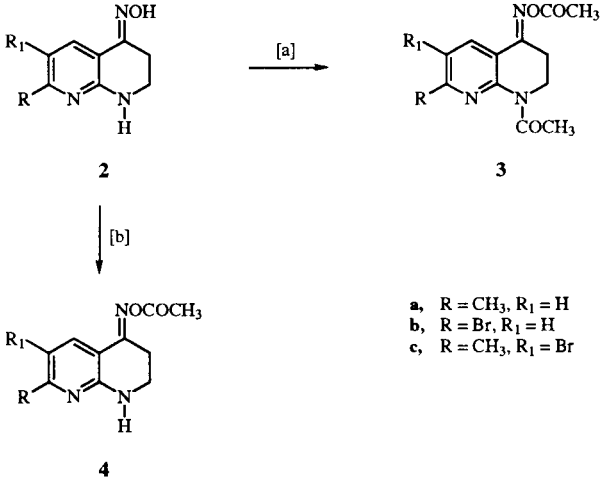
In the course of our research program we required the synthesis of substituted (*E*)-1-acetyl-4(1*H*)-hydroxyimino-2,3-dihydro-1,8-naphthyridines **1** for the study of biologically active compounds.



**1**

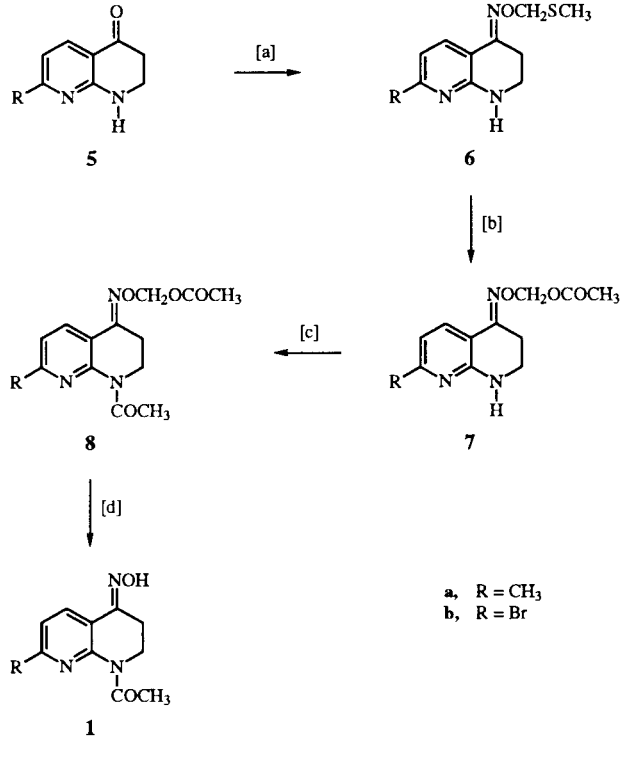
Attempts to prepare compounds **1** by acetylation of (*E*)-oximes **2** [6,7] in hot acetic anhydride were unsuccessful. In this manner the corresponding 1-acetyl-4(1*H*)-acetyloxyimino derivatives **3** were obtained instead. When the reaction of (*E*)-oximes **2** with a large excess of acetyl chloride was carried out at room temperature for 24 hours 4(1*H*)-acetoxyimino derivatives **4** and 10-30% recovery of the (*E*)-oximes **2** were isolated, as showed by tlc analyses (Scheme 1). Mixtures of **3** and **4** were generally obtained instead when the reaction was performed in acetic anhydride or in acetyl chloride in different condition of temperature. For the preparation of derivatives **1** an alternative profitable procedure, starting from ketones **5**, was chosen, in accord with that described in the literature [8] (Scheme 2). The ketones **5** [6,9] were then treated with *O*-(methylthiomethyl)hydroxylamine in pyridine in the presence of an equivalent amount of pyridine hydrochloride at room temperature for 15 hours to give the corresponding (*E*)-oximes **6**. Acidolysis of **6**

Scheme 1



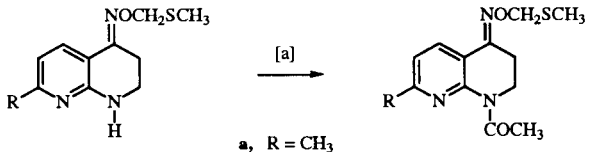
[a] = $(CH_3CO)_2O$, [b] = $CH_3COCl$

Scheme 2



[a] = $H_2NOCH_2SCH_3$, [b] = $CH_3COOH$, $CH_3COONa$, $HgCl_2$, HgO, [c] = $(CH_3CO)_2O$, [d] = $K_2CO_3/H_2O$, $CH_3OH$

Scheme 3



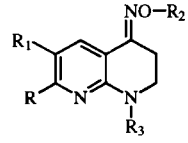

[a] = $(CH_3CO)_2O$

performed in glacial acetic acid, with mercuric chloride, mercuric oxide and sodium acetate, as buffer, resulted in the formation of the *O*-acetoxymethoxy oximes **7**. Compounds **7** were converted into the 1-acetyl derivatives **8** by treatment with acetic anhydride at 80°. Under the same conditions compounds **6** gave the corresponding derivatives **9** (Scheme 3). The target compounds **1** were finally prepared by mild treatment of **8** with aqueous potassium carbonate in methanol at room temperature for 1.5 hours.

All the synthesized compounds were characterized by elemental analysis, ir and $^1H$ nmr data (Table 1,2).

The $^1H$ nmr spectra of oximes **2** show two triplets in the range of δ 3.22-3.35 and δ 2.67-2.76 due to $H_2$ and $H_3$ respectively. The $^1H$ nmr spectra of =N–O– substituted **4**, **6** and **7** show one multiplet in the range of δ 3.43-3.50 due to $H_2$, whereas the $^1H$ nmr spectra of the $N_1$-acetyl derivatives **1**, **3** and **8** exhibit the $H_2$ triplet at lower field, δ 3.73-4.06, due to the deshielding effect of the acetyl group to the $H_2$. The deshielding effect due to substituents on =N–O– was lower. In fact, the $^1H$ nmr spectra of **1** and **2**

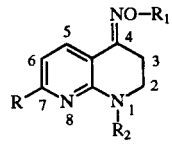
Table 1




| Compound | R | $R_1$ | $R_2$ | $R_3$ | Yield % | mp°C [a] | Empirical Formula | Elemental Analyses Calcd./Found | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | $CH_3$ | H | H | $COCH_3$ | 97 | 176-178 [b] | $C_{11}H_{13}N_3O_2$ | 60.26<br>60.41 | 5.98<br>6.26 | 19.15<br>19.33 |
| **1b** | Br | H | H | $COCH_3$ | 98 | 177-180 [b] | $C_{10}H_{10}N_3O_2Br$ | 42.27<br>42.35 | 3.54<br>3.44 | 14.79<br>14.81 |
| **3a** | $CH_3$ | H | $COCH_3$ | $COCH_3$ | 66 | 105-107 [c] | $C_{13}H_{15}N_3O_3$ | 59.76<br>59.80 | 5.79<br>5.78 | 16.08<br>16.01 |
| **3b** | Br | H | $COCH_3$ | $COCH_3$ | 96 | 130-132 [c] | $C_{12}H_{12}N_3O_3Br$ | 44.19<br>43.95 | 3.71<br>3.52 | 12.88<br>12.89 |
| **3c** | $CH_3$ | Br | $COCH_3$ | $COCH_3$ | 81 | 138-140 [d] | $C_{13}H_{14}N_3O_3Br$ | 45.90<br>46.39 | 4.15<br>4.20 | 12.35<br>12.52 |
| **4a** | $CH_3$ | H | $COCH_3$ | H | 57 | 134-137 [c] | $C_{11}H_{13}N_3O_2$ | 60.26<br>60.19 | 5.98<br>5.84 | 19.15<br>19.24 |
| **4b** | Br | H | $COCH_3$ | H | 82 | 182-183 [c] | $C_{10}H_{10}N_3O_2Br$ | 42.27<br>41.99 | 3.54<br>3.39 | 14.79<br>15.00 |
| **4c** | $CH_3$ | Br | $COCH_3$ | H | 56 | 185-187 [e] | $C_{11}H_{12}N_3O_2Br$ | 44.31<br>44.53 | 4.05<br>3.99 | 14.09<br>14.09 |
| **6a** | $CH_3$ | H | $OCH_2SCH_3$ | H | 70 | 117-118 [f] | $C_{11}H_{15}N_3OS$ | 55.67<br>55.49 | 6.37<br>6.02 | 17.70<br>17.81 |
| **6b** | Br | H | $OCH_2SCH_3$ | H | 36 | 145-146 [f] | $C_{10}H_{12}N_3OSBr$ | 39.74<br>39.74 | 4.00<br>3.94 | 13.90<br>13.52 |
| **7a** | $CH_3$ | H | $OCH_2OCOCH_3$ | H | 48 | 130-132 [c] | $C_{12}H_{15}N_3O_3$ | 57.82<br>57.53 | 6.07<br>6.25 | 16.86<br>16.96 |
| **7b** | Br | H | $OCH_2OCOCH_3$ | H | 61 | 166-168 [d] | $C_{11}H_{12}N_3O_3Br$ | 42.05<br>41.85 | 3.85<br>3.85 | 13.37<br>13.13 |
| **8a** | $CH_3$ | H | $OCH_2OCOCH_3$ | $COCH_3$ | 95 | oil [g] | $C_{14}H_{17}N_3O_4$ | 57.72<br>57.33 | 5.88<br>5.82 | 14.43<br>14.06 |
| **8b** | Br | H | $OCH_2OCOCH_3$ | $COCH_3$ | 98 | 88-89 [c] | $C_{13}H_{14}N_3O_4Br$ | 43.83<br>43.89 | 3.96<br>3.81 | 11.79<br>11.77 |
| **9a** | $CH_3$ | H | $OCH_2SCH_3$ | $COCH_3$ | 87 | 76-77 [h] | $C_{13}H_{17}N_3O_2S$ | 55.89<br>56.07 | 6.13<br>6.35 | 15.04<br>14.86 |
| **9b** | Br | H | $OCH_2SCH_3$ | $COCH_3$ | 79 | 110-111 [d] | $C_{12}H_{14}N_3O_2SBr$ | 41.87<br>41.52 | 4.09<br>4.39 | 12.20<br>11.96 |

[a] Recrystallization solvent. [b] 2-Propanol/water 1/1. [c] Petroleum benzin 100/140°. [d] 2-Propanol. [e] Toluene. [f] Ethanol. [g] Purified by flash chromatography. [h] Ethanol/water 1/2.

Table 2




| Compound | $^1$H NMR Spectral Data (δ) | | | | | | IR Data cm$^{-1}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | $H_1$ | $H_2$ | $H_3$ | $H_5$ | $H_6$ | Others | N-H | NC=O | CC=O |
| **1a** | -- | 3.73 t | 2.66 t | 7.60 d | 6.50 d | 2.25($CH_3$) s<br>2.33($NCOCH_3$) s<br>10.26(NOH) | | 1660 | |
| **1b** | -- | 3.80 t | 2.70 t | 7.60 d | 6.83 d | 2.33($NCOCH_3$) s<br>10.54(NOH) | | 1640 | |
| **2a** | 6.52 | 3.22 m | 2.67 t | 7.75 d | 6.45 d | 2.42($CH_3$) s<br>10.98(NOH) | 3250 | | |
| **2b** | 7.27 | 3.27 m | 2.70 t | 7.83 d | 6.77 d | 11.27(NOH) | 3270 | | |
| **2c** | 6.44 | 3.35 m | 2.76 t | 8.12 s | -- | 2.43($CH_3$) s<br>11.80(NOH) | 3250 | | |
| **3a** | -- | 4.00 t | 2.95 t | 8.26 d | 6.93 d | 2.26($OCOCH_3$) s<br>2.45($NCOCH_3$) s<br>2.51($CH_3$) s | | 1670 | 1780 |
| **3b** | -- | 4.13 t | 3.03 t | 8.59 d | 7.42 d | 2.26($OCOCH_3$) s<br>2.58($NCOCH_3$) s | | 1680 | 1780 |
| **3c** | -- | 4.13 t | 3.03 t | 8.66 s | -- | 2.26($OCOCH_3$) s<br>2.51($CH_3$) s<br>2.66($NCOCH_3$) s | | 1660 | 1750 |
| **4a** | 5.60 | 3.43 m | 2.96 t | 8.26 d | 6.63 d | 2.26($OCOCH_3$) s<br>2.41($CH_3$) s | 3210 | | 1780 |
| **4b** | 6.16 | 3.50 m | 2.96 t | 8.13 d | 6.85 d | 2.26($OCOCH_3$) s | 3260 | | 1780 |
| **4c** | 5.30 | 3.43 m | 2.96 t | 8.43 s | -- | 2.26($OCOCH_3$) s<br>2.53($CH_3$) s | 3250 | | 1770 |
| **6a** | 5.30 | 3.43 m | 2.86 t | 8.10 d | 6.60 d | 2.30($SCH_3$) s<br>2.40($CH_3$) s<br>5.30($OCH_2$) s | 3200 | | |
| **6b** | 5.73 | 3.46 m | 2.86 t | 8.00 d | 6.86 d | 2.30($SCH_3$) s<br>5.30($OCH_2$) s | 3250 | | |
| **7a** | 5.43 | 3.40 m | 2.85 t | 8.06 d | 6.56 d | 2.13($OCOCH_3$) s<br>2.38($CH_3$) s<br>5.86($OCH_2$) s | 3250 | | 1750 |
| **7b** | 5.70 | 3.40 m | 2.93 t | 8.00 d | 6.83 d | 2.13($OCOCH_3$) s<br>5.83($OCH_2$) s | 3250 | | 1760 |
| **8a** | -- | 4.06 t | 2.90 t | 8.28 d | 7.06 d | 2.13($OCOCH_3$) s<br>2.50($NCOCH_3$) s<br>2.56($CH_3$) s<br>5.86($OCH_2$) s | | 1670 | 1750 |
| **8b** | -- | 4.06 t | 2.90 t | 8.30 d | 7.30 d | 2.13($OCOCH_3$) s<br>2.53($NCOCH_3$) s<br>5.86($OCH_2$) s | | 1680 | 1760 |
| **9a** | -- | 4.06 t | 2.90 t | 8.30 d | 7.06 d | 2.30($SCH_3$) s<br>2.50($NCOCH_3$) s<br>2.56($CH_3$) s<br>5.33($OCH_2$) s | | 1660 | |
| **9b** | -- | 4.06 t | 2.90 t | 8.23 d | 7.36 d | 2.30($SCH_3$) s<br>2.50($NCOCH_3$) s<br>5.30($OCH_2$) s | | 1670 | |

show one triplet due to $H_2$ in the range of δ 2.66-2.76, whereas all the compounds =N–O– substituted **3**, **4**, **6**, **7** and **8**, exhibit a triplet due to $H_3$ in the range of δ 2.85-3.03.

Biological Results.

The following activities were investigated: 1) Compounds **2b,c**, **3a,b,c**, **4a** for phytoiatric antimycotic activity. 2) Compounds **1a,b**, **2a**, **4b,c**, **6a,b**, **7a**, **8b**, **9a** for their ability to reactivate acetylcholinesterase inhibited by organophosphates and for their ability to inhibit acetylcholinesterase.

Phytoiatric Antimycotic Activity.

Compounds **2b,c**, **3a,b,c**, **4a** were tested *in vitro* at 200 ppm against fungal plant pathogens of different taxonomic classes, *Botrytis cinerea*, *Fusarium nivale*, *Pythium ultimum*, *Penicillium italicum*, *Colletotrichum lindemuthianum*, *Fusicladium dendriticum*, *Cercosporella herpotricoides* and *Cercospora beticola*. They generally had some activity against one or more of the test fungi.

Compounds **2b,c**, **3a,b,c**, **4a** tested have interesting activity against *F. dendriticum* in general also at 20 ppm.

Reactivation of Phosphylated Acetylcholinesterase and Inhibition of Acetylcholinesterase.

The *in vitro* reactivating potency of compounds **1a,b**, **2a**, **4b,c**, **6a,b**, **7a**, **8b**, **9a** was evaluated with reference to their ability to reactivate the immobilized acetylcholinesterase inhibited by diisopropylfluoro phosphate. No significant ability to reactivate acetylcholinesterase was shown by these compounds. For these last compounds the ability to inhibit the acetylcholinesterase was also evaluated, but these compounds are devoid of this activity.

## EXPERIMENTAL

Chemistry.

All compounds were routinely checked for their structure by ir and $^1$H-nmr spectroscopy. Melting points were determined in a Köfler hot-stage apparatus and are uncorrected. The ir spectra were measured with Perkin-Elmer Infracord Model 1310 as Nujol mulls. The $^1$H-nmr spectra were determined in DMSO-$d_6$ or deuteriochloroform with TMS as the internal standard, on a Varian EM 360A spectrometer or a Fourier transform spectrometer Varian Model CFT 20. Analytical tlc was carried out on Merck 0.2 mm precoated silica-gel glass plates (60 F-254) and location of spots was detected by illumination with a uv lamp. Flash chromatography was carried out on silica gel (60 size 0.04-0.063 mm) at low pressure. Elemental analyses of all synthesized compounds for C, H and N were within ±0.4% of the theoretical values and were performed by our analytical laboratory.

General Procedure for the Preparation of Substituted (*E*)-4(1*H*)-Acetyloxyimino-2,3-dihydro-1,8-naphthyridines **4**.

To 10 ml of acetyl chloride, 1.0 mmole of **2** was added and the stirred mixture was allowed to react at room temperature for 24 hours. The products were separated by one of the following methods and then purified by crystallization (Table 1).

A) The solid was separated by filtration, suspended in dilute ammonium hydroxide, collected by filtration and washed with water to give 30% of unreacted oxime **2a**. After evaporation of the acetyl chloride *in vacuo*, the residue was suspended in dilute ammonium hydroxide, collected and washed with water to obtain **4a**.

B) The solid was separated by filtration suspended in dilute ammonium hydroxide, collected by filtration and washed with water to give **4b,c**. From the organic solution, treated as in A), was recovered a mixture of compounds **4b,c** and unreacted oximes **2b,c** respectively.

General Procedure for the Preparation of Substituted (*E*)-1-Acetyl-4(1*H*)-acetyloxyimino-2,3-dihydro-1,8-naphthyridines **3**.

A suspension of 2.0 mmoles of **2** in 10 ml of acetic anhydride was allowed to react at 80° for 4 hours. After cooling, the solution was evaporated to dryness *in vacuo* to give a solid residue that was purified by crystallization (Table 1).

General Procedure for the Preparation of Substituted (*E*)-4(1*H*)-Methylthiomethoxyimino-2,3-dihydro-1,8-naphthyridines **6**.

A mixture of 10 mmoles of ketone **5**, 15 mmoles of *O*-(methylthiomethyl)hydroxylamine [8] and 15 mmoles of anhydrous pyridine hydrochloride in 20 ml of pyridine was stirred at room temperature for 15 hours. The pyridine was removed *in vacuo* and the residue extracted with ether. The organic solution was evaporated *in vacuo*, the residue was treated with dilute ammonium hydroxide. The solid was then collected by filtration and washed with water to obtain **6** (Table 1).

General Procedure for the Preparation of Substituted (*E*)-4(1*H*)-Acetoxymethoxyimino-2,3-dihydro-1,8-naphthyridines **7**.

Millimoles 3.6 of mercuric chloride, 1.2 mmoles of mercuric oxide and 10 mmoles of potassium acetate were added to a solution of 1.2 mmoles of compounds **6** in 60 ml of acetic acid and the mixture was stirred at 50° for 24 hours. The suspension was diluted with 60 ml of acetone and treated with hydrogen sulfide gas. The mercuric sulfide was filtered and the filtrates were evaporated to dryness *in vacuo*. The solid residue was extracted with ether and the extracts were washed with water, dried (magnesium sulfate) and evaporated *in vacuo* to give **7** (Table 1).

General Procedure for the Preparation of Substituted (*E*)-1-Acetyl-4(1*H*)-acetoxymethoxyimino-2,3-dihydro-1,8-naphthyridines **8**.

A mixture of 2.0 mmoles of **7** in 4 ml of acetic anhydride was stirred at 80° for 4 hours. The solution was evaporated to dryness *in vacuo* to give **8** (Table 1).

General Procedure for the Preparation of (*E*)-1-Acetyl-4(1*H*)-hydroxyimino-2,3-dihydro-1,8-naphthyridines **1**.

To a solution of 2.0 mmoles of **8** in 10 ml of methanol was added 0.3 ml of 10% aqueous potassium carbonate and the mixture was stirred at room temperature for 1.5 hours and evaporated to dryness *in vacuo*. The solid residue was treated with water, collected by filtration to obtain **1** (Table 1).

General Procedure for the Preparation of Substituted (*E*)-1-Acetyl-4(1*H*)-methylthiomethoxyimino-2,3-dihydro-1,8-naphthyridines **9**.

A suspension of 1.0 mmole of **6** in 2.0 ml of acetic anhydride was stirred at 80° for 4 hours. The solution obtained was evaporated to dryness *in vacuo*, the residue treated with water and the solid collected by filtration to give **9** (Table 1).

Acknowledgements.

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