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Synthesis of Isomeric Isoxazolopyridinones

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Summary. Reaction of 4-methylamino-5,6-dihydropyridinone with acetyl chloride yielded exclusively the 3-acetyl derivative. When the methylamino group of the latter was removed by alkaline hydrolysis, a mixture of two hydroxy derivatives was formed. Those cyclized upon treatment with hydroxylamine exclusively to the isoxazolo[4,5-*c*]pyridinone, whereas the 4-methylamino analogue yielded, depending on *pH*, mainly the isoxazolo[4,3-*c*]pyridinone or the isoxazolo[4,5-*c*]pyridinone. The configurations of the latter compounds were established by NMR experiments.

Keywords. 3-Acetyl-4-methylaminopyridin-2-one; Hydrogen bridge bond; 4-Hydroximinopyridin-2-one; 3-(1-Hydroxyethyliden)-piperidin-2,4-dione; Isoxazolo[4,3-*c*]pyridinone; Isoxazolo[4,5-*c*]-pyridinone.

Synthese isomerer Isoxazolopyridinone

Zusammenfassung. Bei der Umsetzung von 4-Methylamino-5,6-dihydropyridinon mit Acetylchlorid entstand ausschließlich das 3-Acetylderivat. Bei der alkalischen Hydrolyse der Methylaminogruppe entstand ein Gemisch zweier Hydroxyderivate. Diese reagieren mit Hydroxylamin zum Isoxazolo[4,5-*c*]pyridinon, während das 4-Methylaminoanaloge in Abhängigkeit vom *pH*-Wert zum Isoxazolo[4,3-*c*]pyridinon oder zum Isoxazolo[4,5-*c*]pyridinon cyclisiert. Die Konfiguration der letzteren Verbindungen wurde durch NMR-Messungen gesichert.

Introduction

Isoxazolo[4,5-*c*]pyridin-4-ones (**1**) are known as hypolipidemic agents [1]. Moreover, they are used as precursors for hypnotics, muscle relaxants, and tranquilizers [2, 3]. Usually they are prepared from isoxazoles [1–5], but a few years ago a dihydropyridin-2(1*H*)-one was reacted with N, α-diphenylnitrone to give selectively the respective isoxazolo[4,5-*c*]pyridin-4-one in excellent yield [6].

Isoxazolo[4,3-*c*]pyridin-4-ones (**2**) are relevant synthons for analogues to herbicides [7–9]. They are available by thermolysis of 3-acetyl-4-azido-2-pyridinones [7–10].

This paper presents the preparation of the two isomeric isoxazolopyridin-4-ones and the feasibility of influencing the isomer ratio.

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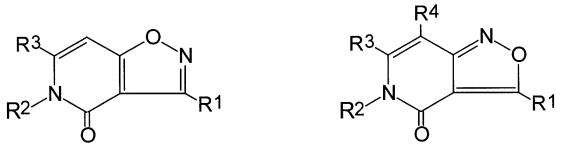


1 2

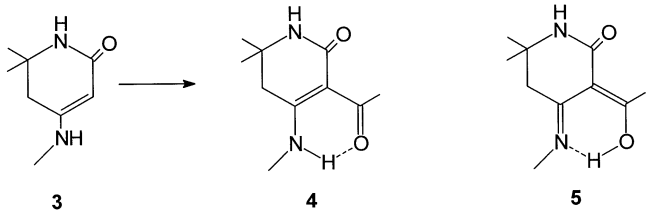
Scheme 1

Results and Discussion

Our method is based on the reaction of 4-substituted 3-acetyldihydropyridin-2-ones with hydroxylamine affording isoxazolo[4,3-*c*]pyridinones or isoxazolo[4,5-*c*]-pyridinones. The configuration of these isomers is directed both by the reaction conditions and the substitution at C-4. 4-Methylamino-5,6-dihydropyridin-2(1*H*)-one **3** [11] serves as starting material. Under *Friedel-Crafts* reaction conditions, the methylamino group of **3** is not attacked, and with acetyl chloride the 3-acetyl derivative **4** is obtained selectively. In its ^{1}H NMR spectrum the hydrogen bond of **4** is characterized by a 6 ppm downfield shift of the signal for the methylamino proton as compared to **3**. The corresponding tautomer **5** is ruled out by a 5.5 Hz coupling between the NH and the methyl proton.

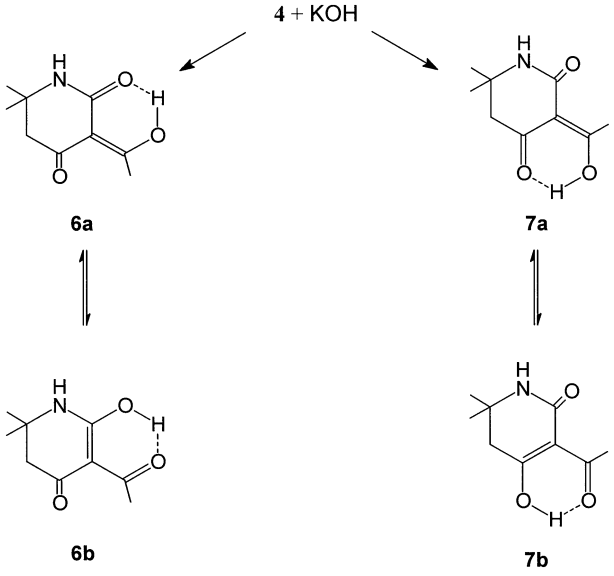
The 4-aminopyridin-2-one **4** is hydrolyzed by potash lye yielding a mixture of two tautomeric hydroxy compounds (**6** and **7**) in a ratio of 4:1. Hydrogen bonds in both structures were indicated by the extreme downfield shift (>17 ppm) of the resonances of the OH groups in their NMR spectra. The signals in the ^{13}C NMR spectra were assigned by means of heteronuclear shift correlation experiments which were optimized for long-range couplings. Crosspeaks in those spectra from OH to ring carbon atom 2 and C-1 of the ethylidene group established the main component to exist in an equilibrium between structures **6a** and **6b**, predominantly favouring **6a**, as indicated by a much smaller cross peak to C-2 in analogy to the cross peak from the OH proton to the carbonyl carbon in salicylaldehyde. Furthermore, we observed a coupling of the C-1 of the ethylidene group which disappeared upon treatment with deuterium oxide. The value of $^{3}J(\mathrm{COH}) = 4.6$ Hz coincides exactly with the corresponding coupling in salicylaldehyde [12].

For the by-product, no such correlations were visible in coupled spectra, and the respective cross peaks were missing in the above mentioned long range experiment. Increasing the number of scans did not lead to improved quality of the spectra due to folding of the large cross peaks of the methyl and methylene groups;



3 4 5

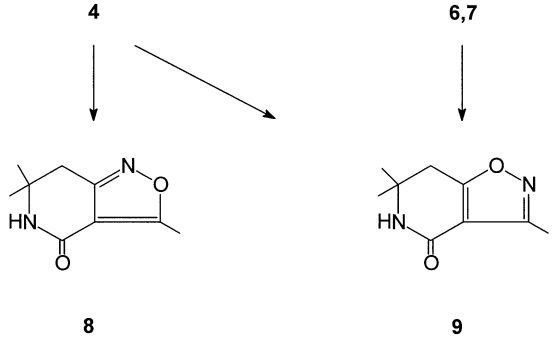
Scheme 2



Scheme 3

its interpretation was not possible beyond all doubt. The problem was solved by a further experiment which was run using real-time digital signal processing to supress peaks coming from outside the region of interest in the ^{1}H domain (digital filtering). For the OH group of the by-product, we obtained two cross peaks with approximately equal intensity to C-4 and the exocyclic carbon, respectively, establishing the equilibrium **7a**, **7b**.

Hydroxylamine has been reported to attack α,β-unsaturated 3-aminoketones at the carbon atom bearing the amino group rather than the carbonyl group [13–15]. However, the 4-methylamino compound **4** gave, depending on reaction conditions, differently composed mixtures of the two possible isoxazolopyridinones **8** and **9**. In faintly acid environment, approximately equal amounts of the isomers **8** and **9** were obtained. The base-catalized reaction yielded the isoxazolo[4,3-*c*]pyridinone **8**, whereas under strongly acidic conditions the isoxazolo[4,5-*c*]pyridinone **9** was formed, most probably due to protonation of the amino group. The hydroxy



Scheme 4

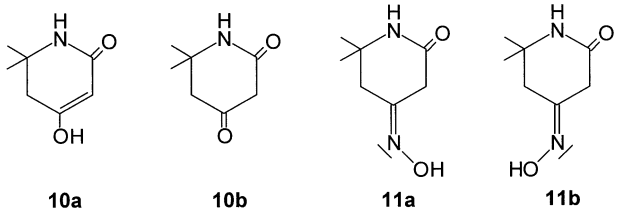
compounds **6** resp. **7** gave exclusively the isoxazolo[4,5-*c*]pyridinone **9** in neutral and faintly acid environment.

Some authors revealed confusion of previously published fused isoxazoles with the corresponding oxazoles or reported about remaining uncertainties concerning that isomer problem when structure elucidation was based solely on spectroscopic methods [8, 16]. Evidence of structure was furnished by alternative syntheses, respectively [8, 16]. We investigated **8** and **9** by means of NMR measurements and finally compared the chemical shifts in ^{13}C NMR spectra to those of 2-methyl-oxazolo- and 3-methyl-isoxazoloquinolones with already confirmed structures [8]. For compounds **8** and **9** we assigned the signals in the ^{13}C NMR spectra with the aid of ge-HMQC spectra which were optimized for 10 Hz. If **8** and **9** were oxazolopyridinones, the ring-atoms bearing the single methyl group should have similar ^{13}C NMR shifts. Actually, it differs by about 13 ppm. The signals for the 3-methyl groups in both compounds appear roughly at 11 ppm, which is also typical for fused 3-methyl-isoxazoles [17–22] and not for 2-methyl-oxazoles resonating usually at 14 ppm [16, 23, 24]. Moreover, an oxazolopyridinone structure is definitely ruled out by comparison with the corresponding shifts for the above-mentioned reference compounds in the ^{13}C NMR spectra, suggesting good correlations only between **8**, **9** and 3-methyl-isoxazoloquinolones.

The oxygen bearing C-3 in **9** is expected to resonate more than 10 ppm [25, 26] downfield from the nitrogen bearing C-3 in **8**. The same effect should be observable for the shifts of C-7a in both compounds. In fact, shift differences of approximately 13 ppm made the distinction between both compounds feasible.

The deacetylated compounds **10a**, **b** and **11a**, **b** were isolated as by-products and in some cases even as major products (see Table). The tautomers **10a**, **b** had already been prepared from the 4-methylaminopyridin-2-one **3** [27]. When measured in *DMSO*-d_6, the oximes **11a**, **b** appear in a ratio of 4.3:1 in the ^{1}H NMR spectrum. The C=NOH fragments were easily identified by their typical chemical shifts [28], exhibiting resonances at 10.6 ppm in the ^{1}H NMR spectra and at 151 ppm in the ^{13}C NMR spectra. Alternatively, they were synthesized from **10a**, **b**. Their resonances in the NMR spectra were assigned by means of ge-HMQC spectra optimized for 10 Hz couplings. The distinction of *syn*- and *anti*-isomers succeeded by means of NOE experiments. Upon irradiation of H-3 in **11A** resp. H-5 in **11B**, we observed NOEs at the NOH groups. Typical upfield shifts [29] in the ^{13}C NMR spectra for C-3 resp. C-5 in *syn* position to the OH group established the assignments.

Dihydropyridin-2(1*H*)-ones are valuable synthons for the preparation of isoxazolopyridin-4-ones. The isomer ratio of the products may be controlled by



Scheme 5

Table 1. Yields of reaction products (given for isolated products unless stated otherwise)

Starting material	Method *A* (basic)	Method *B* (neutral)	Method *C* (faintly acidic)	Method *D* (acidic)
4	**8** (14.5%)	**8** (16.7%)	**8**[a] (23.7%)	**9** (31.9%)
	11a, **b** (55.0%)	**11a**, **b** (65.7%)	**9**[a] (26.6%)	**10a**, **b** (13.3%)
			11a, **b** (3.7%)	**11a**, **b** (23.9%)
6, 7	**10a**, **b** (58.0%)	**9** (51.8%)	**9** (62.7%)	**9** (2.2%)
	11a, **b** (17.1%)	**11a**, **b** (31.1%)		**10a**, **b** (36.8%)
				11a, **b** (41.4%)

[a] Compounds not isolated; yields determined by ^{1}H NMR integration after separation of **11a**, **b**

the substitution of C-4 as well as by the reaction conditions. The formation of both isomers is a helpful support for unequivocal structure elucidation.

Experimental

All melting points (Büchi 510) are uncorrected; IR: Perkin Elmer 2000 FT-IR; NMR: Varian INOVA (400 MHz), internal standard: *TMS*; microanalyses: Microanalytical Laboratory at the Institute of Physical Chemistry, University of Vienna; their values were in satisfactory agreement with the calculated ones; flash chromatography: column diameter 30 mm, layer thickness 40 mm, Merck silicagel 60, 0.040–0.063 mm (230–400 mesh), rate of flow: 30 ml/min, eluent: CH_2Cl_2:CH_3OH = 19:1

3-Acetyl-4-methylamino-6,6-dimethyl-5,6-dihydropyridin-2(1H)-one (**4**; $C_{10}H_{16}N_2O_2$)

Aluminum chloride (0.012 mol) was dissolved in 30 ml of nitrobenzene. Then, 0.011 mol acetyl chloride were added dropwise to the ice-cooled solution. Finally, 0.01 mol of compound **3** were added, and the mixture was stirred at room temperature for 16 h. The solution was diluted with 100 ml $CHCl_3$ and poured on ice. The aqueous layer was neutralized and extracted once with 30 ml $CHCl_3$. The combined organic layers were carefully washed with H_2O, $NaHCO_3$ solution, H_2O, and brine. After drying over Na_2SO_4, the solvents were removed *in vacuo*. The crystalline residue was triturated with 2-propanol, filtered with suction, and recrystallized from 2-propanol.

Yield: 1.46 g (74.4%); m.p: 227 °C; IR (KBr): $\bar{\nu}$ = 3250(w), 3160(w), 1755(s), 1693(s), 1607(s), 1576(m), 1306(s), 1188(s) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.26 (s, 6H, $(CH_3)_2$), 2.50 (s, 2H, 5-H), 2.51 (s, 3H, $COCH_3$), 2.98 (d, J = 5.5 Hz, 3H, NCH_3), 5.41 (s, 1H, NH), 12.32 (br, 1H, N*H*CH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 28.67 $(CH_3)_2$, 29.86 (NCH_3), 31.33 (CO*C*H_3), 38.39 (C-5) 48.56 (C-6), 99.58 (C-3), 167.41 (C-2), 168.08 (C-4), 199.44 (*C*OCH_3) ppm.

3-(1-Hydroxyethyliden)-6,6-dimethylpiperidine-2,4-dione and its tautomers (**6, 7**; $C_6H_{13}NO_3$)

Compound **4** (0.01 mol) was added to an aqueous ethanolic solution of 0.03 mol KOH, and the mixture was refluxed for 8 h. After cooling, the mixture was concentrated to a small volume *in vacuo*. The residue was acidified with HCl and extracted three times with $CHCl_3$. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. The solvent was removed and the residue recrystallized from H_2O. Yield: 1.20 g (65.5%) **6** and 0.30 g **7** (16.4%); m.p.: 109 °C; IR (KBr): $\bar{\nu}$ = 3255(w), 2976(w), 1755(s), 1645(s), 1635(s), 1570(m) cm^{-1}.

6 (main product): ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.33 (s, 6H, $(CH_3)_2$), 2.52 (s, 2H, 5-H), 2.56 (s, 3H, CH_3), 5.72 (br, s, 1H, NH), 17.65 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 24.56

(CH_3), 28.71 ($CH_3)_2$, 50.31 (C-6), 51.09 (C-5), 100.89 (C-3), 173.02 (C-2), 191.50 (C-4), 192.45 (COH) ppm.

7 (by-product): ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.32 (s, 6H, ($CH_3)_2$), 2.61 (s, 2H, 5-H), 2.63 (s, 3H, CH_3), 5.50 (br, s, 1H, NH), 17.65 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 25.71 (CH_3), 28.97 ($CH_3)_2$, 46.68 (C-5), 49.30 (C-6), 105.05 (C-3), 165.60 (C-2), 196.07 (C-4), 197.65 (COH) ppm.

Reaction of **4** *resp.* **6, 7** *with hydroxylamine*

Method A: $NH_2OH \cdot HCl$ (3 mmol) was added to a solution of 6 mmol Na in 50 ml abs. alcohol. The mixture was refluxed for 1 h. The 5, 6-dihydropyridinone (1 mmol) was added, and refluxing was continued for 4 h. The mixture was cooled, diluted with 30 ml ethanol, and neutralized with HCl. The solution was evaporated to dryness. The residue was treated with warm ethanol and filtered to remove the inorganic salt. The solvent was removed *in vacuo*, and the residue was treated with chloroform/ethyl acetate (1:3). The insoluble compounds **10a**, **b** resp. **11a**, **b** were removed by filtration. The filtrate was evaporated and the residue recrystallized. Compounds **10a**, **b** and **11a**, **b** were – if necessary – separated by flash chromatography.

Method B: $NH_2OH \cdot HCl$ (3 mmol) was added to a solution of 3 mmol Na in 30 ml abs. alcohol. The mixture was refluxed for 1 h. The 5, 6-dihydropyridinone (1 mmol) was added, and refluxing was continued for 18 h. The mixture was cooled, diluted with 30 ml ethanol, and the inorganic salt was removed by filtration. Further workup was performed according to method *A*.

Method C: $NH_2OH \cdot HCl$ (3 mmol) was added to a solution of 1.5 mmol Na in 30 ml abs. alcohol. The mixture was refluxed for 1 h. The 5, 6-dihydropyridinone (1 mmol) was added, and refluxing was continued for 12 h. The mixture was cooled and diluted with 30 ml ethanol, and the inorganic salt was removed by filtration. Further workup was performed according to method *A*.

Method D: The 5, 6-dihydropyridinone (1 mmol) was mixed with 3 mmol $NH_2OH \cdot HCl$ and 0.1 ml concentrated HCl in 30 ml absolute alcohol. The mixture was refluxed for 12 h, diluted with 30 ml ethanol, neutralized, and evaporated to dryness. The residue was treated with warm ethanol and filtered. Further workup was performed according to method *A*.

3,6,6-Trimethyl-6,7-dihydro-isoxazolo[4,3-c]pyridin-4(5H)-one (**8**; $C_9H_{12}N_2O_2$)

Yield: see Table; m.p.: 189°C (2-propanol); IR (KBr): $\bar{\nu} = 3203$(m), 1678(s), 1431(m), 1371(m), 1255(m), 1152(m), 797(m) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 400 MHz): 1.24 (s, 6H, ($CH_3)_2$), 2.60 (s, 3H, CH_3), 2.85 (s, 2H, 7-H), 7.85 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz): 11.78 (CH_3), 28.59 ($CH_3)_2$, 33.29 (C-7), 53.55 (C-6), 106.95 (C-3a), 160.66 (C-7a), 161.01 (C-4), 170.73 (C-3) ppm.

3,6,6-Trimethyl-6,7-dihydro-isoxazolo[4,5-c]pyridin-4(5H)-one (**9**; $C_9H_{12}N_2O_2$)

Yield: see Table, m.p.: 173°C (ethanol/water); IR (KBr): $\bar{\nu} = 3207$(m), 1691(s), 1640(m), 1494(s), 1365(m), 1243(m), 1162(m), 781(m) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 400 MHz): 1.25 (s, 6H, ($CH_3)_2$), 2.34 (s, 3H, CH_3), 3.00 (s, 2H, 7-H), 7.60 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz): 10.18 (CH_3), 28.79 ($CH_3)_2$, 34.76 (C-7), 53.97 (C-6), 108.07 (C-3a), 157.39 (C-3), 161.93 (C-4), 175.07 (C-7a) ppm.

4-Hydroxy-6,6-dimethyl-5,6-dihydropyridin-2(1H)-one (**10a**) *resp.*
6,6-Dimethylpiperidin-2,4-dione **10b**

Yield: see Table; m.p. and NMR data agree with those of a sample prepared according to Ref. [27].

4-Hydroximino-6,6-dimethylpiperidin-2-one (**11a**, **b**; $C_7H_{12}N_2O_2$)

A mixture of **10a**, **b** (0.01 mol), 0.035 mol $NH_2OH \cdot HCl$, and 0.03 mol CH_3COONa in 100 ml ethanol/H_2O (19:1) was refluxed for 9 h, neutralized, and evaporated. The residue was triturated with warm ethanol, filtered, and the filtrate was evaporated. Compounds **11a**, **b** were purified by flash chromatography.

Yield: 1.27 g (81.3%), m.p.: 225–227 °C (ethanol/water); $Rf = 0.38$ (dichloromethane/methanol = 9:1); IR (KBr): $\bar{\nu} = 3171$(m), 2980(w), 1637(s), 1446(m), 1430(m), 1259(m), 960(m) cm^{-1};

11a (main component): ^{1}H NMR (*DMSO*-d_6, δ, 400 MHz): 1.14 (s, 6H, $(CH_3)_2$), 2.32 (s, 2H, 5-H), 3.09 (s, 2H, 3-H), 7.89 (s, 1H, NH), 10.63 (s, 1H, NOH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz): 28.88 $(CH_3)_2$, 30.99 (C-3), 41.20 (C-5), 50.64 (C-6), 150.96 (C-4), 167.33 (C-2) ppm.

11b (minor constituent): ^{1}H NMR (*DMSO*-d_6, δ, 400 MHz): 1.15 (s, 6H, $(CH_3)_2$), 2.54 (s, 2H, 5-H), 2.96 (s, 2H, 3-H), 7.82 (s, 1H, NH), 10.60 (s, 1H, NOH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz): 29.48 $(CH_3)_2$, 35.40 (C-5), 36.22 (C-3), 50.64 (C-6), 150.86 (C-4), 168.02 (C-2) ppm.

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