Synthesis and Structure of 3-Acyl-γ-pyridones

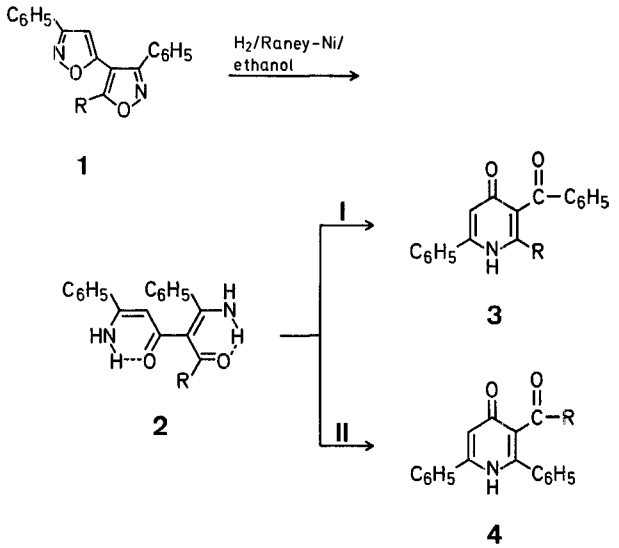
Pierluigi CARAMELLA and Alessandro QUERCI

Istituto di Chimica Organica dell'Università, I-27100 Pavia, Viale Taramelli 10

We wish to report on a very convenient and selective synthesis of 3-acyl-γ-pyridones starting from 1,2-oxazole derivatives. The known synthetic procedures involve the ammonolysis of 3-acyl-γ-pyrons[1,2], or the action of diketene on β-enamino ketones[3]. However, these methods are not generally applicable, on the one hand due to the poor availability of the 3-acyl-γ-pyrons and on the other hand due to the fact that only 6-methyl derivatives can be prepared.

Recently[4], we reported the synthesis of 2,6-dimethyl-γ-pyridonecarboxylic acid esters and amides through hydrogenolytic cleavage of "dimethyldiisoxazolone" derivatives. Since the method seemed to us a very promising entry to γ-pyridones, we investigated the approach to the title compounds from suitable 1,2-oxazole systems.

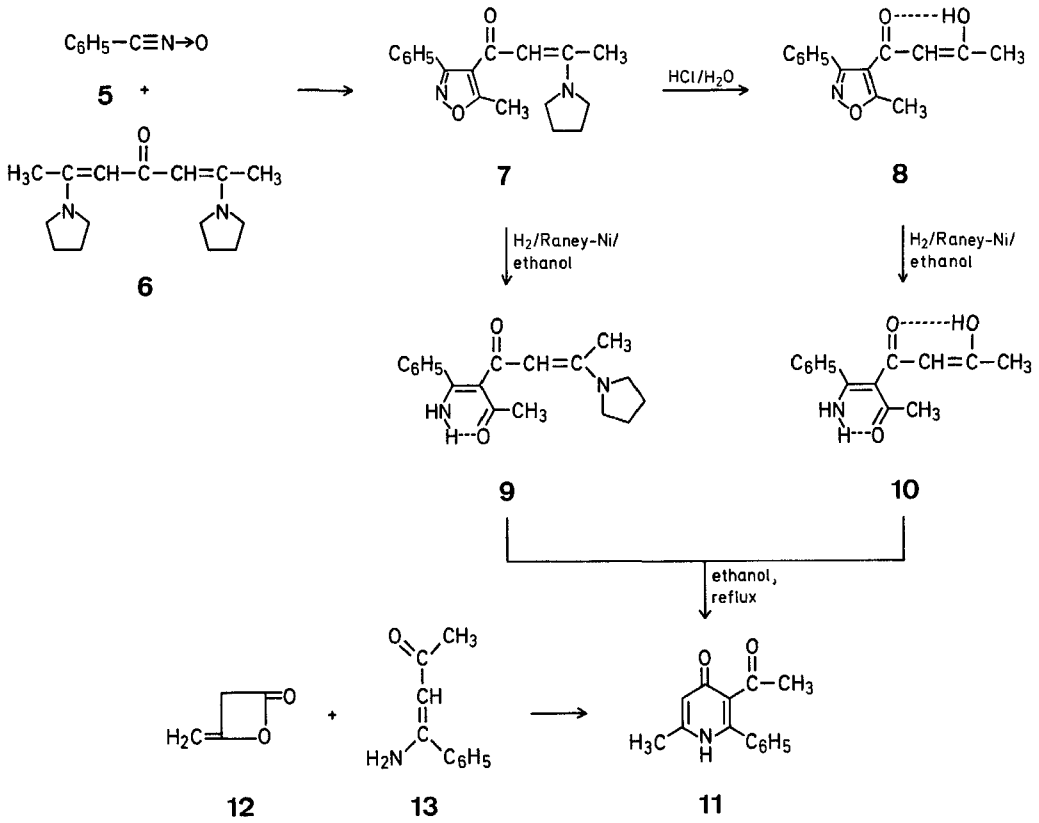
Both rings of the 4,5'-bi-1,2-oxazole derivatives **1a** and **1b** undergo hydrogenolytic cleavage in ethanolic solution in the presence of Raney nickel. The hydrogenation solutions show a long wave-length absorption band at 370 and 327, 361 nm (sh), respectively, assignable to the acyclic intermediates **2a** and **2b**, which disappear within 1–2 hr on boiling of the solutions (evolution of ammonia). On cooling, pyridones **3a** and **4b** separate in 41 and 47% yields, respectively. The formation of **3a** should depend on the easier cyclization on the aldehyde function (Route I) when R = H. With ketone **2b**, Route II predominates, the previously observed cyclization pattern[4] being followed (see Scheme **A**).



a R = H
b R = CH_3

Scheme **A**

1,2-Oxazoles having suitable side chains (e.g. **7** and **8**) may be used in the synthesis. Following a recently proposed general synthetic route to 4-acyl-1,2-oxazoles[5], compound **7** was obtained in 60% yield by the cycloaddition reaction

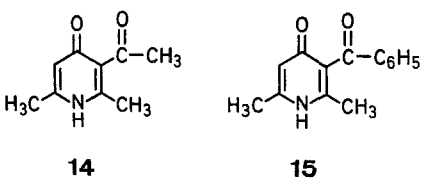


Scheme **B**

of benzonitrile oxide (**5**) and the readily accessible 2,6-dipyrrolidino-4-oxohepta-2,5-diene (**6**); acid hydrolysis afforded diketone **8**. Compounds **7** and **8** take up 1 equivalent of hydrogen (Raney nickel in ethanol). The resultant unstable acyclic intermediates **9** and **10** ($\lambda_{max}^{ethanol}$ = 237, 322 and 253, 323 nm, respectively) cyclize on refluxing of the solutions. From the reaction mixtures, 3-acetyl-6-methyl-2-phenyl-γ-pyridone (**11**) is obtained in 26 and 38% yields, respectively (Scheme **B**).

The structures of the products rely on N.M.R. data (see Table 1). In DMSO-d_6, the 3-acetyl group of **4b**, **11**, and of the model compound **14** readily undergoes deuterium exchange in the presence of D_2O/NaOD, whereas the methyl groups at the 2 and 6 positions are not affected. No exchange was observed with model compound **15** under similar conditions. The I.R. data of the products obtained are in agreement with the assigned structures, the 3-acetyl group absorbing at 1680–1692 cm^{-1} and the 3-benzoyl group at 1652–1665 cm^{-1}.

Compound **3a** is not oxidized by silver oxide/aqueous sodium hydroxide. The structure of compound **11** was confirmed by an independent synthesis by condensation of diketene (**12**) with 1-amino-3-oxo-1-phenyl-1-butene (**13**) according to the method of Ziegler[3].



14 **15**

3-Benzoyl-6-phenyl-γ-pyridone (3a) and 3-Acetyl-2,6-diphenyl-γ-pyridone (4b):

Solutions of **1a** and **1b**[6], respectively, (1.0 g) in 95% ethanol (200 ml) were hydrogenated at ambient temperature and pressure using Raney nickel (2 ml) as the catalyst. Two equivalents of hydrogen were absorbed within 6–10 hr. The catalyst was removed by filtration and the filtrate refluxed for 5 hr. Upon concentration of the solutions, compounds **3a** and **4b**, respectively, separated out.

3a colorless crystals; yield: 41%; m.p. 251–252° (from ethanol).

$C_{18}H_{13}NO_2$	calc.	C 78.53	H 4.76	N 5.06
	found	78.45	4.75	5.12

4b colorless crystals; yield: 47%; m.p. 195–196° (from ethanol).

$C_{19}H_{15}NO_2$	calc.	C 78.87	H 5.23	N 4.84
	found	78.65	5.36	4.84

5-Methyl-4-(1-oxo-3-pyrrolidinobut-2-enyl)-3-phenyl-1,2-oxazole (7):

To a stirred solution of 2,6-dipyrrolidino-4-oxohepta-2,5-diene[7] (32 mmol) and excess triethylamine (60 mmol) in chloroform (100 ml), a solution of benzhydroximic acid chloride (32 mmol) in chloroform (30 ml) was added over a 30 min. period. Stirring was continued for 2 hr and the mixture allowed to stand at room temperature overnight. The solvent was removed and the residue chromatographed on silica gel H using ethyl acetate as the eluent; yield: 65%; colorless crystals, m.p. 120–122° (from cyclohexane).

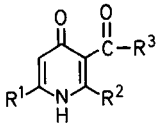
$C_{18}H_{20}N_2O_2$	calc.	C 72.95	H 6.80	N 9.45
	found	72.58	6.81	9.62

I.R. (Nujol): $\nu_{C=O}$ and $\nu_{C=C}$, 1617, 1562, 1530 cm^{-1}.

U.V. (ethanol): λ_{max} = 225 (log ε = 4.18), 336 nm (4.46).

N.M.R. ($CDCl_3$): τ = 2.2–2.7 (m, 5H, phenyl), 5.22 (s, 1H, =CH—), 6.4–6.8 (m, 4H, CH_2—N—CH_2), 7.33 (s, 3H, C-5 ring methyl), 7.43 (s, 3H, side chain methyl), 8.0–8.3 (m, 4H, pyrrolidine CH_2—CH_2).

Table 1. Spectroscopic Data of 3-Acyl-γ-pyridones



Compound	R^1	R^2	R^3	I.R. (Nujol)[b] $\nu_{C=O}$ [cm^{-1}]	U.V. (95% ethanol)[b] λ_{max} [nm] (log ε)	N.M.R. (DMSO-d_6)[a] (τ values)			
						C-5	R^1	R^2	R^3
3a	C_6H_5	H	C_6H_5	1652	250 (4.53), 290 sh (4.14)	3.02 (s)	—	1.80 (s)	—
4b	C_6H_5	C_6H_5	CH_3	1692	251 (4.51), 284 sh (4.08)	2.52 (s)	—	—	7.63 (s)[d]
11	CH_3	C_6H_5	CH_3	1680	238 (4.30), 262 sh (4.15)	3.87 (s)[e]	7.74 (d) (J=0.5 Hz)	—	7.70 (s)[d]
14[c]	CH_3	CH_3	CH_3	1680	261 (3.55)	4.00 (s)[e]	7.81 (d) (J=0.6 Hz)	7.79 (s)	7.60 (s)[d]
15[c]	CH_3	CH_3	C_6H_5	1665	253 (4.35)	4.01 (s)[e]	7.78 (d) (J=0.5 Hz)	7.95 (s)	—

[a] N.M.R. spectra were recorded on a Perkin-Elmer R 12 spectrometer operating at 60 MHz; TMS was used as an internal standard.
[b] 3-Acetyl-2-methyl-6-phenyl-γ-pyridone and 3-benzoyl-2-methyl-6-phenyl-γ-pyridone show I.R. (KBr) carbonyl absorptions at 1690 and 1670 cm^{-1}, respectively, and U.V. maxima (95% ethanol) at 252 nm (log ε = 4.50) and 250 nm (4.56), respectively[1].
[c] Prepared according to Ref.[3]. We thank Dr. T. Kappe for a sample of compound **14**.
[d] disappears in the presence of D_2O/NaOD.
[e] broad.

4-Acetoacetyl-5-methyl-3-phenyl-1,2-oxazole (8):
Compound **7** (0.5 g) was refluxed in dilute hydrochloric acid (10 ml) for 2 hr. On cooling, compound **8** crystallized out; yield: 68%; m.p. 64–66° (from ethanol/water), colorless crystals.

$C_{14}H_{13}NO_3$ calc. C 69.12 H 5.39 N 5.76
found 68.74 5.47 5.66

I.R. (Nujol): $\nu_{C=O}$ and $\nu_{C=C}$, 1596, 1575, 1555, 1538 cm^{-1}.

U.V. (ethanol): λ_{max} = 230 (log ε = 4.07), 307 nm (4.23).

N.M.R. ($CDCl_3$): τ = −5.8 (broad s, 1H, OH), 2.49 (s, 5H, phenyl), 4.69 (s, 1H, =CH—), 7.34 (s, 3H, methyl at C-5), 8.10 (s, 3H, side-chain methyl).

3-Acetyl-6-methyl-2-phenyl-γ-pyridone (11):
Method a, from **7** or **8**, respectively: A solution of compounds **7** or **8** (1.0 g) in 95% ethanol (100 ml) was hydrogenated using Raney nickel (or palladium on carbon) as catalyst at ambient temperature and pressure until 1 equivalent of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate refluxed for 2 and 10 hr, respectively. The solvent was removed and the residue recrystallized from ethyl acetate; yield of **11**: 26 and 38%, respectively; colorless crystals, m.p. 226–227°; the product sublimes at 140–160° (bath)/1 mm.

$C_{14}H_{13}NO_2$ calc. C 73.99 H 5.77 N 6.16
found 73.81 5.83 6.20

Method b, (procedure of Ziegler et al.[3]): A mixture of 1-amino-3-oxo-1-phenyl-1-butene (2 mmol; m.p. 86–87°[8], obtained from the hydrogenolysis of 5-methyl-3-phenyl-1,2-oxazole using Raney nickel as catalyst in ethanol as solvent) and diketene (2 mmol) was heated at 120° for 2 hr. The reaction product was recrystallized from ethyl acetate; yield: 22%.

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