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270. A New Synthesis of β-Lactams

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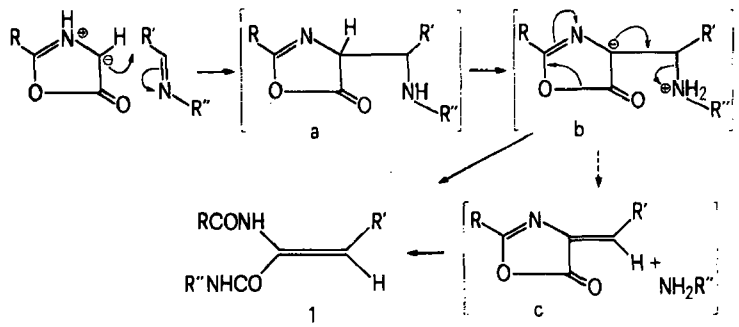
Zusammenfassung. Es wird eine neue Synthese von β-Lactamen durch Umsatz von 4-Alkyl-azlactonen mit acyclischen Iminen beschrieben. Mit einem cyclischen Imin wird dagegen ein Imidazolin-Derivat erhalten.

The reaction of oxazolin-5-ones with different imines is reported in the literature [1–3]. In all cases the products obtained are derived from an initial nucleophilic attack of oxazolone on the imine (*Scheme 1*), and are of type **1**.

Scheme 1



During our work on β-lactam antibiotics, we got interested in the above scheme as we have visualized the possibility of obtaining β-lactams by substituting one of the hydrogen atoms at C(4) of oxazolone by an alkyl group. The intermediate **d** (*Scheme 2*) generated by the initial attack of the oxazolone on an imine, can now lead to an azetidinone **2** and/or an imidazoline derivative **3** as shown in *Scheme 2*. The imidazoline derivative is of interest because of its close relationship to penillic acid (**4a**),

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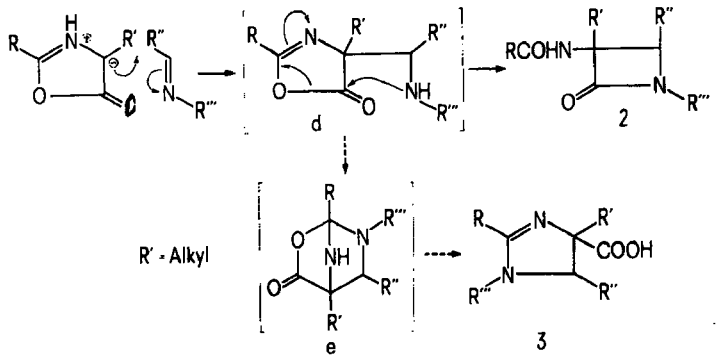
Scheme 2



which is formed by the rearrangement of penicillin through a similar intermediate as **d** [4].

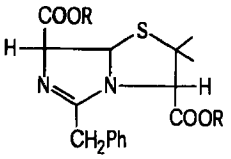
In our present studies we obtained azetidinones of type **2** with acyclic imines, and an imidazoline derivative of type **3** with the cyclic imine **5** derived from penicillin.

The reaction of 2-phenyl-4-methyl-2-oxazolin-5-one (**6a**) with *N*-benzylidene-butylamine in refluxing benzene gave compound **7a** [m.p. 145°; analyzed for $C_{21}H_{24}N_2O_2$; MS. (*m/e*): 336 (M^+); IR.: 1745 (lactam CO) [5], 1670 (amide CO) and 3430 (NH) cm^{-1}; NMR.: 0.92 (3H, *t*, $J = 7$); 1.18 (3H, *s*); 1.20–1.80 (4H, *m*); 3.24 (1H, *m*); 3.64 (1H, m); 5.14 (1H, *s*); 6.11 (1H, br.); 7.28–7.58 (8H, *m*); 7.84 (2.H, *m*) ppm. These data are in agreement with the azetidinone formulation **7a**]. Similarly 2-benzyl-4-methyl-2-oxazolin-5-one (**6b**) and 2-*t*-butyl-4-methyl-2-oxazolin-5-one (**6c**) gave the corresponding azetidinones with *N*-benzylidene-butylamine. The spectral data agree with structures **7b** and **7c**. One common characteristic feature of compounds **7a–c** is that the 2 protons of *n*-butyl in α-position to the ring nitrogen atom appear as anisochronous in the NMR. spectra giving an ABX_2 type pattern ($J_{AB} =$ 14 Hz, $J_{AX} =$ 7 Hz) by coupling with the adjacent methylene protons. Similar observations were made on *N*-benzylic β-lactams [6].

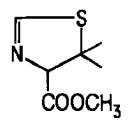
The reaction of oxazolone **6a** with *N*-benzylidene-aniline in refluxing toluene yielded the azetidinone **7d**. Compounds **7a–d** fragment upon electron impact (see Exper. Part) in the pathways established for azetidinones [7], which is additional evidence for the proposed structures.

The reaction of oxazolone **6a** with a cyclic imine, *i.e.* methyl D-5,5-dimethyl-2-thiazoline-4-carboxylate (**5**) in refluxing benzene yielded the crystalline compound **8a** [m.p. 216°; MS. (*m/e*); 348 (M^+); IR.: 1750, 1620 cm^{-1}; NMR.: 1.36 (3H, *s*); 1.44 (3H, *s*); 1.77 (3H, *s*); 3.86 (3H, *s*); 4.36 (1H, *s*); 5.78 (1H, *s*); 7.40–7.72 (6H, *m*) ppm]. From the above data it is quite evident that the type of product obtained in this case is different from the ones obtained from acyclic imines, *e.g.* the usual absorptions for secondary amides (3430 and 1670 cm^{-1}) are absent in the IR. spectrum, and the mass spectrum shows the loss of COOH and CO_2 fragments from the molecular ion. On treatment with diazomethane **8a** gave a methyl derivative **8b** [m.p. 115°; MS. (*m/e*): 362 (M^+); IR.: 1745 and 1625 cm^{-1}; NMR. spectrum shows an additional three proton singlet (3.79 or 3.80 ppm) accounting for a new carbomethoxy group, apart from the other signals of the parent compound]. Based on the above evidence a penillic acid structure **8a** is proposed for this compound. Its IR. absorption at

1620 cm^{-1} agrees well with the imidazoline system [8]. The UV. spectra of **8a** and **8b** correspond to those recorded for benzyl-penillic acid **4a** and its derivative **4b** [9].



4a R = H
4b R = CH_3



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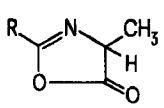
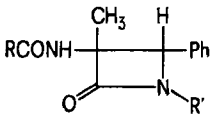
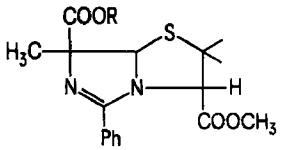


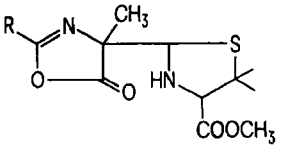
6a R = Ph
6b R = CH_2Ph
6c R = *t*-Butyl



7a R = Ph, R′ = n-Butyl
7b R = CH_2Ph, R′ = n-Butyl
7c R = *t*-Butyl, R′ = n-Butyl
7d R = R′ = Ph



8a R = H
8b R = CH_3



9a R = Ph
9b R = CH_2Ph

Bell et al. [10] had assigned an oxazolone-thiazolidine structure **9b** to the reaction product of oxazolone **6b** and thiazoline **5**. However, in our case, the corresponding structure **9a** can be ruled out on the basis of spectral and chemical evidence: (a) the product from **6a** and **5** does not show the normal IR. absorptions of oxazolones (1820 and 1670 cm^{-1}); one could assume a hydrogen bridge between the NH and the lactone carbonyl in structure **9a** in order to explain the shift of the 1820 band to 1750 cm^{-1}, but the absence of the 1670 cm^{-1} band is difficult to account for; (b) the *ortho*-protons of the phenyl group in **6a** appear at 7.96 ppm whereas in compound **8a** all aromatic protons occur as a multiplet at 7.40–7.72 ppm; (c) the methyl derivative **8b** shows a three proton singlet at 3.79 or 3.80 ppm, in accordance with the presence of a $COOCH_3$ rather than a N—CH_3 group. As expected there are no changes in the 6 μ region of the IR. spectrum compared to the absorptions of **8a**; (d) the product of **6a** and **5** is stable to refluxing methanol, while normally 2-oxazoline-5-ones undergo methanolysis under such conditions. On the basis of the above evidence we prefer structure **8a** for the product of **6a** and **5**.

The formation of azetidinones and imidazolines in the reaction of oxazolones with imines may proceed from a common intermediate of type **d** (*Scheme 2*); this assumption is supported by a recent observation of *Okutome et al.* [11], who demonstrated the formation of an 3-acyl-2-(oxazol-2-in-5-on-4-yl)-thiazolidine compounds

in the reaction of N-acyl-α-aminoacids which is transformed in an oxazolinon under the reaction conditions) with 2-substituted thiazolines in the presence of acetic anhydride.

Experimental Part

All melting points were taken in a *Tottoli* melting-point apparatus and are uncorrected. IR. spectra (bands in cm^{-1}) were determined in chloroform on a *Perkin Elmer* 125. Mass spectra were taken with a *Hitachi* RMU 6 A, operating with an ionization energy of 70 eV, the temperature of the ion source was about 200°. NMR. spectra were taken in deuteriochloroform on a Varian 4 A 100 using TMS as internal reference. Chemical shifts are given in δ (ppm) and the coupling constants in Hz. The UV. spectra were recorded on a *Perkin Elmer* 137. Preparative TLC. was carried out on pre-coated silica gel plates F 254 (*Merck*) and Rf values were determined on 60 F 254 (*Merck*) using chloroform methanol 9:1 as developping solvent system.

General procedure for the preparation of oxalones [12]. – *N*-acyl-α-amino acid (0,01 mol) and acetic anhydride (10 ml) are heated on a boiling water bath for 20 min, the excess acetic anhydride is removed in vacuum and the residue yields on distillation at 80–100°/0,01 Torr the colourless oily oxazolone (80–90%).

In case of oxazolone **6c** this procedure is slightly modified. After the lactonization the volatiles are removed in vacuum. The residue is analytically pure and was used directly in subsequent reactions.

Spectral data of oxazolones – *2-Phenyl-4-methyl-2-oxazolin-5-one* (**6a**). IR.: 1820, 1670. – NMR.: 1.61 (3H, *d*, $J = 7$); 4.46 (1H, *q*, $J = 7$); 7.50 (3H, *m*); 7.96 (2H, *m*). – MS. (*m/e* (%)): 175 (9, M^+), 147 (7), 131 (31), 105 (100), 77 (55).

2-Benzyl-4-methyl-2-oxazolin-5-one (**6b**). – IR.: 1830, 1675. – NMR.: 1.48 (3H, *d*, $J = 7$); 3.80 (2H, *d*, $J = 1.5$; on irradiation at 4.21 the *d* collapsed into a *s*); 4.21 (1H, $t \times q$, $J_{H,CH_3} = 7, J_{H,CH_2} = 1.5$; on irradiation at 3.80 it became a clean *q*); 7.32 (5H, *s*). – MS. (*m/e* (%)): 189 (39, M^+), 161 (2), 146 (3), 145 (4), 136 (2), 119 (7), 118 (8), 92 (22), 91 (100).

2-t-Butyl-4-methyl-2-oxazolin-5-one (**6c**). – IR.: 1825, 1670. – NMR.: 1.33 (9H, *s*); 1.46 (3H, *d*, $J = 7$); 4.03 (1H, *q*, $J = 7$). – MS. (*m/e* (%)): 155 (10, M^+), 140 (5), 127 (7), 112 (11), 111 (22), 96 (16), 85 (13), 84 (8), 69 (13), 57 (100), 55 (43).

Reaction of oxazolones with imines – *1-Butyl-3-benzoylamino-3-methyl-4-phenyl-2-azetidinone* (**7a**). 175 mg (1 mmol) of oxazolone **6a** and 161 mg of *N*-benzylidene-butylamine [13] are dissolved in 5 ml of dry benzene and the mixture is refluxed for 2 h. After the removal of volatiles the residue is separated on preparative TLC. using silica gel as adsorbent and chloroform/methanol as eluent. Compound **7a** is isolated as the main product (others are uncharacterised): 167 mg (50%), m.p. 145°, Rf = 0.62. – UV. (λ_{max}^{EtOH} (ε)): 207 (25020), 224 (19650) nm. – IR.: 3430, 1745, 1675. – NMR.: 0.92 (3H, *t*, $J = 7$); 1.18 (3H, *s*); 1.20–1.80 (4H, *m*); 3.24 (1H, *m*, $J_{gem} = 14$, $J_{vic} = 7$); 3.64 (1 H, *m*, $J_{gem} = 14$, $J_{vic} = 7$); 5.14 (1H, *s*); 6.11 (1H, *br.*); 7.28–7.58 (8H, *m*); 7.84 (2H, *m*). – MS. (*m/e* (%)): 336 (1, M^+), 238 (6), 237 (30), 215 (13), 175 (14), 163 (13), 162 (100), 105 (70), 77 (28).

$C_{21}H_{24}N_2O_2$ (336.42): Calc. C 74.97 H 7.19 N 8.33% Found C 74.69 H 7.10 N 8.36%

1-Butyl-3-methyl-3-phenacetylamino-4-phenyl-2-azetidinone (**7b**). 189 mg (1 mmol) of oxazolone **6b** and 161 mg (1 mmol) of *N*-benzylidene-butylamine are treated as above: 140 mg (40%) **7b**, m.p. 142°, Rf = 0.57. – UV. (λ_{max}^{EtOH} (ε)): 207 (25380), 219 (16600) nm. – IR.: 3420, 1755, 1675. – NMR.: 0.90 (3H, *t*, $J = 7$); 0.96 (3H, *s*); 1.20–1.80 (4H, *m*); 3.00 (1H, *m*, $J_{gem} = 14$, $J_{vic} = 7$); 3.60 (1H, *m*, $J_{gem} = 14$, $J_{vic} = 7$); 3.64 (2H, *s*); 5.00 (1H, *s*); 6.00 (1H, br.); 7.32 (10H, *s*). – MS. (*m/e* (%)): 350 (2, M^+), 322 (2), 251 (34), 215 (26), 189 (13), 162 (100), 133 (34), 91 (35).

$C_{22}H_{26}N_2O_2$ (350.44): Calc. C 75,40 H 7,48 N 7,99% Found C 74,85 H 7,71 N 7,45%

1-Butyl-3-methyl-4-phenyl-3-pivaloylamino-2-azetidinone (**7c**). 155 mg (1 mmol) of oxazolone **6c** and 161 mg (1 mmol) of *N*-benzylidene-butylamine are dissolved in 10 ml of dry benzene and refluxed for 3 h. Working-up as above gives an oily compound **7c**: 110 mg (35%), Rf = 0.62. – UV. (λ_{max}^{EtOH} (ε)): 206 (14720), 220 (9365) nm. – IR.: 3440, 1750, 1675. – NMR.: 0.90 (3H, *t*, $J = 7$); 1.04 (3H, *s*); 1.20–1.80 (4H, *m*); 1.26 (9H, *s*); 3.04 (1H, *m*, $J_{gem} = 14$, $J_{vic} = 7$); 3.60 (1H, *m*,

$J_{gem} = 14$, $J_{vic} = 7$); 4.92 (1H, *s*); 6.06 (1H, br.); 7.36 (5H, *s*). – MS. (*m/e* (%)): 316 (0.5, M^+), 231 (2), 217 (17), 215 (10), 163 (13), 162 (100), 155 (12), 85 (9), 57 (47).

$C_{19}H_{28}N_2O_2$ (316.43): Calc. C 72.11 H 8.92 N 8.85% Found C 71.85 H 9.01 N 8.75%

3-(Benzoylamino)-1,4-diphenyl-3-methyl-2-azetidinone (**7d**). 175 mg (mmol) of oxazolone **6a** and 181 mg (1mmol) of *N*-benzylidene-aniline [14] are dissolved in dry toluene and the mixture is refluxed for 5 h. Working-up in the usual way gives compound **7d**: 0.106 g (30%), Rf = 0.67. – UV. (λ_{max}^{EtOH} (ε)): 204 (47890), 249 (26330) nm. – IR.: 3430, 1750, 1675. – NMR.: 1.26 (3H, *s*); 5.58 (1H, *s*); 6.72 (1H, br.); 7.20–7.54 (13H, *m*); 7.84 (2H, *m*). – MS. (*m/e* (%)): 356 (0.5, M^+), 328 (0.5), 310 (9), 237 (6), 235 (3), 182 (100), 175 (6), 105 (48), 77 (33).

$C_{23}H_{20}N_2O_2$ (356.41): Calc. C 77.50 H 5.66 N 7.86% Found C 77.45 H 5.60 N 7.80%

3-Methoxycarbonyl-4-phenyl-2,2,6-trimethyl-6-(2,3,6,6a-tetrahydroimidazo[5,1-b]thiazoloic) acid (**8a**). 175 mg (1 mmol) of the oxazolone **6a** and 173 mg (1 mmol) of methyl D-5,5-dimethyl-2-thiazoline-4-carboxylate (**5**) [15] are dissolved in 5 ml of dry benzene and the reaction mixture is refluxed for 8 h; during this period a colourless crystalline solid separates from the mixture. After completion of the reaction the crystalline residue, which is pure compound **8a**, is collected by filtration (344 mg (98%)), and recrystallized from chloroform/benzene, m.p. 216°, Rf = 0.18. – UV. (λ_{max}^{EtOH} (ε)): 208 (17280), 232 (12030). – IR.: 1750, 1620. – NMR.: 1.36 (3H, *s*); 1.44 (3H, *s*); 1.77 (3H, *s*); 3.86 (3H, *s*); 4.36 (1H, *s*); 5.78 (1H, *s*); 7.40–7.72 (6H, *m*). – MS. (*m/e* (%)): 348 (7, M^+), 304 (12), 303 (18), 271 (6), 230 (14), 229 (16), 176 (8), 175 (27), 174 (100), 171 (13), 158 (15).

$C_{17}H_{20}N_2O_4S_1$ (348.35): Calc. C 58.67 H 5.79 N 8.04 S 9.21%
Found ,, 58.65 ,, 5.81 ,, 7.93 ,, 9.34%

Methyl 3-methoxycarbonyl-5-phenyl-2,2,7-trimethyl-7-(2,3,7,7a-tetrahydroimidazo-[5,1-b]-thiazoloate (**8b**). 174 mg (0.5 mmol) of compound **8a** is dissolved in ether/methanol and diazomethane added until the persistence of the yellow colour; the solvent is evaporated and the residue chromatographed on silica gel with chloroform as eluent giving compound **8b**: 108 mg (60%), recrystallization from ether/hexane, m.p. 115°, Rf = 0.64. – UV. (λ_{max}^{EtOH} (ε)): 205 (15910), 228 (13980) nm. – IR.: 1745, 1625. – NMR.: 1.28 (3H, *s*); 1.34 (3H, *s*); 1.68 (3H, *s*); 3.79 (3H, *s*); 3.80 (3H, *s*); 4.37 (1H, *s*); 5.70 (1H, *s*); 7.36–7.70 (5H, *m*). – MS. (*m/e* (%)): 362 (17, M^+), 303 (44), 189 (100), 161 (38), 146 (15), 126 (12), 120 (36), 105 (74).

$C_{18}H_{22}N_2O_4S_1$ (362.37): Calc. C 59.66 H 6.12 N 7.73 S 8.85%
Found C 59.46 H 6.16 N 7.76 S 9.02%

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