C-ACYLATION OF AZLACTONE RING

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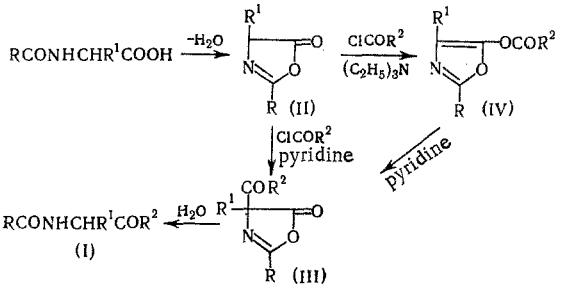
The C-acylation of the azlactone (oxazolinone) ring lies at the base of a simple method for the synthesis of α-acylamino ketones (I) from α-amino acids according to the scheme [1, 2]



The 4-substituted derivatives (III) (R^1 = alkyl) are obtained in high yields by the direct C-acylation of the azlactones (II) (R^1 = alkyl) in pyridine [1, 2], or by the O → C-isomerization under the influence of the same base of the O-acylazlactones (IV) (R^1 = alkyl), which are formed from (II) and $ClCOR^2$ in the presence of triethylamine in tetrahydrofuran [1]. The C-acylation of the 4-unsubstituted derivatives (II) (R^1 = H) in either pyridine or β-picoline proceeds much more poorly. For example, when 2-phenyl–5-oxazolinone (IIa) (R = C_6H_5, R^1 = H) is reacted with $ClCO(CH_2)_2COOCH_3$ (V) in β-picoline the corresponding C-acyl derivative (IIIa) (R = C_6H_5, R^1 = H, R^2 = $(CH_2)_2COOCH_3$) is isolated in a total yield of only 10% [3]. Data on the conditions for the O → C-isomerization of (IV) (R^1 = H) are absent in the literature.

In order to develop a method for the synthesis of (III) (R^1 = H) we first made some unsuccessful attempts to accomplish the O → C-isomerization of (IV) (R^1 = H) under the influence of pyridine bases. We were able to obtain positive results only when BF_3 · etherate was used as a catalyst for the O → C-isomerization of (IV) (R^1 = H).

Employing this method, from (IVa) (R = C_6H_5, R^1 = H, R^2 = $(CH_2)_2COOCH_3$), (IVb) (R = C_6H_5, R^1 = H, R^2 = CH_3), and (IVc) (R = C_6H_5, R^1 = H, R^2 = $(CH_2)_{14}CH_3$) we obtained in yields of 17-46% respectively (IIIa), (IIIb) (R = C_6H_5, R^1 = H, R^2 = CH_3), and (IIIc) (R = C_6H_5, R^1 = H, R^2 = $(CH_2)_{14}CH_3$), the structure of which was confirmed by the characteristic reaction for enol with $FeCl_3$, and also by the hydrolytic cleavage of (IIIa) and (IIIc) to (Ia) (R = C_6H_5, R^1 = H, R^2 = $(CH_2)_2COOCH_3$) and δ-aminolevulinic acid hydrochloride, and (Ic) (R = C_6H_5, R^1 = H, R^2 = $(CH_2)_{14}CH_3$). Acylazlactone (IIIc) is also formed in 31% yield directly from (IIa) by heating it with $ClCO(CH_2)_{14}CH_3$ (VI) and BF_3 · etherate in toluene.

Compounds (IIIa), (IIIb), (IIIc), and (IIId) (R = C_6H_5, R^1 = H, R^2 = $(CH_2)_2OC_2H_5$) were isolated in higher yields (35-60%) by the direct C-acylation of (IIa) employing (V), CH_3COCl, (VI), and $ClCOCH_2CH_2OC_2H_5$ in γ-picoline medium. The yields of (IIIa), (IIIb), (IIIc), and (IIId) drop sharply (Table 1) when other picolines or pyridine itself are used as bases.

A smoother course for the C-acylation of (IIa) in γ-picoline when compared with other picolines and pyridine is probably explained by the steric hindrance introduced by the methyl group for nucleophilic attack of the (IIa) anion on the γ-carbon atom of the acylpyridinium cation, with the formation of the secondary dihydropyridine derivative (VII) (R = H)

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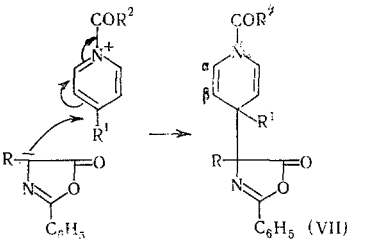
TABLE 1

C-Acylation products (IIa)	Yield, %			
	in picoline			in pyridine
	α	β	γ	
IIIa	0	10	54	0
IIIb	—	—	41	0
IIIc	0	21	54	Traces
IIId	0	8	35	0



In the absence of steric hindrance for nucleophilic attack of the γ-position of the pyridine ring, i.e., when the α- and β-picolines or pyridine are used as the bases, it is possible for the dihydropyridine derivative to be formed, which is incapable of conversion to (III). Actually, soon after mixing (IIa) and (V) in pyridine, we detected the distinct resonance signals of the protons of (VII) (R = R^1 = H, R^2 = $(CH_2)_2COOCH_3$) [δ 3.35 (R^1 = H); 4.50 (R = H), 4.78 ppm (β – H)]* in the reaction mass.

We were unable to isolate (IIIa) from this reaction mixture even when the mixture was allowed to stand at ~20°C for many days or heated at 100°C for many hours. The analogous dihydropyridine derivatives (VII) (R = CH_3) are also formed by the acylation of (II) (R^1 = CH_3). However, being found in equilibrium with (II) (R^1 = CH_3), they are converted completely to (III) (R^1 = CH_3) during the reaction process [1].

EXPERIMENTAL

Preparation of O-Acyl-5-oxazolinones (IVa-c). Using the method described in [1], the reaction of CH_3COCl, (V), and (VI) with (IIa) in tetrahydrofuran, in the presence of triethylamine, respectively gave as oils (IVb), R_f 0.77 (here and subsequently, thin-layer chromatography on SiO_2HF_{254}, benzene–ethyl acetate, 1:1, detection of the spots either with iodine vapors or in UV light); (IVa), R_f 0.71 (benzene–acetone, 1:1). Infrared spectrum ($CHCl_3$): 1670, 1740, 1830 cm^{-1}; (IVc), IR spectrum ($CHCl_3$): 1670, 1760, 1790 cm^{-1}. Compounds (IVa-c) give hippuric acid when heated with aqueous CH_3COOH.

Preparation of (IIIb). To 0.92 g of (IVb) in 10 ml of absolute ether was added 1.2 ml of BF_3·etherate, and the mixture was allowed to stand at ~20°C for ~12 h. The mixture was then evaporated and the residue was treated with Na_2CO_3 solution, filtered, the filtrate was acidified with conc. HCl, and the obtained precipitate was washed with water and dried in the air. We obtained 0.42 g (46%) of (IIIb) with mp 157-164°C, which failed to depress the mixed melting point with an authentic sample [5]. With vigorous stirring, to a solution of 0.5 g of (IIa) in 5 ml of γ-picoline at –5 to 0°C was added 0.25 ml of CH_3COCl in 2 ml of benzene, after which the mixture was stirred for another 3 h, and then poured into a mixture of ice and dilute HCl solution. The obtained oil was extracted with $CHCl_3$, the chloroform extract was washed with Na_2CO_3 solution, the aqueous alkaline solution was acidified with conc. HCl, and the obtained precipitate was filtered, washed with water, and dried in the air. We obtained 0.27 g (41%) of (IIIb) with mp 180-183°C.

Preparation of (IIIa). To 0.59 g of (IVa) in 10 ml of absolute benzene was added 0.8 ml of BF_3·etherate and the mixture was allowed to stand at ~20°C for 12 h, after which the mixture was refluxed for 3 h, evaporated, the residue was treated with Na_2CO_3 solution, filtered, the filtrate was acidified with conc. HCl, and the obtained precipitate was filtered, washed with water, and dried in the air. We obtained 0.1 g (17%) of (IIIa) with mp 168-171°C, which failed to depress the mixed melting point with an authentic specimen [3].

With stirring, to 40 ml of γ-picoline at –5 to 0°C was successively added 4.1 ml of (V) and 5.1 g of (IIa), after which the mixture was allowed to stand at ~20°C for 2.5 h and then poured into a mixture of ice and conc. HCl. We obtained 6.1 g (70%) of (IIIa) with mp 149-160°C. After washing with acetonitrile we obtained 4.7 g (54% yield) of product with mp 170-179°C.

Preparation of (IIIc). To 0.6 g of (IVc) in 10 ml of absolute ether was added 0.4 ml of BF_3·etherate, after which the mixture was allowed to stand at ~20°C for ~12 h, evaporated, 10 ml of anhydrous toluene was added to the residue, the mixture was refluxed for 5 h, again evaporated, and the residue was treated with Na_2CO_3 solution, and then acidified with conc. HCl. The obtained precipitate was dried in the air and then recrystallized from n-hexane. We obtained 0.41 g (30%) of (IIIc) with mp 100-103°C, which failed to depress the mixed melting point with an authentic specimen [6].

*The NMR spectrum was taken on an R-12 instrument. The assignment of the signals of the protons was made on the basis of the data given in [4].

To 0.5 g of (IIa) in 5 ml of anhydrous toluene was added 0.8 ml of BF_3 · etherate, after which the mixture was allowed to stand at ~20°C for 1 h, a mixture of 1 ml of (VI) and 0.4 ml of BF_3 · etherate in 5 ml of toluene, previously held at 20°C for 1 h, was added, and the whole was refluxed for 10 h. After the above indicated work-up we isolated 0.4 g (31%) of (IIIc) with mp 96-99°C.

With vigorous stirring, to a solution of 3 g of (IIa) in 30 ml of γ-picoline at −5 to 0°C was added 6 ml of (VI) in drops, after which the mixture was stirred for another 6 h at 0°C, and then poured into a mixture of ice and dilute HCl solution. The obtained precipitate was dried in the air and then recrystallized from n-hexane. We obtained 3.97 g (54%) of (IIIc) with mp 100-103°C.

Preparation of (IIId). With vigorous stirring, to a solution of 1.5 g of (IIa) in 10 ml of γ-picoline at −5 to 0°C was added 1.5 ml of $ClCOCH_2CH_2OC_2H_5$ [ppm 43-45°C (10 mm)] [7] in drops, after which the mixture was stirred for another 2.5 h at ~0°, poured into a mixture of ice and dilute HCl solution, the precipitate was treated with Na_2CO_3 solution, filtered, the filtrate was acidified with dilute HCl solution, and the obtained powder was washed with water and then dried in the air. We obtained 0.85 g (35%) of (IIId) with mp 118-121°C. After a double reprecipitation from sodium carbonate solution with dilute HCl, mp 124-126°C (decompn.). Found: C 64.54, 64.67; H 5.49, 5.65%. $C_{14}H_{15}NO_4$. Calculated: C 64.45; H 5.45%.

Hydrolytic Cleavage of (IIIa). A mixture of 2 g of (IIIa) and 50 ml of water was refluxed for 1 h, cooled, extracted with benzene, the benzene extract was evaporated, and the residue was dissolved in ether and cooled to −70°C. The obtained crystals were filtered and washed with chilled ether. We obtained 0.82 g (46%) of (Ia) with mp 63-65°C, R_f 0.57 (benzene–acetone, 2:1). Infrared spectrum (KBr): 1630, 1730 cm^{-1} Found: C 62.75, 62.98; H 6.24, 6.08; N 5.66, 5.62%. $C_{13}H_{15}NO_4$. Calculated: C 62.65; H 6.03; N 5.62%.

A mixture of 5.6 g of (IIIa) and 200 ml of dilute (1:1) HCl solution was refluxed for 10 h, cooled, and the obtained benzoic acid was filtered. The mother liquor was refluxed for 0.5 h with active carbon. The filtrate was evaporated in vacuo. We obtained 2.3 g (88%) of δ-aminolevulinic acid hydrochloride with mp 145-149°C, which failed to depress the mixed melting point with an authentic specimen [3].

Hydrolytic Cleavage of (IIIc). A mixture of 1 g of (IIIc) and 20 ml of dilute (1:1) acetic acid solution was refluxed for 1 h, cooled, and the obtained crystals were filtered and dried in the air. We obtained 0.8 g (85%) of (Ic) with mp 91-93°C. After recrystallization from n-hexane, mp 94-96°C, R_f 0.54 (benzene–acetone, 3:1). Found: C 76.82, 76.96; H 10.38, 10.47; N 3.94, 3.93%. $C_{24}H_{39}NO_2$. Calculated: C 77.30; H 10.44; N 3.75%.

Hydrolytic Cleavage of (IIId). A mixture of 1.6 g of (IIId) and 50 ml of water was refluxed for 1.5 h, cooled, extracted with ether, the extract was evaporated, and the residue was dissolved in a small amount of ether and cooled to −70°C. The obtained crystals were filtered and washed with chilled ether. We obtained 0.36 g (25%) of 1-benzoylamino–4-ethoxy–2-butanone with mp 54-55°C, R_f 0.54 (benzene–acetone, 2:1). Infrared spectrum (KBr): 1630, 1720 cm^{-1}. Found: C 66.14, 66.23; H 7.28, 7.26; N 6.17, 6.26%. $C_{13}H_{17}NO_3$. Calculated: C 66.37; H 7.24; N 5.96%.

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CONCLUSIONS

1. The O → C-isomerization of some O-acyl derivatives of 2-phenyl–5-oxazolinone was accomplished under the influence of boron trifluoride etherate.

2. It was found that γ-picoline exerts a beneficial effect on the C-acylation of 2-phenyl–5-oxazolinone with carboxylic acid chlorides.

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