MECHANISM OF THE DAKIN – WEST REACTION WITH CARBOXYLIC ACID CHLORIDES

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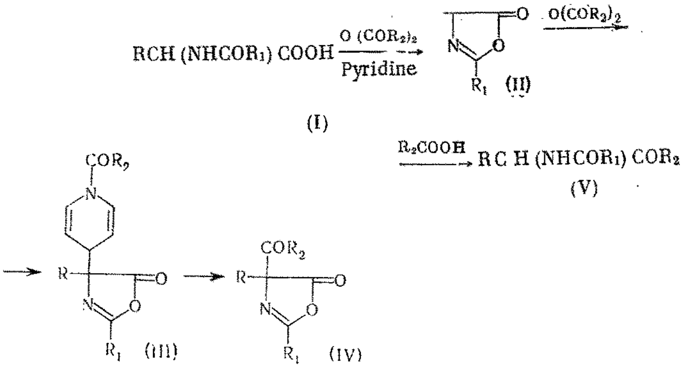
As is known [1-6], the Dakin – West reaction between α-N-acylamino acids (I) and anhydrides in the presence of pyridine proceeds by way of C-acylation of the intermediate azlactones (II) with participation of the dihydropyridine derivatives (III) by the scheme:



This work establishes that this mechanism is also retained upon substituting anhydrides by carboxylic acid chlorides. As follows from PMR spectral data (Figs. 1-3) the reaction of α-N-benzoylalanine (VI) with CH_3COCl in pyridine (~20°C) leads to the formation of 2-phenyl-4-methyloxazolin-5-one (VII), which is subsequently transformed into (III, $R = R_2 = CH_3$, $R_1 = C_6H_5$) and (IV, $R = R_2 = CH_3$, $R_1 = C_6H_5$). Upon reaction of CH_3COCl or CH_3COBr with α-N-formylalanine in pyridine (~20°) 2-[4-(1-acetyl-1,4-dihydropyridinyl)]-3-oxazolin-5-one [7] could be isolated, which was transformed into the C-acylation product under the influence of elevated temperature in pyridine.

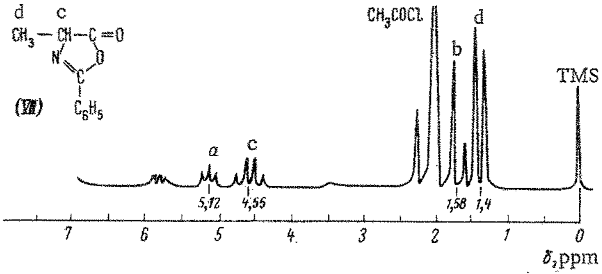


Fig. 1. PMR spectrum of the reaction mixture 60 min after addition of CH_3COCl to $CH_3CH(NHCOC_6H_5)\cdot COOH$ (VI) in pyridine (~20°). Compound (VI): a) CH; b) CH_3.

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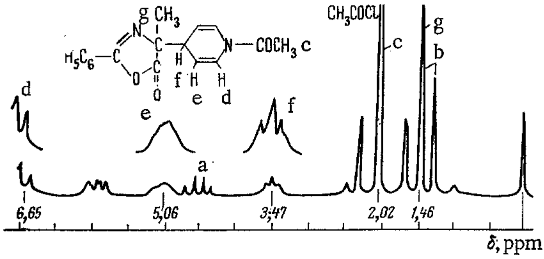


Fig. 2

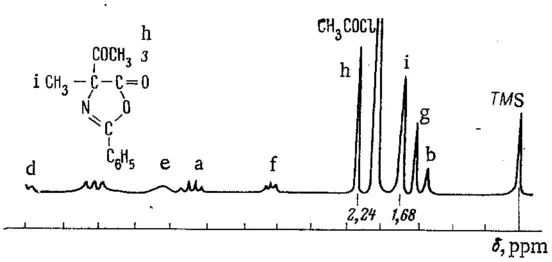


Fig. 3

Fig. 2. PMR spectrum of the reaction mixture 18 min after addition of CH_3COCl to (VII) in pyridine (~20°). Compound (VII): a) CH; b) CH_3.

Fig. 3. PMR spectrum of the reaction mixture 1.5 h after addition of CH_3COCl to (VII) in pyridine (~20°).

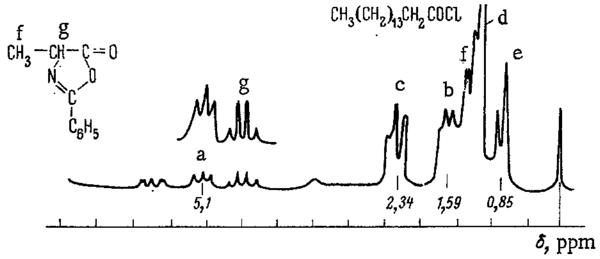
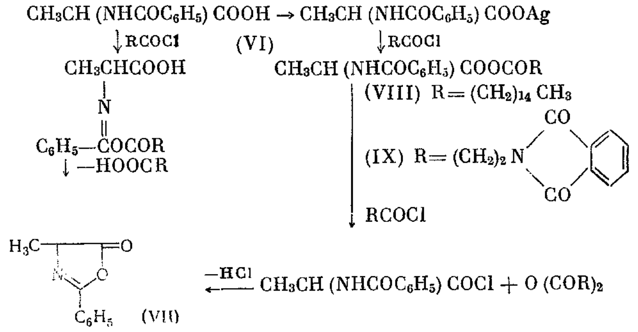


Fig. 4. PMR spectrum of the reaction mixture 10 min after addition of $CH_3(CH_2)_{14}COCl$ to $CH_3CH(NHCO\cdot C_6H_5)COOCOCH_2(CH_2)_{13}CH_3$ (VIII) in pyridine (~20°). Compound (VIII): a) CH; b) CH_3-CH; c) CH_2; d) $(CH_2)_{13}$; e) CH_3.

The participation of (II) in the Dakin – West reaction with acid chlorides is also confirmed by the ability of (VII) to react with CH_3COCl and $CH_3(CH_2)_{14}COCl$ under the usual conditions (Table 1, examples 11, 13).[*] However, hydrolytic cleavage of the intermediates (IV) is required to obtain (V) from (II), and this is attained by heating with dilute HCl or passing the reaction product through a column containing Al_2O_3.

Upon using (I) themselves in the Dakin – West reaction this treatment becomes unnecessary, since the acid R_2COOH necessary for cleavage of (IV) is formed as a result of the cyclization (I) → (II).



Azlactonization of (I) evidently precedes activation of the amide function by way of its acylation. An alternative acylation of the carbonyl group must be excluded in this case, since the mixed anhydrides (VIII) and (IX) are not cyclized into (VII) even upon heating (pyridine, 100°, 2 h); (VII) is formed from (VIII) and

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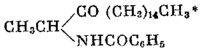
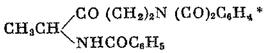
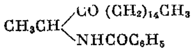
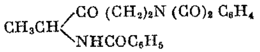
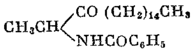
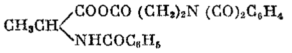
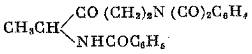
[*] While this work was being prepared a communication appeared in the press [8] in which the reaction of (VII) with RCOCl was also described. The acetylation of (VII) with acetyl chloride in low yield was indicated earlier [9].

TABLE 1

Number	Initial α-N-acylamino acids or their derivatives	Acylating agents	Dakin-West reaction products	Yield, %	
				$\sim 100°$ */1 h	$\sim 20°$/20 h
1	$CH_3CH(NHCHO)COOH$	CH_3COCl	$CH_3CH(NHCHO)COCH_3$*	73 *	0
2	"	CH_3COBr	"	75 †	0
3	"	$(CH_3CO)_2O$	"	42 ‡	0
4	$CH_3CH(NHCOC_6H_5)COOH$	CH_3COCl	$CH_3CH(NHCOC_6H_5)COCH_3$*	55	47
5	"	$(CH_3CO)_2O$	"	76	80
6	"	$CH_3(CH_2)_{14}COCl$	 $CH_3CH{<}\begin{matrix}CO(CH_2)_{14}CH_3{}^*\\ NHCOC_6H_5\end{matrix}$	73 (1,5 h)	46
7	"	$[CH_3(CH_2)_{14}CO]_2O$	"	59	18
8	"	C_6H_5COCl	$CH_3CH(NHCOC_6H_5)(COC_6H_5)$*	46	10
9	"	$(C_6H_5CO)_2O$	"	27	—
10	"	$C_6H_4(CO)_2N(CH_2)_2COCl$	 $CH_3CH{<}\begin{matrix}CO(CH_2)_2N(CO)_2C_6H_4{}^*\\ NHCOC_6H_5\end{matrix}$	56	20
11	VII	CH_3COCl	$CH_3CH(NHCOC_6H_5)COCH_3$	15 †	40
12	VII	$(CH_3CO)_2O$	"	—	70
13	VII	$CH_3(CH_2)_{14}COCl$	 $CH_3CH{<}\begin{matrix}CO(CH_2)_{14}CH_3\\ NHCOC_6H_5\end{matrix}$	73 (1.5 h)	39
14	VII	$[CH_3(CH_2)_{14}CO]_2O$	"	44 (1.5 h)	31
15	VII	$C_6H_4(CO)_2N(CH_2)_2COCl$	 $CH_3CH{<}\begin{matrix}CO(CH_2)_2N(CO)_2C_6H_4\\ NHCOC_6H_5\end{matrix}$	—	20
16	$CH_3CH(NHCOC_6H_5)COOCOC_6H_5$	C_6H_5COCl	$CH_3CH(NHCOC_6H_5)COC_6H_5$	50	0
17	$CH_3CH(NHCOC_6H_5)COOCO(CH_2)_{14}CH_3$	$CH_3(CH_2)_{14}COCl$	 $CH_3CH{<}\begin{matrix}CO(CH_2)_{14}CH_3\\ NHCOC_6H_5\end{matrix}$	54 (1,5 h	46
18	 $CH_3CH{<}\begin{matrix}COOCO(CH_2)_2N(CO)_2C_6H_4\\ NHCOC_6H_5\end{matrix}$	$C_6H_4(CO)_2N(CH_2)_2COCl$	 $CH_3CH{<}\begin{matrix}CO(CH_2)_2N(CO)_2C_6H_4\\ NHCOC_6H_5\end{matrix}$	52 (5 h	36

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*Physicochemical constants are presented in [9].

† Yields are indicated for 4, 5-dimethylimidazolin-2-one, easily formed upon hydrolysis of the Dakin-West reaction product and subsequent carbamidation of the intermediate $CH_3CH(NH_2\cdot NCl)COCH_3$ [9].

‡ Strongly contaminated reaction product.

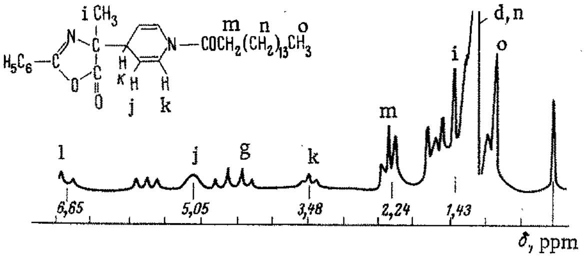

Fig. 5. PMR spectrum of the reaction mixture 1 h after addition of $CH_3(CH_2)_{14}COCl$ to (VIII) in pyridine (~20°).

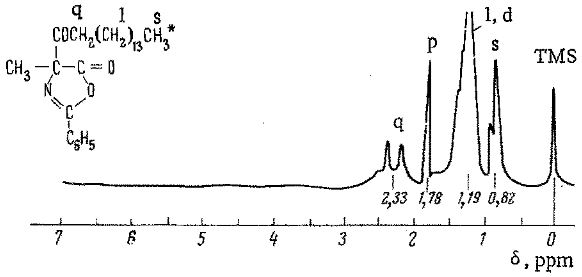

Fig. 6. PMR spectrum of the reaction mixture 30 h after addition of $CH_3(CH_2)_{14}COCl$ to (VIII) in pyridine (~20°).

(IX) only upon their reaction with acid chlorides, probably with participation of transacylation and cyclization reactions. Subsequent transformation of (VIII) into [(IV), R = CH_3, $R_1 = C_6H_5$, $R_2 = (CH_2)_{14}CH_3$] upon reaction with $CH_3(CH_2)_{14}COCl$ in pyridine (~20°) through intermediate stages of (VII) and [(III), R = CH_3, $R_1 = C_6H_5$, $R_2 = (CH_2)_{14}CH_3$] can be followed by PMR spectra (see Figs. 4-6).

The acylating properties of acid chlorides and anhydrides in the Dakin – West reaction are displayed to a different degree depending on the structure of reagents and the experimental conditions. As is seen from data of Table 1, acid chlorides, as a rule, exceed anhydrides in yield of Dakin – West reaction products. An only exception is CH_3COCl, which by virtue of its instability in pyridine [11] gives (V, $R = R_2 = CH_3$, $R_1 = C_6H_5$) with (VI) and (VII) in much lower yield than $(CH_3CO)_2O$ (see Table 1, examples 4, 5, 11, 12).

EXPERIMENTAL

Dakin – West Reaction with N-Formyl-α-alanine. A mixture of 0.3 g of α-N-formylalanine and 0.5 ml of CH_3COCl or CH_3COBr in 5 ml of pyridine was heated for 1 h at 100° and evaporated in vacuum to dryness; benzene extraction of the residue gave 0.3 g of oily 2-formamido-3-butanone. Hydrolysis of the latter with dilute HCl and subsequent treatment with KCNO as described earlier [9] yielded 0.21 g (73%) of 4,5-dimethylimidazolin-2-one having mp 310-313° (dec.). Substitution of CH_3COCl and CH_3COBr by $(CH_3CO)_2O$ led to a sharp decrease in yield of 2-formamido-3-butanone (example 3). A mixture of 0.3 g of α-N-formylalanine and 0.45 ml of CH_3COCl in 3 ml of pyridine was maintained at ~20° for 15 h and then evaporated in vacuum to dryness. Benzene extraction of the residue gave 0.37 g of an oil which was subjected to low-temperature crystallization from ether. We obtained 0.2 g of 2-[4-(1-acetyl-1,4-dihydropyridinyl)]-3-oxazolin-5-one [7], mp 89-93°. After recrystallization from isopropanol the melting point increased to 106-108°. R_f 0.66 (benzene – acetone, 1 : 1). Found: C 60.33; 60.35; H 5.76; 5.51; N 12.80; 12.74%. $C_{11}H_{12}N_2O_3$. Calculated: C 60.00; H 5.45; N 12.70%.

Heating it in pyridine (100°, 1 h) with subsequent hydrolysis with dilute HCl and treatment with KCNO yielded 4,5-dimethylimidazolin-2-one, yield 40%.

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* Obtained according to Steglich and Hofle [10], oil, R_f 0.71 (here and further thin-layer chromatography was on silica gel HF_{254}, benzene – ethyl acetate 5 : 1).

Dakin – West Reaction with α-N-Benzoylalanine. A mixture of 0.003 mole of α-N-benzoylalanine and 0.009 mole of anhydride or acid chloride in 5 ml of pyridine was heated for 1-1.5 h at ~100°, then evaporated in vacuum to dryness, and the residue was extracted with benzene. The benzene extract was transferred to a column of Al_2O_3 (act. III) and the Dakin – West reaction products were eluted with benzene or a mixture of benzene and ethyl acetate, 1 : 1 (examples 4-10). A mixture of 0.003 mole of α-N-benzoylalanine and 0.009 mole of anhydride or acid chloride in 5 ml of pyridine was maintained for 15-20 h at ~20°, then evaporated in vacuum to dryness; the remaining C-acylated azlactone was hydrolyzed by heating with a mixture of 10 ml of dilute HCl, 1 : 1, and 5 ml of acetic acid, and the Dakin – West reaction products were isolated as indicated above (examples 4-8, 10). Methods of identification and physicochemical constants of the Dakin – West reaction products are presented in [9].

The reaction of anhydrides or acid chlorides (0.003 mole) with 2-phenyl-4-methyloxazoline-5-one (VII) (0.002 mole) (examples 11-15) was carried out analogously.

Reaction of Acid Chlorides with Mixed Anhydrides of α-N-Benzoylalanine. To a suspension of 0.003 mole of the Ag salt of α-N-benzoylalanine in 5 ml of pyridine was added 0.003 mole of the acid chloride; the mixture was stirred for 30 min at ~20°, then an additional 0.006 mole of acid chloride was added and further operations were carried out as described above (examples 16-18).

PMR spectra were taken in pyridine on a DA-60-1 instrument. Assignment of proton signals was carried out on the basis of data of Steglich and Höfle [6].

In conclusion we express our gratitude to E. P. Prokof'ev and V. A. Korenevskii for carrying out the spectral investigations.

CONCLUSIONS

1. Acid chlorides enter into the Dakin – West reaction with α-N-acylamino acids in a pyridine medium via intermediate stages of formation of the azlactone and its C-acylation.

2. Upon reaction with α-N-acylamino acids in pyridine (~100°, 1-1.5 or at ~20°, 20 h) acid chlorides give, as a rule, higher yields of Dakin – West reaction products than anhydrides.

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