CATALYTIC ASYMMETRIC SYNTHESIS OF DIPEPTIDES FROM 2-TRIFLUOROMETHYL-Δ^2-AND 2-TRIFLUOROMETHYL-Δ^3-OXAZOLIN-5-ONES

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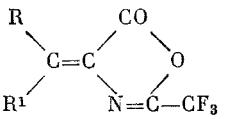
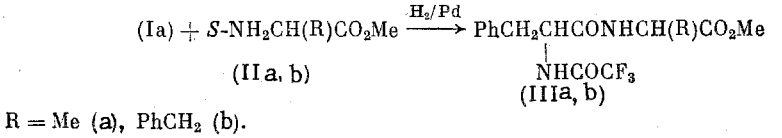
We have shown that the reductive aminolysis (RA) of 2-trifluoromethyloxazolin-5-ones (I) on a Pd–S-α-phenylethylamine (PEA) catalytic system gives trifluoroacetylphenylalanine amides amides, from which optically active α-phenylethylamides of S-amino acids were obtained by selective hydrolysis [1]. In the present work, we studied the RA of (I) by the action of esters of S-amino acids, to prepare optically active dipepetides.

DISCUSSION OF RESULTS

The initial oxazolinones  (Ia, b) were obtained according to [2], R = H, R^1 = Ph (a), R = R^1 = Me (b).

The RA of (Ia) was carried out at 20°C and at 1.2-1.3 atm H_2 in various solvents (scheme 1)

Scheme 1



R = Me (a), $PhCH_2$ (b).

The catalyst was obtained by reducing $PdCl_2$ in situ in the presence of S-(II). The rate of RA of (Ia), determined from the absorption of hydrogen, is described by a first order equation with respect to unsaturated substrate and depends little on the nature of the solvent (Table 1). The yields of trifluoroacetyldipeptides (III) are quantitative, but the stereoselectivity of the reaction is not high: the excess of the RS-diastereomer (III) is 2-15%. The analysis of the reaction products and the ratio of the diastereomers of (III) was determined by PMR and GLC. The signals were assigned according to the enantiomeric GLC analysis of amino acids [3], obtained by hydrolysis of (III). In the PMR spectra of (III), the weak-field MeO signals correspond to SS-(III) in all the dipeptides studied. The ratio between the diastereomers of TFAPheAlaOMe was determined according to the relative intensity of the MeCH signals. The data of the PMR spectra are given in Table 2, and the results of the gas-chromatographic separation of the diastereomers of (III) in Table 3. In the case of (Ib), the reaction leads to the formation of dehydrodipeptides $Me_2C{=}CCONHCH(R)CO_2Me$ (NHCOCF) (IVb), which are not reduced further.

It has already been shown that the RA of (Ia) in the presence of S-PEA and $PdCl_2$ proceeds via the intermediate formation of S-phenylethylamide of trifluoroacetylaminocinnamic acid [1]. We therefore studied the asymmetric hydrogenation of dehydrodipeptides (IV) on catalysts obtained in situ from $PdCl_2$ (a), $PdCl_2$ + S = (II) (b), $PdCl_2$ + S-PEA (c) (Table 4). On all the catalysts, the reduction of (IVa) is characterized by a high degree of conversion, but by an extraordinarily low stereoselectivity. A noticeable effect, possibly due to both diastereo-

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TABLE 1. Reductive Aminolysis of 2-Trifluoromethyl-Δ^2-oxidiazolin-5-ones (I) Carrying out the Reaction in One and Two Stages ((I) 0.5 mmole, (II) 0.75 mmole, solvent 7.5 ml, $PdCl_2$, 0.09 mole)

Oxazolinone	Amino esters S-(II)	Solvent*	Excess of diastereomer of (III), %	Configuration of (III), %	$k.10^3$ min^{-1}
(Ia)	AlaOMe	DME	15	*RS*	0.5
	»	t-BuOH	2 †	*RS*	4.9
	PheOMe	DME	2	*RS*	5.0
	»	DO	11	*RS*	11.3
	»	t-BuOH	4	*RS*	4.7
	»	THF	4	*RS*	5.7
		Two-stage process ‡			
(Ib)	PheOMe	THF	54	*SS*	
	ProOMe	THF	54	*RS*	

*DME – dimethoxyethane, DO – dioxane.
†The formation of excess RS-diastereomer is confirmed by the hydrolysis of (III) followed by chromatographic separation of Phe and Ala and determination of positive dispersion of optical rotation of Phe.

‡ (Ib) $\xrightarrow[Et_3N]{H_2/Pd}$ [Me$_2$CHCH(CO)–N=C(O)–C(CF$_3$)] (V6) $\xrightarrow{S\text{-(II)}}$ Me$_2$CHCHCONHCH(R)CO$_2$Me (III), NHCOCF$_3$

TABLE 2. PMR Spectra of Dipeptides (III) Obtained

Dipeptide (III)	CH_3CH, d	OCH_3, s	CH_2Ph, m	CH, m	C_6H_5, m
TFAPhePheOMe		3.75 * 3.65 †	3.05 * 2.95 †	4.60, 4.75	7.25
TFAPheAlaOMe	1.35 * 1.25 †	3.75 * 3.70 †	3.01	4.40, 4.70	7.25
TFAPheValOMe	0.82 * 0.85 * 0.72 † 0.74 †	3.70 * 3.68 †	3.1	2.1, 4.45 4.8	7.25
TFAValAlaOMe	1.37 * 1.39 † 0.93 ‡	3.70 * 3.68 †		2.1, 4.36 4.53	
TFAValPheOMe	0.91 * 0.93 * 0.74 † 0.78 †	3.75 * 3.70 †	3.1	2.03, 4.28 4.86	7.25
TFAValValOMe	0.95 ‡	3.77 * 3.73 †		2.12, 2.31 4.52, 4.6	

*SS-(III).
†RS-(III).
‡Multiplet $(\underline{Me})_2CH$.

selective and enantioselective action [4], is observed only in the case of chiral metallocomplexing catalyst (c). The catalyst obtained by the reduction of $PdCl_2$ in the presence of S-PEA in $CHCl_3$ (d) was found [4] to be inactive. The reductive of (IVb) did not occur on catalysts (a-d).

TABLE 3. Results of GLC of Dipeptides (III)

Compound (III) being analyzed	Length of column, m	T., °C	Time of analysis, min	Separation criterion of diastereomers, R_S	Order of elution of diastereomers	
					1st peak	2nd peak
TFAPhePheOMe	38	235	60	2.14	*SS*	*RS*
TFAPheAlaOMe	38	174	40	1.15	*SS*	*RS*
TFAPheProOMe	20 *	186	33	1.14	*SS*	*RS*
TFAPheValOMe	20 *	160	32	1.26	*SS*	*RS*
TFAValPheOMe	15	209	15	3.11	*SS*	*RS*
TFAValAlaOMe	50 †	190	39	1.95	*RS*	*SS*
TFAValProOMe	20 *	182	30	3.18	*RS*	*SS*
TFAValValOMe	20 *	180	3	1.25	*SS*	*RS*

*Stationary liquid phase (SLP) – 90% OV-17 + 10% PEG-40M.
†SLP – PEG-40M.

TABLE 4. Hydrogenation of Methyl Esters of N-Trifluoroacetyldehydrodipeptides $PhCH{=}C(NHCOCF_3)CONHCH(R)CO_2Me$ (IVa) on Pd Catalysts

((IV) 0.5 mmole, solvent 7.5 ml, $PdCl_2$ 0.09 mmole, p 1.2 atm, 20°C)

R	Catalyst	Solvent	Degree of conversion, %	Excess RS-(III), %	$k^* \cdot 10^3$, min^{-1}
Me	a	DME	100	8	10
	a	*t*-BuOH	95	8	16
	b	DME	100	8	22
	b	*t*-BuOH	100	5	5
	c	DME	70	20	28
Ph	a	DO	100	8	10
	a	*t*-BuOH	100	2	21
	a	THF	90	2	9
		DME	100	5	10
	b	*t*-BuOH	100	0	5
	c	DME	100	12	19

*A linear dependence of ln C on t is realized with correlation coefficient 0.98-0.99. Coefficient k was determined as arithmetical mean of 2-3 experiments, relative error 10-15%.

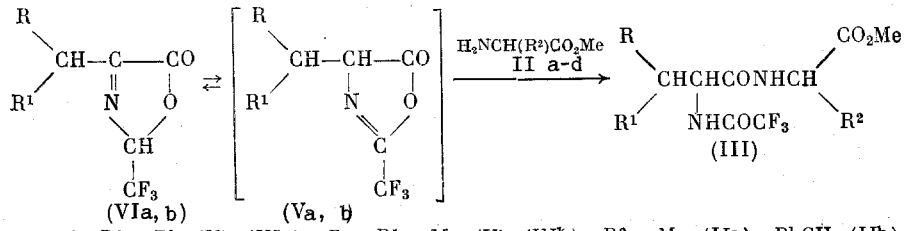
Comparing rate constants, stereodirectivity and stereoselectivity of the RA processes of (Ia) and hydrogenation of (IVa) (compare Tables 1 and 4), it can be assumed that the RA proceeds through an intermediate formation of (IV). Carrying out the RA of (Ib) in two stages showed that in the reduction of (Ib) into (Vb) in the presence of $PdCl_2$ and Et_3N, followed by aminolysis by esters (II), a mixture of peptide (IIIb) (∿7%) and dehydrodipeptide (IVb) with a 1:1 composition and of by-products is obtained. The aminolysis of (Vb) proceeds with a high stereoselectivity: the excess of diastereomer of (IIIb) reaches 54% (GLC analysis), whereby the stereodirectivity of the process depends on the nucleophile (II) used: in the case of S-PheOMe, SS-(IIIb) is preferentially formed, while with S-ProOMe, RS-(IIIb) is preferred (see Table 1). Comparison of these results with the RA data shows that the possibility of the occurrence of RA via the intermediate formation of (V) can be excluded.

The high stereoselectivity of aminolysis of (V) prompted us to study the reaction of its stable isomer of Δ^3-oxazolinone (VI) with S-(II). As the result of aminolysis of (VI), peptides (III) were obtained in quantitative yield (scheme 2)

TABLE 5. Aminolysis of 2-Trifluoromethyl-Δ^3-oxazolin-5-ones (VI) by Methyl Esters of S-Amino Acids (II) ((VI) – 1 mmole, (II), 1.5 mmole, solvent 15 ml)

R	R¹	Amino ester S-(II)	Solvent	Ratio of diastereomers of (III), % SS:RS	Excess of diastereomer of (III)	
					%	configuration
H	Ph	AlaOMe	*t*-BuOH	52 : 48	4	*SS*
		»	DO	67 : 33	34	*SS*
		»	DME	69 : 31	38	*SS*
		ValOMe	DO	77.5 : 22.5	55	*SS*
		PheOMe	*t*-BuOH	53.5 : 46.5	7	*SS*
		»	DO	78 : 22	56	*SS*
		»	THF	74 : 26	48	*SS*
		ProOMe	*t*-BuOH	39 : 61	22	*RS*
		»	DO	26 : 74	48	*RS*
		»	THF	39 : 61	22	*RS*
Me	Me	AlaOMe	*t*-BuOH	55 : 45	10	*SS*
		»	THF	77.5 : 22.5	55	*SS*
		ValOMe	*t*-BuOH	54 : 46	8	*SS*
		»	THF	82.5 : 17.5	65	*SS*
		PheOMe	*t*-BuOH	58.5 : 41.5	17	*SS*
		»	THF	75 : 25	50	*SS*
		»	DO	75 : 25	50	*SS*
		ProOMe	THF	26.5 : 73.5	46	*RS*
		»	*t*-BuOH	35.5 : 64.5	29	*RS*

Scheme 2

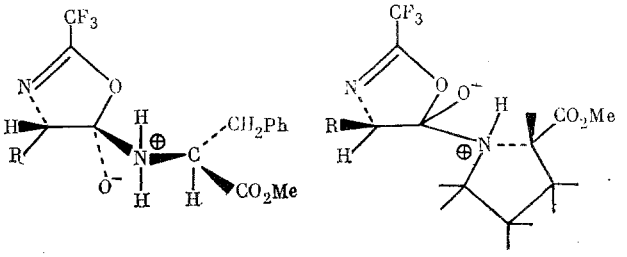


R = H, R¹ = Ph (V), (VIa); R = R¹ = Me (V), (VIb); R² = Me (IIa), $PhCH_2$ (IIb), *i*-Pr (IIc), ProOMe (IId).

The reaction proceeds stereoselectively (Table 5) with preferential formation of SS-(III) in all cases, as well as aminolysis by the action of S-ProOMe. The stereoselectivity depends substantially on the type of solvent: during aminolysis in t-BuOH, the excess of SS-(III) is 4-17%, while in DO, THF and DME it increases to 40-50%. We should note the equal stereoselectivity of aminolysis of Δ^2-oxazolinone (Vb) (see Table 1) and Δ^3-oxazolinone (VIb) (see Table 5) and also the change in stereodirectivity of the processes on transition from S-PheOMe to S-ProOMe. This possibly indicates that the aminolysis of (VI) proceeds via (V) (see scheme 2).

To explain the stereodirectivity of the aminolysis, we shall examine the stereochemistry of the reaction with the nucleophiles studied. According to [5], it can be assumed that the aminolysis of (V) present in equilibrium with (VI) (see scheme 2) proceeds via the intermediate (VII).

The molecular model of intermediate (VIIa) shows that the preferential conformation is determined by the dipseudoequatorial position of substituent R and the amino ester fragment. Thus, the repulsion of the ring oxygen atoms and the CF_3 group from the ester group of the amino ester fragment leads to a higher stability of SS-(VIIa) compared with RS-(VIIa), since in the latter these groups approach closer to each other.



SS-(VIIa) *RS*-(VIIb)

On the other hand, in the case of ProOMe, the RS-diastereomer becomes stabilized due to the pseudoequatorial disposition of the radical R, the amino ester fragment and the carbomethoxyl group in proline. In the SS-intermediate, at least one of the substituents should occupy a pseudoaxial position.

Thus, because of the high stereoselectivity of 2-trifluoromethyl-Δ^3-oxazolin-5-ones by the action of S-amino esters, SS-dipeptides can be obtained starting from racemic amino acids. By crystallization of the aminolysis products of Δ^3-oxazolin-5-ones, diastereomerically pure SS-(III) were isolated: TFAPheAlaOMe; TFAPhePheOMe. Removal of the protective groups gives the corresponding optically pure dipeptides.

EXPERIMENTAL

The PMR spectra were measured on "Varian DA-60-IL" and "Bruker WP-250" spectrometer, using HMDS as internal standard. The IR spectra were run on an UR-20 spectrophotometer, the UV spectra — on a "Specord" spectrophotometer, and the DOR spectra — on a Spectropol-1 spectropolarimeter. The GLC analysis was carried out on a Biochrom-1 chromatograph with glass capillary columns. The ratio between the diastereomers of (III) was determined on a column with OV-17, and the ratio between Phe and Val enantiomers in the form of isopropyl esters of trifluoroacetylamino acids was determined on a column with a chiral phase of tert.-butylamide of N-docosanoyl-L-valine [3].

2-Trifluoromethyl-4-benzylidene-Δ^2-oxazolin-5-one (Ia), 2-trifluoromethyl-4-isopropylidene-Δ^2-oxazolin-5-one (Ib), 2-trifluoromethyl-4-benzyl-Δ^3-oxazolin-5-one (VIa), and 2-trifluoromethyl-4-isopropyl-Δ^3-oxazolin-5-one (VIb) were described in [1].

The methyl esters of N-trifluoroacetyldehydrodipeptides were obtained according to [2]. The yield after recrystallization from the corresponding solvent was 50-60%.

Methyl ester of N-trifluoroacetyldehydrovalylphenylalanine: mp 151-152°C (methanol: water, 1:1). PMR spectrum ($CDCl_3$, δ, ppm): 1.57 s, 1.72 s ($C\underline{H}_3C$), 3.02 d ($C\underline{H}_2CH$), 3.62 s ($OC\underline{H}_3$), 3.94 m ($C\underline{H}$), 7.12 m ($O_6\underline{H}_5$).

Methyl ester of N-trifluoroacetyldehydrovalylalanine: mp. 149-150°C (ethanol:water, 1:1). PMR spectrum ($CDCl_3$, δ, ppm): 1.36 d ($C\underline{H}_3CH$), 1.67 s ($C\underline{H}_3C$), 1.92 s($C\underline{H}_3C$), 3.66 s ($OC\underline{H}_3$), 4.49 m ($CH_3C\underline{H}$).

Methyl ester of N-trifluoroacetyldehydrovalylproline: mp 217-219°C (ethanol:water, 1:1). PMR spectrum ($CDCl_3$, δ, ppm): 1.7 s, 1.95 s ($C\underline{H}_3$), 3.75 s ($OC\underline{H}_3$). $[\alpha]\lambda^{17}$ (λ, nm) (C 6.0, $CHCl_3$): −184° (350), −165° (470), −94.6° (589).

Methyl ester of N-trifluoroacetyldehydrophenylalanylphenylalanine, mp 144-145°C (ethanol: water, 1:1) (cf. [2]). PMR spectrum ($CDCl_3$, δ, ppm): 315 d ($C\underline{H}_2CH$), 3.75 s ($OC\underline{H}_3$), 4.85 quart ($C\underline{H}CH_2$), 6.68 d ($N\underline{H}CH$), 7.35 m ($C_6\underline{H}_5$). IR spectrum ($CHCl_3$, ν, cm^{-1}): 3035, 3400 (NH-val), 1735, 1665 (amide I), 1515 (amide II), 1175 (CF). UV spectrum (C_2H_5OH): λ_{max} 277 nm (log ε 4.34).

Methyl ester of N-trifluoroacetyldehydrophenylalanylalanine, mp 166-167°C (ethanol:water, 1:1). PMR spectrum ($CDCl_3$, δ, ppm): 1.42 d ($C\underline{H}_3CH$), 3.72 s ($OC\underline{H}_3$), 4.56 m ($C\underline{H}CH_3$), 7.0 d (NHCH), 7.33 m ($C_6\underline{H}_5CH$). IR spectrum ($CHCl_3$, ν, cm^{-1}): 3035, 3410 (NH-val), 1735, 1670 (amide I), 1515 (amide II), 1170 (CF). UV spectrum (C_2H_5OH); λ_{max} 217 nm (log ε 4.31).

The reductive aminolysis of (Ia) was carried out in a thermostated reactor, with stirring. A 0.09 mmole portion of $PdCl_2$ in 3 ml of a solvent was reduced by hydrogen in the presence of 0.75 mmole of S-(II) hydrochloride and 0.5 mmole of triethylamine for 10 min.

Then 0.5 mmole of (Ia) in 4 ml of a solvent was introduced into the reactor, and the rate of absorption of hydrogen was measured. At the end of the reaction, the catalyst was separated by centrifugation and the solution was treated according to [1]. The yield of (III) was 89-95%.

The preferential formation of methyl ester of N-trifluoroacetylphenylalanylalanine in an RS-configuration was confirmed by obtainment of R-phenylalanine after the hydrolysis of the peptide (6 N HCl, 7 h in an Ar current) and chromatographic separation of phenylalanine and alanine.

Separation of Phe and Ala. A 0.162 g portion of a mixture of amino acids, obtained after the hydrolysis of (IIIa), was dissolved in 5 ml of water, and the solution was deposited on a 2.9 dm × 13.5 mm column with an IA-1R resin. The alanine was eluted with 45 ml of 2N NH_4OH; phenylalanine was eluted by the following 50 ml of 2N NH_4OH. The separation of the amino acids was controlled by TLC on Silufol UV-254 plates in a butanol:acetic acid:water = 3:1:1 system of solvents. After evaporation of the eluate, 0.079 g of R-Phe was obtained with optical purity of 2.2%. $[\alpha]_{365}^{20}$ + 2.15° (C 2.6, H_2O).

Two-stage process. A 0.5 mmole portion of oxazolinone (Ib) was hydrogenated for 5 h in 7 ml of absolute THF in the presence of 0.75 mmole of triethylamine and 18 mg of $PdCl_2$. A 0.75 mmole portion of the 5-amino acid ester hydrochloride was introduced into the reactor in a hydrogen current, and the mixture was left standing overnight. After separation of the catalyst, the mixture was passed through a column with Dowex 50 × 8 (the H^+-form), evaporated, and analyzed by the GLC method, using an absolute calibration.

Hydrogenation of methyl esters of N-trifluoroacetyldehydrodipeptides (IV) was carried out in a thermostated reactor with stirring. After 0.09 mmole of the catalyst has been prepared, 0.5 mmole of (IV) was introduced into the reactor, and the rate of absorption of hydrogen was measured. The catalyst (a) was separated by centrifugation, the solvent was evaporated, and the product was analyzed. In the remaining cases, the catalyzate was passed through a column with Dowex 50 × 8 (in the H^+-form), the column was washed with the corresponding solvent, and the solution was evaporated.

Catalysts: a) reduction of $PdCl_2$ in a hydrogen current (10 min); b) a 0.018 mmole portion of $PdCl_2$ was reduced in the presence of 0.5 mmole of S-(II) and 0.5 mmole of triethylamine (10 min); c) a 0.018 mmole portion of $PdCl_2$ was reduced in the presence of 0.5 mmole of S-(-)-α-phenylethylamine (10 min); d) the catalyst was obtained according to [4].

Aminolysis of 2-trifluoromethyl-Δ^3-oxazolin-5-ones (VI): a 1 mmole portion of S-amino acid ester hydrochloride and 1.2 mmole of triethylamine were added to 1 mmole of (I) in 15 ml of a solvent. The reaction was controlled according to the disappearance of the 1810 cm^{-1} band in the IR spectra. Triethylamine hydrochloride was filtered, and the solution was passed through a column with Dowex 50 × 8 (in the H^+ form), evaporated, and a mixture of diastereomers of (III) was obtained. After crystallization from methanol, SS-TFAPhePheOMe was obtained, mp 186-187°C; $[\alpha]_{365}^{20}$ +8.8° (C 1, EtOH). After crystallization from an ether – ethyl acetate (1:1) mixture, SS-TFAPheAlaOMe was obtained, mp 154-155°C, $[\alpha]_{365}^{20}$ +26.2° (C 0.9, alcohol).

Removal of protecting groups. The simultaneous removal of the protecting groups was carried out according to [6]. A 1.8 ml portion of 1 N NaOH was added to a solution of 100 mg of SS-(III) in 5 ml of 95% ethanol. The reaction was controlled by TLC on Silufol-UV-254 plates in a $CHCl_3$:CH_3OH = 10:1 system. After 24 h, the solution was acidified with 2.4 ml of 1N HCl, and deposited on a column with Dowex 50 × 8 (in the H^+-form). The resin was washed to a neutral reaction, and the peptide was eluted with 4N NH_4OH. The solution was evaporated. To the resulting oil, add 4 ml 3 N HCl in methanol and evaporate the solution. Yield, 36 g (46%) of SS-phenylalanylphenylalanine hydrochloride, mp 127-128°C, PMR spectrum (CD_3OD, δ, ppm): 3.00 m (CH_2CH), 3.20 m (CH_2CH), 4.08 quart. ($CHCH_2$), 4.65 ($CHCH_2$), 7.20 m (C_6H_5). IR spectrum (KBr, ν, cm^{-1}): 3330, 3240 (NH-val, OH-val), 1670 (amide I), 1550 (amide II). $[\alpha]_{365}^{20}$ +57.5° (C 1.2 H_2O).

SS-Phenylalanylalanine hydrochloride (37 mg, 53%) was obtained in a similar way, $[\alpha]_{365}^{20}$ +12.66° (C 1.2 H_2O). The PMR spectrum in D_2O corresponds to this peptide. IR spectrum (KBr, ν, cm^{-1}): 3430, 3220 (NH-val, OH-val), 3070, 1680 (amide I), 1560 (amide II).

CONCLUSIONS

1. Reductive aminolysis of 2-trifluoromethyl-4-benzylidene-Δ^2-oxazolin-5-one in the presence of S-amino acid esters, $PdCl_2$ and H_2 proceeds via the intermediate formation of RS-peptides.

2. Aminolysis of 2-trifluoromethyl-Δ^3-oxazolin-5-ones with S-AlaOMe, S-ValOMe, S-PheOMe proceeds with a high stereoselectivity, with the formation of SS-diastereomer, so that optically pure SS-PheAla and SS-PhePhe dipeptides could be obtained.

3. Aminolysis of 2-trifluoromethyl-Δ^3-oxazolin-5-ones with S-ProOMe preferentially gives RS-peptides.

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HETERYLADAMANTANES. COMMUNICATION 6.*

SYNTHESIS AND SOME PROPERTIES OF 6-(1-ADAMANTYL)-3-CYANOPYRIDIN-2(1H)-ONE

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We have previously described [1, 2] the isolation of 6-(1-adamantyl)-3-cyanopyridine-2(1H)-thione and its corresponding selenone by reaction of the Na salt of 3-(1-adamantyl)-1-hydroxyprop-1-en-3-one (I) with cyanothioacetamide or cyanoselenoacetamide and have reported some of their properties.

In order to elucidate the effect of the type of exocyclic heteroatom on the structure and properties of adamantyl-substituted pyridines, we have synthesized 6-(1-adamantyl)-3-cyanopyridin-2(1H)-one (II) by reaction of salt (I) with cyanoacetamide in alcohol in the presence of AcOH (for previous communication, see [3]). The structure of pyridone (II), which has been obtained for the first time, was confirmed by the data of IR, UV, and PMR spectroscopy, mass spectrometry and elemental analysis. Comparison of the high-resolution ^{13}C NMR spectrum of pyridone (II) with the spectrum of the analogous 6-(1-adamantyl)-3-cyanopyridine-2(1H)-thione [2] revealed that there are only small differences between them in the chemical shifts of the C^4 and C^5 carbons and the CN groups; there are a displacements of the signals from the C^2 and C^3 carbons upfield ($\Delta\delta$ = 13-15 ppm) and agreement within the limits of experimental error of the spin–spin coupling constant values of $^{13}C^{-1}H$ when the C=O in the pyridine molecule (Table 1).

When pyridone (II) is treated with PCl_5 at 150-170°C, 6-(1-adamantyl)-2-chloro-3-cyanopyridine (III) is formed in 85% yield, having a chlorine atom which is labile and can be replaced by amines to form aminopyridines (IV). In the IR spectra of (IV) there are vibrational bands from the CN group in the region 2220-2230 cm^{-1} and stretching vibrations from the NH group of (IVa) in the region 3360-3420 cm^{-1}. In the PMR spectra of (IV) there are signals in characteristic regions from the protons of all fragments of the molecule, while the signal from the NH group proton in (IVa) appears in the form of a broadened singlet at 5.08 ppm (Table 2).

*For Communication 5, see [1].

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