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REACTION OF 1-ACETYL-5-HYDROXY-2-PHENYLPYRAZOLIDINES WITH AMINO ACID ESTERS*

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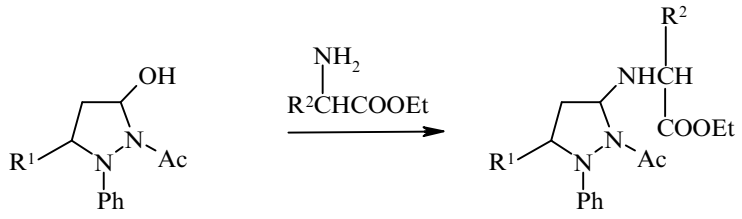
Reaction of 1-acetyl-2-phenyl-5-hydroxypyrazolidines with amino acid esters occurs to give the corresponding N-pyrazolidinyl amino acids under mild conditions.

Keywords: aminopyrazolidines, hydroxypyrazolidines, amino acid esters, N-alkylation, nucleophilic substitution

The hydroxyl group of 5-hydroxypyrazolidines **1** readily undergoes nucleophilic substitution including reactions with different amines [1, 2]. Amino acids have not been included amongst the amines for which this reaction has been studied. Since amino acid derivatives of the pyrazolidines can show a high degree of biological activity we set out with the aim of developing a preparative method for such derivatives **2**.

In the case of the introduction of the glycine residue it was found that the most convenient reactive form of the amino acid is its ester. Heating a benzene solution of the hydroxypyrazolidine **1a** for 30 min with glycine ester leads to decomposition of the starting pyrazolidine, dimerization of the glycine ester to diketopiperazine, and only an insignificant amount of the desired product. Activation of the reaction mixture using high frequency irradiation gave virtually the same results. The optimum conditions proved to be mixing the reagents and holding the mixture without solvent at room temperature in the dark for several days. The only reaction product is 1-acetyl-2-phenyl-3-methyl-5-(α-carbethoxymethylamino)pyrazolidine (**2a**).



1a,b **2a–k**

1a R^1 = Me; **b** R^1 = H; **2a** R^1 = Me, R^2 = H; **b** R^1 = Me, R^2 = Me; **c** R^1 = Me, R^2 = CH_2Ph; **d** R^1 = Me, R^2 = CH_2Ind; **e** – proline ester derivative, R^1 = Me; **f** R^1 = Me, R^2 = CHMeEt; **g** R^1 = Me, R^2 = *i*-Bu; **h** R^1 = Me, R^2 = *n*-Pr; **i** R^1 = H, R^2 = H; **k** R^1 = H, R^2 = CH_2Ph

Similarly to the glycine ester, other amino acid esters were introduced into the reaction. It was found that a change of the structural properties of the amino acids did not cause a marked change in the reaction conditions or the yield of the target compound.

* Dedicated to A. N. Kost on the occasion of his 85th birthday.

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TABLE 1. Parameters of the Compounds Prepared **2a-k**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	IR spectrum, cm^{-1}	R_f*	Yield, %
		C	H				
2a	$C_{16}H_{23}O_3N_3$	62.9 / 63.0	7.6 / 8.0	Oil	3350, 1665, 1740	0.56	78
2b	$C_{17}H_{25}O_3N_3$	63.9 / 63.8	7.9 / 8.0	63*[2]	3350, 1675, 1740	0.57	78
2c	$C_{23}H_{29}O_3N_3$	69.9 / 69.9	7.4 / 7.1	Oil	3350, 1675, 1745	0.82	82
2d	$C_{25}H_{30}O_3N_4$	69.1 / 68.4	7.0 / 7.1	132	3360, 1645, 1730	0.88	48
L-**2d**	$C_{25}H_{30}O_3N_4$	69.1 / 70.4	7.0 / 6.9	154	3350, 1670, 1740	0.89	65
2e	$C_{19}H_{27}O_3N_3$	66.1 / 65.3	7.9 / 7.7	Oil	1680, 1750	0.69	84
2f	$C_{20}H_{31}O_3N_3$	66.5 / 65.9	8.6 / 8.6	Oil	3350, 1675, 1735	0.86	75
2g	$C_{20}H_{31}O_3N_3$	66.5 / 66.4	8.6 / 8.8	Oil	3350, 1675, 1735	0.81	85
2h	$C_{19}H_{29}O_3N_3$	65.7 / 65.6	8.4 / 8.3	Oil	3350, 1670, 1735	0.82	82
2i	$C_{25}H_{30}O_3N_4$			Oil	3350, 1665, 1740	0.36	62
2k	$C_{25}H_{30}O_3N_4$	68.7 / 68.6	6.8 / 6.8	110	3350, 1675, 1740	0.69	78

* In the system benzene–ethyl acetate, 1:1.
*[2] For the crystallized diastereomers.

The starting hydroxypyrazolidine **1a** has two chiral atoms, however it exists as one diastereomeric pair with a trans positioning of the protons in positions 3 and 5 [3]. The reaction of pyrazolidine **1a** with glycine ester gave compound **2a** which also appears as a single diastereomeric pair. Upon substitution of the hydroxyl group by the amino acid residue containing a chiral carbon atom, there were obtained two or four isomers depending upon whether an optically pure (*L*-) or a racemate (*DL*-) amino acid respectively was used.

In the case of the racemic tryptophan derivative **2d** the predominant diastereomeric racemate was isolated in the pure state from the reaction mixture. The same reaction with optically active *L*-tryptophan permitted separation in the pure state of one of the diastereomers (*L*-**2d'**). Investigation of this sample by the ^{1}H NMR spectroscopic method using the nuclear Overhauser effect [4] showed these compounds, as with the majority of other function derivatives of pyrazolidines [5], to have a trans configured pyrazolidine ring

$$[\eta_{3\text{-H}}(4\text{-H}) = 8.6;\ \eta_{5\text{-H}}(4'\text{-H}) = 7.7].$$

A successful separation of the reaction mixture with production of one of the diastereomeric racemates in the pure state was also carried out for derivatives of *D*,*L*-alanine **2b**. In the case of the derivative of *L*-isoleucine **2f** both diastereomers were separated in the pure state (Tables 2 and 3). For compounds **2i** and **2k** it was shown that, for derivatives of pyrazolidine **1b**, the process is accelerated by about ten times.

The ratio of the isomers obtained is determined to a significant degree by the size of the radical in the molecule of the starting amino acid.

Compound	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
Isomer ratio	1:1.5	1:4	1:4	1:2	1:1.5	1:2	1:1.7

TABLE 2. [1]H NMR Spectra of the Compounds Prepared, ppm*.

Compound	Ac (3H), s	3-Me (3H), d	3-H, m	4-H (2H), m	5-H, m	α-H (1H)	EtOOC (5H)	NH, s	R
1	2	3	4	5	6	7	8	9	10
2a	1.16	1.12	4.05	1.97; 1.82	5.21	3.54 dd	4.04 q; 1.14 t	1.92	—
2b	1.88 1.87*[2]	1.13 1.07	4.15	2.05; 1.83	5.27 5.23	3.74 dd	4.04 q; 1.18 t 4.09 q; –	2.16	1.25 d 1.16 d
2b'*[3]	1.98	1.14	4.07	2.05; 1.90	5.31	3.80	4.09 q; 1.20 t	2.13	1.34
2c	1.85 1.77	1.06	4.07	1.96; 1.83	5.19 4.98	4.01 dd	3.98 q; 1.08 t	2.12	3.98 d (CH_2)
2d	1.89 1.94	1.07 1.38	3.92 4.23	2.11; 1.99 1.91; 1.71	5.28 5.40	4.07 dd	3.95 q; 1.03 t 4.26 q; 1.27 t	1.98	8.37 s (NH); 3.12 m (CH_2)
2d'*[3]	1.98	1.13	4.11	1.99; 1.89	5.36	4.04 dd	4.05 q; 1.08 t	2.18	8.09 s (NH); 3.15 m (CH_2)
L-**2d**	1.94 1.87	1.02	3.92 4.20	1.86; 1.81 1.99; 1.64	5.29 5.39	4.07	3.95 q; 1.05 t 4.24 q; 1.25 t	2.10	3.12 m (CH_2); 8.29 (NH) (2.87; 3.25); 8.24 (NH)
L-**2d'***[4]	1.95	1.04	3.92	1.89; 1.82	5.28	4.09	3.95 q; 1.05 t	2.14	3.14 m (CH_2); 8.41

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10
2e	2.07	1.25	4.12	1.90; 1.75	5.70 5.64	3.95 t	4.05 q; 1.30 t	—	3.40 m; 3.15 m; 2.80 m
2f$_1$*[5]	2.00	1.15	4.06	2.07; 1.92	5.25	3.70 m	4.20 q; 1.29 t	—	1.58 m (1.09 m;1.30 m); 0.79 s; 0.84 t
2f$_2$	2.05	1.11	4.00	2.00; 2.04	5.17	3.66	4.11 q; 1.21 t	2.05	1.67 m (1.07 m; 1.38 m); 0.79 s; 0.82 t
2g	2.00 2.06	1.17 1.19	4.06	1.94; 2.14	5.26 5.34	3.78 3.88	4.25 q; 1.29 t 4.17 q; 1.32 t	2.05	0.92 d; 0.96 d; 1.49 m
2h	2.04 1.99	1.17 1.21	4.08	2.07; 1.94	5.38 5.28	3.82	4.25 q; 1.27 t 4.17 q; 1.32 t	—	1.32 m; 1.17 d; 0.92 m
2i	1.98	—	3.76 3.23	2.32; 1.75	5.26	3.60	4.09; 1.19	—	—
2k	1.95	—	4.04; 3.16	2.09; 1.68	5.11	3.68	(COOMe) 3.56	2.04	2.90 m

* Chemical shifts of the aromatic protons in the region 6.8-7.7 ppm.

*[2] In several examples the signals of the various diastereomeric racemates could be separated.

*[3] One pair of diastereomeric racemates was separated from the mixture of isomers.

*[4] One isomer was separated from the mixture of isomers.

*[5] The reaction mixture was separated chromatographically and gave the two diastereomers **2f$_1$** and **2f$_2$**.

TABLE 3. ^{13}C NMR Spectra of the Compounds Prepared, ppm

Compound	Ac	3-Me	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	Ph		C_{α}	COOEt		Other signals	
1	2	3	4	5	6	7		8	9		10	
2a	172.62; 21.26	20.30	61.94	40.19	72.75	*ipso* 152.01 *m* 129.70 *p* 121.84 *o* 115.63		49.05	175.99 (CO) 60.71 (CH_2) 14.50 (Me)		—	
2b	175.66; 21.30* 175.38; 21.28	20.12	62.03 62.10	40.54 41.06	71.67 71.23	*ipso* 152.12 *m* 129.83 *p* 122.01 *o* 115.79	*ipso* 152.44 *m* 129.64 *p* 121.70 *o* 115.58	54.76 54.41	176.38 61.06 14.52	176.38 60.73 14.61	19.22 19.54	
2c	174.24; 21.30	19.96	62.11	40.21	72.10	*ipso* 152.00 *m* 129.65 *p* 121.94 *o* 115.97		61.06	175.97; 60.87; 14.40		39.92; 138.96; 130.39; 128.55; 126.82	
2d*[2]	174.86; 21.44	20.04	61.54	39.88	71.67	*ipso* 152.12 *m* 129.39 *p* 121.85 *o* 113.49		60.14	176.80; 60.84; 14.16		29.49; 136.22; 128.21; 129.39; 122.99; 119.25; 115.49; 112.19; 111.14	
***L*-2d**	174.56; 21.19	19.71	61.35	39.54	71.62	*ipso* 150.70 *m* 129.02 *p* 121.50 *o* 115.09		59.60	176.22; 60.64; 13.93		29.08; 135.88; 127.84; 122.98; 121.39; 118.88; 118.81; 111.37; 110.91	
2e	173.69; 20.90 174.80; 20.60	20.12 19.84	61.95	37.12 36.29	74.66 74.60	*ipso* 148.56 *m* 128.63 *p* 119.93 *o* 112.13	*ipso* 149.23 *m* 127.78 *p* 120.31 *o* 113.56	50.99	177.95 59.92 13.84	176.97 59.82 13.68	45.71 29.25 22.60	— 30.06 22.90

TABLE 3 (continued)

1	2	3	4	5	6	7	8	9	10
2f$_1$*[3]	174.69; 21.10	19.41	61.44	39.58	72.83	*ipso* 150.80 *m* 128.95 *p* 121.43 *o* 115.33	63.59	175.98; 60.24; 14.04	38.82; 24.97; 15.26; 11.61
2f$_2$*[3]	174.60; 21.16	20.19	62.97	40.48	74.19	*ipso* 148.72 *m* 127.68 *p* 122.14 *o* 110.10	63.67	175.96; 60.25; 14.10	38.26; 25.09; 15.80; 11.68
2g	175.95; 21.31	20.40 19.67	61.74 61.72	39.75 49.61	72.49 70.62	*ipso* 151.06 *m* 129.10 *p*121.65 *o* 115.67	58.08 57.17	176.13; 60.55; 14.31	43.05 24.75 22.86
						ipso 150.92 *m* 129.09 *p*121.63 *o* 115.20			43.31 — 23.30
2h	174.90; 20.91	19.23	61.13	39.44	72.30 70.36	*ipso* 150.94 *m* 128.65 *p* 121.28 *o* 114.77	58.37 57.96	175.98; 60.25; 13.98	35.43; 18.16; 13.55
2i	174.47; 19.82	—	51.78	31.99	71.03	*ipso* 149.28 *m* 128.03 *p* 120.21 *o* 113.37	47.22	170.69; 59.36; 12.82	—
2k	174.52; 21.19	—	53.56	39.74	72.18	*ipso* 150.56 *m* 129.51 *p* 121.60 *o* 115.32	51.73	(COOMe) 175.98; 60.41	33.5; 137.8; 129.10; 127.98; 126.29

* In several examples the signals for the different diastereomeric racemates differed in their spectra.

*[2] ^{13}C NMR spectrum was obtained only for the pair of diastereomeric racemates separated from the mixture of isomers.

*[3] The reaction mixture was separated chromatographically to give the two diastereomers **2f$_1$** and **2f$_2$**.

EXPERIMENTAL

IR spectra were recorded on UR-20 and Specord IR-75 instruments for films or solutions in CH_2Cl_2 and ^1H and ^{13}C NMR spectra on a Varian VXR-400 instrument using $CDCl_3$ with HMDS or TMS as internal standard. Monitoring of the course of the reaction and the purity of the compounds obtained was carried out by TLC on Silufol UV-254 or Alufol plates in the systems benzene–ethyl acetate (1:1) or chloroform–methanol (15:1) and visualized by iodine vapor and an alcoholic solution of ferric chloride. Purification of the compounds obtained was carried out using flash chromatography on a dry column using L 5/40 silica gel and a gradient of benzene–ethyl acetate or chloroform–methanol [6]. 1-Acetyl-5-hydroxy-2-phenylpyrazolidines were prepared as described in method [7] and amino acid esters as in [8].

General Method for the Synthesis of 1-Acetyl-5-(α-carbethoxyalkylamino)-2-phenylpyrazolidines 2. The starting pyrazolidine (0.005 mol) and ester (0.005 mol) were mixed without solvent and the mixture was left at room temperature. For speeding the reaction $MgSO_4$ was added in order to bind the water produced in the reaction. Monitoring was carried out by TLC on removed samples. The compounds obtained were purified by chromatography (in the cases of the tryptophan and proline derivatives by chromatography on aluminium oxide since these compounds were decomposed on silica gel). The parameters of the compounds synthesized are given in Table 1 and the NMR spectra in Tables 2 and 3.

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