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UNUSUAL AMINO ACIDS. 5.* SYNTHESIS OF 3,5-DIOXO-PYRAZOLIDINE DERIVATIVES

D. Zicane[1], Z. Tetere[1], I. Rijkure[1], M. V. Petrova[1], E. Gudriniece[1], and U. Kalejs[2]

Monohydrazides of 2-R-4-methyl-4-cyclohexene-1,1-dicarboxylic acids react with trifluoroacetic acid anhydride to give 4-substituted 3,5-dioxopyrazolidines, with phosphorus trichloride to give 4-(2-R-5-chloro-4-methylcyclohexane)-3,5-dioxopyrazolidines, and with acetic anhydride to give 4-(2-R-4-methyl-4-cyclohexene)-3,5-diacetoxypryazoles.

Keywords: 3,5-dioxopyrazolidines, malonic acid, monohydrazides of 2-R-4-methyl-4-cyclohexene-1,1-dicarboxylic acids.

Continuing a study of monohydrazides of 2-R-4-methyl-4-cyclohexene-1,1-dicarboxylic acids (**1a-e**) [2], we more thoroughly investigated the possibilities of using these compounds to synthesize pyrazolidine derivatives. The formation of 3,5-dioxopyrazolidine derivatives, many of which possess biological activity and have found use in medicine [3, 4], might be expected in the cyclization of hydrazides **1a-e**.

Monohydrazides of malonic acid and substituted malonic acids are resistant to intramolecular acylation [5]. This property was also found for hydrazides **1a-e**. Upon heating these compounds to the melting point, only decarboxylation products **2a-e**, analogous to the products synthesized in our previous work from acetylcyclohexenecarboxylic acids and hydrazine hydrate [2], were obtained instead of the expected 3,5-dioxopyrazolidines.

However, upon heating with phosphorus trichloride, hydrazides **1a-e**, by analogy to our previous work for derivatives of malonic and substituted malonic acids [5], give 3,5-dioxopyrazolidine derivatives. We note that the addition of hydrogen chloride to give **3a-e** also proceeds in addition to intramolecular acylation. The ^{1}H NMR spectra of **3a-e** lack signals for =CH protons at 5.37-5.46 ppm, characteristic for **4** and **5**, but display two additional multiplets with integral intensity 2H at 1.70-2.50 ppm. The signals for most of the protons of the six-membered ring in **3-5** are found in this range as a broad, poorly resolved multiplet due the small differences in chemical shifts and large number of coupling constants.

By substituting phosphorus trichloride with trifluoroacetic acid anhydride, we were able to obtain 4-cyclohexene-3,5-dioxopyrazolidines **4a-e** in 65-77% yield. The analogous reaction with acetic anhydride led to acetylated products. The formation of N-acetyl (**5A**) and O-acetyl derivatives (**5B**) is theoretically possible. The ^{1}H NMR spectra of these compounds do not contradict either **5A** or **5B**. The elemental composition of these compounds is the same. The literature data on the acylation of 3,5-dioxopyrazolidine derivatives are contradictory [6-8]. We favor O-acyl derivatives **5B** on the basis of their IR spectra, which show high frequencies for the carbonyl group bands at 1720-1763 cm^{-1} but lack amide carbonyl group bands at 1648-1683 cm^{-1}.

* For Communication 4, see [1].

[1] Riga Technical University, LV-1048 Riga, Latvia; e-mail: gudr@rtu.ktf.lv. [2] BAPEKS, LV-1048 Riga, Latvia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 903-907, July, 2000. Original article submitted February 11, 2000.

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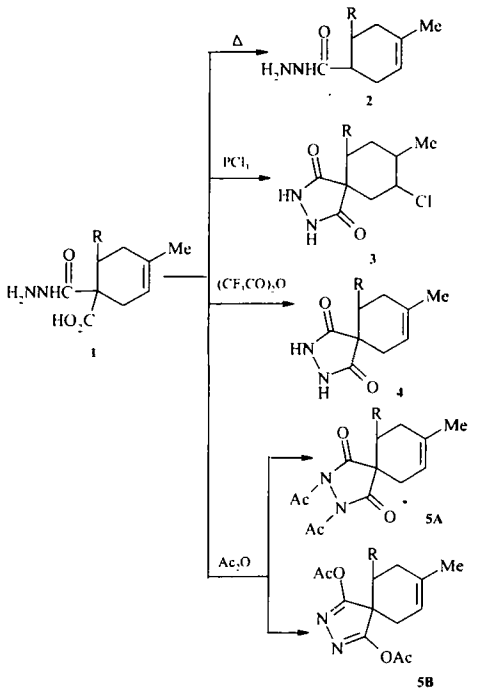

1-5 a R = Ph; **b** C_6H_4F-*p*; **c** C_6H_4Cl-*p*; **d** C_6H_4Br-*p*; **e** $C_6H_4NO_2$-*p*

TABLE 1. Characteristics of Compounds **3-5**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	halogen		
3a	$C_{15}H_{17}ClN_2O_2$	61.71 / 61.54	5.87 / 5.85	9.52 / 9.57	12.21 / 12.11	198-200	60
3b	$C_{15}H_{16}ClFN_2O_2$	57.84 / 57.98	5.26 / 5.19	9.07 / 9.01		210-212	62
3c	$C_{15}H_{16}Cl_2N_2O_2$	54.85 / 55.06	4.31 / 4.93	8.20 / 8.56	22.01 / 21.67	212-213	73
3d	$C_{15}H_{16}BrClN_2O_2$	48.52 / 48.47	4.41 / 4.34	7.52 / 7.54		218-220	70
3e	$C_{15}H_{16}ClN_3O_4$	53.42 / 53.34	4.81 / 4.77	12.56 / 12.44	10.83 / 10.50	193-195	74
4a	$C_{15}H_{16}N_2O_2$	70.52 / 70.29	6.51 / 6.29	11.02 / 10.93		202-204	65
4b	$C_{15}H_{15}FN_2O_2$	66.91 / 65.68	5.82 / 5.51	10.41 / 10.20		215-217	60
4c	$C_{15}H_{15}ClN_2O_2$	62.02 / 61.97	5.31 / 5.20	9.81 / 9.63	12.05 / 12.19	200-202	67
4d	$C_{15}H_{15}BrN_2O_2$	54.00 / 53.75	4.63 / 4.50	8.52 / 8.36	23.51 / 23.84	247-248	68
4e	$C_{15}H_{15}N_3O_4$	59.53 / 59.79	5.05 / 5.02	13.63 / 13.95		241-242	77
5a	$C_{19}H_{20}N_2O_4$	68.12 / 67.05	6.02 / 5.92	8.41 / 8.23		157-158	70
5b	$C_{19}H_{19}FN_2O_4$	64.01 / 63.88	5.51 / 5.37	8.02 / 7.82		182-184	72
5c	$C_{19}H_{19}ClN_2O_4$	61.01 / 60.88	5.32 / 5.11	7.61 / 7.47	8.85 / 9.45	195-196	75
5d	$C_{19}H_{19}BrN_2O_4$	54.10 / 54.42	4.38 / 4.56	6.73 / 6.68	19.01 / 18.86	190-192	87
5e	$C_{19}H_{19}N_3O_6$	59.00 / 59.22	5.03 / 4.97	11.02 / 10.90		172-173	75

TABLE 2. Spectral Characteristics of Products **3-5**

Compound	IR spectrum, cm^{-1}		^1H NMR spectrum, δ, ppm (SSCC, J, Hz)
	C=O	NH	
3a	1662-1674	2931-3100	1.73 (3H, s, CH_3); 1.80-2.02 (3H, m, CH_2, CH); 2.27 (2H, centr. m, CH_2, CH); 2.80 (1H, t, J = 13, CH_2); 3.56 (1H, dd, J = 13, J = 3, CH); 7.22 (5H, centr. m, C_6H_5); 9.40 (2H, br. s, 2NH)
3b	1648-1664	2860-3150	1.71 (3H, s, CH_3); 1.78-1.98 (3H, m, CH_2, CH); 2.25 (2H, centr. m, CH_2, CH); 2.75 (1H, t, J = 13, CH_2); 3.45 (1H, dd, J = 13, J = 3, CH); 7.02 (4H, centr. m, C_6H_4); 10.04 (2H, br. s, NH)
3c	1650-1680	2948-3050	1.76 (3H, s, CH_3); 1.78-2.0 (3H, m, CH_2, CH); 2.4 (2H, centr. m, CH_2, CH); 2.87 (1H, t, J = 13, CH_2); 3.56 (1H, dd, J = 13, J = 3, CH); 7.22 (4H, centr. m, C_6H_4); 9.89 (2H, br. s, NH)
3d	1650-1660	2856, 2932	1.69 (3H, s, CH_3); 1.81-1.98 (3H, m, CH_2, CH); 2.33 (2H, centr. m, CH_2, CH); 2.73 (1H, t, J = 13, CH_2); 3.56 (1H, dd, J = 13, J = 3, CH); 6.98 (4H, m, C_6H_4); 9.73 (2H, br. s, NH)
3e	1662-1681	2950-3050	1.65 (3H, s, CH_3); 1.70-1.76 (3H, m, CH_2, CH); 2.31 (2H, centr. m, CH_2, CH); 2.84 (1H, t, J = 13, CH_2); 3.28 (3H, s, CH_3); 3.72 (1H, dd, J = 13, J = 3, CH); 7.37 (2H, m, J = 8, C_6H_4); 8.1 (2H, m, J = 8, C_6H_4); 9.68 (2H, br. s, NH)
4a	1666-1683	3010-3188	1.73 (3H, s, CH_3); 1.98-2.98 (4H, m, $2CH_2$); 3.25 (1H, dd, J = 12, J = 5.5, =CH–); 5.42 (1H, m, =CH–); 7.24 (5H, centr. m, C_6H_5); 8.70 (2H, br. s, 2NH)
4b	1650-1665	2900-3163	1.72 (3H, s, CH_3); 2.04-2.99 (4H, m, $2CH_2$); 3.17 (1H, dd, J = 12, J = 5, =CH–); 5.37 (1H, m, =CH–); 6.90-7.2 (4H, m, C_6H_4)
4c	1650-1673	2950-3150	1.66 (3H, s, CH_3); 2.01-3.03 (4H, m, $2CH_2$); 3.21 (1H, dd, J = 12, J = 5, =CH–); 5.42 (1H, m, =CH–); 6.66 (2H, br. s, 2NH); 7.22 (4H, centr. m, C_6H_4)
4d	1660-1680	2972-2997	1.66 (3H, s, CH_3); 1.87-2.90 (4H, m, $2CH_2$); 3.11 (1H, dd, J = 12, J = 5, =CH–); 5.37 (1H, m, =CH–); 7.11 (2H, m, J = 8, C_6H_4); 7.55 (2H, m, J = 8, C_6H_4); 10.26 (2H, br. s, 2NH)
4e	1665-1678	2825-3072	1.77 (3H, s, CH_3); 1.96-3.11 (4H, m, $2CH_2$); 3.33 (1H, dd, J = 12, J = 5, =CH–); 5.46 (1H, m, =CH–); 7.4 (2H, m, J = 8, C_6H_4); 8.06 (2H, m, J = 8, C_6H_4); 9.51 (2H, br. s, 2NH)
5a	1730, 1763		1.76 (3H, s, CH_3); 2.13 (3H, s, CH_3); 2.07-3.05 (4H, m, $2CH_2$); 3.29 (1H, dd, J = 12, J = 6, =CH–); 5.44 (1H, m, =CH–); 7.18 (5H, centr. m, C_6H_5)
5b	1726, 1752		1.81 (3H, s, CH_3); 2.1-3.01 (4H, m, $2CH_2$); 2.2 (3H, s, CH_3); 2.56 (3H, s, CH_3); 3.31 (1H, dd, J = 12, J = 5.5, =CH–); 5.41 (1H, m, =CH–); 6.82-7.3 (4H, m, C_6H_4)
5c	1724, 1751		1.76 (3H, s, CH_3); 2.1-2.98 (4H, m, $2CH_2$); 2.22 (3H, s, CH_3); 2.41 (3H, s, CH_3); 3.34 (1H, dd, J = 12, J = 5, =CH–); 5.44 (1H, m, =CH–); 7.04 (4H, centr. m, C_6H_4)
5d	1725, 1748		1.77 (3H, s, CH_3); 2.08-2.98 (4H, m, $2CH_2$); 2.17 (3H, s, CH_3); 2.51 (3H, s, CH_3); 3.33 (1H, dd, J = 12, J = 5.5, =CH–); 5.4 (1H, m, =CH–); 6.95 (2H, m, J = 8, C_6H_4); 7.48 (2H, m, J = 8, C_6H_4)
5e	1730, 1750		1.76 (3H, br. s, CH_3); 2.09-3.07 (4H, m, $2CH_2$); 2.2 (3H, s, CH_3); 2.42 (3H, s, CH_3); 5.41 (1H, m, =CH–); 7.12 (2H, m, J = 8, C_6H_4); 6.95 (2H, m, J = 8, C_6H_4); 8.1 (2H, m, J = 8, C_6H_4)

EXPERIMENTAL

The ^1H NMR spectra were taken on a Bruker WH-90/DS spectrometer at 90 MHz for solutions in either $CDCl_3$ or DMSO-d_6 with HMDS as the internal standard. The IR spectra were taken on Specord-75 spectrometer for mulls in vaseline and hexachlorobutadiene. The purity of the products was checked by thin-layer chromatography on Silufol plates using 9:1:1 chloroform–methanol–glacial acetic acid as the eluent for **4a,d, 5b,d**

and 85:10:5 chloroform–methanol–glacial acetic acid for **3a-e, 4b,c,e, 5a,c,e.** The characteristics of the products are given in Tables 1 and 2.

Monohydrazides of 2-R-4-Methyl-4-cyclohexene-1,1-dicarboxylic Acids (1a,c-e) were obtained according to our previous procedure [2]. Hydrazide **1b** was synthesized analogously in 70% yield; mp 167-170°C (from 2:1 ethanol–water).

Hydrazides of 2-R-4-Methyl-4-cyclohexenecarboxylic Acids (2a-2e). A sample of hydrazides **1a-e** (0.05 mol) was heated on an oil bath until molten. The sample was cooled and water added. The product was filtered off and recrystallized from 1:1 ethanol–water. The yields were 70% (**2a**), 72% (**2b**), 68% (**2c**), 74% (**2d**), and 64% (**2e**). The melting points and ^{1}H NMR spectra of hydrazides **2a,c-e** corresponded to the data for these hydrazides obtained in our previous work [2]; mp of **2b** 152-154°C.

4-(2-R-4-Chloro-4-methylcyclohexane)-3,5-dioxopyrazolidines (3a-e). A mixture of hydrazides **1a-e** (0.004 mol) and phosphorus trichloride (0.012 mol) was heated on a water bath for 1 h and then cooled. Water was added and the mixture was extracted with ethyl acetate. The extract was washed with water until the wash water was neutral. The solvent was distilled off and the residue was recrystallized from 1:1 ethanol–water except for **3a**, which was recrystallized from 1:1 methanol–water.

4-(2-R-4-Methyl-4-cyclohexene)-3,5-dioxopyrazoles (4a-e). A sample of hydrazides **1a-e** (0.05 mol) in trifluoroacetic acid anhydride (12 ml) was heated at reflux for 1.5 h, cooled, and poured onto ice. The mixture was filtered, washed with water until the wash water was neutral, and recrystallized from 1:1 ethanol–water (**4a,b**), 1:1 methanol–water (**4c,e**), and 1:1 acetonitrile–water (**4d**).

3,5-Diacetoxy-4-(2-R-4-methyl-4-cyclohexene)pyrazoles (5Ba-e). A sample of hydrazides **1a-e** (0.05 mol) in acetic anhydride (10 ml) was heated at reflux for 1 h, cooled, and poured onto ice. The mixture was filtered and recrystallized from 2:1 acetonitrile–water (**5a,d**), 1:1 acetonitrile–water (**5b,c**), and 2:1 methanol–water (**5e**).

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