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POLYFUNCTIONAL PYRAZOLES.

3.* SYNTHESIS OF 3-(3-ARYL-4-FORMYL-1-PYRAZOLYL)PROPIONIC ACIDS AND THEIR AMIDES

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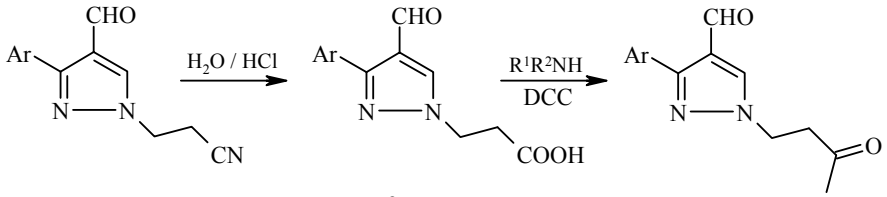
3-(3-Aryl-4-formyl-1-pyrazolyl)propionic acids were synthesized by the reaction of 3-aryl-1-(2-cyanoethyl)-4-formylpyrazoles with concentrated hydrochloric acid. They were converted into the corresponding amides by the carbodiimide method.

Keywords: amides, dicyclohexylcarbodiimide, 3-(4-formyl-1-pyrazolyl)propionic acids, 1-(2-cyanoethyl)-4-formylpyrazoles, hydrolysis.

Earlier [2] we described the synthesis of 3-aryl-1-(2-cyanoethyl)-4-formylpyrazoles and the corresponding thiosemicarbazides. On the basis of the last reactions with monochloroacetic acid and maleic anhydride unsymmetrical azines with 3-aryl-1-(2-cyanoethyl)-4-methylidenepyrazole and 2-thiazolidinylen-4-one fragments having antimicrobial activity were obtained [3].

The present communication presents the results from selective modification of the 2-cyanoethyl substituent in the 4-formylpyrazoles **1a-e** to a 2-carboxyethyl substituent. We showed that during the action of boiling concentrated hydrochloric acid the nitrile group of compounds **1a-e** is readily hydrolyzed and forms 3-(3-aryl-4-formyl-1-pyrazolyl)propionic acids **2a-e** with yields of 78-93%. It is remarkable that cleavage of the C–N bond of neither the β-cyanoethyl nor the β-carboxyethyl substituent with the nitrogen atom of the pyrazole ring was observed under the reaction conditions [4].



1a–e **2a–e** **3a–e**

1, 2 a Ar = Ph, **b** Ar = 4-FC_6H_4, **c** Ar = 4-ClC_6H_4, **d** Ar = 4-BrC_6H_4, **e** Ar = 4-$MeOC_6H_4$;
3a,b,d-g R^1 = H, **c** R^1R^2 = $(CH_2)_2O(CH_2)_2$; **a** Ar = Ph, R^2 = 2-methyl-5-quinolinyl;
b Ar = 4-FC_6H_4, R^2 = 4-$MeOC_6H_4$; **c** Ar = 4-FC_6H_4,; **d** Ar = 4-ClC_6H_4, R^2 = 5-quinolinyl;
e Ar = 4-BrC_6H_4, R^2 = 4-MeC_6H_4; **f** Ar = 4-BrC_6H_4, R^2 = 3-pyridyl;
g Ar = 4-$MeOC_6H_4$, R^2 = Ph

* For Communication 2, see [1].

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The acids **2a-e** are colorless or light-yellow crystalline substances, the structure of which agrees with the results from elemental analysis and the IR and ^{1}H NMR spectra (Tables 1 and 2). The IR spectra of the solid samples contain absorption bands of the C=O bonds of the formyl (1640-1660 cm^{-1}) and carboxyl (1705-1720 cm^{-1}) groups and also broad absorption bands of OH groups with a hydrogen bond (2900-3200 cm^{-1}), and this confirms their dimeric nature [5]. In the ^{1}H NMR spectra the carboxyl group has hardly any effect on the chemical shifts of the 5-CH= proton of the pyrazole ring and leads to slight upfield shifts of the signals for the aldehydic protons (by 0.09-0.22 ppm) and to more pronounced shifts of the signals for the protons of the CH_2 groups (by 0.25-0.45 ppm).

Published data [6, 7] make it possible to regard 3-heterylpropionic acids and their derivatives as subjects with potential biological activity. We attempted the synthesis of 3-(1-pyrazolyl)propionamides, the most suitable approach to which seemed to be through the respective acid chlorides. However, it was found that the reaction of acids of type **2** with thionyl chloride takes place ambiguously, and as a result it is not possible to isolate products with individual structures. For this reason direct acylation of the amines with the acids **2a-e** in the presence of dicyclohexylcarbodiimide (DCC) was used. This made it possible to obtain the amides **3a-e** with yields of 51-83% (Tables 1 and 2).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in tablets with potassium bromide. The ^{1}H NMR spectra were obtained on a Varian Gemini instrument (300 MHz) in DMSO-d_6.

3-(3-Aryl-4-formyl-1-pyrazolyl)propionic Acids (2a-e). To 3-aryl-1-(2-cyanoethyl)-4-formylpyrazole **1a-e** (50 mmol) we added concentrated hydrochloric acid (20 ml). The mixture was heated to boiling and left at room temperature for 12 h. We then added water (50 ml). The precipitate was filtered off, dried, and crystallized from a 1:5 mixture of acetic acid and water.

TABLE 1. The Characteristics of the Synthesized Compounds **2a-e** and **3a-g**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{13}H_{12}N_2O_3$	63.67 / 63.93	4.78 / 4.92	11.31 / 11.48	121-122	82
2b	$C_{13}H_{11}FN_2O_3$	59.33 / 59.54	4.08 / 4.20	10.31 / 10.69	144-145	87
2c	$C_{13}H_{11}ClN_2O_3$	55.77 / 56.01	4.20 / 3.95	9.83 / 10.05	140-141	91
2d	$C_{13}H_{11}BrN_2O_3$	48.13 / 48.30	3.24 / 3.41	8.31 / 8.67	124-125	93
2e	$C_{14}H_{14}N_2O_4$	60.93 / 61.31	4.85 / 5.11	10.07 / 10.21	125-126	78
3a	$C_{23}H_{20}N_4O_2$	71.60 / 71.87	5.28 / 5.20	14.36 / 14.58	169-170	58
3b	$C_{20}H_{18}FN_3O_3$	65.17 / 65.39	4.71 / 4.90	11.18 / 11.44	137-138	76
3c	$C_{17}H_{18}FN_3O_3$	61.51 / 61.62	5.83 / 5.48	12.58 / 12.68	119-120	51
3d	$C_{22}H_{17}ClN_4O_2$	65.03 / 65.26	4.07 / 4.20	13.60 / 13.84	196-197	78
3e	$C_{20}H_{18}BrN_3O_2$	57.90 / 58.22	4.19 / 4.36	9.93 / 10.19	185-186	58
3f	$C_{18}H_{15}BrN_4O_2$	53.76 / 54.13	3.41 / 3.75	13.82 / 14.03	140-141	64
3g	$C_{20}H_{19}N_3O_3$	68.33 / 68.76	5.30 / 5.44	11.80 / 12.03	118-119	67

TABLE 2. The Spectral Characteristics of Compounds **2a-e** and **3a-g**

Compound	IR spectrum, ν, cm^{-1}			^1H NMR spectrum, δ, ppm (*J*, Hz)							
	C=O	O–H	N–H	CH=O (1H, s)	5-CH= (1H, s)	Ar, R^2		β-CH_2 (2H, t, *J* = 7.5)	α-CH_2 (2H, t, *J* = 7.5)	COOH (1H, br. s)	N–H (1H, s)
						arom.	CH_3 (3H, s)				
2a	1645, 1715	2950, 3200		9.86	8.47	7.40-7.44 (3H, m); 7.78-7.81 (2H, m)		4.42	2.88	12.39	
2b	1650, 1710	2900, 3180		9.84	8.51	7.19-7.23 (2H, m); 7.86-7.89 (2H, m)		4.42	2.89	12.44	
2c	1640, 1720	2900, 3150		9.85	8.52	7.44 (2H, d, *J* = 8.7); 7.87 (2H, d, *J* = 8.7)		4.42	2.88	12.40	
2d	1655, 1715	2950, 3200		9.85	8.52	7.61 (2H, d, *J* = 8.5); 7.79 (2H, d, *J* = 8.5)		4.42	2.88	12.41	
2e	1660, 1705	2900, 3130		9.82	8.44	7.77 (2H, d, *J* = 8.6); 6.95 (2H, d, *J* = 8.6)	3.84	4.40	2.87	12.38	
3a	1645, 1660		3360	9.88	8.53	8.18 (1H, d, *J* = 8.8); 7.23-7.82 (9H, m)	2.64	4.60	3.15		10.07
3b	1650, 1655		3320	9.84	8.55	6.88 (2H, d, *J* = 8.6); 7.28-7.30 (2H, m); 7.44 (2H, d, *J* = 8.6); 7.85-7.88 (2H, m)	3.71	4.51	2.96		9.91
3c*	1650, 1665			9.86	8.56	7.28-7.30 (2H, m); 7.88-7.91 (2H, m)		4.54	3.01		
3d	1650, 1660		3290	9.85	8.57	7.34 (1H, dd, J_o = 8.6, J_m = 2.9); 7.46 (2H, d, *J* = 8.7); 7.69-7.93 (5H, m); 8.28 (1H, d, *J* = 8.6); 8.84 (1H, d, *J* = 8.6)		4.59	3.10		10.12
3e	1660, 1675		3350	9.84	8.52	7.05 (2H, d, *J* = 8.6); 7.43 (2H, d, *J* = 8.6); 7.57 (2H, d, *J* = 8.5); 7.82 (2H, d, *J* = 8.5)	2.32	4.51	2.95		9.88
3f	1680, 1700		3260	9.86	8.53	7.25-7.27 ($1H_{pyr}$, m); 7.58 (2H, d, *J* = 8.5); 7.82 (2H, d, *J* = 8.5); 8.03 ($1H_{pyr}$, d, *J* = 8.6); 8.21 ($1H_{pyr}$, d, *J* = 8.6); 8.67 ($1H_{pyr}$, s)		4.55	3.04		10.23
3g	1660, 1670		3250	9.83	8.46	6.96 (2H, d, *J* = 8.6); 7.24-7.27 (3H, m); 7.57-7.59 (2H, m); 7.75 (2H, d, *J* = 8.6)	3.81	4.51	2.99		10.01

* The multiplet signals of the protons of the morpholine ring are at 3.29-3.44 (4H) and 3.52-3.57 ppm (4H).

3-(3-Aryl-4-formyl-1-pyrazolyl)propionamides (3a-g). To a solution of the acid **2a-e** (3 mmol) in THF (15 ml) we added the respective amine (3 mmol) and DCC (0.61 g, 3 mmol). The mixture was stirred at room temperature for 12 h and then at 50°C for 1 h. After cooling the precipitated dicyclohexylurea was filtered off and washed with THF (2 × 10 ml). The filtrate was evaporated, diethyl ether (20 ml) was added to the residue, and the mixture was left for 6 h. The precipitate was filtered off, dried, and crystallized from ethanol.

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