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3-[2-(3,5-Dimethylpyrazolyl)] Succinic Anhydride: Synthone for the Synthesis of Some Heterocycles with Potential Pharmaceutical Activity

M. S. Abd El Halim*[,1], A. Nada[2], and W. A. Gad[2]

[1] Chemistry Department, Faculty of Engineering, Ain Shamis University, Cairo, Egypt
[2] National Research Center, Dokki, Cairo, Egypt

Summary. Aminolysis of 3-[2-(3,5-dimethylpyrazolyl)] succinic anhydride (**1**) leads to **5**. Hydrazine hydrate reacts with **1a** to give 4-(3,5-dimethylpyrazolyl)-1,2,4,5-tetrahydro-3,6-pyridazindione. The structures were confirmed by IR, MS, ^{1}H and ^{13}C NMR.

Keywords. 3,5-Pyrazole derivatives; Synthesis; Aminolysis; Pharmaceutical activity.

3-[2-(3,5-Dimethylpyrazolyl)]-succinanhydrid, ein Synthon für die Synthese einiger Heterocyclen mit potentieller pharmazeutisch nutzbarer Aktivität

Zusammenfassung. Die Aminolyse von 3-[2-(3,5-Dimethylpyrazolyl)]-succinanhydrid (**1**) führt zu **5**. Hydrazinhydrat reagiert mit **1a** zu 4-(3,5-Dimethylpyrazolyl)-1,2,4,5-tetrahydro-3,6-pyridazindion. Die Strukturen wurden mittels IR, MS, ^{1}H-NMR und ^{13}C-NMR überprüft.

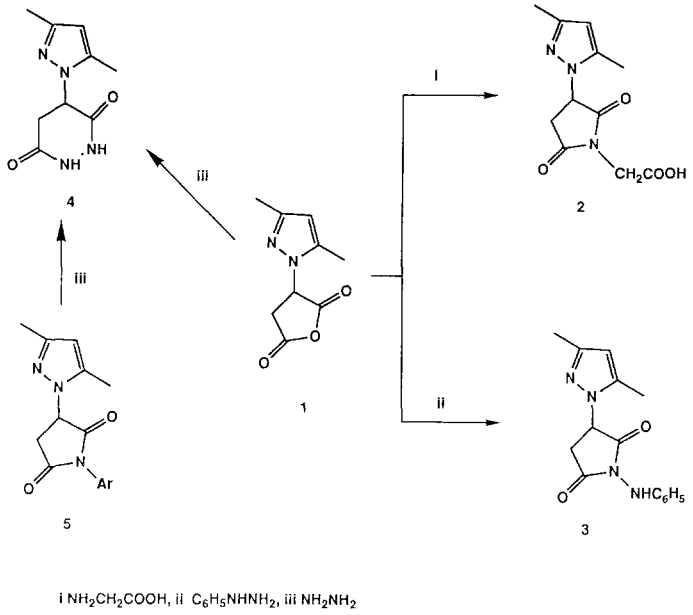
Introduction

A variety of pyrazole derivatives are of considerable pharmacological interest [1,2]. In previous publications [3, 4], we reported efficient procedures for the synthesis of substituted pyrazoles. To extend this work, we have synthesized 1-aryl-2,5-dimethyl pyrazole derivatives which could have analgesic and anti-inflammatory activities [1].

Results and Discussion

The fusion of **1** with glycine leads to the formation of 2-[(3,5-dimethylpyrazolyl) succinic glycine **2**. The reaction of **1** with phenylhydrazine leads to compound **3**. Hydrazinolysis of **1** with hydrazine hydrate yields **4**. Compound **4** was also obtained by the hydrazinolysis of **5a–c** with hydrazine hydrate. The spectroscopic data of **4** favor the 3,6-pyridazinedione structure rather than the 3,6-dihydroxypyridazine one. The IR spectra show a peak at 3190 cm^{-1} for NH stretching and 1665 cm^{-1}

for C=O stretching. The absence of the OH stretching peak is a good evidence for the dione structure. The most important features of the ^{1}H NMR spectrum are the singlets at 8.82 and 8.97 ppm (NH groups) and the absence of low field singlets (Scheme 1).



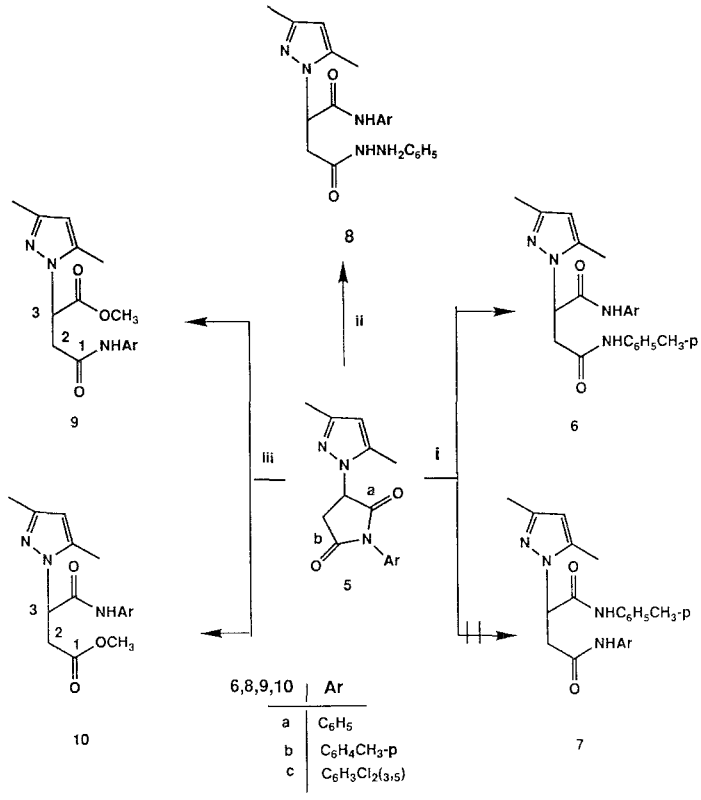
i NH_2CH_2COOH, ii $C_6H_5NHNH_2$, iii NH_2NH_2

Scheme 1

The reaction of **5a–c** with *p*-toluidine at 100–120 °C leads to pyrazolidine ring opening to give two possible dianilides (**6a–c** or **7a–c**). TLC analysis showed the presence of only one compound. We assume **6a–c** to be the product. This assumption is based on the *HSAB* concept [5], the carbonyl group (b) being relatively softer than the carbonyl group (a). Thus, the amino group of *p*-toluidine attacks the carbonyl group (b) by soft-soft attack to give **3a–c** (Scheme 2).

The reaction of **5a–c** with phenylhydrazine gives ring opened products **8a–c** by the attack of phenylhydrazine to the less hindered carbonyl group (b). The *HSAB* concept can again be applied to explain the formation of **8a–c**. Phenylhydrazine, a soft nucleophile, attacks the softer carbonyl group (b). The structures of **8a–c** were confirmed by IR spectra which show two carbonyl bands for anilide and hydrazide at 1710–1690 cm^{-1} and 1670–1600 cm^{-1}, respectively.

Compounds **9a–c** and **10a–c** [3] were found to have the same molecular formula. The IR and ^{1}H NMR spectral data could not differentiate between these compounds. The ^{13}C NMR spectra of **9a–c** and **10a–c** were compared with propionanilide and methyl propionate as reference compounds (Tables 1 and 2). The chemical shift of the α carbon of the ester function is about 2 ppm downfield from that of the anilide; with the β carbon, the effect amounts to about 0.5 ppm. In addition, the fragmentation pattern of the mass spectra of compounds **9a–c**, and **10a–c** are different. Furthermore, the mass spectrum of compound **9c** shows a molecular ion at $m/z = 370$ corresponding to $C_{16}H_{17}N_3O_3Cl_2$. The fragmented ion $m/z = 274$ produced from $[M^+]$ after removal of $C_5H_8N_2$ is due to *retro–Michael* addition.



i $NH_2C_6H_4CH_3$-P, ii $C_6H_5NHNH_2$, iii CH_3OH

Scheme 2

Table 1. ^{13}C NMR spectral data of propionanilide and methylpropionate

Carbon	$CH_3CH_2CONHC_6H_5$ δ(ppm)	$CH_3CH_2COOCH_3$ δ(ppm)
CH_3	9.61	9.07
CH_3	29.4	26.84

The base peak ($m/z = 160$) could be due to the expulsion of ketene from the molecular ion [6, 7]. Compound **10c** may be considered as a highly substituted acid anilide. The charge seems to be retained preferentially in the aromatic system of the acid part of the molecule, and formation of 3,5-dichloroaniline by expulsion of pyrazolyl ketene becomes a secondary process. The high relative abundance of the ion $m/z = 338$ in **10c** with respect to **9c** could be attributed to the easy loss of OCH_3. The base peak ($m/z = 181$) could be due to he explusion of the acylium ion.

Table 2. ^{13}C NMR spectral data of **9a–c** and **10a–c** (δ, ppm)

Compound	Carbon atom	
	2	3
9a	37.46	55.59
10a	35.54	57.53
9b	37.44	55.55
10b	35.64	57.78
9c	37.54	35.33
10c	35.50	57.51

Experimental

Melting points (uncorrected) were determined using a Fisher–Johns apparatus. IR spectra were measured on a Beckman 4220 spectrometer using KBr pellets. ^1H NMR spectra were recorded on a Varian EM-390, ^{13}C NMR spectra on a Varian CFT 200 spectrometer. Mass spectra were taken on a Varian Mat 112 instrument at 70 eV and from 100 to 196 °C operating temperature.

2-(3,5-Dimethylpyrazolyl)-succinyl glycine (**2**)

A mixture of **1** (1.94 g, 0.10 mol) and glycine (0.75 g, 0.10 mol) was heated at 100 °C for 20 minutes. After cooling and trituration with petrol ether (60–80), a solid product resulted which was crystallized from ethanol to give pale yellow crystals (Tables 3 and 4).

1-Anilino-2-(3,5-dimethylpyrazolyl)-pyrrolidine-2,5-dione (**3**)

A mixture of **1** (1.94 g, 0.01 mol) and phenylhydrazine (1.08 g 0.01 mol) in 5 ml *n*-butanol was refluxed for three hours. The solvent was evaporated to dryness and the solid product was recrystallized from benzene to give **3** (Tables 3 and 4).

Table 3. Characterization of compounds **2–4**, **6**, and **8–10**

Compound	M.p. (°C)	Yield (%)	Mol. Formula[a]
2	215	61	$C_{11}H_{13}N_3O_4$
3	106	59	$C_{15}H_{16}N_4O_2$
4	174	69	$C_9H_{12}N_4O_2$
6a	175	61	$C_{22}H_{24}N_4O_2$
6b	189	60	$C_{23}H_{26}N_4O_2$
6c	196	58	$C_{22}H_{22}N_4O_2Cl_2$
8a	203	68	$C_{21}H_{23}N_5O_2$
8b	224	63	$C_{22}H_{22}N_5O_2$
8c	195	57	$C_{21}H_{21}N_5O_2Cl_2$

[a] Elemental (C H) analyses are in accordance with calculated values

Table 4. IR and ^{1}H NMR spectral data of compounds **2**–**4**, **6**, and **8**–**10**

Compound	IR (cm^{-1})	^{1}H NMR ($CDCl_3$, δ (ppm))
2	3000–2500 (OH, acid), 1790, 1735 (C=O)	
3	3280 (NH), 1730 (C=O)	
4	3190 (NH), 1665 (C=O)	2.06 (3H, s), 2.22 (3H, s), 2.85 (2H, d), 5.08 (1H, t), 5.77 (1H, s), 8.82 (1H, s), 8.97 (1H, s)
6a	3340 (NH), 1665 (C=O)	2.09 (3H, s), 2.23 (3H, s), 2.30 (3H, s), 3.21 (2H, d), 5.37 (1H, t), 5.80 (1H, s), 6.97 (1H, t), 7.06 (2H, d), 7.23 (2H, t), 7.44 (2H, d), 7.63 (2H, d)
6b	3330 (NH), 1660 (C=O)	
6c	3320 (NH), 1660 (C=O)	2.07 (3H, s), 2.22 (3H, s), 2.29 (3H, s), 3.14 (2H, d), 5.37 (1H, s), 5.84 (1H, s), 7.06 (2H, d), 7.42 (2H, d), 7.48 (1H, s), 7.52 (1H, d), 7.95 (1H, d)
8a	3240, 3220 (NH), 1720, 1670 (C=O)	
8b	3260, 3210 (NH), 1700, 1670 (C=O)	
8c	3250, 3210 (NH), 1690, 1670 (C=O)	
9a	3200 (NH), 1740, 1670 (C=O)	2.07 (3H, s), 2.27 (3H, s), 3.27 (2H, d), 3.63 (3H, s), 5.38 (1H, t), 7.54 (5H, m), 10.08 (1H, s)
9b	3180 (NH), 1740, 1680 (C=O)	
9c	3100 (NH), 1740, 1670 (C=O)	
10a	3250 (NH), 1720, 1680 (C=O)	2.07 (3H, s), 2.27 (3H, s), 3.18 (2H, d), 3.58 (3H, s), 5.26 (1H, t), 5.84 (1H, s), 7.06 (1H, t), 7.57 (5H, m) 9.96 (1H, s)
10b	3100 (NH), 1740, 1660 (C=O)	
10c	3100 (NH), 1740, 1670 (C=O)	

4-(3,5-Dimethylpyrazolyl)-hexahydropyridazine-3,6-dione (**4**)

A mixture of **1** (1.94 g, 0.01 mol) and hydrazine hydrate (1 ml, 0.02 mol) in 7 ml *n*-butanol was boiled under reflux for four hours. The solvent was evaporated to dryness, and the solid product was crystallized from methanol to give **4** (Tables 3 and 4).

3-(3,5-Dimethylpyrazolyl)-succinic dianilides (**6a**–**c**)

A mixture of **5a**–**c** (0.01 mol) and *p*-toluidine (2.14 g, 0.01 mol) was heated by fusion at 110 °C for 15 minutes and then cooled. After trituration with petrol ether (60–80), the residue was filtered and crystallized from benzene to give **6a**–**c** (Tables 3 and 4).

Compounds **8a**–**c**

A mixture of **5a**–**c** (1.94 g, 0.01 mol) and phenylhydrazine (1.08 g, 0.01 mol) in 10 ml *n*-butanol was refluxed for three hours. The solvent was evaporated to dryness and the solid product was recrystallized from benzene to give **8a**–**c** (Tables 3 and 4).

Mass spectral data of compounds **9a–c** *and* **10a–c**

9a: MS: *m/z* (rel. int. %): 301(63), 269(44), 242(31), 241(6), 209(44), 205(18), 173(59), 159(90), 145(28), 129(13), 122(98), 119(66), 108(44), 103(13), 96(81), 95(79); ^{13}C NMR: 10.40, 13.41, 37.46, 52.40, 55.59, 104.83, 118.89, 123.10, 128.61, 138.91, 139.98, 146.89, 167.61, 169.48 ppm.

10a: ^{13}C NMR: 10.58, 13.39, 35.54, 51.50, 57.53, 105.36, 119.53, 123.66, 128.64, 138.46, 139.56, 146.48, 166.17, 170.50 ppm.

9b: ^{13}C NMR: 10.43, 13.43, 20.35, 37.44, 52.41, 55.55, 104.85, 118.93, 129.00, 131.98, 136.48, 140.00, 146.85, 167.37, 169.52 ppm.

10b: ^{13}C NMR: 10.61, 13.42, 20.35, 35.64, 51.53, 57.58, 105.39, 119.60, 129.03, 132.66, 135.98, 139.60, 146.53, 166.00, 170.54 ppm.

9c: MS: *m/z* (rel. int. %): 374(6), 370(27), 342(4), 338(15), 314(4), 311(5), 310(16), 278(3), 274(10), 242(34), 218(6), 215(37), 209(36), 202(5), 198(7), 192(5), 188(16), 176(9), 172(18), 165(16), 164(23), 161(48), 160(100), 150(68), 146(11), 133(83), 122(57), 111(69), 108(50), 100(11), 98(98), 96(59), 95(74); ^{13}C NMR: 10.44, 14.42, 37.54, 52.49, 55.33, 104.91, 118.93, 120.06, 124.61, 130.62, 131.00, 138.96, 140.05, 146.95, 168.25, 169.37 ppm.

10a: MS: *m/z* (rel. int. %): 374(10), 370(35), 343(8), 342(6), 339(18), 338(61), 246(6), 242(20), 218(6), 214(12), 209(35), 202(14), 198(10), 192(6), 188(14), 181(100), 176(6), 172(14), 165(10), 164(12), 161(35), 160(29), 150(41), 146(8), 133(12), 122(76), 113(41), 111(20), 108(43), 100(16), 98(29), 96(94), 95(98), 81(67); ^{13}C NMR: 10.62, 13.42, 35.50, 51.60, 57.31, 105.46, 119.65, 120.84, 125.23, 130.62, 130.99, 138.57, 139.75, 146.78, 166.69 ppm.

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