STRUCTURE DETERMINATION OF SOME PYRONYLPYRAZOLES, CORRECTION OF THE STRUCTURES DESCRIBED AS PYRANO[4,3-c]PYRAZOLES

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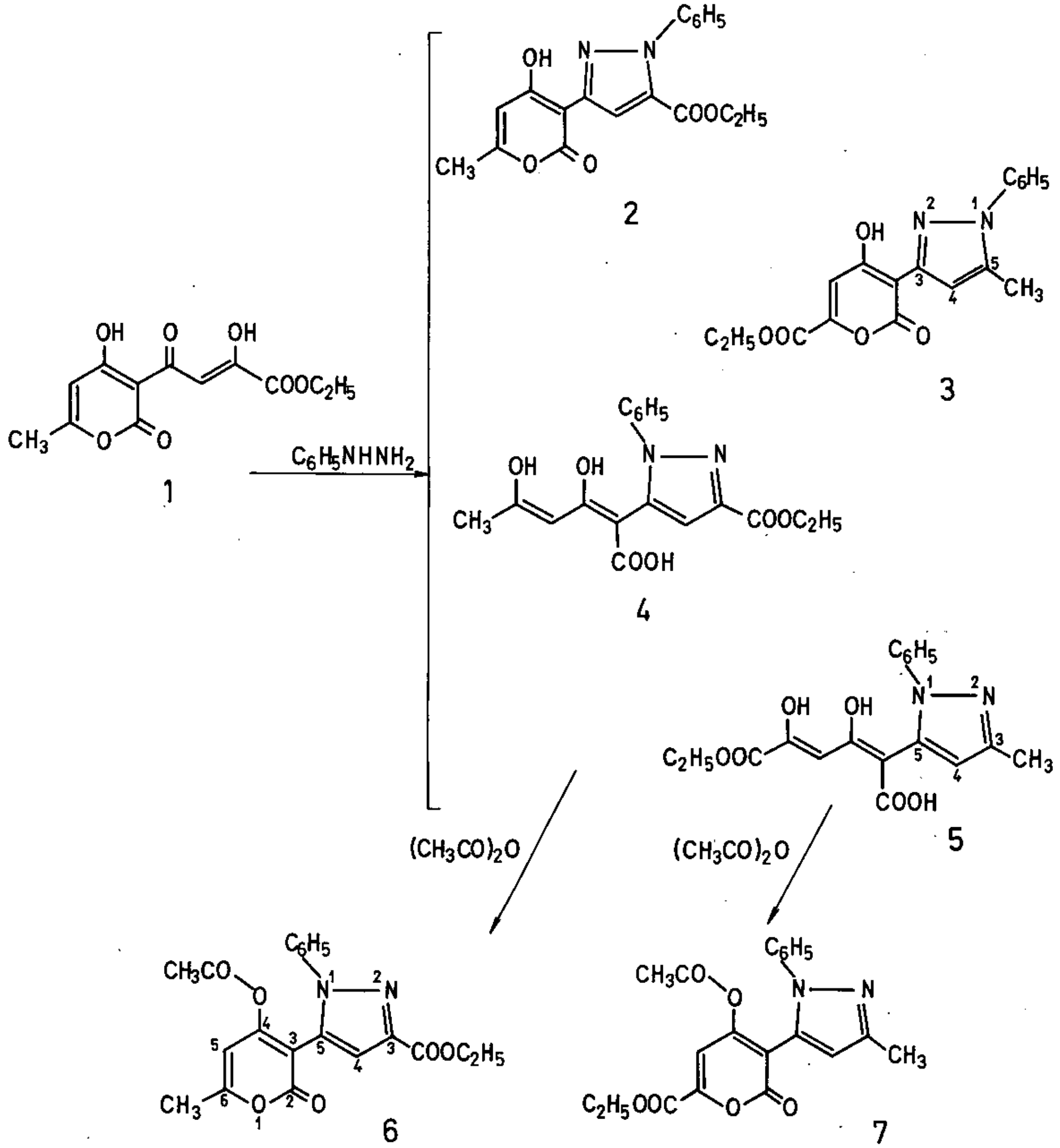
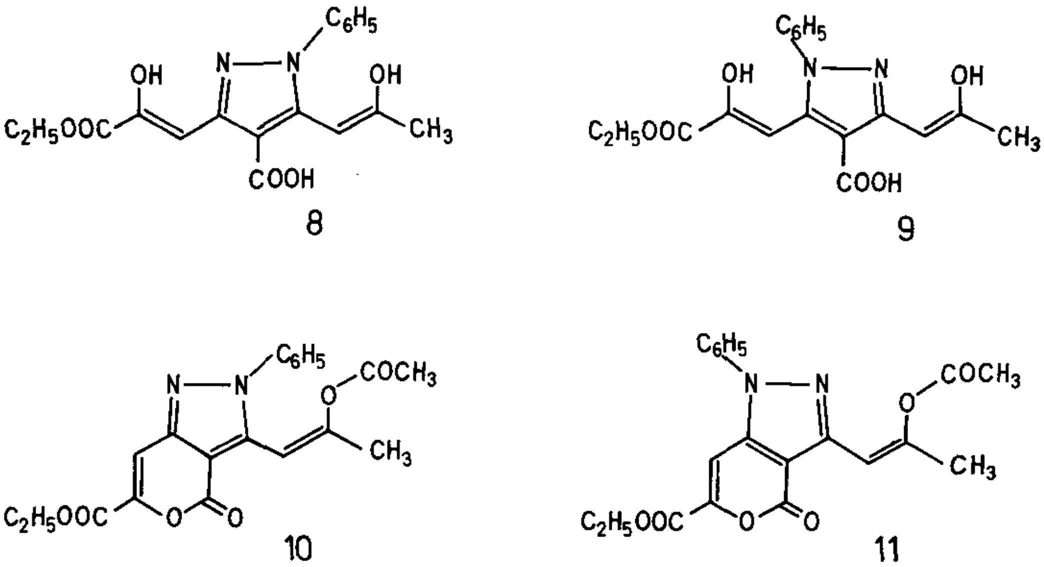
Abstract-Reaction of ethyl 2-hydroxy-4-(4-hydroxy-6-methyl-2-pyron-3-yl)-4-oxo-2-butenoate (**1**) with phenylhydrazine has been reported to give four products. The corrected structures (**4** and **5**) were subsequently established for two of them, which had been reported previously as 3,5-disubstituted *N*-phenylpyrazole-4-carboxylic acids (**8**,**9**). Consequently, the structures of their cyclized products, instead of the reported pyrano[4,3-*c*]pyrazoles (**10**,**11**) are pyronylpyrazoles (**6**,**7**). The structure (**6**) was also confirmed by means of X-ray crystallography.

Recently we reported[1] the synthesis of four pyrazole compounds derived from the compound (**1**) and phenylhydrazine. Two of these compounds were identified as pyronylpyrazoles (**2** and **3**) (Scheme 1), while the structures of **8** and **9** were ascribed to the second isomeric pair (Scheme 2). However, the additional chemical and spectroscopic evidences collected recently offer a new insight into the structures of two carboxylic acids (assigned as **8** and **9**). In this paper we report the revision of the original structural assignment[1] on the basis of ^{1}H and ^{13}C nmr spectroscopy as well as crystallographic analysis.[2] The reinvestigation of the ^{1}H and ^{13}C chemical shift values of all compounds suggested structure **4** of carboxylic acid instead of **8**. Consequently, the structure of cyclized compound produced from this acid with acetic anhydride could not be pyrano[4,3-*c*]pyrazole (**10**), but pyronylpyrazole (**6**). To prove this more rigorously, the structure of the cyclized product was investigated by means of crystallographic analysis which unambigously confirmed the structure (**6**).

Scheme 1



Scheme 2



8 9 10 11

Likewise, in the case of second isomeric acid produced in the same reaction with phenylhydrazine, reassignment of structure (**9**) into **5** was achieved from mass fragmentation pattern[2] as well as by means of ^1H and ^{13}C chemical shift values. On the same basis structure (**7**) was deduced for its cyclized product previously ascribed as **11**.

^1H and ^{13}C Nmr Spectra

Considering the open ring structure of **4** and **5** , several tautomeric forms are theoretically possible. If they exist at all, the presence of the methylene and methine proton signals might be expected, and besides them, even two methyl resonances in the spectrum of compound (**4**) (enol and keto methyl).[3,4] The ^1H nmr spectra of **4** and **5** in $CDCl_3$ solution showed the methine proton signals at δ 5.93 and 6.76 ppm, respectively. The former was split by an allylic coupling (J=0.8 Hz) with enol methyl resonance (δ 2.14 ppm). The OH signals were not observed in the spectrum of **4** at room temperature. They appeared, however, at -46°C as broad bands, centered at δ 11.4, 5.8 and 3.2 ppm. The spectrum of compound (**5**) exhibited the broad signal around 6 ppm due to the OH protons, even at room temperature. The methylene proton signal was not observed in the spectra of both **4** and **5**. The enolized forms of **4** and **5**, indicated by the presented ^{1}H nmr spectral evidence, were supported also by ^{13}C nmr spectral data (Table 1).

Table 1. ^{13}C Nmr Spectral Data[a] ($CDCl_3$, δ/ppm)

Compd	2-Pyrone ring[b]					Pyrazole ring			Substituent[c]		
	C-2	C-3	C-4	C-5	C-6	C-3	C-4	C-5	C=O[d]	3-CH_3	6-CH_3
4	163.9	92.2	169.2	100.5	163.6	143.3	112.1	135.2	162.1	-	19.8
5	161.8	98.4	167.7	107.1	149.1	149.3	109.8	135.2	158.9	13.0	-
6	161.2[e]	104.6	161.3	102.0	164.3	144.5	112.3	133.2	162.1[e]	-	20.2
7	158.5[f]	112.9	158.3[f]	108.5	148.8	149.7	110.3	131.0	159.3[f]	13.5	-

[a] The ^{13}C nmr data of compounds (**2** and **3**) were already published.[1]

[b] Carbons of open ring structures (**4** and **5**) attaining 2-pyrone numeration.

[c] Phenyl carbons: 138.9-140.2(C'-1), 123.3-124.4(C'-2,6), 128.8-129.2(C'-3,5), 127.7-128.7(C'-4); Acetoxy carbons: 166.2(CO), 20.7(CH_3) ppm.

[d] Ester carbonyl carbons, ethoxy carbons: 61.1-62.9(CH_2), 14.1-14.4(CH_3)

[e,f] These values can be interchanged.

We did not find any low-field resonance which could be assigned to the carbon of free keto group. Moreover, a comparison of the chemical shift values of side chain carbons (**4**,**5**) to those of corresponding carbons in 2-pyrone moiety of **2**,**3** and **6**,**7** showed a great similarity. The only carbons significantly affected were C-4 and C-3 of **6** and **7**, where the acetoxy group caused an expected upfield shift of C-4 and downfield shift of C-3. The ^{13}C signals were generally assigned using off-resonance decoupling experiments and chemical shift comparison among compounds studied here. The assignments of *N*-phenylpyrazole and 2-pyrone moieties were also made according to the literature data.[5-8] The substituent effect of the ethoxycarbonyl group on the pyrone ring carbons was assessed by comparing the similar effect in the 6-methoxycarbonyl-2-pyrone.[9]

Crystal Structure Analysis of 6

Figure 1 shows the atomic arrangement of the compound (**6**). The numbering was drawn with ORTEP program.[10] Final positional and thermal parameters are given in Table 2. Selected molecular geometry data are collected in Table 3. Geometrical parameters were calculated and table prepared with CSU program.[11] There is no unusual geometrical features. The skeleton of the structure is described by the three well defined planes of phenyl, pyrazole and 2-pyrone; the estimated standard deviations (e.s.d.) of the least-square planes are 0.03, 0.01 and 0.06, respectively. The angles between two planes pyrazole/phenyl, pyrazole/2-pyrone and phenyl/2-pyrone are 49.7(1)°, 60.0(1)° and 65.5(1)°, respectively. The intermolecular packing arrangement is determined by normal van der Waals contacts with no short interactions. All calculations were performed on an IBM compatible PC-AT computer.

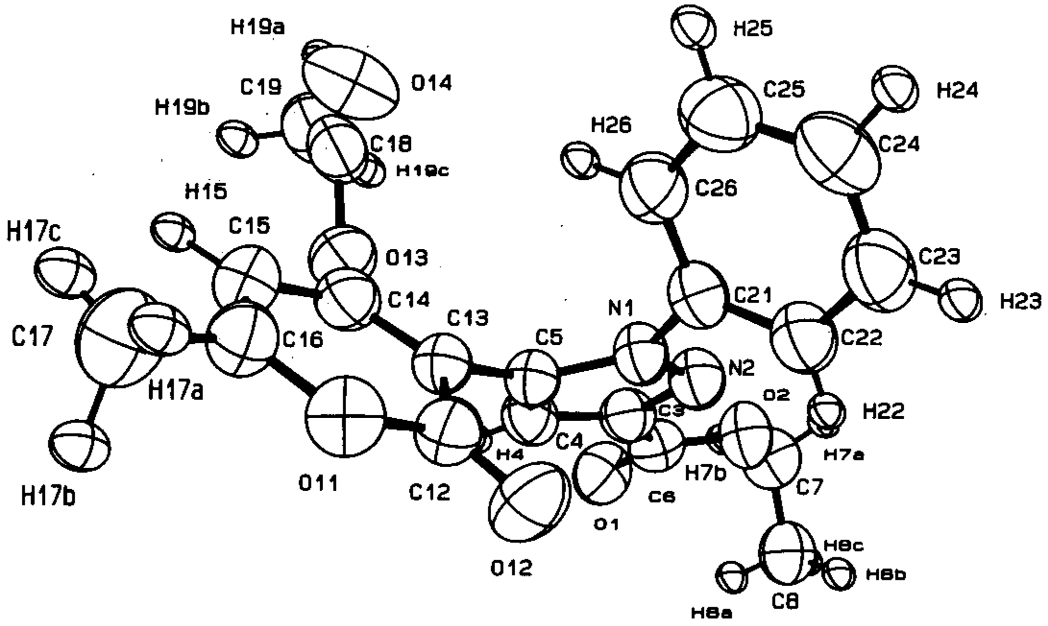


Figure 1.

Table 2. Non-hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Temperature Factors ($\text{Å}^2 \times 10^3$) for Compound (**6**). Values in Parentheses: Estimated Standard Deviations.

$$U_{eq} = \frac{1}{3}\sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

Atom	x/a	y/b	z/c	U_{eq}	Atom	x/a	y/b	z/c	U_{eq}
N1	7092(2)	4074(3)	6984(2)	54(1)	N2	6404(2)	3906(4)	7413(2)	59(1)
C3	5512(3)	3817(4)	6800(2)	58(1)	C4	5625(3)	3918(4)	5989(2)	58(1)
C5	6646(3)	4100(4)	6111(2)	53(1)	C6	4540(3)	3623(4)	7013(3)	61(1)
O1	3731(2)	3535(4)	6468(2)	79(1)	O2	4679(2)	3546(4)	7847(2)	76(1)
C7	3769(4)	3328(6)	8115(3)	81(1)	C8	3249(4)	4799(7)	8151(4)	86(1)
O11	8360(2)	6015(3)	5024(2)	66(1)	C12	7785(3)	5779(5)	5586(2)	60(1)
O12	7804(2)	6777(3)	6090(2)	76(1)	C13	7250(3)	4373(4)	5511(2)	54(1)
O13	6660(2)	2158(3)	4735(2)	70(1)	C14	7278(3)	3419(4)	4870(2)	61(1)
O14	8037(3)	680(4)	5080(2)	105(1)	C15	7866(3)	3721(5)	4305(3)	69(1)
C16	8390(3)	5007(5)	4404(2)	64(1)	C17	9023(4)	5556(7)	3877(4)	87(2)
C18	7133(4)	789(5)	4807(3)	74(1)	C19	6383(5)	-428(6)	4504(3)	91(1)
C21	8151(3)	4079(4)	7462(2)	56(1)	C22	8473(3)	5001(5)	8167(2)	65(1)
C23	9477(3)	4936(6)	8666(3)	74(1)	C24	10148(3)	3973(5)	8453(3)	76(1)
C25	9825(3)	3081(6)	7744(3)	75(1)	C26	8817(3)	3105(5)	7243(3)	66(1)

Table 3. Selected Bond Lengths (Å) and Bond Angles (°) for Compound (**6**). Values in Parentheses: Estimated Standard Deviations

N1-N2	1.340(5)	C12-O12	1.203(5)	N2-N1-C5	112.1(3)	O11-C12-O12	116.0(4)
N1-C5	1.375(4)	C12-C13	1.434(6)	N2-N1-C21	118.3(3)	O11-C12-C13	116.8(3)
N1-C21	1.434(4)	C13-C14	1.355(5)	C5-N1-C21	129.4(3)	O12-C12-C13	127.2(4)
N2-C3	1.336(4)	O13-C14	1.382(5)	N1-N2-C3	104.3(3)	C5-C13-C12	117.3(3)
C3-C4	1.380(5)	C14-C15	1.419(7)	N2-C3-C4	112.1(3)	C5-C13-C14	124.0(3)
C3-C6	1.485(6)	C15-C16	1.333(6)	C3-C4-C5	105.6(3)	C12-C13-C14	118.6(3)
C4-C5	1.367(6)	C16-C17	1.474(8)	N1-C5-C4	105.9(3)	C13-C14-C15	122.4(4)
C5-C13	1.478(6)			N1-C5-C13	121.6(3)	C14-C15-C16	118.2(4)
O11-C12	1.391(5)			C4-C5-C13	132.5(3)	O11-C16-C15	121.3(4)
O11-C16	1.360(5)			C12-O11-C16	122.6(3)		

EXPERIMENTAL

The synthetic procedures, data of elementary analyses, melting points and spectroscopic data (ir, uv, ^{1}H nmr) of all compounds were published in our previous paper.[1] The ^{1}H and ^{13}C nmr spectra were recorded on a JEOL FX 90 Q spectrometer with TMS as an internal standard.

X-Ray Crystallographic Data for 5-(4-Acetoxy-6-methyl-2-pyron-3-yl)-3-ethoxycarbonyl-1-phenylpyrazole (6)[12]

A colorless crystal of approximately 0.49x0.30x0.24 mm was used for the measurements. Throughout the experiment CuKα radiation was used with a graphite crystal monochromator on a Philips PW 1100 four cycle diffractometer. Formula: $C_{20}H_{18}N_2O_6$, formula weight 382.37, monoclinic, space group $P2_1/c$, F(000)=800, Z=4, a=13.734(8), b=8.866(2), c=16.321(7) Å, β=107.13(5)°, V=1900(2) Å^3, D_{calc}=1.337 g cm^{-3}, μ=7.97 cm^{-1}, λ =1.5418 Å. The unit cell dimensions were determined from the angular settings of 25 reflections ($10.8^o < \Theta < 13.4^o$). The intensity data of 2645 reflections (one quarter sphere up to $\Theta=69.82^o$), hkl range from (-16,0,0) to (15,10,19), were measured using ω scan technique. Since significant mosaic spread was noticed for some reflections during preliminary investigations, we applied relatively fast scanning with a constant scan rate (0.04 deg sec^{-1}) and scan width 1.2°, for both strong and weak reflections. The intensity of the primary beam was checked throughout the data collection by monitoring three standard reflections every 120 minutes. The final drift correction factors were between 0.98 to 1.12. Lorentz and polarization (but not absorption) corrections were applied. Thirty reflections, unsuitable for supposed space group $P2_1/c$ were omitted (so that there were 2615 reflections left). Symmetry equivalent reflections were averaged, $R_{int}=\Sigma(I - <I>)/ \Sigma I =0.035$, resulting in 2521 unique reflections of which 2307 were observed with $I > 3\sigma(I)$. The structure was solved by Direct Methods using SIR88.[13] It was refined by full-matrix least squares using SHELX76.[14] Atomic scattering factors were taken from the International Tables for X-ray Crystallography. Isotropic least-squares refinement converged at R=0.126. Final least-squares refinement involved positions and anisotropic thermal parameters for all non-hydrogen atoms. Position parameters for hydrogen atoms, all found by difference Fourier synthesis, were refined. Isotropic temperature factors were not refined for hydrogen atoms. Because of secondary extinction four further reflections were omitted (200, 021, 202, 020) leaving 2303 reflections for analysis. The final conventional agreement factors were R = 0.062 and R_w = 0.069 for 2303 observed reflections and 307 variables. The function minimized was $\Sigma w(F_o-F_c)^2$ with $w = 2.709/\sigma^2(F)$, and $\sigma(F_o)$ from counting statistics. The maximum shift over error ratio in the last full matrix least-square cycle is 2.67 for y coordinate for the atom H19a. The final difference Fourier map showed a residual electron density between -0.25 and 0.19 e/Å^3.

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