

Synthesis and Structure Elucidation of *N*-Methyl-4-(2-benzo- γ -pyronyl)-1,2,3-triazoles

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When diazomethane was reacted with 2-cyano chromones, three isomeric *N*-methyltriazoles were obtained. They were isolated by liquid chromatography with three different solvents for elution. Complete elucidation of the structures was performed both by pmr and cmr spectrography; X-ray analysis is in agreement with the proposed structures.

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A variety of new triazole derivatives with potential biological interest have been described over the past decade [1-9]. The well known antiallergic effects of chromones prompted us to synthesize molecules in which a benzo- γ -pyrone nucleus was bonded with 1,2,3-triazole ring.

Nitriles are generally considered as unreactive towards diazomethane in the absence of a catalyst, however exceptions have been reported concerning compounds possessing electron-attracting groups [10,11].

We previously established that the chromone nucleus behaved as a strongly electron-attracting moiety [12]. So it appeared likely that 2-cyanochromones could react with diazomethane as activated nitriles to yield triazole derivatives, which was evidenced in our first attempts [13]. After-

wards Dean [14] applied this reaction to 2-cyano-6-methylchromone and isolated only a 2-methylated triazole. This result seemed to conform with literature data [10,11,14,15,16]. However Pedersen [17] isolated three isomeric *N*-methylated triazoles when diazomethane was reacted with cyanogen bromide.

So we decided to verify whether such a result could be observed with chromones. 2-Cyano chromones **1** and **2** were reacted with an excess of diazomethane. They first gave prototropic *H*-1,2,3-triazoles, which led to three isomeric *N*-methyltriazoles **A**, **B**, and **C** (Figure 1). They were then isolated by liquid chromatography on silica gel.

In order to facilitate structural comparisons, the same numbering of the atoms of the triazole ring has been used for the three isomers in each series. So structures **A**, **B**, and **C** can be related respectively, to 1,2- and 3-methylated derivatives.

Complete structural elucidation of all compounds has been performed by nmr spectrography and by X-ray analysis.

Major products, first eluted by chromatography, were thought to be 2-methylated derivatives (structure **B**), which was confirmed by X-ray crystallography for chlorinated compound **6** (Figure 2). The pmr data for related compounds [10,18,19,20,21] indicate that H-5 chemical shift is often higher in 1-methyl than in 2- or 3-methyltriazoles. Comparison with our results suggests that structure **A** can be postulated for compounds **5** and **8**. This assumption was confirmed by a nOe study. While irradiating the methyl proton, the H-5 signal intensity was measured with respect to a reference, irradiated off resonance under

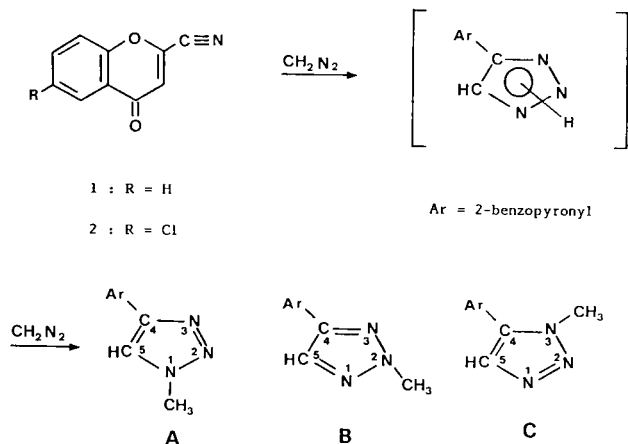
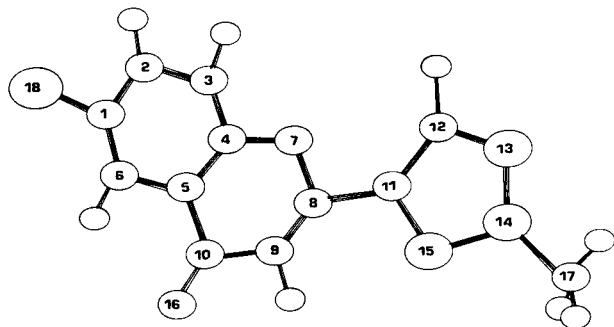
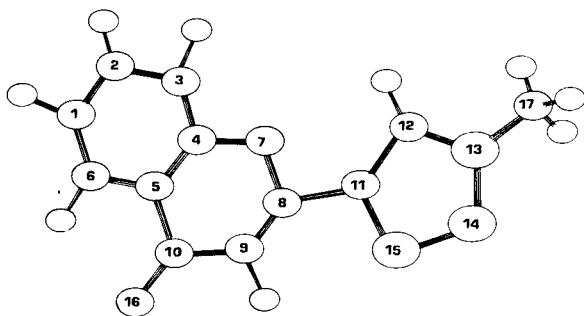


Figure 1

the same conditions. A significant modification of the signal was observed only for compounds **5** and **8**, which is in agreement with structure A.



Compound 6



Compound 5

Figure 2. Projections of the two molecules on the mean-planes of atoms showing the atom labelling scheme. Atoms 7 and 16 are oxygens, atoms 13, 14 and 15 are nitrogens, atom 18 is chlorine.

The ^{13}C nmr spectroscopy provided further information about the structures. Tsoleridis [22] pointed out that C-4 and C-5 chemical shifts of 1,2,3-triazoles were dependent upon the nature of the vicinal nitrogens.

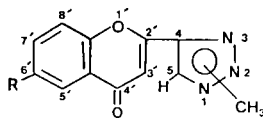
Resonance occurs at higher fields when the carbon atom is bonded to a tricoordinated nitrogen than when it is bonded to a dicoordinated one. The difference can reach 10 ppm. Considering structures A, B, and C, the lowest chemical shift should be exhibited by A for carbon 5 and by C for carbon 4. In relation to Table 1, structure A can be attributed to compounds **5** and **8**, and structure C to compounds **4** and **7**. Furthermore paramagnetic effects created by vicinal nitrogens on carbon 4 can also extend to the benzopyrone carbon 2', but the foreseeable variations in the chemical shifts should not exceed 3 ppm [22,23]. According to Table 1 compounds **4** and **7** show the lowest chemical shifts for C-2', confirming structure C. An additional proof is provided by the ^{13}C - ^1H coupling between carbon 5 and methyl protons, which can be observed for compounds **5** and **8**. Such a possibility can only occur in structure A. The value of 3.5 Hz found for the coupling constant is in agreement with literature [20].

Finally X-ray crystallography confirmed structure A for compound **5** (Figure 2).

Conclusion.

The reaction of diazomethane with 2-cyanochromones gave rise to three isomeric *N*-methyltriazoles. As was presumed, 2-methylated derivative (isomer B) is widely predominant. It is noticeable that the isomer C, although

Table 1
Selective Spectral Data (δ values)



No.	R	nmr ^1H (DMSO- d_6)			nmr ^{13}C (deuteriochloroform)		
		H-5	CH_3	$\text{C}_{2'}$	C_4	C_5	CH_3
3	H	8.65 (s)	4.42 (s)	155.65 (s)	140.62 (d)	132.92 (d)	41.92 (q)
4	H	8.63 (s)	4.52 (s)	152.65 (s)	130.28 (d)	135.19 (d)	37.55 (q)
5	H	9.01 (s)	4.29 (s)	156.91 [a] (s)	139.96 [a] (d)	126.46 [a] (dq)	36.80 [a] (q)
6	Cl	8.62 (s)	4.41 (s)	156.21 (s)	140.68 (d)	133.29 (d)	42.26 (q)
7	Cl	8.62 (s)	4.50 (s)	154.06 (s)	130.06 (d)	135.43 (d)	37.60 (q)
8	Cl	8.98 (s)	4.29 (s)	157.18 [a] (s)	139.67 [a] (d)	126.58 [a] (dq)	39.60 [a] (q)

[a] DMSO- d_6 .

Table 2
Physical and Crystal Data of Compounds 5 and 6

	Compound 5	Compound 6
Chemical Formula	C ₁₂ H ₉ O ₂ N ₃	C ₁₂ H ₈ ClO ₂ N ₃
Formula Weight	227.2	261.7
Crystal dimensions	0.5 x 0.3 x 0.05 mm ³	0.4 x 0.2 x 0.1 mm ³
Symmetry	Monoclinic	Monoclinic
Space group	P2 ₁ /c	C ₂ /c
Unit Cell dimensions		
a =	3.959 (1) Å	20.226 (5) Å
b =	21.004 (3)	7.240 (3)
c =	12.551 (5)	15.918 (5)
β =	84.01 (3)°	99.44 (2)°
ν =	1037.97 Å ⁻³	2299.64 Å ⁻³
Density (calculated)	1.454 g. cm ⁻³	1.512 g. cm ⁻³
Number of molecules per unit cell, Z	4	8
X-radiation used for data collection	λ (CuK α) = 1.54178 Å	
Total number of reflections with $\theta < 65^\circ$	1769	1950
Number of reflections with $I \geq 3 \sigma(I)$	769	1360
Disagreement index, R	0.047	0.044

more hindered, is a little more abundant than the isomer A. The steric control, pointed out by Gilchrist [10] in the alkylation by dimethyl sulfate or isopropyl iodide, does not seem a determining factor in the alkylation by diazomethane.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. Ultraviolet spectra were recorded on a Beckman DB spectrophotometer. Infrared spectra were recorded on a Beckman 4240 spectrophotometer as potassium bromide pellets. The ¹H and ¹³C nmr spectra were acquired on a pulsed wave W. H. 250 BRUKER spectrophotometer, fitted with an ASPECT 3000 calculator. Used frequencies were 250,13 MHz for proton and 62.89 MHz for ¹³C. Chemical shifts, expressed in parts per million with respect to TMS, are indicated in Table 1 for the selective data and in the description of each compound for the others.

For the nOe spectra, degassed solutions were used. The samples were cooled to -78° under vacuum (2.5 · 10⁻³ mm), then the temperature was allowed to rise to 25° while maintaining the reduced pressure. Afterwards argon was introduced. The same process was repeated three times for each sample. Protons relaxation times T₁ were determined. They were all lower than 6 seconds, so a recovery time of 60 seconds (10 T₁) could be used for the Overhauser effect measurement;

Microanalysis for C, H, N, Cl were performed by the Service Central d'Analyses du CNRS (Thiais-France).

N-Methyl-4-(2-benzopyronyl)-1,2,3-triazoles 3, 4, and 5.

To a solution of 5.5 g (0.13 mole) of diazomethane in 600 ml of ethyl ether were added 8.5 g (0.05 mole) of 2-cyanochromone 1 [24]. The mixture was stirred below 5° over 48 hours. After evaporation of ethyl ether, the residue (11.4 g) was chromatographed on a silica gel column (70-230

Table 3
Atomic Positions as Fractional Coordinates (x 10⁴) with the Estimated Standard Deviations in Parenthesis

	Compound 5			Compound 6		
	x	y	z	x	y	z
C(1)	-2305(13)	591(3)	3853(4)	3430(1)	3468(4)	1648(2)
C(2)	-2019(13)	1000(3)	2963(4)	2989(2)	3814(4)	2215(2)
C(3)	-608(13)	1594(2)	3004(4)	2374(2)	4562(4)	1914(2)
C(4)	593(12)	1786(2)	3963(3)	2208(1)	4970(4)	1059(2)
C(5)	315(12)	1399(2)	4858(3)	2654(1)	4679(4)	494(2)
C(6)	-1108(13)	799(2)	4797(4)	3277(1)	3907(4)	806(2)
C(7)	2000(9)	2384(1)	3958(2)	1576(1)	5687(3)	794(1)
C(8)	3286(12)	2596(2)	4862(4)	1395(1)	6135(4)	-37(2)
C(9)	3107(13)	2249(2)	5776(4)	1798(1)	5935(4)	-622(2)
C(10)	1691(13)	1627(2)	5845(4)	2464(1)	5200(4)	-402(2)
C(11)	4728(12)	3217(2)	4709(3)	716(1)	6840(4)	-200(2)
C(12)	5157(13)	3589(2)	3804(4)	271(2)	7186(5)	357(2)
N(13)	6655(10)	4120(2)	4108(3)	-307(1)	7760(4)	-85(2)
N(14)	7206(11)	4090(2)	5163(3)	-198(1)	7755(4)	-881(2)
N(15)	6052(11)	3535(2)	5516(3)	407(1)	7204(4)	-991(2)
O(16)	1591(11)	1286(2)	6650(3)	2851(1)	5026(3)	-919(1)
C(17)	7759(15)	4682(2)	3480(4)	-710(2)	8270(7)	-1591(3)
C(18)	-	-	-	4189.5(4)	2414(2)	2037.2(5)

Table 4
Bond Lengths (Å) and angles (°) (e.s.d.'s in parenthesis)

1	2	3	1 - 2		1 - 2 - 3	
			Compound 5	Compound 6	Compound 5	Compound 6
C(2)	C(1)	C(6)	1.405(8)	1.390(4)	118.6(5)	121.9(2)
Cl(18)	C(1)	C(2)	—	1.736(3)	—	118.2(2)
C(6)	C(1)	Cl(18)	—	1.363(4)	—	119.9(2)
C(3)	C(2)	C(1)	1.369(7)	1.370(4)	121.8(5)	119.2(2)
C(4)	C(3)	C(2)	1.398(7)	1.379(4)	118.1(5)	119.3(2)
C(5)	C(4)	C(3)	1.382(7)	1.389(4)	121.7(4)	121.8(2)
O(7)	C(4)	C(3)	1.374(6)	1.380(3)	115.7(4)	116.4(2)
C(5)	C(4)	O(7)	—	—	122.6(4)	121.8(2)
C(6)	C(5)	C(4)	1.387(7)	1.393(4)	119.2(4)	118.4(2)
C(10)	C(5)	C(4)	1.483(7)	1.465(4)	119.0(4)	119.8(2)
C(6)	C(5)	C(10)	—	—	121.8(4)	121.8(2)
C(1)	C(6)	C(5)	1.391(7)	—	120.6(5)	119.3(2)
C(8)	O(7)	C(4)	1.367(6)	1.353(3)	118.7(4)	118.5(2)
C(9)	C(8)	O(7)	1.355(7)	1.343(4)	122.4(4)	123.6(2)
C(11)	C(8)	O(7)	1.428(7)	1.447(4)	111.4(4)	111.0(2)
C(9)	C(8)	C(11)	—	—	126.2(5)	125.4(2)
C(10)	C(9)	C(8)	1.420(7)	1.437(4)	122.1(5)	121.5(2)
C(5)	C(10)	C(9)	—	—	115.1(4)	114.7(2)
O(16)	C(10)	C(5)	1.236(6)	1.232(3)	120.8(4)	122.1(2)
C(9)	C(10)	O(16)	—	—	124.2(5)	123.3(2)
C(12)	C(11)	C(8)	1.374(7)	1.386(4)	130.1(4)	130.2(2)
N(15)	C(11)	C(8)	1.363(6)	1.337(4)	121.8(4)	121.5(2)
C(12)	C(11)	N(15)	—	—	108.2(4)	108.3(2)
N(13)	C(12)	C(11)	1.338(6)	1.328(4)	105.0(4)	109.0(3)
N(14)	N(13)	C(12)	1.366(6)	1.321(4)	111.0(4)	103.6(2)
C(17)	N(13)	C(12)	1.460(7)	—	129.5(4)	—
N(14)	N(13)	C(17)	—	—	119.5(4)	—
N(15)	N(14)	N(13)	1.312(6)	1.325(3)	106.4(4)	115.5(2)
C(17)	N(14)	N(13)	—	1.451(5)	—	122.4(3)
N(15)	N(14)	C(17)	—	—	—	122.1(2)
C(11)	N(15)	N(14)	—	—	109.4(4)	103.5(2)

mesh), using a Duramat pump Merck. Successive elution of the column with 1,2-dichloroethane, ethyl acetate and ethanol effected the separation of the three isomers **3**, **4** and **5**.

2-Methyl-4-(2-benzopyronyl)-1,2,3-triazole **3**.

Compound **3** eluted first (1,2-dichloroethane), yield 5.8 g (51%), mp 158-159°; tlc (ethyl acetate) R_f = 0.67; uv (ethanol): λ max = 288 nm (ε = 26,300); ir (potassium bromide): 1650 (broad, C=O, C=N, C=C); ¹H-nmr (DMSO-d₆): δ 7.04 (s, H-3', 1H), 7.64 (m, H-6', 1H), 7.85 (dd, H-8', 1H, J = 8.0, 1.5 Hz), 7.97 (m, H-7', 1H), 8.18 (dd, H-5', 1H, J = 8.0, 1.5 Hz); ¹³C-nmr (deuteriochloroform): δ 107.29 (d, C₃), 117.59 (dd, C₈), 123.71 (s, C_{4'}), 124.91 (d, C₆), 125.14 (dd, C₅), 133.42 (dd, C₇), 155.36 (s, C_{8'}), 177.17 (s, C₄).

Anal. Calcd. for C₁₂H₉N₃O₂: C, 63.44; H, 3.96; N, 18.5. Found: C, 63.33; H, 4.02; N, 18.1.

3-Methyl-4-(2-benzopyronyl)-1,2,3-triazole **4**.

Compound **4** eluted second (ethyl acetate), yield 1 g (8.8%), mp 216-217°; tlc (ethyl acetate) R_f = 0.59; uv (ethanol): λ max = 288 nm (ε = 22,200); ir (potassium bromide): 1625 (broad, C=O, C=N, C=C); ¹H-nmr (DMSO-d₆): δ 7.12 (s, H-3', 1H), 7.66 (m, H-6', 1H), 7.93 (dd, H-8', 1H, J = 8.0, 1.5 Hz), 7.99 (m, H-7', 1H), 8.19 (dd, H-5', 1H, J = 8.0, 1.5 Hz); ¹³C-nmr (deuteriochloroform): δ 110.84 (d, C₃), 117.69 (dd, C₈), 123.65 (s, C_{4'}), 125.9 (2 dd, C₅, C₆), 134.35 (dd, C₇), 155.70 (s, C_{8'}), 176.94 (s, C₄).

Anal. Calcd. for C₁₂H₉N₃O₂: C, 63.44; H, 3.96; N, 18.5. Found: C, 63.63; H, 4.08; N, 18.0.

1-Methyl-4-(2-benzopyronyl)-1,2,3-triazole **5**.

Compound **5** eluted third (ethanol), yield 0.75 g (6.6%); mp 266°-267°;

tlc (ethyl acetate) Rf = 0.41; uv (ethanol): λ max = 288 nm (ϵ = 25,400); ir (potassium bromide): 1640 (broad, C=O, C=N, C=C); ^1H -nmr (DMSO- d_6): δ 7.01 (s, H-3', 1H), 7.64 (m, H-6', 1H), 7.80 (dd, H-8', 1H, J = 8.5, 1.5 Hz), 7.97 (m, H-7', 1H), 8.18 (dd, H-5', 1H, J = 8.5, 1.5 Hz); ^{13}C nmr (DMSO- d_6): δ 106.80 (d, C₃), 118.46 (dd, C₈), 123.82 (s, C_{4'}), 125.04 (dd, C₆), 125.87 (dd, C₅), 134.60 (dd, C₇), 154.89 (s, C_{8'}), 176.6 (s, C₄).
 Anal. Calcd. for C₁₂H₉N₃O₂: C, 63.44; H, 3.96; N, 18.5. Found: C, 63.28; H, 3.94; N, 18.2.

N-Methyl-4-(6-chloro-2-benzopyronyl)-1,2,3-triazoles **6**, **7**, and **8**.

To a solution of 3 g (0.071 mole) of diazomethane in 400 ml of ethyl ether were added 5 g (0.024 mole) of 6-chloro-2-cyanochromone **2** [24]. The mixture was stirred below 5° over 48 hours. After evaporation of the ethyl ether, the material (6.4 g) was chromatographed as previously described and the three isomers **6**, **7**, and **8** were separated.

2-Methyl-4-(6-chloro-2-benzopyronyl)-1,2,3-triazole **6**.

Compound **6** eluted first (1,2-dichloroethane), yield 3.1 g (49%), mp 191-192°; tlc (ethyl acetate) Rf = 0.80; uv (ethanol): λ max = 292 nm (ϵ = 22,500); ir (potassium bromide): 1615 (broad, C=O, C=N, C=C); ^1H nmr (DMSO- d_6): δ 7.05 (s, H-3', 1H), 7.88 (d, H-8', 1H, J = 9.0 Hz), 7.99 (dd, H-7', 1H, J = 9.0, 3.0 Hz), 8.07 (d, H-5', 1H, J = 3.0 Hz); ^{13}C nmr (deuteriochloroform): δ 107.56 (d, C₃), 119.60 (d, C₅), 124.92 (s, C_{4'}), 125.00 (dd, C₈), 131.18 (s, C₆), 133.83 (dd, C₇), 154.04 (s, C_{8'}), 176.27 (s, C₄).

Anal. Calcd. for C₁₂H₈ClN₃O₂: C, 55.07; H, 3.06; N, 16.1; Cl, 13.6. Found: C, 54.92; H, 3.11; N, 15.8; Cl, 13.4.

3-Methyl-4-(6-chloro-2-benzopyronyl)-1,2,3-triazole **7**.

Compound **7** eluted second (ethyl acetate), yield 0.55 g (8.6%), mp 187-188°; tlc (ethyl acetate) Rf = 0.64; uv (ethanol): λ max = 292 nm (ϵ = 20,900); ir (potassium bromide): 1625 (broad, C=O, C=N, C=C); ^1H nmr (DMSO- d_6): δ 7.16 (s, H-3', 1H), 8.02 (m, H-7', H-8', 2H), 8.11 (d, H-5', 1H, J = 3.0 Hz); ^{13}C nmr (deuteriochloroform): δ 110.77 (d, C₃), 119.47 (d, C₅), 124.65 (s, C_{4'}), 125.34 (dd, C₈), 132.07 (s, C₆), 134.60 (dd, C₇), 152.94 (s, C_{8'}), 175.79 (s, C₄).

Anal. Calcd. for C₁₂H₈ClN₃O₂: C, 55.07; H, 3.06; N, 16.1; Cl, 13.6. Found: C, 55.03; H, 3.08; N, 15.9; Cl, 13.5.

1-Methyl-4-(6-chloro-2-benzopyronyl)-1,2,3-triazole **8**.

Compound **8** eluted third (ethanol), yield 0.45 g (7.1%) mp 267-268°; tlc (ethyl acetate) Rf = 0.36; uv (ethanol): λ max = 292 nm (ϵ = 24,100); ir (potassium bromide): 1605 (broad, C=O, C=N, C=C); ^1H nmr (DMSO- d_6): δ 7.03 (s, H-3', 1H), 7.85 (d, H-8', 1H, J = 9.0 Hz), 7.98 (dd, H-7', 1H, J = 9.0, 3.0 Hz), 8.10 (d, H-5', 1H, J = 3.0 Hz); ^{13}C nmr (DMSO- d_6): δ 106.08 (d, C₃), 120.91 (d, C₅), 124.05 (s, C_{4'}), 124.94 (dd, C₈), 130.20 (s, C₆), 134.20 (dd, C₇), 154.11 (s, C_{8'}), 175.43 (s, C₄).

Anal. Calcd. for C₁₂H₈ClN₃O₂: C, 55.07; H, 3.06; N, 16.1; Cl, 13.6. Found: C, 55.11; H, 3.12; N, 15.9; Cl, 13.3.

X-Ray Crystallography.

Direct structural information as to the location of the N-methyl group in compounds **3** to **8** can be obtained by X-ray crystallography. Crystals suitable for such a study were obtained only for compound **5** in the non-substituted series and compound **6** in the chlorinated series.

Data Collection.

The intensity data were collected on a CAD-4 Enraf-Nonius automatic diffractometer at room temperature (ω θ scan procedure, scan width 1° (**6**), 3° (**5**), speed ratio θ/ω = 1). No deviations in the intensities of check reflections were observed during the data collection. Corrections were made for Lorentz and polarization effects but not for absorption. The physical and crystal data of both compounds are listed in Table 2.

Determination of the Structures.

The scattering factor tables for non-hydrogen atoms and the anomalous dispersion corrections for Cl were taken from the International Tables for X-ray Crystallography [25] whereas the scattering factors for hydrogens were taken from [26].

Both structures were solved by direct methods using the MULTAN 80

program [27] and classical Fourier techniques. All calculations were carried out on a Mini 6-92 CII-Honeywell-Bull computer. Positional parameters of both molecules are given in Table 3.

Discussion.

These results confirm the structure **A** (N-methyl-1) for compound **5** and **B** (N-methyl-2) for compound **6**.

Projections of the two molecules on least squares planes, showing the atom labelling scheme are depicted on Figure 2. The bond lengths and angles are compared in Table 4.

Both molecules are almost flat. The angle between the two rings is 2.9° in **5** and 5.7° in **6**.

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