Modifications and Extensions of the Pschorr Reaction in Pyrazole Series. Access to the [2]Benzopyrano[4,3-*c*]pyrazole System of Pharmaceutical Interest

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The Pschorr reaction performed under non-classical reaction conditions on the diazonium chloride derived from 2-amino-*N*-methyl-*N*-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)benzamide **1** afforded the epimers (3'*R*,4'*S*)- and (3'*R*,4'*R*)-4'-chloro-2',4'-dihydro-2,5'-dimethyl-2'-phenylspiro[isoindoline-1,3'-3'*H*-pyrazol]-3-one **4a** and **4b**† together with the related enantiomers. The epimers were easily converted under acid conditions into both 4-chloro-3-methyl-5-[2-(methylcarbamoyl)phenyl]-1-phenyl-1*H*-pyrazole **5** and the potentially pharmacologically active 3-methyl-1-phenyl-1*H*-[2]benzopyrano[4,3-*c*]pyrazol-5-one **3**, whereas under base conditions, as well as thermally, only compound **5** was obtained.

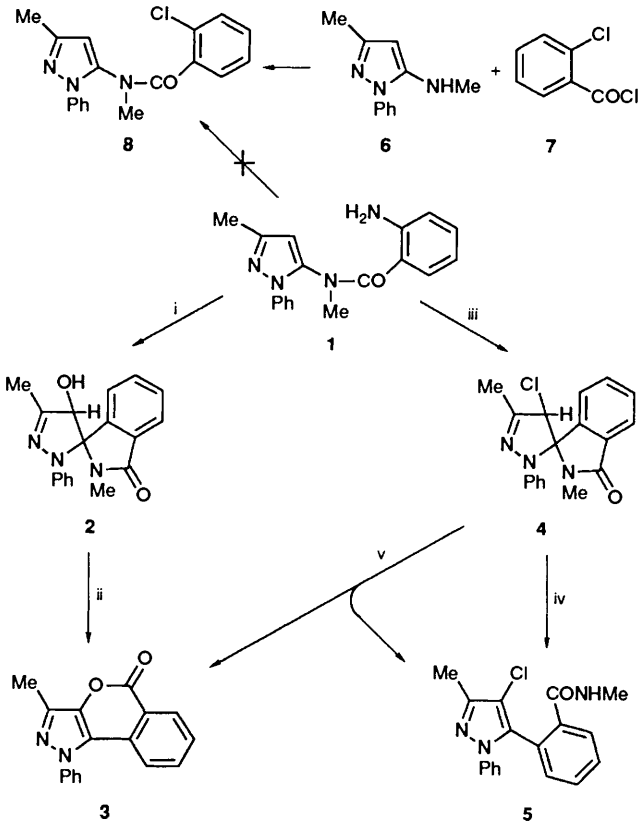
The molecular structure of epimer **4a** and that of the derivative **5** were confirmed by single-crystal X-ray analysis. The crystal of compound **5** is characterized by the presence of two conformational isomers in the unit cell.

Previously we have reported [1] that the diazotization of 2-amino-*N*-methyl-*N*-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)benzamide **1** in dilute aqueous sulfuric acid, followed by the Pschorr reaction at 70 °C, gives rise to the formation of numerous products, among them the spiro compound **2** is isolated in low yield. This product rapidly undergoes thermal conversion into 3-methyl-1-phenyl-1*H*-[2]benzopyrano[4,3-*c*]pyrazol-5-one **3** in good yield (see Scheme 1).

From the literature it is known that different [2]benzopyrano-pyrazole derivatives show a wide variety of pharmacological activities, such as analgesic, anti-inflammatory and antimicrobial.[2] Continuing our research on analgesic and anti-inflammatory agents,[3] it was thought of interest to prepare the spiro derivative **2** under different reaction conditions with respect to the classical Pschorr reaction,[1,4] in order to obtain a greater yield and to transform it into the benzopyranopyrazole **3** with potential pharmacological activity. The modifications concern: (a) slightly acid pH, 6.25, which should increase the reactivity of the 5-position in the pyrazole nucleus, (b) the decomposition of the diazonium salt without heating, in order to reduce formation of classical Pschorr reaction product and by-products, and (c) a prolonged (1 week) reaction time, due to the low decomposition rate of the diazonium salt.

The amine **1** was diazotized at pH 6.25 using hydrochloric acid; the diazonium salt solution was stored at 7 °C for a week and unexpectedly gave a solid chlorine-containing product. The reaction mixture, when analysed by TLC, showed two relevant spots with an area ratio of 1.5:1 and R_{f_1} 0.85, R_{f_2} 0.71. Crystallization gave crystals which analysed for $C_{18}H_{16}ClN_3O$. Moreover, TLC analysis again showed the presence of two spots but the area ratio was now ~3:1.

An examination of the 250 MHz ^{1}H NMR spectrum showed signals for two methyls, *viz.* a singlet at δ 2.67 and a doublet (J 1.78 Hz) at δ 2.24, for one methine as a quadruplet (J 1.75 Hz) at δ 5.29 and, finally, signals for nine aromatic protons. The IR spectrum presented a carbonyl stretching band at 1705 cm^{-1}, shifted towards higher wavenumbers with respect to the starting amide **1**.



Scheme 1 *Reagents and conditions:* i, KNO_2, H_2SO_4; ii, H^+ or 260 °C; iii, KNO_2, HCl; iv, OH^- or 220 °C; v, H_2SO_4

Lastly, the crystalline product is different from the isomeric compound **8** (see Scheme 1).

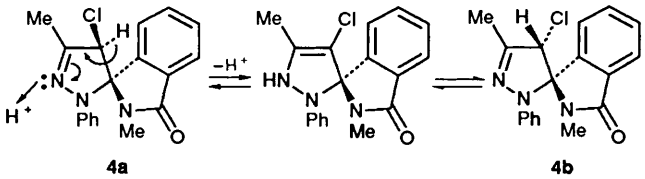
On the basis of the above analytical and spectroscopic data we suggest for the crystalline product the presence of the

† The numbering of the epimers is according to IUPAC recommendations and is different from that used in the crystallographic numbering scheme.

epimers **4a** and **4b** (together, obviously, with their enantiomers) which are the main products of the reaction mixture.

Attempts to separate the two epimers by fractional crystallization were unsuccessful. However, by slow solvent evaporation of a diethyl ether solution of the epimeric mixture at room temperature the epimer **4a** was obtained pure, whose stereochemical structure was elucidated by X-ray analysis.

We could attribute the epimeric form **4b** to the second compound of the mixture (R_f 0.71) on the basis of the following results: (a) analytical data agree with the $C_{18}H_{16}ClN_3O$ formula even if a mixture is analysed, (b) the ^1H NMR spectrum signals are consistent with structure **4b**, (c) HPLC analysis of an acidic methanol solution of the crystallized reaction mixture, kept for 24 h, showed that epimer **4a** underwent interconversion with the second component of the mixture. This could be explained by the C-4′ acid-catalysed epimerization of epimer **4a** into epimer **4b** [5] (see Scheme 2).

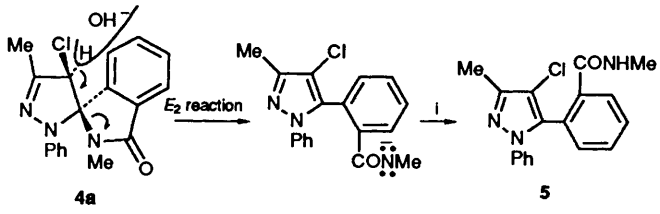


Scheme 2

The formation of the epimers **4a** and **4b** can be rationalized (see Scheme 3) through the formation of carbocation **10**, followed by an electrophilic attack at the 5 position of the pyrazole nucleus and subsequent nucleophilic addition of the chloro anion on the C-4′ pyrazoline position. The different yields of the epimers **4a** and **4b** are due to the presence of the chiral centre at the C-3′ pyrazoline position. The absence of the expected spiro compound **2** in the reaction mixture (see Scheme 1) could be due to the higher nucleophilicity of chloride compared with that of water.[6] Despite the loss of pyrazole aromaticity and the low reactivity of the pyrazole C-5 position, we obtained the epimeric couple due to the easier formation of a 5-membered ring than a 6-membered one.[7]

The reactivity of the epimers **4a** and **4b** (as a mixture) in acid and basic medium, as well as their thermal transformations, were then investigated. By treatment of the crystalline epimeric mixture with 1 mol dm^{-3} alcoholic potassium hydroxide at room temperature for 15 h, or by heating for 8 h, an isomeric product of formula $C_{18}H_{16}ClN_3O$ was formed. On the basis of both spectroscopic measurements and X-ray crystallographic analysis (see below) we assigned structure **5** to this product. The IR spectrum of the compound displayed two carbonyl bands at 1630 and 1650 cm^{-1} as well as two other absorption bands at 3270 and 3360 cm^{-1} attributed to the NH amidic group. The 250 MHz ^1H NMR spectrum showed, in addition to other signals, distinct resonances for a methyl, as doublet at δ 2.71, and for one amidic proton at δ 5.55. Upon D_2O exchange the spectrum lost the broad signal for the NH, and the methyl doublet collapsed to a singlet.

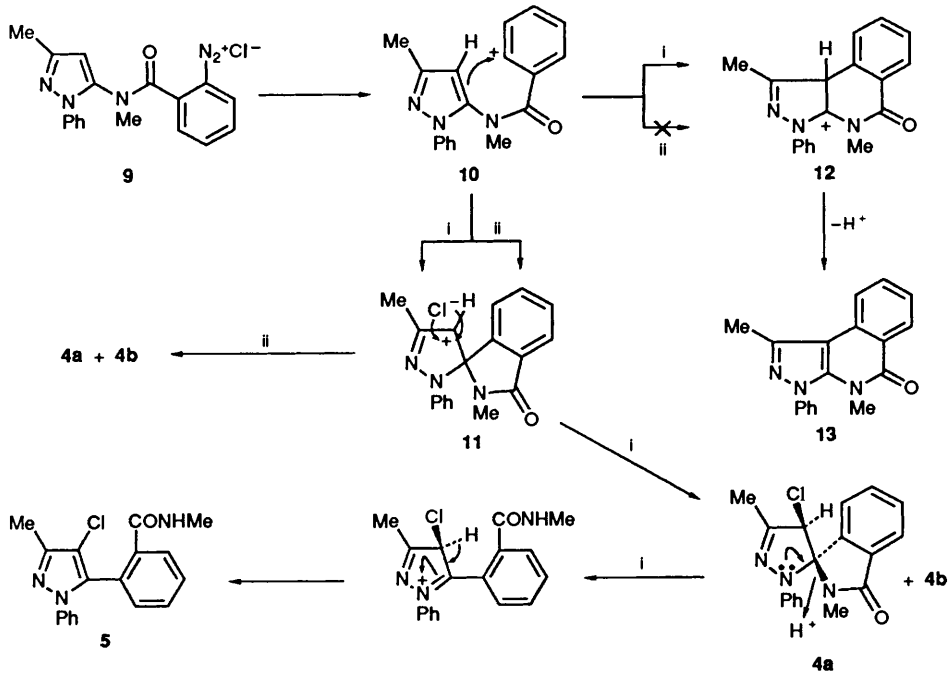
A possible pathway for the formation of compound **5** in basic medium involves the removal of a proton from the C-4′ pyrazoline position, followed by a shift of the C-4′ electrons into the ring and the simultaneous 'elimination' of the methylcarbamoyl moiety as anion (see Scheme 4). This process is very



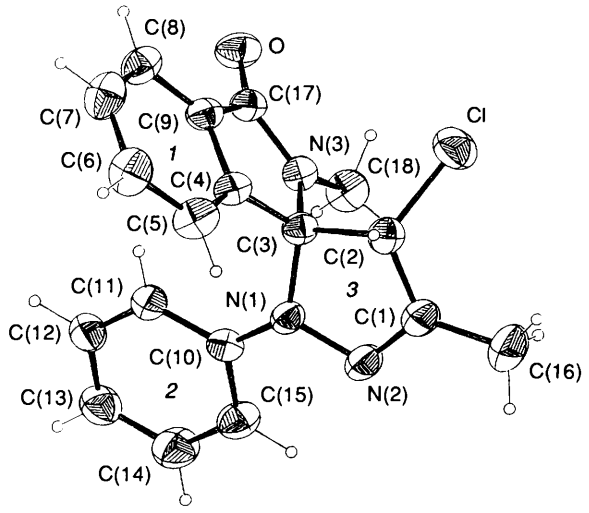
Scheme 4 *Reagents:* i, water

easy for the epimer **4a**, due to the correct *trans* structure, whereas for the epimer **4b**, with a *cis* structure, it is reasonable to consider a preliminary conversion into the epimer **4a**. In acidic medium the reaction pathway for the transformation of the epimers is quite different. Moreover, the pyrazole derivative **5** was obtained together with compound **3** which was identical in all respects with an authentic specimen of 3-methyl-1-phenyl-1*H*-[2]benzopyrano[4,3-*c*]pyrazol-5-one [1] (see Scheme 1). The formation of compound **5** probably occurs by an acid-catalysed ionization of the C1–N2 bond of the isoindolinone ring, assisted by the N-2′ lone pair of the pyrazoline nucleus [8] (see Scheme 3).

The transformation of the epimers **4a** and **4b** into the lactone



Scheme 3 *Conditions:* i, 70 °C; ii, 7 °C



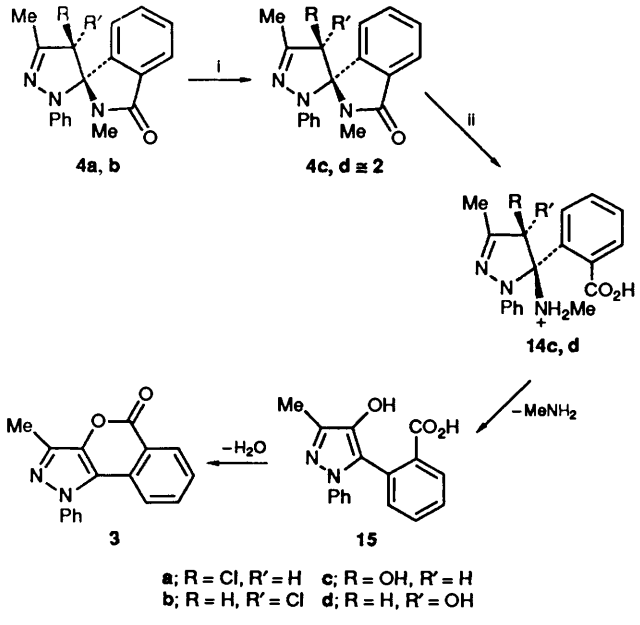
4a

Fig. 1 ORTEP view of compound **4a**

Table 1 Selected bond lenths (Å) and angles (°) for compound **4a**

Cl–C(2)	1.784(3)	N(1)–N(2)	1.405(3)
N(1)–C(3)	1.469(3)	N(1)–C(10)	1.419(3)
N(2)–C(1)	1.285(3)	N(3)–C(3)	1.451(3)
N(3)–C(17)	1.369(3)	N(3)–C(18)	1.449(3)
O–C(17)	1.227(3)	C(1)–C(2)	1.497(4)
C(1)–C(16)	1.481(4)	C(2)–C(3)	1.562(3)
C(3)–C(4)	1.509(3)	C(4)–C(5)	1.380(4)
C(4)–C(9)	1.396(3)	C(5)–C(6)	1.393(4)
C(6)–C(7)	1.399(4)	C(7)–C(8)	1.394(4)
C(8)–C(9)	1.384(4)	C(9)–C(17)	1.476(3)
C(3)–N(1)–C(10)	122.8(2)	N(2)–N(1)–C(10)	116.2(2)
N(2)–N(1)–C(3)	111.4(2)	N(1)–N(2)–C(1)	109.2(2)
C(17)–N(3)–C(18)	123.0(2)	C(3)–N(3)–C(18)	123.3(2)
C(3)–N(3)–C(17)	113.7(2)	N(2)–C(1)–C(16)	123.2(3)
N(2)–C(1)–C(2)	112.1(2)	C(2)–C(1)–C(16)	124.6(3)
Cl–C(2)–C(1)	114.0(2)	C(1)–C(2)–C(3)	102.8(2)
Cl–C(2)–C(3)	114.1(2)	N(3)–C(3)–C(2)	114.4(2)
N(1)–C(3)–C(2)	99.3(2)	N(1)–C(3)–N(3)	114.0(2)
C(2)–C(3)–C(4)	112.4(2)	N(3)–C(3)–C(4)	101.9(2)
N(1)–C(3)–C(4)	115.4(2)	C(3)–C(4)–C(9)	109.5(2)
C(3)–C(4)–C(5)	129.1(2)	C(8)–C(9)–C(17)	130.5(2)
C(4)–C(9)–C(17)	108.1(2)	N(1)–C(10)–C(15)	120.0(2)
N(1)–C(10)–C(11)	121.1(2)	O–C(17)–C(9)	129.1(2)
N(3)–C(17)–C(9)	106.4(2)	N(3)–C(17)–O	124.4(2)

3 is based on the mechanism which involves the preliminary nucleophilic substitution of the chlorine at the C-4′ pyrazoline position, followed by hydrolytic opening of the isoindoline ring to give the acids **14c** and **14d**, elimination of methylamine, and finally the cyclocondensation of hydroxy acid **15** to give lactone **3** (see Scheme 5). This mechanism is supported by the following



Scheme 5 *Reagents:* i, water; ii, H^+, water

experimental evidence: (a) the epimeric mixture **4a**/**4b** afforded the spiro derivative **4c** or **4d** (≡**2**) when refluxed in aq. ethanol solution, (b) the intermediate **4c**/**4d** was easily converted under acidic conditions into the lactone **3**.

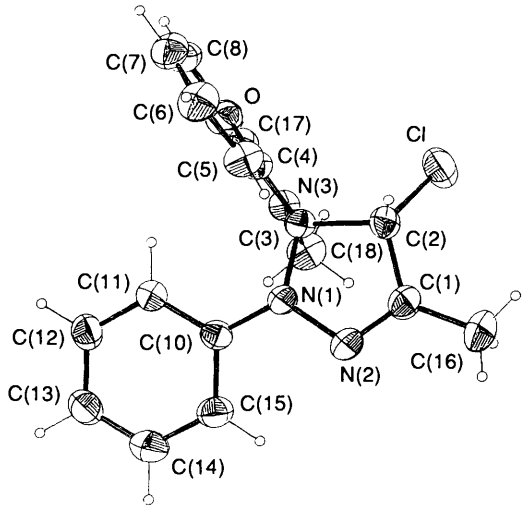
Thermal transformation of the epimers **4a** and **4b** was also studied: on reflux of an ethanolic solution of the mixture **4a**/**4b** for 24 h, compound **5** was formed, whereas by fusion at 210–220 °C for 5 min the epimers were totally transformed into compound **5**. The formation of compound **5** under different reaction conditions is indicative of the pyrazoline system's characteristic tendency to restore, by an elimination process, the aromatic system of the pyrazole nucleus.[9] The difference in the present mechanism is that the restoration of aromaticity does not require loss of a molecular entity, because both substituents at C-3′ are part of the isoindoline ring.

Upon decomposition of the diazonium salt (**9**) at 70 °C (pH 6.25) no epimer was isolated. However, chromatography of the reaction mixture allowed the separation of the pyrazole **5**, which represents indirect experimental evidence for formation of the epimers, and of a second product, identified as 3,4-dihydro-1,4-dimethyl-3-phenylpyrazolo[3,4-*c*]isoquinolin-5-one **13**[1] (see Scheme 3).

Our findings support the view that when the reaction is carried out at 7 °C, only the intermediate **11**, which yields the epimers **4a** and **4b**, is formed, whereas at 70 °C the carbocation **12**, bearing a six-membered ring, is also an intermediate (see Scheme 3) from which the pyrazoloisoquinoline derivative **13** is formed. Apparently, the rearrangement **11** to **12** could take place at 70 °C, due to the greater stability of cation **12** compared with that of spiro cation **11**.

Structure of Epimer **4a**.—Fig. 1 shows an ORTEP view of one molecule with the atom-numbering scheme used. Selected interatomic distances and angles are given in Table 1. The molecular structure is characterized by the two chiral centres at atoms C(2) and C(3) of the pyrazoline ring with conformations 2*S*,3*R* respectively (or 2*R*,3*S*); the space group in which the compound crystallizes is centrosymmetric, consequently both enantiomers are present.

The isoindolinone ring is not planar due to the lack of aromaticity in the five-membered ring, which adopts a puckered conformation. The dihedral angle with the fused benzene ring is 6.09(2)°. The pyrazoline ring (*3*) is characterized by an envelope conformation and the isoindolinonic residue is quasi-orthogonal to it. The phenyl ring *2* [bound to N(1)] is rotated 16.1(5)° with respect to ring *3*. Close examination of bond distances and angles indicates double-bond character for the N(2)–C(1) bond [1.285(3) Å] *versus* the theoretical value for N–Csp^2 = 1.279 Å (Allen *et al.*[10]). The other distances in the pyrazoline ring are close to the values reported for single bonds. In the isoindoline ring the N(3)–C(17) bond length of 1.369(3) Å adjacent to the C=O group is between a single- and a double-bond value as a consequence of some degree of electron delocalization in the amidic group. The other bond distances in the structure present values expected from the literature. The crystal packing is determined by the usual van de Waals contact distances.



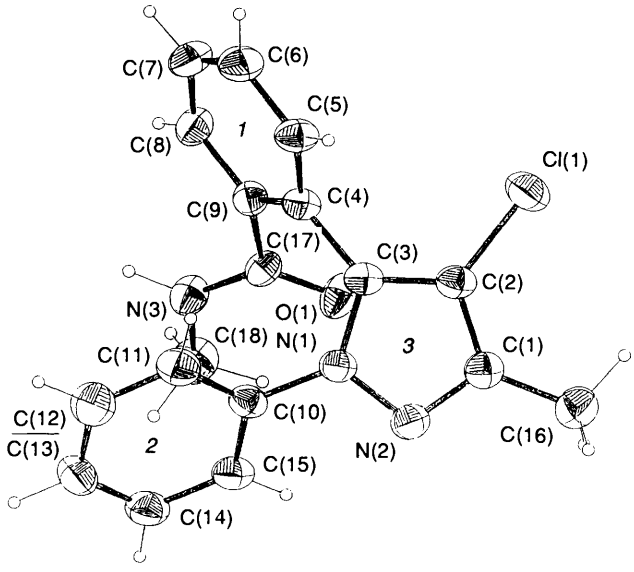
4a

Fig. 2 ORTEP view of molecule **4a** projected onto the plane of the pyrazole moiety

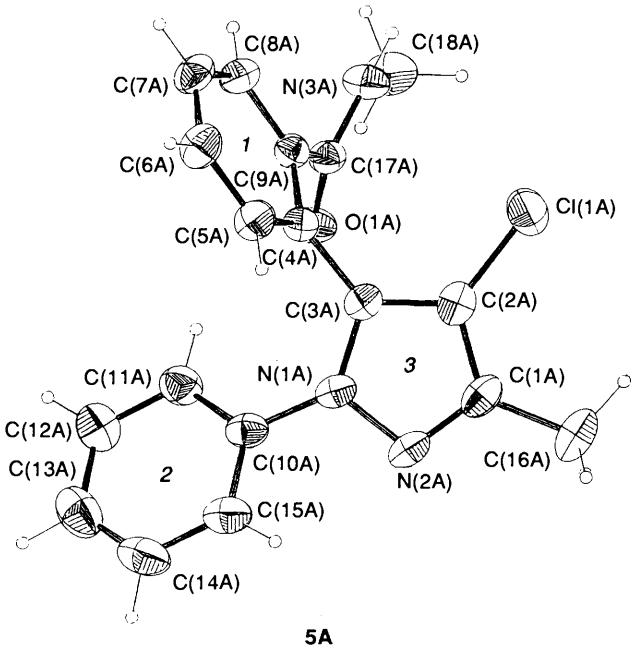
Table 2 Selected bond lengths (Å) and angles (°) for comformers **5** and **5A**

5		5A	
Cl(1)–C(2)	1.736(4)	Cl(1A)–C(2A)	1.713(4)
N(1)–N(2)	1.353(5)	N(1A)–N(2A)	1.380(4)
N(1)–C(3)	1.381(4)	N(1A)–C(3A)	1.382(5)
N(1)–C(10)	1.438(5)	N(1A)–C(10A)	1.432(5)
N(2)–C(1)	1.347(5)	N(2A)–C(1A)	1.325(6)
C(1)–C(2)	1.401(5)	C(1A)–C(2A)	1.412(5)
C(1)–C(16)	1.482(6)	C(1A)–C(16A)	1.501(6)
C(2)–C(3)	1.370(5)	C(2A)–C(3A)	1.379(5)
C(3)–C(4)	1.475(5)	C(3A)–C(4A)	1.486(5)
C(9)–C(17)	1.519(5)	C(9A)–C(17A)	1.507(5)
C(17)–O(1)	1.220(4)	C(17A)–O(1A)	1.230(5)
C(17)–N(3)	1.334(5)	C(17A)–N(3A)	1.339(4)
C(18)–N(3)	1.454(6)	C(18A)–N(3A)	1.457(6)
C(3)–N(1)–C(10)	127.8(3)	C(3A)–N(1A)–C(10A)	131.0(4)
N(2)–N(1)–C(10)	119.9(3)	N(2A)–N(1A)–C(10A)	117.2(4)
N(2)–N(1)–C(3)	112.2(3)	N(2A)–N(1A)–C(3A)	111.1(4)
N(1)–N(2)–C(1)	106.6(3)	N(1A)–N(2A)–C(1A)	105.5(4)
N(2)–C(1)–C(16)	122.5(4)	N(2A)–C(1A)–C(16A)	121.4(4)
N(2)–C(1)–C(2)	108.1(4)	N(2A)–C(1A)–C(2A)	111.3(4)
C(2)–C(1)–C(16)	129.4(4)	C(2A)–C(1A)–C(16A)	127.2(4)
Cl(1)–C(2)–C(1)	125.1(3)	Cl(1A)–C(2A)–C(1A)	127.6(4)
C(1)–C(2)–C(3)	109.2(4)	C(1A)–C(2A)–C(3A)	106.0(4)
Cl(1)–C(2)–C(3)	125.5(3)	Cl(1A)–C(2A)–C(3A)	126.3(4)
N(1)–C(3)–C(2)	104.0(4)	N(1A)–C(3A)–C(2A)	106.1(4)
C(2)–C(3)–C(4)	130.8(4)	C(2A)–C(3A)–C(4A)	129.2(4)
N(1)–C(3)–C(4)	124.5(4)	N(1A)–C(3A)–C(4A)	123.7(4)
C(3)–C(4)–C(9)	121.5(4)	C(3A)–C(4A)–C(9A)	123.0(4)
C(3)–C(4)–C(5)	119.5(4)	C(3A)–C(4A)–C(5A)	117.8(4)
C(8)–C(9)–C(17)	121.7(4)	C(8A)–C(9A)–C(17A)	118.6(4)
C(4)–C(9)–C(17)	118.7(4)	C(4A)–C(9A)–C(17A)	121.6(4)
N(1)–C(10)–C(11)	118.3(4)	N(1A)–C(10A)–C(11A)	120.2(4)
N(1)–C(10)–C(15)	121.8(4)	N(1A)–C(10A)–C(15A)	120.2(4)
C(9)–C(17)–N(3)	116.1(3)	C(9A)–C(17A)–N(3A)	115.9(4)
C(9)–C(17)–O(1)	120.5(4)	C(9A)–C(17A)–O(1A)	120.0(4)
O(1)–C(17)–N(3)	123.4(4)	0(1A)–C(17A)–N(3A)	123.8(4)
C(17)–N(3)–C(18)	120.5(4)	C(17A)–N(3A)–C(18A)	121.1(4)

We have already described the formation of compound **5**, from epimer **4a**, under the action of KOH in ethanolic solution. The reaction product **5** has been crystallized and the unexpected result from its X-ray analysis is the presence, in the same crystal, of two conformers.



5



5A

Fig. 3 ORTEP view of the conformers **5** and **5A**

A ORTEP view of the two molecules (hereinafter **5** and **5A**) is reported in Fig. 3. Their formation can be easily understood if we examine Fig. 2 where a view of a molecule of epimer **4a** projected onto the pyrazole plane is reported. The orthogonal isoindolinone moiety has enough room for rotation clockwise and anticlockwise around the C(3)–C(4) bond, after the breakage of the C(3)–N(3) bond with the formation of the methylcarbamoylphenyl moiety. The two conformers **5** and **5A** differ mainly in the orientation of the methylcarbamoylphenyl moiety, which is directed toward the phenyl group, with a distance N(3)···C(15) of 3.994(5) Å in **5**, and toward the chlorine in **5A**, with a distance N(3A)···Cl of 3.993(4) Å in a rather symmetric fashion with respect to the most hindering moieties (the phenyl on one side and the chlorine on the other). Table 2 gives significant bond distances and angles.

There is electron delocalization in the pyrazole rings whether it is slightly puckered as in **5** or planar as in **5A** [probably as a consequence of the intramolecular C(5)···Cl(1) contact of 3.595(5) Å which could cause some molecular perturbation].

Table 3 Significant geometric parameters for compounds **4a**, **5** and **5A** [angles (°), distances (Å)]

Angles between the planes			
	5	**5A**	**4a**
1 ∧ *2*	117.2(1)	75.9(2)	81.4(1)
1 ∧ *3*	62.5(2)	65.3(2)	96.1(1)
2 ∧ *3*	137.5(2)	34.9(2)	16.1(1)
Significant intramolecular contacts			
	5	**5A**	**4a**
C(5)···Cl(1)	3.595(4)	4.254(4)	>4.0
N(2)···C(15)	2.893(5)	2.868(6)	2.747(3)
N(3)···C(3)	4.061(5)	4.127(5)	bonded
N(3)···Cl(1)	>4.5	3.993(4)	2.964(2)
Pyrazole ring conformation	'slightly puckered'	planar	'envelope'

The benzamide residue is symmetrically orientated with respect to the pyrazole nucleus in structures **5** and **5A**. An additional conformational difference between conformers **5** and **5A** is, as expected, the orientation of the phenyl [C(10) to C(15)] with respect to the pyrazole ring: 137.6(1)° in **5** and 34.9(2)° in **5A**. The greater rotation in conformer **5** is due to the steric requirement of the methylcarbamoyl residue which is pointing in the direction of the phenyl group. Table 3 gives significant geometric parameters for structures **4a**, **5** and **5A**. We notice that a further effect of the formation of conformers **5** and **5A** from **4a** is the rotation of ring *2* with respect to ring *3* in order to allow the C(3)–N(3) cleavage, and the rather symmetric orientation of ring *1* with respect to ring *3* in the conformers **5** and **5A** [62.5(2) and 65.3(2)°, respectively].

Bond distances in both conformers are comparable, and a certain degree of electron delocalization is present in both the O(1)–C(17)–N(3)–Me residues.

The crystal packing illustrated in Fig. 4 shows a hydrogen-bond interaction between N(3)A and O(1) [N(3)A···O(1) 2.917(5) Å, H(3)A···O(1) 1.95(4) Å, N(3)A–H(3)A···O(1) 164(4)°] which represents the strongest interaction between the two conformers. A second, weaker interaction of hydrogen-bond type involves N(3) and O(1)A′ (′ at x, y, $z-1$) [N(3)···O(1)A′ 2.928(5) Å, H(3)···O(1)A′ 2.09(4) Å, N(3)–H(3)···O(1)A′ 142(3)°].

Conclusions. The desired spiro compound **2**, useful as a starting material for the preparation of the potentially pharmacologically active benzopyranopyrazole derivative **3**, was not obtained, whereas, unexpectedly, the chlorine-containing epimers **4a** and **4b** were formed.

It is worthwhile remembering that the epimers **4a** and **4b** were formed only under particular conditions. When the reaction temperature was raised, other compounds were obtained. The formation of compound **5** from epimer **4a** and/or **4b**, with restoration of the aromatic system of the pyrazole nucleus without molecular loss, is a rare example of such a mechanism in pyrazoline chemistry. The molecular structure of compounds **4a** and **5** (in the form of two conformers **5** and **5A**) has shown the easy formation of compound **5** from **4a** and that little energy is required to convert conformer **5** into **5A** since both are present in the same crystal. In addition, the hydrogen-bond interactions among the two forms stabilize the two conformations, at least in the solid state.

Experimental

M.p.s were determined on a Büchi-Tottoli apparatus and are uncorrected. IR spectra were recorded on a JASCO spectrophotometer for solutions in hexachlorobutadiene. ^{1}H NMR spectra were obtained for $CDCl_3$ solutions (tetramethylsilane as internal standard) on a Bruker AC 250F (250 MHz) spectrometer. *J*-Values are given in Hz. Mass measurements at low resolution were obtained on a JEOL JMS-01-SG-2 mass spectrometer operating at 75 eV. HPLC analysis was performed using a Beckman Gold System model 126 pump with a Beckman Gold System model 166 UV detector set at 254 nm. An Ultrasphere octadecylsilyl 5μ 25 cm × 4.6 mm column and, as the eluent, a 70:30 methanol–water mixture, were used for the separation of epimers.

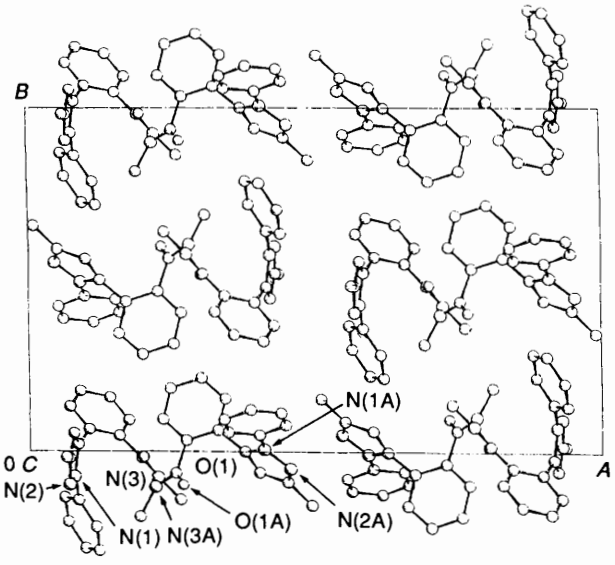


Fig. 4 Unit-cell content for conformer **5**

Decomposition of the Diazonium Chloride **9** *prepared from* 2-*Amino*-N-*methyl*-N-(3-*methyl*-1-*phenylpyrazol*-5-*yl*)*benzamide* **1**.—The pulverized amine **1**[11] (20 mmol) was dissolved in cooled (0–5 °C), 5 mol dm^{-3} hydrochloric acid (12 cm^3), and 2.5 mol dm^{-3} aq. sodium nitrite (4.14 cm^3) was added dropwise to the stirred solution. The solution was stirred for a further 10 min in the ice-bath and was then checked for nitrous acid excess with potassium iodide starch paper; the eventual excess was destroyed by the addition of urea.

The yellow solution was diluted with cold water (0–5 °C) to 600 cm^3, the pH was adjusted to 6.25 with aq. sodium hydrogen carbonate, and stored at 7 °C for a week. The suspension thus obtained was filtered, and the insoluble residue was dried in air and then recrystallized from ethanol (95% v/v) to give the epimeric mixture **4a**/**4b** (2.4 g).

The crystalline product was dissolved at room temperature in diethyl ether and the saturated solution was allowed to evaporate slowly. The crystals at the bottom of the vessel were collected and the procedure was repeated twice more to give the epimer 4′-*chloro*-2′,4′-*dihydro*-2,5′-*dimethyl*-2′-*phenylspiro*[*isoindoline*-1,3′-3′H-*pyrazol*]-3-*one* **4a** in very poor yield, m.p. 156–157 °C (Found: C, 66.5; H, 5.1; N, 12.8. $C_{18}H_{16}ClN_3O$ requires C, 66.31; H, 4.95; N, 12.89%); m/z 325 (M^+); ν_{max}/cm^{-1} 1705 (CO); δ_H 2.24 (3 H, d, *J* 1.78, Me), 2.67 (3 H, s, Me), 5.29 (1 H, q, *J* 1.78, pyrazoline CH) and 6.64–7.93 (9 H, complex signals, Ph and C_6H_4).

Alkaline Isomerization of the Epimers **4a**/**4b** *into* 4-*Chloro*-3-*methyl*-5-[2-(*methylcarbamoyl*)*phenyl*]-1-*phenyl*-1H-*pyrazole* **5**.—*Method* (*a*). The finely pulverized epimeric mixture **4a**/**4b** (500 mg, from one crystallization from ethanol) was dissolved in 1 mol dm^{-3} potassium hydroxide in absolute ethanol (10 cm^3) and the solution was stirred for 15 h at room temperature. The suspension thus obtained was diluted with water to a volume of ~25 cm^3, and the solid material was filtered off, and washed with water. Recrystallization from ethanol (95% v/v) gave compound **5** in 65% yield.

Method (*b*). The epimeric mixture **4a**/**4b** (1.2 g, from one crystallization from EtOH) was refluxed in 1 mol dm^{-3} potassium hydroxide in absolute ethanol (10 cm^3) for 8 h. After storage overnight a crystalline product had separated, and this was filtered off, washed with water, and recrystallized from ethanol (95% v/v) to give *compound* **5** (70%), m.p. 187–189 °C (Found: C, 66.4; H, 4.8; N, 12.85. $C_{18}H_{16}ClN_3O$ requires C, 66.31; H, 4.95; N, 12.89%); *m*/*z* 325 (M^+); ν_{max}/cm^{-1} 3360 and 3270 (NH), 1650 and 1630 (CO); δ_H 2.37 (3 H, s, Me), 2.71 (3 H, d, *J* 5.27, Me), 5.55 (1 H, br s, exchanges slowly with D_2O, NH) and 7.16–7.65 (9 H, complex m, Ph and C_6H_4).

Action of 1.25 *mol* dm^{-3} *Sulfuric Acid on the Epimers* **4a** *and* **4b**.—The epimeric mixture **4a**/**4b** (400 mg, from one crystallization from EtOH) was refluxed in a solution 1.25 mol dm^{-3} sulfuric acid in ethanol–water (1:1 v/v; 20 cm^3) for a period of 3 h. The solution was diluted with water (80 cm^3) and the pH was adjusted to 8 with aq. potassium hydroxide. The solution was extracted with chloroform (2 × 100 cm^3), and the combined extract was dried (Na_2SO_4), and concentrated under reduced pressure. The solid residue was chromatographed by preparative TLC on silica gel [thickness 2 mm; benzene–diethyl ether (1:1) as developer] to give compound **5** together with a product that was identical in all respect (IR, MS, ^1H NMR, mixed m.p.) with an authentic specimen of 3-methyl-1-phenyl-1*H*-[2]benzopyrano[4,3-*c*]pyrazol-5-one **3**.[1]

2-*Chloro*-N-*methyl*-N-(3-*methyl*-1-*phenyl*-1H-*pyrazol*-5-*yl*)-*benzamide* **8**.—A solution of equimolar amounts (10 mmol) of 3-methyl-5-methylamino-1-phenyl-1*H*-pyrazole **6**[12] and *o*-chlorobenzoyl chloride **7** in dry chloroform (100 cm^3) was refluxed for 5 h. After the first hour of reflux, triethylamine (1.6 cm^3) was added in four portions (0.8, 0.4, 2 × 0.2 cm^3, respectively), with an interval of 1 h between each addition.

The solution was evaporated under reduced pressure and the oily residue was washed with water (2 × 100 cm^3). The oil solidified when scratched with cyclohexane, and crystallization from cyclohexane gave *compound* **8** (50%), m.p. 129–131 °C (Found: C, 66.4; H, 5.1; N, 13.0. $C_{18}H_{16}ClN_3O$ requires C, 66.31; H, 4.95; N, 12.89%); *m*/*z* 325 (M^+); ν_{max}/cm^{-1} 1660 (CO); δ_H 2.15 (3 H, s, Me), 3.35 (3 H, s, Me), 6.12 (1 H, s, pyrazole H) and 6.30–7.60 (9 H, complex m, Ph and C_6H_4).

Chlorolysis of the Epimers **4a**/**4b**.—The epimeric mixture **4a**/**4b** (700 mg) was refluxed in a water–ethanol solution (35 cm^3; 1:1 v/v) for 30 min. The solution thus obtained was concentrated under reduced pressure to half its original volume and the separate solid material was filtered off. After several crystallizations a crystalline product, identified on the basis of physical, as well as spectroscopic, data (60% yield) as 2′,4′-dihydro-4′-hydroxy-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazol]-3-one **2**[1] was obtained.

Action of 1.25 *mol* dm^{-3} *Sulfuric Acid on the Spiro Derivative* **2**.—A sample (200 mg) of spiro derivative **2** was refluxed in a solution 1.25 mol dm^{-3} sulfuric acid in ethanol–water (1:1 v/v; 10 cm^3) for a period of 3 h. The suspension was allowed to cool at room temp. and was then placed in freezer for 30 min. The insoluble product was filtered off, and washing successively with saturated aq. sodium hydrogen carbonate and water. The product was identical with an authentic specimen of 3-methyl-1-phenyl-1*H*-[2]benzopyrano[4,3-*c*]pyrazol-5-one **3**[1] (45% yield).

HPLC.—An aliquot (20 mm^3) of a methanolic solution of the crystalline epimeric mixture was injected into the chromatographic system. Retention times were 9.80 and 11.01 min for **4b** and **4a**, respectively, with a peak: area ratio of 1:4.11. The above methanolic solution was acidified with hydrochloric acid and stored for 24 h. An aliquot (20 mm^3) was injected and the obtained chromatogram showed for epimers **4b** and **4a** a peak: area ratio of 1:1.30.

Table 4 Final atomic co-ordinates (× 10^4) for non-hydrogen atoms, with standard deviations for compound **4a**

Atom	*x*	*y*	*z*
Cl	1355.8(5)	564.9(8)	5237.2(7)
N(1)	1552(1)	4340(2)	3820(2)
N(2)	1636(1)	4582(2)	5121(2)
N(3)	615(1)	2382(2)	3109(2)
O	−148(1)	1129(2)	1511(2)
C(1)	1792(2)	3387(3)	5702(2)
C(2)	1837(1)	2164(3)	4815(2)
C(3)	1450(1)	2808(2)	3522(2)
C(4)	1864(1)	2287(2)	2453(2)
C(5)	2647(2)	2531(3)	2233(3)
C(6)	2876(2)	1980(4)	1136(3)
C(7)	2328(2)	1168(3)	306(3)
C(8)	1538(2)	918(3)	533(2)
C(9)	1312(1)	1508(2)	1607(2)
C(10)	1153(1)	5433(2)	3041(2)
C(11)	976(2)	5256(3)	1759(2)
C(12)	598(2)	6356(3)	1004(3)
C(13)	406(2)	7637(3)	1521(3)
C(14)	587(2)	7808(3)	2805(3)
C(15)	957(2)	6739(3)	3570(3)
C(16)	1958(3)	3272(4)	7089(3)
C(17)	509(1)	1595(2)	2024(2)
C(18)	−51(2)	2793(3)	3758(3)

Crystallographic Measurements.—*Crystal data*. Compound **4a**, $C_{18}H_{16}ClN_3O$, M = 325.80, monoclinic, space group $P2_1/a$, a = 16.656(3), b = 9.328(2), c = 10.767(3) Å, β = 98.72(4)°, V = 1653.5(7) $Å^3$, Z = 4, D_C = 1.309 g cm^{-3}, F(000) 680, μ = 1.99 cm^{-1} for Mo-Kα radiation, λ = 0.710 69 Å.

Crystal data. Compound **5** $C_{18}H_{16}ClN_3O$, M = 325.80, triclinic, space group $I\bar{1}$(we used $I1$ in order to have a more reduced cell), a = 24.141(4), b = 14.923(3), c = 9.229(3) Å, α = 97.10(4), β = 99.09(4), γ = 90.02(4)° (standard lattice obtainable with transformation matrix from $I\bar{1}$ to $P\bar{1}$ −1,0,1/−1,−1,0/−1,1,0: a = 9.229, b = 14.017, c = 14.616 Å, α = 62.78, β = 104.37, γ = 97.31°), V = 3257(1) $Å^3$, Z = 4 (the asymmetric unit consists of two conformers), D_C = 1.329 g cm^{-3}, F(000) 1360, μ = 1.99 cm^{-1} for Mo-Kα radiation, λ = 0.710 69 Å.

Suitable crystals of the compounds studied were obtained from ethanol. Unit-cell and intensity data were obtained by using a Philips PW1100 diffractometer. Reflections were measured at 294 K by the θ/2θ scan method with a scan speed of 1.80° min^{-1}, scan width 1.20°. Background counts at both ends of the scan after 20 s. Owing to the low absorption coefficients no absorption corrections were applied to the intensity data. The structures were solved by direct methods employing the SHELX 86 program.[13] For compound **4a**, hydrogen atoms except those of the methyls were introduced at the positions indicated by Fourier difference and were refined with isotropic thermal parameters, while co-ordinates of methyl hydrogens were calculated at tetrahedral positions (d_{C-H} 0.98 Å and U 0.08 $Å^2$). The hydrogen atoms in compound **5** were all introduced at the corresponding idealized positions (d_{C-H} 0.98 Å and U 0.08 $Å^2$). The non-hydrogen atoms were refined anisotropically. The final Fourier difference maps showed no significant peaks. In both structures the final shift/error quotient in refinement was less than 0.04. Final R = 0.049, R_w = 0.066 (for **4a**) with w = $[\sigma^2(F_o) + 0.011\ 376(F_o)^2]^{-1}$; R = 0.059 for **5** (w = 1). Calculations were performed using SHELX 76.[14] Atomic scattering factors were taken from ref. 15. ORTEP program was used for

Table 5 Final atomic co-ordinates ($\times 10^4$) for non-hydrogen atoms, with standard deviations for compounds **5** and **5A**

Atoms	*x*	*y*	*z*
Cl(1)	841(1)	1 661(1)	2 126(1)
N(1)	784(1)	−718(2)	−77(3)
N(2)	696(1)	−956(2)	1 237(4)
O(1)	1 992(1)	−153(2)	524(3)
N(3)	2 236(1)	−746(2)	−1 642(4)
C(1)	692(2)	−184(3)	2 159(4)
C(2)	777(2)	538(2)	1 376(4)
C(3)	849(1)	205(2)	−31(4)
C(4)	1 044(2)	654(2)	−1 201(4)
C(5)	715(2)	1 322(3)	−1 839(5)
C(6)	901(2)	1 779(3)	−2 902(5)
C(7)	1 413(2)	1 587(3)	−3 328(5)
C(8)	1 742(2)	925(3)	−2 703(4)
C(9)	1 569(2)	466(3)	−1 633(4)
C(10)	840(2)	−1 405(2)	−1 280(4)
C(11)	1 143(2)	−2 172(2)	−963(5)
C(12)	1 190(2)	−2 848(3)	−2 103(5)
C(13)	952(2)	−2 780(3)	−3 531(5)
C(14)	649(2)	−2 013(3)	−3 840(5)
C(15)	597(2)	−1 328(3)	−2 714(5)
C(16)	638(2)	−172(3)	3 739(4)
C(17)	1 952(1)	−177(2)	−814(4)
C(18)	2 620(2)	−1 382(3)	−965(5)
Cl(1A)	3 766(1)	−903(1)	2 428(1)
N(1A)	4 093(1)	66(2)	6 576(3)
N(2A)	4 548(1)	−490(2)	6 517(4)
N(3A)	2 191(1)	−1 013(2)	3 226(4)
O(1A)	2 672(1)	−961(2)	5 552(3)
C(1A)	4 492(2)	−876(2)	5 128(5)
C(2A)	4 000(2)	−595(2)	4 274(4)
C(3A)	3 752(2)	11(2)	5 218(4)
C(4A)	3 284(2)	633(2)	4 859(4)
C(5A)	3 414(2)	1 553(3)	4 950(4)
C(6A)	3 007(2)	2 162(3)	4 526(5)
C(7A)	2 465(2)	1 859(3)	3 956(5)
C(8A)	2 330(2)	951(3)	3 852(4)
C(9A)	2 731(2)	332(2)	4 316(4)
C(10A)	4 010(2)	486(2)	8 004(4)
C(11A)	3 468(2)	573(3)	8 346(5)
C(12A)	3 397(2)	943(3)	9 753(5)
C(13A)	3 855(2)	1 228(3)	10 821(5)
C(14A)	4 387(2)	1 134(3)	10 481(5)
C(15A)	4 468(2)	779(3)	9 072(5)
C(16A)	4 909(2)	−1 542(3)	4 626(5)
C(17A)	2 541(2)	−619(2)	4 403(4)
C(18A)	1 909(2)	−1 871(3)	3 264(5)

drawings.[16] Final positional parameters for compounds **4a** and **5** are given in Tables 4 and 5, respectively.*

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* *Supplementary material* (see section 5.6.3 of Instructions for Authors, in the January issue). Additional material available from the Cambridge Crystallographic Data Centre comprises the hydrogen atomic co-ordinates, thermal parameters, and remaining bond lengths and angles.

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