Consecutive Pschorr–Sandmeyer reactions in a pyrazole series. Part 2.[1] Access to the [2]benzopyrano[4,3-*c*]pyrazole system of pharmaceutical interest

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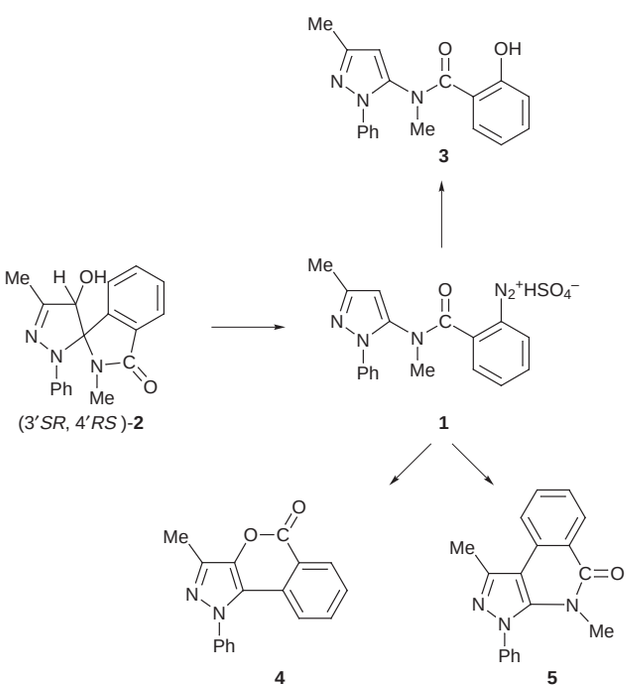
The diazonium salts obtained from 2-amino-*N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)benzamide were reacted with cuprous oxide or copper at 5 or 25 °C under different pH conditions. Cuprous oxide at 25 °C and pH 6.25 yielded the racemic epimers (3′*SR*,4′*RS*)- and (3′*SR*,4′*SR*)-4′-hydroxy-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazol]-3-ones 2 and 10 respectively, (*RS*)-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazole]-3,4′-dione 9 and *N*-methylphthalimide 8. The thermal transformation of 2 and 10 into the potentially pharmacologically active 3-methyl-1-phenyl[2]benzopyrano[4,3-*c*]pyrazol-5(1*H*)-one 4 was strongly dependent on the structure of the two epimers. When 1 was reacted with cuprous oxide or copper sulfate and sodium halide (chloride or bromide), in the presence of ascorbic acid as initiator, a mixture of epimers (3′*SR*,4′*RS*)- and (3′*SR*,4′*SR*)-4′-chloro(or bromo)-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazol]-3-ones 6b and 7b (or 6c and 7c) was obtained. The same epimers were obtained when the diazonium halides (chloride and bromide) 1b,c obtained from 2-amino-*N*-methyl-*N*-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)benzamide were treated with the appropriate classical Sandmeyer catalysts. The formation of the spiro compounds is based on consecutive Pschorr and Sandmeyer reactions. The X-ray crystal structures of the epimers 2 and 10 have been determined, confirming the given formulations.

Previously we reported on the Pschorr reaction performed at 70 °C on diazonium hydrogen sulfate **1** derived from 2-amino-*N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)benzamide[2,3] (see Scheme 1). From the mixtures, the products outlined in Scheme 1 were isolated. Despite the loss of pyrazole aromaticity and the low reactivity of the pyrazole C-5 position, the spiro compound **2** was obtained. This compound rapidly underwent thermal conversion[3] into [2]benzopyrano[4,3-*c*]pyrazol-5-one **4**. In the literature it is reported that benzopyranopyrazole derivatives show a wide range of pharmacological properties such as analgesic,[4] antiinflammatory, antimicrobial,[4] myelopoiesis[5] and immunomodulating[6] activities. Moreover, they are central benzodiazepine and adenosine receptor ligands.[7,8]

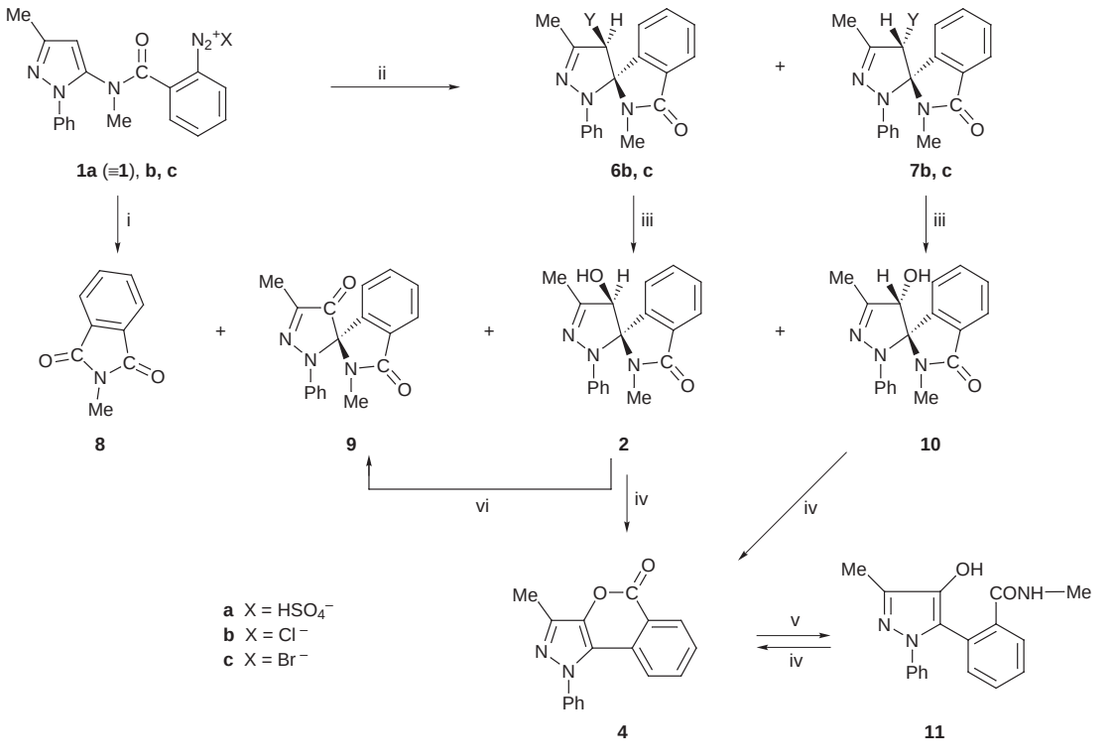


Scheme 1

It is well established that thermal decomposition of benzenediazonium salts in acidic solution produces phenyl cations,[9–11] whereas decompositions which are catalyzed by copper metal or cuprous oxides are radical in character.[12–14] In view of the pharmaceutical interest in benzopyranopyrazole derivatives and also to extend the study of the Pschorr reaction in the pyrazole series, we have investigated the radical decomposition of the diazonium hydrogen sulfate **1** catalyzed by copper or cuprous oxide under different conditions.

Starting from cuprous oxide at 25 °C and pH 6.25, four products were isolated and identified (see Scheme 2, one enantiomeric form is represented for all the racemic compounds), on the basis of analytical, spectral and physical data, as (3′*SR*,4′*RS*)- and (3′*SR*,4′*SR*)-4′-hydroxy-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazol]-3-ones (**2** and **10**),† (*RS*)-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazole]-3,4-dione **9** and *N*-methylphthalimide **8**. No evidence was obtained for the formation of **5**, the product of the classical Pschorr cyclization. This result confirms our previous findings[1] on the non-catalyzed decomposition of **1b** (see Scheme 2) at 7 °C.

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



Scheme 2 *Reagents and conditions*: (X = HSO_4^-) i, Cu_2O, pH 6.25; ii, Cu_2O/NaY, $CuSO_4$/ascorbic acid/NaY (Y = Cl, Br); (X = Cl^-) ii, $CuCl_2^-$ (Y = Cl); (X = Br^-) ii, $CuBr_2^-$ (Y = Br); iii, H_2O; iv, 255–260 °C; v, $MeNH_2$; vi, MnO_2

The racemic spiro compound **2** was identical to that isolated under thermal conditions[3] and was found to be the epimeric form of **10**. In fact, both compounds' analyses gave formulae of $C_{18}H_{17}N_3O_2$, and they have IR, ^{1}H NMR and ^{13}C NMR spectra that are very similar. The most significant features of the ^{1}H NMR spectrum of **10**, determined at 250 MHz, were the doublets of the 4′-hydroxy group, at δ 6.11, and the pyrazoline H-4′, at δ 4.99. By addition of deuterium oxide, these resonance signals of the CH–OH system collapsed to a single peak. ^{13}C NMR spectra obtained by the 90-DEPT technique confirmed a secondary carbon atom in both spiro compounds with resonance values of δ 81.02 and 82.51 for **10** and **2**, respectively. The structures of the epimers were also characterized by single-crystal X-ray analysis (see below). The formation of the epimers is shown in Scheme 3, and involves consecutive Pschorr-type cyclization and Sandmeyer hydroxylation. The last reaction probably occurs *via* transfer of H_2O from the aqueous cupric ions, which are considered as ligand radical transfer agents.[15]

The (*RS*)-2′,4′-dihydro-2,5′-dimethyl-2′-phenyl[isoindoline-1,3′-3′*H*-pyrazole]-3,4′-dione **9** was obtained in trace amounts, probably by oxidation of the racemic spiro compounds **2** and **10** with hydrate cupric ions and/or hydrogen atom abstraction due to species such as **12** and **13** (see Scheme 3). However, when compound **2** was stirred in an acidic aqueous solution of copper sulfate for 24 h production of **9** was not observed, supporting the second hypothesis. Otherwise, compound **9** can be prepared in moderate yield (40%) by oxidation of **2** with manganese dioxide.

The decoupled ^{13}C NMR spectrum was very informative of the structure of **9**. It showed two signals at δ 195.9 and 168.2, respectively, attributable to two carbonyl groups, whereas the signal at about δ 82 for the CH–OH carbon atom was missing. Compound **8** was identified as *N*-methylphthalimide by comparison with an authentic specimen. As the structure of **8** is in part based on the isoindoline moiety of the radical intermediate **13**, its formation should take place *via* this species.

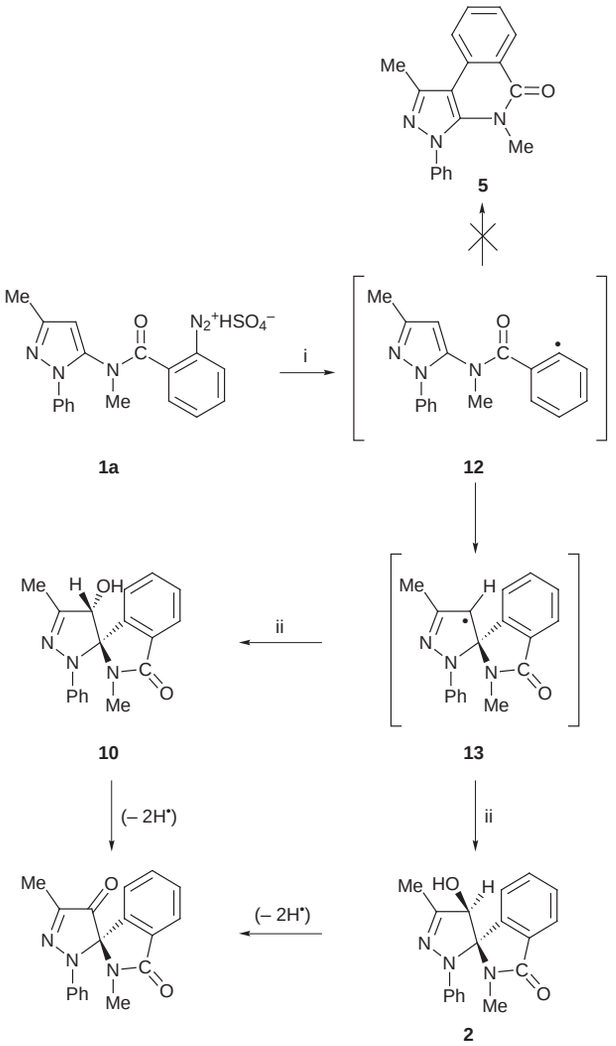
The radical decomposition of diazonium salt **1** was performed under other experimental conditions and all the results are summarized in Table 1. The formation of **2** in very low yields was slightly influenced by temperature and pH variations. The poor yields are probably due to the low concentration of aqueous copper(II) and its moderate reactivity for water ligand transfer. In fact, when the decomposition of the diazonium salt *via* Cu_2O catalysis was performed in 1 M NaCl or NaBr solution, the yields of the halogenated spiro compounds (see Scheme 2) increased significantly, expecially for the bromo derivative. This is due to the formation of different Cu^{II} complexes with Cl^- or Br^-, which are more effective as radical ligand transfer reagents ($Cl^\bullet$ or $Br^\bullet$ radicals)[16] than $[Cu(H_2O)_6]^{2+}$. The halogenated spiro compounds were also formed as a mixture of racemic epimers. The chloro epimers mixture was identical to that obtained in HCl media, in the absence of a copper(I) catalyst and with a long reaction time (one week).[1] The **6c** and **7c** bromo epimers mixture analyzed as $C_{18}H_{16}BrN_3O$ and had a ^{1}H NMR spectrum which showed signals for both. Lastly, these were hydrolyzed in water–ethanol solution to give a mixture of the spiro compounds **2** and **10** (TLC) from which **2** was isolated by crystallization.

Table 1 Reaction conditions for the formation of **2**

Entry	Catalysts	pH	*T*/°C	*t*/h	Yield (%)
1	Cu_2O	6.25	25	20	13
2	Cu_2O	6.25	5	20	12
3	Cu_2O	1.3	25	20	14
4	Cu	6.25	25	20	11
5	Cu	1.3	25	20	16
6[a]	Cu_2O	1.3	25	20	11

[a] In this case **1** was initially transformed into the diazonium fluoroborate, which was used as crude product.

The formation of the halogenated spiro compounds was also investigated employing the classical Sandmeyer catalysts or carrying out the reaction under homogenous catalysis with copper(II) ions and ascorbic acid as reducing agents.[16] In both cases an epimeric mixture was obtained, with yields comparable to that obtained under cuprous oxide catalysis, with a considerable reduction of the reaction time.



Scheme 3 Suggested reaction pathway of the cuprous oxide or copper catalyzed decomposition of diazonium salt. *Reagents and conditions*: i, Cu_2O or Cu at 25 or 5 °C, 1 h; ii, $Cu(H_2O)_n^{2+}$

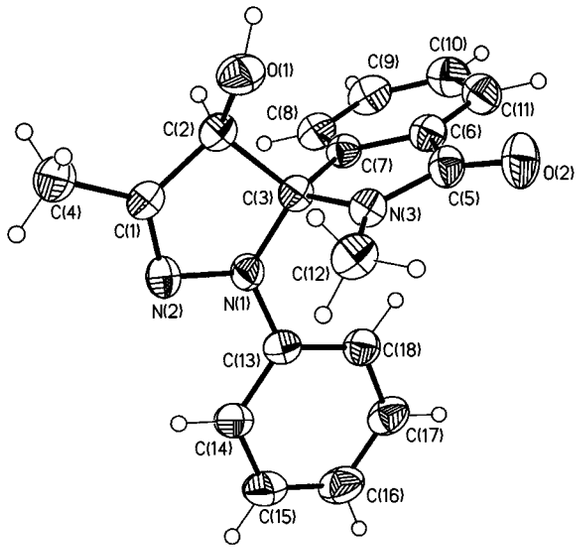
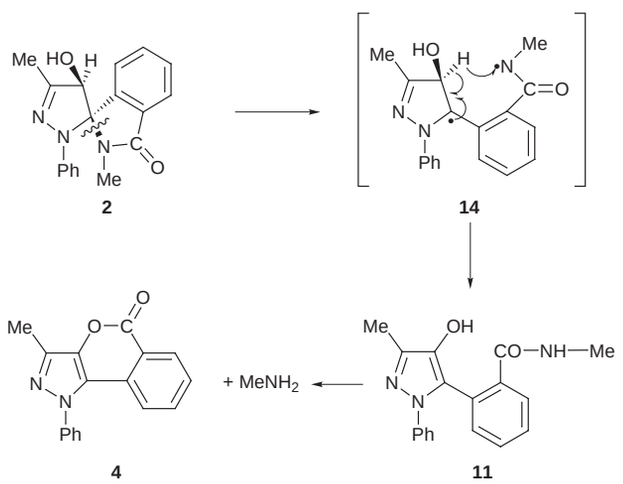


Fig. 1 ORTEP view of epimer **2**



Scheme 4 Suggested mechanistic pathway of the thermal transformation of **2** at 255–260 °C for 5 min

Compound **2** rapidly undergoes thermal conversion into 3-methyl-1-phenyl[2]benzopyrano[4,3-*c*]pyrazol-5(1*H*)-one **4** in good yield [3] (Scheme 1). It appears that the best route to obtain **2** is the hydrolysis in ethanol–water of the epimeric mixture of **6c** and **7c**, easily obtained with copper sulfate and ascorbic acid (see Scheme 2).

The thermal conversion of the epimers **2** and **10** was studied in order to elucidate the reaction pathway. Both compounds were melted under the same thermal conditions to give compound **4** with 52 and 7.5% yields, respectively (HPLC results).

The conversion of the epimer **2** to the benzopyrano derivative **4** was much easier than for **10**, due to the appropriate *trans* structure of the leaving groups. GLC–MS measurements established that **2** affords 1-phenyl-3-methyl-4-hydroxy-5-[2-(*N*-methylcarbamoyl)phenyl]-1*H*-pyrazole **11** together with derivative **4** when heated at 260 °C (injector temperature). Moreover, **11** (see below) was converted into **4** when heated under the same conditions which converted **2** into **4** (255–260 °C) (HPLC and GLC–MS results).

This suggests that the reaction pathway for the formation of derivative **4** from **2** involves a preliminary isoindolinone ring opening to give the intermediate species **14**, which undergoes an intramolecolar hydrogen atom migration and pyrazoline aromatization to form **11** which, in turn, affords **4** (see Scheme 4).

Compound **11** was obtained by reacting the [2]benzopyran derivative **4** with methylamine in ethanol solution at room temperature (see Scheme 2). This reactivity is indicative of the possible biological action of this compound on protein and other biomolecules containing a reactive amino group.

Structure of (3′*SR*,4′*RS*)-4′-hydroxy-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazol]-3-one 2 and (3′*SR*,4′*SR*)-4′-hydroxy-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazol]-3-one 10

A perspective view of the X-ray structure of **2** is shown in Fig. 1. The molecular structure, characterized by the two chiral centers C2 and C3 of the pyrazoline ring, has the same (2*R*,3*S*) [or (2*S*,3*R*)] configuration as the analogous chloro derivative, whose crystal structure has been already reported [1] (both enantiomers are present as the compound crystallizes in a centrosymmetric space group). The puckered conformation of the isoindoline ring is the same as in the previously quoted chloro derivative, with a major torsion of the phenyl ring bound to N(1) [23.4(1)°] with respect to the pyrazoline moiety [it was 16.1(5)° in the chloro derivative [1]]. A comparison of the corresponding bond distances and angles does not show significant variations. The main difference is related to the crystal packing, where pairs of centrosymmetrically related molecules are linked by intermolecular hydrogen bonds [O(1) · · · O(2)′ = 2.737(2) Å; H · · · O(2)′ = 1.80(3) Å and O(1)–H · · · O(2)′ = 175(3)°; ′ at $-x$, $1-y$, $1-z$] to form cyclic dimers.

Epimer **10** (see Fig. 2) differs from **2** in its configuration [(2*S*,3*S*) or (2*R*,3*R*)] at the chiral centers C(2) and C(3) (in this case

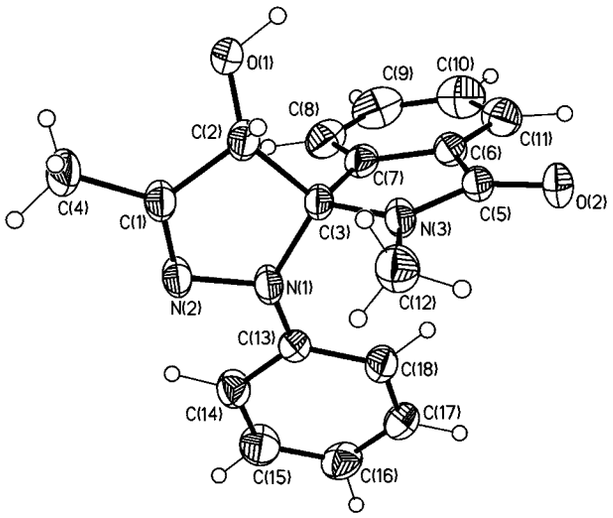


Fig. 2 ORTEP view of epimer **10**

both enantiomers are also present in the crystal). This causes differences, mainly related to the torsion angle of the phenyl ring bound to N(1) [2.2(2)°] with respect to the pyrazoline ring [it was 23.4(1) in **2**] which has a more pronounced half chair conformation with respect to epimer **2**. Significant geometrical parameters for epimers **2** and **10** are reported in Table 2. The crystal packing is different. The hydrogen bond interaction between O(1) and O(2′) [O(1)···O(2′) = 2.684(5) Å, H···O(2′) = 1.80(7) Å, O(1)–H···O(2′) = 167(7)°; ′ at 3/2 − *x*, 1/2 − *y*, 1/2 − *z*] produces chain formation in the direction of the *b* crystallographic axis, instead of dimers as in **2**.

Conclusion

The radical species **12** formed by decomposition of diazonium salts **1a**–**c** under different conditions did not afford the expected products of the Pschorr or Sandmeyer reactions; instead the spiro compounds **2**, **10**, **6b**,**c** and **7b**,**c** were obtained.

Their formation is due to the more rapid ring closure in the species **12**, to form the radical intermediate **13**, than the transfer of the water or halide ligands which were instead transferred to **12**; consequently the spiro compounds were formed. The presence of the chiral center at the C(3)′ pyrazoline position influenced the yields of the epimeric spiro compounds. Their formation can be considered as an example of consecutive Pschorr and Sandmeyer reactions on unclassical positions.

The molecular structures of **2** and **10** show the presence of a racemic mixture in both crystal cells. Geometrical parameters are comparable in both derivatives; the different orientation of the hydroxy group causes some differences in the conformation of the pyrazoline moiety, which has a more pronounced half chair conformation in **10** than in **2**. This could be associated to the different crystal packing of the two epimers, where the intermolecular hydrogen bond [O(1)–H···O(2′)] determines dimer formation in **2** and chain formation in **10**.

Experimental

Mps were determined on a Buchi-tottoli apparatus and are uncorrected. IR spectra were recorded on a JASCO spectrophotometer for Nujol mulls. ^{1}H NMR spectra were obtained for $CDCl_3$ or DMSO 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-SG2 mass spectrometer operating at 75 eV. GLC–MS measurements were carried out with a 3400-CX Varian gas chromatograph fitted with a Saturn 3 mass spectrometer. The capillary column used was a nonpolar RTX-5 (Restec, USA) of 30 m length, 0.25 mm i.d. and 0.25 μm stationary phase thickness (5% diphenyl- and 95% dimethylpolysiloxane). The carrier gas was helium with 11 psi entrance pressure; the injector temperature was 260 °C. The column temperature was programmed as follows: the initial temperature was set to 200 °C and maintained for 3 min, and then a linear heating rate of 5 °C min^{-1} was applied so as to obtain a final temperature of 265 °C. HPLC analysis was performed using a Perkin-Elmer series 10 liquid chromatograph. A C_{18} Perkin-Elmer 25 cm × 4.6 mm column and, as the eluent, a 1 : 1 acetonitrile–water mixture, were used for the separation of compounds. The flux was 2.00 cm^3 min^{-1} and the UV detector was set at 254 nm.

Table 2 Selected bond lengths (Å) and angles (°) for the epimers **2** and **10**

	2	**10**
O(1)–C(2)	1.404(3)	1.403(5)
O(2)–C(5)	1.235(2)	1.230(6)
N(1)–C(3)	1.470(2)	1.458(5)
N(1)–C(13)	1.402(3)	1.403(7)
N(1)–N(2)	1.393(3)	1.408(7)
N(2)–C(1)	1.272(3)	1.287(7)
N(3)–C(3)	1.478(3)	1.465(5)
N(3)–C(5)	1.347(3)	1.357(7)
N(3)–C(12)	1.451(4)	1.453(7)
C(1)–C(2)	1.500(3)	1.488(6)
C(1)–C(4)	1.492(4)	1.498(9)
C(2)–C(3)	1.564(3)	1.575(8)
C(3)–C(7)	1.507(4)	1.508(7)
C(5)–C(6)	1.471(3)	1.479(7)
C(6)–C(7)	1.386(3)	1.384(6)
N(1)–N(2)–C(1)	109.5(2)	107.9(4)
C(5)–N(3)–C(12)	123.7(2)	123.8(4)
C(3)–N(3)–C(12)	123.2(2)	122.5(4)
C(3)–N(3)–C(5)	113.0(2)	113.4(4)
N(2)–N(1)–C(13)	118.1(2)	117.9(4)
N(2)–N(1)–C(3)	112.1(2)	112.2(3)
C(3)–N(1)–C(13)	125.0(2)	126.4(4)
N(2)–C(1)–C(4)	122.8(2)	122.2(5)
N(2)–C(1)–C(2)	114.3(2)	114.1(4)
C(2)–C(1)–C(4)	122.8(2)	123.6(4)
O(1)–C(2)–C(1)	109.5(2)	113.3(4)
C(1)–C(2)–C(3)	101.9(2)	101.6(4)
O(1)–C(2)–C(3)	115.9(2)	114.0(4)
N(1)–C(3)–C(2)	101.8(2)	100.3(4)
N(3)–C(3)–C(2)	111.2(2)	112.0(4)
N(3)–C(3)–N(1)	112.0(2)	113.2(4)
C(2)–C(3)–C(7)	114.7(2)	112.3(4)
N(1)–C(3)–C(7)	115.8(2)	117.8(4)
N(3)–C(3)–C(7)	101.6(2)	101.7(4)
O(2)–C(5)–N(3)	124.9(2)	126.8(4)
N(3)–C(5)–C(6)	107.2(2)	106.2(4)
O(2)–C(5)–C(6)	127.9(2)	127.0(5)
C(5)–C(6)–C(7)	108.7(2)	108.9(4)
C(3)–C(7)–C(6)	109.3(2)	109.2(4)

Diazonium hydrogen sulfate 1a prepared from 2-amino-*N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)benzamide

The pulverized amine[2] (10 mmol) was dissolved in cooled (0–5 °C) 2.5 mol dm^{-3} sulfuric acid (20 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 15 min in the ice bath and was then checked for excess nitrous acid with potassium iodide starch paper; the eventual excess was destroyed by the addition of urea.

Diazonium fluoroborate prepared from 2-amino-*N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)benzamide

The amine (10 mmol) was dissolved in cooled (0–5 °C) 2.5 mol dm^{-3} sulfuric acid (20 cm^3) and diazotized as above. In this case the eventual excess of nitrous acid was not destroyed. The

solution (0–5 °C) was treated with sodium fluoroborate (4.8 g in 20 cm^3) under stirring and the solid product formed was filtered off and washed with ice-cold water. Purification was carried out by dissolving the crude product in boiling acetone, quickly cooling the solution in an ice-salt mixture and adding light petroleum (bp 40–60 °C) until complete precipitation (75%), mp 143 °C (Found: C, 53.32; H, 4.19; N, 16.93%. $C_{18}H_{16}BF_4N_5O$ requires C, 53.35; H, 3.95; N, 17.29%); *m/z* 309 ($M^+ - N_2 - BF_3$); λ_{max}/cm^{-1} 2280 (N_2^+), 1645 (CO), 1050 (br, BF); δ_H(DMSO-d_6) 2.19 (3H, s, Me), 3.40 (3H, s, Me), 6.50 (1H, s, pyrazole), 7.28–8.78 (a set of signals, Ph and C_6H_4).

Procedures for decomposition of diazonium hydrogen sulfate 1a

Run 1. The diazonium salt solution was diluted with cold water (0–5 °C) to 300 cm^3 and the pH was adjusted to pH 6.25, first with 30% (w/v) aq. sodium hydroxide (until pH 4.5) and then with aq. sodium hydrogen carbonate. At this point cuprous oxide (Fluka) (1.5 g) was added to the solution and the obtained suspension was stirred for a period of 20 h at 25 °C, filtered, and the air-dried insoluble residue extracted with chloroform (200 cm^3) under magnetic stirring for 30 min. The insoluble material was separated by filtration and the solution was evaporated under reduced pressure to give a complex mixture (2.8 g) which was chromatographed on silica gel, using a Jobin Yvon preparative liquid chromatograph: ethyl acetate–light petroleum (bp 40–70 °C) (1 : 1 v/v) as eluent, silica gel (200 g, 230–400 mesh); column pressure 10 bar; fractions each 50 cm^3. The first seven fractions were discarded and fractions 8–11 were evaporated under reduced pressure to give 250 mg of a mixture which was rechromatographed on silica gel (60 g, >400 mesh) using ethyl acetate–light petroleum (1 : 4 v/v) as eluent. Fraction 7 was evaporated and the product crystallized from cyclohexane, to give 50 mg of (*RS*)-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazole]-3,4′-dione **9**, mp 163–165 °C (Found: C, 70.92; H, 5.06; N, 13.67%. $C_{18}H_{15}N_3O$ requires C, 70.80; H, 4.95; N, 13.76%); *m/z* 305 (M^+); λ_{max}/cm^{-1} 1745–1695 (multiple bands, 2 × CO); δ_H($CDCl_3$) 2.29 (3H, s, Me), 2.83 (3H, s, Me), 6.89–7.18 (6H, m, C_6H_5 and isoindoline proton), 7.40–7.57 (2H, m, isoindoline protons), 7.94 (1H, d, isoindoline H-4); δ_C(decoupled) 10.23 (Me), 25.52 (Me), 115.40–142.44 (aromatic and pyrazoline carbons), 168.16 (CO), 195.87 (CO).

Fractions 12–23 of the first chromatographic procedure were discarded whereas fractions 24–38 afforded a residue which was crystallized from ethanol to give a product identical in all respects with (3′*SR*,4′*RS*)-4′-hydroxy-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazol]-3-one **2**,[3] yield 220 mg; δ_C(DMSO-d_6)(90-DEPT) 82.51 (pyrazoline C-4), 114.36–132.62 (aromatic carbons); δ_C(decoupled) 12.56 (Me), 82.43 (pyrazoline C-4), 87.02, 114.30–152.85 (aromatic and pyrazoline carbons), 166.17 (CO).

Further elution gave fractions 39–61 from which a residue was obtained (300 mg). The residue was crystallized from ethyl acetate–light petroleum (bp 40–70 °C) and the crystalline product was chromatographed on silica gel (100 g, >400 mesh), chloroform–diethyl ether (2 : 3 v/v) as eluent, column pressure 10 bar, fraction each 50 cm^3. Fractions 13–21 left a quasi-pure residue which was purified by preparative TLC on silica gel [thickness 2 mm; chloroform–diethyl ether (2 : 3) as developer] to give the racemic epimer **10** (60 mg), mp 213–214 °C (Found: C, 70.40; H, 5.65; N, 13.60%. $C_{18}H_{17}N_3O_2$ requires C, 70.34; H, 5.58; N, 13.67%); *m/z* 307 (M^+); λ_{max}/cm^{-1} 3270 (OH), 1690 (CO); δ_H(DMSO-d_6) 2.15 (3H, s, Me), 2.76 (3H, s, Me), 4.99 (1H, d, *J* 7.3, pyrazoline H-4), 6.10 (1H, d, *J* 7.3, pyrazoline OH, exchangeable with D_2O), 6.58 (2H, d, C_6H_5 *o*-protons), 6.70 (1H, t, C_6H_5 *p*-proton), 7.00 (2H, t, C_6H_5 *m*-protons), 7.39 (1H, m, H-7), 7.52 (2H, m, H-5,6), 7.73 (1H, m, H-4); δ_C(90-DEPT) 81.03 (pyrazoline C-4), 114.60–131.30 (aromatic carbons); δ_C(decoupled) 13.17 (Me), 24.39 (Me), 81.04 (pyrazoline C-4), 88.85, 114.63–152.39 (aromatic and pyrazoline carbons), 165.98 (CO).

Isolation of N-*methylphthalimide* **8**.—The mother liquors of the suspension obtained from the decomposition of diazonium salt **1** were extracted with chloroform (3 × 150 cm^3) and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was boiled in 15 cm^3 of ethanol for a few minutes and the suspension filtered. The filtrate was evaporated under reduced pressure and crystallized from ethanol. The crude product (100 mg) was chromatographed on silica gel using the above preparative liquid chromatograph: silica gel (100 g, 230–400 mesh), ethyl acetate–light petroleum (bp 40–70 °C) (1 : 9) as eluent, elution pressure 10 bar, fractions each 50 cm^3. The solid residue from fractions 11–27 was chromatographed by preparative TLC on silica gel [thickness 2 mm, eluent as the above chomatography] to give a product, which was crystallized from ethanol, identical in all respects (IR, MS, ^{1}H NMR, mixed mp) with an authentic specimen of *N*-methylphthalimide.

Runs 2–5. The diazonium salt solution as Run 1 was adjusted to pH 6.25, or left unneutralized (pH *ca.* 1.3), and then treated with the appropriate catalyst: cuprous oxide (1.5 g) or copper powder[17] (1.5 g). The suspension was stirred for 20 h at the indicated temperature (see Table 1). The work-up for each reaction mixture was as Run 1, except for the chromatographic procedure, which was not employed. Compound **2** was obtained by crystallization from ethanol (see Table 1). TLC of the mother liquors showed the presence of **10** but no attempt was made to isolate this compound or any other compounds from the mixture.

Run 6. *Decomposition of diazonium tetrafluoroborate with cuprous oxide*.—The crude diazonium tetrafluoroborate obtained from 3.06 g (10 mmol) of the starting amine was dissolved in 0.16 mol dm^{-3} sulfuric acid (400 cm^3) (pH *ca.* 1.3) and then cuprous oxide (1.5 g) was added. The suspension was stirred for 20 h at 25 °C. The work-up was as for Runs 2–5.

Epimeric mixtures of (3′*SR*,4′*RS*)- and (3′*SR*,4′*SR*)-4′-chloro-(or bromo)-2′,4′-dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazol]-3-one 6b and 6c (or 7b and 7c)

The diazonium salt solution was diluted with cold 1 mol dm^{-3} sodium chloride (or sodium bromide) cold solution (0–5 °C) to 300 cm^3. Cuprous oxide (1.5 g) was added and the suspension was stirred at 25 °C for 20 h and then filtered. The solid product was dried between porous plates.

Epimers **6b** and **7b**: the solid was crystallized from ethanol to give **6b** and **7b** as a mixture identical to that previously obtained[1] (46% yield).

Epimers **6c** and **7c**: the solid was crystallized from anhydrous methanol (freezer) to give a mixture of **6c** and **7c** (50% yield), mp 140–141 °C (Found: C, 58.66; H, 4.44; N, 11.52%. $C_{18}H_{16}BrN_5O$ requires C, 58.39; H, 4.35; N, 11.35%); λ_{max}/cm^{-1} (Nujol) 1701 (CO); δ_H($CDCl_3$) 2.29 and 2.31 (3H, s, Me), 2.68 and 2.63 (3H, s, Me), 5.08 and 5.42 (1H, s, pyrazoline CH), 6.67 (2H, m, C_6H_5 *o*-protons), 6.84 (1H, t, C_6H_5 *p*-proton), 7.04 (2H, m, C_6H_5 *m*-protons), 7.62 (3H, m, H-5,6,7), 7.92 (1H, m, H-4).

Actions of some classical Sandmeyer catalysts on the diazonium salts 1b and 1c

The diazonium chloride (or bromide) was prepared from 3.06 g (10 mmol) of 2-amino-*N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)benzamide in 5 mol dm^{-3} aqueous HCl (or HBr) following the procedure as for **1a**. The obtained diazonium salt solution was slowly added under stirring into a cooled solution (ice bath) containing the halogenated cuprous complexes ($CuCl_2^-$ or $CuBr_2^-$) obtained from 13 mmol of $CuSO_4 \cdot 5H_2O$.[13] Cooling was interrupted and the temperature was allowed to rise to 15 °C. At this point the suspension was gradually heated to 60 °C and the gummy material which separated was washed

with water and crystallized from ethanol, to give epimers **6b** and **7b** as a mixture (30% yield) or from anhydrous methanol, to give epimers **6c** and **7c** as a mixture (45% yield).

Decomposition of diazonium salt 1a by copper sulfate/sodium halide and ascorbic acid as initiator

The reaction was carried out following the procedure of Hanson[16] which has been modified by us. To the diazonium salt solution **1a** prepared from 3.06 g (10 mmol) of amine and diluted to 500 cm^3 with a cold (0–5 °C) solution of $CuSO_4 \cdot 5H_2O$ (0.3 mol dm^{-3}) and sodium chloride (or bromide) (0.75 mol dm^{-3}) was then added ascorbic acid (0.44 g, 2.5 mmol) and stirring was continued for 1 h at room temperature. The suspension was filtered off and the solid product was dried between porous plates and crystallized as above (45% yield for a mixture of epimers **6b** and **7b**, and 50% yield for a mixture of epimers **6c** and **7c**).

(*RS*)-2′,4′-Dihydro-2,5′-dimethyl-2′-phenylspiro[isoindoline-1,3′-3′*H*-pyrazole]-3,4-dione 9 *via* oxidation of epimer 2

The crude epimer **2** (500 mg, 1.63 mmol) was reacted with manganese dioxide (425 mg, 4.89 mmol) in anhydrous acetone (10 cm^3) under reflux for 6 h. The suspension was filtered off, and the filtrate was evaporated under reduced pressure and chromatographed following the flash chromatography procedure: ethyl acetate–light petroleum (bp 40–70 °C) (2 : 8 v/v) as eluent, silica gel (56 g) 230–430 mesh, fractions each 50 cm^3.

The first 8 fractions of eluent were discarded and fractions 9–13, when evaporated under reduced pressure, gave a residue (380 mg) which, crystallized from cyclohexane, afforded **9** (40% yield).

1-Phenyl-3-methyl-4-hydroxy-5-[2-(*N*-methylcarbamoyl)phenyl]-1*H*-pyrazole 11

500 mg of 1-phenyl-3-methyl-1*H*-[2]benzopyrano[4,3-*c*]pyrazol-5-one were dissolved under stirring (24 h, room temp.) in an ethanolic methylamine solution (33% w/v, 20 cm^3). The solution was evaporated under reduced pressure and the residue was crystallized from ethanol to give compound **11** (50% yield), mp 217–218 °C (Found: C, 70.13; H, 5.58; N, 13.73%. $C_{18}H_{17}N_3O_2$ requires C, 70.34; H, 5.58; N, 13.67%); *m*/*z* 307 (M^+); ν_{max}/cm^{-1} 3340 (OH), 3170 (br, NH), 1615 (br, CO); δ_H(DMSO-d_6) 2.18 (3H, s, Me), 2.63 (3H, d, *J* 3.7, Me), 6.98–7.51 (9H, a set of signals, Ph and C_6H_4), 8.24 (1H, apparent q, exchangeable with D_2O, NH), 8.51 (1H, s, exchangeable with D_2O, OH).

Hydrolysis of the epimers 6c/7c

The epimeric mixture of **6c/7c**, obtained from 3.06 g (10 mmol) of the starting amine, was refluxed in a water–ethanol mixture (150 cm^3; 1 : 1 v/v) for 30 min. The solution thus obtained was concentrated under reduced pressure to 1/3 its original volume and extracted with chloroform (2 × 100 cm^3). The combined extract was dried (Na_2SO_4) and the residue was crystallized from ethanol to give **2** impure for **10** (overall yield 40%).

HPLC

Thermal transformation of epimers 2 and 10. A small amount of epimer was melted at 255–260 °C for 5 min into a melting point capillary (Büchi 530 melting point apparatus). The clean capillary tract was cut and the remaining part was triturated. The obtained material was suspended in 1 cm^3 of HPLC grade methanol and the suspension was filtered. An aliquot (20 mm^3) was injected into the chromatographic system. The peak areas were corrected by applying an internal corrective factor method.

Thermal tranformation of 11 in 4. Following the above procedure, the formation of **4** from **11** was detected.

GLC–MS: thermal transformation of 2 in 11 and 11 in 4. Compounds **2** and **11** were dissolved in CH_3Cl and injected into the GLC–MS apparatus.

Crystallographic measurements

Crystal data for 2. $C_{18}H_{17}O_2N_3$, $M = 307.36$, triclinic, space group $P\bar{1}$, $a = 10.157(3)$, $b = 10.939(3)$, $c = 7.733(2)$ Å, $\alpha = 93.63(3)$, $\beta = 106.25(3)$, $\gamma = 63.10(3)°$, $V = 764.5(4)$ $Å^3$, $Z = 2$, $D_x = 1.33$ g cm^{-3}, $F(000)$ 324, $\mu = 0.89$ cm^{-1} for Mo-Kα radiation, $\lambda = 0.710\ 73$ Å.

Crystal data for 10. $C_{18}H_{17}O_2N_3$, $M = 307.36$, monoclinic space group $C2/c$, $a = 21.051(5)$, $b = 7.753(3)$, $c = 22.026(5)$ Å, $\beta = 118.90(5)°$, $V = 3147(2)$ $Å^3$, $Z = 8$, $D_x = 1.30$ g cm^{-3}, $F(000)$ 1296, $\mu = 0.87$ cm^{-1} for Mo-Kα radiation, $\lambda = 0.710\ 73$ Å.

Reflections were collected using a Philips PW1100 diffractometer[18] with graphite-monochromated Mo-Kα radiation. The orientation matrix and cell dimensions were determined by least-squares refinement of the angular positions of 30 reflections. Two standard reflections were monitored every 200 reflections and no significant decay was observed during data collection. All intensities were corrected for Lorentz polarization. Structure solution was by direct methods (SIR 92).[19] Structures were refined by full-matrix least-squares using anisotropic temperature factors for all non-hydrogen atoms. Hydrogen atoms were located from difference Fourier maps and refined anisotropically.

For **2** the 3101 measured reflections ($2\theta_{max} = 52°$) yelded 2703 unique and 2582 reflections with $F_o^2 \geqslant 3\sigma F_o^2$. 277 parameters were refined, the final conventional R was 0.055 [$R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$] based on F values, $wR' = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{\frac{1}{2}} = 0.154$ (on F^2), $S = 1.07$.

For **10** the 2840 measured reflections ($2\theta_{max} = 50°$) yielded 1959 unique and 1888 reflections with $F_o^2 \geqslant 3\sigma F_o^2$. 215 parameters were refined and the final conventional R was 0.079 [$R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$] based on F values, $wR' = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{\frac{1}{2}} = 0.166$ (on F^2), $S = 1.30$.

Calculations were performed with the SHELX-93 program,[20] using the scattering factors enclosed therein. The program for the ORTEP drawings was taken from ref. 21.‡

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‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/242.

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