# Nonclassical *Pschorr* and *Sandmeyer* Reactions in Pyrazole Series

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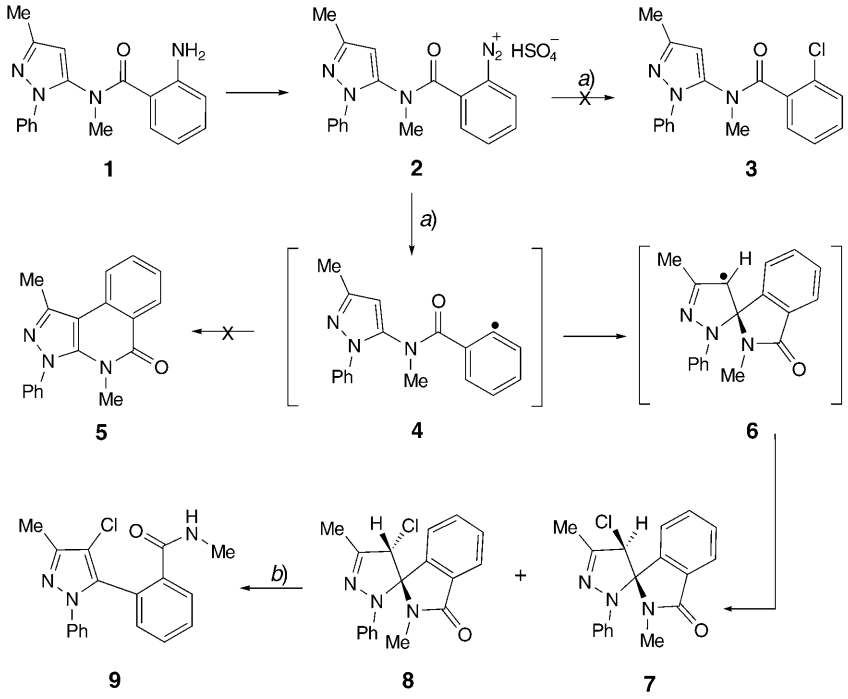
The diazonium salt derived from 4-amino-*N*,1,3-trimethyl-*N*-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-1*H*-pyrazole-5-carboxamide (**14**) was reacted with a mixture of $CuSO_4$ and NaCl, with ascorbic acid as an initiator to afford the planar derivative 4,6-dihydro-1,4,6,8-tetramethyl-3-phenyldipyrazolo[3,4-*b*:4′,3′-*d*]pyridin-5(3*H*)-one (**16**) and its unexpected isomer 4,6-dihydro-3,4,6,8-tetramethyl-1-phenyldipyrazolo[4,3-*b*:4′,3′-*d*]pyridin-5(1*H*)-one (**17**), as well as the epimers (3*S*,4*S*)- (or (3*S*,4*R*)-) and (3*S*,4*R*)- (or (3*S*,4*S*)-) 4-chloro-2,4-dihydro-1′,3′,5,5′-tetramethyl-2-phenylspiro[pyrazole-3,4′(1′*H*)-pyrrolo[3,4-*c*]pyrazol]-6′(5′*H*)-one (**18a** and **b**, respectively). Epimers **18a** and **b** were converted under basic conditions to 4′-chloro-*N*,1,3,3′-tetramethyl-1′-phenyl-[4,5′-bi-1*H*-pyrazole]-5-carboxamide (**19**). The structures of isomers **16** and **17** determined by single-crystal X-ray analysis are also reported. Linear dichroism (LD) measurements for the above isomers suggest that **17** intercalates into DNA, and **17** exhibited antiproliferation activity against human NCI-H460 pulmonary carcinoma cells.

**Introduction.** – Previously, we reported the transformation of diazonium salt **2**, derived from 2-amino-*N*-methyl-*N*-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)benzamide (**1**). This reaction was carried out with $CuSO_4$ and NaCl, with ascorbic acid as a reducing agent (*Scheme 1*). The diazonium sulfate **2** afforded neither the chloro derivative **3**, the product of the classical *Sandmeyer* reaction, nor the tricyclic derivative **5**, the expected product of the competitive *Pschorr* ring closure. Instead, we obtained epimers **7** and **8**, the formation of which can be considered examples of consecutive nonclassical *Pschorr* and *Sandmeyer* reactions [1], presumably *via* radical intermediates **4** and **6** (*Scheme 1*). The isomeric product **9** was formed by treatment of the mixture of epimers **7** and **8** with 1M alcoholic KOH, with restoration of the aromatic system of the pyrazole nucleus [2].

In continuation of our research on pyrazole chemistry, we thought it of interest to investigate the above reaction to establish the role of the aryl-diazonium moiety in the reaction pathway. Here, we describe the $CuSO_4$/ascorbic acid-catalyzed decomposition in the presence of NaCl of the diazonium sulfate **15**, which bears a pyrazole-diazonium moiety in place of the benzene-diazonium in **2** (*Scheme 2*).

**Results and Discussion.** – Pyrazolecarbonyl chloride **11**, obtained *in situ*, was reacted with *N*,3-dimethyl-1-phenyl-1*H*-pyrazol-5-amine (**12**) to give nitro derivative **13**, which, in turn, was reduced to the corresponding amine **14**. The pyrazole-diazonium salt **15**, obtained from **14**, was reacted under the same conditions as applied to **2** to afford the tricyclic isomers **16** and **17** and the chlorinated epimers **18a** and **b**

*Scheme 1*



*a*) $CuSO_4$/ascorbic acid/NaCl. *b*) KOH.

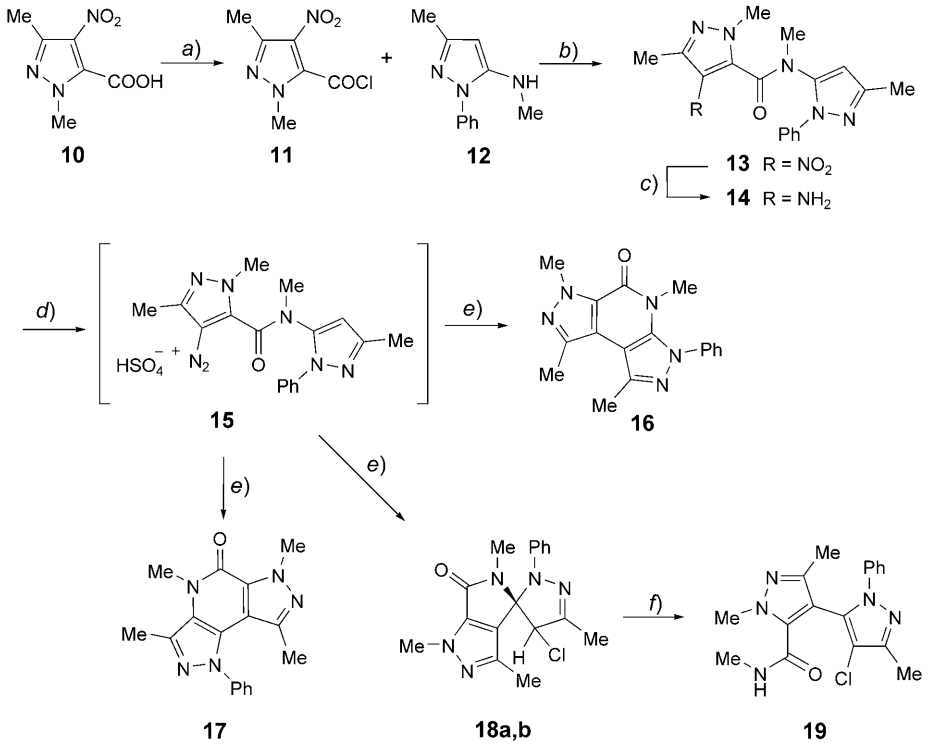
(*Scheme 2*). The new compounds were characterized by means of analytical and spectral data and, in the case of isomers **16** and **17**, by X-ray analysis.

The $^1$H-NMR spectra of **16** and **17** showed signals consistent with four Me groups as shown in the structures. The spectrum of compound **16** showed for the Me groups at 3-positions of the two pyrazole nuclei, two closely spaced resonance signals at $\delta$ 2.59 and 2.62, whereas the corresponding Me groups in isomer **17** produced signals at $\delta$ 1.47 and 2.69. The high-field signal at $\delta$ 1.47 is due to the Me group located in the shielding zone of the Ph ring. Further, the pyridinone Me group of **16** but not **17** exhibited carbonyl diamagnetic anisotropy.

The $^1$H-NMR spectra of epimers **18a** and **b** showed signals at $\delta$ 5.93 and 5.82, respectively, due to the pyrazoline H-atom, as well as those of the four Me groups at $\delta$ 2.19–3.91 and 2.03–3.86, respectively. The relative configuration of the pyrazoline C(5)-atom was not determined. A possible mechanism for formation of isomers **16** and **17** and epimers **18a** and **b** is proposed in *Scheme 3*.

On the basis of the experimental results, the radical intermediates **20** and **21** (*Scheme 3*) are more reactive than the analogous species **4** and **6** (*Scheme 1*). In fact, in the intermediate **20**, the radical attack at C(4) and C(5) of the pyrazole nucleus takes place to afford the tricyclic system **16** and the radical spiro-species **21**, respectively, whereas the intermediate **4** is transformed to only the spiro-intermediate **6**. Species **21**

*Scheme 2*




Reagents: *a*) $SOCl_2$ reflux. *b*) $Et_3N/CHCl_3$ reflux. *c*) Fe/AcOH. *d*) $KNO_2/H_2SO_4$. *e*) $CuSO_4$/ascorbic acid/NaCl. *f*) KOH.

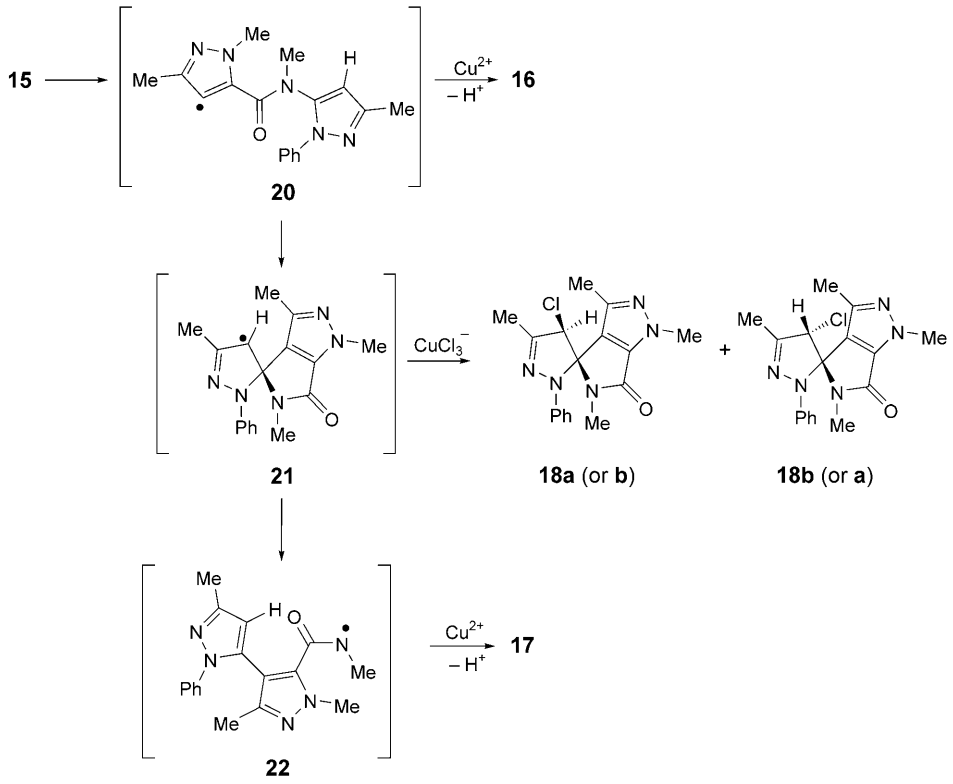
produces both epimers **18a** and **b** and rearranges *via* the *N*-centered radical **22** to form **17**, an isomer of **16**, whereas **6** is transformed only to the epimeric couple **7** and **8**.

Finally, epimer **18a** was reacted with KOH in EtOH solution to give the derivative **19** (*Scheme 2*). The same result was obtained from reaction of a mixture of **18a** and **b**; conversion of **18b** was confirmed by TLC analysis. The mechanism of the reaction is probably similar to that proposed for the formation of compound **9** from **8** (*Scheme 1*) [2]. This transformation represents a new way to obtain the 5,4′-bipyrazole system.

ORTEP [3] Views of isomers **16** and **17** are shown in *Figs. 1* and *2*. The isomers have in common a tricyclic system with the pyrazolo[3,4-*c*]pyridin-4-one moieties equally substituted, but differ in the point of closure of the ring to give the Me- and Ph-substituted pyrazole. In fact, **17** can be thought of as being derived from **16** by a 180° rotation along an ideal axis passing through N(2) and the mid-point of the C(8)–C(9) bond, with exchange of the relative ring-junction atoms.

The crystal structure of **17** is characterized by the presence of a molecule of $H_2O$ of crystallization, which bridges adjacent molecules *via* H-bond interactions involving two N-atoms of pyrazole at the two terminal parts of the tricyclic system with contact distances N(5) · · · O($H_2O$) 2.92(1) Å and O($H_2O$) · · · N(2′) 2.94(1) Å (N(5) · · ·

Scheme 3. *Suggested Mechanism for the Transformation of* **15**




H(111)–($H_2O$) 1.87 Å, 156(6)° and ($H_2O$)–H(112)···N(2′) 2.34 Å, 133(8)°; at $1.5 - x$, $-1/2 + y$, $1.5 - z$). The presence of $H_2O$ gives rise to infinite chains that develop along the *b* axis (*Fig. 3*), while, in **16**, which has no crystallized $H_2O$, the molecules are oriented parallel to the (101) plane, as shown in *Fig. 4*.

Finally, we thought it of interest to verify whether the nearly planar heteroaromatic isomers **16** and **17** are able to intercalate into DNA. Due to the very low solubility of the compounds, particularly **16**, only the somewhat more-soluble **17** could be investigated. The interaction of **17** with DNA was evaluated by means of linear dichroism (LD) experiments according to *Vedaldi et al.* [4]. The presence of a small negative band in the 300–350 nm region of the LD spectrum (*Fig. 5*), corresponding to the maximum absorption range of the compound, was observed, suggesting that the chromophore of the compound lies parallel to the base pairs of the macromolecule, thus indicating intercalation into the macromolecule. Isomer **17** was also active against proliferation of human NCI-H460 pulmonary carcinoma cells with a $IC_{50}$ value of 30 μg/ml. Presumably, the antiproliferation activity is correlated to DNA intercalation.

**Conclusions.** – The radical intermediate **20** derived from diazonium salt **15** exhibits chemical behavior different from that reported for radical **4** obtained from diazonium

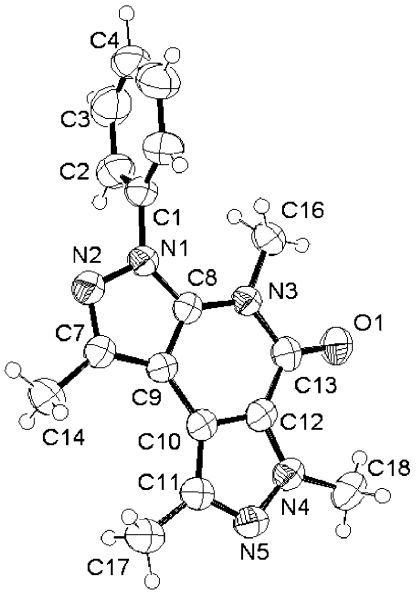



Fig. 1. *ORTEP* [3] *Drawing of the crystal structure of* **16** (ellipsoids at 50% probability; arbitrary numbering)

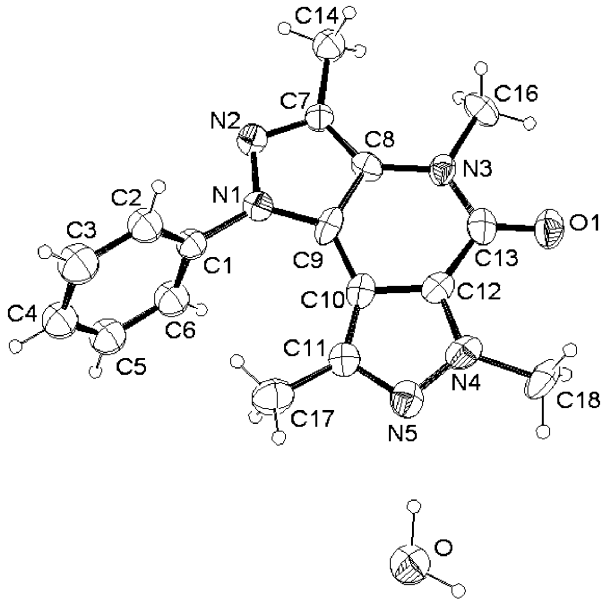



Fig. 2. *ORTEP* [3] *Drawing of the crystal structure of* **17** (ellipsoids at 50% probability, arbitrary numbering)

salt **2**. This difference is related to the presence of a dimethyl-substituted pyrazole radical in **20** in place of a phenyl radical in **4**. The transformation of **20** is based on intramolecular attack of the radical moiety on C(4) and C(5) of the phenyl-substituted

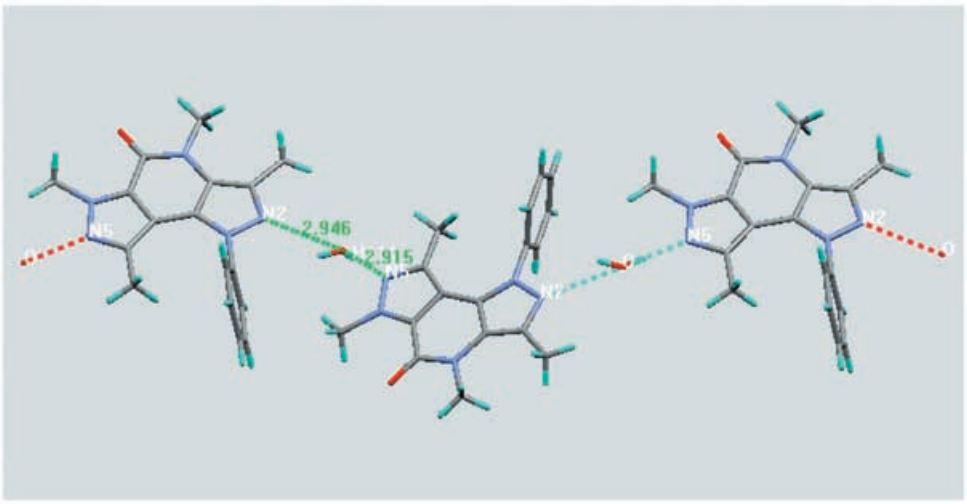



Fig. 3. *Chain arrangement of the molecules in* **17**

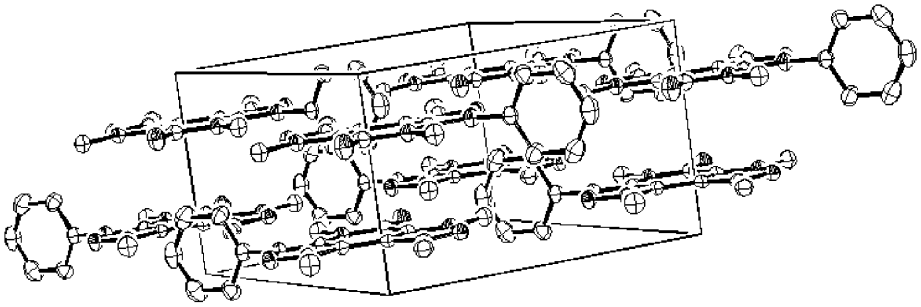


Fig. 4. *Crystal packing of* **16**

pyrazole ring. To find **17** among the isolated products was quite unexpected, as it forms as a result of consecutive transformations of **20**. Isomerization of epimers **18a** and **b** to **19** under basic conditions represents a new way to obtain the 4,5′-bipyrazole system. Finally, isomer **17** showed, to some extent, DNA-intercalation, as well as moderate antiproliferation activity against human NCI-H460 pulmonary carcinoma cells.

## Experimental Part

*General*. M.p.: *Büchi 530* capillary melting-point apparatus; uncorrected. IR Spectra: *Perkin-Elmer Spectrum RXI-FT* spectrophotometer; hexachlorobutadiene solns.; $\nu$ in $cm^{-1}$. $^1$H-NMR Spectra: *Bruker AC-E 250F* (250 MHz); in ($D_6$)DMSO; $\delta$ in ppm rel. to $Me_4Si$ as internal standard. MS: *Waters AutoSpec-Ultima* orthogonal T.O.F. mass spectrometer; 75 eV; *m*/*z* (%). Microanalyses (C, H, N) were performed in the laboratories of the Dipartimento di Scienze Farmaceutiche-Università di Catania. Compound **17** was dried in a cell thermostatted at 150° under vacuum 4 h before analysis.

*1,3-Dimethyl-4-nitro-1*H*-pyrazole-5-carbonyl Chloride* (**11**). *1,3-Dimethyl-4-nitro-1*H*-pyrazole-5-carboxylic acid* (**10**; 1.85 g, 10 mmol) [5] was reacted with $SOCl_2$ (12 ml) under reflux for 5 h. The soln. was evaporated under reduced pressure and the oily residue obtained was dissolved in abs. benzene (20 ml). The soln. was

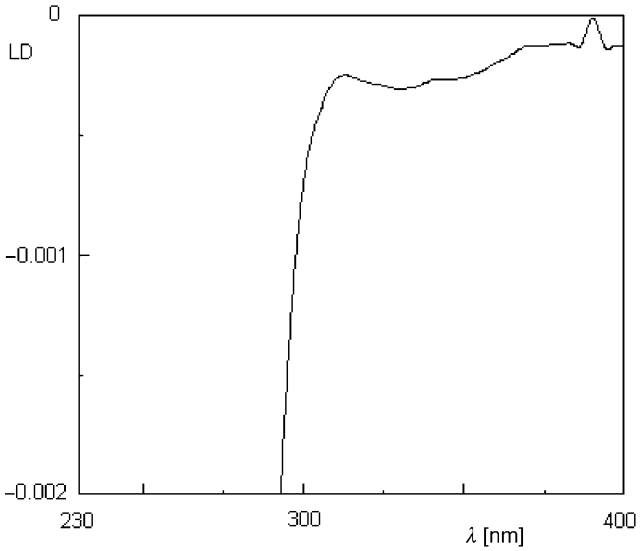



Fig. 5. *Linear dichroism spectrum of* **17**–*DNA complex* (optical path 1 mm)

evaporated under reduced pressure. This last part of the procedure was repeated and the oily residue was used in the next step.

N,*1,3-Trimethyl*-N-*(3-methyl-1-phenyl-1*H-*pyrazol-5-yl)-4-nitro-1*H-*pyrazole-5-carboxamide* (**13**). A soln. containing equimolar amounts of **11** and N,*3-dimethyl-1-phenyl-1*H-*pyrazol-5-amine* (**12**; 1.87 g, 10 mmol) [6] in dry $CHCl_3$ (100 ml) was refluxed for 5 h. After the first hour, $Et_3N$ (1.6 ml) was added in four portions (0.8, 0.4, $2 \times 0.2$ ml, resp., with intervals of 1 h between additions). The soln. was evaporated under reduced pressure, and the solid residue was washed with $H_2O$ ($2 \times 100$ ml) and crystallized from EtOH to afford **13** (1.06 g, 30%). Crystalline colorless solid. M.p. 136–137°. IR: 1664 (CO). $^1$H-NMR: 2.13 (*s*, Me); 2.78 (*s*, Me); 3.53 (*s*, Me); 6.21 (*s*, H–C(4) of pyrazole); 7.16–7.57 (*m*, 5 arom. H). MS: 354 ($M^+$). Anal. calc. for $C_{17}H_{18}N_6O_3$: C 57.62, H 5.12, N 23.72; found: C 57.47, H 5.19, N 23.59.

*4-Amino*-N,*1,3-trimethyl*-N-*(3-methyl-1-phenyl-1*H-*pyrazol-5-yl)-1*H-*pyrazole-5-carboxamide* (**14**). A susp. of Fe filings (8 g) in 5% aq. AcOH (10 ml) was heated at *ca.* 100° under stirring on the water bath of a rotavapor until $H_2$ evolution ceased. The $NO_2$ derivative **13** (4.6 g, 13 mmol) was added in four portions, with intervals of 20 min between additions. After the last addition, stirring was continued at 100° for 1 h, then the mixture was cooled to r.t. The pH of the susp. was adjusted to 7–8 with a sat. soln. of $NaHCO_3$. The solid was separated by filtration, air dried overnight, and then extracted with boiling $CHCl_3$ ($3 \times 50$ ml). The combined extracts were evaporated under vacuum, leaving an oily residue that solidified by addition of a small amount of $Et_2O$ to give practically pure **14** (3.12 g, 74%). Crystalline colorless solid. M.p. 122–124° ($Et_2O$). IR: 3429–3335 (multiple bands), 1634 (CO). $^1$H-NMR: 1.89 (*s*, Me); 2.20 (*s*, Me); 2.85 (*s*, Me); 3.36 (*s*, Me); 3.73 (*s*, $NH_2$ (exchangeable with $D_2O$)); 6.52 (*s*, H–C(4) of pyrazole); 7.13–7.47 (*m*, 5 arom. H). MS: 324 ($M^+$). Anal. calc for $C_{17}H_{20}N_6O$: C 62.95, H 6.21, N 25.91; found: C 62.71, H 6.31, N 25.75.

*1,3-Dimethyl-5-{[methyl(3-methyl-1-phenyl-1*H-*pyrazol-5-yl)amino]carbonyl}-1*H-*pyrazole-4-diazonium Sulfate* (**15**). Pulverized **14** (1.49 g, 4.6 mmol) was dissolved in cooled (0–5°) 5N $H_2SO_4$ (9.2 ml), and 2.5M aq. $NaNO_2$ (1.92 ml) was added dropwise to the stirred soln. The soln. was stirred for a further 15 min in an ice bath and then checked for excess $HNO_2$ with KI-starch paper; excess $HNO_2$ was destroyed by addition of urea.

*(3*S*,4*S*)- or (3*S*,4*R*)-4-Chloro-2,4-dihydro-1′,3′,5,5′-tetramethyl-2-phenylspiro[3*H*-pyrazole-3,4′(1′*H*)-pyrrolo[3,4-*c*]pyrazol]-6′(5′*H*)-one* (**18a**). To a cold (0–5°) soln. (220 ml) of $CuSO_4 \cdot 5\ H_2O$ (0.3M) and NaCl (0.75M), first the soln. of **15** obtained from the previous procedure, and then ascorbic acid (205 mg, 1.6 mmol) were added under stirring. The mixture was stirred for 1 h at r.t. and then filtered. The solid product obtained was dried (anh. $CaCl_2$) for 24 h and then processed by flash chromatography (FC) [7] (external diameter of the column 5 cm, silica gel (0.040–0.063 mm, 170 g), AcOEt/light petroleum ether 6:4 (40–70°)); 50 ml fractions were collected. The initial ten fractions were discarded and *Fr. 11–16* were evaporated under reduced pressure

to give 500 mg of a mixture that was crystallized from $Et_2O$ to give **18a** (160 mg). Crystalline colorless solid. M.p. 156–158°. IR: 1708 (CO). $^1$H-NMR: 2.19 (*s*, Me); 2.21 (*s*, Me); 2.47 (*s*, Me); 3.91 (*s*, Me); 5.93 (*s*, H–C(4) of pyrazole); 6.82–7.21 (*m*, 5 arom. H). MS: 343 ($M^+$). Anal. calc. for $C_{17}H_{18}ClN_5O$: C 59.39, H 5.28, N 20.37; found: C 59.17, H 5.40, N 20.03.

*4,6-Dihydro-1,4,6,8-tetramethyl-3-phenyldipyrazolo[3,4-*b:*4′,3′-*d*]pyridin-5(3*H*)-one* (**16**). *Fr. 21–26* were evaporated under vacuum, and the residues crystallized from AcOEt to give **16** (100 mg): Colorless crystalline solid. M.p. 241–243°. IR: 1649 (CO). $^1$H-NMR: 2.58 (*s*, Me); 2.61 (*s*, Me); 3.09 (*s*, Me); 4.18 (*s*, Me); 7.53 (*s*, 5 arom. H). MS: 307 ($M^+$). Anal. calc. for $C_{17}H_{17}N_5O$: C 66.43, H 5.57, N 22.79; found: C 66.57, H 5.60, N 22.60.

*4,6-Dihydro-3,4,6,8-tetramethyl-1-phenyldipyrazolo[4,3-*b:*4′,3′-*d*]pyridin-5(1*H*)-one* (**17**). *Fr. 32–38* were evaporated under vacuum, and the residues crystallized from AcOEt to give **17** (90 mg). White crystalline solid. M.p. 220–222°. IR: 1646 (CO). $^1$H-NMR: 1.46 (*s*, Me); 2.61 (*s*, Me); 3.75 (*s*, Me); 4.20 (*s*, Me); 7.57 (br. *s*, 5 arom. H). MS: 307 ($M^+$). Anal. calc. for $C_{17}H_{17}N_5O$: C 66.43, H 5.57, N 22.79; found: C 66.65, H 5.45, N 22.87.

*(3*S*,4*R*)- or (3*S*,4*S*)-4-Chloro-2,4-dihydro-1′,3′,5,5′-tetramethyl-2-phenylspiro[3*H*-pyrazole-3,4′(1′*H*)-pyrrolo[3,4-*c*]pyrazol]-6′(5′*H*)-one* (**18b**). The residue obtained by evaporation of the mother liquors of *Fr. 11–16* were processed by FC [7] (external diameter of column 3.5 cm, silica gel (0.004–0.063 mm, 70 g), $Et_2O$/light petroleum ether 7:3 (40–70°)); 50 ml fractions were collected. The first eight fractions were discarded, and *Fr. 17–19* were evaporated to afford a small amount of practically pure **18b**. IR: 1705 (CO). $^1$H-NMR: 2.03 (*s*, Me); 2.20 (*s*, Me); 2.70 (*s*, Me); 3.86 (*s*, Me); 5.81 (*s*, H–C(4) of pyrazole); 6.70–7.19 (*m*, 5 arom. H). MS: 343 ($M^+$).

*4′-Chloro-*N*,1,3,3′-tetramethyl-1′-phenyl[4,5′-1*H*-bipyrazole]-5-carboxamide* (**19**). Epimer **18a** (80 mg) was dissolved in 1M KOH in abs. EtOH (5 ml) and the soln. was stirred for 15 h at r.t. The obtained soln. was diluted with $H_2O$ to a volume of 25 ml and then extracted with $Et_2O$ (3 × 25 ml). The combined extracts were dried ($Na_2SO_4$) and evaporated to afford a solid residue. Crystallization from AcOEt/light petroleum ether (40–70°) gave compound **19** (60 mg, 75%). Colorless crystalline solid. M.p. 111–112°. IR: 3231 (NH), 1671 (CO). $^1$H-NMR: 1.67 (*s*, Me); 2.27 (*s*, Me); 2.60 (*s*, Me); 3.84 (*s*, Me); 7.24–7.41 (*m*, 5 arom. H); 7.9 (br. *s*, NH (exchanges very slowly with $D_2O$)). MS: 343 ($M^+$). Anal. calc. for $C_{17}H_{18}ClN_5O$: C 59.39, H 5.28, N 20.37; found: C 59.60, H, 5.41, N 20.21.

*X-Ray Crystallography.* The crystal data for **16** and **17** are given in *Table 1*, and significant bond lengths are listed in *Table 2*. The intensity data were collected on a *CAD4* diffractometer with graphite monochromated Mo$K_\alpha$ radiation ($\lambda$ 0.71073 Å). The cell parameters were determined and refined by least-squares fit of 20 high-angle reflections. The structures were solved by direct methods with Sir-92 [8] and conventional *Fourier* synthesis (SHELX-97) [9]. The refinement of the structures was made by full-matrix least-squares on $F^2$. All non-H-atoms were refined anisotropically. The H-atom positions were detected in a difference *Fourier* synthesis and refined with isotropic thermal factors. The supplementary crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* (CCDC deposition numbers 253865 and 253866).

*Linear Dichroism (LD) Measurements.* The LD spectra of DNA solns. ($4 \times 10^{-3}$ M) containing 2 mM NaCl and 1 mM EDTA were measured in the absence and presence of excess **17** on a *Jasco J500* CD spectrometer converted for LD according to *Wada* and *Kozawa* [10]. Briefly, a quartz cylinder was immersed in a cylindrical cell with two quartz windows. The sample soln. was illuminated with plane-polarized light of incidence perpendicular to the cell axis. When the inner cylinder rotates, the long, stiff DNA molecules are oriented in the flow. The LD spectrum is the difference between the absorption spectra recorded with and without cylinder rotation (*i.e.*, with the molecules oriented randomly or ordered, resp.).

*Antiproliferation Assay.* Compound **17** was tested *in vitro* for the antiproliferation activity against the human NCI-H460 cell line. Cells were suspended at a density of $4 \times 10^5$ cells per ml in minimum essential medium (*Eagle MEM*, *Sigma*) supplemented with 10% fetal calf serum (FCS) and antibiotics, transferred (100 µl per well) to 96-well plate and incubated for 4 d at 37° in a humidified atmosphere containing 5% $CO_2$. After this incubation time, the cells reached confluence, the medium was removed and replaced with *RPMI-1640* (without phenol red but with FCS, 0.025% glutamine, and antibiotics) with or without test compound and incubated at 37° for 3 d. At the end of this incubation time, the antiproliferation activity was determined by means of the MTT ((3-(4, 5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide); thiazolyl blue) assay [11] and expressed as the $IC_{50}$ value (test concentration at which the cell proliferation was inhibited to a level 50% of that of the untreated control).

We are grateful to Prof. *S. Caffieri* (Padova University) for the LD measurements, to Dr. *D. Schillaci* (Palermo University) for the antiproliferation test and to the *Ministero dell'Istruzione, dell'Università e della Ricerca* (*MIUR*, Research fund ex 60%) for financial support.

Table 1. *Crystal and Refinement Data for* **16** *and* **17**

| | **16** | **17** |
|---|---|---|
| Formula | $C_{17}H_{17}N_5O$ | $C_{17}H_{19}N_5O_2$ |
| Molecular weight | 307.36 | 323.36 |
| Temperature [K] | 293(2) | 293(2) |
| Wavelength [Å] | 0.71073 | 0.71073 |
| Crystal system | monoclinic | monoclinic |
| Space group | $P2_1/m$ | $P2_1/n$ |
| Cell parameters | | |
| $a$ [Å] | 10.460(2) | 7.226(7) |
| $b$ [Å] | 6.898(2) | 20.362(8) |
| $c$ [Å] | 10.820(2) | 11.421(4) |
| $\beta$ [°] | 108.81(5) | 96.74(5) |
| $V$ [Å$^3$] | 739.0(3) | 1668.8(9) |
| $Z$ | 2 | 4 |
| Calc. density [g cm$^{-3}$] | 1.381 | 1.287 |
| Absorption coeff. (mm$^{-1}$) | 0.091 | 0.088 |
| $F(000)$ | 324 | 688 |
| Scan technique | $\omega/2\theta$ | $\omega/2\theta$ |
| Crystal size [mm] | $0.5 \times 0.5 \times 1$ | $0.3 \times 0.3 \times 1$ |
| $\theta$ range [°] | 2.06–24.98 | 2.00–19.98 |
| Limiting indices | $12 \geq h \geq -12$, $8 \geq k \geq -1$, $12 \geq l \geq -12$ | $6 \geq h \geq -6$, $19 \geq k \geq 0$, $10 \geq l \geq 0$ |
| Refls. collected | 1919 | 1642 |
| Unique refls. | 1411 | 1548 |
| Completeness to $\theta$ | 99.9% | 99.7% |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data, restraints, parameters | 1411, 0, 148 | 1548, 0, 175 |
| Goodness-of-fit on $F^2$ | 1.038 | 0.997 |
| $R$ ($I > 2\sigma(I)$) | $R_1 = 0.0508$, $wR_2 = 0.1280$ | $R_1 = 0.0554$, $wR_2 = 0.1340$ |

Table 2. *Significant Bond Lengths* [Å] *for* **16** *and* **17**

| | **16** | **17** |
|---|---|---|
| N(1)–N(2) | 1.370(4) | 1.352(9) |
| N(1)–C(9) | | 1.37(1) |
| N(1)–C(8) | 1.349(5) | |
| N(2)–C(7) | 1.308(5) | 1.34(1) |
| C(9)–C(8) | 1.384(5) | 1.39(1) |
| C(7)–C(8) | | 1.35(1) |
| C(9)–C(7) | 1.400(5) | |
| N(1)–C(1) | 1.426(5) | 1.433(8) |
| N(3)–C(13) | 1.408(5) | 1.36(1) |
| C(10)–C(12) | 1.389(6) | 1.40(1) |
| C(12)–C(13) | 1.445(6) | 1.48(1) |
| C(10)–C(9) | 1.443(5) | 1.43(1) |
| O(1)–C(13) | 1.212(5) | 1.23(1) |
| N(5)–C(11) | 1.333(5) | 1.35(1) |
| N(3)–C(8) | 1.378(5) | 1.40(1) |
| N(3)–C(16) | 1.452(5) | 1.475(9) |
| N(4)–N(5) | 1.344(5) | 1.36(1) |
| N(4)–C(12) | 1.354(5) | 1.34(1) |
| C(10)–C(11) | 1.403(5) | 1.36(1) |
| N(4)–C(18) | 1.454(5) | 1.50(1) |
| C(11)–C(17) | 1.468(6) | 1.46(1) |

## REFERENCES

[1] G. Daidone, B. Maggio, D. Raffa, S. Plescia, F. Benetollo, G. Bombieri, *J. Chem. Soc., Perkin Trans 1* **1998**, 2891.
[2] G. Daidone, S. Plescia, B. Maggio, V. Sprio, F. Benetollo, G. Bombieri, *J. Chem. Soc., Perkin Trans 1* **1993**, 285.
[3] C. K. Johnson, ORTEP 11, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.
[4] D. Vedaldi, P. Rodighiero, F. Orsini, V. Lucchini, F. Dall'Acqua, S. Caffieri, G. Bombieri, F. Benetollo, *Eur. J. Med. Chem.* **1991**, *26*, 875.
[5] V. Papesch, R. M. Dodson, *J. Org. Chem*. **1965**, *30*, 199.
[6] S. Plescia, G. Daidone, V. Sprio, E. Aiello, G. Dattolo, G. Cirrincione, *J. Heterocycl. Chem.* **1978**, *15*, 1278.
[7] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. **1978**, *43*, 2923.
[8] A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Gagliardi, G. Polidori, *J. Appl. Crystallogr*. **1994**, *27*, 435.
[9] G. M. Sheldrick, SHELX-97. Program for the refinement of crystal structures, University of Göttingen, Germany, 1997.
[10] A. Wada, S. Kozawa, *J. Polymer Sci.* **1964**, *A2*, 853.
[11] J. Carmichael, W. G. DeGraff, A. P. Gazdar, J. D. Minna, J. B. Mitchel, *Cancer Res.* **1987**, *47*, 936.

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