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The Crystal and Molecular Structure of 1,3-dimethyl-pyrazole-5-carboxylic acid

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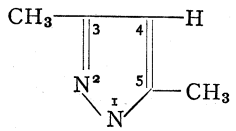
Cristallografia. — *The Crystal and Molecular Structure of 1,3-dimethyl-pyrazole-5-carboxylic acid* (*). Nota di ELISABETTA FORESTI SERANTONI, ROMANO MONGIORGI e LODOVICO RIVA DI SANSEVERINO, presentata (**) dal Socio P. GALLITELLI.

RIASSUNTO. — La struttura di un secondo derivato pirazolico ad azione lipolitica fra quelli studiati da Bizzi, Codegoni e Garattini (1967) è stata determinata con metodi diffrattometrici.

L'acido 1,3-dimetil-pirazol-5-carbossilico ha simmetria monoclina, $P2_1/a$, $a = 9{,}67$ (2), $b = 14{,}22$ (4), $c = 4{,}90$ (1) Å, $\beta = 93{,}20°$ (8), e analogamente all'amide dell'acido 3-metil-pirazol-4-bromo-5-carbossilico ha una struttura decisamente planare. L'impacchettamento è caratterizzato da un singolo legame ad idrogeno che genera catene illimitate di molecole planari ed ha una interessante somiglianza con quello dell'acetil-4-bromo-pirazolo (Lapasset *et al.*, 1972).

INTRODUCTION

Work by Rubessa (1967), Bizzi, Codegoni and Garattini (1967) and others reported there has shown how influential 3,5-dimethyl-pyrazole and its derivatives are as powerful inhibitors of lipolysis of adipose tissue.



A first crystallographic investigation of 3-methyl-4-bromo-pyrazole-5-carboxyamide revealed the planar structure of this compound, which was thought to be correlated with its weak biological activity (Foresti *et al.*, 1970).

More recently careful attention has been given to slight anomalies in the stereochemistry of nitrogen atoms involved in cyclic compounds, resulting in a proposed correlation with biological activity, as in the case of cephalosporins (Sweet and Dahl, 1970) and of pyrazoline cycles (Aubagnac *et al.*, 1972 and *l.c.*). An interesting conclusion has been finally proposed by Whinnery and Watson (1972), who underlined the role of nitrogen atom belonging to a pentatomic ring.

More accurate data for pyrazole cycles were already required in our earlier work but the pyrazole analysis itself, which had been started, was

(*) Lavoro eseguito con il contributo del Consiglio Nazionale delle Ricerche.
(**) Nella seduta del 12 maggio 1973.

stopped when the papers by Berthou *et al.* (1970) and Larsen *et al.* (1970) appeared, witnesses of the relevance attributed to the related parameters. Within this framework the analysis of a second pyrazole derivative, 1,3–dimethyl–pyrazol–5–carboxilic acid, has now been completed.

Crystal data

$C_6H_8N_2O_2$, 1,3–dimethyl–pyrazol–5–carboxylic acid, M.W. 140.14, a = = 9.67 (2), b = 14.22 (4), c = 4.90 (1) Å, β = 93.20° (8), V = 761.8, Z = 4, D_c = 1.387, D_m = 1.37 gr. cm.$^{-3}$, space group $P2_1/a$, radiation CuKα. By equi-inclination photographic methods layers $hk0$–4 and 1–2 kl were collected from two crystals whose size in each of the three dimensions was roughly 0.2 mm. 1187 intensities were measured by a Nonius Mark I microdensitometer.

Structure solution and refinement

1140 I_{hkl} were used to calculate normalized structure factor magnitudes $|E_{hkl}|$. By selecting 228 values greater than 1.7 the program Tanfiz (Kennard *et al.*, 1971) produced 8 sets of signs using the tangent formula on three origin and three symbolic reflections (Karle and Karle, 1966). The lowest agreement factor R_{Karle} indicated which E map was to give the correct molecular model for the non-hydrogen atoms (R = 0.27). Ten cycles of block diagonal least squares refinement lowered the R factor to 0.108. Hydrogen positions were not easily recognizable from the difference map. Only atoms external to the ring have marked anisotropy (fig. 1).

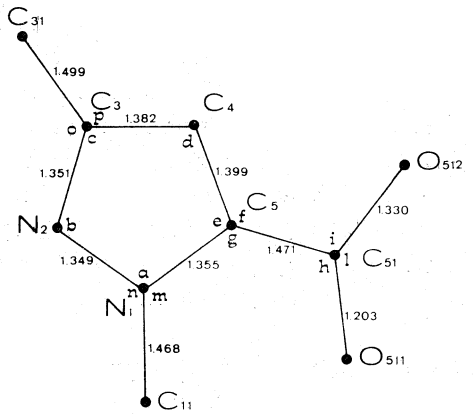


Fig. 1.

a = 111°.03;	h = 124°.36;
b = 106°.80;	i = 110°.99;
c = 109°.52;	l = 124°.65;
d = 106°.36;	m = 129°.95;
e = 106°.28;	n = 118°.97;
f = 129°.19;	o = 120°.97;
g = 124°.52;	p = 129°.49.

In Table I atomic parameters are reported. A list of observed and calculated structure factors is obtainable from the authors.

TABLE I

Atomic parameters.

ATOM	$x \cdot 10^4$	$y \cdot 10^4$	$z \cdot 10^4$	B (Å^2)
$O_{(511)}$	5928 (4)	1349 (2)	3249 (7)	(*)
$O_{(512)}$	6648 (3)	2811 (2)	2322 (6)	(*)
$N_{(1)}$	4121 (3)	2204 (2)	7139 (7)	3.18
$N_{(2)}$	3387 (3)	2822 (2)	8570 (7)	3.16
$C_{(5)}$	4977 (3)	2658 (2)	5481 (7)	2.95
$C_{(3)}$	3781 (4)	3693 (2)	7818 (8)	3.18
$C_{(51)}$	5888 (4)	2187 (2)	3600 (8)	(*)
$C_{(11)}$	3867 (4)	1192 (3)	7463 (9)	(*)
$C_{(4)}$	4782 (4)	3621 (3)	5922 (8)	3.28
$C_{(31)}$	3128 (5)	4555 (3)	8958 (9)	(*)

Standard deviations in parenthesis.

(*) Anisotropic temperature factors following the general formula:

$$\exp [-1/4 (B_{11} h^2 a^{*2} + B_{22} k^2 b^{*2} + B_{33} l^2 c^{*2} + 2 B_{12} hka^* b^* \cos \gamma^* + 2 B_{13} hla^* c^* \cos \beta^* + 2 B_{23} klb^* c^* \cos \alpha^*)]$$

ATOM	$B_{(11)}$	$B_{(22)}$	$B_{(33)}$	$B_{(12)}$	$B_{(13)}$	$B_{(23)}$
$O_{(511)}$	6.13	3.37	5.14	.06	1.45	—.88
$O_{(512)}$	4.57	3.82	3.80	—.11	1.06	—.21
$C_{(51)}$	3.80	3.53	2.69	.08	.08	—.22
$C_{(11)}$	4.62	2.88	4.88	—.32	.81	.16
$C_{(31)}$	4.80	3.22	5.05	.07	1.57	—.19

DISCUSSION

Distances and angles are shown in fig. 2. Consulting Table II, where values from the most recent structure determinations of the pyrazole ring are listed, there seems to be good agreement with our results. In this respect, although C(3)—C(4) is generally greater than C(4)—C(5), we believe that our assignment of atomic numbering follows the general trend. In fact Berthou *et al.* (1970) have ascertained the quasi-symmetric geometry of the pyrazole ring and Larsen *et al.* (1970) have finally differentiated a pyridine side and a pyrrole side in the molecule, fixing in this way the position of the N-hydrogen. Further-

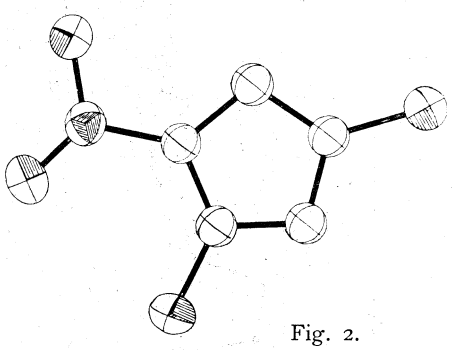


Fig. 2.

more, it is confirmed here that the longest C—N bond is related to the pyrrole type nytrogen atom.

TABLE II

Comparison of bond distances in the pirazole ring.

	(1)	(2)	(3)	(4)
$N_{(1)}$–$N_{(2)}$	1.341 Å	1.344 Å 1.344	1.35 Å 1.35	1.349 Å
$N_{(2)}$–$C_{(3)}$	1.329	1.325 1.322	1.34 1.33	1.351
$C_{(3)}$–$C_{(4)}$	1.382	1.391 1.389	1.37 1.38	1.382
$C_{(4)}$–$C_{(5)}$	1.376	1.364 1.351	1.36 1.36	1.399
$C_{(5)}$–$N_{(1)}$	1.333	1.345 1.352	1.33 1.33	1.355

Data from: (1) Larsen *et al.*, 1970; (2) Reimann *et al.*, 1967 and Mighell *et al.*, 1969; (3) Berthou *et al.*, 1970; (4) present work.

While no intramolecular hydrogen bond is observed, an intermolecular contact of 2.71 Å allows the molecules to form continuous ribbons, as illustrated by figs. 3 and 4. The next shortest contact between O(512) and N(1)

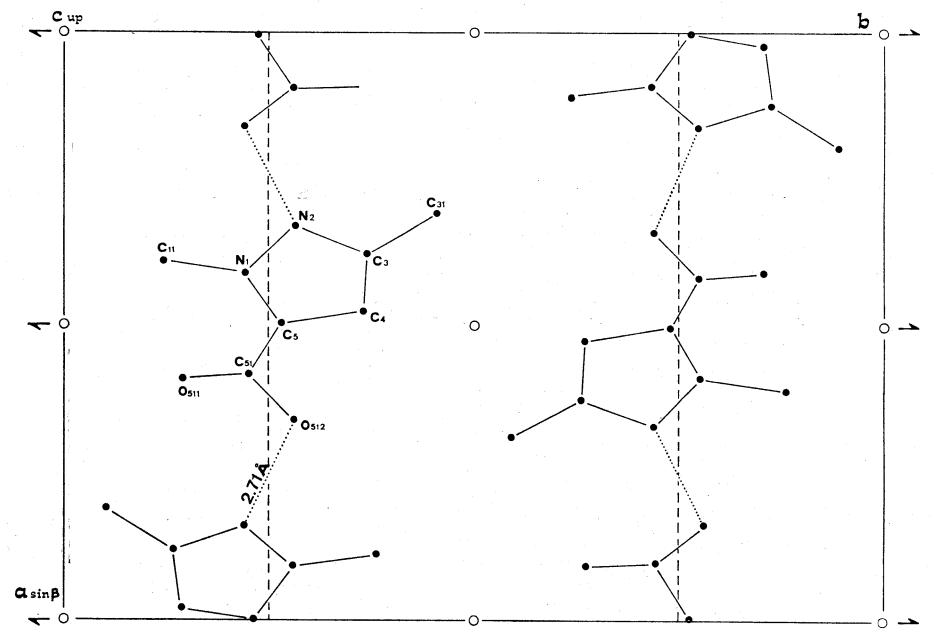


Fig. 3.

is 3.26 Å (at $1/2 + x$, $1/2 - y$, $1 - z$). This packing is strikingly similar to that of acetyl-4-bromo-pyrazole (Lapasset *et al.*, 1972).

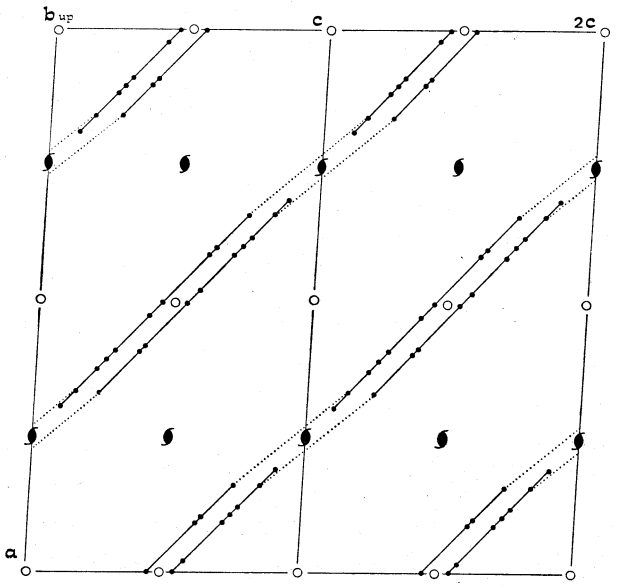


Fig. 4.

It may already be deduced that the molecule is planar, with extended aromatization; some geometric data are reported in Table III and IV.

TABLE III

n	ΔP_1	ΔP_2	ΔP_3	ΔP_4
$O_{(511)}$	—0.08 Å	—0.001 Å	—	—
$O_{(512)}$	0.04	—0.001	—	—
$N_{(1)}$	0.04	—	0.014 Å	—
$N_{(2)}$	0.02	—	—0.004	—0.002 Å
$C_{(3)}$	0.00	—	—	0.008
$C_{(4)}$	0.02	—	—	—0.003
$C_{(5)}$	0.02	—0.001	—0.005	—
$C_{(11)}$	0.01	—	—0.005	—
$C_{(31)}$	—0.06	—	—	—0.003
$C_{(51)}$	—0.01	0.003	—	—

TABLE IV

Angles between	P_2	P_3	P_4
P_1	3.2°	0.4°	2.0°
P_2	—	2.8°	5.1°
P_3	—	—	2.4°

Planes defined by: P_1, full molecule; P_2, O(511), O(512), C(51), C(5); P_3, C(11), N(1), N(2), C(5); P_4, C(31), C(3), N(2), C(4).

The only exceptional feature in the molecular geometry is the extremely low value for angle *i*, which is certainly due to the steric hindrance produced by the hydrogen bond (see also fig. 3).

The observed planarity of this compound, rather active biologically, raises some doubts as to the suggested correlation between planarity and weak activity for this kind of compound. It seems therefore worthwhile to compare the existing results with those observable from similar pyrazole derivatives.

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