On the Oxidizability of 1-Methyl-1,2,3,4-tetrahydropyrimido-[1,2-a]indole-10-carboxaldehyde and its Crystal Structure

Aldo Andreani

Istituto di Chimica Farmaceutica e Tossicologica, Università di Bologna,
Via Belmeloro 6, I-40126 Bologna, Italy

Lucedio Greci* and Giorgio Tosi

Dipartimento di Scienze dei Materiali e della Terra, Facoltà di Ingegneria,
Via Brecce Bianche, I-60131 Ancona, Italy

Paolo Sgarabotto and Franco Ugozzoli

Istituto di Strutturistica Chimica, Università di Parma,
C.N.R. Centro di Studio per la Strutturistica Diffrattometrica, Viale delle Scienze,
I-43100 Parma, Italy
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The study of the molecular geometry of 1-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole-10-carboxaldehyde as determined by X-ray analysis and the electrochemical properties of that compound are reported. These are compared with those of a number of indole-3-carboxaldehyde, differently substituted at 1 and 2 position. This was done in order to understand the unsuccessful attempts to convert the title compound into the corresponding acid. The result indicate that this anomalous behaviour may be attributed to easy oxidizability of the pyrimido ring nitrogen.

Introduction.

In the course of our study on the pharmacological behaviour of new 2-chloroindoles [1-9], we planned the synthesis of compound **3** and its corresponding acid. A literature survey revealed contradictory reports.

Compounds **3** [10] and **6** [11] were described as products of the reaction between the aldehyde **1** and the chloroalkylamine **2** (Scheme 1). When the reaction was repeated according to ref [10], two products, whose analytical and spectroscopic data were consistent with compounds **5** and

6 described by Coppola and co-worker [11], were isolated. The attainment of **5** together with **6** confirmed the intermediate formation of **4**. In fact, it is well known that tetra-alkylammmonium salts are able to form *N*-alkylated indoles [12].

Since our original purpose was to synthesize a series of carboxylic acids, the oxidation of compound **6** was attempted. While aldehydes such as **5** can be easily converted into their acids [1,4,9], several attempts to transform the aldehyde **6** under different conditions were unsuccessful. Furthermore, compound **6** behaves very dif-

Scheme 1
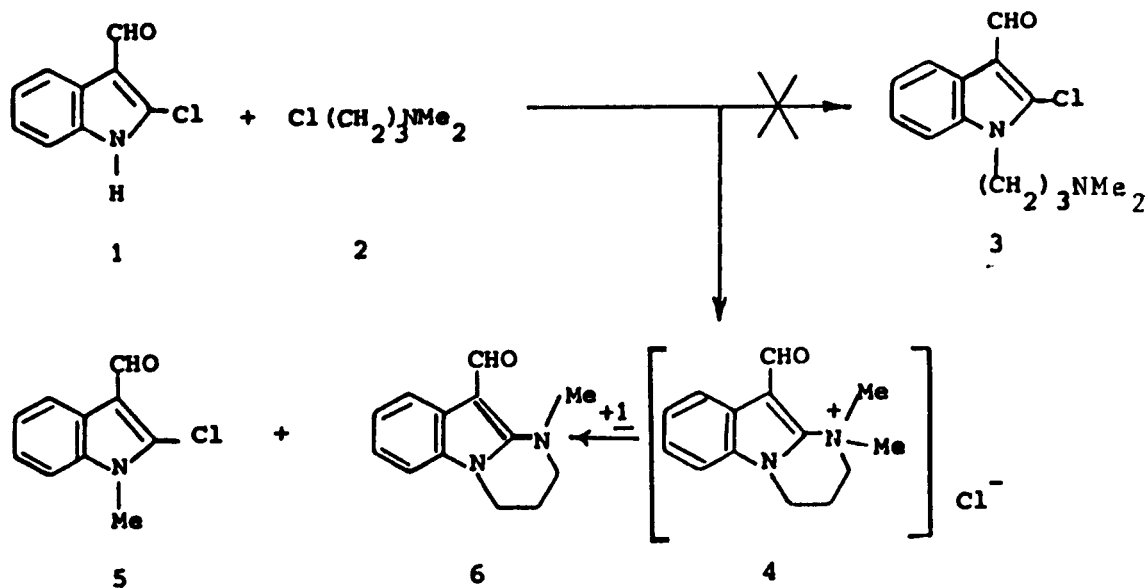
ferently towards 2,4-dinitrophenylhydrazine to form the corresponding hydrazone if it is compared with aldehydes such as **5** [13]. This unusual behaviour and the uncertainty about the structure of the isolated products suggested to verify the structure of **6** by X-ray analysis and an electrochemical study of a number of indole aldehydes including compound **6**.

Results and Discussion.

Aldehydes such as **5** and **7a-c** (see Table 1) can be easily transformed into the corresponding acid by potassium permanganate oxidation [1,4,9] but all attempts to oxidize compound **6** to the corresponding acid failed. These results might be attributed to a different oxidability of **6** with respect to **5** and **7a-c** or to a particular structure of **6**.

Table 1

Oxidation Potentials (E_p) of **5**, **6** and **7a-c**

Compound	R₁	R₂	E_p(V)	n [a]	E_p (V)
6	– –	– –	0.37	1.1	1.20
5	Me	Cl	1.30	3.4	– –
7a	Ph	Cl	1.34	4.0	– –
7b	CH₂Ph	H	1.16	1.3	1.37
7c	H	H	1.15	1.6	1.35

[a] Number of electron involved in the first step.

Block

CHO

R₂

N

R₁

7

a: R₁ = Ph ; R₂ = Cl

b: R₁ = CH₂Ph; R₂ = H

c: R₁ = R₂ = H
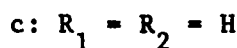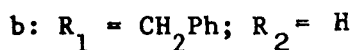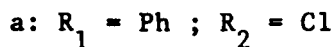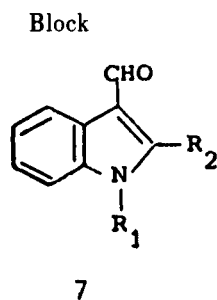
Aldehydes **5a** and **7a** undergo anodic oxidation in two very close irreversible steps at *ca.* 1.3V involving about four electrons per molecule [14] whereas compounds **7b** and **7c** show two different irreversible steps of the same height: the first at 1.15V and the second one at about 1.35V involving *ca.* three electrons [14] per molecule (Table 1). Thus, compounds **5** and **7a-c** do not show sub-

stantial differences in their behaviour under anodic oxidation and all give the corresponding carboxylic acid by potassium permanganate treatment. Compound **6** under anodic oxidation shows two different irreversible monoelectronic steps: the first at 0.37V and the second one at 1.2V. The first value means that the amine nitrogen of the six-membered ring causes the low oxidability of **6**; furthermore, as no products were isolated in all experiments done, we conclude that the potassium permanganate oxidation produces a complete breaking of the molecule.

Table 2

Fractional Coordinates (x10⁴, x10³ for hydrogen), Equivalent Isotropic Thermal Parameters (x10⁴ Å²) for Non Hydrogen Atoms and U_{iso} (x10³ Å²) for Hydrogen Atoms

$$U_{eq} = \frac{1}{3} \, \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* (a_i \cdot a_j)$$

Atom	x/a	y/b	z/c	U_{eq}
O(1)	4810(3)	6975(2)	2455(5)	633(15)
N(1)	4641(3)	3747(2)	2504(5)	376(15)
N(2)	6744(4)	4198(2)	2745(5)	432(14)
C(1)	4920(4)	5322(3)	2455(6)	357(14)
C(2)	3599(4)	5116(3)	2284(6)	370(16)
C(3)	2511(5)	5666(3)	2109(6)	464(18)
C(4)	1344(4)	5228(4)	2009(7)	562(20)
C(5)	1242(5)	4254(4)	2079(7)	537(20)
C(6)	2299(4)	3693(3)	2247(7)	473(20)
C(7)	3456(4)	4144(3)	2336(6)	378(18)
C(8)	4879(4)	2733(3)	2586(8)	496(19)
C(9)	6222(5)	2559(4)	2116(1)	869(34)
C(10)	7115(5)	3219(4)	3012(1)	724(27)
C(11)	5527(4)	4441(3)	2573(6)	370(17)
C(12)	5424(5)	6244(4)	2508(7)	491(20)
C(13)	7728(5)	4892(4)	2914(1)	573(23)
H(3)	257(4)	642(5)	210(6)	31(11)
H(4)	51(4)	565(4)	183(7)	77(15)
H(5)	33(4)	393(5)	201(7)	79(15)
H(6)	223(5)	294(3)	233(6)	50(13)
H(81)	472(6)	248(5)	401(6)	112(21)
H(82)	425(6)	238(4)	158(6)	105(20)
H(91)	631(7)	263(3)	59(7)	273(50)
H(92)	647(6)	185(4)	255(9)	96(18)
H(101)	711(6)	308(5)	452(7)	178(34)
H(102)	805(5)	311(4)	251(7)	95(18)
H(12)	639(4)	626(3)	249(6)	59(14)
H(131)	758(4)	535(3)	406(7)	69(16)
H(132)	858(6)	457(4)	319(9)	119(25)
H(133)	780(5)	533(4)	178(7)	94(22)

As far as the molecular geometry is concerned, bond distances and angles are given in Table 3 and an arbitrary numbering scheme used in the crystal analysis is shown in
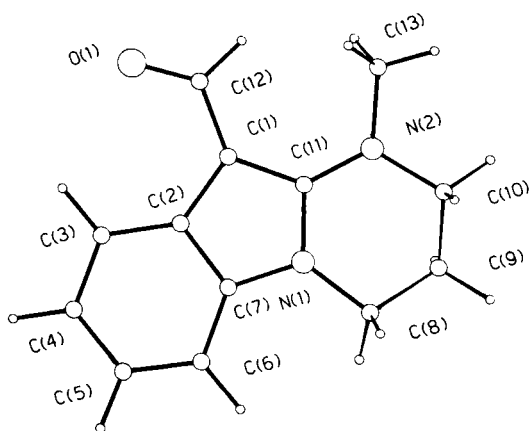
Figure 1.   Projection of the molecule on the plane of the indole ring.

Table 3

Bond Distances (Å) and Angles (°),
with Estimated Standard Deviations in Parantheses

a) Bond Distances

O(1)-C(12)	1.231(6)	C(1)-C(12)	1.420(7)
N(1)-C(7)	1.386(5)	C(2)-C(3)	1.402(7)
N(1)-C(8)	1.469(5)	C(2)-C(7)	1.395(6)
N(1)-C(11)	1.368(5)	C(3)-C(4)	1.392(7)
N(2)-C(10)	1.461(6)	C(4)-C(5)	1.394(8)
N(2)-C(11)	1.345(6)	C(5)-C(6)	1.384(7)
N(2)-C(13)	1.444(7)	C(6)-C(7)	1.391(6)
C(1)-C(2)	1.440(6)	C(8)-C(9)	1.503(7)
C(1)-C(11)	1.414(6)	C(9)-C(10)	1.464(8)

b) Bond Angles

C(7)-N(1)-C(8)	124.1(3)	C(3)-C(4)-C(5)	121.1(4)
C(7)-N(1)-C(11)	109.5(3)	C(4)-C(5)-C(6)	121.0(5)
C(8)-N(1)-C(11)	126.3(3)	C(5)-C(6)-C(7)	117.1(4)
C(10)-N(2)-C(11)	120.9(4)	N(1)-C(7)-C(2)	107.9(4)
C(10)-N(2)-C(13)	116.9(4)	N(1)-C(7)-C(6)	128.3(4)
C(11)-N(2)-C(13)	121.8(4)	C(2)-C(7)-C(6)	123.8(4)
C(2)-C(1)-C(11)	105.6(4)	N(1)-C(8)-C(9)	108.6(4)
C(2)-C(1)-C(12)	124.0(4)	C(8)-C(9)-C(10)	114.2(5)
C(11)-C(1)-C(12)	130.4(4)	N(2)-C(10)-C(9)	113.0(5)
C(1)-C(2)-C(3)	134.2(4)	N(1)-C(11)-N(2)	118.7(4)
C(1)-C(2)-C(7)	108.0(4)	N(1)-C(11)-C(1)	109.0(4)
C(3)-C(2)-C(7)	117.8(4)	N(2)-C(11)-C(1)	132.3(4)
C(2)-C(3)-C(4)	119.3(4)	O(1)-C(12)-C(1)	125.6(5)

c) Selected Torsion Angles

C(11)-C(1)-C(12)-O(1)	−177.5(5)	C(8)-N(1)-C(11)-N(2)	−0.5(6)
C(2)-C(1)-C(12)-O(1)	1.5(8)	C(11)-N(1)-C(8)-C(9)	−18.3(6)
C(12)-C(1)-C(2)-C(3)	1.0(8)	N(1)-C(8)-C(9)-C(10)	42.4(6)
C(12)-C(1)-C(11)-N(2)	−0.9(8)	C(8)-C(9)-C(10)-N(2)	−49.5(7)
C(13)-N(2)-C(11)-C(1)	2.2(8)	C(11)-N(2)-C(10)-C(9)	30.1(7)
C(8)-N(1)-C(7)-C(6)	1.2(7)	C(10)-N(2)-C(11)-N(1)	−5.0 (6)

Figure 1. This represents a projection of the molecule on the plane of the indole ring. The conformational geometry of the molecule can be deduced from the torsion angles listed in Table 3. The intramolecular bond lengths and angles in the indole nucleus are in line with the hybridization expected for the atoms involved and are also reasonably in agreement with those of analogous compounds previously studied [15]. The fused two-rings indolic system is almost planar, the dihedral angle between the mean planes of the two individual rings being 179.2°. A significant deviation from planarity is observed only for C(1) atom which is out of the indole mean plane of 0.014(4) Å.

The average angle around N(2) of 119.9° indicates that the N(2) atom should be considered in a sp² hybridization state; on the other hand an analysis in terms of piramidality for N(2) atom shows that this atom deviates from the plane containing the three atoms attached to it by 0.054(4) Å. The molecular dimensions, of the carbaldehyde group, indicate that weak repulsive forces between the oxygen atom of the carbonyl group and the benzene ring cause a slight but significant distorsion of the valency angle O(1)-C(12)-C(1) from the expected 120°. In addition there is a slight deviation of the atoms of this plane from the plane of the indole group; the dihedral angle between the O(1)-C(12)-C(1) plane and the two-fused ring mean plane is 2.4(3)°.

The conformational analysis indicates that the tetrahydropyrimido ring adopts a half-chair conformation with a considerable degree of distorsion (given by tg θ_2 = 1.294). A quantitative evaluation of this ring deviation from the ideal symmetry can be derived from the asymmetry parameters proposed by Duax et al [16]. They show that reasonable symmetry is due to the presence of a pseudo-mirror plane through C(11) and a twofold rotational axis intersecting N(1)-C(11) bond. The packing of the molecules in the crystal is determined by van der Waals interactions only. No evidence exists for hydrogen bonds and there are no intermolecular contacts shorter than the respective van der Waals diameters.

The results derived from X-ray crystal structure analysis show that, in the solid state, there are no reasons related to either the conformation of the molecule or to steric hindrance which would prevent the oxidation of the aldehyde group to the corresponding acid. Thus, the anomalous behaviour of **6** may be attributed to the amine nitrogen of the six-membered ring, which is in agreement with the electrochemical results.

EXPERIMENTAL

Compounds **6** [10,11], **7a** [4], and **7b** [9] were prepared as described in the literature. Compound **7c** was an Aldrich commercial product.

Attempted Oxidation of **6** with Potassium Permanganate.

The oxidation was carried out as already described in the literature

[1,4,9]. Potassium permanganate (2 g, 12.5 mmoles in 30 ml of water) was added to a solution of 6 (1 g, 4.67 mmoles in 200 ml of acetone), at room temperature and under stirring. After 12 hours the mixture was filtered and the acetone evaporated. The precipitate (0.35 g), which was identified as starting material, was filtered off. The filtrate was neutralized with 2N hydrochloric acid and extracted with chloroform (2 x 50 ml). No products were isolated after evaporation of the solvent.

Electrochemical Measurements.

The oxidation potentials were measured by recording the voltamperograms with a three-electrodes multipolarograph (Amel 471). The reversibility of the oxidation process was evaluated by recording the cyclic voltamperograms with an oscillographic polarograph (Amel 448). The working electrode was a pulsed [17] platinum disc (Amel 492) of about 1 mm in diameter. The reference electrode assembly was silver/0.1 M silver perchlorate-acetonitrile/ fine porosity fritted glass disk. A platinum wire served as the counter electrode. Acetonitrile (Erba, spectrophotometer grade), used as a solvent, was purified by distillation on calcium hydride, phosphorus pentoxide and then on calcium hydride again. Triethylammonium perchlorate (Erba, RS grade for polarography), used as supporting electrolyte, was vacuum dried at 60°, for three days. Argon (99.99%) was used to deoxygenate the investigated solutions, which were in the concentration of ca. 1 x 10^{-3} M in acetonitrile-triethylammonium perchlorate 0.1 M.

Crystal Structure of 6.

Crystals, obtained from ethanol solution, were colourless prisms, roughly of 0.16 x 0.10 x 0.72 mm, elongated on [001]. Lattice parameters were calculated using a least squares procedure [18] which involves angle settings of 28 carefully centered reflections.

Crystal Data.

$C_{13}H_{14}N_2O$, M = 214.3. Monoclinic, a = 10.668(2), b = 14.258(3), c = 7.014(1) Å, β = 92.2(1)°; Z = 4; D_c = 1.33 g, cm^{-3}; U = 1066.1 Å^3; Cu-Kα radiation, λ = 1.5418 Å, μ(Cu-Kα) = 6.48 cm^{-1}. Space group P2$_1$/n (C^5_{2h}, N°14) from systematic absences.

X-Ray measurements were performed at T = 298K on a Siemens AED single-crystal diffractometer in the range 3° ≤ θ ≤ 70° using Ni filtered Cu-Kα radiation. Intensity data were collected using a θ-2θ scan procedure with the scan width ranging from (θ - 0.60)° to (θ + 0.60 + 0.142 tg θ)°. The intensities I_{hkl} were determined by analyzing the reflection profiles with the Lehman and Larsen procedure [19].

A total of 2295 symmetry independent reflection were measured, of which 756 having $I_{hkl} \geq 2\sigma (I_{hkl})$ [$\sigma (I)$ based on statistic counting] were retained as "observed" and used in the structure solution and refinement. One standard reflection was measured every 50 collected reflections to monitor crystal decomposition and instrumental linearity. The calculated intensities I_{hkl} were corrected for Lorentz and polarization effects. No corrections for absorption effects were performed.

Structure Analysis and Refinement.

The structure was solved by direct methods using the computer program system written by Sheldrick [20]. The structure was refined by a few cycles of full-matrix anisotropic least-squares refinement with a resulting R of 0.085. The hydrogen atoms were included in the refinement with geometrically calculated positional parameters. The weighting function was of the form $1/w = \sigma^2 (F_o) + 0.005 F_o$. The final agreement factor R was 0.045, R_w = 0.044. Positional parameters together with their standard deviations are given in Table 2. The atomic scattering factors for oxygen, nitrogen and carbon were from ref [21] and those of hydrogen from ref [22]. All calculations were carried out on the CDC Cyber 76 of

Consorzio per la Gestione del Centro di Calcolo Interuniversitario dell'Italia Nord-Orientale, Casalecchio, Bologna. Observed and calculated structure factors thermal parameters, analysis of the planarity, and puckering and asymmetry parameters are available on request.

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