Synthesis of 1-Cyano-2-methylisoindole.
A New Route to Isoindoles [1]

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The reaction of o-phthaldehyde with potassium cyanide and methylamine hydrochloride afforded 1-cyano-2-methylisoindole (1) in 92% yield. Possible mechanism and supporting nmr, ir, mass spectrum and single X-ray structure analysis for 1 are discussed. The X-ray study revealed that the true structure of 1 can best be represented as a resonance hybrid of the canonical forms a, b, c and d.

Although isoindoles were first prepared in 1951 [2,3], this area of chemistry had received very limited attention in the literature until 1969. However, since 1970 considerable attention has been focused on their preparation and certain derivatives of isoindoles have served as important synthetic intermediates in the elaboration of certain natural products [4-22].

We wish to report that the reaction of o-phthaldehyde with potassium cyanide and methylamine hydrochloride in methyl alcohol afforded 1-cyano-2-methylisoindole (1) in 92% yield. Since it has been reported that the reaction
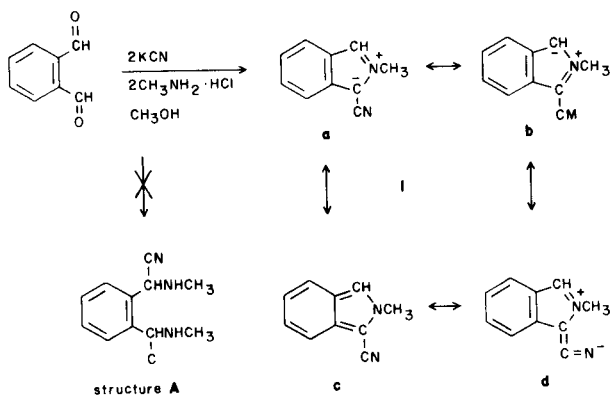
of benzaldehyde with potassium cyanide and methylamine hydrochloride furnished α-methylaminophenylacetonitrile [23], the formation of product A had to be considered in the above reaction. Based on elemental analysis and molecular weight, structure A was ruled out. By reviewing the elemental analysis and the mass spectrum data the compound isolated in this reaction had a molecular weight of 156 with an empirical formula of $C_{10}H_8N_2$. From this data we considered the possible structures as being the resonance hybrid of the canonical forms a, b, c, d or structure B shown below:
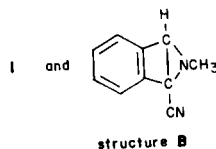
structure B

Since the nmr via Varian T-60, ir and mass spectral data could not completely substantiate the proposed structure 1, an X-ray crystallographic study was undertaken.

The X-ray crystal structure analysis shows that the title compound does not adopt structure B. An examination of Figure 1 (an ORTEP drawing of the molecular structure) and Figure 2 (a drawing showing selected bond distances and angles) clearly indicates that structure B is not adopted since the bond distance of 2.233 Å between C_1 and C_8 is much too long to be considered bonding [24]. Moreover, the crystal structure shows that all non-hydrogen atoms are planar to within ± 0.07 Å. This planarity would not be observed for structure B. The crystal structure can best be described as a hybrid of the resonance structures (a, b, c, d) shown as 1. If one examines only the six-membered ring portion of the structure, then the resonance form c seems to predominate the structure. This resonance form is the one chosen by Simons and co-workers [9d] to describe the structure dimethylacetylenedicarboxylate-1-(ethylthio)-2-n-propylisoindole. There appears to be bond localization in the six-membered ring. However, the bonding in the five-membered ring portion of the molecule does not strongly support resonance structure c. The bond distances C_1-C_2 and C_8-C_7, which should have localized double bond character, average to 1.401 Å which is nearly equal to the average of 1.409 Å for C_2-C_3 and C_7-C_6 bonds which should have more localized single bond character in the six-membered ring. The N_1-C_1 and N_1-C_8 bond distances average 1.361 Å which is in the range for shortened (partially double bonds) found in heterocyclic systems [16,24]. Moreover, it is noteworthy to observe that the normal N_1-C_{10} single bond distance is 1.460 Å. The delocalization of the lone pair of electrons in structure a would lead to

$$(-\overset{..}{\underset{..}{C}} \overset{+}{=} C \equiv N \longleftrightarrow -C = C = N^-)$$

the canonical form d. Consideration of this resonance form was based on the bond distances for 1 reported in this paper. It certainly apears that a bonding form for isoindoles shown only as structure C does not adequately describe this system. This crystal structure analysis supports a bonding model for isoindoles with delocalized bonding and substantial aromatic character.

Table 1

Atomic Coordinates ($\times 10^4$) for Compound **1** [a,c]

Atom	X	Y	Z
N1	3683(2)	2067(4)	1608(1)
N2	2614(4)	6681(5)	445(2)
C1	2853(3)	3997(4)	1665(2)
C2	2229(3)	4090(4)	2437(2)
C3	1309(3)	5666(5)	2832(2)
C4	869(3)	5244(6)	3603(2)
C5	1315(4)	3262(6)	4012(2)
C6	2215(4)	1713(5)	3647(2)
C7	2698(3)	2112(4)	2848(2)
C8	3588(3)	913(5)	2308(2)
C9	2732(3)	5477(5)	994(2)
C10	4544(4)	1390(5)	896(2)
H3 [b]	1051	7179	2580
H4	156	6649	3887
H5	968	2758	4610
H6	2559	187	3913
H8	4245	−559	2380
H10,1	5411	137	1005
H10,2	3841	918	431
H10,3	5430	2670	750

[a] Figures in parenthesis are the estimated standard deviations in the least significant figures. [b] Hydrogen atoms were included as fixed contributions with isotropic temperatures of $5.0 = e^{-\beta \sin^2 \theta / \lambda}$. [c] Atoms labeled according to Figure 1.
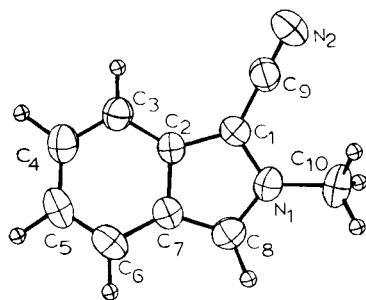

Figure 1. An Ortep drawing showing the molecular configuration **1**.

Figure 2. Selected bond distances and angles for **1**.

Once the correct structure for **1** became known, the nmr, ir and mass spectral data became more meaningful and thus provided additional support for the proposed structure **1**. We are deeply indebted to Dr. W. H. Urry of the University of Chicago for the 350 MHz nmr spectrum of **1** (Figure 3) which is in complete agreement with our proposed structure **1**. The electron impact and isobutane

350 MHZ nmr spectrum of **1** in perdeuteriobenzene

Figure 3

Table 2

Refined Anisotropic Thermal Parameters for Compound **1** [a,b]

Atom	B11 [c]	B22	B33	B12	B13	B23
N1	3.17(10)	4.24(12)	3.44(11)	0.22(7)	0.16(8)	−0.58(8)
N2	8.44(18)	6.18(14)	4.32(14)	0.02(12)	1.21(12)	1.31(12)
C1	3.16(11)	3.80(12)	3.27(13)	−0.23(9)	−0.01(8)	0.21(9)
C2	2.66(10)	3.86(13)	2.97(12)	−0.06(8)	−0.04(8)	−0.20(8)
C3	3.66(12)	4.36(14)	3.91(15)	0.14(9)	0.27(9)	−0.34(9)
C4	4.10(14)	6.25(17)	4.04(15)	0.51(11)	0.57(11)	−0.56(12)
C5	4.47(15)	7.31(19)	3.05(14)	−0.38(13)	0.64(11)	0.26(13)
C6	4.25(14)	5.55(14)	3.85(15)	−0.34(12)	−0.07(10)	1.10(12)
C7	2.88(11)	4.24(14)	3.46(12)	−0.009(9)	0.06(9)	0.04(9)
C8	3.58(12)	4.07(13)	4.30(16)	0.26(11)	−0.19(11)	−0.05(10)
C9	4.57(14)	4.48(13)	3.65(14)	−0.23(10)	0.78(11)	−0.11(12)
C10	4.04(13)	6.39(16)	4.52(15)	0.60(12)	0.99(11)	−1.66(13)

[a] Figures in parenthesis are the estimated standard deviations in the least significant figures. [b] Atoms labeled according to Figure 1. [c] The anisotropic temperature parameter is of the form: $B_{ij} = \exp[-\frac{1}{4}(\beta_{11}h^2 a^{*2} + \beta_{22}k^2 b^{*2} + \beta_{33}l^2 c^{*2} + 2\beta_{12}hka^*b^* + 2\beta_{13}hla^*c^* + 2\beta_{23}klb^*c^*)]$.
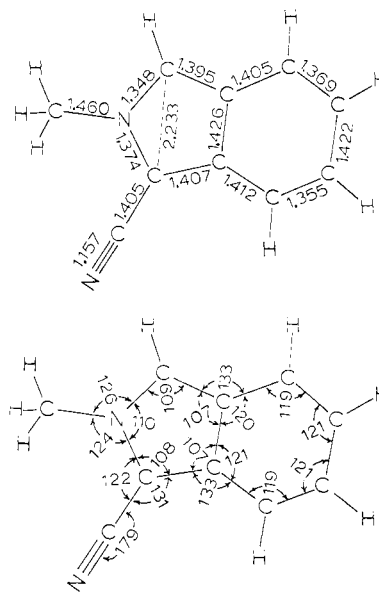
Scheme I

Table 3

Bond Distances and Bond Angles for Compound **1** [a,b,c]

Bond Distances, Å

N1-C1	1.374(3)	C8-H8	1.08
-C8	1.348(4)	C3-H3	1.03
C10	1.460(4)	C4-H4	1.16
C1-C2	1.407(4)	C5-H5	1.08
C2-C3	1.414(4)	C6-H6	1.06
-C7	1.426(4)	C10-H10,1	1.06
C3-C4	1.355(4)	-H10,2	0.97
C4-C5	1.422(5)	-H10,3	1.11
C5-C6	1.369(4)		
C6-C7	1.405(4)		
C7-C8	1.395(4)		
C9-C1	1.405(4)		
C9-N2	1.157(4)		

Bond Angles, degrees

C1-N1-C8	110.2(2)	H8-C8-N1	119
-C10	124.3(2)	C7	132
C8-N1-C10	125.2(2)	H3-C3-C2	123
N1-C1-C2	107.6(2)	-C4	118
-C9	121.6(2)	H4-C4-C3	114
C2-C1-C9	130.8(2)	-C5	125
C1-C2-C3	133.0(2)	H5-C5-C4	126
-C7	106.4(2)	-C6	112
C3-C2-C7	120.5(2)	H6-C6-C5	125
C2-C3-C4	118.6(3)	-C7	116
C3-C4-C5	121.2(3)	N1-C10-H10,1	116
C4-C5-C6	121.5(3)	-H10,2	114
C5-C6-C7	118.6(3)	-H10,3	110
C6-C7-C8	133.3(3)	H10,1-C10-H10,2	106
-C2	107.6(2)	-H10,3	96
C8-C7-C2	119.7(2)	H10,2-C10-H10,3	114
C7-C8-N1	108.6(2)		
C1-C9-N1	179.1(3)		

[a] Figures in parenthesis are the estimated standard deviations. [b] Hydrogen atoms were included as fixed contributions and were not refined. [c] Atom labeling scheme is given in Figure 1. The hydrogen atoms are numbered according to the carbon atoms to which they are bonded.

chemical ionization mass spectra furnished the molecular weight data in the form of M.$^+$ 157 and (M + 1)$^+$ 157, respectively. Furthermore, the fragmentation pathway of **1** (see experimental) is consistent with the proposed structure. Moreover, the presence of the aromatic CH (3120-3000 cm^{-1}) and cyano (2200 cm^{-1}) absorption bands in the ir spectra furnished additional evidence for our proposed structure **1**. The proposed mechanism for this unusual reaction is depicted in Scheme I.

EXPERIMENTAL

The nmr spectrum was obtained with a 350 MHz spectrometer by Dr. W. H. Urry of the University of Chicago. The chemical shifts are reported in δ using tetramethylsilane as reference. The melting point was taken upon a Fischer-Johns block and is uncorrected. The electron impact mass spectra was determined with a Varian-MAT CH-7A mass spectrometer operating at an ionizing potential of 70 eV using the direct insertion probe technique with a source temperature of 250°. This instrument was operated in the CIMS mode to obtain the chemical ionization mass spectrum of **1**. The infrared spectrum was obtained with a Beckman IR-12 spectrophotometer. The X-ray for **1** was determined by using a Syntex P2$_1$ diffractometer and the XTL structure determination system.

1-Cyano-2-methylisoindole (**1**).

To a stirred solution containing 39.1 g (0.6 mole) of potassium cyanide in 200 ml of water, 45.9 g (0.68 mole) of methylamine hydrochloride was added in one portion. To this stirred solution at 20°, a solution containing 40.2 g (0.3 mole) of a freshly prepared o-phthaldehyde in 200 ml of methyl alcohol was added in one portion. An exothermic reaction resulted causing a temperature rise from 20° to 49°. The reaction mixture was stirred at 25-30° for 24 hours. After cooling to 5°, 1000 g of ice water was added and stirring continued at 0-10° for 30 minutes. The solid was collected by filtration, washed with water until the washings were neutral to litmus and air-dried at 25-30°. Compound **1**, mp 95-96°, was obtained in 92% yield. After two recrystallizations from isopropyl alcohol, **1** melted at 100-101°; ir (potassium bromide): 3120-3000 (ArCH), 2200 (CN), 1800-1600 (ArC=C), 1500-1300 (Ar ring modes) and 800-700 (CH wag on o-substituted ring) cm^{-1}; electron impact ms: m/e (relative intensity) M.$^+$ 156 (100), 155 (36) (M.$^+$H), 141 (63) (M.$^+$CH$_3$), 129 (11) (M.$^+$HCN), 115 (51) (M.$^+$CH$_3$CN); isobutane chemical ionization ms: m/e 157 (M + 1)$^+$; nmr (see Figure 3).

Anal. Calcd. for C$_{10}$H$_8$N$_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.89; H, 5.11; N, 17.82.
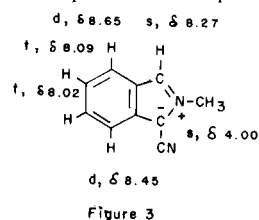
Crystal Data for **1**.

A single crystal of **1** measuring 0.4 × 0.25 × 0.25 mm was sealed in a glass capillary to prevent possible decomposition. The crystal was examined on a Syntex P2$_1$ diffractometer ad found to have the following parameters: Lattice constants = a = 8.129(2)Å, b = 6.341(6)Å, c = 16.269(8)Å, β = 93.05(2)Å; Crystal Class = monoclinic, Space group = P2$_1$/a, Unit Cell volume = 837.4 Å^3. Density (Calcd.) = 1.24 g cm^{-1}, Z = 4, mass absorption coefficient = 0.8 cm^{-1} (MoK$_\alpha$- radiation).

X-Ray Data Collection, Structure Determination, and Refinement.

The computer programs used for Crystal characterization, data collection, structure determination and refinement were those of the Syntex P2$_1$ Fortran Data Collection System and the XTL Structure Determination System [25]. Intensity data were recorded for 974 unique reflections (0° ≥ 2$\theta$$_{MoK\alpha}$- ≤ 43.0°) using the θ-2θ scan technique and variable scan rates from 1.0-18.0°/minute. No absorption correction (μ = 0.8 cm^{-1} for MoK$_\alpha$-) was necessary and the intensity data were reduced to a set of relative F$_o$ after corrections for Lorentz and polarization effects.

Atomic coordinates for the twelve non-hydrogen atoms were obtained from an E-map calculated using the phase set having the highest figures of merit from the program MULTAN [25]. The twelve atoms were refined using full-matrix least-squares and isotropic thermal parameters to give R$_1$ = 0.12 [26]. After refinement using anisotropic thermal parameters the eight hydrogen atoms were located from a difference Fourier map.

The eight hydrogen atoms were included as fixed contributions in final refinement and were given isotropic temperature factors of 5.0. The final full-matrix least-squares refinement employing anisotropic temperature parameters for all non-hydrogen atoms gave R$_1$ = 0.055 and R$_2$ = 0.098 [27] for 905 reflection having F$_o$-6.0σ(F$_o$). A counter weighting scheme with p = 0.070 was used in the refinement. A final difference Fourier showed no features of significance. The supplemental material is listed in Tables 1-3.

Acknowledgement.

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[24] "International Tables for X-Ray Crystallography", Vol III, Kynoch Press, Birmingham, England, Table 4.2.

[25] Syntex Analytical Instruments (Nicolet XRD), 10040 Babb Road, Cupertino, California 95014.

[26] R$_1$ = $\Sigma |F_o| - |F_c|/\Sigma |F_o|$.

[27] R$_2$ = $[\Sigma \omega (|F_o| - |F_c|)^2/\Sigma \omega |F_o|^2]^{1/2}$.