

Synthesis and Structure of New Substituted 2-Dicyanomethylene-1,2-dihydropyridines

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The synthesis of substituted 2-dicyanomethylene-1,2-dihydropyridines **3b-e** and 2-dicyanomethylene-2,3,4,5-tetrahydropyridine **4** is accomplished from malononitrile dimer and propenenitriles **2**. All structures were determined by nmr techniques; however to put our structural assignment for 6-amino-3-cyano-5-ethoxycarbonyl-2-dicyanomethylene-1,2-dihydropyridine **3d** on a firm and unequivocal basis we decided to perform X-ray diffraction analysis of this compound.

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In the last few years we have been investigating the photo-oxidation of 2-dicyanomethylene-1,2-dihydropyridines **3a** as a new synthetic procedure of 2-pyridinecarboxylates [1]. The scope of this synthetic approach, has stimulated in us a renewed interest for the preparation of compounds of type **3**. In a previous paper [2] we have reported the reaction of malononitrile dimer **1** with benzylidene malononitriles and amine in chloroform/tetrahydrofuran as a procedure of synthesis of compounds **3a**. We report herein the synthesis of the new 2-dicyanomethylene-1,2-dihydropyridines **3b-d** and 2-dicyanomethylene-2,3,4,5-tetrahydropyridine **4** by reaction of the 2-amino-1,1,3-tricyanopropene with the corresponding substituted propenenitrile **2** in ethanol-sodium ethoxide. Compound **3e** was obtained by oxidation of **4** with DDQ. The structure of the products isolated in this work was confirmed by analytical and spectral data. Thus, a mixture (9:2) of two epimeric forms through C3 was established for compound **4** based on acetone-*d*₆ 500 MHz ¹H-nmr spectra. The more abundant isomer showed three signals

at 4.15 (dd, $J_{H4,H5} = 13$ Hz and $J_{H4,H3} = 4.5$ Hz, H4), 4.40 (d, $J_{H3,H4} = 4.5$ Hz, H3) and 4.78 (d, $J_{H5,H4} = 13$ Hz, H5) ppm, whereas the minor one showed its set of resonances at 4.07 (dd, $J_{H4,H5} = 11$ Hz and $J_{H4,H3} = 10$ Hz, H4), 4.42 (d, $J_{H5,H4} = 11$ Hz, H5) and 4.52 (d, $J_{H3,H4} = 10$ Hz, H3) ppm.

After we published our first work [2] about the utilization of malononitrile dimer in pyridine synthesis, Fahmy and co-workers have assigned the structure **5** to the product obtained from **1** and **2d** in ethanol-triethylamine [3]. Given the similarity between **5** and **3d** on melting point and spectral data, a X-Ray diffraction analysis of **3d** was made necessary to put our assignment on a firm and unequivocal basis.

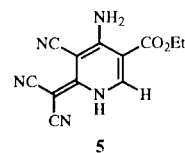
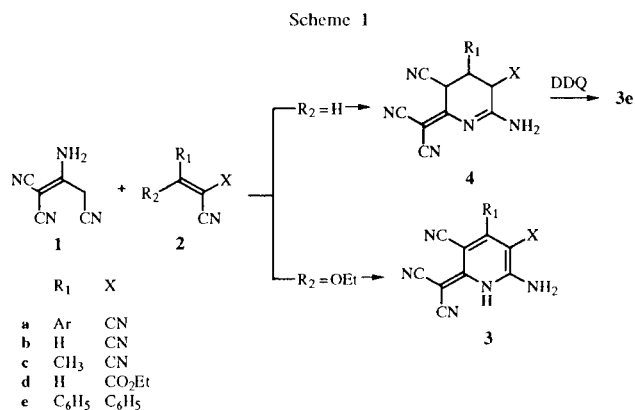


Figure 1



X-ray Crystallographic Work.

Well developed from DMF yellow crystal of **3d** was subjected to the X-ray investigation. The compound crystallizes with a molecule of solvent. Figure 2 shows a view of the molecule with the atomic labelling used in the crystallographic study. Table 1 collects the experimental and crystallographic data and Tables 2,3 and 4 show the geometrical features. The central ring is planar; N12 lies in this plane, while the ethyl ester and the dicyanomethylene group form angles of 2.9(2)^o and

Table 1

Crystal Data, Data Collection and Structure Refinement

Crystal data

Formula	C ₁₂ N ₅ O ₂ H ₉ .CH ₃ CH ₃ NCO
Crystal size (mm)	0.38x0.32x0.21
Symmetry	Monoclinic, P2 ₁ /n
Unit cell determination	Least-squares fit from 57 reflexions (4< θ <32°)
Unit cell dimensions	15.939(2), 8.188(1), 13.421(1) Å β = 107.74(1)°
Packing: V(A ³), Z	1668.3(3), 4
D _c (g. cm ⁻³), M, F(000)	1.3072, 328.330, 688.0
μ (cm ⁻¹)	7.549

Experimental data

Technique	Four circle diffractometer: Seifert XRD 3000S Bisecting geometry Graphite oriented monochromator: Cu K α 1.5418 Å w/2 θ scan
Scanning range for θ	2<2 θ <100
Number of reflexions :	
Measured	1707
Observed	1148 ($I > 2\sigma(I)$ criterion)
Range of hkl	-15/15 0/8 0/13
Absorption	No correction applied

Solution and refinement

Solution	Direct methods
H atoms	Fourier synthesis and geometrical calculations
Refinement	L.s. on Fobs; H atoms fixed.
Variables	217
w-scheme	Empirical as to give no trends in <w Δ^2 F> vs. < F _o > and <sin θ / λ >
Final max. shift/error	0.005
Final R and Rw	0.062, 0.071
Computer and programs	Vax 11/750, MULTAN80 [5], XRAY80 [6], PESOS [7], PARST [8]
Scattering factors	Int. Tables for X-Ray Crystallog [9]
Anomalous dispersion	Int. Tables for X-Ray Crystallog [9]

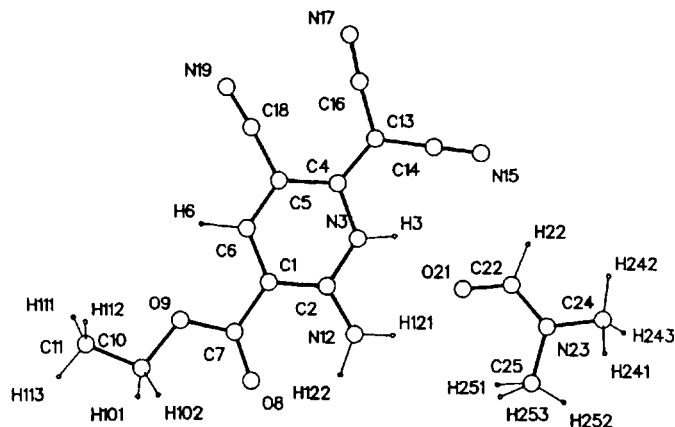


Figure 2. Pluto [10], view of the molecule showing the atomic numbering.

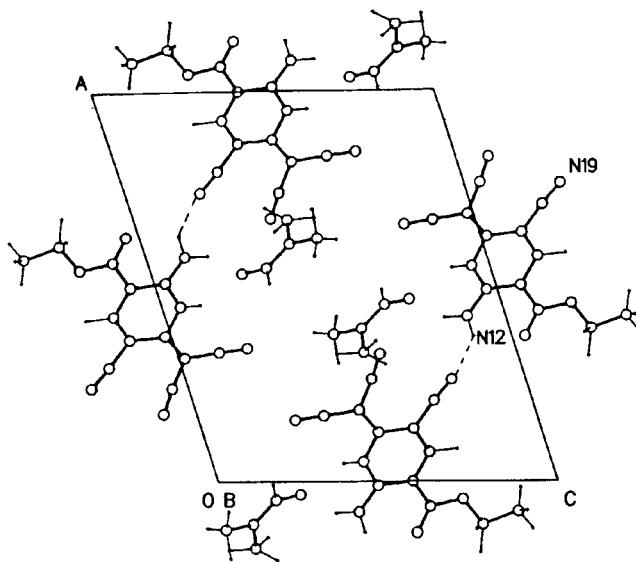


Figure 3. Packing of the molecules viewed down the b axis.

Table 2
Bond distances (Angstrom)

C1 - C2	1.41 (1)	O9 - C10	1.46 (1)
C1 - C6	1.40 (1)	C10 - C11	1.48 (1)
C1 - C7	1.45 (1)	C13 - C14	1.42 (1)
C2 - N3	1.35 (1)	C13 - C16	1.42 (1)
C2 - N12	1.33 (1)	C14 - N15	1.15 (1)
N3 - C4	1.39 (1)	C16 - N17	1.14 (1)
C4 - C5	1.42 (1)	C18 - N19	1.15 (1)
C4 - C13	1.39 (1)	O21 - C22	1.24 (1)
C5 - C6	1.37 (1)	C22 - N23	1.32 (1)
C5 - C18	1.44 (1)	N23 - C24	1.46 (1)
C7 - O8	1.22 (1)	N23 - C25	1.45 (1)
C7 - O9	1.34 (1)		

Table 3
Bond angles (degrees)

C6 - C1 - C7	122.0 (4)	C1 - C7 - O8	125.4 (5)
C2 - C1 - C7	121.0 (4)	O8 - C7 - O9	122.0 (5)
C2 - C1 - C6	116.9 (4)	C7 - O9 - C10	116.9 (4)
C1 - C2 - N12	124.3 (4)	O9 - C10 - C11	106.5 (6)
C1 - C2 - N3	118.8 (4)	C4 - C13 - C16	124.0 (4)
N3 - C2 - N12	116.9 (4)	C4 - C13 - C14	121.9 (5)
C2 - N3 - C4	126.5 (4)	C14 - C13 - C16	113.9 (5)
N3 - C4 - C13	118.8 (4)	C13 - C14 - N15	178.5 (7)
N3 - C4 - C5	113.7 (4)	C13 - C16 - N17	176.5 (6)
C5 - C4 - C13	127.4 (4)	C5 - C18 - N19	176.4 (6)
C4 - C5 - C18	121.7 (4)	O21 - C22 - N23	123.5 (5)
C4 - C5 - C6	121.4 (4)	C22 - N23 - C25	122.2 (5)
C6 - C5 - C18	116.8 (4)	C22 - N23 - C24	120.5 (5)
C1 - C6 - C5	122.5 (4)	C24 - N23 - C25	117.1 (5)
C1 - C7 - O9	112.6 (5)		

Table 4
Hydrogen Bonds

Donor-H	Donor...Acceptor	H...Acceptor	Donor-H.....Acceptor
N3 - H3 0.876 (.004) 1.030	N3O21 (0) 2.790 (.005)	H3...O21 (0) 2.073 (.003) 1.961	N3 - H3...O21 (0) 138.41 (0.29) 135.43 (**)
C6 - H6 1.115 (.005) 1.080	C6...O9 (0) 2.706 (.007)	H6...O9 (0) 2.346 (.004) 2.350	C6 - H6...O9 (0) 96.27 (0.28) 97.13 (**)
N12 - H121 0.920 (.004) 1.030	N12....O21 (0) 2.801 (.006)	H121...O21 (0) 2.021 (.004) 1.936	N12 - H121...O21 (0) 141.58 (0.30) 139.56 (**)
N12 - H122 1.017 (.004) 1.030	N12....O8 (0) 2.732 (.006)	H122...O8 (0) 2.165 (.004) 2.159	N12 - H122...O8 (0) 113.31 (0.23) 112.99 (**)
N12 - H122 1.017 (.004) 1.030	N12....N19 (1) 2.942 (.006)	H122...N19 (1) 2.075 (.005) 2.065	N12 - H122...N19 (1) 141.66 (0.25) 141.43 (**)

(**) Values normalized following G. A. Jeffrey and L. Lewis, *Carbohydr. Res.*, **60**, 179 (1978); R. Taylor and O. Kennard, *Acta Cryst.*, **B39**, 133 (1983).

Equivalent positions:

- (0) X,Y,Z
(1) +X-1/2,-Y+1/2,+Z-1/2

4.3(2)^o respectively with the plane of the six membered ring. Therefore the entire molecule is rather planar, the maxima deviations being 0.13(1)Å for N19 and 0.23(1)Å for C11. The molecule is stabilized by a framework of intermolecular and intramolecular hydrogen bonds between the oxygen atoms and the N atoms of the heterocyclic and the amino groups (see Table 4). The oxygen of the dimethylformamide is connected to N3 through H3 and with N12 through H12/N12 is also interacting with O8 and N19, this one through the symmetry -1/2+x, 1/2-y, -1/2+z. There is another intramolecular hydrogen bond between C6-H6 ... O9 [4]. The packing of the molecules, which are held together by hydrogen bonds and Van der Waals forces, is shown in Figure 3.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1310. ¹H-nmr spectra were recorded on a Varian FT-80 and a Varian Unity 500 spectrometers.

Synthesis of Compounds 4 and 3b,c,d.

A solution of sodium (0.01 g-atom) in ethanol (60 ml),

3-amino-1,1,3-tricyanopropene (0.01 mole) and the corresponding substituted propenenitrile 2 (0.01 mole) was treated as described in each case.

6-Amino-3-cyano-2-dicyanomethylene-4,5-diphenyl-2,3,4,5-tetrahydropyridine (4).

The mixture was refluxed for 45 hours and then left to cool. The solid product formed (2.35 g) on addition over ice-water acidified with drops of 35% hydrochloric acid, was chromatographed on a silica gel column; chloroform elution gave a product (1.8 g, 53%) which recrystallized from ethanol-ethyl acetate yielded crystals of mp 251-253^o; ir (potassium bromide): $\nu = 3440, 3300, 3230$ (NH₂, NH); 2200 (CN); 1640 (C=C, C=N) cm⁻¹; ¹H-nmr (acetone-d₆): for more abundant epimer, $\delta = 4.15$ (1H, dd, J_{H4,H5} = 13 Hz and J_{H4,H3} = 4.5 Hz, H4), 4.40 (1H, d, J_{H3,H4} = 4.5 Hz, H3) and 4.78 (1H, d, J_{H5,H4} = 13 Hz, H5), 7.2-7.9 (m, H_{arom}), 7.58 and 8.88 (2H, NH); for least abundant epimer, $\delta = 4.07$ (dd, J_{H4,H5} = 11 Hz and J_{H4,H3} = 10 Hz, H4), 4.42 (d, J_{H5,H4} = 11 Hz, H5), 4.52 (d, J_{H3,H4} = 10 Hz, H3), 7.2-7.9 (m, H_{arom}), 6.44 and 8.79 (2H, NH).

Anal. Calcd. for C₂₁H₁₅N₅ (337.4): C, 74.76; H, 4.47; N, 20.75. Found: 74.33; H, 4.74; N, 20.94.

6-Amino-3,5-dicyano-2-dicyanomethylene-1,2-dihydropyridine (3b).

The mixture was stirred at room temperature for 24 hours. The solid product thus formed (0.95 g) was recrystallized from ethanol-water (250 ml, 8:2) giving the sodium salt of 3b (0.75 g); this salt was dissolved by heating in ethanol-water (250 ml, 8:2) and acidified with drops of 35% hydrochloric acid giving a precipitate (0.56 g, 26%) of 3b, mp > 300^o; ir (potassium bromide): $\nu = 3370, 3310, 3220$ (NH₂, NH); 2210, 2190 (CN); 1635 (C=C, C=N) cm⁻¹; ¹H-nmr (DMSO-d₆): $\delta = 7.57$ (3H, NH+NH₂), 8.10 (1H, s).

Anal. Calcd. for C₁₀N₄O₆ (208.2): C, 57.69; H, 1.93; N, 40.37. Found: C, 57.66; H, 1.70; N, 40.76.

6-Amino-3,5-dicyano-4-methyl-2-dicyanomethylene-1,2-dihydropyridine (3c).

The reaction mixture was refluxed under nitrogen for 33 hours and then precipitated over ice-water acidified with 35% hydrochloric acid, yielding a precipitate (0.9 g, 40%) of 3c, mp > 300^o; ir (potassium bromide): $\nu = 3430, 3320, 3210$ (NH₂, NH); 2200, 2160 (CN); 1625 (C=C, C=N) cm⁻¹; ¹H-nmr (DMSO-d₆): $\delta = 2.25$ (s, 3H), 6.67 (b, 3H).

Anal. Calcd. for C₁₁H₆N₆ (222.2): C, 59.46; H, 2.72; N, 37.82. Found: C, 59.01; H, 2.41; N, 38.21.

6-Amino-3-cyano-5-ethoxycarbonyl-2-dicyanomethylene-1,2-dihydropyridine (3d).

After refluxing the reaction mixture for 4 hours, a precipitate of the sodium salt of 3d (1.64 g) was formed. The salt was dissolved in ethanol-water (200 ml, 8:2) and acidified with 35% hydrochloric acid. The precipitate which formed (1.37 g) was recrystallized from DMF giving 0.70 g of yellow crystals, yield 31%, mp > 300^o; ir (potassium bromide): $\nu = 3357, 3221$ (NH₂, NH); 2228, 2207 (CN); 1705 (C=O); 1640 (C=C, C=N) cm⁻¹; ¹H-nmr (DMSO-d₆): $\delta = 1.28$ (t, 3H), 4.26 (c, 2H), 8.13 (s, 1H), 7.4-8.5 (b, 3H, NH+NH₂).

Anal. Calcd. for C₁₂H₉N₅O₂ (255.2): C, 56.47; H, 3.55; N, 27.44. Found: C, 55.97; H, 3.70; N, 26.98.

6-Amino-3-cyano-4,5-diphenyl-2-dicyanomethylene-1,2-dihydropyridine (3e).

To a solution of DDQ (0.4 g, 1.8 mmol) in absolute ethanol (40 ml.), **4** (0.33 g, 1 mmol) was added. The mixture was refluxed for 1 hour. The precipitate formed was filtered and washed by refluxing in acetone, giving 0.26 g. (78%) of a pure white solid mp > 300°; ir (potassium bromide): $\nu = 3485, 3361$ (NH₂ + NH), 2224 (CN), 1612 (C=C, C=N) cm⁻¹; ¹H-nmr (DMSO-d₆): $\delta = 6.1-8.3$ (13H, H_{arom} + NH + NH₂).

Anal. Calcd. for C₂₁H₁₃N₅ (335.4): C, 75.21; H, 3.91; N, 20.88. Found: C, 75.13; H, 4.25; N, 21.03.

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