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Reaction of 4-Cyano-1,3-dihydroxy-5,6,7,8-tetrahydroisoquinolines with Vilsmeier Reagent: Structure and Mechanism of Formation of [2,7]naphthyridines[1]

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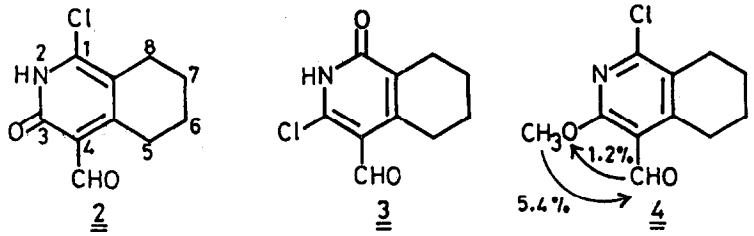
ABSTRACT: Reaction of 4-cyano-1,3-dihydroxy-5,6,7,8-tetrahydroisoquinoline 1, with Vilsmeier reagent gave the chloro aldehyde 2, dichloro [2,7]naphthyridine, 5 and monochloro [2,7]naphthyridine 8, identified by spectral data [Mass, ^{1}H & ^{13}C NMR, NOE and HETERO COSY]. Structure 5 has been confirmed by X-ray crystal structure analysis. Reaction of 1a-f, similarly, gave the corresponding compounds 2a-f, 5a-f and 8a-f. The starting tetrahydroisoquinolines, 1a-f were synthesised by the reaction of the corresponding ß-keto esters with cyanoacetamide. Reaction of 8 with $POCl_3$ gave in almost quantitative yield, the dichloro compound 5. An acceptable mechanism has been proposed for the formation of the products.

The Vilsmeier reagent,[2-9] a mild reagent for formylating a variety of substrates, is also useful to bring about many substitutive cyclization and condensation to make it a versatile synthetic tool. This has been applied to many carbocycles as well as hetero aromatic, hetero nonaromatic[2-9] systems. We have recently reported[10] the novel decyanation reaction of 4-cyano-1,3-dialkoxy-5,6,7,8-tetrahydroisoquinolines under Vilsmeier reaction conditions. In continuation of this work, we have now studied the reaction of 4-cyano-1,3-dihydroxy-5,6,7,8-tetrahydroisoquinolines with Vilsmeier reagent[$POCl_3$-DMF] and the interesting results obtained leading to a facile synthesis of [2,7]naphthyridine ring system are discussed in this paper.

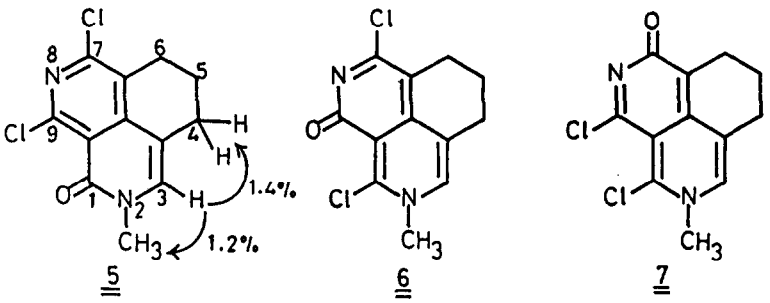
Reaction of 4-cyano-1,3-dihydroxy-5,6,7,8-tetrahydroisoquinoline[11] (1 mmol) with anhydrous $POCl_3$ (6 mmol) and DMF (1.6 ml) at 90° for 9 hrs[12] followed by treatment with sodium acetate resulted in the formation of a

mixture of compounds from which three compounds, designated A, B and C, have been isolated by rigorous column chromatography followed by preparative TLC. The least polar compound A, (33%) showed signals in the ^1H NMR at δ 10.41 (-CHO) & 12.26 (D_2O exchangable) in addition to the upfield protons of the tetrahydroisoquinoline moiety. On the basis of the spectral data, two structures (2 & 3) could be considered for this compound. The long range coupled heteronuclear (^{13}C-^1H) correlation spectrum[13] (LRCOSY) of compound A revealed long range couplings (^3J) between aromatic carbon C-1 (δ 157.61) with the C_8 benzylic protons(δ2.73), aromatic carbon C-4 (δ111.67) with C_5 benzylic protons(δ 3.14) and the C-3 amide carbonyl (>N-C=O, δ 163.57) with the aldehyde proton. On this basis, structure 2 was assigned to compound A. Methylation of compound 2 in presence of Ag_2O/CH_3I gave a methoxy derivative. (4, δ 4.01) which showed significant NOE (5.3%) to the aldehyde proton confirming the assigned structure 2.



2 3 4

The medium polar compound B (15%) analysing for $C_{12}H_{10}ON_2Cl_2$ showed an IR absorption at 1665 cm^{-1}. The significant signals in the ^1H NMR spectrum are at δ 3.56 (s,3H) and 7.14(t,1H,J=1.2Hz)[14] in addition to signals in the upfield region. The signal at δ 7.14 showed considerable NOE to the signals at δ 3.56 and 2.68(dt, J=7.2Hz, J=1.2Hz, 2H). On the basis of the above spectral data, three alternate structures, 5, 6 & 7 could be considered for this compound. A fully coupled heteronuclear (^{13}C-^1H) correlation spectrum[15] (FUCOUP) of compound B revealed long range couplings (^3J) of the C-3 carbon (δ 134.95) with the N-CH_3 (δ 3.56) as well as the benzylic C_4-2H (δ 2.68) protons. Of the two downfield carbons carrying chlorines (δ149.14 and 148.86), only one (δ148.86) showed long range (^3J) coupling to the benzylic C_6-2H protons (δ 2.98). Further, the long range couplings (^3J) of the amide carbonyl (δ 163,83) with N-CH_3 as well as C_3-H



proton (δ7.14) are also observed. On this basis, structure 5 was tentatively assigned to compound B. X-ray crystal structure analysis (Fig.1) unambiguously confirmed this structure.

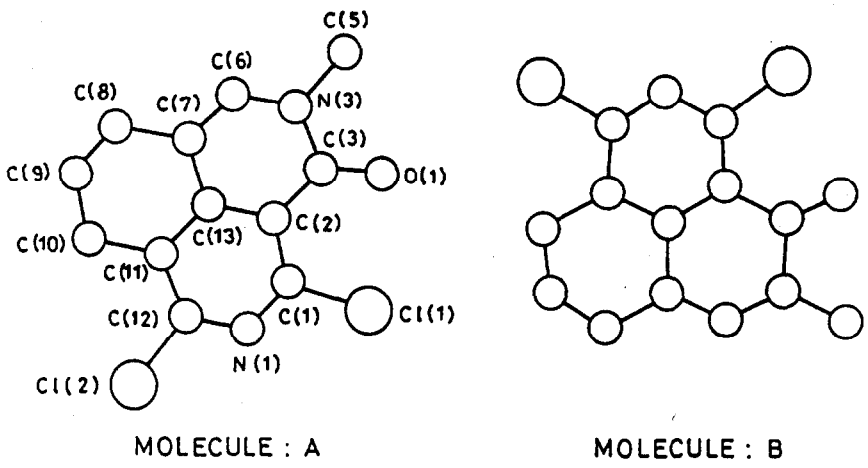


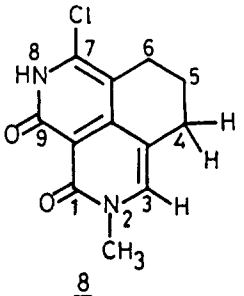
Fig.1 A PLUTO[16] diagram of the two molecules in the asymmetric unit (Crystallographic numbering used).

The most polar compound C (8%) analysing for $C_{12}H_{11}O_2N_2Cl$ also showed the presence of an amide carbonyl (IR, 1659 cm^{-1}). In the ^1H NMR spectrum, compound C showed a broad signal at δ 13.25 (1H, D_2O exchangable) in addition to all the signals seen in the spectrum of compound 5. Silver salt methylation (CH_3I) of compound C gave a methoxy derivative. A long range coupled heteronuclear (^{13}C-^1H) correlation spectrum[13]

Table - 1. Spectroscopic and analytical data of 1a-f

Compound	m.p. (°C)	IR (cm^{-1})	^1H NMR (90 MHz, DMSO-d_6)	Analytical data	Mass (% intensity)
1a	286	3346 2224 1629	1.13(d,3H),1.21-1.84 (m,3H),2.32-3.22(m,4H), 7.88 (bs, 2H).	Calcd for $C_{11}H_{12}N_2O_2$ C,64.70;H,5.88;N,13.73. Found: C,64.32;H,5.90;N,13.52.	
1b	246	3418 2218 1629	1.12(d,3H),1.17-2.15 (m,3H),2.28-3.18(m,4H), 7.78 (bs, 2H).	Calcd for $C_{11}H_{12}N_2O_2$ C,64.70;H,5.88;N,13.73. Found: C,64.52;H,5.82;N,13.62.	204(M^+,75) 189(60) 162(100) 134(30)
1c	242	3364 2224 1623	1.06(t,3H),1.26-2.26 (m,5H),2.76-3.34(m,4H), 7.64 (bs, 2H).	Calcd for $C_{12}H_{14}N_2O_2$ C,66.06;H,6.42;N,12.84. Found: C,65.95;H,6.39;N,12.78.	
1d	302	3360 2224 1615	1.02(s,9H),1.24-2.16 (m,3H),2.52-2.92(m,4H), 7.62 (bs, 2H).	Calcd for $C_{14}H_{18}N_2O_2$ C,68.29;H,7.32;N,11.38. Found: C,68.03;H,7.48;N,11.05.	246(M^+,40) 231(15) 190(70) 175(25) 57(100)
1e	296	3300 2230 1644	2.03(qn,3H),2.78(t,2H) 3.42(t,2H),7.05(bs,2H)	Calcd for $C_9H_8N_2O_2$ C,61.36;H,4.55;N,15.91. Found: C,61.19;H,4.57;N,15.78.	
1f	269	3586 2226 1635	1.44-1.72(m,6H),2.94 (t,2H),3.02(t,2H), 7.18 (bs, 2H).	Calcd for $C_{11}H_{12}N_2O_2$ C,64.70;H,5.88;N,13.73. Found: C,64.59;H,5.82;N,13.64.	

(LRCOSY) of compound C revealed ^{3}J coupling of C-7 (δ 150.41) with the benzylic C_6-2H protons (δ 2.84). Also the C-3 carbon (δ 132.89) correlated with the N-CH_3 (δ3.59) as well as C_4-2H protons (δ 2.66). On the basis of the spectral data, structure 8 was tentatively assigned to compound C in preference to the alternate structure 9. The methoxy derivative could therefore be represented by structure, 10.



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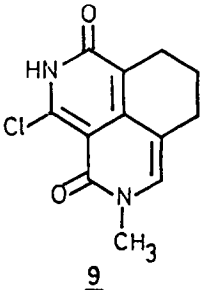

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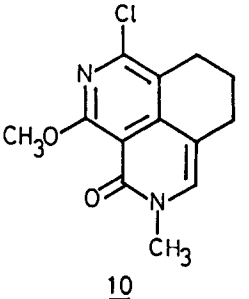

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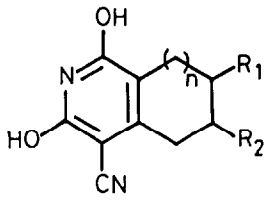
In order to explore the generality of this reaction, we carried out the reaction with a variety of substrates,1a-f. These compounds (Table-1) could be prepared by the reaction of the corresponding ß-keto esters with cyanoacetamide by the general method.[11]

Reaction of 4-cyano-1,3-dihydroxy-5,6,7,8-tetrahydroisoquinolines (1a-f) with $POCl_3$/DMF at 90° followed by the workup, gave the expected compounds 2a-f, 5a-f & 8a-f, characterised by spectral data.



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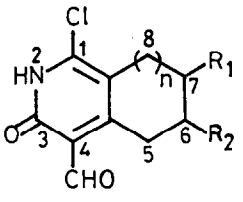

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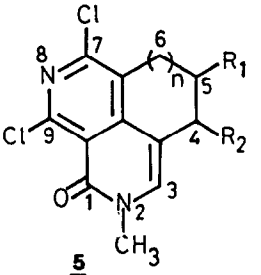

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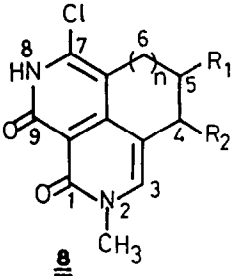

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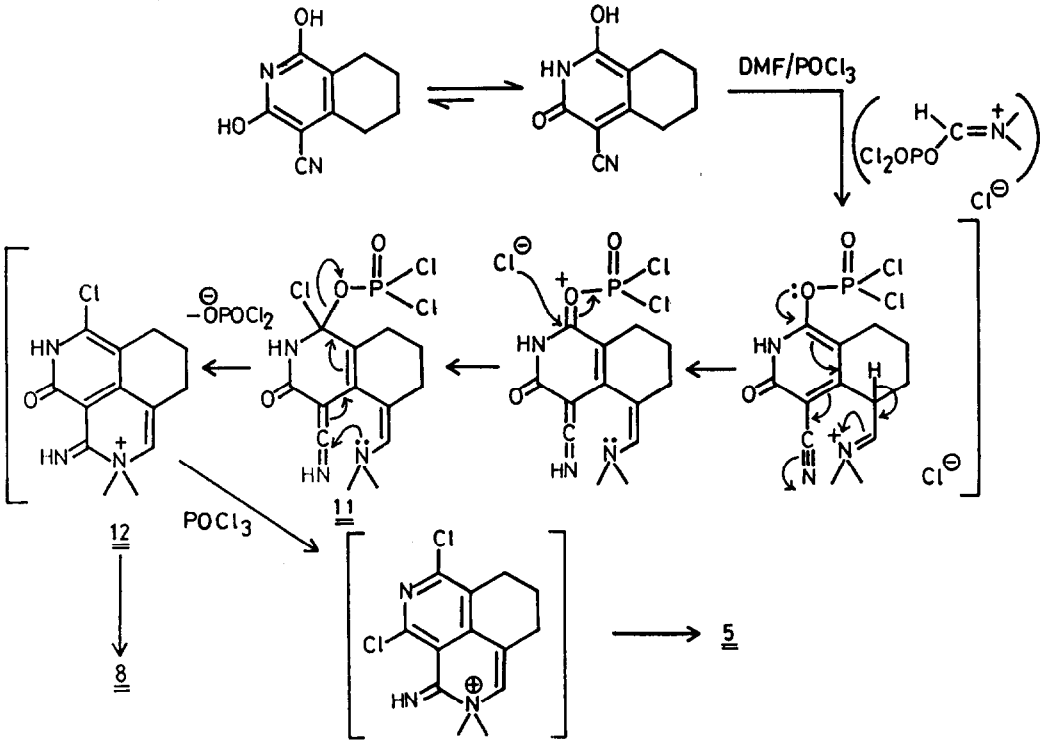
(a) R_1 = H , R_2 = CH_3 ; n = 1 (c) R_1 = Et , R_2 = H ; n = 1 (e) R_1 = R_2 = H ; n = 0

(b) R_1 = CH_3, R_2 = H ; n = 1 (d) R_1 = t-Bu , R_2 = H ; n = 1 (f) R_1 = R_2 = H ; n = 2

MECHANISM OF THE REACTION

(a) Chloro aldehyde 2: The formation of the chloro aldehyde 2 could be visualised through a decyanation followed by chlorination reaction as reported[10] by us in the synthesis of 1-chloro-3-alkoxy-4-formyl-5,6,7,8-tetrahydroisoquinolines.

(b) [2,7]naphthyridines 5 & 8: As seen from the scheme, the formation of the [2,7]naphthyridine ring system in 5 & 8 from 1 could proceed by the initial attack of the Vilsmeier complex at the benzylic C-5 position. Facile attack at the benzylic carbon in Vilsmeier reactions is well documented in the literature.[17,18] Chlorination followed by attack of the lone pair of nitrogen on to the ketenimine (11) with concomitant elimination of dichlorophosphate group results in the formation of the intermediate 12, which gives compound 8 on workup. Formation of the dichloro compound 5 can be visualised by further chlorination of the



Scheme

intermediate 11, followed by workup. The fact that the isolated compound 8, gives compound 5, in almost quantitative yield, on reaction with $POCl_3$ substantiates our conjecture. Reaction of 4-cyano-1,3-dichloro-5,6,7,8-tetrahydroisoquinoline with $POCl_3$/DMF at 90° followed by work up, gave back the starting material. This confirms our assumption that the attack of Vilsmeier complex is the first step of the reaction.

Reaction of 4-cyano-1,3-dihydroxy-5,6,7,8-tetrahydroisoquinolines with Vilsmeier reagent, thus, led to a convenient onestep synthesis of [2,7]naphthyridine skeleton. Alkaloids[19] containing this ring system possess biological activity and few syntheses of this ring system have been reported.[20] The biological activity of the synthesised compounds as also further extension of this reaction would be explored.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR (cm^{-1}) were recorded on Perkin-Elmer Model 781 spectrometer. NMR spectra were recorded on a Varian T-60, Jeol FX-90Q, 22.49MHz (^{13}C), Bruker ACF-200, 50.31 MHz (^{13}C), Bruker WH-270, 67.87 MHz (^{13}C) and Bruker WH-400, 100.61 MHz (^{13}C) spectrometers with Me_4Si (TMS) as internal standard (δ = 0 ppm). MS (70eV) were recorded on a Jeol MS-DX 303 spectrometer fitted with a built-in direct inlet system. Analytical and preparative TLC were carried out using silica gel. Column chromatography was carried out using silica gel.

Preparation of tetrahydroisoquinolines 1a-f

General Procedure: A solution of potassium hydroxide (0.1 mol) in 20 ml of methanol was added over 1 hr at room temperature to a stirring mixture of 2-carbethoxy cycloalkanones, (0.1 mol) and cyanoacetamide (0.1 mol) in 200 ml of methanol. The reaction mixture was refluxed for 8 hrs. Upon cooling the suspension, precipitated salt was filtered, washed with methanol and dissolved in hot water. The hot solution was filtered and immediately brought to pH 2-3 with concentrated hydrochloric acid. After 2 hrs, the resulting precipitate was filtered, washed with water, dried and crystallised (EtOH). (Table-I) (yield, 60-70%)

Reaction of tetrahydroisoquinolines with Vilsmeier Reagent

General Procedure: Substrate (2 mmol) was dissolved in dry N,N-dimethylformamide(DMF) (3.2 ml) and stirred at 0°C. Freshly distilled anhydrous phosphoryl chloride (1.84g, 12 mmol) was added dropwise and stirred for 0.5 hr. The mixture was heated at 90°C for 9 hrs. It was cooled to 0°C, quenched by adding saturated sodium acetate solution and warmed on a steam bath for 30 min. Then it was cooled and extracted with chloroform. The chloroform extract was thoroughly washed with water and dried over anhydrous sodium sulphate. The product obtained after removal of solvent yielded 60% crude material, which was chromatographed over silica gel. Elution with $CHCl_3$ gave the chloro aldehyde, 1. Further elution with $CHCl_3$-EtOAc (9:1) gave a mixture of [2,7]naphthyridines 5 & 8, which was again separated by preparative TLC [$CHCl_3$-EtOAc; 8:1].

Reaction of 1: gave 1-chloro-4-formyl-5,6,7,8-tetrahydroisoquinolin-3(2H)

-one, 2 (least polar, 140mg, 33%) m.p. 169°C (chloroform); IR (Nujol) 3335, 1690, 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32-1.86 (m, 4H), 2.73 (t, J=6.3Hz, 2H), 3.14 (t, J=6.3Hz, 2H), 10.41(s, 1H, -CHO), 12.26(bs, 1H,-NH); ^{13}C NMR (100.61MHz, $CDCl_3$) δ 21.42(t),21.81(t),25.63(t),26.38(t),111.67(s), 124.57(s), 154.01(s), 157.61(s), 163.57(s), 193.11(d); MS m/e (relative intensity) 213(M+2,25%),211(M^+,75),196(20),183(100),168(20),91(25);Analysis cacld for $C_{10}H_{10}O_2NCl$: C,56.87; H,4.74; N,6.64. Found: C,56.65; H,4.79; N, 6.49; 5,6-dihydro-4H-benzo[de]-7,9-dichloro-2-methyl[2,7]naphthyridin-1-one, 5 (medium polar, 80mg, 15%) m.p. 228°C (chloroform);IR (Nujol) 1665, 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.96(qn, J=6.7Hz, 2H), 2.68(dt,J=7.2Hz, J=1.2Hz,2H),2.98(t,J=6.7Hz,2H),3.56(s,3H,-NMe), 7.14(t,J=1.2Hz,1H); ^{13}C NMR (67.87MHz, $CDCl_3$) δ21.41(t), 26.01(t),26.56(t), 37.50(q),111.10(s), 126.50 (s), 134.95(d), 145.25(s), 148.86(s),149.14(s),159.34(s), 163.83(s); MS m/e (relative intensity) 272(M+4, 11%), 270(M+2, 66), 268(M^+, 100), 253(25); Analysis calcd for $C_{12}H_{10}ON_2Cl_2$: C,53.73; H,3.73; N,10.45. Found: C,53.52; H,3.80;N,10.22; 5,6-dihydro-4H-benzo[de]-7-chloro-2-methyl[2,7]naphthyridin -1,9(8H)-dione, 8 (highly polar, 30mg, 8%): m.p. 239°C (chloroform); IR (Nujol) 1659, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ1.93(t, J=6.2Hz, 2H), 2.66(t, J=6.2Hz, 2H), 2.84(t, J=6.2Hz, 2H), 3.59(s, 3H, -NMe), 7.04(t, J=1.4Hz, 1H), 13.25(bs, 1H, -NH); ^{13}C NMR (100.61MHz, DMSO-d_6) δ22.36(t), 28.11(t), 29.74(t), 36.45(q), 104.28(s), 115.66(s), 119.13(s), 132.89(d), 143.40(s), 150.41(s), 163.23(s), 163.88(s); MS m/e (relative intensity) 252(M+2, 33%), 250(M^+, 100), 213(15), 188(15), 89(10); Analysis calcd for $C_{12}H_{11}O_2N_2Cl$: C,57.60; H,4.40; N,11.20. Found: C,57.32; H,4.49; N,11.15.

Compound 2 (422mg, 2 mmol), silver oxide (232mg, 1 mmol) and methyl iodide (40% molar excess) were refluxed in benzene (15 ml) for 8 hrs. The reaction mixture was cooled and the silver iodide formed was filtered off. The benzene solution was washed with an ice-cold solution of 10% NaOH followed by water and dried over Na_2SO_4. The crude product obtained after the removal of solvent was purified by column chromatography (eluent: Benzene) to give the methylated compound 4 (160mg, 71%); m.p. 211°C (benzene-hexane); IR (nujol) 1690, 1655 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.73-1.90 (m, 4H), 2.53-2.83 (t, J=7.2Hz, 2H), 2.90-3.23 (t, J=7.2Hz, 2H), 4.01 (s, 3H, $-OCH_3$), 10.41 (s, 1H, -CHO); MS m/e 225, 227 (M^+, 100, 33), 212(15), 210(44), 198(13), 196(28), 190(8); Analysis calcd for $C_{11}H_{12}O_2NCl$ C,58.67; H,5.33; N,6.22. Found: C,58.44; H, 5.22; N,6.24.

Reaction of 1a : gave 1-chloro-4-formyl-6-methyl-5,6,7,8-tetrahydroisoquinolin-3(2H)-one, 2a (least polar, 160mg, 36%) m.p. 175°C (chloroform); IR (nujol) 1689, 1632 cm^{-1}; ^1H NMR (90MHz, $CDCl_3$) δ 1.14 (d, J=7.2Hz, 3H, 6-Me), 1.27-1.97 (m, 3H), 2.42-3.44 (m, 4H), 10.41 (s, 1H, Ar-CHO), 12.28 (bs, 1H, -CONH), ^{13}C NMR (22.49 MHz, $CDCl_3$) δ21.40 (q), 26.27 (t), 27.57 (d), 29.74 (t), 33.75 (t), 111.54(d, J=3.6Hz), 124.11 (s), 154.01 (s), 156.40(s), 163.55(s), 193.02 (d); MS m/e (relative intensity) 227(M+2,17%), 225(M^+, 51), 210(100), 197(20), 91(20); Analysis calcd for $C_{11}H_{12}O_2NCl$: C, 58.66; H, 4.88; N, 6.22. Found C,58.45; H,4.79; N,6.19; 5,6-dihydro -4H-benzo[de]-7,9-dichloro-2,4-dimethyl[2,7]naphthyridin-1-one, 5a (medium polar, 85mg, 15%): m.p. 186°C (chloroform); IR (nujol) 1665, 1625 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ1.29 (d, J=7.2Hz, 3H, 4-Me), 1.58-2.03 (m, 2H), 2.87-3.04 (m, 3H), 3.58 (s, 3H, -CONMe), 7.13 (d, J=1.2Hz, 1H); ^{13}C NMR (67.87 MHz, $CDCl_3$) δ19.74 (q), 24.35 (t), 28.58 (d), 29.76 (t), 37.51 (q), 115.93 (s), 116.12 (s), 125.78 (s), 133.77 (d), 144.58 (s), 148.75 (s), 149.12(s), 159.02 (s); MS m/e (relative intensity) 286(M+4,5%),284(M+2,30), 282(M^+,45),224(25); Analysis calcd for $C_{13}H_{12}ON_2Cl_2$: C,55.32;H,4.26;N,9.93. Found: C, 55.12; H, 4.10; N, 9.82; 5,6-dihydro-4H-benzo[de]-7-chloro-2,4-dimethyl[2,7]naphthyridin-1,9(8H)-dione, 8a (highly polar, 35mg, 7%) ; m.p. 218°C; IR (nujol) 1665, 1625 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, J=6.9Hz, 3H, 4-Me), 1.61-1.75 (m, 2H), 2.64-3.03 (m, 3H), 3.61 (s, 3H, -CONMe), 7.05 (d, J=1.2Hz, 1H), 13.34 (bs, 1H, -CONH); Analysis calcd for $C_{13}H_{13}O_2N_2Cl$: C,59.10; H,4.92; N,10.61. Found C,59.02; H,4.89; N,10.45.

Reaction of 1b : gave 1-chloro-4-formyl-7-methyl-5,6,7,8-tetrahydroisoquinolin-3(2H)-one, 2b (least polar, 155mg, 34%); m.p. 122°C; IR (nujol) 1686, 1632 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.03 (d,J=7.2Hz,3H,7-Me), 1.27-2.35 (m, 3H), 2.80-3.47 (m, 4H), 10.32 (s, 1H, -CHO), 12.24 (bs, 1H,-CONH); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 21.61 (q), 25.84 (t), 28.10 (t), 29.41 (t), 34.62 (d), 111.76 (d, J=9.6Hz), 124.44 (s), 154.12 (s), 155.6 (s), 163.44(s), 193.24(d); MS m/e (relative intensity) 227(M+2,33%),225(M^+,100), 210(85), 197(95), 182(45), 91(20); Analysis calcd for $C_{11}H_{12}O_2NCl$ C,58.66; H,4.88; N,6.22. Found: C,58.62; H,4.83; N,6.20; 5,6-dihydro-4H-benzo[de]-7,9-dichloro-2,5-dimethyl[2,7]naphthyridin-1-one,5b(medium polar,75mg,13%); m.p. 229°C; IR (nujol) 1665, 1615 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.18 (d, J=7.2Hz, 3H, 5-Me),1.82-2.19(m, 1H),2.21-3.25(m, 4H),3.56(s,3H,-CONMe), 7.13 (t, J=1.2Hz, 1H); MS m/e (relative intensity) 286(M+4,5%),284(M+2,30), 282(M^+,45), 267(100), 238(20); Analysis calcd for $C_{13}H_{12}ON_2Cl_2$: C,55.32; H,4.26; N,9.93. Found: C,55.17; H,4.17; N,9.77; 5,6-dihydro-4H-benzo[de]-7-chloro-2,5-dimethyl[2,7]naphthyridin-1,9(8H)-djone, 8b (highly polar, 38mg, 7%); m.p. 221°C; IR (nujol) 1662, 1625 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ1.17 (d, J=6.6Hz, 3H, 5-Me) 1.84-2.17 (m, 1H), 2.29-3.34 (m, 4H), 3.55 (s, 3H, -CONMe), 7.02 (d, J=1.2Hz, 1H), 13.21 (bs, 1H, -CONH); MS m/e (relative intensity) 266(M+2,33%),264(M^+,100),223(95),167(10), 77(20); Analysis calcd for $C_{13}H_{13}O_2N_2Cl$: C,59.10; H,4.92; N,10.61. Found: C,58.98;H,4.78;N,10.38.

Reaction of 1c: gave 1-chloro-4-formyl-7-ethyl-5,6,7,8-tetrahydroisoquinolin-3(2H)-one, 2c (least polar, 162mg, 34%); m.p. 125°C; IR (nujol) 1680, 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.08 (t, J=6.2Hz, 3H, 7-CH_2CH_3), 1.32-2.35 (m, 5H), 2.84-3.46 (m, 4H), 10.32 (s, 1H, -CHO), 12.36 (bs, 1H, -CONH); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 11.21(q), 25.95(t), 27.03 (t), 28.76(d), 32.56(t), 34.62 (t), 111.87 (d, J=9.6Hz), 124.33 (s), 154.66 (s), 156.18(s), 163.44(s), 193.02(d); MS m/e (relative intensity) 241(M+2,22%), 239 (M^+, 66), 210 (100), 196(25), 182(20), 91(20) ; Analysis calcd for $C_{12}H_{14}O_2NCl$: C, 60.25; H, 5.86; N, 5.86. Found: C, 59.98; H, 5.82; N, 5.83; 5,6-dihydro-4H-benzo[de]- 7,9-dichloro-5-ethyl-2-methyl[2,7]naphthyridin-1-one, 5c (medium polar, 90mg, 15%); m.p. 178°C; IR (nujol) 1668, 1632 cm^{-1}; ^1H NMR (270 MHz,$CDCl_3$) δ 1.03 (t, J=6.9Hz, 3H, 7-CH_2CH_3), 1.25-1.87(m, 3H), 2.15-3.22 (m, 4H), 3.54 (s, 3H, -CONMe), 7.13 (t, J=1.2Hz, 1H); ^{13}C NMR (67.87MHz, $CDCl_3$) δ 11.21 (q), 28.01 (t), 31.36 (d), 32.23 (t), 33.75 (t), 37.32 (q), 110.78 (s), 116.09 (s), 126.06 (s), 134.95 (d), 144.91 (s), 148.49 (s), 149.17(s), 158.78(s); MS m/e (relative intensity) 300(M+4,11%), 298(M+2,66),296(M^+,100), 281(5), 218(20); Analysis calcd for $C_{14}H_{14}ON_2Cl_2$ C, 56.76; H, 4.73; N, 9.46. Found: C, 56.23; H, 4.54; N, 9.22; 5,6-dihydro-4H-benzo[de]-7-chloro-5-ethyl-2-methyl[2,7]naphthyridin-1,9(8H)-djone, 8c (highly polar, 34mg, 6%); m.p. 209°C; IR (nujol) 1668, 1615 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.01 (t, J=6.6Hz, 7-CH_2CH_3), 1.25-1.97 (m, 3H), 2.16-3.15 (m, 4H), 3.58(s,3H,-CONMe), 7.02 (t, J=1.2Hz, 1H), 13.18 (bs, 1H, -CONH); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 11.54 (q), 28.33(t), 31.36(t), 31.69(t), 34.72 (d), 36.57 (q), 104.39 (s), 114.79 (s), 118.37 (s), 133.10 (d), 143.83 (s), 150.03(s), 163.44(s), 163.98(s); MS m/e (relative intensity) 280(M+2,33%), 278(M^+, 100), 224(30), 156(10), 42(20); Analysis calcd for $C_{14}H_{15}O_2N_2Cl$ C,60.43; H,5.40; N,10.10. Found: C, 60.18; H, 5.32; N, 10.01.

Reaction of 1d: gave 7-t-butyl-1-chloro-4-formyl-5,6,7,8-tetrahydroisoquinolin-3(2H)-one, 2d (least polar, 165mg, 31%); m.p. 135°C; IR (nujol) 1678, 1615 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1,06 (s, 9H, t.Bu), 1.22-2.48 (m, 3H), 2.82-3.62 (m, 4H), 10.34 (s, 1H, -CHO); 12.22 (bs,1H, -CONH) ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 22.59(t), 26.92(q), 28.00(d), 32.23(s), 43.28 (t), 111.76 (d, J=9.6Hz), 124.76 (s), 154.66 (s), 155.86 (s), 163.12 (s), 192.91 (d); MS m/e (relative intensity) 269 (M+2, 33%), 267 (M^+, 100), 251(15), 210(45), 196(20), 182(15), 57(45); Analysis calcd for $C_{14}H_{18}O_2NCl$ C,62.92; H,6.74; N,5.24. Found: C,62.88; H, 6.69; N, 5.22; 5,6-dihydro-4H-benzo[de]-5-t-butyl-7,9-dichloro-2-methyl[2,7]naphthyridin-1-one,5d (medium polar, 78mg, 12%); m.p. 235°C; IR (nujol) 1658, 1632 cm^{-1}; ^1H NMR (200 MHz,

$CDCl_3$) δ 1.03 (s, 9H, t.Bu), 2.13-2.37 (m, 1H), 2.55-3.33 (m, 4H), 3.55 (s, 3H, -CONMe), 7.15 (t, J=1.2Hz, 1H); ^{13}C NMR (50.31MHz, $CDCl_3$) δ 27.05 (q), 27.84 (d), 32.16 (t), 37.35(q), 42.79 (s), 111.87 (s), 116.31 (s), 126.99 (s), 134.38 (d), 144.70 (s), 148.73 (s), 159.13(s); MS m/e (relative intensity) 328(M+4,11%), 326(M+2,66), 324(M^+,100), 309(5),267(55); Analysis calcd for $C_{16}H_{18}ON_2Cl_2$: C,59.26; H,5.56; N,8.64. Found: C,59.10; H,5.38; N, 8.43; 5,6-dihydro-4H-benzo[de]-5-t-butyl-7-chloro-2-methyl[2,7]naphthyridin -1,9(8H)-dione, 8d (highly polar,36mg, 6%); m.p. 243°C ; IR (nujol) 1668, 1590 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ1.03 (s,9H,t.Bu), 1.33-1.63(m,1H), 2.25-2.44(m,2H), 2.71-3.15(m,2H), 3.59(s,3H,-CONMe), 7.05 (t,J=1.2Hz,1H), 13.16 (bs,1H,-CONH); ^{13}C NMR(22.49MHz, $CDCl_3$) δ27.36, 28.11, 29.74, 32.45, 36.45, 43.03, 104.28, 115.66, 119.13, 132.89,143.40,150.41,163.23,163.88; Analysis calcd for $C_{16}H_{19}O_2N_2Cl$: C,62.74;H,6.21;N,9.15. Found:C,62.59;H,6.06;N,9,10.

Reaction of 1e: gave 2-chloro-5-formyl-3,4-cyclopentenopyridin-6(1H)-one,2e (least polar, 80mg, 20%); m.p. 162°C; IR (nujol) 1690, 1636 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.28 (qn, 2H), 3.03 (t, J=6.8Hz, 2H), 3.21 (t, J=6.8Hz, 2H), 10.33 (s, 1H, -CHO), 12.23 (bs, 1H, -CONH) ; Analysis cacld for $C_9H_8O_2NCl$: C, 54.82; H, 4.06; N,7.11. Found: C,54.69; H,4.01; N,7.08; 6,8-dichloro-4,5-dihydro-2-methyl[2,7]acenaphthyridin-1-one, 5e (*medium* polar, 90mg, 18%); m.p. 256°C; IR (nujol) 1660, 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 3.14-3.33(m, 4H),3.57(s, 3H, -CONMe),7.17(t, J=1.7Hz, 1H); MS m/e (relative intensity) 258(M+4,11%),256(M+2,66),254(M^+,100),218(15), 184(20), 155(10),71(25); Analysis cacld for $C_{11}H_8ON_2Cl_2$: C,51.97; H,3.15; N,11.02. Found : C, 51.87; H, 3.12; N, 10.98 ; 6-chloro-4,5-dihydro-2-methyl[2,7] acenaphthyridin-1,8(7H)-dione, 8e (highly polar, 46mg, 10%); m.p. 264°C; IR (nujol) 1666, 1595 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.12-3.41 (m, 4H), 3.59 (s, 3H,-CONMe), 7.03 (t, J=1.6Hz, 1H), 13.13 (bs, 1H,-CONH); Analysis calcd for $C_{11}H_9O_2N_2Cl$:C,55.93;H,3.81;N,11.86. Found:C,55.87;H,3.72;N,11.78.

Reaction of 1f: gave 2-chloro-5-formyl-3,4-cycloheptenopyridin-6(1H)-one,2f (least polar, 160mg, 36%); m.p. 148°C;IR (nujol) 1692, 1638 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.52-1.81 (m, 6H), 2.97-3.25 (m, 4H), 10.37(s, 1H,-CHO), 12.45 (bs, 1H, -CONH); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 26.38(t), 28.11 (t), 29.41(t), 31.15(t), 113.17(d, J=9.6Hz), 129.31(s), 152.82 (s), 161.82 (s), 163.66(s), 193.24(d); MS m/e (relative intensity) 227(M+2,33%),225(M^+,100), 207(35), 197(35), 182(35), 172 (75) ; Analysis calcd for $C_{11}H_{12}O_2NCl$: C,58.67; H,5.33; N,6.22. Found: C, 58.58; H, 5.23; N, 6.20; 3a,7a-butano-8,10-dichloro-2-methyl[2,7]naphthyridin-1-one, 5f(medium polar, 60mg, 11%); m.p. 246°C; IR (nujol)1660, 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.93- 2.64 (m, 4H), 3.12-3.34 (m, 4H), 3.56 (s, 3H, -CONMe), 7.16 (t, J=1.3Hz, 1H); Analysis calcd for $C_{13}H_{12}ON_2Cl_2$: C, 55.32; H,4.26; N,9.93. Found: C, 55.12; H, 4.09; N, 9.98; 3a,7a-butano-8-chloro-2-methyl[2,7]naphthyridin-1,10(9H) -dione, 8f (highly polar, 30mg, 6%); m.p. 253°C;IR (nujol) 1667, 1595 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.91-2.62 (m, 4H), 3.09-3.36 (m, 4H), 3.56(s, 3H, -CONMe), 7.06 (t, J=1.3Hz, 1H), 13.12 (bs, 1H, -CONH); Analysis calcd for $C_{13}H_{13}O_2N_2Cl$ C,59.10; H,4.92; N,10.61. Found: C,59.08; H,4.88; N,10.48.

Chlorination of 8 with $POCl_3$: A mixture of compound 8 (250mg, 1 mmol) and $POCl_3$ (230mg, 1.5 mmol) was refluxed in 20 ml of benzene for 3 hrs. The reaction mixture was cooled, washed with water and dried over Na_2SO_4. The crude product obtained was purified by column chromatography (eluent: chloroform) to give chlorinated compound 5 (240mg, 90%). This was identical (mixed m.p., comparision IR & NMR) with the dichloro compound 5.

X-ray analysis of compound 5

$C_{12}H_{10}ON_2Cl_2$, monoclinic, $P2_1$, a=8.797 (1), b=7.019 (1), c=18.219 (2) A, β=95.9°(1); λ =1.5418A (CuKα), 2536 intensities collected on a CAD4 diffractometer, 2112 observed reflections I>3σ(I). The structure was solved using MULTAN87[21] and refined by full matrix least squares using SHELEX76.[22]

Hydrogen atoms were stereochemically fixed with an isotropic thermal factor equivalent to that of the bonded atoms. Final R factor is 0.073. There are two molecules in the asymmetric unit and on refinement it was found that one of the atoms C(9') of molecule B which has a large temperature factor [U_{iso} = 0.1265(70)] and appears to be disordered. Atomic coordinates, distances and angles will be deposited with the Cambridge Crystallographic Data Bank.

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