A SPONTANEOUS RING CLOSURE REACTION AS A NEW ROUTE TO ISOQUINOLINE DERIVATIVES

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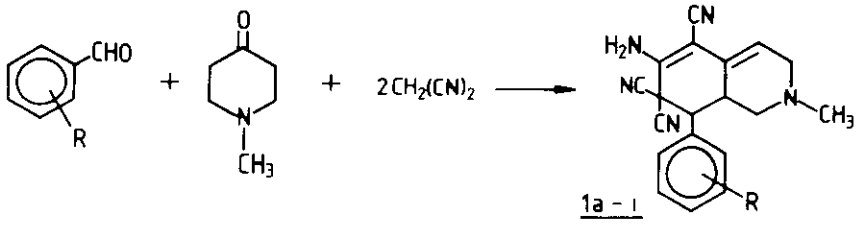
Abstract - A spontaneous reaction takes place between benzaldehydes, malononitrile and N-methyl-4-piperidone to yield the compounds 1a-i which can be aromatized to the new dicyano-1,2,3,4-tetrahydroisoquinolinamines 2a-e. Tetrahydro-2,7-naphthyridines 3a,b were also isolated as by-products.

The recent interest in the synthesis of cyclohexadiene derivatives by a base catalyzed dimerization reaction of alkylidenemalononitriles[1-4], prompts us to report our results on a new cyclization reaction of N-methyl-4-piperidone with benzaldehydes and malononitrile to give the hexahydroisoquinoline derivatives 1a-i.



1a - i

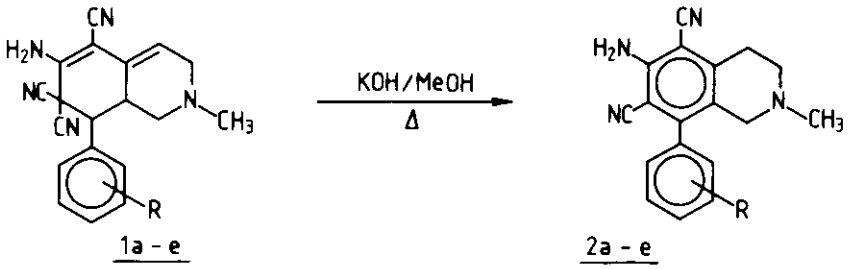
The necessary base catalysis for the ring closure reaction was brought about by N-methyl-4-piperidone and the weakly exothermic reaction proceeded smoothly in good yields when stoichiometric amounts of the starting materials were treated in methanol. Spectral data for the products, hexahydroisoquinolines, summarized in Table 1 were in good agreement with those expected for the assigned structures

Table 1: Preparation of hexahydroisoquinolines (1).

	R[a]	Yield %[b]	M.p. °C [c]	^{1}H-NMR	IR(KBr)cm^{-1}
1a	H	95	197-198(d)	δ(DMSO-d_6)-2.10(s,3H); 2.73-3.70(6H);5.65(m,H);7.45 (s,6H,arom.,NH_2)	2211(CN) 3330,3420(NH)
1b	p-CH_3	83	188-191(d)	δ(DMSO-d_6)=2.10(s,3H);2.30 (s,3H);2.93-3.37(6H);5.66 (m,H);7.38(m,6H,arom.,NH_2)	2211(CN) 3328,3420(NH)
1c	p-OCH_3	93	192-193(d)	δ(DMSO-d_6)=2.13(s,3H);2.87-3.92(6H);3.80(s,3H);5.65 (m,H);7.22(m,6H,arom.,NH_2)	2211(CN) 3330,3423(NH)
1d	m-OCH_3	47	204-206(d)	δ(DMSO-d_6)=2.13(s,3H);2.70-3.87(6H);3.77(s,3H);5.64(m,H) 7.13(m,4H);7.42(s,2H)	2211(CN) 3333,3420(NH)
1e	p-Cl	94	190-192(d)	δ(DMSO-d_6)=2.13(s,3H);2.67-3.93(6H);5.68(m,H);7.53 (m,6H,arom.,NH_2)	2212(CN) 3329,3423(NH)
1f	o-OCH_3	44	185-187(d)[d]	δ(DMSO-d_6)=2.13.(s,3H);2.95-4.40(6H);3.80(s,3H);5.68 (m,H);7.37(m,6H,arom.,NH_2)	2212(CN) 3330,3415(NH)
1g	o-Cl	78	187-189(d)[d]	δ(DMSO-d_6)=2.12(s,3H);2.82-4.04(6H);5.70(m,H);7.54(m,4H) 7.75(s,2H)	2212(CN) 3327,3424(NH)
1h	p-NMe_2	59	195-197(d)[d]	δ(DMSO-d_6)=2.11(s,3H);2.70-3.70(6H);2.93(s,6H);5.63 (m,H);7.15(q,4H);7.40(s,2H)	2210(CN) 3312,3411(NH)
1i	o-NO_2	72	188-189(d)[d]	δ(CF_3COOH)=3.30(s,3H);3.33-5.00(6H);6.97(s,H);8.00 (m,6H,arom.,NH_2)	2211(CN) 3334,3419(NH)

[a] MS showed correct M^+, [b] Crude product. [c] Recrystn. from n-BuOH. [d] 1, ½ n-BuOH.

1a-i, which were also supported by transforming 1 to 2, as follows. When heated in MeOH containing KOH, dehydrocyanation of 1 took place accompanied by aromatization due to isomerization of the Δ^4 double bond to afford the tetrahydroisoquinolines 2a-2e in 35~17% yields, as shown in Table 2.



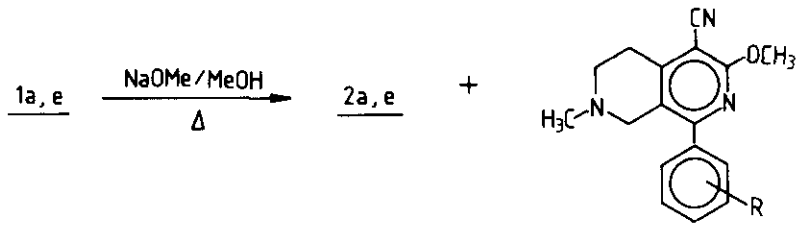
1a - e　　2a - e

Table 2: Preparation of tetrahydroisoquinolines (2).

	R[a]	Yield %[b]	M.p. °C [c]	^{1}H-NMR	IR(KBr) cm^{-1}
2a	H	35	251-253(d)	δ($CDCl_3$)=2.30(s,3H);2.67 (m,2H);3.07(m,4H);5.04(s,2H) 7.33(m,5H)	2212(CN) 3400,3312(NH)
2b	p-CH_3	24	250-253(d)	δ(DMSO-d_6)=2.19(s,3H);2.40 (s,3H);2.93(m,4H);3.37(m,2H) 6.44(s,2H);7.24(q,4H)	2212(CN) 3423,3312(NH)
2c	p-OCH_3	21	218-220(d)	δ(DMSO-d_6)=2.17(s,3H);2.90 (m,4H);3.37(m,2H);3.84(s,3H); 6.41(s,2H);7.12(q,4H)	2212(CN) 3426,3332(NH)
2d	m-OCH_3	17	231-233(d)	δ(DMSO-d_6)=2.20(s,3H);2.97 (m,4H);3.30(s,2H);3.80 (s,3H);6.37(s,2H);7.06(m,4H)	2212(CN) 3425,3332(NH)
2e	p-Cl	31	258-261(d)	δ($CDCl_3$)=2.33(s,3H);2.77 (m,2H);3.13(m,4H);5.17 (s,2H);7.33(q,4H)	2212(CN) 3424,333(NH)

[a] Showed correct M^+ and all the compounds gave correct microanalyses. [b] Crude product. [c] Recrystn. from 1-butanol

When NaOMe was used instead of KOH in the aromatization reaction of 1, 2 were obtained in very lower yield. This may be connected with formation of tetrahydro-2,7-naphthyridines in a competing reaction. Small quantities of the crystalline products 3a and 3b precipitated on addition of water to the methanol solution when 2a and 2e, respectively, had been filtered off.



3a, b

When 1b, c, f-i were stirred with a great excess of NaOMe in MeOH at 0°C a microcrystalline product soon precipitated. Although its structure has not yet been completely determined, spectroscopic data (including MS) and microanalysis indicate that it could be an addition compound of 1 and MeOH.

EXPERIMENTAL

6-Amino-2-methyl-8-phenyl-5,7,7-tricyano-1,2,3,7,8,9-hexahydroisoquinoline (1a)-(Typical example). Malononitrile (6.7 g, 0.1 mol) and benzaldehyde (5.3 g, 0.05 mol) were dissolved in methanol (50 ml) and N-methyl-4-piperidone (5.7 g, 0.05 mol) was added with stirring. From the cooled reaction mixture there was obtained a microcrystalline precipitate which was washed with methanol, dried, and recrystallized from n-butanol. Found: C 72.09; H 5.49; N 22.16. Calcd for $C_{19}H_{17}N_5$: C 72.36; H 5.43; N 22.21. Yield and physical data are given in Table 1.

6-Amino-5,7-dicyano-2-methyl-8-(p-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (2b)(typical example). One pellet of KOH (0.2 g) was added to a boiling suspension of 1b (0.66 g, 0.002 mol) in methanol (10 ml). After reflux for ½ h the solution was cooled to give crystals which were collected by suction filtration, washed with water and methanol, dried, and recrystallized from 1-butanol. Found: C 75.54; H 6.01; N 18.52. Calcd for $C_{19}H_{18}N_4$: C 75.47; H 6.00; N 18.53. Yield and physical data are given in Table 2.

4-Cyano-3-methoxy-7-methyl-1-phenyl-5,6,7,8-tetrahydro-2,7-naphthyridine (3a). Yield 9%, m.p. 205-208°C. ^{1}H-NMR: $\delta(CDCl_3)$=2.33(s,3H,N-CH_3); 2.92 (4H,-$(CH_2)_2$-); 3.20(s,2H,CH_2); 4.67(s,3H,OCH_3); 7.45(m,5H,arom.). IR(KBr): 2218 cm^{-1}(CN). MS: m/e 279.1373.calc for $C_{17}H_{17}N_3O$: m/e 279.1371.

1-(4-Chlorophenyl)-4-cyano-3-methoxy-7-methyl-5,6,7,8-tetrahydro-2,7-naphthyridine (3b). Yield 3%, m.p. 189-192°C. ^{1}H-NMR;$\delta(CDCl_3)$=2.30(s,3H,N-CH_3);2.90 (4H, $(CH_2)_2$); 3.16(s,2H,CH_2); 4.05(s,3H,OCH_3); 7.40(q,4H,arom.). IR(KBr):2218cm^{-1} (CN). Found: C 64.31; H 5.09; N 13.58. Calcd for $C_{17}H_{16}ClN_3O$: C 65.07; H 5.14; N 13.39.

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