SYNTHESIS AND REACTIONS OF ISOQUINOLINES IV. [1] REACTIONS OF 3-CHLOROISOQUINOLINE-4-CARBALDEHYDES

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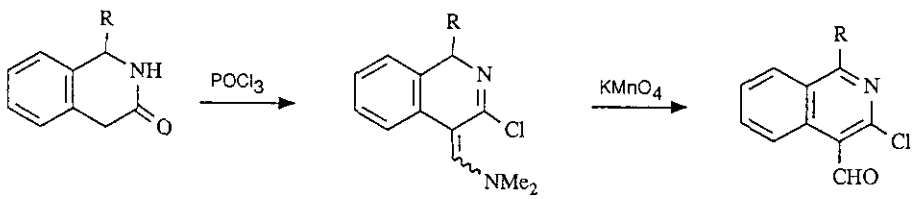
Dedicated to Prof. Wilhelm Bartmann on the occasion of his 60th birthday

Abstract - 3-Chloroisoquinoline-4-carbaldehydes 2 are versatile intermediates for various functional manipulations as e.g. oxidation or reduction of the formyl group or nucleophilic substitution of the chloro substituent leading to products with interesting pharmacological properties.

After a century of research on isoquinoline chemistry mainly derived from the interest in the alkaloid field [2,3] compounds with special substitution patterns are still a matter of concern for synthetic as well as pharmaceutical chemists. 3-Chloroisoquinoline-4-carbaldehydes 2 have been almost unknown in the literature with just one exception [4]. Recently we developed a convenient and versatile synthesis of these derivatives from 1,4-dihydro-3(2H)-isoquinolinones 1 by a two-step procedure involving a Vilsmeier-Haack reaction followed by subsequent oxidation with potassium permanganate under acidic conditions [5-7]. Formally the aldehydes 2 are vinylogous acid chlorides and as such amenable to various synthetic transformations [8]. The incorporation of the ß-chlorovinylaldehyde element into an heteroaromatic ring system increases its stability and attenuates its reactivity towards nucleophilic reagents at the ß-carbon.

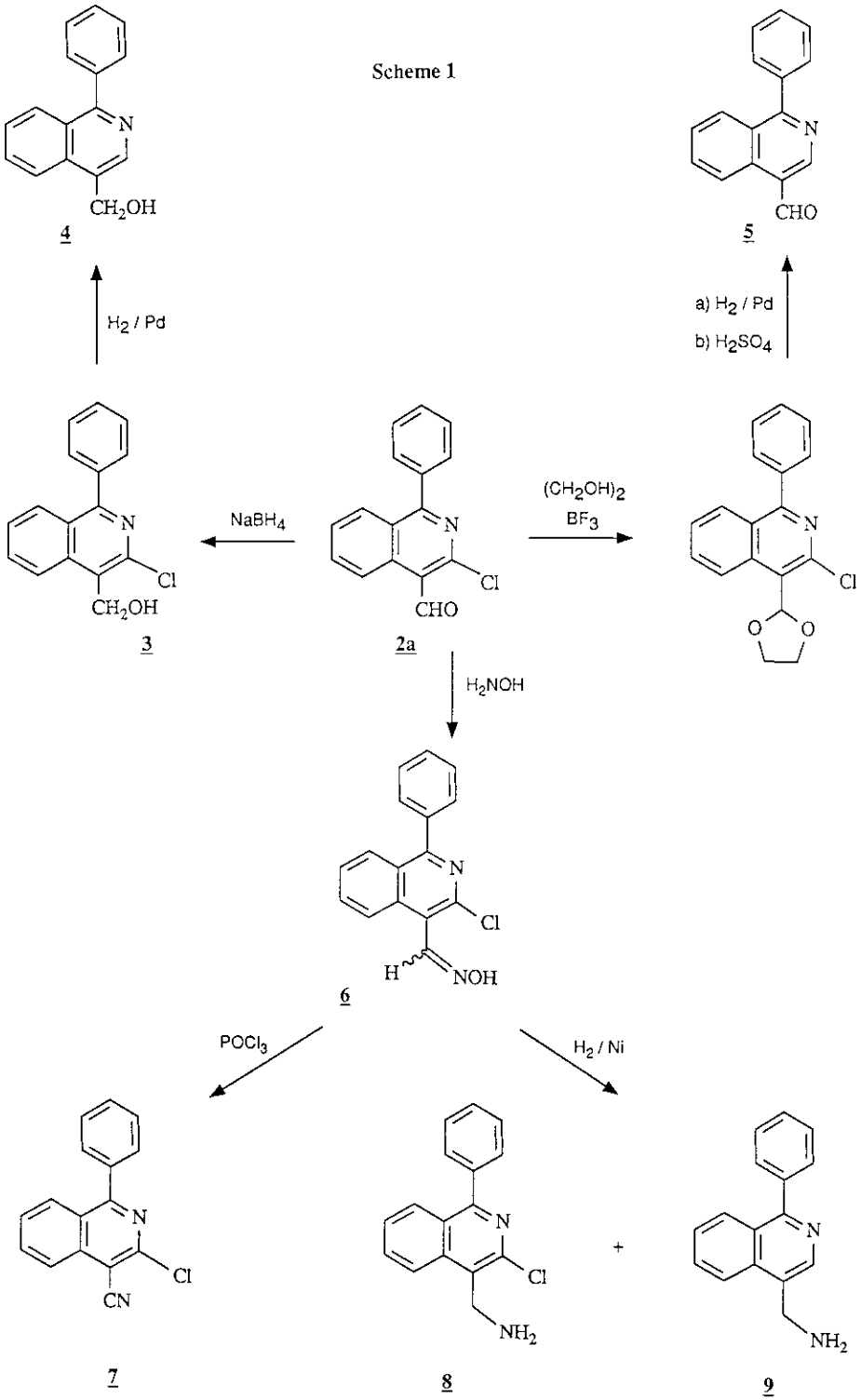


1 2

(a:R=C_6H_5; b:R=H)

Scheme 1 illustrates the synthetic opportunities starting e.g. from 3-chloro-1-phenylisoquinoline-4-carbaldehyde 2a:

Scheme 1


4
5
H_2 / Pd
a) H_2 / Pd
b) H_2SO_4
3
2a
$NaBH_4$
$(CH_2OH)_2$
BF_3
H_2NOH
6
$POCl_3$
H_2 / Ni
7
8
9

2a is reduced by sodium borohydride to the alcohol 3 which can be dehydrogenated to 4 by catalytic hydrogenation over palladium on charcoal. Dehalogenated aldehyde 5 is accessible from 2a by protection, catalytic hydrogenation and deprotection. Treatment of 2a with hydroxylamine yields oxime 6 which can be further transformed either to nitrile 7 by dehydration with phosphorus oxychloride in pyridine or to the amines 8 and 9 by stepwise catalytic hydrogenation (see Table 1 for physical data).

The chloro substituent of 2a can be substituted by a lot of different nucleophiles, e.g. by heating with excess alcohol, phenol, thiophenol or amine in toluene or dimethylformamide in the presence of sodium carbonate, leading to 3-substituted isoquinoline-4-carbaldehydes 10. Even primary amines give clean substitution products because intermediate Schiff bases are hydrolyzed upon work-up (see Table 2 for examples and physical data).

The 3-substituted isoquinoline-4-carbaldehydes 10 are very versatile intermediates for further elaboration as illustrated by the examples shown in Scheme 2 and Table 3:

The formyl function can be reduced to an alcohol 11 by sodium borohydride or oxidized to the acid 12c (Nu = O-Ph) by potassium permanganate. With Nu = amine these oxidation conditions lead to decomposition. Moreover, the formyl group can be transformed to a nitrile via the intermediate oxime or reduced to the primary amine as exemplified in the Scheme. Nitrile 14f is also obtained by nucleophilic substitution with N-methylpiperazine from 7. Hydrolysis of 14f to the amide 16f is easily accomplished by reaction with concentrated sulfuric acid in excellent yield. Finally, Wittig-Horner reaction of 10f and subsequent reduction with DIBAL leads to the vinylogous aldehyde 17f, whereas Wolff-Kishner reduction provides the 4-methyl derivative 18f. Most of the nucleophilic substitution reactions of 2a need temperatures above 100°C. In contrast, the reactivity of the 1,2-dihydroisoquinoline derivative 19 [5] is so high that the analogous reaction leading to 20 takes place even at room temperature (see Table 4). Scheme 3 contains two more examples demonstrating that these reactions are also applicable to 1-unsubstituted (2b, R = H) and partially hydrogenated 3-chloroisoquinoline-4-carbaldehydes (22) [5].

Scheme 2

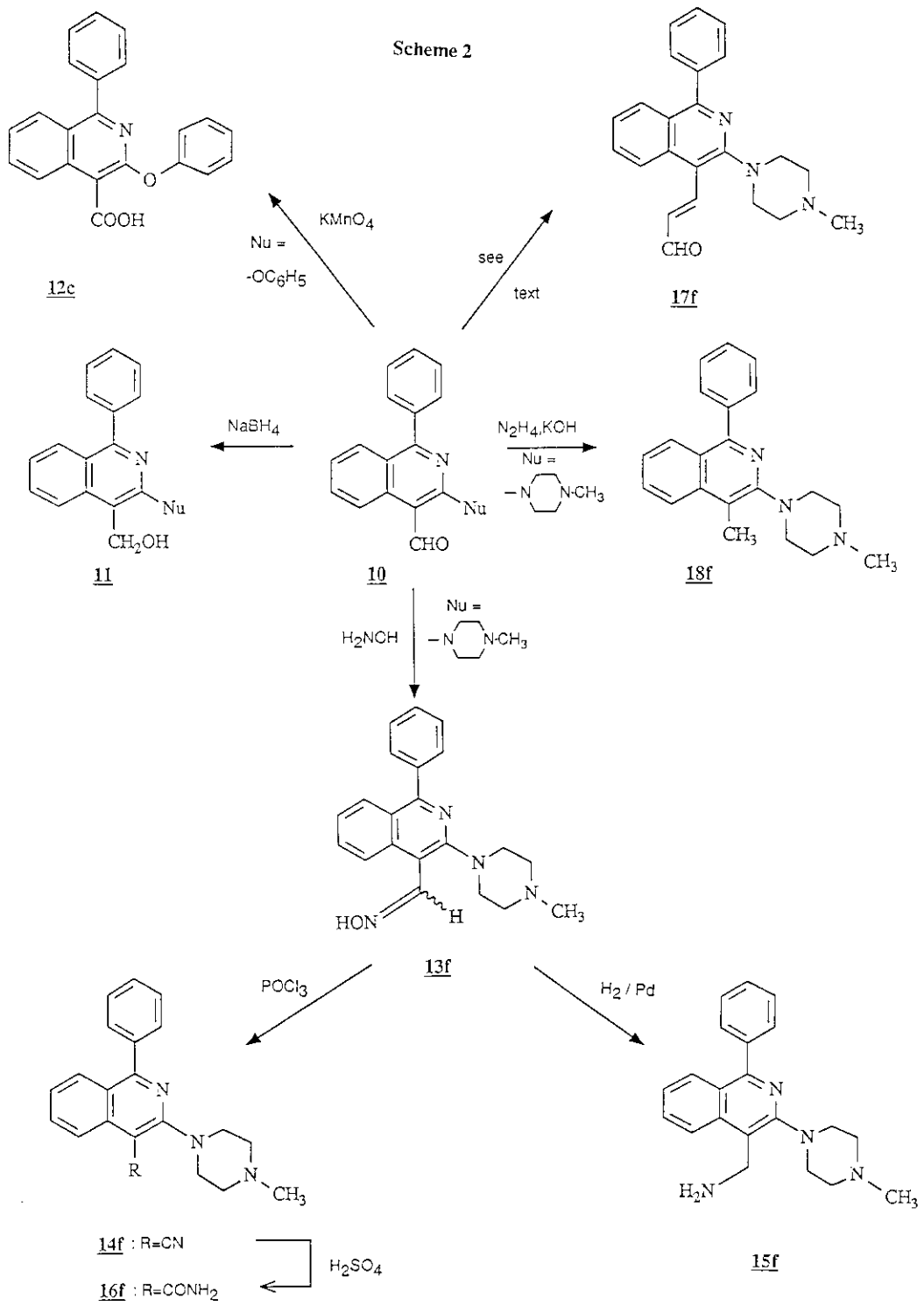

KMnO4
Nu =
-OC6H5
see
text
NaBH4
N2H4,KOH
Nu =
H2NCH
Nu =
POCl3
H2 / Pd
H2SO4
12c
17f
11
10
18f
13f
14f : R=CN
16f : R=CONH2
15f

Table 1: Isoquinoline Derivatives Prepared from 3-Chloro-1-phenylisoquinoline-4-carbaldehyde **2a**

Product	Yield[a] (%)	mp[b] (°C)	Molecular formula[c]	Ms (70 eV)[d] m/z (M^+, %)		^{1}H-Nmr ($CDCl_3$/TMS)[e] δ, J (Hz)
3	90	150-152	$C_{16}H_{12}ClNO$	269	(100)	4.05 (s,2H,CH_2); 6.37 (s,1H,OH); 7.20-9.00 (m,9H,arom)
4	66	117-119	$C_{16}H_{13}NO$	235	(75)	2.65 (s,1H,OH); 5.09 (s,2H,CH_2); 7.20-8.40 (m,9H,arom); 8.53 (s,1H,H-3)
5	86	153-155[f]	$C_{16}H_{11}NO$	233	(78)	7.20-8.40 (m,8H,arom); 8.96 (s,1H,H-3); 9.30 (dd,J≈ 8.0, ≈2.0,H-5); 10.40 (s,1H,CHO)
6	77	152-154	$C_{16}H_{11}ClN_2O$	282	(50)	7.30-8.30 (m,8H,arom); 8.46 (s,1H,OH); 8.86 (s,1H, CH=); 8.85 (dd,J≈ 8.0,≈2.0,H-5)
7	96	189-192	$C_{16}H_9ClN_2$	263(M^+-H)	(100)	7.30-8.50 (m,9H,arom)
8	65	101-103	$C_{16}H_{13}ClN_2$	268	(22)	1.94 (s,2H,NH_2); 4.45 (s,2H,CH_2); 7.30-8.40 (m,9H,arom)
9	98	238-240[g]	$C_{16}H_{14}N_2$	234	(40)	2.50 (s,2H,NH_2); 4.40 (s,2H,CH_2); 7.30-8.40 (m,9H,arom); 8.66 (s,1H,H-3)

a) Yields not optimized, isolated pure products.

b) Uncorrected, measured on a Büchi melting point apparatus (Dr. Tottoli).

c) Satisfactory microanalyses obtained. C ± 0.40, H ± 0.30, N ± 0.20, Cl ± 0.30.

d) Recorded on a Kratos MS 30 or Kratos 902 S Spectrometer.

e) Obtained on a Varian T 60 or Bruker WP 60 Spectrometer at 60 MHz.

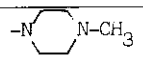
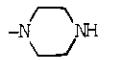
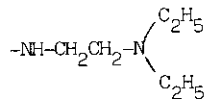
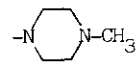
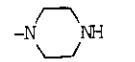
f) Lit. 11: mp 153-154°C.

g) mp of the hydrochloride.

Table 2: 3-Substituted 1-Phenylisoquinoline-4-carbaldehydes Prepared from 3-Chloro-1-phenylisoquinoline-4-carbaldehyde **2a**

Product	Nu	Yield[a] (%)	mp[b] (°C)	Molecular formula[c]	Ir(KBr)[f] $\tilde{\nu}_{C=O}$ (cm^{-1})	Ms (70eV)[d] m/z (M^+, %)		^{1}H-Nmr ($CDCl_3$/TMS)[e] δ, J (Hz)
10a	$-OC_4H_9$	48	93- 95	$C_{20}H_{19}NO_2$	1662	305	(65)	0.80-2.10 (m,7H,$CH_2CH_2CH_3$); 4.64 (t,J≈6.0,2H,CH_2O); 7.10-8.00 (m, 7H,arom); 8.05 (dd,J≈ 8.0,<1.0, 1H,H-8); 9.35 (dd,J≈8.0, <1.0,1H, H-5); 10.85 (s,1H,CHO)
10b	$-O-CH_2CH_2-N(CH_3)_2$	61	72- 75	$C_{20}H_{20}N_2O_2$	1618	321(M+H)	(13)	2.37 (s,6H,CH_3); 2.84 (t,J≈6.0, 2H,CH_2N); 4.77 (t,J≈6.0,2H,CH_2O); 7.10-8.20 (m,8H,arom); 9.37 (dd,J≈ 8.0,<1.0,1H,H-5); 10.87 (s,1H,CHO)
10c	$-O-C_6H_5$	85	181-185	$C_{22}H_{15}NO_2$	1665	325	(28)	6.80-8.30 (m,12H,arom); 8.10 (dd,J≈8.0,<1.0,1H,H-8); 9.37 (dd,J≈ 8.4,<1.0,1H,H-5); 10.95 (s,1H,CHO)
10d	$-S-CH_2CH_2-N(CH_3)_2$	45	97-100	$C_{20}H_{20}N_2OS$	1678	336	(0.7)	2.26 (s,6H,CH_3); 2.70 (t,J≈7.0, 2H,CH_2N); 3.53 (t,J≈7.0,2H,CH_2S); 7.20-8.30 (m,7H,arom); 8.30 (dd,J≈ 8.0,<1.0,1H,H-8); 9.07 (dd,J≈8.0,<1.0,1H,H-5); 10.95 (s,1H,CHO)
10e	$-S-C_6H_5$	80	126-128	$C_{22}H_{15}NOS$	1669	341	(30)	7.10-8.10 (m,12H,arom); 8.17 (dd,J≈8.0,<1.0,1H,H-8); 9.07 (dd,J≈ 8.0,<1.0,1H,H-5); 11.04 (s,1H,CHO)

Table 2 Continued

10f		84	152-154	$C_{21}H_{21}N_3O$	1658	331	(25)	2.37 (s,3H,CH_3); 2.60 (t,J≈7.0, 4H,CH_2); 3.85 (t,J≈7.0,4H,CH_2); 7.30-8.10 (m,8H,arom); 9.20 (dd, J≈ 8.0,<1.0,1H,H-5); 10.30 (s,1H, CHO)
10g		52	147-149	$C_{20}H_{19}N_3O$	1660	317	(58)	1.75 (s,1H,NH); 3.07 (t,J≈7.0,4H, CH_2); 3.80 (t,J≈7.0,4H,CH_2); 7.10-8.20 (m,8H,arom); 9.20 (dd, J≈ 8.0,<1.0,1H,H-5); 10.30 (s,1H, CHO)
10h		100	72- 74	$C_{22}H_{25}N_3O$	1631	347	(9)	1.07 (t,J≈7.0,6H,CH_3); 2.10-2.90 (m,6H,CH_2N); 3.87 (t,J≈7.0,2H, CH_2N); 7.00-8.00 (m,8H,arom); 8.29 (dd,J≈ 8.0,<1.0,1H,H-5); 10.00 (s,1H,NH); 10.84 (s,1H,CHO)
21		45	oil	$C_{15}H_{17}N_3O$		255	(47)	2.37 (s,3H,CH_3; 2.58 (t,J≈7.0, 4H,CH_2N); 3.72 (t,J≈7.0,4H,CH_2N); 7.20-8.00 (m,3H,arom); 9.00 (s,1H,H-1); 9.04 (dd,J≈ 8.0, ≈1.0,1H,H-5); 10.24 (s,1H,CHO)
23		25	oil	$C_{20}H_{23}N_3O$		321	(0.8)	1.2-4.1 (m,17H,CH_2+NH); 7.10-7.80 (m,5H,arom); 10.20 (s,1H,CHO)

a,b,d,e) Refers to a,b,d,e in Table 1.

c) Satisfactory microanalyses obtained: C ± 0.40, H ±0.30, N ± 0.20, S ±0.40.

f) Recorded on a Perkin-Elmer 683 Infrared Spectrophotometer.

Table 3: Compounds Prepared from 3-Substituted 1-Phenylisoquinoline-4-carbaldehydes **10**

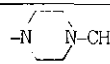
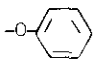
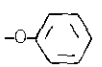
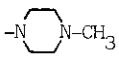
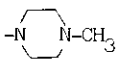
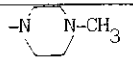
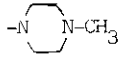
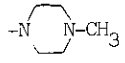
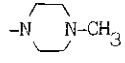
Product	R (pos.4)	Nu	Yield[a] (%)	mp[b] (°C)	Molecular formula[c]	Ms (70 eV)[d] m/z (M^+, %)		^{1}H-Nmr ($CDCl_3$/TMS)[e] δ, J (Hz)
11f	CH_2OH		98	153-155	$C_{21}H_{23}N_3O$	333	(100)	2.35 (s,3H,CH_3); 2.40-2.90 (m, 4H,CH_2N); 3.10-3.60 (m,4H,CH_2N); 5.29 (s,2H,CH_2O); 5.76 (s,1H, OH); 7.20-8.20 (m,9H,arom)
11c	CH_2OH		97	131-136	$C_{22}H_{17}NO_2$	327	(100)	2.03 (t,J≈6.0,1H,OH); 5.24 (d, J≈6.0,2H,CH_2O); 6.80-8.00 (m, 12H,arom); 8.10 (dd,J=7.6,≈2.0, 1H,H-8); 8.23 (dd,J= 7.6,≈2.0, 1H,H-5)
11h	CH_2OH	$-NH-(CH_2)_2-N(C_2H_5)_2$	82	109-111	$C_{22}H_{27}N_3O$	349	(2)	1.00 (t,J=6.8,6H,CH_3); 2.20-2.90 (m,6H,CH_2N); 3.66 (t,J≈7.0,2H, CH_2N); 5.06 (s,2H,CH_2O); 5.56 (s,1H,NH); 6.90-8.10 (m,9H, arom)
12c	CO_2H		29	195-197	$C_{22}H_{15}NO_3$	341	(58)	6.90-8.00 (m,12H,arom); 8.06 (dd,J≈ 6.0,≈2.0,1H,H-8); 8.18 (dd,J≈ 6.0,≈2.0,1H,H-5)
13f	CH=NOH		98	234-235	$C_{21}H_{22}N_4O$	346	(0.1)[f]	2.82 (s,3H,CH_3); 3.00-3.90 (m, 8H,CH_2N); 7.30-8.20 (m,8H,arom); 8.46 (s,1H,CH=N); 8.90 (dd,J ≈8.0,≈1.0,1H,H-5); 11.20 (s,1H, NH^+); 11.57 (s,1H,OH)[f]
14f	CN		92	143-145	$C_{21}H_{20}N_4$	328	(22)	2.36 (s,3H,CH_3); 2.57 (t,J≈7.0,4H, CH_2N); 4.02 (t,J≈7.0,4H,CH_2N); 7.10-8.10 (m,9H,arom)

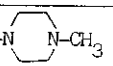
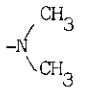
Table 3 continued

15f	CH_2NH_2		90	122-125	$C_{21}H_{24}N_4$	332	(33)	1.65 (s,2H,NH_2); 2.34 (s,3H, CH_3); 2.56 (t,J≈7.0,4H,CH_2N); 3.30 (t,J≈7.0,4H,CH_2N); 4.32 (s,2H,CH_2N); 7.10-7.90 (m, 8H,arom); 8.02 (dd,J≈ 8.0,≈2.0, 1H,H-5)
16f	$CONH_2$		98	187-188	$C_{21}H_{22}N_4O$	346	(16)	2.33 (s,3H,CH_3); 2.50 (t,J≈7.0, 4H,CH_2N); 3.55 (t,J≈7.0,4H, CH_2N); 6.25 (s,1H,NH); 6.65 (s, 1H,NH); 6.90-8.20 (m,8H,arom); 8.31 (dd,J≈ 8.0,<1.0,1H,H-5)
17f	CH=CH-CHO		78	130-133	$C_{23}H_{23}N_3O$	357	(25)	2.36 (s,3H,CH_3); 2.57 (t,J≈7.0, 4H,CH_2N); 3.50 (t,J≈7.0,4H, CH_2N); 6.70-8.40 (m,11H,9H, arom+CH=CH); 9.74,9.86 (s,1H,CHO)
18f	CH_3		60	112-114	$C_{21}H_{23}N_3$	317	(20)	2.36 (s,3H,CH_3); 2.58 (s+t, J≈7.0,7H,CH_3+CH_2N); 3.30 (t, J≈7.0,4H,CH_2N); 7.10-8.20 (m,9H,arom)

a-e) Refers to a-e) in Table 1.

f) Spectrum of the hydrochloride.

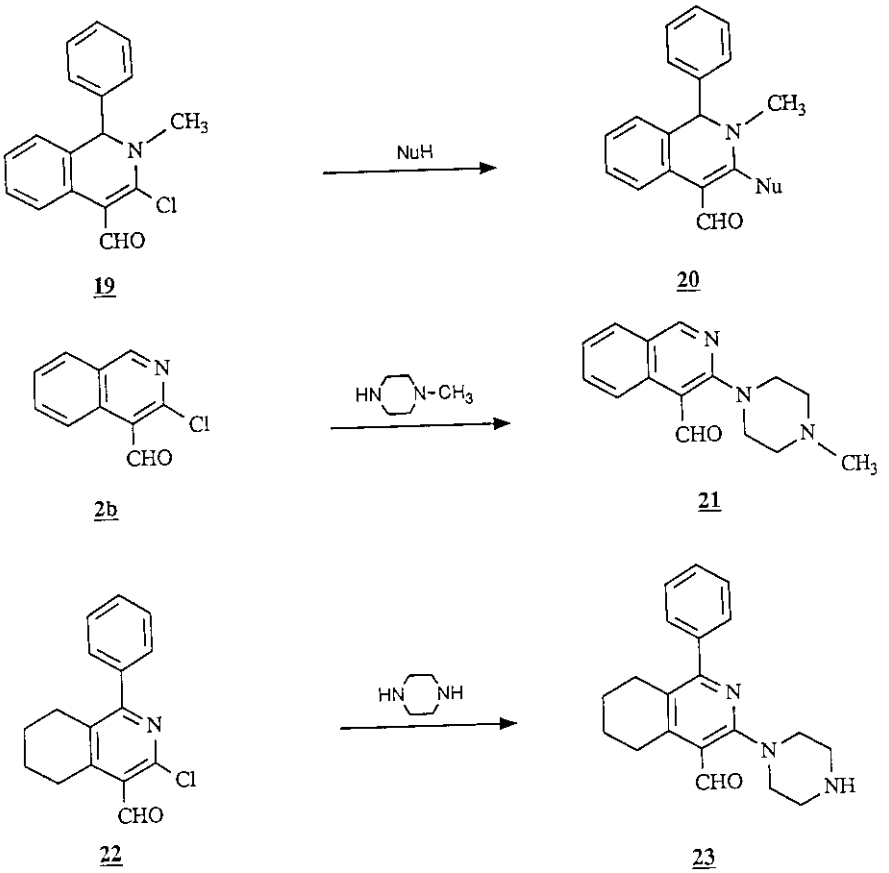
Table 4: Isoquinoline Derivatives **20** Prepared from 3-Chloro-2-methyl-1-phenyl-1,2-dihydroisoquinoline-4-carbaldehyde **19**

Product	Nu	Yield[a] (%)	mp[b] (°C)	Molecular formula[c]	Ir (KBr)[f] $\tilde{\nu}_{C=O}$ (cm^{-1})	Ms (70 eV)[d] m/z (M^+, %)	^{1}H-Nmr ($CDCl_3$/TMS)[e] δ, J (Hz)
20a		40[g]	184–187	$C_{22}H_{25}N_3O$	1615	347 (45)	2.30 (s,3H,CH_3); 2.40 (m,4H,CH_2N); 3.25 (s,3H,CH_3); 3.50 (m,4H,CH_2N); 5.32 (s,1H,H-1); 6.80–7.50 (m,8H, arom); 8.30 (dd,J≈8.0,<1.0,1H,H-5); 9.45 (s,1H,CHO)
20b		41	160–161	$C_{23}H_{19}NO_2$	1632	341 (40)	2.96 (s,3H,CH_3); 5.53 (s,1H,H-1); 6.70–7.50 (m,13H,arom); 8.77 (dd,J ≈8.0, 2.0,1H,H-5); 9.75 (s,1H,CHO)
20c		50	162–164	$C_{23}H_{19}NOS$	1634	357 (36)	3.17 (s,3H,CH_3); 5.42 (s,1H,H-1); 6.50–7.60 (m,13H,arom); 8.77 (dd,J ≈8.0,≈2.0,1H,H-5); 9.27 (s,1H,CHO)
20d		35[g]	163–166	$C_{19}H_{20}N_2O$	1608	292 (100)	3.07 (s,3H,CH_3); 3.23 (s,6H,CH_3); 5.30 (s,1H,H-1); 6.80–7.60 (m,8H, arom); 8.20 (dd,J≈3.0,<1.0,1H,H-5); 9.30 (s,1H,CHO)

a–f) Refers to a–f) in Table 2.

g) Yield based upon 2-methyl-1-phenyl-1,4-dihydro-3(2H)-isoquinolinone (lit. 12).

Scheme 3



In summary, our results prove that 3-chloroisoquinoline-4-carbaldehydes 2 are versatile intermediates for various functional manipulations leading to products with interesting pharmacological properties [9,10].

ACKNOWLEDGEMENT

We thank Mrs. S. Granata and K. Wagner for their experimental assistance.

EXPERIMENTAL

3-Chloro-4-hydroxymethylene-1-phenylisoquinoline (3).

To a suspension of 3-chloro-1-phenylisoquinoline-4-carbaldehyde 2a (26.8 g, 0.1 mol) in tetrahydrofuran (300 ml) and water (300 ml) at 0°C sodium borohydride (3.8 g, 0.1 mol) is added in portions. The reaction mixture is stirred at room temperature 3 h, the solvent evaporated and the residue crystallized from water. 3 is filtered off and recrystallized from ethanol; yield 20.6 g, mp 150-152°C. Another 3.6 g, mp 149-152°C is recovered from the mother liquor. Total yield: 24.2 g (90 %).

4-Hydroxymethylene-1-phenylisoquinoline (4).

To a suspension of 2a (5.4 g, 0.02 mol) in ethanol (200 ml) sodium hydroxide (1.6 g, 0.04 mol) in water (4 ml) and palladium on charcoal (10 %, 1.0 g) are added. Hydrogenation takes place at room temperature under normal pressure during 2 h. The catalyst is filtered off, the filtrate distributed between ethyl acetate and saturated aqueous sodium chloride, the organic phase is separated, dried and evaporated to yield 3.1 g (66%) of 4, mp 117-119°C.

1-Phenylisoquinoline-4-carbaldehyde (5).

A mixture of 2a (13.4 g, 0.04 mol), ethylene glycol (12.4 g, 0.2 mol) and boron trifluoride diethyl ether complex (1.5 ml) is heated to reflux 5 h and the water distilled off. The solution is then extracted with aqueous sodium hydrogen carbonate, dried, evaporated to dryness and the residue hydrogenated at room temperature in methanol (300 ml)/ methanolic ammonia (2 N, 100 ml) over palladium on charcoal (10 %, 0.5 g). After filtration and the usual work-up the intermediate acetal is hydrolyzed with dilute sulfuric acid. The product is collected by filtration, yielding 8.3 g (71 %), mp 153-155°C (lit. [11] 154-155°C).

3-Chloro-1-phenylisoquinoline-4-aldoxime (6).

To a solution of 2a (53.6 g, 0.2 mol) in pyridine (150 ml) at 0°C hydroxylamine hydrochloride (55.6 g, 0.8 mol) is added and the reaction stirred 1 h at 0°C and one h at room temperature.

The pyridine is evaporated in vacuo and the residue distributed between toluene and water. Evaporation of the toluene phase gives 60 g of brownish crude material which is crystallized from diisopropyl ether. *Yield : 43.2 g (77 %)*, mp 152-154°C.

3-Chloro-4-cyano-1-phenylisoquinoline (7).

To a solution of 6 (7.6 g, 0.027 mol) in pyridine (100 ml) phosphorus oxychloride (10.3 g, 0.067 mol) is added dropwise at 0°C. After 14 h at room temperature a precipitate has formed. The reaction mixture is hydrolyzed by addition of water and the precipitate collected by filtration. Yield 6.9 g (96 %), mp 191-193°C (from ethanol).

4-Aminomethylene-3-chloro-1-phenylisoquinoline (8) and 4-aminomethylene-1-phenylisoquinoline (9).

Aldoxime 6 (40.0 g, 0.14 mol) is dissolved in dimethylformamide (250 ml) and methanolic ammonia (2 N, 250 ml) and shortly hydrogenated (20 min) at room temperature over Raney nickel (30 g). *The catalyst is filtered off*, the remaining solution evaporated in vacuo and the residue crystallized as hydrochloride from ethanolic hydrogen chloride. After transformation to the free bases the mixture of 8 and 9 (5:1, 35g) is separated by *chromatography on silica gel* (chloroform/methanol 8/2). Yield: 24.8 g (65 %) of 8, mp 101-103°C, hydrochloride mp 295°C (dec.) and 2.7 g (12 %) of 9, oily, hydrochloride mp 238-240°C. The aldoxime can be reduced to pure 9 by longer exposure to hydrogen (yield 98 %).

Typical procedure:

3-(4-Methylpiperazin-1-yl)-1-phenylisoquinoline-4-carbaldehyde (10f).

A mixture of 2a (20.0 g, 0.075 mol) and N-methylpiperazine (22.5 g, 0.214 mol) in toluene (200 ml) is heated to reflux for 4 h. The solution is washed with water, dried and evaporated in vacuo. The residue is treated with diisopropyl ether and the crystalline 10f collected by filtration. Yield : 20.9 g (84 %), mp 152-154°C, hydrochloride mp 220-230°C (dec.). For reasons of better solubility dimethylformamide can also be used as solvent. Sodium carbonate is added to the reaction mixtures with alcohols and thiols. *In the case of 10h 2 N sulfuric acid is* added to the reaction mixture, stirring continued at room temperature for 2 h and the intermediate Schiff base hydrolyzed subsequently.

4-Hydroxymethylene-3-(4-methylpiperazin-1-yl)-1-phenylisoquinoline (11f).

This compound is obtained from 10f (10.0 g, 0.03 mol) according to the procedure described for the production of 3. Yield 9.8 g (98 %), mp 153-155°C, hydrochloride mp 223-225°C (dec.).

3-Phenoxy-1-phenylisoquinoline-4-carboxylic acid (12c).

To a solution of 10c (13.4 g, 0.04 mol) in acetone (300 ml) and aqueous buffer (pH 7, 100 ml) at 40°C potassium permanganate (18.0 g, 0.076 mol) is added in portions. After 4 h sodium hydrogen sulfite (5 g) is added, the solution filtrated and concentrated to a volume of about 100 ml. This solution is diluted with water (200 ml) and adjusted to pH 4 by addition of hydrochloric acid. The solution is extracted with ethyl acetate, the organic phase dried and evaporated. Yield : 3.9 g (29 %), mp 195-197°C (dec.).

3-(4-Methylpiperazin-1-yl)-1-phenylisoquinoline-4-aldoxime (13f).

This compound is obtained from 10f (16.6 g, 0.05 mol) according to the procedure described for the production of 6. Yield 17.2 g (99 %), mp 234-235°C (dec.); hydrochloride mp 235°C (dec.).

4-Cyano-3-(4-methylpiperazin-1-yl)-1-phenylisoiquinoline (14f).

This compound is obtained from 7 (21.1 g, 0.08 mol) according to the procedure described for the production of 10f. Yield 24.2 g (92 %), mp 143-145°C.

4-Aminomethylene-3-(4-methylpiperazin-1-yl)-1-phenylisoquinoline (15f).

A solution of 13f (9.8 g, 0.028 mol) in methanolic ammonia (2 N, 600 ml) is hydrogenated over Raney nickel (2g) at room temperature under normal pressure. The catalyst is filtered off, the solution evaporated and the residue crystallized. Yield 8.35 g (90 %), mp 122-125°C; hydrochloride mp 250-251°C (dec.).

3-(4-Methylpiperazin-1-yl)-1-phenylisoquinoline-4-carboxamide (16f).

To concentrated sulfuric acid (150 ml) 14f (16.3 g, 0.05 mol) is slowly added and heated to 80°C for 5 h. After cooling the reaction mixture is poured onto ice (2000 ml) and sodium hydroxide added until the pH is basic. 16f is collected by filtration and recrystallized from ethanol. Yield 15.6 g(90 %), mp 187-188°C; dihydrochloride mp 148-150°C (dec.).

3-[3-(4-Methylpiperazin-1-yl)-1-phenylisoquinoline-4-yl]-2-propenal (17f).

The phosphonate anion derived from sodium hydride (0.6 g, 0.025 mole, 55 %) and diethyl cyanomethylenephosphonate (4.43 g, 0.025 mole) in dimethoxyethane (75 ml) is treated at room temperature with a solution of 10f (8.3 g, 0.025 mole) in dimethoxyethane (100 ml). After 12 h at room temperature water is added for hydrolysis and the reaction mixture extracted with toluene (200 ml). The toluene phase is dried rigorously and a solution of diisobutylaluminium hydride (20 %, 22 ml) is added at 0°C. After 1 h at 0°C water is added for hydrolysis, the toluene phase separated, dried over sodium sulphate and evaporated to give 6.8 g (78 %) of 17f, mp 130-133°C.

4-Methyl-3-(4-methylpiperazin-1-yl)-1-phenylisoquinoline (18f).

A mixture of 10f (1.65 g, 0.005 mole), hydrazine hydrate (98 %, 0.75 g, 0.015 mole) and potassium hydroxide (1.12 g, 0.02 mole) in triethyleneglycol (10 ml) is heated to 170°C for 3 h. After cooling toluene and water are added, the organic phase is separated, dried over sodium sulphate and evaporated. The residue is crystallized from ether. Yield 0.95 g (60 %), mp 112-114°C; hydrochloride mp 273-275°C (dec.).

Typical procedure:

2-Methyl-1-phenyl-3-phenylthio-1,2-dihydroisoquinoline-4-carbaldehyde (20c).

A mixture of 2a (42.5 g, 0.15 mole), thiophenol (18.2 g, 0.165 mole) and potassium carbonate (22.8 g, 0.165 mole) in toluene (300 ml) is stirred at room temperature overnight. The toluene phase is extracted several times with water, dried over sodium sulphate, filtrated and evaporated. The residue is crystallized by treatment with ether. Yield 26.4 g (50 %), mp 162-164°C.

REFERENCES

1. Part III : B. Renger, E. Konz, and W. Rüger, Synthesis, 1988, 683.
2. M. Shamma, The Isoquinoline Alkaloids, Academic Press, New York, 1972.
3. G. Grethe (ed.), The Chemistry of Heterocyclic Compounds, Isoquinolines Part I, John Wiley, New York, 1981.
4. T. Koyama, T. Hirota, Y. Shinohara, M. Yamato, and S. Ohmori, Chem. Pharm. Bull., 1975, 23, 497.
5. W. Bartmann, E. Konz, and W. Rüger, Synthesis, 1988, 680.
6. W. Bartmann, E. Konz, H. Kruse, and H.M. Geyer, German Patent DOS 2811312, Chem. Abstr., 1980, 92, 6430m.
7. W. Bartmann, E. Konz, and H. Kruse, German Patent DOS 2811361, Chem. Abstr., 1980, 92, 6431n.
8. C. Jutz, Advances in Organic Chemistry, Vol. 9, Iminium Salts in Organic Chemistry, Part 1, E.C. Taylor (ed.), John Wiley, New York, 1976, p. 225.
9. W. Bartmann, E. Konz, and H.M. Geyer, German Patent DOS 2818403, Chem. Abstr., 1980, 92, 94262m.
10. W. Bartmann and E. Konz, German Patent DOS 2818423, Chem. Abstr., 1980, 92, 110874v.
11. J.B. Wommack, T.G. Barbee, Jr., D.J. Thoennes, M.A. McDonald, and D.E. Pearson, J. Heterocycl. Chem., 1969, 6, 243.
12. J. Finkelstein and A. Brossi, J. Heterocycl. Chem., 1967, 4, 315.

Received, 24th October, 1988