SYNTHESIS AND REACTIONS OF ISOQUINOLINE DERIVATIVES V.[1] SYNTHESIS AND REACTIONS OF 3-CHLOROISOQUINOLINE-4-CARBOXYLIC ACIDS

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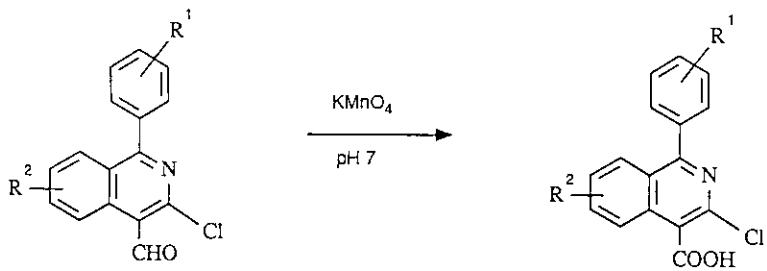
Abstract - Derivatives of 3-chloroisoquinoline-4-carboxylic acid are easily accessible by potassium permanganate oxidation of the corresponding aldehydes. Conditions have been developed for selective reduction, substitution and decarboxylation reactions leading to 3-substituted isoquinoline derivatives with interesting pharmacological properties.

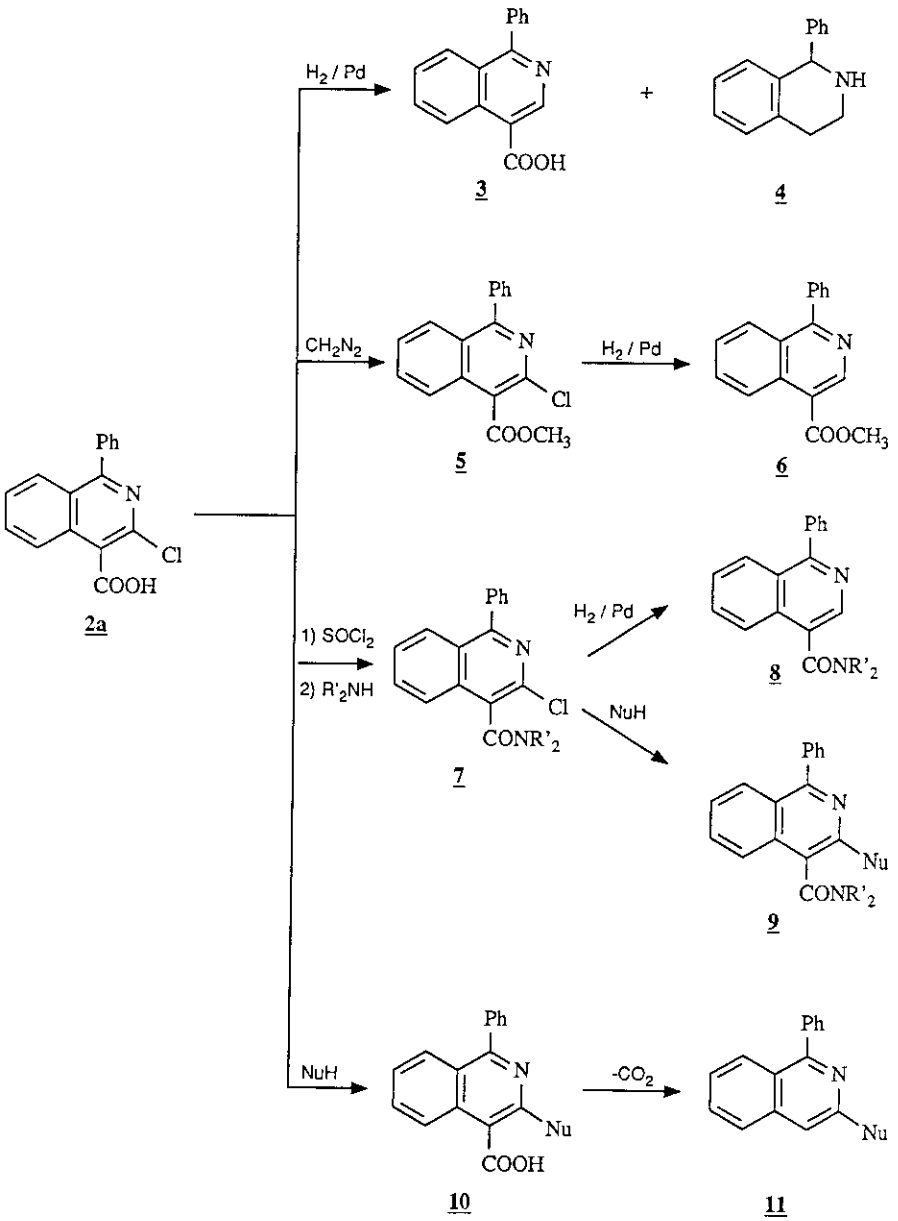
In continuation of our efforts to define easily accessible routes to isoquinoline derivatives with special substitution patterns [1] and interesting pharmacological properties we directed our attention to the synthesis of 3-substituted isoquinoline-4-carboxylic acids. We have already reported that 3-chloroisoquinoline-4-carbaldehydes 1 are oxidized in good yield to the corresponding 3-chloroisoquinoline-4-carboxylic acids 2 by the action of potassium permanganate in acetone/water at pH 7 [2,3].



1 2

As the aldehydes 1 are easily accessible from 1,4-dihydro-3(2H)-iso-quinolinones [2], the carboxylic acids 2 constitute very versatile starting materials for further elaboration. Scheme 1 illustrates some of the opportunities starting from 3-chloro-1-phenylisoquinoline-4-carboxylic acid 2a.

Scheme 1


Ph
N
Cl
COOH
2a
H2 / Pd
3
4
NH
CH2N2
5
COOCH3
6
1) SOCl2
2) R'2NH
7
CONR'2
8
NuH
9
Nu
-CO2
10
11

Catalytic reduction of 2a over palladium in methanolic ammonia leads to the dehalogenated acid 3 in a very sluggish reaction. Under harsher conditions 1-phenyl-1,2,3,4-tetrahydroisoquinoline 4 is formed as the main product. However, 3 is accessible by another route : Hydrogenation of the ester 5 which is obtained from 2a by esterification with diazomethane, leads to the dehalogenated ester 6 in a very clean and uniform reaction; 6 can be saponified to 3 afterwards.

Reaction of 2a with thionyl chloride to the intermediate carboxylic acid chloride followed by treatment with amines gives access to the amides 7 which in turn can be catalytically dehalogenated to the amides 8. Compounds 8 are also obtained by an alternate sequence of reactions starting from the acid 3 by treatment with first thionyl chloride and then amines. The amide function in position 4 is activating the neighbouring chlorine atom towards nucleophilic displacement as is demonstrated by the formation of 9 with amines under relatively mild conditions (t = 100 - 120 °C). In contrast, the direct treatment of 2a with amines in diglyme as solvent needs temperatures of about 140 °C, and the nucleophilic substitution is accompanied by decarboxylation leading to 3-amino-1-phenylisoquinoline derivatives 11 [4-6]. Nucleophilic displacement by alcohols or thiols, however, does allow the isolation of the carboxylic acids 10 which lose carbon dioxide only at temperatures of about 200 - 250 °C.

This difference in reactivity between amines on the one hand vs. alcohols and thiols on the other hand can be interpreted by assuming amino acids 12 as intermediates: 12 can be protonated at position 4 by ammonium compounds present in the reaction mixture thereby facilitating the elimination of carbon dioxide accompanied by rearomatization. This protonation/decarboxylation sequence is not as efficiently favored with oxygen or sulfur substituents in position 3. Thus the acids 10f-i are isolable.

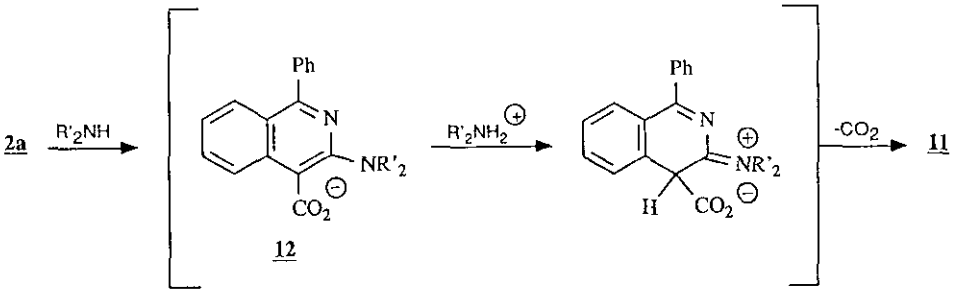


Table 1: Isoquinoline-4-carboxylic Acid Derivatives

Product	R^1	R^2	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)
2a	H	H	73	214-216	$C_{16}H_{10}ClNO_2$	283	(100)	7.20-8.30 (m,9H,arom+COOH)[f]
2b	2-CH_3	H	87	170-180	$C_{17}H_{12}ClNO_2$	296	(M^+-H,6)	2.11 (s,3H,CH_3); 7.00-8.20 (m,8H,arom); 8.73 (s,1H,COOH)
2c	2-F	H	87	193-196	$C_{16}H_9ClFNO_2$	301	(100)	6.90-8.30 (m,8H,arom+COOH)
2d	3-NO_2	H	69	237-239	$C_{16}H_9ClN_2O_4$	328	(12)	5.74 (s,1H,COOH); 7.30-8.80 (m,8H,arom)
2e	4-CF_3	H	61	258-260	$C_{17}H_9ClF_3NO_2$	351	(9)	7.20-8.20 (m,8H,arom); 9.00 (s,1H,COOH)
2f	2-F, 6-Cl	H	75	106-110	$C_{16}H_8Cl_2FNO_2$	335	(100)	6.80-8.20 (m,7H,arom+COOH)[f]
2g	H	5-CH_3	65	226-228	$C_{17}H_{12}ClNO_2$	297	(100)	2.82 (s,3H,CH_3); 7.10-8.10 (m,8H,arom+COOH)
2h	H	6-CH_3	78	268-272	$C_{17}H_{12}ClNO_2$	297	(100)	2.45 (s,3H,CH_3); 6.40 (s,1H,COOH); 6.90-8.05 (m,8H,arom)
2i	H	6-Cl	30	268-271	$C_{16}H_9Cl_2NO_2$	317	(M^+-H,100)	5.65 (s,1H,COOH); 7.20-7.80 (m,6H, arom); 7.95 (s,1H,H-5); 8.05 (d,J≈6.0, 1H,H-8)
2j	H	6,7-di-CH_3O	58	235-237	$C_{18}H_{14}ClNO_4$	343	(100)	3.84 (s,3H,CH_3O); 4.02 (s,3H,CH_3O); 6.60-7.90 (m,7H,arom+COOH)
2k	2-CH_3	6-Cl	85	258-260	$C_{17}H_{11}Cl_2NO_2$	331	(100)	2.07 (s,3H,CH_3); 7.00-7.90 (m,6H,arom); 8.04 (m,2H,H-5+COOH)
21	2-F	6-F	74	232-234	$C_{16}H_8ClF_2NO_2$	319	(100)	6.95-8.10 (m,7H,arom); 8.75 (s,1H,COOH)
14			38	251-253	$C_{10}H_6ClNO_2$	207	(100)	7.60-8.50 (m,4H,arom); 9.30 (s,1H,H-1)[f]
17			34	205-209	$C_{16}H_{14}ClNO_2$	287	(70)	1.50-2.10 (m,4H,CH_2); 2.40-3.10 (m,4H, CH_2); 4.40 (s,1H,COOH); 7.45 (s,5H,arom)

a) Yields not optimized, isolated pure products.

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

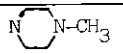
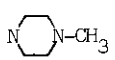
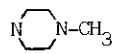
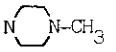
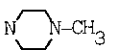
c) Satisfactory microanalyses obtained: C ± 0.40; H ± 0.30; N ± 0.30; Cl ± 0.40

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

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

f) Spectrum recorded in DMSO-d_6.

Table 2: 1-Phenylisoquinoline-4-carboxamides **7**, **8** and **9** Prepared from **2a**

Product	NR'_2	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)
7a		Cl	96	164–167	$C_{21}H_{20}ClN_3O$	365 (11)	2.38 (s,3H,CH_3); 2.20–4.30 (m,8H, CH_2N); 7.30–8.30 (m,9H,arom)
7b	$NHCH_2CH_2N(C_2H_5)_2$	Cl	98	167–169[h]	$C_{22}H_{24}ClN_3O$	381 (5)[h]	1.23 (t,J≈7.0,6H,CH_3); 2.80–4.00 (m,8H,CH_2N); 7.40–8.20 (m,9H, arom); 9.17 (t,J=4,1H,NH)[f]
7c	NH_2	Cl	98	218–221	$C_{16}H_{11}ClN_2O$	282 (100)	6.90+6.94 (2s,2H,NH_2); 7.20–8.30 (m,9H,arom)
8a		H	98	218–230[g]	$C_{21}H_{21}N_3O$	331 (14)[g]	2.32 (s,3H,CH_3); 2.10–4.20 (m,8H, CH_2N); 7.20–8.30 (m,9H,arom); 8.54 (s,1H,H-3)
8b	$NHCH_2CH_2N(C_2H_5)_2$	H	98	115–118[h]	$C_{22}H_{25}N_3O$	347 (1)[h]	1.21 (t,J≈7,6H,CH_3); 3.00–3.40 (m, 6H,CH_2N); 3.67 (q,J≈7,2H,CH_2N); 5.20 (s,1H,NH); 7.20–9.30 (m,10H, arom)[f]
8c	NH_2	H	90	225–227	$C_{16}H_{12}N_2O$	248 (84)	3.30 (s,2H,NH_2); 7.40–8.40 (m,8H, arom); 8.45 (dd,J≈8,≈2,1H,H-5); 8.72 (s,1H,H-3)
9a			84	156–158	$C_{26}H_{31}N_5O$	429 (75)	2.54 (s,6H,CH_3); 2.10–2.80 (m,8H, CH_2N); 3.20–4.40 (m,8H,CH_2N); 7.20–8.30 (m,9H,arom)
9b	$NHCH_2CH_2N(C_2H_5)_2$		56	204–206[g]	$C_{28}H_{29}N_3O_2$	439 (5)	0.95 (t,J≈7,6H,CH_3); 2.30–2.80 (m, 6H,CH_2N); 3.62 (q,J≈6,2H,CH_2N); 6.90–8.50 (m,15H,NH+14H,arom)
9c	NH_2		42	105–107	$C_{21}H_{22}N_4O$	346 (16)	2.33 (s,3H,CH_3); 2.50 (t,J≈5,4H, CH_2N); 3.55 (t,J≈5,4H,CH_2N); 6.20+ 6.55 (2s,2H,NH_2); 6.90–8.20 (m, 8H,arom); 8.31 (dd,J≈8,≈1,1H,H-5)

a-f) Refers to a-f) in Table 1. g) hydrochloride salt. h) oxalate salt.

Table 3: 3-Substitued 1-Phenylisoquinoline-4-carboxylic Acid Derivatives Prepared from 2a

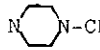
Product	Nu	Yield[a] (%)	mp[b] (°C)	Molecular formula[c]	Ms (70 eV)[d] m/z (M^+,%)	^{1}H-Nmr ($CDCl_3$/TMS)[e] δ, J (Hz)
3	H	70	244-247	$C_{16}H_{11}NO_2$	249 (62)	7.40-8.20 (m,8H,arom); 9.00 (dd,J≈8, ≈1,1H,H-5); 9.13 (s,1H,H-3); 13.60 (S,1H,COOH)
5	Cl	98	110-113	$C_{17}H_{12}ClNO_2$	297 (32)	4.00 (s,3H,CH_3); 7.20-7.80 (m,8H,arom); 8.00 (dd,J≈8,≈1,1H,H-5)
6	H	91	oil	$C_{17}H_{13}NO_2$	263 (95)	4.00 (s,3H,CH_3); 7.10-8.20 (m,8H,arom); 9.75 (dd,J≈8,≈2,1H,H-5); 9.92 (s,1H,H-3)
10f	OC_4H_9	68	115-117	$C_{20}H_{19}NO_3$	321 (95)	0.70-2.20 (m,7H,$CH_3CH_2CH_2$);4.73 (t,J≈6, 2H,CH_2O); 7.20-8.30 (m,8H,arom); 9.20 (d, J≈8,1H,H-5); 9.60 (s,1H,COOH)
10g	O- 	29	195-197	$C_{22}H_{15}NO_3$	341 (58)	6.90-8.00 (m,12H,arom); 8.06 (dd,J≈8,≈1, 1H,H-8); 8.18 (dd,J≈8,≈1,1H,H-5)
10h	S- 	55	238-240	$C_{22}H_{15}NO_2S$	357 (100)	7.10-8.20 (m,14H,arom); 11.00 (s,1H,COOH)[f]
10i	$OCH_2CH_2N(CH_3)_2$	95	154-156	$C_{20}H_{20}N_2O_3$	336 (1.8)	2.30 (s,6H,CH_3); 2.80 (t,J≈5,CH_2N);4.54 (t, J≈5,CH_2O); 7.10-8.00 (m,9H,arom)[g]
			288-290[g]			
10j	OH	46	220-222	$C_{16}H_{11}NO_3$	265 (10)	6.80-8.00 (m,8H,arom); 9.15 (d,J≈8,1H,H-5)

a,b,d,-f) Refers to a,b,d-f in Table 1.

c) Satisfactory microanalyses obtained: C ± 0.40; H ± 0.30; N ± 0.30; Cl ± 0.40; S ± 0.40.

g) sodium salt, spectrum in D_2O.

Table 4: 3-Substituted 1-Phenylisoquinoline Derivatives 11

Product	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)
11a		81	278-281[g]	$C_{20}H_{21}N_3$	303 (23)	2.34 (s,3H,CH_3); 2.40-2.80 (m,4H,CH_2N); 3.50-3.80 (m,4H,CH_2N); 6.72 (s,1H,H-4); 7.00-8.10 (m,9H,arom)
11b		95	107-118	$C_{19}H_{19}N_3$	289 (42)	1.68 (s,1H,NH); 2.80-3.20 (m,4H,CH_2N); 3.40-3.80 (m,4H,CH_2N); 6.73 (s,1H,H-4); 7.00-8.10 (m,9H,arom)
11c	NH_2	80	109-111	$C_{15}H_{12}N_2$	220 (100)	4.50 (s,2H,NH_2); 6.74 (d,J≈1,H-4); 6.90-8.10 (m,9H,arom)
11d	$NHCH_2CH_2CH_2N(CH_3)_2$	41	67- 68	$C_{20}H_{23}N_3$	305 (19)	1.60-2.60 (m,8H,$(CH_3)_2NCH_2CH_2$); 3.10-3.60 (q,J≈6,2H,CH_2N); 4.92 (t,J≈4,1H,NH); 6.52 (s,1H,H-4); 6.80-7.90 (m,9H,arom)
11e	$N(CH_3)CH_2CH_2NHCH_3$	95	248-250[g]	$C_{19}H_{21}N_3$	291 (8)[g]	1.45 (s,1H,NH); 2.36 (s,3H,CH_3); 2.83 (t,J≈6,2H,CH_2N); 3.10 (s,3H,CH_3); 3.81 (t,J≈6;2H,CH_2N); 6.56 (s,1H,H-4); 6.80-8.00 (m,9H,arom)
11f	OC_4H_9	40	59- 61	$C_{19}H_{19}NO$	277 (36)	0.90 (t,J≈7,3H,CH_3); 1.10-2.10 (m,4H,CH_2CH_2); 4.34 (t,J≈6,2H,CH_2O); 6.92 (s,1H,H-4); 7.05-8.10 (m,9H,arom)
11g	O- 	65	123-125	$C_{21}H_{15}NO$	297 (50)	6.60-8.10 (m,15H,arom)[f]
11h	S- 	95	82- 84	$C_{21}H_{15}NS$	313 (82)	7.00-8.20 (m,15H, arom)
11i	$OCH_2CH_2N(CH_3)_2$	95	202-204[g]	$C_{19}H_{20}N_2O$	292 (0.7)[g]	2.91 (s,6H,CH_3); 3.30-3.80 (m,2H,CH_2N); 4.70-5.00 (m,2H,CH_2O); 7.04 (s,1H,H-4); 7.10-8.10 (m,9H,arom); 12.90 (s,1H,NH^+)[g]
11j	OH	97	207-209[h]	$C_{15}H_{11}NO$	221 (100)	6.80-8.00 (m,10H,arom);8.70 (s,1H,OH)
11k	Cl	98	86- 87	$C_{15}H_{10}ClN$	239 (76)	7.30-8.20 (m,10H,arom)

a-f) Refers to a-f) in Table 3. g) hydrochloride salt. h) lit. 7: mp 205-206°C.

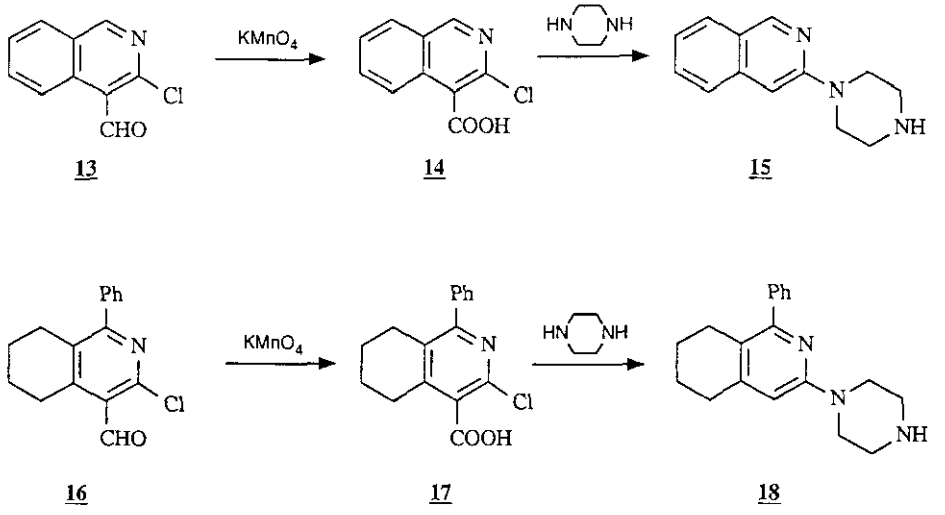
The above interpretation is supported by several experimental results :

a) Acidic cleavage of 3-butoxy-1-phenylisoquinoline-4-carboxylic acid 10f with pyridine hydrochloride at 170 °C is accompanied by decarboxylation leading to 11j in good yield [7].

b) 11j upon treatment with phosphorus oxychloride at 230 °C gives access to 11k. In contrast to 2a, the substitution of the chloro substituent by amines in 11k needs much higher temperatures and longer reaction times [8,9]. Therefore, 11k does not seem to be an intermediate on the way from 2a to 11.

Scheme 2 illustrates that the methods described above are also applicable to 1-unsubstituted and partially hydrogenated isoquinoline derivatives : 3-chloroisoquinoline-4-carboxylic acid 14 and 3-chloro-1-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carboxylic acid 17 are easily obtained by potassium permanganate oxidation of the corresponding aldehydes 13 and 16 [2]. Reaction with amines, e.g. piperazine, leads to substitution and decarboxylation products 15 and 18, respectively.

Scheme 2



In summary, 3-chloroisoquinoline-4-carboxylic acid derivatives prove to be easily accessible and versatile intermediates for the creation of 3-substituted isoquinolines with interesting pharmacological properties [3,10-12].

ACKNOWLEDGEMENT

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

EXPERIMENTAL

Typical procedure:

3-Chloro-1-phenylisoquinoline-4-carboxylic acid (2a).

To a suspension of 3-chloro-1-phenylisoquinoline-4-carbaldehyde [2] (53.3g, 0.2 mol) in acetone (1500 ml) and phosphate buffer (500 ml, pH 7) at 40 °C potassium permanganate (40.0 g, 0.25 mol) is added in portions during 2 h. The reaction mixture is stirred at 40 °C for further 2 h, cooled and sodium hydrogen sulfite (10 g) added. The precipitate is filtered off, the remaining solution concentrated by evaporation and acidified by addition of hydrochloric acid. 2a is collected by filtration and recrystallized from ethanol. Yield : 41.1 g (73 %), mp 214 - 216 °C.

Methyl 3-chloro-1-phenylisoquinoline-4-carboxylate (5).

A suspension of 2a (28.4 g, 0.1 mol) in methylene chloride (250 ml) is treated with excess diazomethane in ether in an ice bath. After 4 h at room temperature the remaining diazomethane is destroyed by addition of glacial acetic acid, the organic phase extracted with saturated aqueous sodium hydrogen carbonate and water, dried and evaporated. Yield : 29.1 g (98 %), mp 110 - 113 °C.

Methyl 1-phenylisoquinoline-4-carboxylate (6) and 1-phenylisoquinoline- 4-carboxylic acid (3).

A mixture of 5 (10.0 g, 0.033 mol) and triethylamine (20 ml) in methanol (250 ml) is hydrogenated over palladium on charcoal (10 %, 0.8 g) at room temperature under normal pressure during 5 h. The catalyst is filtered off, the remaining solution washed with water, dried and evapo-

rated, yielding oily 6 (8.1 g, 91 %). Saponification with sodium hydroxide in methanol and usual work-up gives the acid 3, mp 244 - 247 °C.

Typical procedure:

1-(3-Chloro-1-phenylisoquinoline-4-carbonyl)-4-methylpiperazine (7a).

A mixture of 2a (10.6 g, 0.0375 mol) and thionyl chloride (300 ml) is heated to reflux for 4 h. Excess thionyl chloride is distilled off and the crude acid chloride dissolved in chloroform (75 ml). This solution is added dropwise to a solution of N-methylpiperazine (11.3 g, 0.113 mol) in chloroform (100 ml) at room temperature. The reaction mixture is stirred overnight, the solvent is evaporated, the residue treated with water, collected by filtration, triturated in saturated aqueous sodium hydrogen carbonate (2000 ml), again collected by filtration, washed with water and dried. Yield : 13.3 g (96 %), mp 164 - 167 °C; hydrochloride, mp 255 - 256 °C.

Typical procedure:

1-Phenyl-3-phenylthioisoquinoline-4-carboxylic acid (10h).

A mixture of 2a (28.3 g, 0.1 mol), sodium carbonate (41.5 g, 0.3 mol) and thiophenol (13.2 g, 0.12 mol) in dimethylformamide (200 ml) is heated to reflux during 20 h. After cooling water and toluene are added, the aqueous phase is separated, acidified by addition of hydrochloric acid, the product collected by filtration and recrystallized from ethanol. Yield : 19.5 g (55 %), mp 238 - 240 °C (dec.).

3-Hydroxy-1-phenylisoquinoline-4-carboxylic acid (10j).

A mixture of 2a (85.0 g, 0.3 mol) and sodium hydroxide (300 g) in n-butanol (600 ml) is heated at 100 °C during 2 h. After cooling the solution is diluted with ether (500 ml) and the precipitate collected by filtration. This crude material is dissolved in water (20 l) and acidified to pH 2 by addition of hydrochloric acid. A new precipitate is formed which is again collected by filtration (55 g). 3-Butoxy-1-phenylisoquinoline-4-carboxylic acid 10f (1.8 g, mp 119 - 121 °C from methanol) is extracted from the crude product by stirring with methanol, the residue is purified by recrystallization from dimethylformamide. Yield : 36.6 g (46 %), mp 220 - 222 °C (dec.).

Typical procedure:

3-(4-Methylpiperazin-1-yl)-1-phenylisoquinoline (11a).

A mixture of 2a (30.0 g, 0.116 mol) and N-methylpiperazine (90 ml) is heated to 150 °C during 6 h. After cooling toluene and water are added, the organic phase is separated, washed several times with water, dried and evaporated, leaving 32.0 g of a brownish oil, which is pure on tlc (methanol/chloroform 2/8, Rf = 0.5). Dissolution in acetone and treatment with ethanolic hydrogen chloride gives 11a-hydrochloride (31.8 g, 81 %), mp 278 - 281 °C.

Typical procedure:

3-Hydroxy-1-phenylisoquinoline (11j).

Carboxylic acid 10j (36.6 g, 0.138 mol) is slowly heated to 220 °C and retained 1 h at that temperature. After cooling the residue is treated with little ethyl acetate leaving 29.9 g (97 %) of 11j, mp 207 - 209 °C. 11j is also obtained from 1-phenyl-1,4-dihydro-3(2H)-isoquinolinone [13] by treatment with palladium on charcoal in 1,4-diisopropylbenzene at 175 °C in 16 % yield.

3-(2-Dimethylaminoethoxy)-1-phenylisoquinoline (11i).

Sodium (4.6 g, 0.2 mol) is dissolved in 2-dimethylaminoethanol (80 ml) and 11k (4.8 g, 0.02 mol) is added at 50 °C. The reaction mixture is heated at 140 °C during 3 h. After usual work-up with toluene and water 11i is obtained as an yellowish oil (5.6 g, 95 %) ; hydrochloride mp 202 - 204 °C.

3-Chloro-1-phenylisoquinoline (11k).

A mixture of 11j (40.0 g, 0.18 mol) and phosphorus oxychloride (340 ml) is heated to 230 °C in an autoclave during 24 h. Excess reagent is distilled off and the residue hydrolyzed by cautious addition of ice-water. 11k is extracted with toluene. Yield 42.3 g (98 %), mp 85 - 97 °C.

3-(Piperazin-1-yl)isoquinoline (15).

A mixture of 14 (2.0 g, 0.01 mol) and piperazine (20 g) in diglyme (100 ml) is heated to reflux during 4 h. The solvent is distilled off in vacuo and the residue treated with water and extracted with toluene. 15 is isolated from the toluene phase (1.8 g, 85 %), mp 95 - 96 °C; hydrochloride mp 276 - 277 °C.

1-Phenyl-3-(piperazin-1-yl)-5,6,7,8-tetrahydroisoquinoline (18).

This compound is obtained from 17 by the procedure described above for the synthesis of 15. Yield : 41 % oily product, hydrochloride mp 240 - 243 °C.

REFERENCES

1. Part IV : E. Konz and W. Rüger, Heterocycles, preceding paper in this issue.
2. W. Bartmann, E. Konz, and W. Rüger, Synthesis, 1988, 680.
3. W. Bartmann and E. Konz, German Patent DOS 2818423, Chem. Abstr., 1980, 92, 110874v.
4. J.L. Neumeyer, K.K. Weinhardt, R.A. Carrano, and D.H. McCurdy, J. Med. Chem., 1973, 16, 808.
5. T. Okano, S. Goya, and Y. Tsuda, Yakugaku Zasshi, 1966, 86, 544 ; Chem. Abstr., 1966, 65, 15319f.
6. A.J. Liepa, Aust. J. Chem., 1982, 35, 1391.
7. D.W. Jones, J. Chem. Soc. (C), 1969, 1729.
8. A.R. Osborn, K. Schofield, and L.N. Short, J. Chem. Soc., 1956, 4191.
9. R.D. Haworth and S. Robinson, J. Chem. Soc., 1948, 777.
10. W. Bartmann, E. Konz, and H.M. Geyer, German Patent DOS 2818403, Chem. Abstr., 1980, 92, 94262m.
11. E. Konz, H. Kruse, and F. Hock, German Patent DOS 3227741, Chem. Abstr., 1984, 100, 174683y.
12. E. Konz and J. Kaiser, German Patent DOS 3233424, Chem. Abstr., 1984, 101, 38362m.
13. G. Deak, K. Gall-Istok, L. Hazai, and L. Sterk, Synthesis, 1975, 393.

Received, 24th October, 1988