ISOQUINOLINE-BASED AMINO ACID DERIVATIVES

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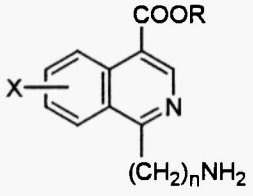
Abstract: A series of 1-aminoalkylisoquinoline-4-carboxylates (**9**) was synthesized by acylation of an appropriate phenethylamine derivative (**4**) with a phthaloyl-protected amino acid (**5**) followed by a Bischler-Napieralski cyclization and oxidation. N-Alkyl analogs **16** were prepared by reaction of the 1-chloromethylisoquinoline **12** with an alkylamine.

Introduction

The isoquinoline nucleus can be found in a wide variety of naturally occurring alkaloids as well as being used as biologically active agents (1,2). Recently, we required a series of isoquinolines functionalized with an aminoalkyl group at the 1-position and a carboxylate at the 4-position (**1**). Isoquinolines with a 4-carboxy function (3,4,5) or a 1-aminomethyl group (6,7,8) are separately known but it appears that isoquinolines containing both functionalities in the same molecule are unknown.



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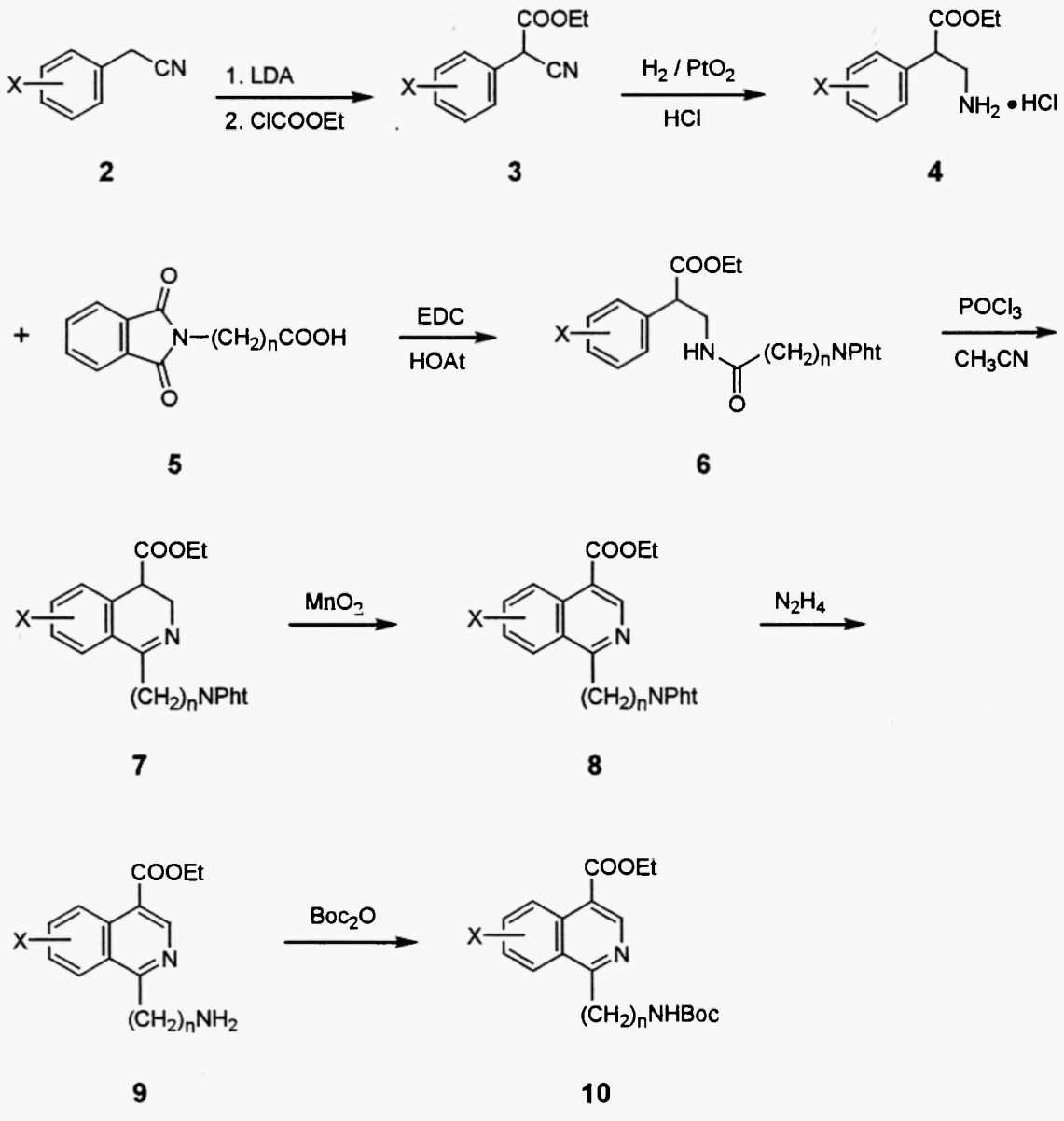
Synthetically, 1-aminomethylisoquinolines can be accessed by catalytic reduction of the corresponding 1-cyano derivative (6,7), however, this method would not be suitable for the introduction of 1-aminoalkyl groups with longer carbon chains. After careful consideration of the generality of the synthetic route, we chose a classical Bischler-Napieralski cyclization (9) to form the

isoquinoline core. The resulting 3,4-dihydroisoquinoline could then be aromatized to the desired heterocycle.

Results and Discussion

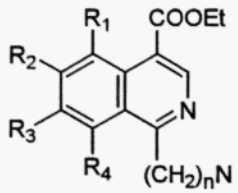
The starting phenethylamine derivative (**4**) with the requisite ester in the appropriate location was conveniently prepared by deprotonation of phenylacetonitrile **2** with two equivalents of LDA followed by alkylation with ethyl chloroformate. Catalytic hydrogenation of **3** in the presence of HCl furnished **4** in 55 – 100% overall yields. Coupling of **4** with phthaloyl-protected amino acid **5** afforded amide **6** in high yields (see Table 1).

Scheme 1



Compounds **6** were cyclized with phosphorus oxychloride under standard Bischler-Napieralski conditions to give the 3,4-dihydroisoquinoline 7. This material typically was directly aromatized in the following step, however **7b**, **7d** and **7j** were purified by crystallization and characterized. Dehydrogenation of 7 with MnO_2 produced the key isoquinoline **8** in moderate overall yield from **6** (Scheme 1).

Table 1. Percent Yields of Chemical Transformations Shown in Scheme 1



Cmpd.	R_1	R_2	R_3	R_4	n	6[a]	8[a b]	10[a b]
a	H	OCH_3	H	H	1	97	35	32
b	H	OCH_3	OCH_3	H	1	90	46	81
c	H	OCH_3	OCH_3	H	2	77	76	22
d	H	OCH_3	OEt	H	1	84	34	78
e	H	OEt	OCH_3	H	1	97	39	62
f	H	OCH_3	OPr	H	1	88	49	48
g	H	OCH_3	OH	H	1	87	—	—
h	H	OCH_3	OTBS	H	1	(c)	66	68
i	H	OCH_3	H	OCH_3	1	89	61	21
j	OCH_3	H	H	OCH_3	1	62	26[d]	49
k	OCH_3	OCH_3	OCH_3	H	1	85	20	80
l	H	OCH_3	OCH_3	OCH_3	1	80	63	78

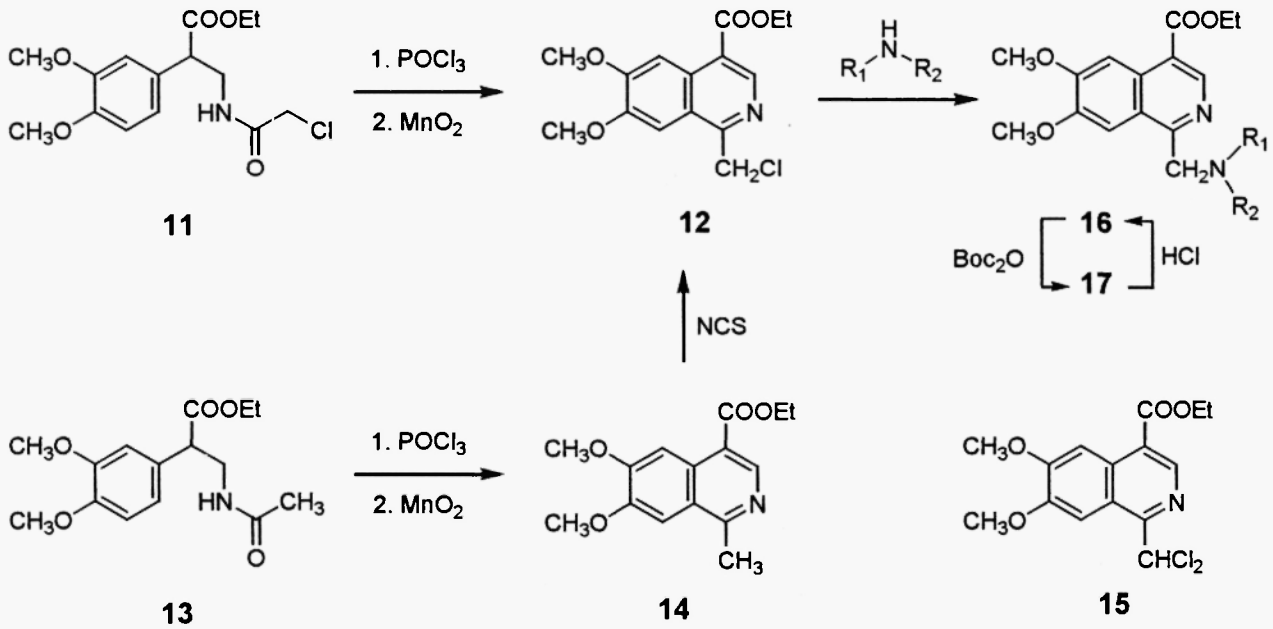
(a) For melting points see reference 10
(b) Overall yield of two steps
(c) **7g** was converted to **7h** before aromatization to **8h**
(d) Based on consumed starting material

Hydrazinolysis of the phthaloyl group under standard conditions (5 equiv. N_2H_4, EtOH) produced erratic results especially on larger scales (>200 mg). We have found that using 15 equivalents of hydrazine in CH_2Cl_2/EtOH (9:1) gave consistent results regardless of the scale of the reaction. In order to facilitate purification of the amine **9** it was converted to its Boc derivative **10** and then flash chromatographed. The Boc protecting group was then removed with either anhydrous

HCl in ethanol (0°C, 5 min) or trifluoroacetic acid in methylene chloride (room temperature, 4 hr) to furnish pure **9** as its di-HCl or di-TFA salt.

N-Alkyl analogs were prepared by displacement of the halogen of the chloromethylisoquinoline **12** with various amines (Scheme 2). Compound **12** was synthesized in 11% yield by a Bischler-Napieralski cyclization of **11** followed by aromatization with MnO_2. Alternatively, **12** can be accessed by chlorination of the 1-methylisoquinoline **14** with NCS/AIBN. Under these reaction conditions both mono- and dichloro derivatives were formed. They were separable by flash chromatography and provided **12** in 23% yield and **15** in 36% yield. The 1-chloromethylisoquinoline **12** was then reacted with methylamine, dimethylamine and *n*-propylamine to give **16a** (R_1 = H, R_2 = CH_3), **16b** (R_1 = R_2 = CH_3) and **16c** (R_1 = H, R_2 = *n*-Pr). In the cases of **16a** and **16c**, they were converted to their N-Boc derivatives **17** (R_1 = Boc) for purification and analytical purposes. The Boc group was then removed with anhydrous HCl to regenerate the pure amine **16**.

Scheme 2



11 **12** **16** **17** **13** **14** **15**

Experimental

General Procedure for the Preparation of 3

To a solution of 10.1 g (100 mmole) of diisopropylamine in 120 ml of THF at –30°C was added 6.4 g (100 mmole) of *n*-butyllithium (1.6M in hexane). The mixture was cooled to –78°C then a solution of 50 mmole of **2** in 80 ml of THF was added dropwise. After stirring the mixture for 15 min a solution of 51 mmole of ClCOOEt in 10 ml of THF was added dropwise at which point a thick gum

formed. The mixture was stirred at -78°C for 15 min then saturated NH_4Cl was added. The organic material was extracted into MTBE and the solution was dried over sodium sulfate. The solvent was removed under reduced pressure to furnish the product **3** (12).

General Procedure for the Preparation of 4

A solution of 44 mmole of **3** and 3.8 ml of concentrated HCl in 150 ml of ethanol was hydrogenated at 50 psi over 1.1 g of platinum oxide for 24 hr. The catalyst was removed by filtration and the solvent evaporated under reduced pressure to give **4** (12).

General Procedure for the Preparation of 6

To a mixture of 3.45 mmole of **4**, 3.5 mmole of **5**, 3.45 mmole of EDC and 3.45 mmole of HOAt in 20 ml of DMF was added 3.5 mmole of triethylamine. The yellow mixture was stirred at room temperature for 18 hr at which point the solution became light straw-colored. The DMF was removed under vacuum and ethyl acetate was added to the residue. The mixture was washed with 10% $NaHCO_3$, water and saturated NaCl. The organic phase was dried over sodium sulfate and the solvent removed under reduced pressure to furnish **6**. The material was recrystallized from methylene chloride/MTBE (12).

General Procedure for the Preparation of 8

To a solution of 28.6 mmole of **6** in 200 ml of acetonitrile was added dropwise 9.5 g of $POCl_3$ and the resulting mixture was stirred at 80-85°C for 48 hr. The solvent was removed under reduced pressure and 2N NaOH was added to the residue. The mixture was extracted with ethyl acetate, the organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to give **7**. This material was dissolved in 200 ml of benzene and 30 g of activated MnO_2 was added. The mixture was refluxed for 1 hr in a flask fitted with a Dean-Stark trap. After filtering the MnO_2 through Celite, the solvent was removed under reduced pressure to give **8**. The material was recrystallized from methylene chloride/ethyl acetate (12).

General Procedure for the Hydrazinolysis of 8

To a solution of 2 mmole of **8** in 50 ml of methylene chloride/ethanol (10:1) was added 15 equivalents of anhydrous hydrazine and the mixture was stirred at room temperature for 24 hr. The solvent was removed under reduced pressure and the solid residue was partitioned between methylene chloride and water. The organic phase was washed with water (2x) and dried over sodium sulfate. The solvent was removed under reduced pressure to give **9**.

General Procedure for the Preparation of 10

To a solution of 2.5 mmole of **9** and 4 mmole of triethylamine in 20 ml of methylene chloride was added 3 mmole of Boc_2O. After stirring the mixture for 2.5 hr, the solvent was removed under reduced pressure and the residual solid was flash chromatographed using methylene chloride/ethyl acetate (4:1) to elute pure **10** (12). The same procedure was used for the conversion of **16** to **17**.

General Procedure For Removal of the Boc Group

Into a solution of **10** in $EtOH/CH_2Cl_2$ (8:2) at 0°C was bubbled HCl gas for 2-5 min. The solution was concentrated and ether was added. The resulting precipitate was filtered and washed with ether to afford pure **9** as its dihydrochloride salt. The same procedure was used for the conversion of **17** to **16**.

Ethyl 6,7-Dimethoxy-1-methylisoquinoline-4-carboxylate (14)

The acetyl derivative **13**, which was prepared by treating **4b** with acetic anhydride in the presence of triethylamine, was converted to **14** according to the general procedure for the preparation of 8 to give 1.5 g (54%) of a yellow solid, mp 141-142°C; ^1H nmr ($CDCl_3$): δ 9.00 (s, 1H), 8.51 (s, 1H), 7.33 (s, 1H), 4.47 (q, 2H), 4.08 (s, 3H), 4.05 (s, 3H), 2.95 (s, 3H), 1.46 (t, 3H). Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.25; H, 6.22; N, 5.03.

Chlorination of 14

A mixture of 3.5 g (12.7 mmole) of **14**, 2.2 g (16.5 mmole) of N-chlorosuccinimide and 0.4 g of AIBN in 100 ml of CCl_4 was refluxed for 18 hr. TLC showed some unreacted **14** remaining so an additional 0.6 g of N-chlorosuccinimide and 0.1 g of AIBN was added and refluxing was continued for an additional 10 hr. The solvent was removed under reduced pressure and the residue flash chromatographed using methylene chloride/ethyl acetate (100:1) to elute the products, 1.6 g (36%) of **15**, mp 108-110°C, ^1H nmr ($CDCl_3$): δ 8.98 (s, 1H), 8.50 (s, 1H), 8.00 (s, 1H), 7.22 (s, 1H), 4.48 (q, 2H), 4.09 (s, 6H), 1.46 (t, 3H). Anal. Calcd. for $C_{15}H_{15}NO_4Cl_2$: C, 52.34; H, 4.39; N, 4.07; Cl, 20.60. Found: C, 52.21; H, 4.20; N, 3.95; Cl, 20.96.

Also 0.7 g (23%) of **12**, mp 172-173°C, ^1H nmr ($CDCl_3$): δ 9.02 (s, 1H), 8.50 (s, 1H), 7.46 (s, 1H), 5.09 (s, 2H), 4.47 (q, 2H), 4.08 (s, 6H), 1.45 (t, 3H). Anal. Calcd. for $C_{15}H_{16}NO_4Cl$: C, 58.17; H, 5.21; N, 4.52; Cl, 11.45. Found: C, 58.07; H, 5.10; N, 4.42; Cl, 11.74.

Reaction of 12 With Amines

Methylamine or dimethylamine was condensed in 15 ml of THF at −78°C until a volume increase of 3-5 ml was observed. To this was added dropwise a solution of 120 mg of **12** in 15 ml of THF. The mixture was allowed to warm to room temperature and stirred there for 2 hr (11). The solvent was

removed under reduced pressure and the residue partitioned between methylene chloride and water. The organic phase was dried over sodium sulfate and the solvent evaporated to give **16**.

References

(1) M. Shamma, The Isoquinoline Alkaloids, Chemistry and Pharmacology, Academic Press, New York, 1972.

(2) F. G. Kathawala, G. M. Coppola and H. F. Schuster (Eds.), Heterocyclic Compounds, Isoquinolines, Part 2, John Wiley, New York, 1990.

(3) W. Bartmann, E. Konz and W. Ruger, Heterocycles 29, 707 (1989).

(4) H. Suzuki and H. Abe, Synthesis 763 (1995).

(5) L. Wessjohann, L. Skattebol and A. de Meijere, J. Chem. Soc., Chem. Commun., 574 (1990).

(6) A. Kubo, Y. Kitahara, S. Nakahara, R. Iwata and R. Numata, Chem. Pharm. Bull. 36, 4355 (1988).

(7) K. Matsuo, M. Okumura and K. Tanaka, Chem. Pharm. Bull. 30, 4170 (1982).

(8) M. Croisy-Delcey, C. Huel and E. Bisagni, J. Heterocyclic Chem. 25, 655 (1988).

(9) W. M. Whaley and T. R. Govindachari, Organic Reactions, Vol. 6, John Wiley, New York, 1951.

(10) Melting points of crystalline products: **3e**, 59-61°; **4b**, 171-174°;**4d**, 119-122°; **4e**, 134-135°; **4f**, 102-105°; **4g**, 159-162°; **4i**, 165-167°; **4l**, 135-135°; **6b**, 151-153°; **6c**, 140-143°; **6d**, 145-148°; **6e**, 149-151°; **6f**, 132-135°; **6i**, 151-153°; **6j**, 111-115°; **6k**, 45-47°, **6l**, 182-184°; **7b**, 178-181°; **7d**, 155-158°; **7j**, 202-204°; **8b**, 230-232°; **8c**, 195-198°; **8d**, 193-196°; **8e**, 251-252°; **8f**, 190-191°; **8h**, 154-156°; **8i**, 201-203°; **8j**; 200-203°; **8k**, 66-67°; **8l**, 163-164°; **10a**, 110-113°; **10b**, 169-171°; **10c**, 187-192°; **10d**, 149-152°; **10e**, 147-149°, **10f**, 130-131°; **10h**, 130-131°; **10i**, 163-164°; **10j**, 141-144°; **10k**, 154-155°; **10l**, 118-120°; **17a**, 98-100°; **17c**, 110-112°; The following are di-HCl salts: **9a**, 177-179° [dec]; **9b**, 225-228° [dec]; **9d**, 260-262°; **9e**, 242-243°; **9f**, 206-208°, **9g**, 193° [dec]; **9i**, 147-149°; **9j**, 156-159°; **9k**, 151-153°, **9l**, 187-188°; **16a**, 220-222°; **16b**, 209-211°; **16c**, 95° [dec].

(11) In the case of **16c**, 5 ml of *n*-propylamine was used and the reaction stirred at room temperature 21 hr.

(12) Representative ^{1}H nmr spectra: **3b** ($CDCl_3$): δ 7.02-6.82 (m, 3H), 4.65 (s, 1H), 4.25 (q, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 1.29 (t, 3H). **4b** (DMSO): δ **8**.29 (s, broad, 3H), 6.98-6.77 (m, 3H), 4.10 (m, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.40 (m, 1H), 3.03 (m, 1H), 1.15 (t, 3H). **6b** ($CDCl_3$): δ 7.88 (m, 1H), 7.75 (m, 1H), 6.77 (s, 3H), 6.25 (t, broad, 1H), 4.30 (s, 2H), 4.16, (m, 2H), 3.87 (s, 3H), (3.83, s 3H), 3.82 (m, 1H), 3.68 (t, 2H), 1.22 (t, 3H). **7b** ($CDCl_3$): δ 7.87 (m, 2H), 7.70 (m, 2H), 7.10 (s, 1H), 6.81 (s, 1H), 4.89 (s, 2H), 4.17 (q, 2H), 4.08 (m, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.72 (m, 1H), 3.60 (t, 1H), 1.23 (t, 3H). **8b** ($CDCl_3$): δ 8.97 (s, 1H), 8.52 (s, 1H), 7.93 (m, 2H), 7.77 (m, 2H), 7.46 (s, 1H), 5.48 (s, 2H), 4.41 (q, 2H),

4.07 (s, 6H), 1.41 (t, 3H). **9b** (di-HCl salt) (D_2O): δ 8.85 (s, 1H), 7.64 (s, 1H), 7.07 (s, 1H), 4.77 (s, 2H), 4.43 (q, 2H), 3.99 (s, 3H), 3.78 (s, 3H), 1.50 (t, 3H). **10b** ($CDCl_3$): δ 9.02 (s, 1H), 8.50 (s, 1H), 7.37 (s, 1H), 6.25 (s, broad, 1H), 4.93 (d, 2H), 4.46 (q, 2H), 4.08 (s, 3H), 4.02 (s, 3H), 1.59-1.45 (m, 12H).

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