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A Synthesis of Functionalized Indoline 2,2-Biscarboxylates

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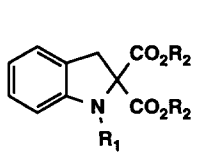
Abstract: *A synthetic approach to a structurally novel series of indoline 2,2-biscarboxylates is described that employs a tandem bis-alkylation strategy to cyclize the indoline heteroring from the bromide 7 and diethyl bromomalonate. The indolines thus prepared may be N-deprotected and further functionalized on the indoline nitrogen.* Copyright © 1996 Elsevier Science Ltd

Indoline 2,2-biscarboxylates (**1**) are almost unknown in the literature, despite the fact that numerous other nitrogen- and oxygen-containing heterocyclic 2,2-biscarboxylate ring systems have been investigated as synthetic intermediates and as components of biologically active molecules, a notable example being the selective β_3-andrenergic agonist BTA-243 (**2**).[1] The only reports of indoline compounds structurally related to **1** is that of compounds such as **3**,[2] some of which were evaluated for antimicrobial activity. Because of their close relationship to proline, pyrrolidine biscarboxylates (**4**) have been well studied, and are generally prepared by the reaction of a bromo-(3-bromopropyl)malonate ester with an amine, or by the reaction of an aminomalonate ester with a 1,3-dihalide,[3] but these methods are not suitable for the preparation of analogous benzo-fused compounds such as **1**.



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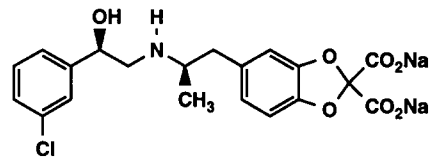

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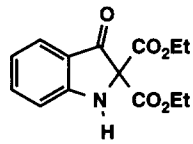

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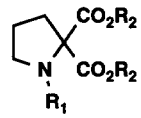

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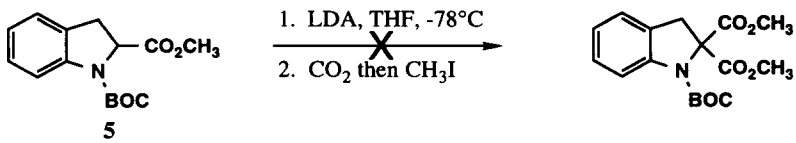
A route to **1** was thus devised *de novo*. Attempts to functionalize the readily available indoline mono-ester **5**[4] with a second carboxy group via the ester enolate were unsuccessful.[5] Trapping experiments using Me_3SiCl and D_2O suggested that the ester enolate (generated from **5** and LDA) suffered decomposition to a ketene, and that metalation of the benzylic methylene of **5** occurred competitively, or was in equilibrium with, enolate formation.



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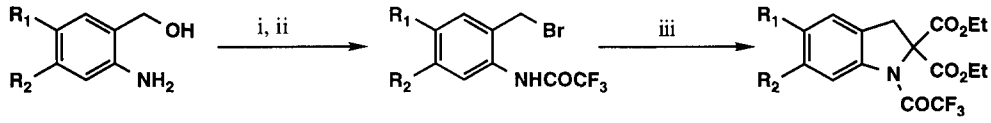
A route that constructed the indoline ring system at the last step, with the bis(alkoxycarbonyl) functionality already in place, was then sought. A two step route to the indoline precursor **8** was found using straightforward methodology (Scheme 1). Thus, the *o*-aminobenzyl alcohol **6** was converted to the N-trifluoroacetamide **7**,[6] after which the alcohol was converted to the benzylic bromide **8** with PBr_3.[7] Subsequently, a tandem bis-alkylation of **8** with diethyl bromomalonate in the presence of base, in which both reactants serve sequentially as nucleophile and electrophile, resulted in cyclization of the indoline ring to afford the key protected indoline **9**.[8]

Scheme 1

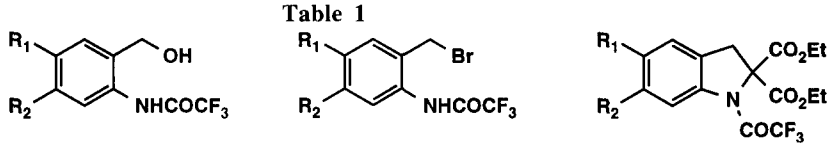


6 **8** **9**

(i) TFAA, Et_3N, Et_2O, 0 °C; (ii) PBr_3, Et_2O, CH_2Cl_2, 35 °C; (iii) $BrCH(CO_2Et)_2$, KOtBu, THF, 5 °C.

Experimentation revealed that optimum yields of **9** were attained when a premixed solution of **8** and diethyl bromomalonate, and a separate solution of potassium *tert*-butoxide, were added simultaneously to the reaction flask with cooling. For example, the addition of the base to the premix of **8** and diethyl bromomalonate resulted in a 15% loss of yield. The use of other bases, such as sodium hydride or diisopropylethylamine, were considerably less effective. Not surprisingly, the major by-product was tetra(carboethoxy)ethylene, formed by the dimerization of diethyl bromomalonate with base.[9] Very little if any dimerized **8** was noted in the crude product if diethyl bromomalonate was used in a 50 mole percent excess over **8**; however, when only one equivalent of diethyl bromomalonate was used, dimerization of **8** became a serious complication. The reaction was applied successfully to several substrates **8** (Table 1).

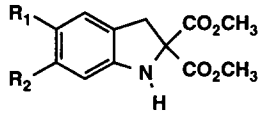
Table 1



Substituents R_1, R_2	Yield[a] of **7** (mp)	Yield[a] of **8** (mp)	Yield[a] of **9**
a: $R_1 = R_2 = H$	91% (75 - 76)	84% (121 - 122)	60%[b]
b: R_1 = Br, R_2 = H	70% (99 - 101)	93% (133 - 135)	63%
c: R_1 = H, R_2 = Cl[c]	95% (89 - 90)	83% (126 - 127)	62%
d: R_1 = Me, R_2 = H	86% (89 - 90)	77% (127 - 128)	66%
e: R_1 = Cl, R_2 = H	70% (120 - 121)	77% (108 - 109)	76%

[a] All yields represent isolated yields of pure products. All products gave satisfactory ^1H NMR and mass spectra and were homogeneous by tlc and GC. [b] All compounds **9** were oils. [c] The precursor amino alcohol was prepared as described by Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C. R. *J. Med. Chem.*, **1993**, *36*, 3397 - 3408.

The trifluoroacetamide residue of **9** was cleaved by magnesium methoxide in methanol with concomitant transesterification to afford the indoline **10**.[10] Attempts to N-functionalize **10b** with acylating agents by traditional methods failed; however, it was found that the N-lithio anion of **10b** (generated from **10b** with $LiN(SiMe_3)_2$) could be cleanly acylated with an acyl chloride or sulfonyl chloride to give **11b**.[11] Alkylation (eg, with benzyl bromide) was slower and was complicated by the formation of the rearrangement product **12b**.[12] This was overcome by the use of an excess of the alkylating agent, the addition of DMF to the reaction solvent, or by the use of a more reactive alkylating agent such as the alkyl sulfate or tosylate.[13, 14]



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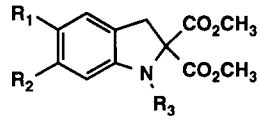

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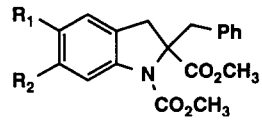

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References and Notes

1. (a) Bloom, J. D.; Claus, T. H. *Drugs of the Future* **1994**, *19*, 23 - 26; (b) Bloom, J. D.; Claus, T. H.; DeVries, V. G.; Dolan, J. A.; Dutia, M. D. US Patent 5,061,727.

2. (a) Azadi-Ardakani, M.; Alkhader, M. A.; Lippiatt, J. H.; Patel, D. I.; Smalley, R. K.; Higson, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1107 - 1112; (b) Martinet, A. *Ann. Sci. Univ. Besancon, Chim.* **1968**, *3*, 41 - 54 (*Chem. Abstr.* **1970**, *72*, 90188f).

3. (a) Curran, T. P.; McEnaney, P. M. *Tetrahedron Lett.* **1995**, *36*, 191 - 194; (b) v. Braun, J.; Leistner, W. *Chem. Ber.* **1926**, *59*, 2323 - 2329; (c) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1958**, 736 - 741; (d) Willstaetter, R.; Ettlinger, F. *Justus Liebigs Ann. Chem.* **1903**, *326*, 91 - 116; (e) Van Heyningen, E. *J. Am. Chem. Soc.* **1954**, *76*, 3043 - 3044.

4. Prepared from ethyl 5-bromoindole-2-carboxylate by reduction with Mg in MeOH (Pak, C. S.; Yon, G. H.; Youn, I. K. *Tetrahedron Lett.* **1986**, *27*, 2409 - 2410) and subsequent reaction with BOC_2O (THF, reflux).

5. Unsuccessful attempts were made to carboxylate **5** using LDA, LiHMDS, NaHMDS, and NaH as bases; and using CO_2, dimethyl carbonate, methyl cyanoformate, and methyl chloroformate as the electrophiles. The N-methyl and N-benzyl indoline monocarboxylates **5** behaved similarly.

6. Acidification of the NH was necessary for the alkylation to occur; the trifluoroacetamide was chosen for the higher yields it afforded and its ease of subsequent removal. See Hodge, P.; Harland, P. A.; Maughan, W.; Wildsmith, E. *Synthesis* **1984**, 941-943. Methanesulfonamides and acetamides failed to afford the desired cyclized products.

7. Typical procedure: A solution of 14.09 g (69.7 mmol) of **6b**[15] and 13.7 mL (97 mmol) of Et_3N in 240 mL of Et_2O was cooled to 0 °C. A solution of 10.8 mL (76.7 mmol) of TFAA in 10 mL of Et_2O was added dropwise, and the mixture was then stirred for 1 h at 0 °C. The mixture was then washed with dilute H_2SO_4, water (3 x), dried ($MgSO_4$), and concentrated to afford an oil that was crystallized by adding hexanes and cooling in ice. Filtration gave 14.51 g (70%) of **7b**, mp 99 - 101 °C. ^1H NMR ($CDCl_3$): δ = 10.02 (br, 1 H); 8.09 (d, 1 H); 7.50 (d of d, 1 H); 7.34 (d, 1 H); 4.81 (s, 2 H). MS (EI): *m/z* = 297, 299 (M^+, Br isotopes). A solution of **7b** (48.7 mmol) in 110 mL of Et_2O and 80 mL of CH_2Cl_2 was treated with 2.59 mL (27.25 mmol) of PBr_3 at 25 °C. The mixture was stirred at 25 °C for 5 min, then heated under reflux for 30 min. The reaction mixture was

poured into a mixture of Et_2O and ice water. The layers were separated and the Et_2O was washed with water, brine, dried (Na_2SO_4) and concentrated to give an oil that was crystallized by the addition of hexanes. The solid was filtered, washed, and dried to give 18.5 g (93%) of **8b**, mp 133 - 135 °C. ^1H NMR ($CDCl_3$): δ = 8.32 (br, 1 H); 7.79 (d, 1 H); 7.56 (d of d, 1 H); 7.54 (s, 1 H); 4.43 (s, 2 H).

8. Typical procedure: A solution of 9.46 g (26.2 mmol) of **8b** and 6.70 mL (39.31 mmol) of diethyl bromomalonate in 180 mL of THF was cooled to 5 °C under N_2. A cold (5 °C) solution of KOtBu (65.5 mL, 65.5 mmol, 1 M in THF) and the solution of **8b** were added simultaneously in rapid streams to a flask immersed in an ice bath with vigorous stirring. The mixture was stirred for 45 min at 5 °C, then was poured into a mixture of EtOAc and dilute HCl. The EtOAc was separated, washed with water, brine, dried (Na_2SO_4), and concentrated to give an oil, which was chromatographed on silica (4:1 EtOAc - hexanes) to give 7.22 g (63 %) of **9b** as an oil. ^1H NMR ($CDCl_3$): δ = 7.42 - 7.36 (m, 3 H); 4.29 (q, 4 H); 3.75 (br s, 2 H); 1.29 (t, 6 H). MS (EI): *m/z* = 437, 439 (M^+, Br isotopes).

9. Identified by its ^1H NMR, mp, and mass spectrum: (a) Villemin, D.; Alloum, A. B. *Synth. Commun.* **1992**, *22*, 3169 - 3179; (b) Beelitz, K.; Hohne, G.; Praefcke, K. *Z. Naturforsch.* **1978**, *33b*, 417 - 419.

10. Typical procedure: A solution of 0.87 g (35.8 mmol) of Mg in 15 mL of dry CH_3OH was treated with 3.14 g (7.17 mmol) of **9b** and was stirred under N_2 at 25 °C for 1.5 h. The reaction mixture was diluted with EtOAc and added to a mixture of EtOAc and water. The EtOAc was separated, washed with water, brine, dried (Na_2SO_4) and concentrated to a solid residue. This was dissolved in hot EtOAc and precipitated by the addition of hexanes to give 1.424 g (63%) of **10b**, mp 113 - 155 °C. ^1H NMR ($CDCl_3$): δ = 7.16 - 7.13 (m, 2 H); 6.58 (d, 1 H); 4.95 (br, 1 H); 3.78 (s, 6 H); 3.64 (s, 2 H). MS (EI): *m/z* = 313, 315 (M^+, Br isotopes).

11. Typical procedure: A solution of 0.307 g (0.98 mmol) of **10b** in 5 mL of dry THF was cooled to -70 °C under N_2 and treated with $LiN(SiMe_3)_2$ (1.08 mL, 1.08 mmol, 1 M in THF). The mixture was stirred for 5 min at -70 °C, then for 10 min at -10 °C. $PhSO_2Cl$ (0.138 mL, 1.08 mmol) was added in one portion and the mixture was stirred for 2.5 h at -10 °C. The mixture was then poured into EtOAc and dilute H_3PO_4, and the EtOAc was separated, washed with water, brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2) to give 0.410 g (92%) of **11b** ($R_3 = SO_2Ph$). ^1H NMR ($CDCl_3$): δ = 8.10 (m, 2 H); 7.60 - 7.46 (m, 3 H); 7.22 - 7.16 (m, 2 H); 6.93 (d, 1 H); 3.88 (s, 6 H); 3.77 (s, 2 H). MS (EI): *m/z* = 453, 455 (M^+, Br isotopes).

12. The identity of **12** was confirmed by independent synthesis.

13. For example, **11b** ($R_3 = CH_2Ph$) was prepared according to the procedure given above (11) from 0.314 g (1 mmol) of **10b**, 1.1 mL of 1 M $LiN(SiMe_3)_2$, 0.238 mL (2 mmol) of $PhCH_2Br$, and 0.150 g (1 mmol) of NaI in 4 mL of THF and 4 mL of DMF; yield 0.222 g (55%). ^1H NMR ($CDCl_3$): δ = 7.27 - 7.21 (m, 5 H); 7.13 (m, 1 H); 6.95 (d, 1 H); 6.02 (d, 1 H); 4.59 (s, 2 H); 3.71 (s, 2 H); 3.66 (s, 6 H). MS (EI): *m/z* = 403, 405 (M^+, Br isotopes).

14. Results of N-functionalization of **10b** to give **11b** (R_1 = Br, R_2 = H): (a) $R_3 = SO_2Ph$; 92%; (b) R_3 = COPh; 100%; (c) $R_3 = CH_2Ph$; 55%; (d) $R_3 = COCH_3$; 95%; (e) $R_3 = COCH_2Ph$; 54%; (f) $R_3 = CH_2CH_3$; 33%; (g) $R_3 = CH_3$; 41%.

15. This was prepared from 2-aminobenzyl alcohol by bromination with 1 eq. of 2,4,4,6-tetrabromocyclohexa-2,5-dienone in Et_2O at 0 °C; yield 86%, mp 111 - 112 °C. See *Org. Syn., Coll. Vol. VI*, p 181.

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