(rel intensity) 353 ($M^+$, 12), 77 (base peak). Anal. Calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.32; H, 5.46; N, 11.67.

**12**: colorless needles (ethyl acetate); mp 250–252 °C; IR (KBr) 2235, 2160, 1678 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 2.50 (1 H, dd, $J_{gem}$ = 13.6 and $J_{3-4}$ = 8.8 Hz, one of 3-H), 2.87 (1 H, dd, $J_{gem}$ = 14.3 and $J_{2-1}$ = 7.3 Hz, 2-H (exo)), 3.00 (1 H, dd, $J_{gem}$ = 14.3 and $J_{2-1}$ = 1.1 Hz, 2-H (endo)), 3.15 (1 H, dd, $J_{gem}$ = 13.6 and $J_{3-4}$ = 8.8 Hz, the other of 3-H), 3.21 (1 H, dd, $J_{gem}$ = 16.1 and $J_{5-4}$ = 8.1 Hz, one of 5-H), 3.32 (1 H, q, $J_{4a-5}$ = $J_{4a-4}$ = 8.1 Hz, 4a-H), 3.35 (1 H, dd, $J_{gem}$ = 16.1 and $J_{5-4a}$ = 8.1 Hz, the other of 5-H), 3.69 (1 H, ddd, $J_{1-2}$ = 7.3, 1.1, and $J_{1-9b}$ = 4.4 Hz, 1-H), 3.95 (1 H, dt, $J_{4-3}$ = 8.8 and $J_{4-4a}$ = 8.1 Hz, 4-H), 4.15 (1 H, d, $J_{9b-1}$ = 4.4 Hz, 9b-H), 7.3–7.6, 8.03 (9 H, m, Ar); $^{13}C$ NMR ($CDCl_3$) 30.05, 31.42, 34.47, 40.55 (1-, 2-, 3-, 4-, and 5-C) 55.85, 59.35 (5b- and 10b-C), 78.32 (9b-C), 120.25, 121.02 (each CN), 123.42, 125.67, 127.32, 127.50, 128.58, 129.35, 132.97, 135.33, 135.75 (each Ar), 198.01 (COPh); MS, *m/z* (rel intensity) 248 ($M^+$ – 105, 5), 84 (11), 83 (12), 69 (16), 44 (base peak). Anal. Calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 77.93; H, 5.21; N, 11.57.

# Synthesis and Rearrangement of Spiro[indan-2,3′-1′,2′,3′,4′-tetrahydroisoquinolin-1′-ones]: A New Approach to Benzo[*b*]phenanthridinones

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*Received June 7, 1988*

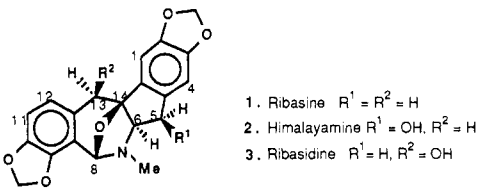
An efficient stereoselective synthesis of spiro[indan-2,3′-1′,2′,3′,4′-tetrahydroisoquinolin-1′-ones] **4** based on the intramolecular aldol condensation of the dicarbonyl compound **11** is described. The potential of compounds of type **4** as starting materials for the preparation of various ring systems by acid-catalyzed rearrangement was also studied. The results clearly indicate the strong tendency to undergo rearrangement by migration of C-1, affording benzo[*b*]phenanthridinones **5** in very good yield. The course of the process proved to be independent of the stereochemistry at C-4′, as was evidenced by the formation of the same product, **15d**, from the C-4′ epimers **12** and **13**. However, all attempts to force rearrangement of C-4′ or the nitrogen atom to C-1 to form indanobenzazepinones (**6** or **7**) resulted only in substitution and epimerization at C-1.

## Introduction

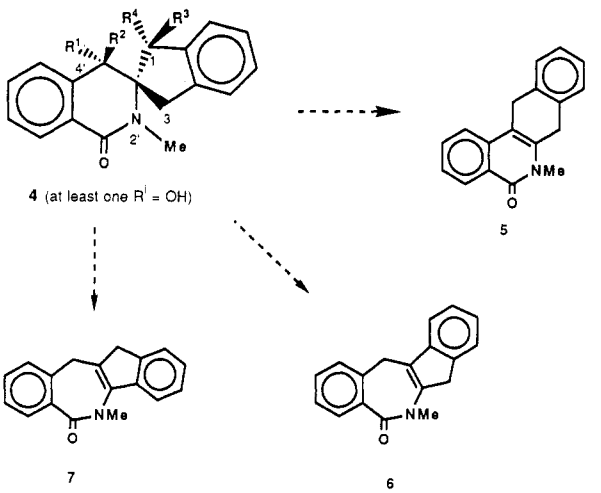
Ribasine (**1**)[1] was recently reported as the parent compound of a new class of alkaloids having the structure of 8,14-epoxy-indano[2,1-*c*][2]benzazepine. So far two other members, himalayamine (**2**)[2] and ribasidine (**3**),[3] both hydroxy derivatives of ribasine, are known (Scheme I).

The limited quantities of these alkaloids present in natural sources, together with the novelty of their skeleton and their potential pharmacological interest, make their synthetic preparation highly desirable.[4] We accordingly decided to explore the acid catalyzed rearrangement of spiro[indan-2,3′-1′,2′,3′,4′-tetrahydroisoquinolin-1′-ones] of the general type **4** (Scheme II). We reasoned that different ring systems could be obtained depending on the position of the hydroxyl group(s) and on the relative stereochemistry of the chiral centers in **4**. In particular, the migration of the carbon atoms C-1 or C-3 in 4′-hydroxy-substituted spiro compounds was expected to result in the formation of benzo[*b*]phenanthridinones **5**.[5] Alternatively, with a hydroxy group at C-1 in **4**, it was thought that indanobenzazepinones **6** (the basic nucleus of the ribasine alkaloids) or the isomeric **7** might be formed by migration of respectively C-4′[6] or the nitrogen atom[7] to C-1.

**Scheme I**




**Scheme II**




(1) Boente, J. M.; Castedo, L.; Cuadros, R.; Saá, J. M.; Suau, R.; Perales, M.; Martínez-Ripoll, M.; Fayos, J. *Tetrahedron Lett.* **1983**, *24*, 2029.

(2) Allais, D. P.; Guineaudeau, H.; Freyer, A. J.; Shamma, M.; Ganguli, N. C.; Talapatra, B.; Talapatra, S. K. *Tetrahedron Lett.* **1983**, *24*, 2445.

(3) Boente, J. M.; Campello, M. J.; Castedo, L.; Domínguez, D.; Saá, J. M.; Suau, R.; Vidal, M. C. *Tetrahedron Lett.* **1983**, *24*, 4481.

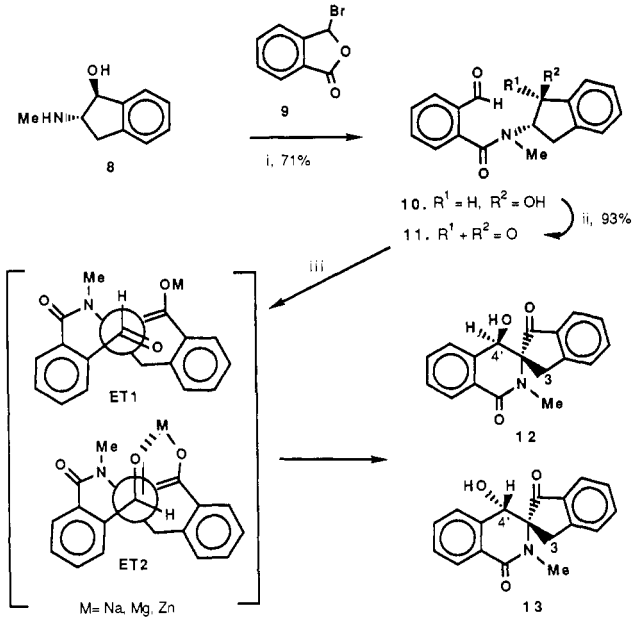
(4) For the first total synthesis of the basic skeleton of the ribasine alkaloids, see: Alonso, R.; Castedo, L.; Domínguez, D. *Tetrahedron Lett.* **1986**, *27*, 3539.

(5) Compounds of type **5** are isomers of the very well-known naturally occurring benzo[*c*]phenanthridine alkaloids; for a review, including synthesis, see: Simánek, V. Benzophenanthridine Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26.

(6) Analogous rearrangements to those proposed for the formation of **5** and **6** have been observed in the acid-catalyzed transpositions of the carbocyclic systems spiro(4,5)decanol-6 and spiro(4,5)decanol-1; see: Arnal, C.; Bessiere, J.; Christol, H.; Vanel, R. *Bull. Soc. Chim. Fr.* **1967**, 2479 and 2485.

0022-3263/89/1954-0424$01.50/0 

**Scheme III**[a]




[a] Reagents: (i) $Et_3N$/THF; (ii) PCC/$CH_2Cl$; and (iii) (a) THF–NaOH, room temperature (12:13, 6:1); (b) $MgCl_2$/THF, reflux (12:13, 1:9).

## Results and Discussion

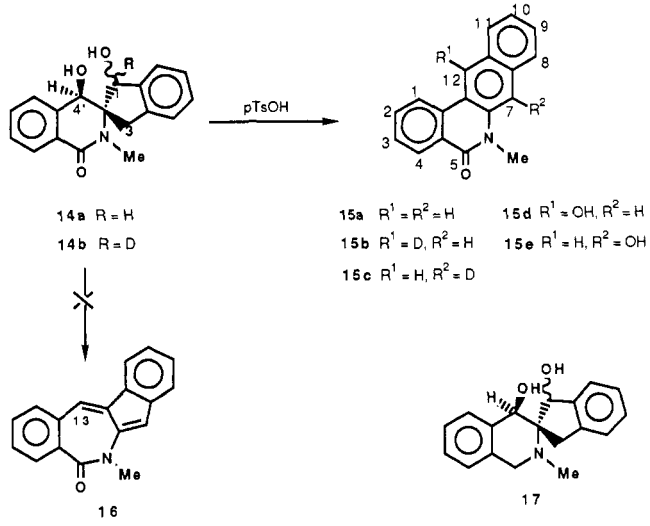
This research was initiated by studying the preparation of the C-4′-epimeric spiro compounds **12** and **13**, which we planned to obtain by intramolecular aldol condensation of dicarbonyl compound **11** (Scheme III). Diketone **11** was synthesized starting from (+)-(1S,2S)-2-(methylamino)-1-indanol (**8**)[8] and 3-bromophthalide (**9**).[9] Their condensation[10] in tetrahydrofuran (THF) in the presence of triethylamine led to amide **10**[11] in 71% yield. Subsequent oxidation of the benzylic hydroxyl group with PCC gave the ketone **11**,[11,12] whose strong tendency to undergo intramolecular aldol condensation was evidenced by its partial conversion to spiro compounds **12** and **13** during isolation by filtration through Florisil, alumina, or silica gel. The best results were obtained with Celite; **11** was produced in 93% yield with only traces of **12** and **13**.

The desired spiro compounds (**12** and **13**) were obtained in quantitative yield as a 6:1 mixture (according to $^1H$ NMR integration of the crude reaction mixture) by treatment of a THF solution of dicarbonyl compound **11** with sodium hydroxide. In order to gain information about the relative stereochemistry of the two compounds, the influence of chelating metals in the reaction mixture was investigated.[13] It was thought that their presence would increase the importance of the transition state ET2, which leads to a stabilized chelate from which **13** is derived after quenching. As expected, the Lewis acid catalyzed aldol condensation of **11** promoted by $MgCl_2$ or $ZnCl_2$ gave a quantitative yield of a 1:9 mixture of **12** and **13**. In contrast, with sodium enolates it appears that chelation is minimal and the aldolates equilibrate to form the isomer in which the two oxygen atoms are as far apart as possible, giving an **12** to **13** ratio of 6:1. The assignment of relative stereochemistry for the spiro derivatives was further confirmed by nuclear Overhauser difference spectroscopy,[14] which showed that only for spiro compound **13** did irradiation of the H-3 proton that appears at higher field result in enhancement (9%) of the singlet due to H-4′ (Scheme III). Additional evidence came from the $^{13}C$ NMR spectra of the two epimers, in which the C-3 signal in **13** appears 3.2 ppm downfield compared to **12**. This can be related to the relative stereochemistry between the 4′-hydroxy group and C-3, which is anti in **13** (γ-anti effect) and gauche in **12** (γ-gauche effect).[15]

Having found how to generate both the epimeric spiro derivatives, **12** and **13**, we were in a position to initiate rearrangement studies. Sodium borohydride reduction of **12** afforded the dialcohol **14a** as a 9:1 mixture of epimers at C-1. Its treatment with pTsOH in refluxing toluene gave a major product (79% overall yield) that according to its spectroscopic data (including NOE studies) might have the structure of either benzo[b]phenanthridinone **15a**[16] or indanobenzazepinone **16**.

In order to study more closely the rearrangement reaction and confirm the structure of the product, we decided to investigate the behavior of the deuteriated compound **14b** under the same conditions as had been used with its

**Scheme IV**




(7) The migration of an amide nitrogen to an electron-deficient center in the rearrangement of a cyclohexadienyl system has been reported: Hey, D. H.; Jones, G. H.; Perkins, M. J. *J. Chem. Soc., Perkin Trans 1* **1972**, 1162.

(8) McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1983**, *48*, 2675.

(9) Koten, I. A.; Sauer, R. J. *Organic Synthesis* **1962**, *42*, 26.

(10) Sloan, K. B.; Koch, S. A. M. *J. Org. Chem.* **1983**, *48*, 635.

(11) The $^1H$ NMR data reveal slow rotation about the amide bond in compounds **10** and **11**: Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517.

(12) The possibility of constructing the indanobenzazepine nucleus of the ribasine alkaloids by intramolecular dicarbonyl coupling of compound **11** was considered. However, although a variety of metallic systems were tried, all attempts at cyclization were unsuccessful.

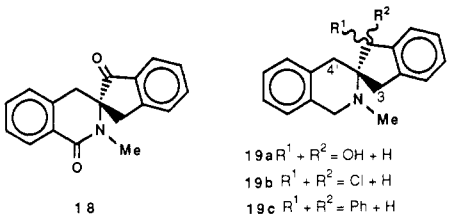
(13) For a comprehensive discussion of aldol stereoselection, see: Heathcock, C. H. Stereoselective Aldol Condensations. In *Comprehensive Carbanion Chemistry*, Part. B; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984.

(14) Initial NOEDIF experiments performed with **12** and **13** in $CDCl_3$ proved to be of little value due to the proximity of the signals of the H-3 protons and the methyl group. The use of acetone-$d_6$ separates these resonances, allowing selective irradiation.

(15) It is well-known that the γ-gauche effect of a hydroxy group is more shielding than the γ-anti. See, for example: (a) Duddeck, H. In *Topics in Stereochemistry*, Eliel, E. L., Wilen, S. H., Allinger, N. L., Ed.; Willey: New York, 1986; Vol. 16, p 219. (b) Eliel, E. L.; Bailey, W. F.; Kopp, L. D.; Willer, R. L.; Grant, D. M.; Bertrand, R.; Christensen, K. A.; Dalling, D. K.; Duch, M. W.; Wenkert, E.; Schell, F. M.; Cochran, D. W. *J. Am. Chem. Soc.* **1975**, *97*, 322. (c) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866.

(16) Hey and Perkins have summarized the confused earlier literature on the identification of *N*-methylbenzophenanthridinones: Hey, D. H.; Jones, G. H.; Perkins, M. J. *J. Chem. Soc., Perkin Trans 1* **1972**, 105. The compound they describe as **15a** has a melting point very close to that of our isolated amide, but the correspondence between the chemical shifts in the $^1H$ NMR spectra is not total.

Scheme V




analogue **14a**. The deuterium atom would be lost in the formation of indanobenzazepinone **16** (migration of C-4′) but retained if C-1 or C-3 migrated to give the deuteriated benzo[*b*]phenanthridinones **15b** or **15c**, respectively. If retained, its position in the final benzo[*b*]phenanthridinone (C-7 or C-12) would also show the pathway followed by the rearrangement (Scheme IV).

When deuteriated dialcohol **14b**[17] was treated with pTsOH in refluxing toluene, a single product was quantitatively obtained. Its $^1$H NMR spectrum was very similar to that of the rearrangement product of **14a**, except for the singlet at lowest field, which was now very weak, indicating the presence of a deuterium atom in place of the more deshielded proton (which according to NOE data corresponds to H-12). The amide **15b** had thus been obtained by migration of carbon atom C-1 (in anti position with respect to the leaving group) in preference to C-4′. This result suggested that the relative position of the hydroxy group at C-4′ of the spiro compound might determine which carbon atom migrates, C-1 or C-3.

To test the above hypothesis, we studied the rearrangement of the C-4′ epimers **12** and **13**, which would afford 12- and/or 7-hydroxy-substituted benzo[*b*]-phenanthridinones **15d** and/or **15e**, by migration of C-1 and/or C-3, respectively. The same compound, 12-hydroxybenzo[*b*]phenanthridinone **15d**,[18] was nevertheless obtained from both **12** and **13**, which means that the reaction is not affected by the relative stereochemistry at C-4′ and may take place via a common benzyl carbocation intermediate.

Further rearrangement studies were carried out with the major C-1 epimer of the dialcohol **17**, which was obtained by crystallization of the crude product of the lithium aluminum hydride (LAH) reduction of the spiro derivative **12** (Scheme IV). Treatment of **17** with pTsOH in refluxing toluene gave **15a** as a result of rearrangement and oxidation processes.

The strong tendency of spiro compounds of type **4** to undergo rearrangement to benzo[*b*]phenanthridinones in good yield might be related to the aromatization process that takes place in the course of this conversion. This would explain the failure of this reactions to afford indanobenzazepinones. To force the reaction to give the benzazepine skeleton, we therefore applied it to amino alcohol **19a**, in which the lack of a leaving group at C-4′ blocks the benzo[*b*]phenanthridinone formation pathway (Scheme V). In the first experiments, which were carried out with the mixture of epimers obtained by reduction of compound **18**[4] with LAH, **19a** was unaltered by treatment with either pTsOH (0.5 equiv) in refluxing benzene or $BF_3$·$OEt_2$ (0.5–2 equiv). Treatment of the major epimer of **19a** with concentrated HCl at 95 °C for 12 h gave chloro compound **19b** together with starting material and its C-1 epimer. When **19a** was refluxed in benzene with 20 equiv of pTsOH for 80 h, **19c** was obtained as a mixture of epimers.

(17) In this experiment we used the major epimer of **14b**, obtained by crystallization of the crude mixture of the reaction of the spiro compound **12** with $NaBD_4$.

(18) Structure **15d** is firmly supported by NOE studies that show a reciprocal nuclear Overhauser effect between the proton at C-7 and the methyl group.

## Conclusion

The stereoselectivity of the intramolecular aldol condensation of dicarbonyl compound **11** can be controlled by the use of chelating or nonchelating conditions. Rearrangement studies resulted in transformation of the spiro compounds **4** in high yield into benzo[*b*]phenanthridinones by migration of C-1. To judge by the results obtained with compounds **12** and **13**, this reaction is unnaffected by the stereochemistry at C-4′. This result suggests the attractive possibility of using the same strategy for the formation of benzo[*a*]- and benzo[*c*]phenanthridines from spiro[indan-1,3′-1′,2′,3′,4′-tetrahydroisoquinolin-1′-ones). In contrast, all attempts to obtain 2-benzazepines by migration of C-4′ have been unsuccessful, the only products isolated were the result of epimerization and substitution at C-1.

## Experimental Section

**General Methods.** $^1$H NMR spectra were recorded on a Brucker WM-250 spectrometer in $CDCl_3$. $^{13}$C NMR spectra were measured at 62.83 MHz. Chemical shifts are reported (ppm) downfield from tetramethylsilane ($\delta$). Coupling constants are in hertz. IR spectra were obtained on a Pye Unicam 1100 spectrometer. Mass spectra were measured with a Kratos MS-25 spectrometer at an ionization voltage of 70 eV. Melting points are uncorrected. All air-sensitive reactions were run under dried deoxygenated argon in oven-dried glassware with magnetic stirring; reagents were added by syringe through septa. All solvents for air- or moisture-sensitive reactions were dried by standard procedures.

**(+)-(1*S*,2*S*)-2-[*N*-Methyl-*N*-(2′-formylbenzoyl)amino]-1-indanol (10).** To a solution of (+)-(1*S*,2*S*)-2-(methylamino)-1-indanol (**8**)[8] (8.28 g, 50.8 mmol) in dry THF (250 mL) were added 3-bromophthalide (**9**)[9] (14 g, 66 mmol) and $Et_3N$ (7.1 mL, 50.9 mmol). After 24 h of stirring at room temperature, the triethylamine hydrobromide formed was filtered off and washed with THF. Evaporation of the solvent and column chromatography (silica gel, $Et_2O$) gave amide **10** (10.6 g, 71%) as a white solid: mp 69–72 °C: $[\alpha]^{20}_D$ +4.2° (*c* 4.5, MeOH); $^1$H NMR $\delta$ 2.76 and 3.15 (s each, 3 H, NMe of the minor and major rotamers, respectively), 4.07 (m, H-2 of the major rotamer), 5.2–5.4 (m, H-1 of the major rotamer and H-2 of the minor rotamer), 5.5 (m, H-1 of the minor rotamer), 7.1–8.0 (m, 8 H, ArH), and 10.03 and 10.06 (s each, ArCHO of the major and minor rotamer, respectively); IR (KBr) 1620, 1695, 3400 cm$^{-1}$; MS, *m*/*z* (rel intensity) 295 ($M^+$, 1), 277 ($M^+$ – 18, 8), 133 (100). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.81; N, 4.74. Found: C, 73.17; H, 5.83; N, 4.72.

**(−)-(2*S*)-2-[*N*-Methyl-*N*-(2′-formylbenzoyl)amino]-1-indanone (11).** A solution of amide **10** (600 mg, 2.04 mmol) and PCC (550 mg, 1.25 equiv) in $CH_2Cl_2$ (50 mL) was stirred for 12 h at room temperature. After filtration, the residue was washed with $CH_2Cl_2$ (3 × 7 mL), and isopropyl alcohol (0.5 mL) was added to the filtrate. After stirring for 0.5 h, the solvents were evaporated and the residue treated with $CH_2Cl_2$ (50 mL), filtered, washed with aqueous 10% HCl (10 mL), dried ($Na_2SO_4$), and evaporated to give an oil, which was filtered through a column of Celite and eluted with ethyl ether. Dicarbonyl compound **11** was obtained as a colorless oil (93%): $[\alpha]^{20}_D$ −9.8° (*c* 1.9, MeOH); $^1$H NMR $\delta$ 2.80 and 2.98 (s each, 3 H, NMe of the major and minor rotamer, respectively), 3.24 (d, $J$ = 6.8, H-3 of the minor rotamer), 3.45 (dd, $J$ = 17.0 and 5.4, H-3 of the major rotamer), 3.70 (dd, $J$ = 17.0 and 8.2, H-3 of the major rotamer), 4.39 (t, $J$ = 6.8, H-2 of the minor rotamer), 5.07 (m, H-2 of the major rotamer), 7.3–8.1 (m, 8 H, Ar H), 10.16 (s, 1 H, ArCHO); IR (film) 1630, 1720 cm$^{-1}$; MS, *m*/*z* (rel intensity) 293 ($M^+$, 61), 275 ($M^+$ – 18, 6), 160 (100), 133 (12); HRMS, calcd for $C_{18}H_{15}NO_3$ 293.1052, found 293.1071.

**Spiro[1-oxoindan-2,3′-(*N*-methyl-4′-hydroxy-1′,2′,3′,4′-tetrahydroisoquinolin-1′-one)] (12). Method A.** A solution of amide **10** (240 mg, 0.81 mmol) and PCC (220 mg, 1.26 equiv) in $CH_2Cl_2$ (10 mL) was stirred for 14 h at room temperature. After evaporation of the solvent, the residue was treated with a mixture of 10% aqueous NaOH–THF (1:1) (14 mL). After 1 h of stirring

at room temperature, the solvent was evaporated, and the residue was washed with $CH_2Cl_2$ (4 × 15 mL). The colorless organic phase obtained was washed with brine, dried ($Na_2SO_4$), and concentrated. Crystallization from EtOH gave **12** (170 mg, 71%): mp 228–230 °C; $^1H$ NMR δ 2.85 (s, 3 H, NMe), 2.94 (d, $J$ = 17.8, 1 H, H-3), 3.41 (s, b, 1 H, OH), 3.64 (d, $J$ = 17.8, 1 H, H-3), 5.51 (s, b, 1 H, H-4), 7.3-8.1 (8 H, ArH); $^{13}C$ NMR δ 30.1 ($NCH_3$), 33.6 (C-3), 70.3 (C-4′), 72.8 (C-2), 164.6 (C-1′), 203.5 (C-1); IR (KBr) 3300, 1720, 1630 and 1580 $cm^{-1}$; MS, $m/z$ (rel intensity) 293 ($M^+$, 47), 275 (5), 248 (8), 160 (100), 133 (36). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.16; N, 4.78. Found: C, 73.77; H, 5.38; N, 4.61.

**Method B.** To a solution of ketone **11** (22 mg) in THF (1 mL) was added solid NaOH (7 mg). After stirring for 3 h at room temperature, the solvents were evaporated and the solid residue was extracted with $CH_2Cl_2$ to give a 6:1 mixture of **12** and **13** in quantitative yield ($^1H$ NMR integration).

**Spiro[1-oxoindan-2,3′-(*N*-methyl-4′-hydroxy-1′,2′,3′,4′-tetrahydroisoquinolin-1′-one)] (13).** $MgCl_2$ (50 mg) was added to a solution of the ketone **11** (160 mg) in THF (20 mL), and the mixture was refluxed for 12 h. The solvent was removed, and brine and $CH_2Cl_2$ were added. The aqueous phase was extracted with $CH_2Cl_2$, and the organic extracts were dried ($Na_2SO_4$) and concentrated to give a 1:9 mixture of **12** and **13**. PTLC on silica gel (EtOH–$CH_2Cl_2$, 2:98) yielded the major compound **13** (140 mg, 88%), which was crystallized from MeOH: mp 204–206 °C; $^1H$ NMR δ 2.99 (s, 3 H, NMe), 3.09 (d, $J$ = 17.9, 1 H, H-3), 3.18 (d, $J$ = 17.9, 1 H, H-3), 3.81 (s, b, 1 H, OH), 4.47 (d, $J$ = 4.6, 1 H, H-4′), 7.3–8.2 (8 H, ArH); $^{13}C$ NMR δ 30.7 ($NCH_3$), 36.8 (C-3), 71.3 (C-4′), 71.8 (C-2), 164.6 (C-1′), 201.1 (C-1); IR (KBr) 1580, 1600, 1640, 1720, and 3300 $cm^{-1}$; MS, $m/z$ (rel intensity) 293 ($M^+$, 41), 275 (4), 248 (6), 160 (100), 105 (24). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.16; N, 4.78. Found: C, 73.60; H, 5.21; N, 4.62. Similar results were obtained by using $ZnCl_2$.

**Spiro[1-hydroxyindan-2,3′-(*N*-methyl-4′-hydroxy-1′,2′,3′,4′-tetrahydroisoquinolin-1′-ones)] (14a).** $NaBH_4$ (9 mg, 0.24 mmol) was added to a suspension of spiro compound **12** (50 mg, 0.17 mmol) in MeOH (3 mL). After being stirred for 1.5 h, the solvent was evaporated and the solid residue was treated with a mixture of $CH_2Cl_2$ and distilled water. The aqueous phase was extracted with more $CH_2Cl_2$, and the organic extracts were mixed, dried, and concentrated. The **major epimer** (46 mg, 91%) was obtained by direct crystallization from EtOH: mp 244–246 °C; $^1H$ NMR ($CDCl_3$ + $CD_3OD$) δ 2.82 (s, 3 H, NMe), 3.65 (s, 2 H, H-3), 4.39 (s, 1 H, H-1), 4.78 (s, 1 H, H-4′), 7.2–7.6 (m, 7 H, ArH), 7.84 (d, $J$ = 7.3, 1 H, ArH); IR (KBr) 1630, 3360 $cm^{-1}$; MS, $m/z$ (rel intensity) 295 ($M^+$, 1), 277 ($M^+$ – 18, 100), 105 (78). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.81; N, 4.74. Found: C, 72.96; H, 5.87; N, 4.65. The **minor epimer** was separated by PTLC on neutral alumina of the mother liquids of crystallization (2 mg, 4%) as a white solid: mp 237–239 °C; $^1H$ NMR δ 2.35 (s, b, 1 H, OH), 2.80 (s, b, 1 H, OH), 2.89 (s, 3 H, NMe), 3.23 (d, $J$ = 17.5, 1 H, H-3), 3.66 (d, $J$ = 17.5, 1 H, H-3), 5.12 (d, $J$ = 4.9, 1 H, H-4′), 5.22 (d, $J$ = 5.9, 1 H, H-1), 7.2–7.6 (m, 7 H, ArH), 8.08 (d, $J$ = 7.3, 1 H, ArH); IR (KBr) 1620, 3340, 3430 $cm^{-1}$; MS, m/z (rel intensity) 295 ($M^+$, 2), 277 ($M^+$ – 18, 100), 105 (76).

**Spiro[1-deuterio-1-hydroxyindan-2,3′-(*N*-methyl-4′-hydroxy-1′,2′,3′,4′-tetrahydroisoquinolin-1′-ones)] (14b).** These were obtained from **12** (50 mg, 0.17 mmol) and $NaBD_4$ (14 mg, 0.39 mmol) following the procedure described for **14a**. **Major epimer** (40 mg, 79%): mp 242–244 °C (EtOH); $^1H$ NMR δ 2.75 (d, $J$ = 8.5, 1 H, OH at C-4′), 2.96 (s, 3 H, NMe), 3.67 (s, 2 H, H-3), 4.44 (d, $J$ = 8.5, 1 H, H-4′), 7.28–7.53 (m, 7 H, ArH), 8.05 (d, $J$ = 7.3, 1 H, ArH); IR (KBr) 1630, 3350 $cm^{-1}$; MS, $m/z$ (rel intensity) 296 ($M^+$, 73), 105 (100). Anal. Calcd for $C_{18}H_{16}DNO_3$: C, 72.95; H, 6.12; N, 4.73. Found: C, 72.86; H, 5.81; N, 4.68. **Minor epimer** (2 mg, 4%): mp 238–240 °C ($CH_2Cl_2$–EtOH); $^1H$ NMR δ 2.58 (s, b, 1 H, OH), 2.84 (s, 3 H, NMe), 3.06 (s, b, 1 H, OH), 3.20 (d, $J$ = 17.5, 1 H, H-3), 3.65 (d, $J$ = 17.5, 1 H, H-3), 5.19 (s, b, 1 H, H-4′), 7.2–7.6 (m, 7 H, ArH), 8.02 (d, $J$ 7.9, 1 H, ArH); IR (KBr) 2920, 3340, 3440 $cm^{-1}$; MS $m/z$ (rel intensity) 296 ($M^+$, 1), 278 ($M^+$ – 18, 100). Anal. Calcd for $C_{18}H_{16}DNO_3$: C, 72.95; H, 6.12; N, 4.73. Found: C, 72.92; H, 5.96; N, 4.56.

***N*-Methylbenzo[*b*]phenanthridinone (15a).** $NaBH_4$ (30 mg, 0.79 mmol) was added to a suspension of alcohol **12** (103 mg, 0.35 mmol) in MeOH (3 mL). After 0.5 h of stirring, the reaction mixture was concentrated to dryness, the solid residue was dissolved, and the organic layer was treated with distilled water. The organic phase was dried and the solvent evaporated. The crude **14a** obtained was refluxed in dry toluene (10 mL) in the presence of pTsOH (50 mg). Compound **15a** was isolated by PTLC (silica gel; EtOH–$CH_2Cl_2$, 2:98) (72 mg, 79% overall yield): mp 200 °C (EtOH); $^1H$ NMR δ 3.90 (s, 3 H, NMe), 7.45–7.65 (m, 3 H, ArH), 7.73 (s, 1 H, H-7), 7.80 (m, 1 H, ArH), 7.91 (d, $J$ = 7.6, 1 H, H-8), 7.98 (d, $J$ = 7.5, 1 H, H-11), 8.45 (dd, $J$ = 8.5 and 0.5, 1 H, H-1), 8.56 (dd, $J$ = 7.9 and 1.1, 1 H, ArH), 8.76 (s, 1 H, H-12); IR (KBr) 1625, 1650 $cm^{-1}$; MS, $m/z$ (rel intensity) 259 ($M^+$, 100). Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.06; N, 5.40. Found: C, 83.42; H, 5.10; N, 5.36.

**12-Deuterio-*N*-methylbenzo[*b*]phenanthridinone (15b).** A solution of the major epimer of spiro derivative **14b** (55 mg, 0.19 mmol) and pTsOH (50 mg) in dry toluene (3 mL) was refluxed for 5 min. The solvent was evaporated and the residue was dissolved in $CH_2Cl_2$. The organic solution was washed with a saturated aqueous solution of $NaHCO_3$, dried, and concentrated to give essentially pure **15b** in quantitative yield. Crystallization from EtOH afforded long white needles, mp 196 °C: $^1H$ NMR δ 3.80 (s, 3 H, NMe), 7.44–7.57 (m, 3 H, ArH), 7.60 (s, 1 H, H-7), 7.74 (td, 1 H, ArH), 7.85 (d, $J$ = 7.8, 1 H, H-8), 7.90 (d, $J$ = 7.8, 1 H, H-11), 8.33 (d, $J$ = 7.9, 1 H, H-1), 8.52 (dd, $J$ = 7.7 and 1.0, 1 H, H-4), 8.62 (s, 7% of 1 H, H-12); IR (KBr) 1650 $cm^{-1}$; MS, $m/z$ (rel intensity) 260 ($M^+$, 100), 259 ($M^+$ – 1, 22). Anal. Calcd for $C_{18}H_{12}DNO$: C, 83.05; H, 5.42; N, 5.38. Found: C, 83.04; H, 5.24; N, 5.13.

**12-Hydroxy-*N*-methylbenzo[*b*]phenanthridinone (15d).** A solution of spiro compound **12** (50 mg, 0.17 mmol) and pTsOH (50 mg) in toluene (15 mL) was refluxed for 4 h. The solvent was evaporated and the yellow residue was dissolved in $CH_2Cl_2$. The organic phase was washed with an aqueous solution of $NaHCO_3$ and then extracted with 10% aqueous NaOH (20 mL). On acidification of the aqueous phase with dilute HCl (1:1), the yellow color disappeared and a white solid precipitated. Extraction with $CH_2Cl_2$, drying, and concentration gave **15d** in quantitative yield as a white solid, which crystallized from $CH_2Cl_2$: mp 252–254 °C; $^1H$ NMR δ 3.87 (s, 3 H, NMe), 7.40 (s, 1 H, H-7), 7.56 (m, 3 H, ArH), 7.79 (t, 1 H, ArH), 7.91 (d, $J$ = 7.7, ArH), 8.06 (d, $J$ = 7.7, 1 H, ArH), 8.61 (d, $J$ = 8.2, 1 H, ArH), 9.30 (d, $J$ = 8.4, 1 H, ArH); IR (KBr) 1620, 3300 $cm^{-1}$; MS, $m/z$ (rel intensity) 275 ($M^+$, 100), 246 (18). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.46; H, 4.77; N, 5.04. The same result was obtained starting with the spiro compound **13**.

**Spiro[1-hydroxyindan-2,3′-(*N*-methyl-4′-hydroxy-1′,2′,3′,4′-tetrahydroisoquinolines)] (17).** LAH (13 mg, 0.34 mmol) was added to a solution of the keto alcohol **12** (100 mg, 0.34 mmol) in THF (6 mL), and the reaction mixture was refluxed for 3 h. A saturated aqueous solution of $Na_2SO_4$ (5 mL) was added and the liquid phase was decanted off. The solid was exhaustively washed with THF and $CH_2Cl_2$, the solvents were evaporated, and the residue was dissolved in $CH_2Cl_2$. The solution was washed with brine, dried ($Na_2SO_4$), and evaporated to yield diol **17** as a mixture of C-1 epimers which were separated by PTLC (alumina; EtOH–$CH_2Cl_2$, 2:98). *Major epimer* (lower $R_f$) (60 mg, 63%): $^1H$ NMR δ 2.66 (s, 3 H, NMe), 3.23 (d, $J$ = 15.9, 1 H, H-3), 3.38 (d, $J$ = 15.9, 1 H, H-3), 3.92 (d, $J$ = 16.8, 1 H, H-1′), 4.28 (s, 1 H, H-1 or H-4′), 4.31 (d, $J$ = 16.8, 1 H, H-1′), 4.68 (s, 1 H, H-1 or H-4′), 7.1–7.4 (m, 8 H, ArH); IR (KBr) 3420, 3560 $cm^{-1}$; MS, $m/z$ (rel intensity) 281 ($M^+$, 27), 144 (100). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.72; H, 6.84; N, 4.93. **Minor epimer** (higher $R_f$) (15%): $^1H$ NMR δ 2.26 (s, 3 H, NMe), 3.11 (d, $J$ = 17.3, 1 H, H-3), 3.33 (d, $J$ = 17.3, 1 H, H-3), 3.83 (d, $J$ = 17.0, 1 H, H-1′), 4.02 (d, $J$ = 17.0, 1 H, H-1′), 5.01 (s, 1 H, H-1 or H-4′), 5.24 (s, 1 H, H-1 or H-4′), 7.0–7.6 (m, 8 H, ArH); IR (KBr) 3010–3060, 3350 $cm^{-1}$; MS, $m/z$ (rel intensity) 281 ($M^+$, 35), 263 ($M^+$ – 18, 22), 144 (100).

**Spiro[1-hydroxyindan-2,3′-(*N*-methyl-1′,2′,3′,4′-tetrahydroisoquinolines)] (19a).** This was obtained as a mixture of epimers starting from ketone 18[4] (50 mg, 0.18 mmol) and following the same procedure as for the preparation of diols **17**. The **major epimer** (higher $R_f$; alumina; $CH_2Cl_2$) (22 mg, 46%) was crystallized from EtOH: mp 181 °C; $^1H$ NMR δ 2.53 (s, 3 H, NMe), 2.63 (d, $J$ = 17.3, 1 H), 2.70 (d, $J$ = 17.3, 1 H), 2.76 (d, $J$ = 14.9, 1 H), 3.27 (d, $J$ = 14.9, 1 H), 4.04 (d, $J$ = 17.1, 1 H, H-1′),

4.11 (d, $J$ = 17.1, 1 H, H-1'), 4.59 (s, 1 H, H-1), 6.96 (d, $J$ = 6.58, 1 H, ArH), 7.1-7.3 (m, 6 H, ArH), 7.44 (d, $J$ = 6.08, 1 H, ArH); IR (KBr) 1620, 3420 $cm^{-1}$; HRMS calcd for $C_{18}H_{19}NO$ 265.1467, found 265.1459. The **minor epimer** was obtained as an oil (12 mg, 25%): $^1H$ NMR $\delta$ 2.38 (d, $J$ = 16.9, 1 H), 2.53 (s, 3 H, NMe), 2.79 (d, $J$ = 15.3, 1 H), 3.08 (d, $J$ = 15.3, 1 H), 3.24 (d, $J$ = 16.9, 1 H), 3.91 (d, $J$ = 16.7, 1 H, H-1'), 4.11 (d, $J$ = 16.7, 1 H, H-1'), 5.41 (s, 1 H, H-1), 6.9-7.4 (m, 8 H, ArH); IR (KBr) 1460, 3460 $cm^{-1}$; MS, $m/z$ (rel intensity) 265 ($M^+$, 95), 264 (91), 247 ($M^+$ - 18, 5), 146 (100); HRMS calcd for $C_{18}H_{19}NO$ 265.1467, found 265.1458.

**Spiro[1-chloroindan-2,3'-(*N*-methyl-1',2',3',4'-tetrahydroisoquinoline)] (19b).** A solution of the major epimer of amino alcohol **19a** (13 mg, 0.05 mmol) in concentrated HCl (3 mL) was maintained for 24 h at 95 °C. Addition of 10% aqueous KOH resulted in a white precipitate, which was extracted with $CH_2Cl_2$ (4 × 10 mL). The organic extracts were dried ($Na_2SO_4$) and concentrated to give an oil, which was chromatographed on neutral alumina (PTLC, $CH_2Cl_2$). Chloro derivative **19b** (6 mg, 43%) was obtained as a colorless oil together with some of the starting material and its C-1 epimer: $^1H$ NMR $\delta$ 2.56 (s, 3 H, NMe), 2.70 (s, 2 H), 2.85 (d, $J$ = 15.0, 1 H), 3.37 (d, $J$ = 15.0, 1 H), 4.13 (d, $J$ = 17.9, 1 H, H-1'), 4.23 (d, $J$ = 17.9, 1 H, H-1'), 5.03 (s, 1 H, H-1), 6.93 (d, 1 H, ArH), 7.1-7.5 (m, 7 H, ArH); MS, $m/z$ (rel intensity) 285 ($M^+$, 31), 283 (93), 282 (100).

**Spiro[1-phenylindan-2,3'-(*N*-methyl-1',2',3',4'-tetrahydroisoquinolines)] (19c).** A solution of the major epimer of amino alcohol **19a** (36 mg, 0.14 mmol) and pTsOH (516 mg, 2.71 mmol) in benzene (15 mL) was refluxed for 80 h. The reaction mixture was washed with distilled water, dried ($Na_2SO_4$), and concentrated. The residue was chromatographed on neutral alumina (PTLC, $CH_2Cl_2$). The **lower $R_f$ epimer** of **19c** was obtained as an oil (27%): $^1H$ NMR $\delta$ 2.34 (s, 3 H, NMe), 2.41 (d, $J$ = 16.0, 1 H), 2.65 (d, $J$ = 16.0, 1 H), 2.97 (d, $J$ = 16.5, 1 H), 3.25 (d, $J$ = 16.5, 1 H), 4.00 (s, 2 H), 4.62 (s, 1 H, H-1), 6.6-7.8 (m, 13 H, ArH); MS, $m/z$ (rel intensity) 325 ($M^+$, 88), 324 (100); HRMS calcd for $C_{24}H_{23}N$ 325.1830, found 325.1811. The **higher $R_f$ epimer** of **19c** was also obtained as an oil (20%): $^1H$ NMR $\delta$ 2.31 (s, 3 H, NMe), 2.83 (d, $J$ = 16.9, 1 H), 2.89 (d, $J$ = 16.9, 1 H), 2.96 (d, $J$ = 15.4, 1 H), 3.60 (d, $J$ = 15.4, 1 H), 3.86 (s, 2 H), 4.04 (s, 1 H, H-1), 6.9-7.3 (m, 13 H, ArH); MS, $m/z$ (rel intensity) 325 ($M^+$, 100); HRMS calcd for $C_{24}H_{23}N$ 325.1830, found 325.1824.

**Acknowledgment.** We gratefully acknowledge the support provided for this project by a grant from the Comision Asesora and by a Spanish Government Fellowship (FPI) awarded to R. Alonso.

# Synthesis and Characterization of Masked Aminopyrazolecarboxylic Acid Synthons

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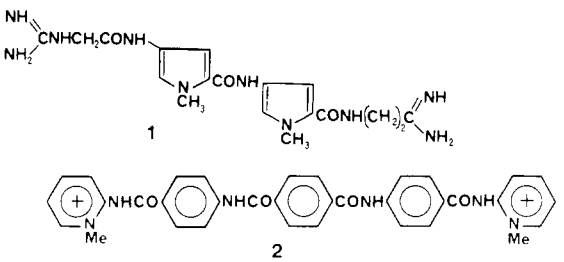
*Received June 15, 1988*

The synthesis of the masked aminopyrazolecarboxylic acid synthons (**11a,b** and **12a,b**) from pyrazole-3,5-dicarboxylic acid (**6**) and the determination of their structures by X-ray crystallography are detailed. The compounds are useful for the synthesis of polypyrazolecarboxamides analogous to the DNA minor groove binding antibiotics distamycin A and netropsin.

Compounds that bind to DNA by lodgement in the minor groove are of particular interest because of their high specificity for AT-rich base sequences.[1-3] The best studied compounds of this class are the polypyrrolecarboxamides, such as netropsin (**1**)[4] and the polybenzamides (e.g. **2**).[1] Apart from their interest as DNA-binding ligands, compounds such as **1** and **2** have potential therapeutic value as antitumor agents. Problems with the polybenzamides include insolubility and chronic toxicity,[5] while the polypyrrolecarboxamides are rather unstable.[4,6] For these reasons we have considered the synthesis of polypyrazolecarboxamides.

In the synthesis of all such oligomeric carboxamides, the key problem is the preparation of a synthon that contains both elements of the oligomer-linking amide moiety (amino and carboxylic acid) in such a form (or with such protection) that either can be selectively elaborated or demasked. In the case of the polybenzamides[7] the problem is a straightforward one, beginning with 4-nitrobenzoic acid (**3**), and an efficient synthesis of the corresponding nitropyrrolecarboxylic acid (**4**) has been the starting point for many polypyrrolecarboxamide syntheses.[8-10] Since the




oligomer unit of the polypyrazolecarboxamides is asymmetric, a completely general synthesis of these compounds

† Deceased.

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