Benzo- and Indoloquinolizine Derivatives. I. Synthesis of 4b,5,6,7,8,8a,10,11,16,16b-Decahydrodibenz[*f,h*]indolo[2,3-*a*]quinolizine

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Two 4b 5,6,7,8,8a,10,11,16,16b-decahydrodibenz[*f,h*]indolo-[2,3-*a*]quinolizine epimers have been synthesized starting from *trans*-1,2,3,4,4a,10b-hexahydrophenanthridine. The structural assignment of both isomers is discussed by use of ir and pmr spectroscopy.

In the frame of a study of the spectroscopic and physiological properties of benzo- and indoloquinolizine derivatives, we synthesized two 4b,5,6,7,8,8a,10,11,16,16b-decahydrodibenz[*f,h*]indolo[2,3-*a*]quinolizine epimers **9** and **10**.

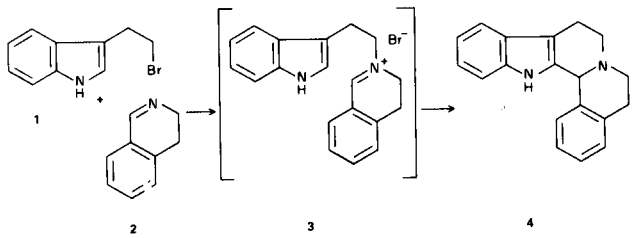
Different members of the benz[*h*]indolo[2,3-*a*] ring system have been prepared by oxidative or reductive cyclizations, involving an electrophilic attack of an iminium group on the indole ring (see reference (1) and references therein).

By this method I. W. Elliott (1) prepared 5,6,8,9,14,14b-hexahydrobenz[*h*]indolo[2,3-*a*]quinolizine **4**, starting from tryptophyl bromide and 3,4-dihydroisoquinoline. The intermediate dihydroisoquinolinium bromide cyclised to **4** upon heating (Scheme 1).

On the basis of these results we devised a stereospecific reaction scheme with an iminium cyclisation as an intermediate step (Scheme 2). The synthesis of the key intermediate, *trans*-1,2,3,4,4a,10b-hexahydrophenanthridine **7**, is essentially the same as described by T. Masamune (2), with somewhat modified conditions and reactants giving excellent results. Special care was devoted to the stereochemical purity of *trans*-2-phenylcyclohexylamine **5**.

The small quantity of *cis*-isomer (*ca.* 10%), present in the hydrogenation product, was removed by fractional

SCHEME 1



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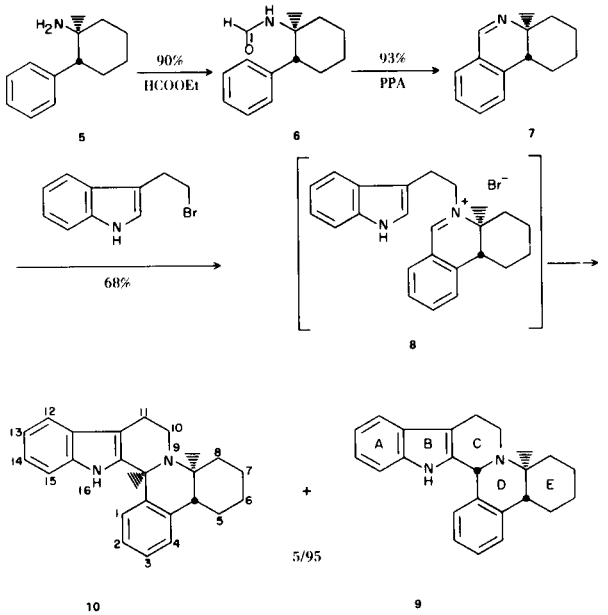

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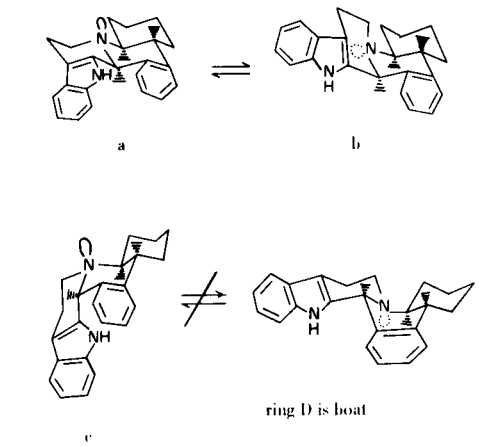

crystallization until the peak of this isomer was no longer detectable by gas chromatography.

The cyclisation of the formamide **6** with phosphorus pentoxide in refluxing tetralin gives only 15% of the *trans*-1,2,3,4,4a,10b-hexahydrophenanthridine **7** (2). By the use of PPA this yield was raised to 93%.

The reaction between **7** and tryptophyl bromide gave the phenanthridinium salt **8** (not isolated) which was cyclised in refluxing acetic acid. The two isomers **9** and **10** were formed which were isolated in a 95/5 proportion.

Compound **9** was obtained by repeated crystallisation of the free bases in ethanol. Column chromatography of the mother liquors gave the other isomer **10**. The products should be epimeric at $C_{16}b$ (Scheme 3).

The infrared spectrum of neither **9** nor **10** showed Bohlmann bands. This is not surprising in view of the strong steric interactions in the *trans*-quinolizidine structure a.

The assignment of stereochemistry to both isomers was made possible by the chemical shift of their $C_{16}b$ proton in pmr. This signal appears at δ = 5.33 ppm for **9** and at δ = 5.18 ppm for **10**. As axial protons absorb at higher fields than equatorial ones (3), this would mean a *trans*-quinolizidine structure for isomer **10** and a *cis*-quinolizidine structure for isomer **9**.

This is confirmed by the shift of the signals in trifluoroacetic acid. Axial protons next to the nitrogen atom experience a much stronger shift than do the equatorial ones (4). This shift is 0.61 ppm for **9** (δ = 5.94 ppm) and 1.02 ppm for **10** (δ = 6.2 ppm).

Interactions in compound **10** are the following: i) conformation a: strong interactions between N-H (indole) and C_1-H; ii) conformation b: interactions between N-H (indole) and C_1-H are smaller but strong interactions appear between C_{10}-H_{ax} and C_4b-H_{ax}.

In compound **9** the following interactions occur: i) conformation c: no interactions between N-H and C_1-H, no abnormal interactions at C_8a-H; ii) conformation d: very strong interactions between N-H (indole) and C_1-H, between C_8-methylene and C_{10}-methylene and other torsion interactions due to the boat form.

The preferential formation of compound **9** could be attributed to less interactions in conformation **9c** than in both conformations of compound **10**.

Synthesis of the corresponding D/E *cis* compounds is in progress.

EXPERIMENTAL

trans-2-Phenylcyclohexylamine **5**.

The reaction was carried out as described by T. Masamune (2). To isolate the amine, water was added carefully to the cooled reaction mixture until the precipitate dissolved. The ethanol was evaporated under vacuum and the water solution was continuously extracted with ether. The yield after distillation was 78-80%, b.p. 130-132°/11 mm. The GLC chromatogram taken with a Varian Aerograph 1520 B showed the presence of 10% *cis*-isomer (SE 30 analytical column, injector 190°, column temperature 100°, flame ionisation detector 240°). Repeated crystallisation in petroleum ether (40-60) removed this impurity. The constant m.p. was 58-59° (lit. (2): 60-61°). The hydrochloride salt melted at 247-248° (lit. (2): 249-251°).

trans-1-Formylamino-2-phenylcyclohexane **6**.

2-Phenylcyclohexylamine (10 g.) was refluxed in 200 ml. of ethyl formate and a few drops of acetic acid. After 18 hours reflux, the ethyl formate was evaporated and the formamide was recrystallised from cyclohexane-petroleum ether (40-60), yield 90%, m.p. 87-87.5° (lit. (2): 88-90°).

trans-1,2,3,4,4a,10b-Hexahydrophenanthridine **7**.

trans-1-Formylamino-2-phenylcyclohexane (10 g.) was heated with 100 g. of PPA at 160-170° for 5 hours. The cooled reaction mixture was decomposed with ice and carefully basified. Extraction with ether and distillation of the residual brown oil gave 93% of **7**, b.p. 102°/0.3 mm. The white oil solidified on cooling and the hydrochloride salt melted at 220-222° (lit. (2): 220-222°).

4b,5,6,7,8,8a,10,11,16,16b-Decahydrodibenz[*f,h*]indolo[2,3-*a*]-quinolizine **9**, **10**.

Tryptophyl bromide (3.65 g.) (5) and *trans*-hexahydrophenanthridine (3.0 g.) were heated under nitrogen at 100-120° (bath temperature) for 4 hours. Glacial acetic acid (100 ml.) was added and the solution was refluxed overnight. The precipitated hydrobromide salt was filtrated and the free base liberated with dilute sodium hydroxide. The product was recrystallised from ethanol until a constant m.p. (161-163°), **9** was obtained (2.67 g.). The acetic acid filtrate was evaporated, treated with base, and the ether extract, together with the ethanolic mother liquors was chromatographed on a column of alumina (Type E, Merck).

Elution with ether gave two fractions. The first fraction was identical with the main product **9** (0.75 g.). Recrystallisation of the second fraction gave **10**, m.p. 202-206° (0.21 g.), yield 68% (64% **9** and 4% **10**); tlc (alumina, ether-chloroform 1/1): **9** R_f = 0.52, **10** R_f = 0.32. The high resolution mass spectra of both compounds indicated a M^+ = 328 with a $C_{23}H_{24}N_2$ composition, the ir spectra showed no significant differences for compounds **9** and **10**; ν (cm^{-1}) = 3330, 3020, 2920, 2840, no Bohlmann bands, 1450, 737.

Nmr spectra (deuteriochloroform): 9 δ (ppm) = 7.8 (NH); 7.6-7.0 (8 H arom); 5.33 (H_{16b}); 3.8-1 (14 H aliph); 10 δ (ppm) = 8.3 (NH); 7.6-7.0 (8 H arom); 5.18 (H_{16b}); 3.3-1.2 (14 H aliph).

Spectra.

Infrared spectra were taken on a Perkin Elmer 257, the nmr spectra on a BRUKER HFX 90 and the mass spectra on a A.E.I. MS 902 S apparatus.

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