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# ON THE COURSE OF THE ACID CATALYZED B/D TRANS/CIS ISOMERIZATION OF 2-PHENYL-BENZAZEPINE ALKALOIDS (1)

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The various 2-phenyl-1.2.4.5-tetrahydro-3H-3-benzazepine alkaloids (e.g.I) isolated from Papaver species or prepared by partial synthesis belong to two groups differing in the relative configuration at C-1 and C-2 (2). The members of one of these groups,e.g. isorhoeagenine, are transformed with boiling 1 n hydrochloric acid into the acid stable bases, e.g. rhoeagenine, a representative of the other group. Although the conformation of the flexible, 7-membered N-heterocyclic ring B is unknown, it has been deduced from the NMR data, that the protons at C-1 and C-2 should possess the trans configuration in the compounds of the acid unstable group and the cis configuration in the compounds of the other (3). Recently (4), the absolute configuration at C-1 and C-2 has been determined in an unambigous manner for one member of the cis series, the rhoeagenine methiodide, by means of a X-ray analysis.

The centre of chirality on which this B/D trans/cis isomerization occurs might be C-1 or C-2. On this point a conclusion cannot be drawn from pertinent literature, due to the lack of experimental evidence. A mechanism had been proposed, involving epimerization at C-2 (5). Contrarily, ORD results (6,7) have been interpreted favouring the same configuration at C-2 in both the trans and cis series.

This prompts us to state alpinigenine (B/D trans,I) (8,9) and 1-epi-alpinigenine (cis,II) to possess different stereochemistry at C-1, a result gained by chemical degradations as follows. EMDE degradation of O-methyl-alpinigenine (Ia) and 1-epi-alpinine (IIa), respectively, resulted in the elimination of the chi-

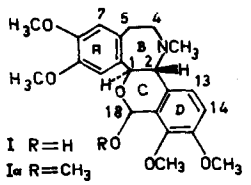
rality at C-2 in the EMDE-products III which proved to be identical in every respect except the sign of optical rotation. Thus they are forming a pair of enantiomers. The components of it have opposite configuration at C-1 (as well as C-18). Further, concerning stereochemical relations at C-18, there is no accordance with earlier conclusions drawn from NMR spectra (10) of benzazepine bases belonging to the same groups, trans-18-epi and cis as Ia and IIa, respectively.

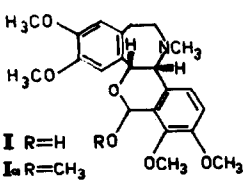
Table: NMR spectra [a] of compounds II, IIa, III and IV

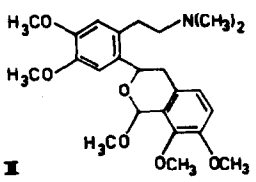
| proton at | II 60 mc | IIa 60 mc | III[b] 100 mc | IV[b] 60 mc |
|---|---|---|---|---|
| C-13+14 | 6.79 (2H, AB-q, J=8.2) | 7.05 (2H, AB-q, J=8.5) | 6.86 (2H, AB-q, J=8.5) | 6.82 (2H, AB-q, J=8.5) |
| C-10 | 6.60 (2H, AB-q collapsing to t J= 2.4) | 6.89 (1H,s) | 7.09 (1H,s) | 6.65 + 6.61 (2H, 2s) |
| C- 7 | | 6.73 (1H,s) | 6.72 (1H,s) | |
| C-18 | 6.26 (1H,s) | 5.86 (1H,s) | 5.81 (1H,s) | 2.87 (3H,s) |
| OH | 4.54 (1H) | - | - | not detected |
| C- 1 | 4.47 (1H,d, J=1.4) | 5.20 (1H,d, J=2.5) | 5.41 (1H,q, Jaa = 11 Jae = 5) | 4.72 (1H,s) |
| C- 2 | 3.67 (1H,d, J =1.4) | 3.83 (1H,d, J =2.5) | not detected | not detected |
| $OCH_3$ (aromat.) | 3.85,3.83,3.75 (12H) | 3.93,3.90,3.89, 3.88 (12H) | 3.95 to 3.85 (12H) | 3.90 to 3.85 (12H) |
| $OCH_3$ (acetal.) | - | 3.61 (3H,s) | 3.58 (3H,s) | - |
| $NCH_3$ | 2.17 (3H,s) | 2.29 (3H,s) | 2.30 (6H,s) | 2.31 (6H,s) |

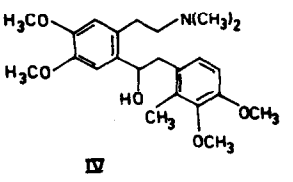
[a] $CDCl_3$, reference: TMS; s = singlet, d = dublet, t = triplet, q =quadruplet, $\delta$-values in ppm

[b] In the table, for sake of clearness, the numbering of protons in the compounds III and IV is the same as in II and IIa.



In the first series of experiments the acetal Ia (8) was transformed to its methiodide with $CH_3J$ in acetone by heating under reflux for 18 hours, 95% th., mp. 208-211 (decomp.), $[\alpha]_D^{22}$ = + 189.1° ($CH_3OH$, c =0.638). The latter in aqueous solution was treated with sodium amalgame at room temp. The main product,(+)-(1ξ :3R )-1.7.8-trimethoxy-3-[4.5-dimethoxy-2-(β-dimethylamino-ethyl)-phenyl]-isochromane (III), 67% th., m.p.86-88° (hexane), $[\alpha]_D^{22}$ +14.3° ($CH_3OH$, c =0.838), was formed by hydrogenolysis of the benzylic C-2-N bond. The NMR spectrum(table) for the proton at C-1 shows a quadruplet indicative for the introduction of a second proton at C-2. The mass spectrum is in accordance with the proposed structure III.

Isomerization could be accomplished by boiling alpinigenine (I) in 1 n hydrochloric acid solution under reflux for 90 min (11). Crystallizations from methanol removed some starting material and afforded 1-epi-alpinigenine (II),(yield 55%) m.p.175-176°, $[\alpha]_D^{22}$+ 110° ($CH_3OH$, c = 0.851). The NMR exhibited a small coupling constant $J_{1,2}$ = 1.4 characteristic for the B/C-cis series; MS revealed m/e 401 ($M^+$) and the other fragments usually formed from phenylbenzazepine bases (8, 12). This compound is apparently identical with iso-alpinigenine, characterized by a $R_F$-value only (5).

The methyl ether IIa was prepared from II as usual, 86% th., m.p. 106-107°, $[\alpha]_D^{21}$ + 193.3° ($CH_3OH$, c = 0.794). NMR (table) and MS represent all the features typical for acetalic rhoeadine type alkaloids, see (12). The corresponding methiodide was quantitatively formed with $CH_3J$ in methanol (4 hrs. at reflux temp.), m.p. 211-214° (decomp.); $[\alpha]_D^{23}$ + 186.0° ($CH_3OH$, c = 0.967) and degraded as described above yielding 38% th. III, m.p. 86-88°, $[\alpha]_D^{22}$ - 15.1° ($CH_3OH$, c = 0.820); identical in other parameters with the dextrorotatory material obtained from alpinigenine(I) (IR,NMR,MS, and thin layer chromatography).

The enantiomeric properties of both samples were confirmed by the ORD-curves taken in $CH_3OH$, cotton effect at 282 nm $\Delta\varepsilon$= + 1.01 (for the first from I) and -1.01 respectively.

It should be mentioned that the low yield of III in the second reduction is due to additional hydrogenolytic fission of ring D forming IV in 35% yield, m.p. 121-123°, $[\alpha]_D^{23}$ - 4.6° ($CH_3OH$, c = 0.939). The proposed structure (IV) is

based mainly on NMR (table) and MS.

This results described above constitute an independend chemical evidence concerning the stereochemical relations between the two series of phenylbenzazepine bases and, consequently, on the ground of correlation with rhoeagenine(4) allow the specification of the absolute configuration for alpinigenine as I and 1-epi-alpinigenine as II which will be discussed in our full paper.

For all new compounds adequate values from C,H,N-analysis have been obtained.

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