CONDENSATION OF 2-HYDROXYTRYPTAMINE WITH DIMETHYL 4-ETHYL-4-FORMYLPIMELATE

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Abstract - Condensation of 2-hydroxytryptamine (1) with dimethyl 4-ethyl-4-formylpimelate (2) yielded the stereoisomeric oxindoles, 8A, 8B, 8C, and 8D which were separated and their stereochemistry assigned. The compounds 8A-D or their N-methyl derivatives, 5A-D could be selectively reduced to the oxindole-amines 9 or 3 by treatment with phosphorus oxychloride followed by sodium borohydride but the amines were isomerised under the reaction condition.

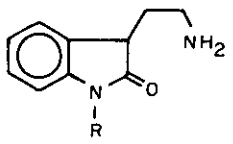
The condensation of 2-hydroxytryptamine (1) with dimethyl 4-ethyl-4-formylpimelate (2) is a potentially useful route for the total synthesis of several indole alkaloids. In an attempted synthesis of the alkaloid vincatine (3)[1], the reaction of 1-methyl-2-hydroxytryptamine (4) with 2 was reported[2] to yield two stereoisomers of the oxindole 5. Condensation of 1 with 2 was later used for the total synthesis of (±) - vincadifformine (6)[3] and (±) - quebrachamine (7)[4]. This reaction was also reported to yield two isomers of 8, the more polar one being amenable to cyclisation to vincadifformine[3] or aspidospermidine[4] skeleton. A recent publication[5] by the French group prompted us to report the work carried out in this laboratory on the condensation of 1 with 2, which showed that the reaction yields all the four possible isomers of 8.

Reaction of 2-hydroxytryptamine (1) with the ester 2 in refluxing methanol in presence of acetate buffer (pH 4.6) yielded, as reported[2,3] earlier, two products (ratio 6:4, total yield 76%) separable by thin layer or column chromatography over silica gel. The nmr spectra, however, indicated that each of them is a mixture of two compounds which could be resolved by reversed phase HPLC (μ-Bondapak C-18, MeOH:H_2O/2:1). We have also been able to successfully separate the four isomers 8A-D by fractional crystallisation, their relative proportion (by HPLC) being A:B:C:D = 18:22.5:32:27.5. The corresponding N-methyl derivatives 5A-D were prepared by methylation with MeI/NaH in DMF.

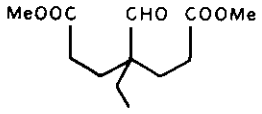
As expected, the uv spectra of all the compounds 8A-D and 5A-D were almost superimposable[6]. The mass spectra of the isomers 8A-D were also almost identical [for 8A, m/z 370 (M^+, 100%), 341 (M-Et, 6%), 339 (M-OMe, 11%), 283 (M-CH_2CH_2COOMe, 6%), 225 (a, 16%), 212 (b, 23%), 196 (c, 39%), 159 (d, 59%) and 138 (e, 67%)], with appropriate mass shifts in the spectra of the N-methyl derivatives. The ir spectra of the compounds were also very close. Since the chemical shifts of the C-21 methine proton in all the eight compounds were observed in the narrow range of δ 4.12-4.20 (Table) all of them must have the same stereochemistry at the C/D ring junction, i.e. trans. The C-7 configuration of the isomers could be unambiguously deduced by comparison of the ^{13}C chemical shifts of C-7 and C-9 with those reported for model compounds[7]. A distinction between the isomers 8A and 8B and between 8C and 8D could be made from the chemical shifts of the C-17 and C-19 which were expected to resonate at higher field in the axial isomer than in the corresponding equatorial isomer[8]. The shielding of the CH_3-CH_2- groups in the pmr spectra of 8B and 8C can then be explained as due to anisotropy of the aromatic ring.

The isolation of all the four possible isomers of 8 thus, disproves the earlier contention[2] that two of the isomers are unlikely to be produced because of steric interactions. We have also observed that the lactams 8A-D are not isomerised by acetic acid or pyridine at 100°C, the usual conditions for equilibration of oxindole alkaloids[9].

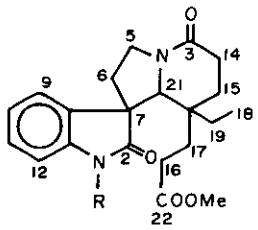
For the synthesis of indole alkaloids, it is necessary to selectively reduce the δ-lactam functions of 5 and 8. Diborane or lithium aluminium hydride reduction of 5 and 8 have been reported to cleave the C_7-C_{21} bond[1,4]. Potassium borohydride reduction of a derivative of 9 was also reported[4] to cleave this bond. We could, however, achieve the desired reduction by treatment of the lactams 5 and 8 with $POCl_3$ followed by sodium borohydride reduction[10] when the oxindole amines 3 and 9 were produced in reproducible yields of 60-65%. However, the stereochemical integrity was not preserved during the reduction. In fact, reduction of any of the isomers of 5 or 8 produced apparently the same mixture of the isomers of 3 or 9. It could be confirmed that isomerisation of 5 and 8 did not take place during the $POCl_3$ treatment. Evidently, the different stereoisomers of 3 and 9 are equilibrated under the conditions of borohydride reduction. Thus, though the δ-lactam group in 5 and 8 could be selectively reduced, the stereospecific synthesis of vincatine (3) could not be achieved. That goal could, however, be reached by an alternative route reported in the succeeding communication[8].



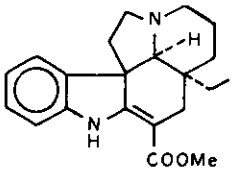
1, R = H
4, R = Me



2



5, R = Me
8, R = H



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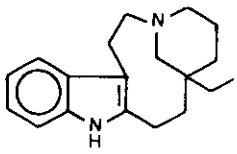

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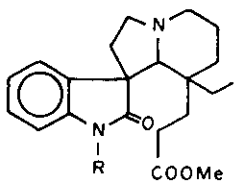
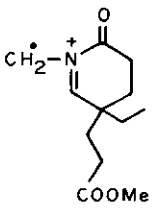
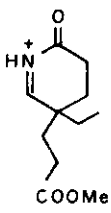


3, R = Me
9, R = H



a



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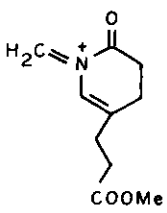

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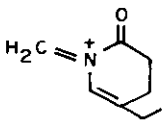

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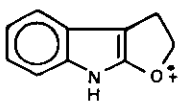

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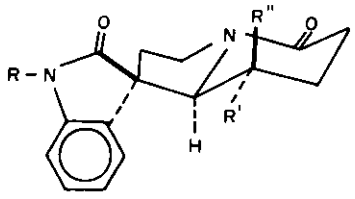
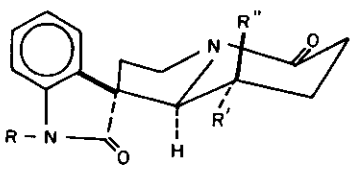


5C, 8C R' = CH_2CH_2COOMe, R'' = Et
5D, 8D R' = Et, R'' = CH_2CH_2COOMe



5A, 8A R' = Et, R'' = CH_2CH_2COOMe
5B, 8B R' = CH_2CH_2COOMe, R'' = Et

Table. Physical data of the lactams 8A-D and 5A-D

Compound	mp (°C)	ir (nujol), cm^{-1}	pmr (90/100 MHz), δ $CDCl_3$			
			CH_3CH_2	OMe	21-H	NH/NMe
8A*	122-124	3413,1705,1618	0.86	3.60	4.20	9.46
8B*	238-240	3100,1718,1613	0.63	3.63	4.20	9.56
8C**	236-238	3236,1720,1646,1616	0.74	3.56	4.16	9.43
8D**	256-258	3170,1720,1611	0.56	3.56	4.20	9.35
5A	126-128	1730,1706,1643,1613	0.83	3.60	4.16	3.30
5B	152-154	1730,1706,1643,1613	0.58	3.70	4.20	3.30
5C	198-200	1738,1693,1640,1613	0.74	3.52	4.12	3.22
5D	212-214	1724,1693,1635,1613	0.57	3.63	4.13	3.24

*Isolated from the less polar product. **Isolated from the more polar product.

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6. For 8A, $\lambda_{max.}$ (EtOH) (Log ε) : 209 (4.50), 256 (3.88) and 286 (3.20) nm.

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