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Meisenheimer Rearrangement of 2-Ethyl-1,4,5,10b-tetrahydro-2*H*-azetopyrido[3,4-*b*]indole *N*-Oxides. Formation of 3,6-Epoxy-1,2,3,4,5,6-hexahydroazocino[5,6-*b*]indoles

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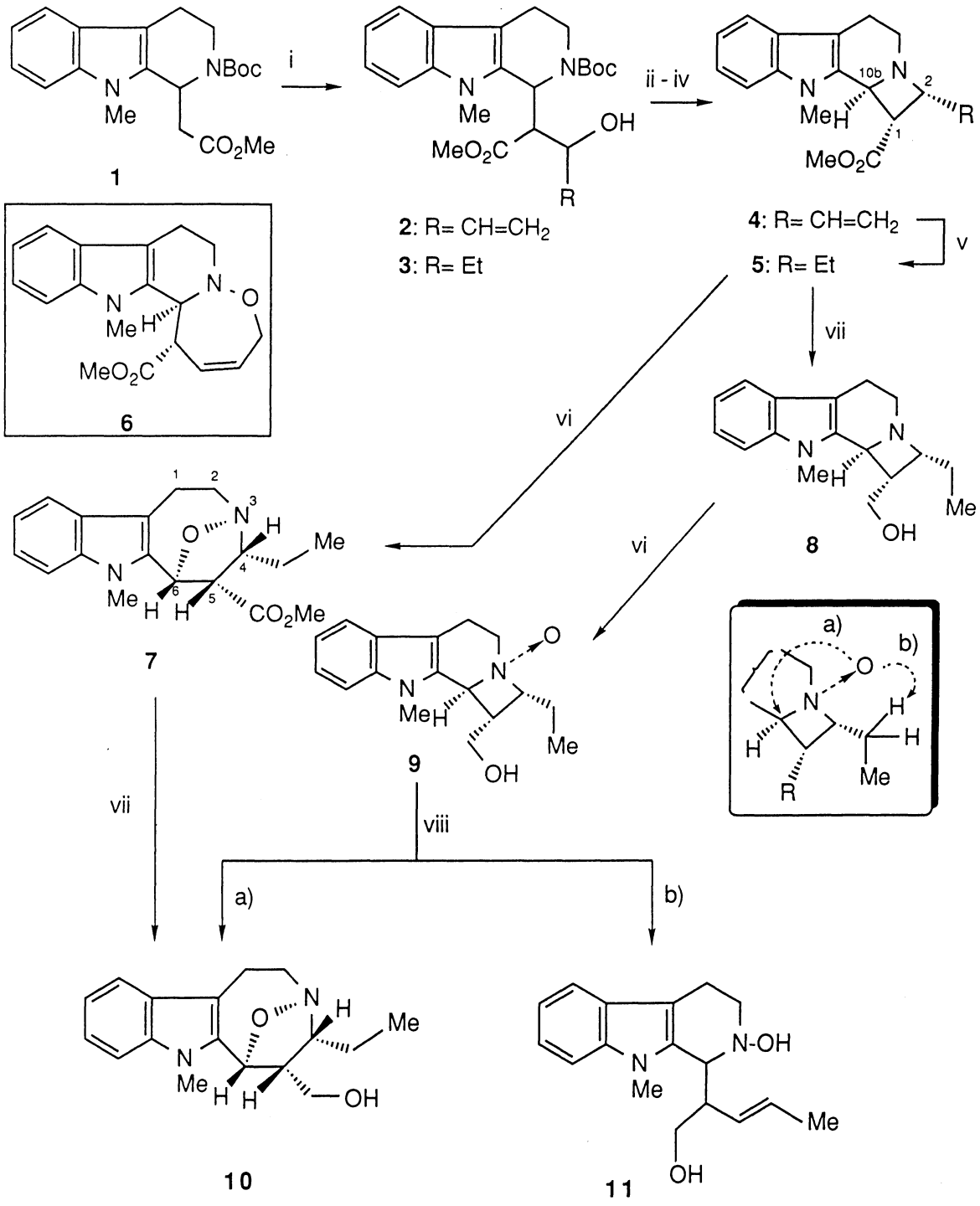
Oxidation of 2-ethyl-1-methoxycarbonyl-1,4,5,10b-tetrahydro-2*H*-azetopyrido-indole with *m*-chloroperbenzoic acid (*m*CPBA) at room temperature gives 3,6-epoxyhexahydroazocino[5,6-*b*]indole *via* Meisenheimer rearrangement of the intermediate *N*-oxide. On the other hand, oxidation of the corresponding 1-hydroxymethyl derivative forms the *cis*-*N*-oxide which then undergoes rearrangement at 55 °C in THF to yield a mixture of azocino[5,6-*b*]indole and *N*-hydroxytetrahydro-β-carboline .

Two representative reactions of *N*-oxides are Meisenheimer rearrangement and Cope elimination. Since the first report on the conversion of tertiary *N*-oxides to trisubstituted hydroxylamines,[1] this rearrangement has extensively been studied by many investigators.[2] Among them, the Meisenheimer rearrangement of cyclic and heterocyclic *N*-oxides has provided an entry to a variety of 1,2-oxazine heterocycles.[3] However, this rearrangement usually requires high reaction temperature. In a recent communication we reported a Meisenheimer rearrangement of 2-ethenyl-1,4,5,10b-tetrahydro-2*H*-azeto[3,4-*b*]indole **4**, prepared from allyl alcohol **2** by the following sequences: i) methanesulfonyl chloride (MsCl) /Et_3N, ii) dry HCl gas in EtOAc, iii) 1,8-diazabicyclo[5.4.0.]-7-undecene (DBU) / DMSO in 54% overall yield, by treatment with *m*CPBA under ice-coolig to give tetrahydopyridooxazepine **6** in 80% yield.[4] Thus, this reaction was regarded as being significant for the preparation of 12(*S*)carba-eudistomin[5] analogs. This paper presents a facile synthesis of 3,6-epoxyhexahydroazocino[5,6-*b*]indoles **7** and **10** by Meisenheimer rearrangement of 2-ethyl derivatives **5** and **8** of **4**.



Reagents and Conditions: i, CH_2=CHCHO or $MeCH_2CHO$ / LDA / -78 °C; ii, MsCl / Et_3N; iii, 2.3 mol dm^{-3} HCl / EtOAc; iv, DBU / DMSO; v, 5% Pd-$BaSO_4$ / H_2 / in MeOH; vi, *m*CPBA in CH_2Cl_2 / r.t.; vii, $LiAlH_4$; viii, 55 °C in THF

Aldol condensation of tetrahydro-β-carbolineacetate **1** with propionaldehyde [lithium diisopropylamide (LDA) / -78 °C] gave alcohol **3**, which was subjected to the same sequence as described for the preparation of **4**. The crude oil finally obtained was purified by SiO_2 column chromatography to give an oily product **5** in 63% overall yield, whose structure was assigned to be 2-ethyltetrahydro-2*H*-azetopyridoindole by comparison of ^{1}H-NMR spectrum with that of **4** as well as by an alternative synthesis of **5** by catalytic hydrogenation (5% Pd-$BaSO_4$ / H_2 in MeOH) of **4**. Oxidation of **5** with *m*CPBA (1.2 equiv.) in CH_2Cl_2 at room temperature afforded a crystalline product **7**[6] in 60% yield, whose MS [*m/z* 314 (M^+)] indicated incorporation of an oxygen atom in **5**. The ^{1}H-NMR spectrum showed the signals of H-6 at δ 5.84 (d, *J*=4.0 Hz) and H-5 at δ 3.86 (dd, *J*=4.0 and 9.0 Hz). The latter signal collapsed to a doublet (*J*=9.0 Hz) by irradiation of the former signal. On the basis of these results, the structure of **7** was supposed to be a unique and new ring system of 3,6-epoxy-1,2,3,4,5,6-hexahydroazocino[5,6-*b*]indole derivative. Although stereochemical problems of **7** could not be resolved clearly by the measurements of nuclear Ovehauser effects (NOE), the dihedral angles estimated by an inspection of the Dreiding model of compound **7** between H-4 and H-5 (φ=110-120°) and between H-5 and H-6 (φ=0-5°) were well consistent with the observed *J*-values. *N*-Oxidation of **5** from the α–side[4] *via* path a) followed by the Meisenheimer [1,2]-rearrangement may also provide the evidence for *cis* structure between C-4, C-5, and C-6 of **7**.

Reduction of **5** with $LiAlH_4$ gave alcohol **8**. On the contrary to the result of **5**, **8** was oxidized with mCPBA (1.2 equiv.) at room temperature to yield the *cis*-*N*-oxide **9** [*m/z* 286 (M^+)] in quantitative yield. The *cis*-stereochemistry of **9** was clarified primarily on the basis by ^{1}H-NMR spectrum in which methylene protons of the ethyl group in **8** [δ 1.60 (2H, m)] shifted downfield to δ 1.85 and 2.30 (each 1H, each m), respectively. Heating a solution of **9** in THF at 55 °C for 3 h gave a mixture of Meisenheimer rearranged product **10** (44%) *via* path a) and *N*-hydroxytetrahydro-β-carboline **11** (27%) *via* path b), the latter of which resulted from a Cope elimination. It was thought that formation of the Cope elimination product **11** substantiated the structure of **9**. The assignment of structure of **10** was supported by analytical and spectroscopic data as well as by an alternative synthesis of **10** by reduction of **7** with $LiAlH_4$. Exact reason for the significant difference of the stability between the *N*-oxide of **5** and the *N*-oxide **9** is not clear at this stage, but it is interesting to note that *m*CPBA oxidation of the corresponding 2-ethenyl derivative of **8** took place to give a mixture of Meisenheimer [2,3]-rearranged product (oxazepine derivative) and [1,2]-rearranged product (isoxazolidine derivative) at C-2.[7]

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References

1) J. Meisenheimer, *Chem. Ber.*, **52**, 1668 (1919).

2) R. F. Kleinschmidt and A. C. Cope, *J. Am. Chem. Soc.*, **66**, 1929 (1944); R. A. W. Johnstone, "Mechanisms of Molecular Migrations," ed by B. S. Thyagarajan, Interscience Inc., New York (1969), Vol.2 , pp. 249-266 ; N. Jr. Castagnoli, J. Cymerman Craig, A. P. Melilian, and S. K. Roy, Tetrahedron, **26**, 4319 (1970).

3) J. B. Bemner, E. J. Browne, P. E. Davies, and Le van Thuc, *Aus. J. Chem.*, **33**, 833 (1980); J. B. Bremner, "Studies in Natural Products Chemistry," ed by Atta-ur-Rahman, Elesevier, Inc., Amsterdam (1990), pp. 467-502.

4) T. Kurihara, M. Doi, K. Hamaura, H. Ohishi, S. Harusawa, and R. Yoneda, *Chem. Pharm. Bull.*, **39**, 811 (1991).

5) M. P. Kirkup, B. B. Shankar, S. McCombie, A. K. Granguly, and A. T. McPhail, *Tetrahedron Lett.*, **30**, 6809 (1989),

6) Compound **7**: IR ($CHCl_3$) 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.02 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.30 and 1.58 (each 1H, each m, $C\underline{H}_2CH_3$), 2.97 (2H, m, 1-CH_2), 3.07 (1H, q, J=9.0 Hz, H-4), 3.60 (1H, m, 2-CH), 3.67 and 3.75 (each 3H, each s, $COOCH_3$ and/or NCH_3), 3.80 (1H, m, 2-CH), 3.86 (1H, dd, J=4.0 and 9.0 Hz, H-5), 5.84 (1H, d, J=4.0 Hz, H-6), 7.02-7.28 (3H, m, Ar-H), and 7.46 (1H, d, J=7.5 Hz, H-8); ^{13}C-NMR ($CDCl_3$) δ 12.0 (q), 21.6 (t), 24.0 (t), 29.9 (q), 52.1 (q), 58.5 (t), 60.3 (d), 70.4 (d), 76.8 (d), 108.6 (d), 112.0 (s), 118.0 (d), 119.4 (d), 121.2 (d), 126.9 (s), 136.0 (s), 140.0 (d), and 171.0 (s).

7) Unreported results. Similar isoxazolidine structure is shown in Ref. 4.

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