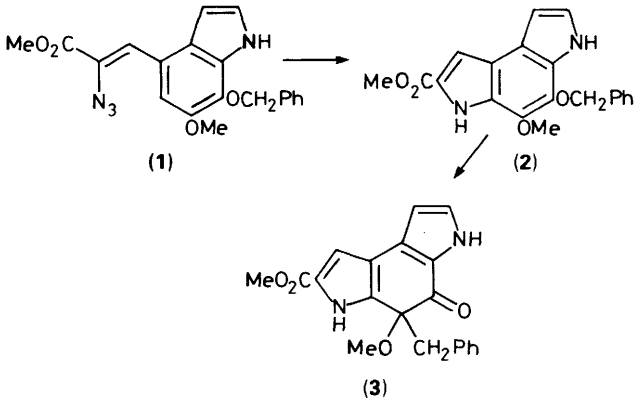
A Mild Uncatalysed Dearomatisation Reaction

Richard E. Bolton, Christopher J. Moody, and Charles W. Rees
Department of Chemistry, Imperial College of Science, Technology, and Medicine, London SW7 2AY

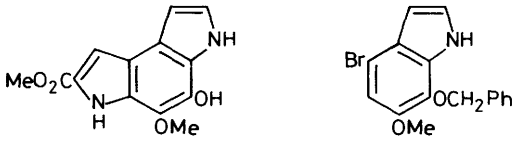
Mild heating of the pyrroloindole (**2**) causes intramolecular migration of the benzyl group from oxygen to ring carbon to give the dienone (**3**) in which the benzene aromaticity has unexpectedly been destroyed.

A key step in the synthesis of the naturally occurring pyrroloindole phosphodiesterase inhibitors PDE-1 and PDE-11 was thermolysis of the azidocinnamate (**1**) to give the desired pyrrolo[3,2-*e*]indole (**2**).[1] In boiling toluene (110 °C) the yield was virtually quantitative, but in xylene (140 °C), the normal solvent for such azide decompositions, the yield of (**2**) was reduced and it was accompanied by another, more polar, product which accounted for the rest of the starting material. The ^{1}H n.m.r. spectrum of the second product showed that the benzylic methylene group was not attached to oxygen, and the methoxy group was not attached to an aromatic ring; there was an AB quartet accounting for two protons centred at δ 3.42 and the ^{13}C n.m.r. spectrum indicated an extra carbonyl group.* This all suggested a structure in which the benzyl group had migrated from oxygen to carbon, disrupting the aromaticity of the central ring. Of the possible structures, (**3**) seemed the most likely since in this both pyrrole rings had retained their aromaticity. The polar product was finally recrystallised from nitromethane to give crystals suitable for *X*-ray diffraction, and this confirmed that structure (**3**) was indeed correct.[2]

When the pure pyrroloindole (**2**) was heated in xylene it isomerised in high yield to (**3**), the benzyl group apparently migrating *via* a 'disallowed' thermal 1,3-shift from oxygen to carbon. We investigated the possibility of catalysis, and an intermolecular pathway, at a lower temperature by heating (**2**) in toluene in the presence of an excess of benzyl bromide, but there was no rearrangement under these conditions. Rearrangement in xylene in the presence of benzyl bromide showed no differences in the ratio of starting material to product when the reaction was interrupted before completion, again suggesting an intramolecular process.



When the benzyl group was removed from compound (**2**) by hydrogenolysis to give the phenol (**4**), the n.m.r. spectrum showed no sign of the keto form, with the phenolic proton remaining visible even after warming the solution for several days. The phenolic structure (**4**) is presumably more stable than the keto form analogous to (**3**).



The rate of rearrangement of (**2**) to (**3**) was measured in bromo[$^2H_5$]benzene at 120 and 140 °C by following the appearance of the new methoxy signal at δ 2.82 and the disappearance of the benzylic methylene group at δ 5.29 in the ^{1}H n.m.r. spectrum. At 120 °C the rearrangement was slow (10% reaction in 12 h) but clean, without detectable decomposition of the product, and the reaction was first order in (**2**). At 140 °C ($t_{\frac{1}{2}}$ = 4.5 h) the reaction was first order for *ca.* 50% of its course, but thereafter product decomposition was significant (n.m.r.). When the dienone (**3**) was heated at 140 °C in bromo[$^2H_5$]benzene or [$^2H_6$]-DMSO there was no detectable reversion to the benzylic ether (**2**).

* *Methyl 5-benzyl-5-methoxy-4-oxo-3,4,5,6-tetrahydro-3H,6H-pyrrolo-[3,2-e]indole-7-carboxylate* (**3**), m.p. 219—220 °C, $\lambda_{max.}$(EtOH) 225sh (log ε 4.19), 233sh (4.08), 262sh (4.04), 272 (4.13), and 305 nm (4.17); $\nu_{max.}$(Nujol) 3 280br (NH), 1 680s (CO), 1 640s, 1 595w, 1 515, 1 490w, 1 450, 1 410, 1 380, 1 340w, 1 310, 1 300w, 1 270, 1 220, 1 205, 1 190w 1 160, 1 075, 1 000, 960, 940w, 910w, 890, 850, 800, 780, 750, and 705 cm^{-1}; δ_H[250 MHz; $(CD_3)_2SO$] 2.82 (3 H, s, OMe), 3.28 (1 H, d, *J* 12.5 Hz, CH_2Ph), 3.55 (1 H, d, *J* 12.5 Hz, CH_2Ph), 3.80 (3 H, s, CO_2Me), 6.13 (1 H, t, *J* 2 Hz, 8-H), 6.58—6.67 (2 H, m, *o*-Ph), 6.86 (1 H, d, *J* 2 Hz, 1-H), 6.89—6.98 (3 H, m, *m*- and *p*-Ph), 7.03 (1 H, t, *J* 2.8 Hz, 7-H), 10.42 (1 H, br s, NH), and 11.04 (1 H, br s, NH); δ_C[62.9 MHz; $(CD_3)_2SO$] 44.45, 50.88, 51.70, 80.93, 104.05, 109.05, 117.75, 123.26, 125.85, 125.98, 127.24, 128.89, 129.19, 129.78, 134.33, 160.57, and 184.59; *m/z* (200 °C) 350 (M^+, 8%), 320 (12), 318 (12), 285 (15), 259 (100), 227 (50), 199 (7), 184 (9), 106 (14), 91 (71), and 77 (9).

Thermal rearrangement of (**2**) into (**3**) involves conversion of the benzene ring into a non-aromatic dienone, and as such occurs under remarkably mild conditions, a hallmark of aromatic rings being their high thermal stability.[3] Conversion of phenol ethers into dienones normally requires catalysis or substantial relief of steric strain; migration of benzyl groups in aryl benzyl ethers occurs at much higher temperatures (*ca.* 260 °C) in low yield,[4] even though the products regain their aromaticity. Compounds like (**2**), dioxygenated across relatively weak aromatic bonds (such as the 9,10-bond of phenanthrene), are known but their rearrangement to keto derivatives has not been reported.[5] A few stable dienones have been isolated in uncatalysed Claisen allyl ether rearrangements, such as the conversion of 1-allyl-2-allyloxynaphthalene into 1,1-diallylnaphthalen-2(1*H*)-one (55%) in dimethylaniline at 194 °C.[6]

We attribute the ready conversion of the aromatic ether (**2**) into the dienone (**3**) under such relatively mild conditions to a coincidence of steric and electronic factors which destabilise the former and stabilise the latter. The starting material is sterically congested with its four contiguous pyrrole NH and ether groups, and this compression is relieved in the dienone-forming transition state. Furthermore, these same substituents enhance the electron density on the central ring thus perturbing its aromatic stability, whilst the product (**3**) has retained the pyrrole rings intact and *both* are now stabilised by conjugation with α-carbonyl groups.[7] It is interesting to note that the indole (**5**), lacking one of the pyrrole rings, survived heating under reflux in mesitylene (165 °C) and showed no evidence of rearrangement.[1]

The rearrangement of (**2**) to (**3**) is unusual and was initially surprising, since the aromaticity of the central benzene ring is destroyed under mild conditions. However, given steric and electronic factors, such as those operating here, which destabilise the aromatic precursor and stabilise the product, this type of rearrangement could well prove to be more general.

Acknowledgements

We thank Dr. D. J. Williams for the *X*-ray structure determination and the S.E.R.C. for a studentship (R. E. B).

References

1 R. E. Bolton, C. J. Moody, C. W. Rees, and G. Tojo, *J. Chem. Soc., Perkin Trans 1*, 1987, 931.
2 D. J. Williams, Imperial College, unpublished results.
3 L. T. Scott, *Acc. Chem. Res.*, 1982, **15**, 52.
4 H. Hart and H. S. Eleuterio, *J. Am. Chem. Soc.*, 1954, **76**, 519; M. Z. A. Badr and H. A. H. El-Sherief, *Can. J. Chem.*, 1972, **50**, 259; M. Z. A. Badr and M. M. Aly, *Tetrahedron*, 1972, **28**, 3401.
5 M. B. Rubin and P. Zwitkowits, *J. Org. Chem.*, 1964, **29**, 2362.
6 J. Green and D. McHale, *Chem. Ind. (London)*, 1964, 1801.
7 R. A. Jones, in 'Comprehensive Heterocyclic Chemistry,' Pergamon Press, Oxford, 1984, vol. 4, p. 201.

Received 17*th July* 1989; *Paper* 9/03015H;