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The vinylogous Witkop cyclisation

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Abstract

The first example of a vinylogous Witkop cyclisation produces a novel azonino[*c*,*d*]indole, a carbocyclic analogue of the tumour-promoting indolactam family of natural products. A similar reaction previously reported to give azecino[*c*,*d*]indoles leads only to azocino[*c*,*d*]indoles, even when the radical centre is stabilised by the presence of halogens. © 1999 Elsevier Science Ltd. All rights reserved.

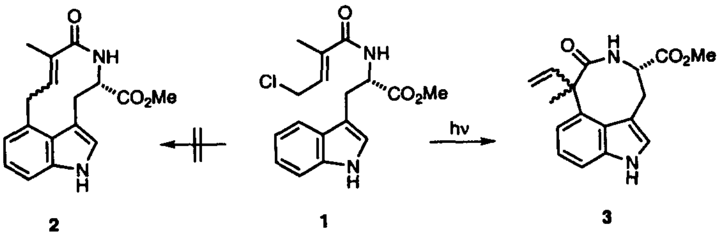
Keywords: cyclisation; indoles; radical reactions.

The Witkop cyclisation, first described in 1966,[1] involves the photoionisation of a haloacetamidoalkyl aromatic compound which, through the intermediacy of a diradical cation, leads to the formation of a new ring (Scheme 1).[2] A key application of this reaction has been in the synthesis of extracyclic indoles, where it is of interest because it can result in unusual products whose ring closure would not have been effected in the ground state, for example cyclisation from the indole 3- to the 4-position.[3]

$$Ar(CH_2)_nNHCOCH_2Cl \xrightarrow{h\nu} \overset{+\bullet}{Ar}(CH_2)_nNHCO\dot{C}H_2 \longrightarrow Ar(CH_2)_nNHCOCH_2 + HCl$$

Scheme 1.

A vinylogous modification of this reaction was reported in 1977 by Anderson and Lawton wherein chlorotiglyltryptophan **1** was irradiated and the products assigned the azecino[*c*,*d*]indole structures **2**.[3c] More recently, Endo and co-workers published a revision of this result, in which the actual products of the above photoreaction were shown to be azocino[*c*,*d*]indoles **3** (Scheme 2).[3k]



Scheme 2.

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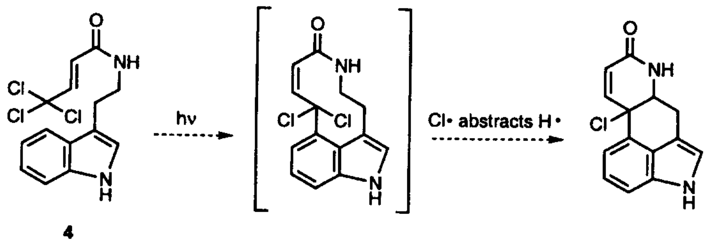
The reaction however as originally envisaged could, we proposed, afford the shortest yet synthetic access to the ergoline skeleton (Scheme 3) if the well-documented stabilising influence of halogens on the radical centre[3i] could shift the reactivity in favour of the larger-ring products. Trichlorocrotonyltryptamine **4** was thus prepared by acylation of tryptamine with the known acid chloride. Any increase in single electron density at the halogenated carbon was however not reflected in the outcome of the reaction, where the only product observed was the ordinary Witkop product **5**,[4] the structure of which was confirmed by X-ray crystallography (Fig. 1).[5]



Scheme 3.

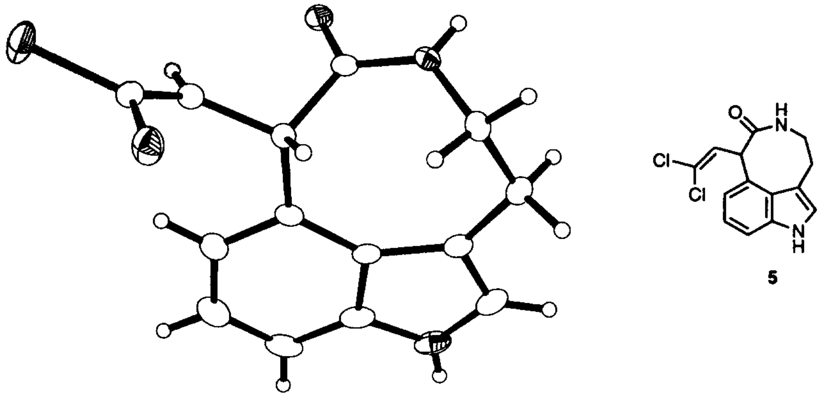
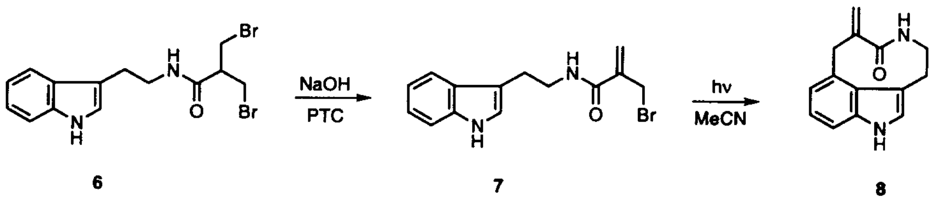


Figure 1. Chemical structure and X-ray crystal structure of compound **5**

The question still remained as to whether a vinylogous Witkop cyclisation was an achievable reaction. This could be tested by irradiation of a haloisobutenyl tryptamine **7**, which, if successful, should only give one cyclic product, i.e. azoninoindole **8**. Although chloromethacrylic acid is known,[6] its acid chloride did not react cleanly with tryptamine due to a competing S_N2' reaction. We therefore prepared dibromoisobutanoic acid from malonic ester, formaldehyde and HBr,[7] and reaction of its acid chloride with tryptamine gave **6**. Elimination of hydrogen bromide from **6** cleanly provided photolysis precursor **7**, irradiation of which gave the expected product **8** in a reproducible 41% yield (Scheme 4).[8] Interestingly, tricycle **8** is C-analogous to the diazoninoindole skeleton of the well known indolactam family of tumour promoters[9] and in the continuation of this work we look forward to producing variously substituted analogues of **8** for assay of biological activity.



Scheme 4.

Acknowledgements

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4. 7-(1,1-Dichloroethen-2-yl)-1,3,4,5,6,7-hexahydroazocino[4,5,6-*cd*]indol-6-one **5**: Through a solution of *E*-3-trichloromethyl-*N*-[2-(1*H*-indolyl-3-yl)ethyl]acrylamide **4** (610 mg, 1.84 mmol) in acetonitrile (500 mL) in a quartz vessel was bubbled nitrogen for 15 min, and the solution was then irradiated at 254 nm for 1 h. The solvent was evaporated and the residue chromatographed on silica (9:1 hexane:ethyl acetate→ethyl acetate) to give the product **5** (150 mg, 28%), mp 196°C (dec); (found C, 56.66; H, 4.14; N, 9.22. $C_{14}H_{14}Cl_2N_2O$ requires C, 56.97; H, 4.10; N, 9.49); δ_H (400 MHz, $CDCl_3$) 3.23 (1H, ddd, *J* 4.6, 8.1, 15.7, 4-H), 3.47 (1H, m, 3-H), 3.66 (1H, m, 3-H), 4.06 (1H, m, 4-H), 5.58 (1H, d, *J* 8.6, 7-H), 5.63 (1H, br s, 5-H), 6.96 (1H, d, *J* 7.4, 8-H), 6.98 (1H, d, *J* 8.6, Cl_2CCH), 7.03 (1H, m, 2-H), 7.14 (1H, t, *J* 7.8, 9-H), 7.26, (1H, d, *J* 8.1, 10-H) and 8.13 (1H, br s, 1-H); δ_C (67.8 MHz, DMSO-d_6) 26.6 (3-C), 41.1 (4-C), 46.1 (7-C), 110.8 (2a-C), 110.9 (10-C), 115.8 (8-C), 119.9 (Cl_2C), 121.1 (9-C), 124.3 (2-C), 125.0 (7a-C), 128.7 (Cl_2CCH), 129.5 (10b-C), 136.6 (10a-C) and 172.0 (6-C); *m/z* (EI) 294 (M^+, 100%).
5. Crystal data for **5**: $C_{14}H_{12}Cl_2N_2O$, M=295.16, triclinic, a=7.286(2), b=8.539(3), c=10.971(3) Å, α=110.95(3), β=99.24(2), γ=89.96(3)°, V=628.0(3) Å^3, T=150 K, space group $P\bar{1}$ (no. 2), Z=2, μ (Mo-Kα)=0.508 mm^{-1}. 3138 reflections measured on a Stoe Stadi-4 four circle diffractometer, 2210 unique (R_{int}=0.0387). Final R_1 and wR_2 values were 0.0465 and 0.0831 (all data).
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8. 7-Methylene-3,4,5,6,7,8-hexahydro-1*H*-azonino[4,5,6-*cd*]indol-6-one **8**: 2-Bromomethyl-*N*-[2-(1*H*-indolyl-3-yl)ethyl]-acrylamide **7** (443 mg, 1.44 mmol) in acetonitrile (300 mL) was irradiated as described above and chromatographed on silica (2:1 hexane:ethyl acetate→ethyl acetate) to give the product **8** (133 mg, 41%), mp 270–272°C; δ_H (250 MHz, DMSO-d_6, 60°C) 3.15 (2H, br, 3-H), 3.40 (2H, br, 4-H), 4.00 (2H, br, 8-H), 5.20 (2H, br s, $=CH_2$), 6.79 (1H, d, *J* 6.8, 9-H), 6.98 (1H, t, *J* 7.5, 10-H), 7.08 (1H, d, *J* 2.1, 2-H), 7.23 (1H, d, *J* 8.0, 11-H) and 10.80 (1H, br s, 1-H); δ_C (126 MHz, DMSO-d_6) 25.0 (3-C), 38.7 (8-C), 41.7 (4-C), 110.2 (11-C), 111.0 (3-C), 114.4 ($=CH_2$), 120.7 (9-C and 10-C), 123.6 (2-C), 126.7 (8a-C), 129.2 (11b-C), 137.2 (11a-C), 146.0 (7-C) and 171.3 (6-C); HRMS (EI): found *m/z* 226.1116 (M^+, 100%). $C_{14}H_{14}N_2O$ requires *m/z* 226.1106.
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