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# INDOLE AS A TOOL IN SYNTHESIS. CONSTRUCTION OF MEDIUM-SIZED RINGS BY ITERATIVE INDOLIZATION-OXIDATION

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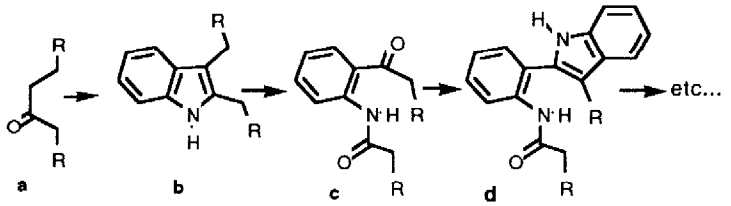
***Summary***: Application to cycloöctanone of two successive sequences of Fischer indolization and oxidation gave compound **10** with a 14-membered ring .

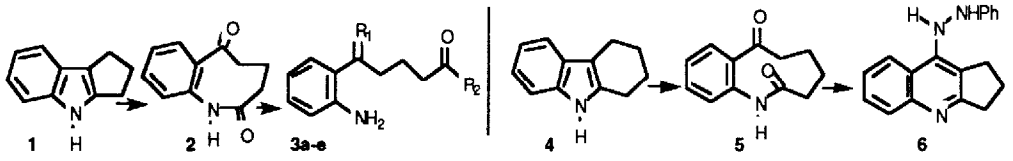
Fischer indolization[1] is a highly potent method for annulation of an aniline unit to a linear or a cyclic ketone: **a -> b** (scheme 1). The 2,3 double bond of indole is easily broken under conditions which mimick the biological oxidation of tryptophan to N-formylkynurenin. Such oxidations of indolic compounds have been extensively studied by Witkop[2] and, more recently, by Japanese authors[3]; they are best performed by ozone, by photosensitized oxidation, or by a peracid, and a ketoamide **c** with an anthranilic moiety results. The newly generated keto group in **c** is available for a second Fischer indolization to **d**, and thus iteration of the two-reaction sequence should allow the construction of a polyanthranilate chain.




scheme 1

In a continuation of our research on the use of indole as a tool in synthesis[4], we undertook an exploratory study of this simple methodology. Its application to cyloalcanones seemed of interest, in view of the possibility of constructing medium-sized rings containing anthranilate units. Recently, cyclic polyanthranilates have been suggested as possible bioprecursors of the cholecystokinin inhibitors asperlicins[5].

Unlike its alpha-substituted derivatives, cyclopentanone itself is easily indolized to the cyclopentano[1,2-b]-indole **1** (scheme 2) , oxidation of which ($O_3$) yields the benzo-öctopine derivative **2**[2b]. As already observed by Witkop[2b], the lactam group in **2** is highly sensitive to nucleophiles.




| | $R_1$ | $R_2$ | | $R_1$ | $R_2$ | | $R_1$ | $R_2$ |
|---|---|---|---|---|---|---|---|---|
| **3a** | N-NH-Ph | NH-NH-Ph | **3c** | O | OMe | **3e** | O | O$^t$Bu |
| **3b** | O-$(CH_2)_2$-O | O-$(CH_2)_2$-OH | **3d** | O | OEt | **3f** | O | OH |

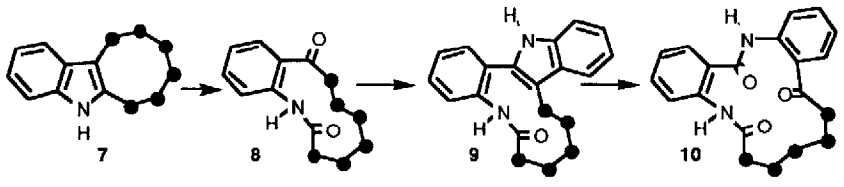
scheme 2

Treatment with phenylhydrazine yielded the phenylhydrazone-hydrazide **3a**. Similarly, attempted dioxolanation of the ketogroup (with a view to selective reduction of the lactam) gave the dioxolane ester **3b**, while methanol, ethanol and even $^t$butanol yielded esters **3c,3d** and **3e** respectively. These esters are rather unstable, and were rapidly hydrolyzed to the acid **3f**. This reactivity of lactam **2** is ascribed to the strain in the octopine ring, and the facile hydrolysis of the esters probably results from participation of the enolized keto group in the reaction. Nevertheless, the ß-lactam like behaviour[6] of compound **2** is noteworthy.

The tetrahydrocarbazole **4** obtained by indolization of cyclohexanone yielded the known[2b] ketolactam **5** upon oxidation. Further progress was not possible, as treatment of **5** with phenylhydrazine gave the cyclized quinoline **6**. The well precedented[7] transannular cyclization of compounds like **5** to quinolones, best exemplified by Winterfeldt in his

biomimetic synthesis of camptothecin[8], is favoured here by the initial formation of a phenylhydrazone.

The cycloöctanone series was fortunately more rewarding (scheme 3):




scheme 3

Fischer indolization to indole **7**[2b] was quantitative. Ozonization of **7** in methylene chloride at-60°C, followed by reduction with dimethyl sulfide gave the crude ketolactam **8** (88 %), which was purified by crystallisation from MeOH (**8**: mp,159-160°C; UV, 222, 246, 284 nm; ms, m/z 231 ($M^{\cdot+}$), 188, 174, 120 (100%); $^1H$ nmr, ppm, 1.4(m,4H), 1.7(m,4H), 2.73(t,2H), 2.82(t,2H), 7.0-7.2(m,3H), 7.4-7.6(m,2H); $^{13}C$ nmr, ppm, 125.5, 126.14, 126.73, 130.09, 133.44, 138.11 (aromatics), 172.53 (lactam), 205.98 (ketone), 21.55, 22.55, 23.35, 24.50, 35.55, 38.46 (six methylene groups)).

A second indolization step transformed **8** into the unstable tetracyclic indole **9**, which was not isolated but submitted to ozonization to yield compound **10** (38% from **8**), whose spectroscopic characteristics are fully consistent with the depicted structure containing two anthranilate units in a 14-membered ring: uv nm (log e), 220(4.31), 250(4.04), 300(3.50); $M^{\cdot+}$ = 336.1498 (calc,336.1473); ms, m/z 120 (100%), 216. Its $^1H$ nmr spectrum (27°C) shows five methylene groups: the two methylenes adjacent to the carbonyls appear as triplets at 2.50 and 3.18 ppm, respectively, while the three remaining methylenes give a triplet (1H) at 1.86 ppm and a multiplet (5H) at 1.68 ppm. The lactam NHs are sharp singlets at 9.78 and 10.75 ppm and the aromatic protons ortho to the carbonyls are deshielded as doublets at 7.54 and 8.20 ppm. The remaining aromatic protons resonate as complex multiplets in the region 6.6-7.4 ppm. In the $^{13}C$ nmr spectrum the two methylenes adjacent to carbonyl groups appear at 36.61 and 37.96 ppm, and are readily distinguished from the remaining three methylenes at 22.99, 23.65 and 25.17 ppm. The lactam carbonyls appear at 178.00 ppm (benzamide) and 170.96 ppm, and the keto group is at 205.56 ppm. The quaternary aromatic carbons give signals at 120.76, 132.74, 136.20 and 138.35 ppm, while the eight remaining aromatic carbons are at 122.52, 123.10, 125.75, 126.03, 126.33, 126.91, 131.15, and 132.95 ppm.

Iteration of the process with a view to the incorporation of a third anthranilate unit and formation of a 17-membered ring is under current study.

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