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Synthesis of Two New Heteroaromatic β-Carboline-Fused Pentacycles. Observation of a New Intercalating Agent

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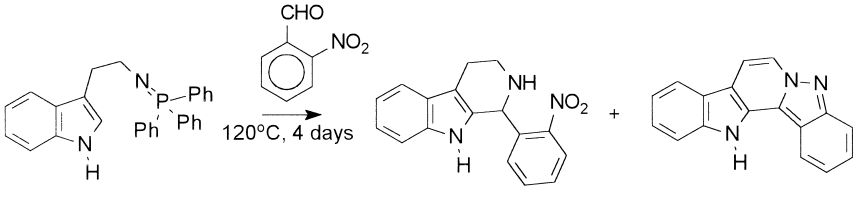
Abstract—Five-step synthetic routes of two new polyfused heterocycles: indazolo[3,2-*a*]-ß-carboline (**3**) and benzo[4′,5′][1,2,3]triazino[6,1-*a*]-ß-carbolinium salt (**10**) applying Pd(0)-catalyzed cross-coupling reaction have been elaborated.

The 9*H*-pyrido[3,4-*b*]indole (β-carboline) core is the main structural unit of many biologically active alkaloids and synthetic molecules of therapeutic interest. Besides the traditional methods (Pictet–Spengler and Bischler–Napieralski cyclisations) imino- phosphoranes[1] have emerged as versatile building blocks for the preparation of such heterocycles. In continuation of our program towards the synthesis of biologically active 1,2,3,4-tetrahydro-β-carboline derivatives[2] we found that the iminophosphorane of tryptamine (**1**) could successfully be used for such purposes. Thus, treatment of **1** with *o*-nitrobenzaldehyde at 120 °C in a sealed tube for 4 days afforded two products simultaneously: besides the expected tetrahydro-ß-carboline **2** (31%),[3] a hitherto unknown pentacyclic ring system, indazolo[3,2-*a*]-β-carboline **3** was also isolated in 15% yield.

As polycyclic *N*-heteroaromatics may exhibit intercalating properties[4,5] and from this point of view compounds of such type came more and more into focus of interest, we decided to elaborate a more convenient and easily reproducable straightforward synthetic pathway to this ring system and to study its intercalating ability.

This synthesis has been accomplished by application of a well established ring fusion strategy elaborated recently by us for various related aza-heterocycles and alkaloids.[6,7] Thus, ß-carboline-1(2H)-one (**4**) was treated with triflic anhydride to give a triflate[8] which was subjected to Suzuki-coupling[9] with *o*-pivaloyl-aminophenylboronic acid to yield the 1-aryl substituted β-carboline derivative **5** (mp >250 °C; 52%). Removal of the pivaloyl group by treatment of **5** with 40% sulfuric



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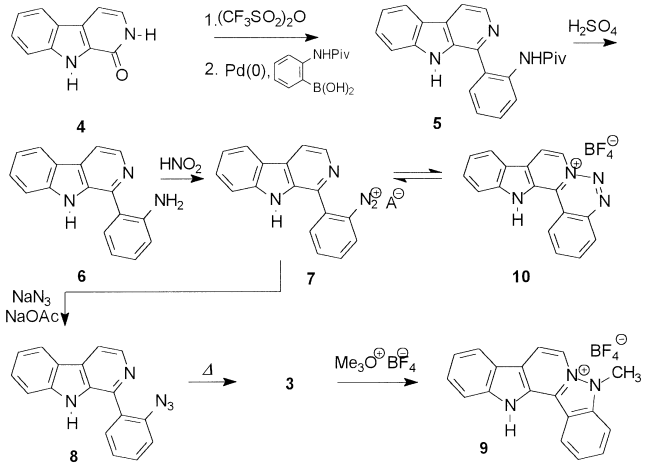
acid at reflux temperature (i.e., preparation of the amino compound **6** prepared earlier by Rocca et al.[10] by an independent route), and subsequent diazotation gave the diazonium salt **7**. Treatment with sodium azide under weakly basic conditions (sodium acetate buffer) afforded the azide **8**[11] in 66% yield. Heat-treatment of **8** gave rise to formation (by generation of a nitrene) of the desired pentacyclic compound **3** in 58% yield which proved to be identical (NMR spectrum and mp)[12] with the sample obtained from **1**. In order to obtain a derivative of this new ring system suitable for biological investigations **3** was methylated by trimethyloxonium tetrafluoroborate in dichloromethane to give the 5-methyl substituted salt (**9**)[13] in good yield.



An interesting extension of this synthetic work was provided by investigating the intermediate diazonium salt **7** in more detail. In one of our early studies[14] we described that *o*-substituted α-pyridylphenyldiazonium salts can form a valence bond isomeric equilibrium with a fused *v*-triazinium salt, and these equilibria can be sensitively shifted by changing the substituents. In order to check whether or not such a ring closure of **7** takes place the product of the diazotation reaction of **6** was also isolated in crystalline form (mp 130–2°C; 96%)[15] and was investigated by IR and NMR spectroscopy. These spectra unambiguously revealed that the isolated product is entirely in the triazinium form **10**, and neither the crystals nor its solutions contain detectable amount of the diazonium isomer **7**. To the best of our knowledge, this ring closed product: benzo[4′,5′][1,2,3]triazino[6,1-*a*]-β-carbolinium salt (**10**) also represents a new ring system. It is interesting to note that two fused quaternary ring systems closely related to **10**: pyrido[2,1-*a*]-β-carbolinium and pyridazino[3,2-*a*]-β-carbolinium salts have been described and proved to be potent antitumor compounds.[16,17]

The fact that an equilibrium between **7** and **10** exists is also revealed by the finding that treatment of the ring-closed **10** with sodium azide under the same conditions as in the transformation of the open-chained **7**, the same product (i.e., **8**) was obtained.

The intercalating property of the two new water-soluble polycycles (**9** and **10**) was investigated by determination of the increase of T_m point.[18] As a model DNS, T_{20}–dA_{20} duplex was used[19] ($T_m = 45.7\,^{\circ}C$) The results of several measurements significantly revealed that the methyl substituted compound **9** is highly active: a T_m point increase of 20.6 °C was found, while the triazinium salt **10** proved to be inactive.

Extension of the synthesis for further related derivatives as well as detailed biological investigation of the new heterocyclic ring systems is in progress.

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3. (**2**) ^{1}H NMR (CDC_{l3} 300 MHz) δ ppm 8.25 (NH, s, 1H), 7.83 (H5, dd, 7 Hz, 1.8 Hz, 1H), 7.52 (H3′, dd, 9 Hz, 2 Hz, 1H), 7.41 (H6′, dd, 9 Hz, 1.7 Hz, 1H), 7.4–7.12 (m, 4H), 7.33 (H8, dd, 7.2 Hz, 1.6 Hz, 1H), 5.65 (H1, s, 1H), 3.15 (H3, m, 2H), 2.87 (H4, m, 2H); ^{13}C NMR (CDC_{l3} 75 MHz) δ ppm 149.8, 136.4, 135.9, 132.9, 132.2, 131.2, 128.6, 126.9, 124.2, 122.0, 119.5,118.3, 111.1, 110.9, 52.0, 41.6, 22.1.
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11. (**8**) ^{1}H NMR ($CDCl_3 + C_6H_6$-d_6 400 MHz) δ ppm 8.54 (H3, d, 5 Hz, 1H), 8.22 (NH, s, 1H), 8.04 (H5, m, 1H), 7.84 (H4, d, 5 Hz, 1H), 7.56 (H3′, m, 1H), 7.42 (H7, td, 7 Hz, 1 Hz, 1H), 7.33 (H5′, m, 1H), 7.25 (H8, dt, 8 Hz, 1 Hz, 1H), 7.21 (H6, td, 7 Hz, 1 Hz, 1H), 7.17 (H4′, t, 6.5 Hz, 1H), 7.16 (H6′, d, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ ppm 140.7, 140.6, 139.4, 138.1, 134.5, 132.3, 130.5, 130.3, 129.7, 128.8, 125.6, 122.0, 121.9, 120.4, 119.1, 114.5, 111.8;, IR (KBr) ν cm^{-1} 2126, 2095, 1626, 1497, 1321, 1298, 1238, 748.
12. (**3**) mp >240 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6 400 MHz) δ ppm 12.1 (NH, s, 1H), 8.62 (H4, dd, 8 Hz, 1 Hz, 1H), 8.54 (H7, d, 7Hz, 1H), 8.00 (H9, d, 8 Hz, 1H), 7.79 (H8, d, 7 Hz, 1H), 7.70 (H1, d, 8 Hz, 1H), 7.62 (H12, dd, 8 Hz, 1 Hz, 1H), 7.43 (H2, td, 8Hz, 1Hz, 1H), 7.35 (H11, m, 1H), 7.20 (H10, td, 7 Hz, 1 Hz, 1H), 7.17 (H3, td, 8 Hz, 1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ ppm 147.4, 138.6, 128.3, 126.1, 123.9, 123.5, 121.0, 119.9, 119.1, 119.0, 118.4, 118.0, 113.7, 113.4, 112.8, 110.7, 108.4; IR (KBr) ν cm^{-1} 3307, 1542, 1456, 1377, 1367, 1212, 725.

13. (**9**) ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm 13.0 (NH, s, 1H), 9.19 (H7, d, 7Hz, 1H), 8.97 (H1, dd, 8 Hz, 1 Hz, 1H), 8.74 (H8, d, 7 Hz, 1H), 8.42 (H9, d, 8 Hz, 1H), 8.09 (H4, dd, 8 Hz, 1 Hz, 1H), 8.01 (H3, td, 7 Hz, 1 Hz, 1H), 7.80 (H12, dd, 8Hz, 1Hz, 1H), 7.72 (H2, td, 7 Hz, 1 Hz, 1H), 7.68 (H11, td, 8 Hz, 1 Hz, 1H), 7.44 (H10, m, 1H), 4.45 (CH_3); ^{13}C NMR (DMSO-d_6) δ ppm 141.4, 139.0, 132.3, 128.7, 127.7, 124.3, 123.6, 122.3, 122.2, 121.8, 121.4, 120.4, 116.5, 113.8, 113.3, 112.6, 109.7, 34.0.
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15. (**10**) ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm 13.2 (NH, s, 1H), 9.78 (H8, d, 6.5Hz, 1H), 9.18 (H1, d, 8 Hz, 1H), 9.09 (H9, d, 6.5 Hz, 1H), 8.83 (H4, dd, 8 Hz, 1 Hz, 1H), 8.59 (H10, dt, 8 Hz, 1 Hz, 1H), 8.52 (H2, td, 8 Hz, 1 Hz, 1H), 8.36 (H3, td, 8Hz, 1Hz, 1H), 7.90 (H13, dt, 8 Hz, 1 Hz, 1H), 7.84 (H12, td, 8 Hz, 1 Hz, 1H), 7.52 (H11, td, 8 Hz, 1 Hz, 1H).
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