COUPLING REACTIONS OF 1,2-BIS(2-INDOLYL)ETHANE. FORMATION OF INDOLO[2,3-*c*]CARBAZOLES.

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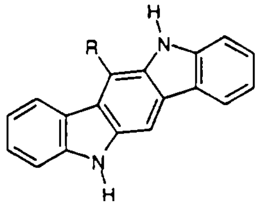
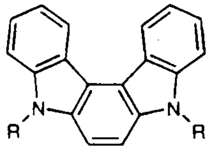
Abstract: 2-Methylindole has been coupled to 1,2-bis(2-indolyl)ethane **6**, which in turn has been further coupled to indolo[2,3-*c*]carbazole **3**. Attempts to couple **6** with CoF_3 in trifluoroacetic acid gave the 7-membered compounds **8** and **9** as the main products.

Indolo[3,2-*b*]carbazole **1** has been intensely studied due to its high affinity[3,4] to the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) receptor and also as a consequence of its presence[5,6] in the gastrointestinal tract of humans after consumption of cruciferous vegetables. Recently a derivative, 6-formylindolo[3,2-*b*]carbazole **2**, (obtained by UV-irradiation of aqueous solutions of tryptophan) has been isolated and found to possess considerably higher affinity to the TCDD receptor than TCDD itself.[7]

Several synthetic pathways to indolo[3,2-*b*]carbazole and many of its derivatives are available.[8,9] All the other possible isomers are known except indolo[2,3-*c*]carbazole **3**.

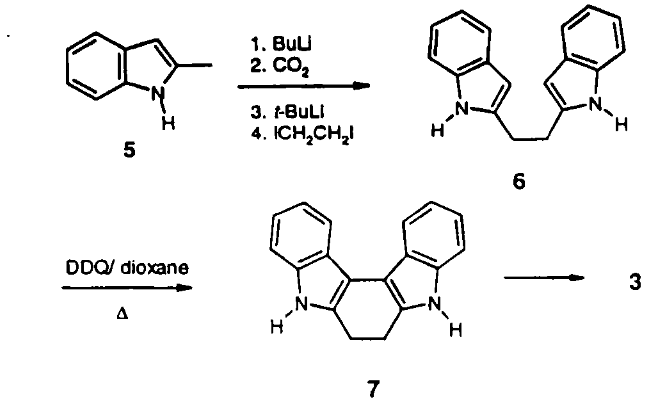


1 R=H
2 R=CHO

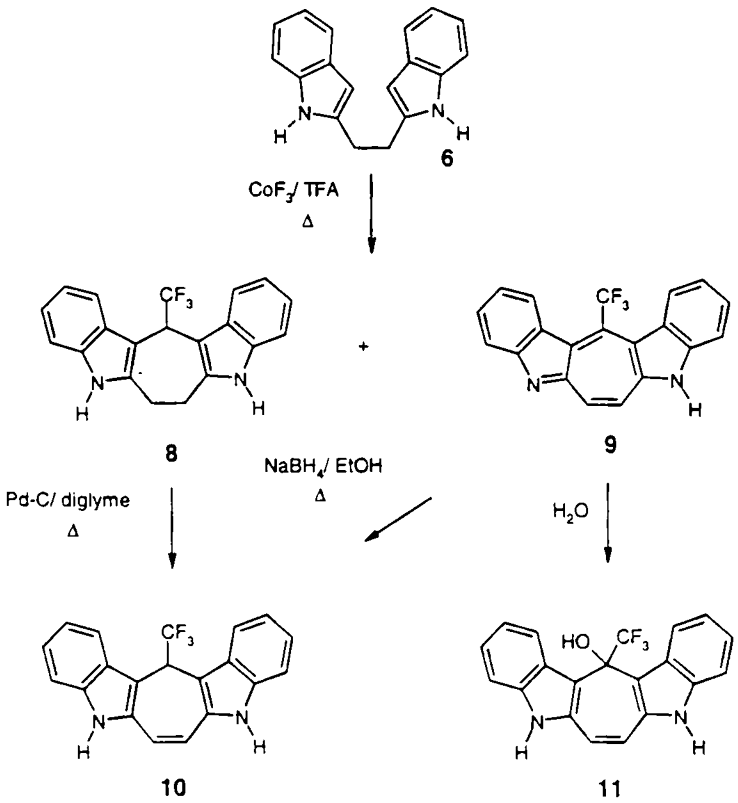


3 R=H
4 H=CH_3

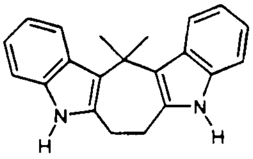
Only one derivative, *N,N'*-dimethylindolo[2,3-*c*]carbazole **4**, formed (without co-formation of *N,N'*-dimethylindolo[3,2-*b*]carbazole) by irradiation of *N,N'*-dimethyl-*N,N'*-diphenyl-1,4-phenylenediamine has previously been described.[10,11] In this context it is of interest that double Fischer indolization of the bisphenylhydrazone of 1,4-cyclohexanedione yields[9] the linear isomer and none of the angular isomer. With this background we have now developed a rational approach to this ring system as outlined below.



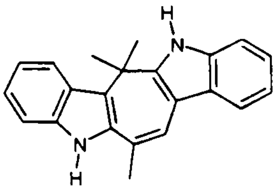
For the coupling of the N-carboxylated dianion[12] obtained from 2-methylindole **5** coupling with 1,2-diiodoethane (yield 48%) was superior in terms of yield and convenience, compared with several other coupling reagents such as iodine or tetraiodomethane. As the yield of 3,3-coupled products from **6**[13] (predominantly **7**[14]) was very low, presumably due to incorporation of DDQ in the starting indole **6** (a reaction that has previously been observed for simple indoles[15]), coupling was also attempted with $Pd(OAc)_2$ which gave a mixture of **7** and **3** in unacceptably low yields. At this point it was decided to try cobalt trifluoride (in trifluoroacetic acid), a reagent which previously has been successfully used[16] for coupling of various activated aromatics, such as 1-methoxynaphtalene.



Refluxing **6** for 18 h with one equivalent of cobalt trifluoride in trifluoroacetic acid did not lead to the expected compounds **7** and **3**, but gave two main products, **8**[17] and **9**[18], both containing a 7-membered ring. The ^{1}H-NMR spectra of **8** and **7** display a coupling pattern for the methylene protons suggesting that the molecules are not planar and undergo rapid conformational changes in analogy with certain substituted dihydrophenanthrenes.[19] The alternative preparation of **8** by refluxing **6** with trifluoroacetaldehyde ethyl hemiacetal and trifluoroacetic acid as catalyst in ethanol suggest formation of trifluoroacetaldehyde in the reaction of **6** with cobalt trifluoride in trifluoroacetic acid. Under acidic conditions, several other carbonyl compounds, e.g. acetone, gave the analogous 7-membered product **12**[20] in excellent yield. A similar compound **13** formed from 2-(α-hydroxyisopropyl)-indole by acid induced dimerization has been reported previously.[21]



12



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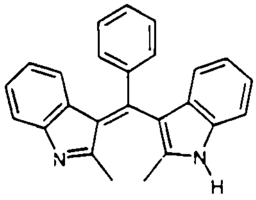

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The red dye **9** has an interesting feature; the indole units are equivalent according to ^{1}H-NMR and ^{13}C-NMR indicating a fast prototropy. Treatment of **9** with sodium borohydride in hot ethanol gave the leuco-compound **10**, whereas treatment of **9** with water yielded the colourless hydrate **11** in quantitative yield. These properties of **9** are analogous to those of the rosindoles[22] e.g. **14** studied already by Emil Fischer.

Acknowledgements.

We thank Prof. R. Lavilla, University of Barcelona, Spain, for provision of a sample of **6**, which gave spectra identical with ours. The trifluoroacetaldehyde ethyl hemiacetal used was a generous gift from Central Glass Co., Saitama, Japan.

References and notes.

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(11a) A possible cyano derivative has been obtained[11b] by Clifton and Plant as early as 1951. However, the structure has never been confirmed.

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(13a) This compound has previously been obtained by Lavilla[13b] as a minor product (in 5% yield) by treatment of the dilithium salt of 2-methylindole-*N*-carboxylic acid with *N*-methylpyridinium salts. Spectral data for compound **6**: IR(KBr): 3391, 1458, 1415, 1290, 788, 746 cm^{-1}. ^{1}H-NMR (DMSO-d$_6$) δ 3.17 (4H, s), 6.20 (2H, s), 6.95 (4H, m), 7.29 (2H, d), 7.40 (2H, d), 11.02 (2H, s) ppm; ^{13}C-NMR (DMSO-d$_6$) δ 27.3 (t), 98.2 (d), 110.5 (d), 118.5 (d), 119.1 (d), 120.0 (d), 128.2 (s), 135.9 (s), 139.3 (s) ppm. MS *m/z* (relative intensity) 260 (72), 130 (100). Mp>260 °C.

(13b) Lavilla, R.; Gotsens, T.; Rodriguez, S.; Bosch, J. *Tetrahedron* **1992**, *48*, 6445-6454.

(14) Compound **7** gave the following spectral data: ^{1}H-NMR (DMSO-d$_6$) δ 3.13 (4H, m), 6.98 (4H, m), 7.28 (2H, d), 8.12 (2H, d), 11.11 (2H, s) ppm; ^{13}C-NMR (DMSO-d$_6$) δ 25.3 (t), 109.6 (s), 110.2 (d), 118.4 (d), 120.2 (d), 122.6 (d), 128.8 (s), 134.3 (s), 136.7 (s) ppm.

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(17) Spectral data for compound **8**. IR(KBr): 3395, 1462, 1334, 1252, 1159, 1140, 1105, 855, 740 cm^{-1}. ^{1}H-NMR (DMSO-d$_6$) δ 3.04 (2H, m), 3.34 (2H, m), 5.42 (1H, m), 7.05 (4H, m), 7.31 (2H, d), 7.77 (2H, d), 11.15 (2H, s) ppm; ^{13}C-NMR (DMSO-d$_6$) δ 24.4 (t), 36.0 (m), 103.4 (s), 110.5 (d), 118.0 (d), 120.5 (d), 121.2 (d), 128.6 (s), 134.0 (s), 137.9 (s) ppm. The carbon of the CF$_3$-group is undetectable due to very slow relaxation. MS *m/z* (relative intensity) 340 (46), 271 (100). Mp>260 °C.

(18) Spectral data for compound **9**. IR(KBr): 1670, 1373, 1194, 1127, 1115, 761 cm^{-1}. ^{1}H-NMR (DMSO-d$_6$) δ 5.95 (1H, m), 7.63 (2H, s), 7.82 (2H, s), 7.94 (2H, d), 8.45 (2H, s), 8.92 (2H, s) ppm; ^{13}C-NMR (DMSO-d$_6$) δ 113.7 (d), 122.8 (s), 123.8 (d), 124.8 (s), 125.1 (d), 127.9 (d), 130.5 (d), 139.6 (s), 148.4 (s) ppm. Slow relaxation made it impossible to detect the carbon of the CF$_3$-group and the adjacent carbon as well. MS *m/z* (relative intensity) 336 (100). Mp>260 °C.

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(20) Compound **12** gave the following NMR-data: ^{1}H-NMR (DMSO-d$_6$) δ 1.96 (6H, s), 3.05 (4H, s), 6.95 (4H, m), 7.25 (2H, d), 7.77 (2H, d), 10.70 (2H, s) ppm; ^{13}C-NMR (DMSO-d$_6$) δ 27.5 (q), 31.4 (t), 37.9 (s), 111.2 (d), 118.2 (d), 119.0 (s), 120.1 (d), 121.4 (d), 128.0 (s), 134.4 (s), 135.6 (s) ppm.

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