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# A NOVEL ACCESS TO BIS-CARBAZOLE ALKALOIDS : SUBSTITUENT EFFECT ON THE EFFICIENCY AND REGIOSELECTIVITY IN $BF_3$-$Et_2O$ MEDIATED INTERMOLECULAR COUPLING OF PYRANOCARBAZOLE ALKALOIDS

Amit Chakrabarti and D.P. Chakraborty*
Department of Chemistry
Bose Institute, 93/1, A.P.C. Road, Calcutta 700 009
India

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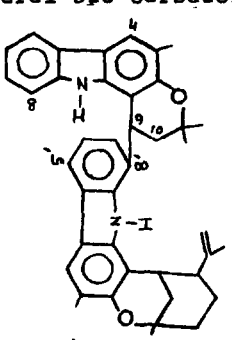
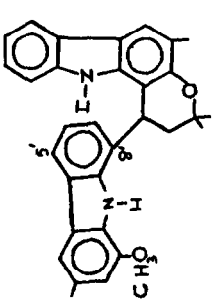
**Abstract** : Whereas the presence of electron releasing groups(+I) on the aromatic part and/or heteronitrogen atom facilitate $BF_3$-$Et_2O$ mediated intermolecular coupling of pyranocarbazoles 2(a-c) thereby affording binary pyranocarbazoles 3(a-c) in 17-35% yield, electron withdrawing groups (-I) prevent such coupling under similar experimental conditions.

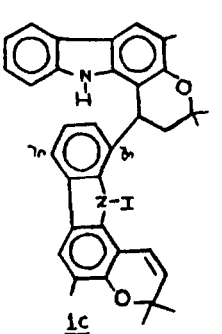
Monomeric carbazoles of various carbon skeletons have been known since 1962[1,2]. From the biomimetic hydroxylation studies on 3-methylcarbazole Chakraborty *et al.*[3,4] predicted the occurrence of dimeric carbazole alkaloids in plants which became a reality after the report of the isolation of murrafoline from *Murraya euchrestifolia* by Furukawa *et al.*[5] Murrafoline (1a) contained a murrayazolidine unit in which a dihydrogirinimbine (upper half) unit was attached at 8 position. Several bis-carbazoles with a dihydrogirinimbine moiety attached at 6 or 8 position of another monomeric carbazole have been reported by Furukawa *et al.* The position 6 or 8 of the carbazole nucleus is more nucleophilic than position 5 or 7. This led us to the idea that an electrophilic centre generated at the benzylic position of the 2:2 dimethyl-$\Delta^3$-pyran system (Scheme-I) could provide the required electrophile which after attacking at 6 or 8 position and subsequent ringclosure could afford the bis-alkaloid with dihydrogirinimbine unit attached at 6 or 8 position as found in many natural bis-carbazole alkaloids.




1a

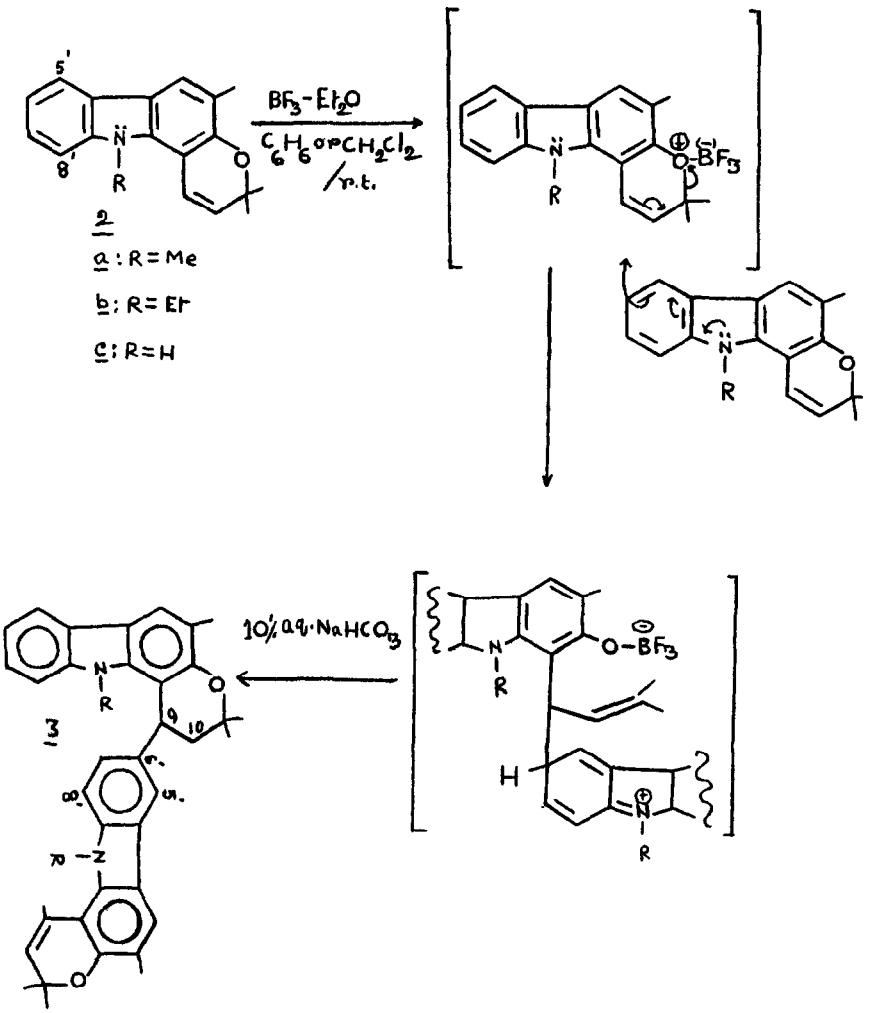



1b




1c

**Scheme-I**



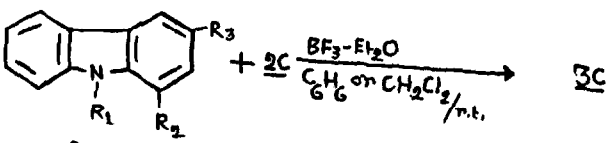
Prompted by this idea we designed the $BF_3$-etherate mediated intermolecular coupling reaction of N-substituted girinimbine 2(a-b), girinimbine 2c and substituted carbazoles 2(d-e). In the present communication we report the synthesis of bis-carbazole alkaloids built on the said monomeric units.

In a typical experimental procedure N-methylgirinimbine 2a in dry benzene or methylenechloride was treated with $BF_3$-$Et_2O$ (Table-1, experimental) at room temperature. After ten minutes of stirring the reaction mixture, usual work up and chromatography afforded an amorphous white solid 3a; m.p.:191° (decompose); UV:239, 293, 331, 349, very similar to 2a; MS:554($M^+$), 553(100%), 539, 278, 276, 263, 261. The $^1$HNMR spectrum of 3a contained signals attributed to two N-methyl groups ( $\delta$3.93 and 3.43), two aryl methyl groups ( $\delta$2.33 and 2.16). The signals for the ortho coupled H-5 proton ( $\delta$7.86, J=6.9 Hz) and the meta coupled broad singlet for H-5' proton[5] ( $\delta$7.75) together with the sharp singlets for H-4 and H-4' protons at $\delta$7.58 and 7.46 account for all the low field aromatic protons[2] of H-5, H-5' and H-4, H-4' respectively. The data show that the protons at H-6' is substituted. The oxygen linked 6-proton signals at $\delta$1.41 together with the two vinylic proton doublets at $\delta$5.55 and 6.60 (J=9.9 Hz each) respectively, could explain the presence of a 2:2 dimethyl-$\Delta^3$-pyran ring system in 3a while the signals at $\delta$1.29 and 1.40 (3H each) together with methylenic proton signals at $\delta$1.97 and 2.31 (1H each) and one benzylic proton multiplet at $\delta$5.03 (1H,m) as evident from the spectra, could account for a 2:2 dimethyl dihydro pyran system in 3a in which one of the benzylic protons has been substituted. The data therefore establish the linkage of a girinimbine unit and dihydrogirinimbine unit through 9 and 6' position as in 3a. In conformity with the structure, the mass spectral peaks at m/z 278 and 276 could arise from the upper and lower halves of 3a respectively (Scheme-I).

The reaction was consistent with substrates 2(b-c) when binary pyranocarbazoles 3(b-c) were obtained under similar experimental condition (Table-1, Schem-I, Experimental). However in all cases of 3(a-c), coupling has been found to occur through 6' and 9 positions (Scheme-I) as has been envisaged by Furukawa *et al.*[5], unlike that of naturally occuring binary pyranocarbazoles e.g. murrafoline-C(1c), -B(1b).

The same strategy was extended to attempt intermolecular coupling between girinimbine 2c and murrayanine (1-methoxy-3-formylcarbazole) 2d under similar experimental condition, with a view to synthesising an analogue of murrafoline-8(1b). Unfortunately no coupled product except 3c(26%) could be isolated from the reaction products. Attempted coupling between 2c and 2e also remained unsuccessful producing only 3c(20%). (Scheme-II)

Scheme-II




2

d ; $R_1$=H; $R_2$=$OCH_3$; $R_3$=CHO

e ; $R_1$=$SO_2Ph$; $R_2$=$R_3$=H

Table-1

| Run | 2(m.p) | $BF_3$-$Et_2O$ (ml) | Time | Product[b] 3(%yield[a]) ($C_6H_6$) | (m.p) ($CH_2Cl_2$) |
|---|---|---|---|---|---|
| 1 | a[6](142°) | 0.5ml | 10 mints. | a(30)(191°-decom.) | (32) |
| 2 | b[6](128-29°) | 0.5ml | 10 mints. | b(35)(181°-decom.) | (27) |
| 3 | c[7](171°) | 0.5ml | 10 mints. | c(liquid)(17) | (21) |

a = Yields are referred to the amount of homogeneous product obtained by column chromatography.

b = Products 3(a-b) are new and gave satisfactory microanalytical data in support of their structures.

It is thus evident that electron releasing groups ($CH_3$, $OCH_3$) on the aromatic part and/or heteronitrogen atom of the carbazole system facilitate electrophilic attack efficiently and regioselectively on the electron rich C-6 position of the attacking entity. On the other hand the presence of electron withdrawing groups decreases the nucleophilicity of the C-6 or C-8 position preventing facile coupling as has been observed with our case (Scheme-II). This fact also provides some rationale for the non-availability of bis-alkaloids with dihydrogirinimbine unit attached at 5 or 7 position of the second monomeric unit in nature or during Nafion 117 induced coupling reactions reported by Furukawa et al.

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## EXPERIMENTAL

All M.ps. are uncorrected and were determined on a Toshniwal melting point apparatus. $^1H$ NMR spectra were recorded in a Bruker CXP 300 MHz instrument using $CDCl_3$ as the solvent and TMS as the internal standard. UV spectra were recorded in spectroscopic grade ethanol (95%) by a UV-160 Shimadzu spectrophotometer. Mass spectra were obtained with a AEIMS 30 mass spectrometer. N-alkyl girinimbines were prepared by the method reported[6].

Reaction of 1(a-c) with $BF_3$-$Et_2O$ : Substrates 1a(1.0 gm; 3.61 mmole), 1b(1.0 gm; 3.43 mmole) and 1c(1.0 gm; 3.80 mmole) were dissolved in dry benzene and methylene chloride separately (50 ml in each run) in 100 ml round bottom flasks under separate experimental set up. Distilled $BF_3$-$Et_2O$ (0.5 ml in each run) was added to the experimental solutions with mechanical stirring at room temperature. The mouths of the flasks were protected with $CaCl_2$ guard tubes. Immediate green coloration of the experimental solutions was observed. The stirring was continued for 10 minutes[8] in each run. The reaction products were then washed with 10% aqueous sodium bicarbonate solution. During washing the deep green colour of the reaction products disappeared quickly. They were then extracted with methylene chloride. The concentrated extracts were then chromatographed over columns of silica gel [60-120 mesh; Merck] 7. Elution of columns with n-hexane-benzene (4:1) yielded binary carbazoles 2(a-c). Identical product formation was observed in each case with the same substrate in both the solvent system (Table-1).

Product 3a : (n-hexane-benzene; 4:1) amorphous solid; m.p.:191° (decompose); UV:239, 293, 331, 349; $^1$H NMR $\delta$ (ppm):1.29(3H,s), 1.40(3H,s), 1.41 (6H,s), 1.97(1H,m), 2.16(3H,s), 2.31(1H,m), 2.33(3H,s), 3.43(3H,s), 3.93 (3H,s), 5.03(1H,m), 5.55(1H,d,J=9.9 Hz), 6.55-6.58(3H,m), 6.60(1H,d,J= 9.9 Hz), 6.61-6.63(2H,m), 7.46(1H,s), 7.58(1H,bs), 7.75(1H,bs) and 7.86(1H, d,J=6.9 Hz); MS; m/z(rel. int.):554($M^+$) (90), 553(100), 539(48), 538(95), 496(48), 495(32), 278(60), 276(20), 263(60), 261(40), 244(49), 243(47). For 3a: $C_{38}H_{38}N_2O_2$; cal; C:82.31%, H:6.85%, N:5.05% and O:5.77%; Found: C:83.01%, H:6.81%, N:5.15% and O:5.72%.

Product 3b : (n-hexane-benzene; 4:1) amorphous solid; m.p.:181° (decompose); UV:240, 291, 333, 349; $^1$H NMR $\delta$ (ppm):1.33-1.45(6H,m), 1.53(3H,s), 1.50 (3H,s), 1.57(3H,s), 1.58(3H,s), 1.91(1H,m), 2.08(1H,m), 2.45(3H,s), 2.41 (3H,s), 4.33-4.45(4H,m), 4.93(1H,m), 5.50(1H,d,J=10.1 Hz), 6.51-6.79(3H,m), 6.85(1H,d,J=10.0 Hz), 6.90-7.06 (2H,m), 7.48(1H,s), 7.56(1H,s), 7.73(1H,s), and 7.87(1H,d,J=7.1Hz); MS:m/z(rel. int.); 582($M^+$) (90), 581(100), 567(95), 553(40), 538(20), 292(40), 290(35), 277(18), 263(60). For 3b: $C_{40}H_{42}N_2O_2$; cal; C:82.47%, H:7.21%, N:4.81% and O:5.49%; Found: C:82.46%, H:7.19%, N: 5.01% and O:5.44%.

Product 3c : (n-hexane-benzene; 4:1) liquid; UV:239, 292, 329, 348; $^1$H NMR $\delta$ (ppm):1.36(3H,s), 1.40(3H,s), 1.45(3H,s), 1.50(3H,s), 2.00(1H,m), 2.25 (1H,m), 2.41(6H,s), 4.93(1H,m), 5.60(1H,d,J=10.0 Hz), 6.79(1H,d,J=9.9 Hz), 7.13(1H,s,$D_2O$ exchangeable), 7.20-7.41(5H,m), 7.48(1H,s), 7.58(1H,s), 7.75 (1H,s), 7.86(1H,s,$D_2O$ exchangeable), and 7.93(1H,d,J=8.4 Hz); MS:m/z (rel. int.):526($M^+$) (99), 525(100), 511(50), 496(30), 264(50), 262(30), 249(65), 247(60). For 3c: $C_{36}H_{34}N_2O_2$; cal; C:82.12%, H,6.46%, N:5.32% and O:6.08%; Found; C:82.03%, H: 6.46%, N:5.40% and O:6.10%.

## REFERENCES AND FOOT NOTES

1. Kapil, R.S., Academic Press, New York, 1971, 13, (R.H.F. Manske, Ed.), 273.
2. Chakraborty, D.P., Fortsch. d. chem. Org. Naturst, 1977, 34, 279.
3. Chakraborty, D.P., Planta Medica, 1980, 39, 97.
4. Roy, Shyamali, Ghosh, S., Guha, R. and Chakraborty, D.P., Indian J. Chem., 1982, 218, 617.
5. Furukawa, H., Wu. T.-S and Kuoh. C. -S, Chem. Pharm. Bull., 1985, 33, 2611 and the references cited therein.
6. Chakrabarti, A. and Chakraborty, D.P., Tetrahedron Letters, 1988, 29, 6625.
7. Chakraborty, D.P., Barman, B.K. and Bose, P.K., Science and Culture (India), 1964, 30, 445.
8. A long time stirring decreases the product yield by increasing polymerisation in each case.