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EFFECT OF SODIUM NAPHTHALENIDE, A KEY SET REAGENT, ON 3-SUBSTITUTED INDOLES

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Abstract — Action of the single electron transfer (SET) reagent sodium naphthalenide on 3-substituted indoles revealed that indoles with electron-donating substituents do not respond whereas indoles with electron-withdrawing substituents easily react, yielding several products depending upon the substituent.

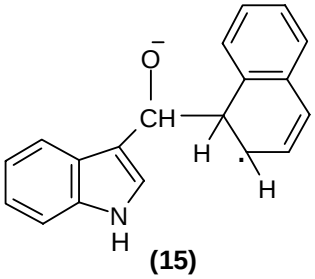
INTRODUCTION

Radical-mediated reactions often serve as the key step in the overall synthetic strategy of a wide range of molecules. Till now, little effort has been made for synthesizing indole derivatives of diverse biological importance through single electron transfer reaction. Such reluctance is explicable in terms of highly electron-rich system of the indole ring which have little tendency to accept an electron. The tendency to form an indolyl radical anion by accepting an electron can be increased by introducing an electron-withdrawing substituent at C-3 of indole ring.

Six C-3 substituted indole derivatives *viz.* 3-formylindole (**2**), 3-trifluoroacetylindole (**3**), 3-benzoylindole (**4**), 3-acetylindole (**5**), skatole (**6**), and 3-ethylindole (**7**) were chosen to study the effect of sodium naphthalenide [Na Naph, (**1**)], a useful single electron transfer (SET) reagent[1-5] on them. Except skatole and 3-ethylindole all the other compounds reacted. 3-Trifluoroacetylindole, 3-acetylindole, and 3-benzoylindole gave a single product each – whereas four products (**8**-**11**) in the ratio (7:6:2:1) were obtained in the case of 3-formylindole (Scheme 1)[6].

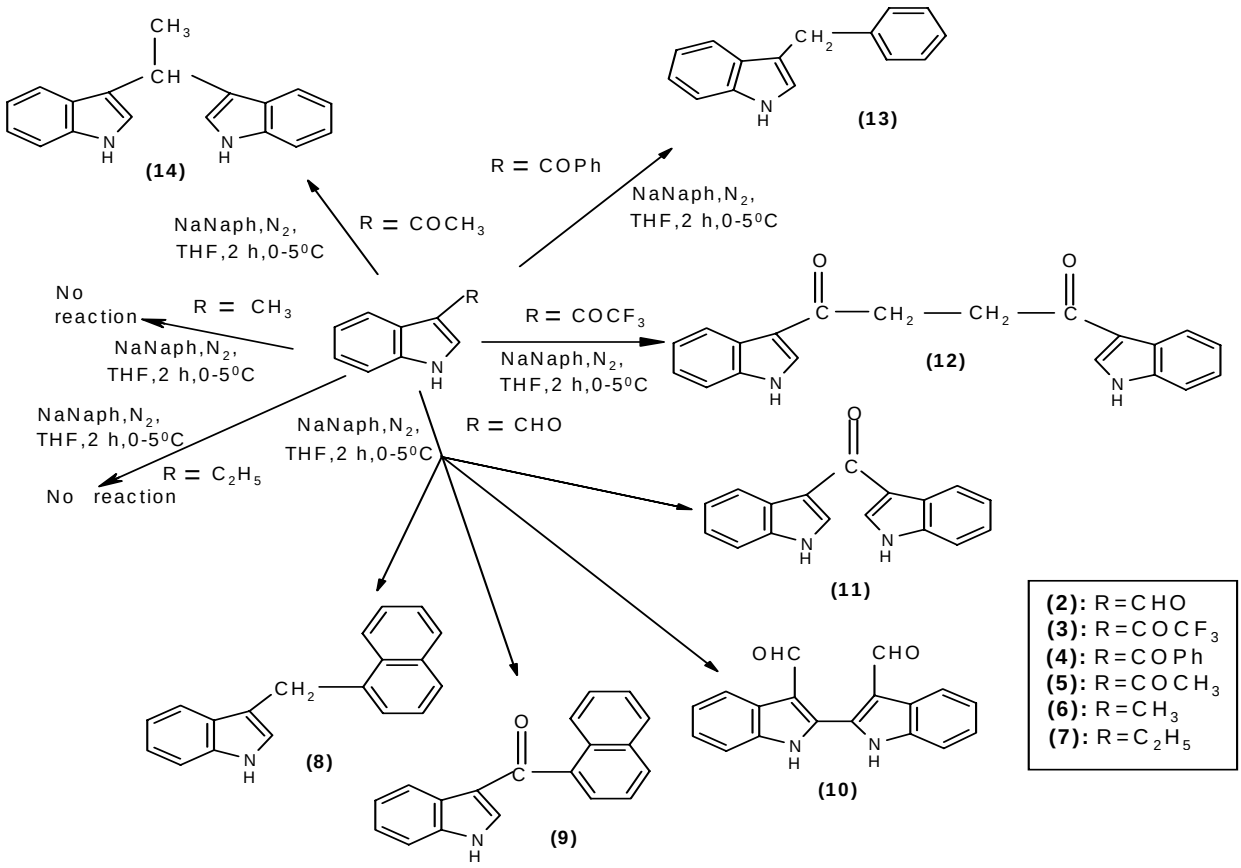
RESULTS AND DISCUSSION

Compounds (**8**) and (**9**) were derived from coupling of the substrate with naphthalenide radical. The plausible mechanism involved the formation of a new bond between Na-naphthalenide anion and electron-deficient carbon atom of aldehyde group to give an intermediate anion radical (**15**).



(15)

Aromaticity of naphthalene ring is regained by hydrogen rearrangement, loss of hydroxide and a further SET from naphthalenide radical anion forms a secondary carbanion which on acidification during work-up



Scheme 1

yields the product (**8**). The structure of **8** has been confirmed by X-Ray crystallographic analysis.[7] The ORTEP projection is shown in Figure 1. Product (**9**) is also formed from the same anion radical (**15**) by abstraction of hydrogen radical, protonation and subsequent liberation of hydrogen. Product (**10**) is formed by dimerization at the 2,2´-positions of the radical anion of **2** initially generated by SET from sodium naphthalenide. Product (**11**) arises from dimerization of this initially generated radical anion with

coupling between 2-position of one unit with the 3-aldehyde group of the other, followed by loss of the other -CHO group. From the reaction between sodium naphthalenide [Na Naph, (**1**)] and **3**, compound (**12**) has been obtained in high yield (94%) as the sole product (Scheme 1). The interesting fact of this reaction is that though the starting material is a fluorinated compound (**3**), the dimeric product (**12**) is totally devoid of fluorine; this has been confirmed by the F^{19}-NMR spectroscopy. This apparently surprising result could be rationalized mechanistically as suggested by Stocker *et al.*[8a,b] for a nearly similar type of defluorination. The mechanism involved radical dimerization and stepwise replacement of fluorine by hydrogen. A single reduction product (**13**) has been isolated from the reaction between **1** and **4** in high yield (87%). Similarly, the reaction between **1** and **5** also yielded a single product (**14**) with high selectivity (84%). In both cases, simple radical-ion mechanisms were followed. An interesting feature of

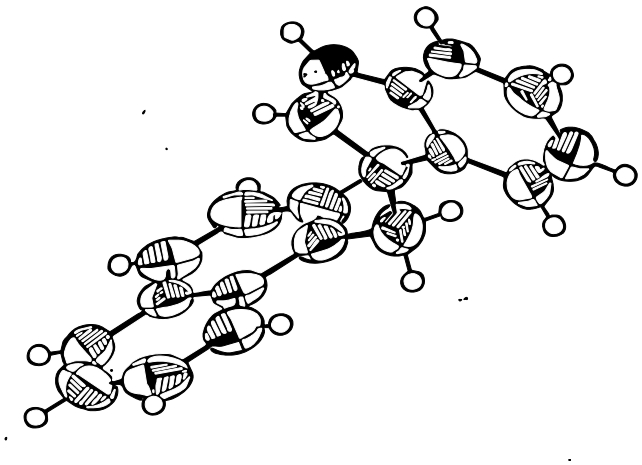


Figure. 1: X-Ray crystallographic structure of **8** (ORTEP projection)

this study is that though the reactions between **1** with **3, 4** and **5** are highly selective but selectivity is almost lost in case of the reaction between **1** and **2**. This might be due to the fact that (a) generally aldehydes are more reactive than ketones and (b) possible formation of 3-alkylidene-3*H*-indolium cation[9] as well as radical anion (**15**) which can react in several ways to form different products (**8-11**).

CONCLUSION

This work clearly shows that construction of different indole derivatives following SET reaction is an efficient, simple and high yielding process, provided electron-withdrawing substituents are present on the indole ring-system. From the sequence of the reactions it can be presumed that when electron-donating groups are present at the 3-position of the indole ring, i.e. for **6** and **7** due to +R effect of the methyl and ethyl group respectively, the five-membered ring becomes more electron rich and as a result electron transfer from reagent to substrate do not take place. However, in presence of electron-withdrawing

groups, i.e. for the compounds (**2, 3, 4** and **5**), the five-membered ring became comparatively less electron rich, as a result LUMO energy is lowered, consequently electron transfer from reagent to substrate becomes easier.

EXPERIMENTAL

General procedure for the synthesis of compounds (8-14)

A deep green solution of sodium napthalenide (**1**) was prepared at 0ºC by treating 1.01 g (0.043 mol) of sodium with 4.08 g (0.032 mol) of naphthalene in dry THF (50 mL) under dry nitrogen atmosphere. Reactions were carried out by adding a solution of the substrate to an excess of the reagent in THF at 0-5ºC till the persistence of the green color of the reagent and allowing to warm up to 20-25ºC with continuous stirring. The reaction mixtures were quenched with a citrate buffer (pH – 4.5) and extracted with 3 x 25 mL of chloroform. The chloroform extracts were washed successively with 10% sodium bicarbonate solution and water, dried over sodium sulfate and evaporated under reduced pressure to leave a residue which was purified by column chromatography to isolate the pure products (**8-14**).

The melting points were recorded on an electrically heated Köfler Block apparatus and are uncorrected. The UV spectra were measured on a Hitachi U-3501 spectrophotometer in 95% aldehyde-free spectral methanol. IR spectra were recorded in KBr discs on a Perkin-Elmer RX1 FT-IR spectrophotometer and MS spectra (EIMS) were recorded on a JEOL-AX 500 mass spectrometer. HRMS spectra were recorded on a Finnigan MAT-H-SQ-30 mass spectrometer. Elemental analyses were performed at the departmental facilities. Column chromatography was performed using neutral alumina (Acme's) whereas preparative TLC was performed using silica gel (Loba Chemié, 100-200 mesh). NMR spectra (both one and two dimensional) were recorded on a Bruker DRX 500 NMR spectrometer (11.7 tesla), equipped with an Silicon Graphics INDY computer using Bruker DISR 871 software. The spectra were recorded in BBI (Broad Band Inverse) probe with 5 mm NMR sample tube at 27ºC temperature. The actual frequency are 500.134 MHz and 125.770 MHz respectively for ^{1}H and ^{13}C-NMR.

3-(Naphth-1-ylmethyl)indole (8) : needle-shaped colorless crystals (petroleum ether (60-80ºC)/benzene), yield 38%, mp 121ºC, R_f = 0.52 (petroleum ether (60-80ºC)/benzene 1:1), silica gel G. Anal. Calcd for $C_{19}H_{15}N$: C, 88.68: H, 5.88: N, 5.44, Found: C, 88.64: H, 5.79: N, 5.37; UV (λ_{max}^{EtOH}): 226.5 (log ε 4.70), 282.5 (log ε 4.00); IR (KBr disc, cm^{-1}): 3416, 1452, 789 and 742; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (1H, d, J=8.2 Hz), 7.82 (1H, d, J=7.7 Hz), 7.71 (1H, d, J=7.7 Hz), 7.60 (1H, d, J=7.9 Hz), 7.57 (1H, s), 7.36-7.43 (2H, m), 7.30-7.35 (2H, m), 7.22 (1H, d, J=8.1 Hz), 7.16 (1H, t, J=7.3 Hz), 7.09 (1H, t, J=7.4 Hz), 6.50 (1H, d, J=1.0 Hz), 4.48 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.32, 136.83,

134.40, 132.71, 129.13, 127.96, 127.38, 127.16, 126.41, 126.20, 126.02, 124.94, 123.32, 122.57, 119.91, 119.52, 115.82, 111.64, 29.43; MS (70 ev): m/z 257 (M^+, 28.8%), HRMS: m/z 257.1204 (M^+, 87.3%).

3-(1-Naphthylcarbonyl)indole (9) : crystalline bright yellow solid, (benzene/ethyl acetate 3:1), yield 33%, mp 216ºC, R_f = 0.52 (benzene/ethyl acetate 3:2), silica gel G. Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11: H, 4.83: N, 5.16, Found: C, 84.06: H, 4.91: N, 5.21; UV (λ_{max}^{EtOH}): 213.5 (log ε 4.74), 256.5 (log ε 4.31); IR (KBr disc, cm^{-1}): 3410, 1705, 1616, 1460, 776, 741; ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.52 (1H, br s), 8.14 (1H, m, faint correlation with NH), 7.90-8.02 (3H, m), 7.79 (1H, m), 7.49-7.60 (2H, m), 7.24 (1H, m), 7.12 (1H, t, J=7.7 Hz), 6.99 (1H, m), 6.89 (1H, m), 6.64 (1H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.40, 139.94, 138.38, 136.82, 136.57, 135.27, 133.09, 132.96, 132.84, 131.78, 129.96, 129.59, 128.87, 126.52, 125.99, 125.42, 124.18, 115.23, 112.52; MS (70 ev): m/z 271 (M^+, 80.5%), HRMS: m/z 271.0992 (M^+, 64.5%).

3,3´-Diformyl-2,2´-biindoyl (10) : yellow microcrystalline solid, yield 11%, mp 158ºC (5% ethyl acetate in benzene as a mixture with **11** and finally purified by extensive preparative TLC), R_f = 0.50 (benzene/ethyl acetate 1:1), silica gel G. Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99: H, 4.20: N, 9.72, Found: C, 74.87: H, 4.17: N, 9.76; UV (λ_{max}^{EtOH}): 207.5 (log ε 4.77), 242.5 (log ε 4.46), 259.5 (log ε 4.39), 295.5 (log ε 4.44) and 448 (log ε 3.34); IR (KBr disc, cm^{-1}): 3167, 1635, 1444, 790 and 760; ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.45 (2H, br s), 10.01 (2H, s), 8.26 (2H, m), 7.85 (2H, m), 7.47 (2H, m), 7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.44, 136.75, 136.08, 123.98, 123.18, 121.86, 120.94, 118.35, 111.55; MS (70 ev): m/z 288 (M^+, 26.9%).

Bis(3-indolyl) ketone (11) : pale yellow microcrystalline solid, yield 6%, mp 287ºC (obtained in 5% ethyl acetate in benzene eluates as a mixture with **10** and finally purified by extensive preparative TLC), R_f = 0.46 (benzene/ethyl acetate 1:1), silica gel G. Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44: H, 4.65: N, 10.76, Found: C, 78.19: H, 4.84: N, 10.59; UV (λ_{max}^{EtOH}): 216.5 (log ε 4.24), 251.0 (log ε 3.73), 270.5 (log ε 3.70), 325.0 (log ε 3.71); IR (KBr disc, cm^{-1}): 3404, 1701, 1453 and 745; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.75 (2H, s), 8.22 (2H, d, J=2.7 Hz), 8.11 (2H, d, J=2.7 Hz), 7.45 (2H, d, J=6.9 Hz), 7.11-7.20 (4H, m); ^{13}C NMR (125 MHz, DMSO-d_6): δ 182.42, 136.63, 131.62, 126.66, 122.47, 121.55, 120.91, 117.44, 111.67; MS (70 ev): m/z 260 (M^+, 100%).

1,4-(3,3´-Diindolyl)-1,4-dioxobutane (12) : colorless needle-shaped crystals (benzene/ethyl acetate 3:1), yield 94%, mp 189ºC, R_f = 0.53 (benzene/ethyl acetate 1:1), silica gel G. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C,

75.93: H, 5.10: N, 8.85, Found : C, 75.64: H, 5.08: N, 8.82; UV (λ_{max}^{EtOH}): 295.5 (log ε 4.43), 240.0 (log ε 4.45), 208.5 (log ε 4.80); IR (KBr disc, cm^{-1}): 3236, 1640, 1432, 749; ^{1}H NMR (500 MHz, pyridine-d_5): δ 14.22 (2H, s), 10.03 (2H, d, J=7.8 Hz), 9.83 (2H, s), 8.70 (2H, d, J=8.0 Hz), 8.43-8.55 (4H, m), 4.77 (4H, s), ^{13}C NMR (125 MHz, pyridine-d_5): δ 196.10, 139.23, 134.85, 128.19, 124.01, 123.65, 123.63, 119.22, 113.78, 35.67; MS (70 ev): m/z 318 (M^++2, 39.2%).

3-Benzylindole (13) [10] **:** white microcrystalline solid (10% petroleum ether (60-80ºC) in benzene eluates), yield 87%, mp 144ºC, R_f = 0.46 (benzene), silica gel G. Anal. Calcd for $C_{15}H_{13}N$: C, 86.92: H, 6.32: N, 6.76, Found : C, 86.81: H, 6.30: N, 6.68; UV (λ_{max}^{EtOH}): 284.0 (log ε 4.07), 226.0 (log ε 4.74); IR (KBr disc, cm^{-1}): 3416, 2914, 1452, 788, 742; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (1H, br s), 7.51 (1H, d, J=7.9 Hz), 7.34 (1H, d, J=8.1 Hz), 7.24-7.28 (4H, m), 7.16-7.19 (2H, dist. t), 7.07 (1H, t, J=7.5 Hz), 6.90 (1H, s), 4.11 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.62, 136.88, 129.10, 128.73, 127.89, 126.28, 122.73, 122.46, 119.77, 119.57, 116.27, 111.47, 32.01; MS (70 ev): m/z 207 (M^+, 63.9%): HRMS : m/z 207.1105 (M^+, 77.8%).

1,1-Bis(3-indolyl)ethane (14)[11,12] **:** white microcrystalline solid (5% ethyl acetate in benzene), yield 84%, mp 198ºC, R_f = 0.49 (benzene/ethyl acetate 9:1), silica gel G. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.05: H, 6.19: N, 5.44, Found: C, 83.12: H, 6.11: N, 5.42; UV (λ_{max}^{EtOH}): 290.0 (log ε 3.85) and 282.0 (log ε 3.92) and 221.0 (log ε 4.67); IR (KBr disc, cm^{-1}): 3408, 1453, 740; ^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.11 (2H, br s), 7.39 (2H, d, J=8.0 Hz), 7.34 (2H, d, J=8.1 Hz), 7.15 (2H, t, J=7.4 Hz), 6.99 (2H, t, J=7.4 Hz), 6.91 (2H, d, J=1.3 Hz), 2.14 (1H, s), 2.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.26, 126.51, 123.51, 122.34, 121.74, 119.85, 119.06, 111.77, 26.99, 25.17; MS (70 ev): m/z 260 (M^+, 25.1%).

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7. Crystal data for compound (**8**) : $C_{19}H_{15}N$, *Mw* 257.12, triclinic, space group *P*-1; Z=4, crystal size: 0.1 x 0.2 x 0.2 mm, n_b. of Fobs(all) 3693, n_b. of observed Fobs (>4 sig.) 2486, R factor (%) all 0.0901, R factor (%) obs. 0.0772, Max/min residual Density(in e-) +0.53/-0.30, a = 10.30, b = 12.52, c = 13.38 (Å degrees), α = 111.9, β = 116.8, γ = 71.6. X-Ray crystallographic data were recorded with an automated four-circle Philips-PW 1100 diffractometer, operating with Cu-K_α radiation (1.541 Å). The structure was solved by direct method and refined with isotropic, then anisotropic thermal factors by Full-Matrix-Least-Squares procedure. Crystallographic data for this structure have been deposited at the Cambridge Crystallographic Data Centre (CCDC 234174). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].
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