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TRANSFORMATION OF 2-ETHYL-1-*m*-FLUOROPHENYL-β-CARBOLINE BY THE ACTION OF DIMETHYL ACETYLENEDICARBOXYLATE IN THE PRESENCE OF INDOLES. NEW METHOD OF SYNTHESIS OF BISINDOLYLARYLMETHANES

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The direction of the tandem transformations of 1-substituted 2-ethyltetrahydro-β-carbolines by the action of dimethyl acetylenedicarboxylate (DMAD) depends on the type of solvent used and the electronic effects of the substituents at C-1 [1]. The major direction of these reactions in methanol is opening of the tetrahydropyridine fragment with participation of a solvent molecule, leading to 2-methoxyalkylindoles and 2-methoxybenzylindoles [1]. In acetonitrile, 3-(dimethoxycarbonylvinylethylamino)-2-vinylethylindole was obtained from 1-methyltetrahydro-β-carboline, while the corresponding azocinoindole was obtained from the 1-benzyl derivative [2]. Multicomponent mixtures, which could not be separated into pure products, were obtained in the reaction of 1-fluorophenylcarbolines in dichloromethane. This behavior suggests that cleavage of the C(1)–N bond occurs in ammonium zwitter-ion **A** during the reaction leading to zwitterion **B** with a secondary carbocationic site. In order to prove this hypothesis, we carried out the reaction of 1-*m*-fluorophenyl-β-carboline **1** with DMAD in methylene chloride in the presence of indole **2a** and its 5-methoxy derivative **2b** as "traps" for cation **B**.

The expected (fluorophenyl)bis(indolyl)methanes **3a** and **3b** were isolated from the reaction mixtures in 40 and 45% yield, respectively. As might have been anticipated, the electrophilic substitution in indoles **2** proceeded at C-2. Bisindolylmethanes **3** may be transformed in an electrophilic substitution reaction into condensed ten-membered azaheterocycles, namely, azecines.

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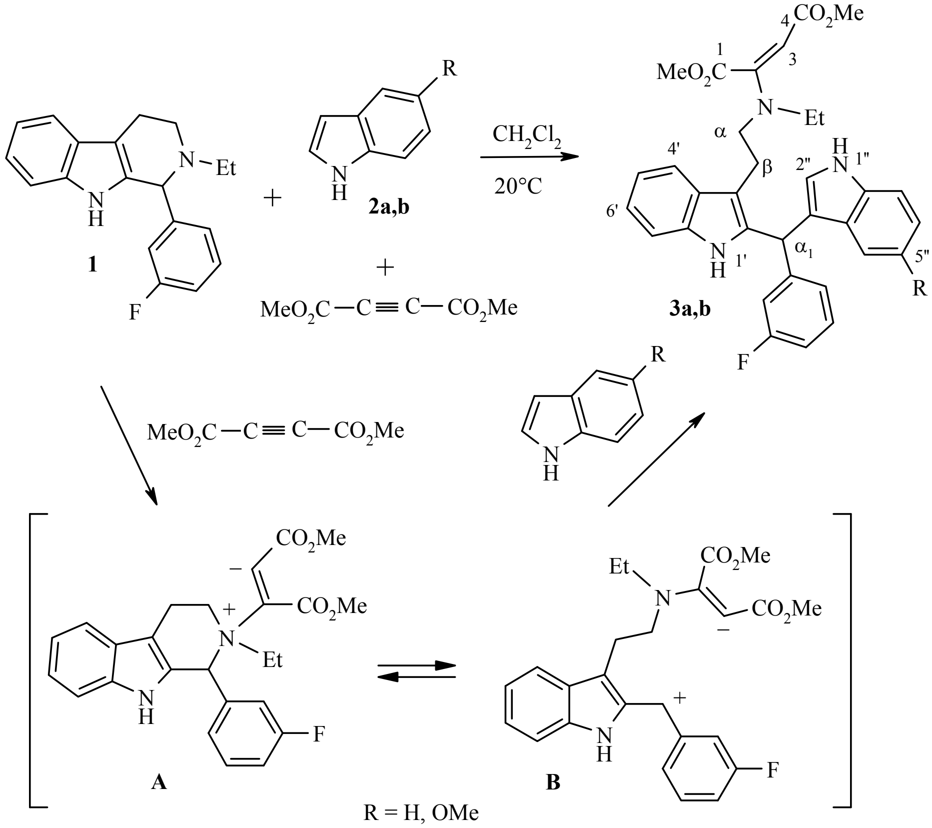
The structure of these compounds was supported by the spectral data. The IR spectra were taken on an INFRALYUM FT-801 Fourier-transform spectrometer for KBr pellets. The ^{1}H and ^{13}C NMR spectra were taken on a Bruker WP-400 spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ with TMS as the internal standard. The ESI mass spectra were taken on an Agilent 1100 Series LC/MSD Trap System VI mass spectrometer.



R = H, OMe

Reaction of β-Carboline 1 with Dimethyl Acetylenedicarboxylate and Indoles 2a,b (General Method). Indoles **2a** or **2b** (1.70 mmol) and DMAD (2.04 mmol) were added to a solution of β-carboline **1** (1.70 mmol) in absolute dichloromethane (20 ml). The reaction was carried out for 2-30 days. The reaction was monitored by thin-layer chromatography on Silufol plates with 1:2 ethyl acetate–hexane as the eluent. The solvent was distilled off. The residual oil was separated by flash chromatography on a 450 mm×20 mm column packed with silica gel 60A (0.04-0.06 mm) using 1-30% ethyl acetate in hexane as the eluent. The reaction mixture was placed onto the column in chloroform.

Dimethyl Ester of (2*E*)-2-[(2-{2-[(3-Fluorophenyl)(1H-indol-3-yl)methyl]-1H-indol-3-yl}ethyl)(ethyl)amino]butene-2-dioic Acid (3a) was obtained in 40% yield as an orange-yellow oil, R_f 0.19 (Silufol, 1:2 ethyl acetate–hexane). IR spectrum (neat), ν, cm^{-1}: 1737 (CO_2CH_3), 1676 (CO_2CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.90 (3H, t, *J* = 6.9, $NCH_2C\underline{H}_3$); 2.87 (2H, q, *J*= 6.9, NCH_2CH_3); 2.93-3.01 (3H, m, CH_2-α and CH-β); 3.05-3.15 (1H, m, CH-β); 3.55 (3H, s, 4-CO_2CH_3); 3.74 (3H, s, 1-CO_2CH_3); 4.52 (1H, s, H-3); 5.87 (1H, s, H-α_1); 6.64 (1H, d, *J* = 2.5, H-2''); 6.85-6.95 (4H, m, H Ar); 7.00 (1H, d, *J* = 7.5, H Ar); 7.03-7.08 (3H, m, H Ar); 7.10-7.16 (4H, m, H Ar); 7.72 (1H, s, NH-1''); 8.14 (1H, br. s, NH-1'). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 22.7, 40.4, 45.7, 50.6, 50.8, 52.9, 55.9, 83.2, 108.2, 111.2, 111.6, 113.9 (d, $^2J_{C-F} = 22$); 115.5 (d, $^2J_{C-F} = 22$); 116.4, 118.1, 119.1, 119.7, 120.0, 121.6, 122.6, 124.2, 124.3, 126.5, 128.7, 130.2 (d, $^3J_{C-F} = 8.0$); 135.1, 136.4, 136.8, 145.1 (d, $^3J_{C-F} = 8.0$); 153.8, 163.1, (d, $^1J_{C-F} = 246.0$); 166.3, 168.5. ESI mass spectrum, *m/z*: 554 [M$^+$ + 1]. Found, %: C 71.55; H 5.86; N 7.61. $C_{33}H_{32}FN_3O_4$. Calculated, %: C 71.59; H 5.83; N 7.59.

Dimethyl Ester of (2*E*)-2-[(2-{2-[(3-Fluorophenyl)(5-methoxy-1H-indol-3-yl)methyl]-1H-indol-3-yl}ethyl)(ethyl)amino]butene-2-dioic Acid (3b) was obtained in 45% yield as a yellow oil, R_f 0.32 (Silufol, 1:1 ethyl acetate–hexane). IR spectrum (neat), ν, cm^{-1}: 1731 (CO_2CH_3), 1665 (CO_2CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.96 (3H, t, *J* = 6.9, $NCH_2C\underline{H}_3$); 2.93 (2H, q, *J* = 6.9, $NC\underline{H}_2CH_3$); 2.99-3.04 (3H, m, CH_2-α and CH-β); 3.13-3.16 (1H, m, CH-β); 3.62 (3H, s, 4-$CO_2C\underline{H}_3$); 3.64 (3H, s, 1-$CO_2C\underline{H}_3$); 3.82 (3H, s, 5"-OCH_3); 4.57 (1H, s, H-3); 5.88 (1H, s, H-α_1); 6.60 (1H, s, H-2"); 6.70 (1H, s, H Ar); 6.85 (1H, dd, *J* = 8.6, *J* = 1.7, H Ar); 6.93-6.99 (2H, m, H Ar); 7.06 (1H, d, *J* = 8.3, H Ar); 7.11-7.15 (1H, m, H Ar); 7.19-7.23 (2H, m, H Ar); 7.28 (2H, d, *J* = 8.9, H Ar); 7.53-7.58 (1H, m, H Ar); 7.81 (1H, s, NH-1"); 8.11 (1H, br. s, NH-1'). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 12.4, 22.7, 40.4, 45.7, 50.6, 50.8, 52.9, 55.9, 83.4, 101.2, 108.3, 111.2, 112.3, 112.8, 114.0, (d, $^2J_{C\text{-}F}$ = 22.0); 115.6 (d, $^2J_{C\text{-}F}$ = 20.0); 116.3, 118.2, 119.8, 121.7, 124.2, 124.8, 127.0, 128.7, 130.2 (d, $^3J_{C\text{-}F}$ = 8.0); 132.0, 135.2, 136.4, 145.2 (d, $^2J_{C\text{-}F}$ = 7.0); 153.8, 154.4, 163.2 (d, $^1J_{C\text{-}F}$ = 247.0); 166.3, 168.4. ESI mass spectrum, *m/z*: 584 [M^++1]. Found, %: C 70.02; H 5.84; N 7.23. $C_{34}H_{34}FN_3O_5$. Calculated, %: C 69.97; H 5.87; N 7.20.

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