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Electrophilic Substitution Reactions of Indole Alkaloids with α,β-Unsaturated Carbonyl Compounds in the Presence of K10 Montmorillonite*

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Abstract—Reactions of indole, 1-methylindole, and 3-methylindole with dimethyl acetylenedicarboxylate in the presence of K10 montmorillonite as a catalyst led to the formation of the corresponding dimethyl 2,2-bis-(indolyl)butanedioates. The reaction of 2-methylindole with dimethyl acetylenedicarboxylate gave dimethyl 2-(2-methyl-1*H*-indol-3-yl)maleate and dimethyl 2-methyl-1*H*-1-benzoazepine-3,4-dicarboxylate. Dimethyl 1,5-dimethyl-1*H*-1-benzoazepine-3,4-dicarboxylate was obtained by treatment of 1,3-dimethylindole with dimethyl acetylenedicarboxylate using K10 clay as a catalyst.

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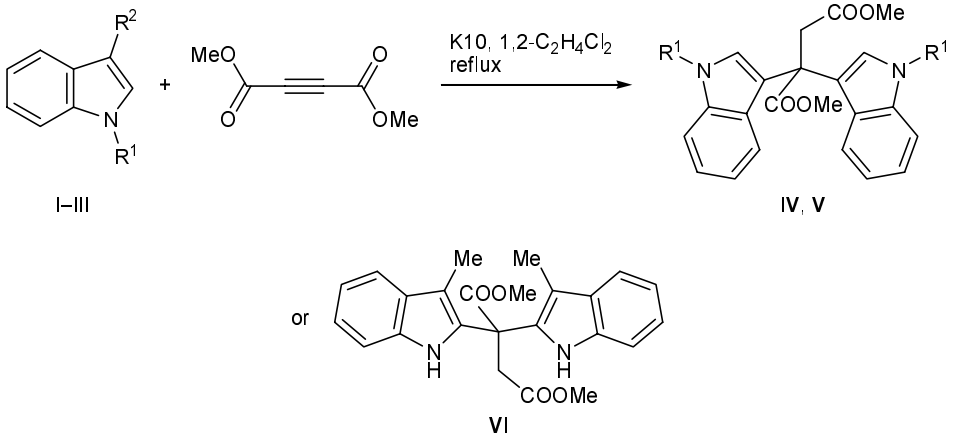
Over the past decade, a number of bis-indole alkaloids were isolated from marine environment; these alkaloids were found to exhibit diverse biological activity, including antibacterial, antiviral, and cytotoxic [1, 2]. Bis(indolyl)alkyl moiety is a structural fragment of many natural products possessing important biological properties [3–5]. Bis(indolyl)alkanes are usually synthesized by reactions of indoles with various aldehydes and ketones in the presence of Lewis acids or protic acids [4–9]. Among a variety of methods, syntheses from indoles and aromatic and aliphatic aldehydes and ketones in the presence of Lewis or Brønsted acids or K-10 montmorillonite were extensively studied [10]. Acid-catalyzed conjugate addition of indoles requires careful control of the acidity to prevent side reactions, such as dimerization or polymerization. Furthermore, many of these procedures involve strongly acidic conditions, expensive reagents, long reaction time, and laborious isolation of the target products. The yields of the latter are often low due to dimerization of indoles or polymerization of vinyl ketones [1, 11]. It is known that K10 montmorillonite

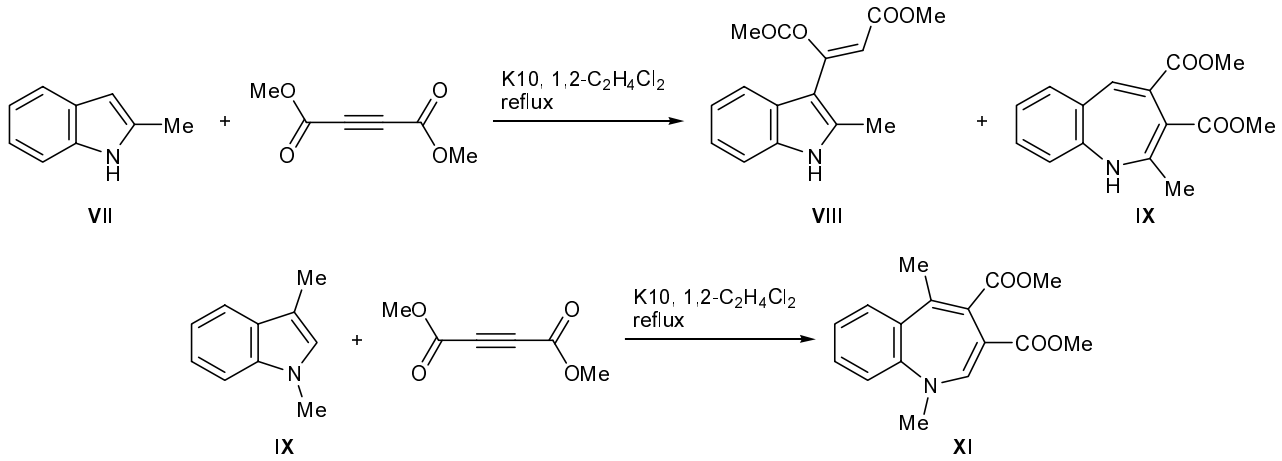
Scheme 1.



I, **IV**, $R^1 = R^2 = H$; **II**, **V**, $R^1 = Me$, $R^2 = H$; **III**, $R^1 = H$, $R^2 = Me$.

* The text was submitted by the authors in English.

Scheme 2.



and structurally modified clays based thereon are used as both Brønsted and Lewis acid catalysts in various industrially important organic reactions [12–15].

Taking into account a need of cheaper and more efficient Lewis acid catalyst for reactions like Michael addition, in the present work we examined K10 montmorillonite as catalyst in reactions of indole and methyl-substituted indoles with α,β-unsaturated carbonyl compounds. As the latter, we used dimethyl acetylenedicarboxylate.

Treatment of indole (**I**), 1-methylindole (**II**), and 3-methylindole (**III**) with dimethyl acetylenedicarboxylate (DMAD) in dichloroethane in the presence of K10 montmorillonite led to the formation of the corresponding dimethyl 2,2-bis(indolyl)butanedioates. Insofar as the C^3 atom in the indole molecule is the most active in electrophilic substitution processes [12, 16], the reactions of DMAD with indole and 1-methylindole occurred just at that position to give dimethyl 2,2-bis(indol-3-yl)- and bis(1-methylindol-3-yl)butanedioates **IV** and **V** in 63 and 57% yield, respectively (Scheme 1).

In the molecule of 3-methylindole, the 3-position is occupied by methyl group; therefore, the addition of dimethyl acetylenedicarboxylate occurred at the C^2 atom to form dimethyl 2,2-bis(3-methylindol-2-yl)-butanedioate (**VI**) in 43% yield (Scheme 1). From the reaction mixture obtained by heating 2-methylindole (**VI**) and dimethyl acetylenedicarboxylate in dichloroethane in the presence of K10 montmorillonite we isolated 27% of dimethyl 2-(2-methyl-1*H*-methylindol-3-yl)maleate (**VIII**) and 45% of dimethyl 2-methyl-1*H*-1-benzoazepine-3,4-dicarboxylate (**IX**) (Scheme 2). In an analogous reaction of dimethyl acetylenedicarboxylate with 1,3-dimethylindole (**X**), the only product was dimethyl 1,5-dimethyl-1*H*-1-benzoazepine-3,4-dicarboxylate (**XI**) (yield 69%).

EXPERIMENTAL

The melting points were determined on an Electrothermal A 9100 melting point apparatus and are uncorrected. The NMR spectra were recorded on a Bruker DPX-400 spectrometer. The IR spectra were measured in KBr on a Jasco FTIR 300E spectrometer. The mass spectra (electron impact) were run on an HP Agilent 6890 CS–5973N GC–MS system. The elemental compositions were determined using a LECO CHNS-932 analyzer.

Dimethyl 2,2-bis(1*H*-indol-3-yl)butanedioate (IV). Indole (**I**), 0.468 g (4 mmol), was dissolved in 60 ml of 1,2-dichloroethane, 6.084 g of K-10 montmorillonite was added, and 1 ml (8 mmol) of dimethyl acetylenedicarboxylate was then added dropwise using a syringe. The mixture was heated for 5 h under reflux (the progress of the reaction was monitored by TLC) and filtered, the catalyst was washed with methylene chloride, the filtrate was combined with the washings and evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (chloroform–ethyl acetate, 3 : 1), followed by recrystallization from hexane–chloroform. Yield 0.95 g (63%), mp 158–160°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 1720 (CO). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.8 t (2H, 5-H), 7.0 t (2H, 6-H), 7.2–7.3 m (6H, 2-H, 4-H, 7-H), 8.1 s (2H, NH), 3.79 s (6H, OCH_3), 3.49 s (2H, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 376 (22) $[M]^+$, 317 (100) $[M - CO_2CH_3]$, 303 (19) $[M - CH_2CO_2CH_3]$, 244 (19) $[M - C_5H_8O_4]$, 128 (10) $[M - C_{11}H_{14}O_4N]$,

116 (29) [C_8H_6N]. Found, %: C 69.81; H 5.55; N 7.64. $C_{22}H_{20}N_2O_4$. Calculated, %: C 70.20; H 5.36; N 7.44. *M* 376.411.

Dimethyl 2,2-bis(1-methyl-1*H*-indol-3-yl)butanedioate (V) was synthesized in a similar way from 0.524 g (4 mmol) of 1-methylindole (reaction time 3 h). The product was purified by flash chromatography on silica gel (cyclohexane–chloroform, 3:2), followed by recrystallization from hexane–chloroform. Yield 0.92 g (57%), mp 194–196°C. IR spectrum, ν, cm^{-1}: 1740 (CO), 1370 (NCH_3). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.8 t (2H, 5-H), 7.1 t (2H, 6-H), 7.2–7.3 m (6H, 2-H, 4-H, 6H, 7-H), 3.76 s (6H (NCH_3), 3.74 s (2H, CH_2), 3.49 s (6H, OCH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 404 (25) $[M]^+$, 345 (100) [$M - CO_2CH_3$], 331 (39) [$M - CH_2CO_2CH_3$], 272 (21) [$M - C_5H_8O_4$], 215 (9) [$M - C_{11}H_{11}NO_4$], 142 (9) [$M - C_{14}H_{16}O_4N$]. Found, %: C 71.42; H 5.21; N 7.05. $C_{24}H_{24}N_2O_4$. Calculated, %: C 71.15; H 5.02; N 6.97. *M* 404.46.

Dimethyl 2,2-bis(3-methyl-1*H*-indol-2-yl)butanedioate (VI) was synthesized in a similar way from 0.524 g (4 mmol) of 3-methylindole (reaction time 5 h). The product was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate, 3:2), followed by recrystallization from hexane–chloroform. Yield 0.69 g (43%), mp 174–175°C. IR spectrum, ν, cm^{-1}: 3390 (NH), 1710 (CO). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.08–7.1 t (2H, 5-H), 7.13–7.17 t (2H, 6-H), 7.25 d (2H, 7-H), 7.5 d (2H, 4-H), 2.0 s (6H, CH_3), 3.8 s (6H, OCH_3), 3.54 s (2H, CH_2), 8.8 s (2H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 404 (2) $[M]^+$, 274 (25) [$M - C_9H_8N$], 273 (100) [$M - C_9H_9N$], 143 (22) [$M - C_6H_7O_4$], 130 (39) [C_9H_8N], 115 (20) [C_8H_5N]. Found, %: C 71.42; H 5.21; N 7.05. $C_{24}H_{24}N_2O_4$. Calculated, %: C 71.15; H 5.02; N 6.97. *M* 404.46.

Dimethyl 2-(2-methyl-1*H*-indol-3-yl)maleate (VIII) and dimethyl 2-methyl-1*H*-1-benzoazepine-3,4-dicarboxylate (IX). The reaction was carried out as described above for compound **IV** using 0.524 g (4 mmol) of 2-methylindole; the reaction mixture was heated for 4 h under reflux. The products were separated by flash chromatography on silica gel using cyclohexane–ethyl acetate (3:2) as eluent and were purified by recrystallization from hexane–chloroform.

Compound **VIII**. Yield 0.29 g (27 %), mp 134–136°C. IR spectrum, ν, cm^{-1}: 3390 (NH), 1720 (CO). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7 1–7.3 m (3H, 5-H, 6-H, 7-H), 7.7 d (1H, 4-H), 8.4 s (1H, NH), 6.2 s (1H, (C=CH), 4.0 s (3H, OCH_3), 3.8 s (3H, OCH_3), 2.4 s (3H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 273 (72) $[M]^+$, 214 (53) [$M - CO_2CH_3$], 154 (100) [$M - C_4H_7O_4$], 130 (9) [C_9H_8N], 115 (11) [C_8H_5N]. Found, %: C 65.58; H 5.59; N 5.41. $C_{15}H_{15}NO_4$. Calculated, %: C 65.93; H 5.53; N 5.12. *M* 273.28.

Compound **IX**. Yield 0.49 g (45%), mp: 120–122°C. IR spectrum, ν, cm^{-1}: 3360 (NH), 1710 (CO). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.1 m (2H, 7-H, 8-H), 7.3 m (3H, 5-H, 6-H, 9-H), 8.3 s (1H, NH), 3.8 s (3H, OCH_3), 3.6 s (3H OCH_3), 2.1 s (3H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 273 (45) $[M]^+$, 214 (32) [$M - CO_2CH_3$], 199 (12) [$M - C_3H_6O_2$], 154 (100) [$M - 2CO_2CH_3$]. Found, %: C 65.58; H 5.59; N 5.41. $C_{15}H_{15}NO_4$. Calculated, %: C 65.93; H 5.53; N 5.12. *M* 273.28.

Dimethyl 1,5-dimethyl-1*H*-1-benzoazepine-3,4-dicarboxylate (XI). The reaction was carried out in a similar way with 0.58 g (4 mmol) of 1,3-dimethylindole. The product was purified by flash chromatography on silica gel (chloroform–1,2-dichloroetane–hexane, 2:4:4), followed by recrystallization from hexane–chloroform. Yield 0.79 g (69 %), mp 102–103°C. IR spectrum: ν(CO) 1710 cm^{-1}. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.11 (1H, 7-H), 7.2–7.3 m (3H, 2-H, 8-H, 9-H), 7.5 d (1H, 6-H), 3.8 s (3H, NCH_3), 3.50–3.49 d (6H, CO_2CH_3), 2.2 s (3H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 287 (63) $[M]^+$, 228 (25) [$M - CO_2CH_3$], 168 (100) [$M - 2CO_2CH_3 - H$], 154 (8) [$M - C_5H_9O_4$], 139 (6) [$M - C_6H_{12}O_4$]. Found, %: C 68.92; H 5.87; N 4.94. $C_{16}H_{17}NO_4$. Calculated, %: C 68.89; H 5.96; N 4.88. *M* 286.30.

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