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Rearrangement and Degradation of 3a,7a-Dihydroindole Esters

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The purpose of this paper is to report that pyrroles **1a-c** also gave the 1:2 adducts **3a-c** when refluxed with dimethyl acetylene dicarboxylate in ether (or ether with $AlCl_3$) and rearrangement and degradation of 3a,7a-dihydroindole esters **3a-c** as 1:2 molar [4+2] cycloadducts were investigated. The electrons in compound **3a** are assumed to move as in its resonance structure A which should results in the formation of transition state B. Next, cleavage of the C-C bond between the carbonyl carbon atom and the **3a** carbon atom and the 1,3-shift of the hydrogen atom from 7a position into 2 position will occur easily to form an aromatized stable indole compound **4a**.

Keywords: Indole, Indoline, Rearrangement, Degradation, 1,3-Shift, Three-membered cyclic transition state structure.

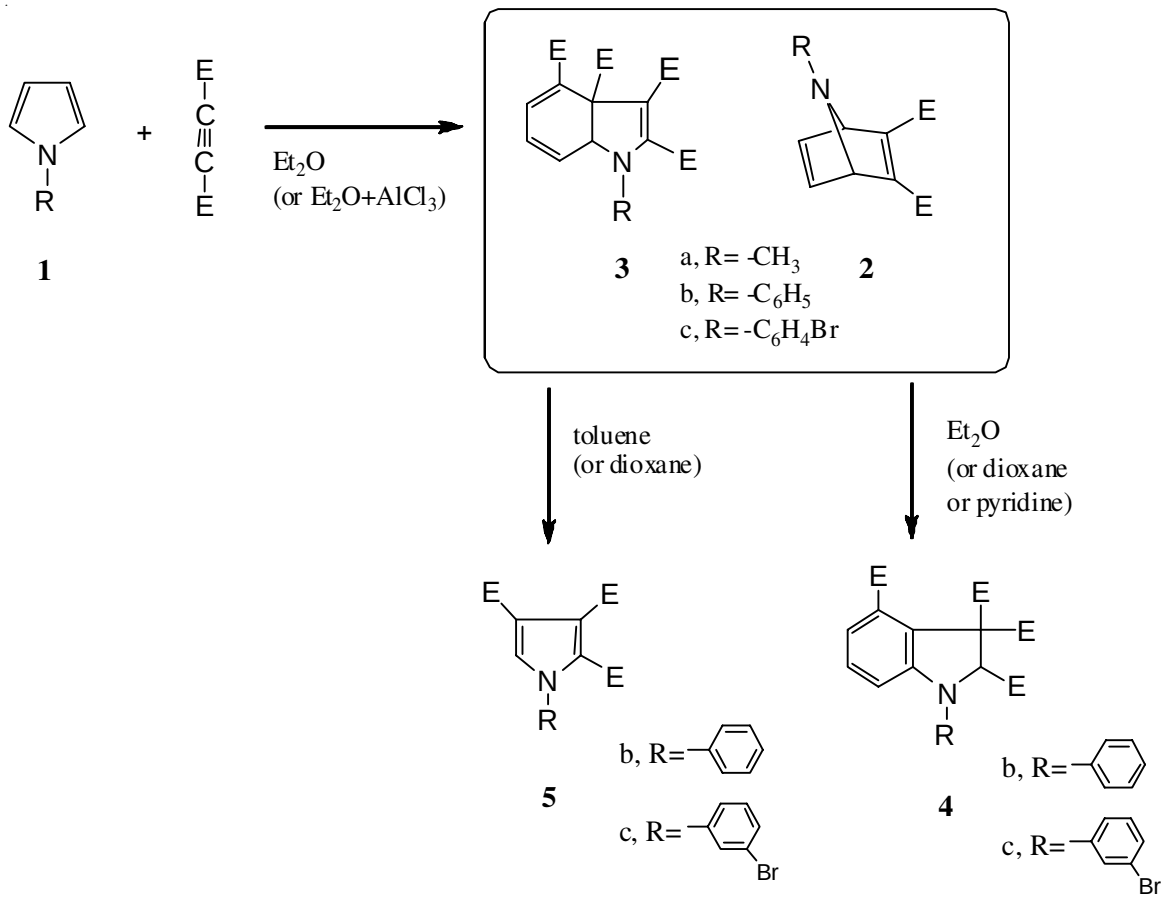
INTRODUCTION

Pyrroles are found in a variety of biological contexts, as parts of cofactors and natural products. Common naturally produced molecules containing pyrroles include vitamin B12, bile pigments like bilirubin and biliverdin and the porphyrins of heme, chlorophyll, chlorins, bacteriochlorins and porphyrinogens [1]. Other pyrrole-containing secondary metabolites are pyrroloquinoline quinone (PQQ), makaluvamine M, *etc.* Moreover, pyrroles are also found in several drugs, *viz.*, atorvastatin, ketorolac and sunitinib. One of the first syntheses of pyrrole-containing molecules was that of haemin, synthesized by Emil Fischer in 1929 [2]. The reaction of pyrroles with common dienophiles seems to follow two different pathway, that is, [4+2] cycloaddition or a Michael-type addition at the α position of pyrroles [3]. Pyrroles which have aryl or electron-withdrawing substituents on the nitrogen gave 1:1 adducts of type 2 with dimethyl acetylene dicarboxylate (DMAD). With an N-alkyl group, the 1:1 adduct of type 2 reacted further with dimethyl acetylene dicarboxylate to give a 1:2 adduct of type 3 [4]. On the other hand, pyrrole (**1a**) itself was reported to give a Michael-type 1:1 adduct 5, though the structure was not thoroughly established [5]. The purpose of this paper is to report that pyrroles **1** also gave the 1:2 adducts **3** when refluxed with dimethyl acetylene dicarboxylate in ether (or ether with $AlCl_3$) for 4 days and rearrangement and degradation of 3a,7a-dihydroindole esters 3 as 1:2 molar [4+2] cycloadducts were researched (**Scheme-I**).

EXPERIMENTAL

Melting points were determined using an electronthermal capillary melting point apparatus and uncorrected. Thin layer chromatography (TLC) was performed on glass plates coated with silicon oxide (silica gel $60F_{254}$) and compounds were visualized using a UV lamp. ^1H NMR and ^{13}C NMR spectra were obtained with Bruker AC 2000 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/Mass (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use. All the starting materials were purchased from Aldrich, Fluka, Lancaster, or TCI chemical companies and used as received.

General procedure for the synthesis of 2a-c and 3a-c: A solution of 1-phenylpyrrole (0.429 g, 3 mmol) and dimethyl acetylene dicarboxylate (0.825 g, 6 mmol) in ether (20 mL) was refluxed for 167 h, during which time some white precipitate formed. After 167 h, the reaction mixture was allowed to stir at room temperature and monitored by TLC to establish completion of the reaction. The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product. After flash chromatography, 1,2-dimethylcarboxylate-7-phenyl-7-aza-bicyclo[2,2,1]-1,3-hexadiene **2b** (0.184 g, 21.5 %) and tetramethyl 3a,7a-dihydro-1-phenylindole-2,3,3a,4-tetracarboxylate **3b** (0.310 g, 24.2 %) were obtained. In case of the reaction in ether with $AlCl_3$ (0.01 g) as an acid catalyst, **2b** (0.195 g, 22.8 %) and **3b** (0.321 g, 25.1 %) were obtained. 1,2-Dimethyl carboxylate-7-phenyl-7-aza-bicyclo[2,2,1]-1,3-hexadiene (**2b**): R_f; 0.42 (TLC eluent; hexane:EtOAc = 5:3, v/v) ^1H NMR ($CDCl_3$); δ 3.80 (s, 6H, OCH_3), 5.43 (dd, 2H, N-C-H), 6.12 (dd, 2H, =C-H), 7.3-7.8



Scheme-I

(m, 5H, phenyl H); IR (KBr, ν_{max}, cm^{-1}): 2950 (C-H), 1850 s (C=O), 1600 s (aromatic C=C), 1280 s, 1250 s, 1215 (O-C=O); UV (EtOH); λ_{max} 223 nm. Tetramethyl 3a,7a-dihydro-1-phenylindole-2,3,3a,4-tetracarboxylate (**3b**); R_f; 0.23 (TLC eluent; hexane:EtOAc = 5:3, v/v) ^{1}H NMR ($CDCl_3$); δ 3.70 (s, 3H), 3.73 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H, all OCH_3), 5.40 (d, 1H, $C_{7a}H$), 6.05 (d, 1H, C_5H), 6.95-7.40 (m, 5H, phenyl H); IR (KBr, ν_{max}, cm^{-1}): 2958 s (C-H), 1750 s, 1730 s, 1700 s (C=O), 1593 (aromatic C=C), 1270 s, 1250 s (O-C=O); UV (EtOH); λ_{max} 235 nm. 1,2-dimethyl carboxylate-7-*m*-bromophenyl-7-aza-bicyclo[2,2,1]-1,3-hexadiene (**2c**); R_f; 0.48 (TLC eluent; hexane:EtOAc = 5:3, v/v) ^{1}H NMR ($CDCl_3$); δ 3.85 (s, 6H, OCH_3), 5.40 (dd, 2H, N-C-H), 6.34 (dd, 2H, =C-H), 6.8-7.6 (m, 4H, phenyl H); IR (KBr, ν_{max}, cm^{-1}): 2955 s (C-H), 1732 s, 1725 s (C=O), 1595 s (aromatic C=C), 1315 s, 1265 s, 1210 s (O-C=O); UV (EtOH); λ_{max} 243 nm. Tetramethyl 3a,7a-dihydro-1-*m*-bromphenyl-indole-2,3,3a,4-tetracarboxylate (**3c**); R_f; 0.22 (TLC eluent; hexane:EtOAc = 5:3, v/v) ^{1}H NMR ($CDCl_3$); δ 3.60 (s, 3H), 3.70 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H, all OCH_3), 5.41 (d, 1H, $C_{7a}H$), 5.75 (dd, 1H, C_6H), 6.05 (dd, 1H, C_7H), 6.2 (d, 1H, C_5H), 6.85-7.3 (m, 4H, phenyl H); IR (KBr, ν_{max}, cm^{-1}): 2970 s (C-H), 1755 s, 1740 s, 1710 s (C=O), 1595 s, 1570 s (aromatic C=C), 1250 s, 1280 s (O-C=O); UV (EtOH); λ_{max} 280 nm.

General procedure for the rearrangement of 3a,7a-dihydroindole esters (3): A solution of tetramethyl 3a,7a-dihydro-1-phenylindole-2,3,3a,4-tetracarboxylate **3b** (0.251 g, 5.9×10^{-4} mol) in pyridine (20 mL) was refluxed for 300 h. The pyridine was distilled off under aspirator pressure and the residual light brown oil was dissolved in methanol, decolourized with charcoal and kept in a refrigerator overnight, giving white prisms. The prisms were collected and recrystallized from methanol and dichloromethane to give tetramethyl-1-phenyl-indoline-2,3,3,4-tetracarboxylate (**4b**) (15.5 %) as white prisms. In case of Et_2O or dioxane as a solvent, **4b** (Et_2O; 10.5 %, dioxane; 12.7 %) respectively was obtained. Tetramethyl-1-phenyl-indoline-2,3,3,4-tetracarboxylate (**4b**); R_f; 0.35 (TLC eluent; hexane:EtOAc = 5:3, v/v) ^{1}H NMR ($CDCl_3$); δ 3.75 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 4.02 (s, 3H, all OCH_3), 5.04 (d, 1H, C_2H), 5.04 (s, 1H, C_2H), 7.21-7.73 (m, 8H, phenyl H); IR (KBr, ν_{max}, cm^{-1}): 3130 s (C-H), 3070 s, 3030 s (aromatic C-H), 2955 s (C-H), 1755 s, 1740 s, 1735 s, 1725 s (C=O), 1600 s (aromatic C=C), 1295 s, 1245 s, 1220 s (O-C=O); UV (EtOH); λ_{max} 228 nm. Tetramethyl-1-*m*-bromophenylindoline-2,3,3,4-tetracarboxylate (**4c**); R_f; 0.34 (TLC eluent; hexane: EtOAc = 5:3, v/v) ^{1}H NMR ($CDCl_3$); δ 3.75 (s, 3H), 3.82 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H, all OCH_3), 5.06 (s, 1H, C_2H), 7.11-8.21 (m, 7H, phenyl H); IR (KBr, ν_{max}, cm^{-1}): 3100 s, 3010 s (aromatic C-H), 2960 s, 2940 s (C-H), 1755 s, 1750 s, 1730 s, 1720 s (C=O), 1615 s, 1590 s, 1580 s (aromatic C=C), 1300 s, 1235 s, 1205 s (O-C=O); UV (EtOH); λ_{max} 288.5 nm.

General procedure for chemical degradation of 3: A solution of tetramethyl 3a,7a-dihydro-1-phenylindole-2,3,3a,4-tetracarboxylate **3b** (0.30 g, 7×10^{-4} mol) in toluene (20 mL) was refluxed for 150 h. After 150 h, the reaction mixture was allowed to stir at room temperature and monitored by TLC to

establish completion of the reaction. Toluene was distilled off under aspirator pressure. The residue was purified by flash chromatography on silica gel to afford the desired product. After flash chromatography tetramethyl-1-phenylpyrrole-2,3,4-tricarboxylate (**5b**) (0.055 g, 25 %) was obtained. In case of dioxane on behalf of toluene **5b** (22 %) was obtained. Tetramethyl-1-phenylpyrrole-2,3,3-tricarboxylate (**5b**); R_f; 0.4 (TLC eluent; hexane:EtOAc = 5:3, v/v) ^{1}H NMR ($CDCl_3$); δ 3.75 (s, 3H), 3.89 (s, 3H), 4.05 (s, 3H, all OCH_3), 7.21-7.65 (m, 5H, phenyl H), 7.15 (s, 1H, pyrrole H); IR (KBr, ν_{max}, cm^{-1}): 3150 s, 3005 s (aromatic C-H), 2960 s (C-H), 1750 s, 1720 s (C=O), 1600 s (aromatic C=C), 1290 s, 1250 s, 1220 s (O-C=O); Mass; *m/e* 77 (105), 288 (100), 317 (44.9) UV (EtOH); λ_{max} 219.5 nm. Tetramethyl-1-*m*-bromophenylpyrrole-2,3,4-tricarboxylate (5c); R_f; 0.48 (TLC eluent; hexane:EtOAc = 3:2, v/v) ^{1}H NMR ($CDCl_3$); δ 3.65 (s, 3H), 3.79 (s, 3H), 3.95 (s, 3H, all OCH_3), 7.05 (s, 1H, pyrrole H), 7.25-7.80 (m, 4H, phenyl H); IR (KBr, ν_{max}, cm^{-1}): 3160 s, 3090 s, 3805 s (aromatic C-H), 2950 s (C-H), 1750 s, 1745 s, 1725 s, 1717 s (C=O), 1590 s (aromatic C=C), 1290 s, 1255 s, 1255 s (O-C=O).

RESULTS AND DISCUSSION

Although the adduct **3** began to form in 2 days, the yield increased to 7 % in 5 days and could be improved to 30 % by removing the product and refluxing for a longer period of time (7 days). The yield of **3a** was more them 60 % under identical conditions.

As shown in Table-1 in case of ether with $AlCl_3$ in behalf of ether 1:1 and 1:2[4+2] cyclo adducts were obtained in high yield. Compound **3a** were reported to isomerize to the indoline derivate **4a** in 4 % yield upon heating at 180 °C for 6 h in the presence of 5 % palladium-charcoal [6]. The isomerization could be carried out as efficiently as 74 % by refluxing **3a** in xylene for 24 h.

TABLE-1
PHYSICAL DATA FOR 1:1 AND 1:2 [4+2] CYCLO ADDUCTS

Pyrrole	R	Solvent	Reflux time (h)	Yield* (%)	
				2	**3**
1a	CH_3	Ether	165	a: 23.0	a: 21.6
		Ether + $AlCl_3$	165	25.0	32.0
1b		Ether	167	b: 21.5	b: 24.2
		Ether + $AlCl_3$	167	24.7	27.3
1c		Ether	158	c: 19.7	c: 20.3
		Ether + $AlCl_3$	158	23.2	25.6

*Isolated yield

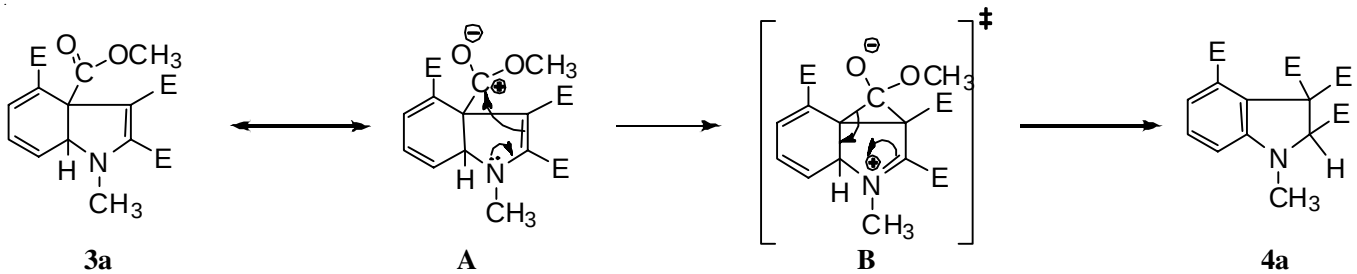
As shown in Table-2, the synthesis of indolines **4b**, **c** in ether (or dioxane) was tried. Yields of those are very low. Plausible mechanism from indole **3** to indoline **4** is as follows. This unequivocally suggests that the transition state for the rearrangement is highly restricted, that is the degree of freedom for the structure of the transition state is much less. A first speclation, the most plausible from for a transition state having such larger negative entropy, is a cyclic structure [7,8]. It is well known that a transition state characterized by a larger negative entropy may possess a three-membered cyclic structure [9]. However, just the fact that the transition state might possess a cyclic form, even if unavoidable, is not enough nor adequate to satisfy all the data mentioned above, Now, the fact that the first-order rate constant becomes large as the polarity of the solvent increase requires a charge separation in the transition state [9,10], no matter what the structure of the transition state might be. Thus, it can be deduced that the most feasible transition state for the rearrangement could be some sort of cyclic form in which charges are separated concomitantly. The propriety of the above speculation is seen from an examination of the electron shifts shown in **Scheme-II**. The electrons in compound **3a** are assumed to move as in its resonance structure A which should results in the formation of transition state B, structure B as the transition state has a three-membered cyclic form and at the same time the charges are well separated as is required by the foregoing experimental results. Next, cleavage of the C-C bond between the carbonyl carbon atom and the **3a** carbon atom and the 1,3-shift of the hydrogen atom from 7a position into 2 position will occur easily to form an aromatized stable indoline compound **4a**. At this state, it can not be determined whether or not the cleavage and the 1,3-shift occur simultaneously. But no matter which may happen, it does not seem to be significant for the mechanism.

TABLE-2
PHYSICAL DATA FOR INDOLINE DERIVATIVES

Indoline	R	Solvent	Reflux time (h)	Yield* (%)
4b		Ether	840	10.5
		Dioxane	840	12.7
		Pyridine	840	16.3
4c		Ether	900	6.2
		Dioxane	900	11.3
		Pyridine	900	15.7

*Isolated yield

The conversion of indoles **3b,c** to pyrroles **5b,c** provides the definite evidence that pyrrole **5b,c**, like 1-substituted pyrroles, undergoes initial Diels-Alder addition (Table-3). Present results



3a **A** **B** **4a**

Scheme-II

TABLE-3
PHYSICAL DATA FOR PYRROLE DERIVATIVES

Pyrrole	R	Solvent	Reflux time (h)	Yield* (%)
5b		Toluene	150	25.0
		Dioxane	150	22.7
5c		Toluene	150	22.5
		Dioxane	150	19.8

*Isolated yield

are a similar type of pyrroles **5b,c** formed from the reaction raised a suspicion of the structures of them. Although the NMR spectra and chemical degradation products are well consistent with pyrrole structure, it seemed to need an unambiguous proof.

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