Studies on Heterocyclic Analogs of Azulene. VIII.[1] Reaction of 2-Alkoxycyclohepta[*b*]pyrroles with Dimethyl Acetylenedicarboxylate

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Synopsis. 2-Alkoxycyclohepta[*b*]pyrroles reacted with dimethyl acetylenedicarboxylate to give tetramethyl 2-alkoxy-3*H*-2a-azacyclopenta[*ef*]heptalene-3,4,5,6-tetracarboxylates in benzene and dialkyl 2-(2-alkoxycyclohepta[*b*]pyrrol-1-yl)fumarate in alcoholic solvents.

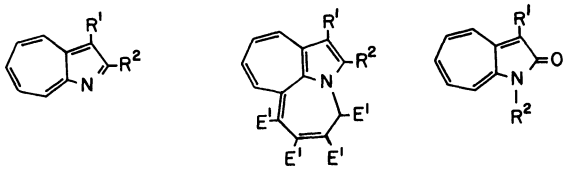
We have previously reported that ethyl 2-chlorocyclohepta[*b*]pyrrole-3-carboxylate (**1a**) reacts with dimethyl acetylenedicarboxylate (DMAD) in benzene giving 1-ethyl 3,4,5,6-tetramethyl 2-chloro-3*H*-2a-azacyclopenta[*ef*]heptalene-1,3,4,5,6-pentacarboxylate (**2a**) *via* a 1,8-dipolar intermediate.[2,3] As nature of substituents and/or reaction conditions appear to play important roles for the cycloadditions of nitrogen-heterocycles with DMAD,[4] we studied the reactions of 2-alkoxycyclohepta[*b*]pyrroles with DMAD in both of benzene and alcoholic solvents.

Treatment of ethyl 2-ethoxycyclohepta[*b*]pyrrole-3-carboxylate (**1b**) with an excess of DMAD in benzene gave 59% yield of 1-ethyl 3,4,5,6-tetramethyl 2-ethoxy-3*H*-2a-azacyclopenta[*ef*]heptalene-1,3,4,5,6-pentacarboxylate (**2b**) along with 29% yield of cyclohepta[*b*]-pyrrol-2(1*H*)-one (**3a**).[5] The structure of **2b** was assigned from the similarity of its spectroscopic properties with those of **2a**.[3] When the reaction of **1b** with DMAD was carried out in boiling abs MeOH, dimethyl 2-(3-ethoxycarbonyl-2-oxo-1,2-dihydrocyclohepta[*b*]pyrrol-1-yl)fumarate (**3b**) was obtained in 94% yield, whose structure was assigned by means of its spectroscopic properties as well as elemental analyses. The ester groups are presumed to have a (*E*)-configuration from the chemical shift of a vinyl proton ($\delta=7.40$) [*e.g.* the vinyl proton of dimethyl 2-(2-oxo-1,2-dihydro-1-pyridyl)fumarate is seen at $\delta=7.05$].[6] Reaction of **3a** with DMAD yielded **3b**, and this supports the structure. Compound **3b** was also obtained in excellent yield from the reaction of **1a** with DMAD in abs MeOH.

Whilst the reaction of 2-methoxycyclohepta[*b*]pyrrole-3-carbonitrile (**1d**) with DMAD in benzene proceeded less efficiently to give only 25% yield of **2c**, with 84% of the starting **1d** being recovered, the reaction in abs EtOH is accompanied by transesterification to furnish diethyl 2-(3-cyano-2-oxo-1,2-dihydrocyclohepta[*b*]pyrrol-1-yl)fumarate (**3d**) despite the absence of acidic or basic materials. Reaction of **3c** with diethyl acetylenedicarboxylate (DEAD) to give **3d**, and this supports the structure.

When the acetylenic ester was absent, **1** did no change in an alcoholic solvent.

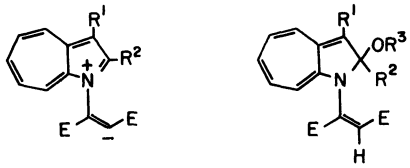
It is obvious that the reactions of 2-alkoxycyclohepta[*b*]pyrroles with DMAD give a cycloadduct in benzene, but they follow a different course in alcohols. It is conceivable that the yilde (**4**) reacts with an alcohol to produce an acetal (**5**), which must be hydrolyzed to cyclohepta[*b*]pyrrol-2(1*H*)-one (**3**) by a trace amount of water fortuitously present in the reaction mixture.



1 **2** **3**

$E^1=CO_2Me$, $E^2=CO_2Et$

1a: $R^1=E^2$, $R^2=Cl$
1b: $R^1=E^2$, $R^2=OEt$
1c: $R^1=CN$, $R^2=Cl$
1d: $R^1=CN$, $R^2=OMe$
2a: $R^1=E^2$, $R^2=Cl$
2b: $R^1=E^2$, $R^2=OEt$
2c: $R^1=CN$, $R^2=OMe$
3a: $R^1=E^2$, $R^2=H$
3b: $R^1=E^2$, $R^2=(E)$-CE^1=CHE^1
3c: $R^1=CN$, $R^2=H$
3d: $R^1=CN$, $R^2=(E)$-CE^2=CHE^2



4 **5**

Experimental

Melting points were uncorrected. ^1H NMR spectra were taken with Hitachi R-24B spectrometer (60 MHz) for solutions in $CDCl_3$ with TMS as internal standard. UV spectra were measured for solutions in $CHCl_3$ and IR spectra for Nujol mulls. Kieselgel 60 was used for chromatography unless otherwise stated. Yields are based on consumed starting materials.

Synthesis of 1b. **1a** (1.00 g) was added to a sodium ethoxide solution prepared from Na (0.40 g) and abs EtOH (20 ml). The mixture was heated under reflux for 2 h, cooled, acidified with dil HCl, and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on alumina with benzene–chloroform to give **1b** [0.914 g, 82%, yellow needles (from petroleum ether), mp 68—69 °C. UV_{max} 289 nm (log ε 4.67), 335 (3.82), 348 (3.71), 368 (3.61), 424 (3.27), 428 (3.26). IR 1675 cm^{-1} (C=O). ^1H NMR $\delta=1.45$ (3H, t, $J=7$ Hz, Me), 1.57 (3H, t, $J=7$ Hz, Me), 4.43 (2H, q, $J=7$ Hz, CH_2), 4.77 (2H, q, $J=7$ Hz, CH_2), 7.5—7.9 (3H, m, H-5,6,7), 8.15—8.4 (1H, m, H-8), 9.1—9.4 (1H, m, H-4). Found: C, 68.51; H, 6.20; N, 5.80%. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71%].

Synthesis of 1d. 2-Chlorocyclohepta[*b*]pyrrole-3-carbonitrile[7] (**1c**) (2.00 g) was added to a sodium methoxide solution prepared from Na (1.20 g) and abs MeOH (50 ml). The mixture was heated under reflux for 2 h and worked up as for **1b** to give **1d** [1.84 g, 94%, yellow needles (from MeOH), mp 186—187.5 °C. UV_{max} 285 nm (log ε 4.65), 334 (3.72), 347 (3.63), 369 (3.58), 423 (3.25), 430 (3.25). IR

2200 cm^{-1} (CN). ^1H NMR δ=4.32 (3H, s, OMe), 7.7—8.0 (3H, m, H-5,6,7), 8.2—8.5 (2H, m, H-4,8). Found: C, 71.68; H, 4.41; N, 15.25%. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21%].

Reaction of ***1b*** *with DMAD.* (*a*): A mixture of **1b** (1.00 g) and DMAD (4.06 g) in benzene (30 ml) was heated under reflux for 8 d. The solvent was evaporated and the residue was chromatographed with benzene–ethyl acetate (95 : 5) to give **1b** (0.305 g) followed by **2b** (0.873 g, 59%), which crystallized from cyclohexane as red prisms, mp 140—141 °C [UV_{max} 258 nm (log ε 4.37), 320^{sh} (3.89), 465 (4.01), IR 1740, 1730, 1710, and 1695 cm^{-1} (C=O), ^1H NMR δ= 1.37 (3H, t, J=7 Hz, Me), 1.41 (3H, t, J=7 Hz, Me), 3.72 (3H, s, OMe), 3.75 (3H, s, OMe), 3.83 (6H, s, OMe), 4.23 (2H, q, J=7 Hz, CH_2), 4.34 (2H, q, J=7 Hz, CH_2), 6.3—6.95 (3H, m, H-7,8,9), 6.48 (1H, s, H-3), 7.82 (1H, dd, J=10 and 3 Hz, H-10). Found: C, 49.51; H, 6.39; N, 3.18%. Calcd for $C_{26}H_{27}NO_{11}$: C, 49.43; H, 6.34; N, 3.26%]. Elution with ethyl acetate gave **3a** (0.147 g, 29%), yellow needles (from EtOH), mp 188.5—190 °C (lit,[5] mp 189—190 °C).

(*b*): A mixture of **1b** (1.00 g) and DMAD (4.06 g) in abs MeOH (50 ml) was heated under reflux for 4 d. The solvent was evaporated and the residue was chromatographed with benzene to give **1b** (0.13 g). Elution with chloroform gave **3b** (1.195 g, 94%), which crystallized from cyclohexane as yellow prisms, mp 119—121 °C [UV_{max} 277 nm (log ε 4.48), 432 (4.26), IR 1735, 1695, and 1670 cm^{-1} (C=O), ^1H NMR δ=1.42 (3H, t, J=7 Hz, Me), 3.63 (3H, s, OMe), 3.80 (3H, s, OMe), 4.43 (2H, q, J=7 Hz, CH_2), 6.8—7.75 (4H, m, H-5,6,7,8), 7.40 (1H, s, vinyl-H), 9.28 (1H, d, J=10 Hz, H-4). Found: C, 60.17; H, 4.78; N, 3.79%. Calcd for $C_{18}H_{17}NO_7$: C, 60.16; H, 4.77; N, 3.90%].

Reaction of ***3a*** *with DMAD.* A mixture of **3a** (1.00 g) and DMAD (2.00 g) in benzene (80 ml) was heated under reflux for 2 d. The solvent was evaporated and the residue was chromatographed with chloroform to give **3b** (1.030 g, 78%). Elution with ethyl acetate gave **3a** (0.205 g).

Reaction of ***1a*** *with DMAD.* A mixture of **1a** (1.00 g) and DMAD (4.22 g) in abs MeOH (40 ml) was heated under reflux for 6 h. The solvent was evaporated and the residue was chromatographed with chloroform to give **3b** (1.465 g, 98%).

Reaction of ***1d*** *with DMAD.* (*a*): A mixture of **1d** (1.00 g) and DMAD (4.00 g) in benzene (70 ml) was heated under reflux for 6 d. The solvent was evaporated and the residue was chromatographed with benzene–ethyl acetate (95 : 5) to give **1d** (0.837 g) followed by **2c** (0.101 g, 25%), which crystallized from cyclohexane as red needles, mp 101—103 °C [UV_{max} 285^{sh} nm (log ε 4.05), 459 (3.75), IR 2200 (CN) and 1740 and 1725 cm^{-1} (C=O), ^1H NMR δ=3.70 (3H, s, OMe), 3.73 (3H, s, OMe), 3.80 (6H, s, OMe), 4.30 (3H, s, OMe), 6.40 (1H, s, H-3), 6.7—7.1 (3H, m, H-7,8,9), 7.6—7.8 (1H, m, H-10). Found: C, 59.09; H, 4.39; N, 5.84%. Calcd for $C_{23}H_{20}N_2O_9$: C, 58.97; H, 4.30; N, 5.98%].

(*b*): A mixture of **1d** (0.500 g) and DMAD (2.00 g) in abs EtOH (70 ml) was heated under reflux for 2 d. The solvent was evapoated and the residue was chromatographed with benzene to give **1d** (0.140 g). Elution with benzene–chloroform (1 : 1) gave **3d** (0.367 g, 55%), which crystallized from ligroine–dichloromethane as yellow leaflets, mp 118—119 °C [UV_{max} 276 nm (log ε 4.37), 430 (4.10), IR 2210 (CN) and 1730 and 1690 cm^{-1} (C=O), ^1H NMR δ=1.13 (3H, t, J=7 Hz, Me), 1.29 (3H, t, J=7 Hz, Me), 4.12 (2H, q, J= 7 Hz, CH_2), 4.31 (2H, q, J=7 Hz, CH_2), 7.15—7.85 (4H, m, H-5,6,7,8), 7.40 (1H, s, vinyl-H), 7.93 (1H, d, J=10 Hz, H-4). Found: C, 63.76; H, 4.71; N, 8.46%. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23%]. Elution with MeOH gave **3c** (0.098 g, 29%), yellow needles (from ethyl acetate), mp 313 °C (lit.[7] mp 313 °C).

Reaction of ***3c*** *with DEAD.* A mixture of **3c** (0.100 g) and DEAD (0.35 g) in benzene (60 ml) was heated under reflux for 2 d and cooled. The product crystallized out of the solution was collected and recrystallized to give **3c** (0.087 g). The mother liquid was evaporated and the residue was chromatographed with chloroform to give **3d** (0.016 g, 80%). Elution with MeOH gave **3c** (0.003 g).

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