# Cycloaddition of Dimethyl Acetylenedicarboxylate to Indoles. Isolation of a [2 + 2] Adduct



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Thermal reaction of 1,2,3-trimethylindole (**1**) and 1,3-dimethylindole (**5**) with dimethyl acetylenedicarboxylate in the presence of boron trifluoride etherate gave cyclobutene derivatives **2** and **7** that were isolated for the first time in good yields under themal conditions. In a polar solvent and with an excess of catalyst, 4-methoxy-2,4a-dihydro-4a,9-dimethyl-2-oxacarbazole **4** was obtained in yields up to 72%.

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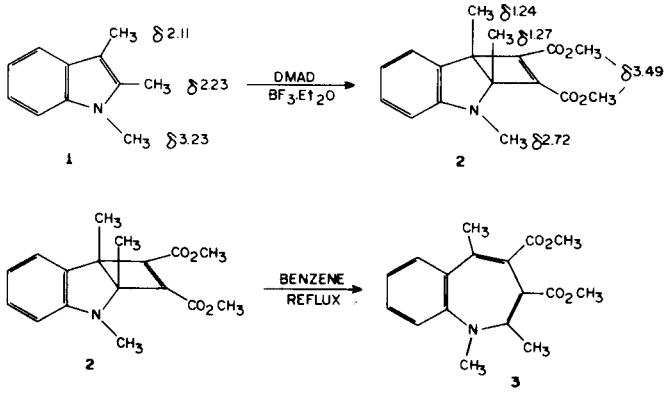
The reaction of indoles with dimethyl acetylenedicarboxylate (DMAD) has been extensively studied [1] because of the high versatility of the compounds isolated. One of these compounds is benzazepine. It has been suggested that this compound is formed *via* a cyclobutene intermediate which then undergoes a ring-opening [2,3]. Taylor *et al.* [4] have reported that in boron trifluoride etherate catalyzed reaction of 1,3-dimethylindole and DMAD, the cyclobutene intermediate was detected in a three component mixture. Neckers *et al.* [5] repeated this reaction and isolated a red oil in only 0.6% yield which was identified as the cyclobutene component. Good yields of cyclobutene derivatives were reported however in a photosensitized cycloaddition of DMAD to activate indoles [6]. We are now reporting our results of cycloaddition of indoles to DMAD in wich we isolate the cyclobutene derivatives in good yields.

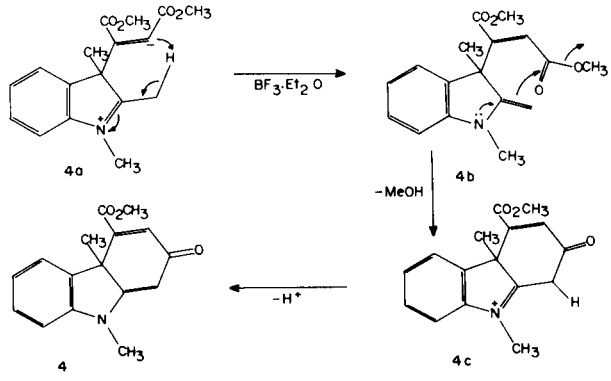
## Results and Discussion.

The reaction of 1,2,3-trimethylindole (**1**) with DMAD, without solvent but in the presence of three drops of boron trifluoride etherate, was carried out for 24 hours at 20° under nitrogen and gave, after purification by flash chromatography, a red oil in 82% yield. The structural assignment was suggested by the pmr spectrum, which showed an upfield chemical shift of the methyl groups when compared with 1,2,3-trimethylindole. On heating, the red oil was smoothly converted to 3,4-bis(methoxycarbonyl)-1,2,5-trimethyl-6,7-1*H*-1-benzazepine (**3**) [7], which may be reasonably interpreted as the formation of the ring-expanded product by thermal decomposition. These observations led to the formulation of the red oil product as 6,7-bis(methoxycarbonyl)-1,2,3-trimethyl-3,4-benzo-2-azabicyclo[3.2.0]hepta-3,6-diene (**2**). Taylor *et al.* [4] had reported that "attempts to isolate the cyclobutene were unsuccessful". When the reaction was repeated using an excess of boron trifluoride etherate (0.3 ml) catalyst, the products isolated were the cyclobutene **2** (50%) and another solid product (40%) with a molecular ion of 269 which is consistent with the loss of methanol and compatible with the dienone structure **4** indicated by other authors [4]. Further insight into the mechanism of formation of the dienone **4** was obtained when the reaction was carried out with a larger excess of boron trifluoride etherate (0.6 ml), where the yield of **4** increased to 60%. These results demonstrate a participation of the catalyst in the formation of the intermediate **4b** that led to the elimination of methanol. Much better yields (72%) of the dienone **4** were achieved when the reaction was carried out in a polar solvent (acetonitrile) containing 0.6 ml of boron trifluoride etherate where the intermediate **4a** is better stabilized.

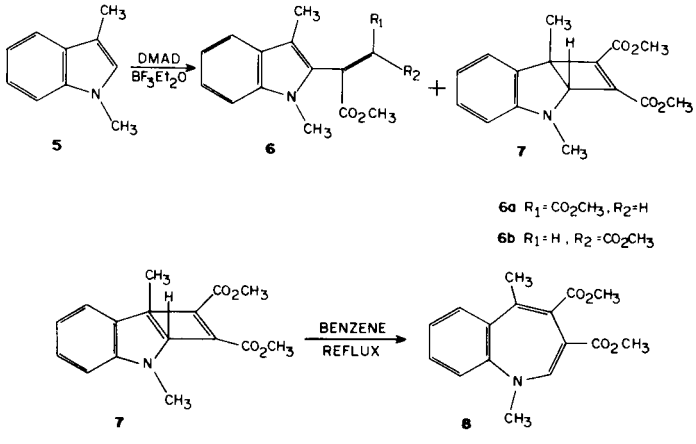



When the cycloadduct **2** was heated under reflux for 10 hours, it was converted to the benzazepine **3** in 83% yield. In the literature, isomerization reactions of [2 + 2]-cycloadducts of enamines and acetylenic esters to the corresponding Michael adducts (structures of type **4a**) have been reported [8,9,10]. Brannock *et al.* [8] and Reinhoudt *et al.* [10] have explained this reaction as a [2 + 2]-cycloreversion followed by a slow irreversible formation of the Michael adduct. We have looked for this type of conversion of the cyclobutene **2** in polar and non polar solvents, with and without boron trifluoride etherate, and have never isolated the dienone **4**, only the benzazepine **3**. This suggested that the ring-opening of the cyclobutene in our case occurs by a concerted mechanism.

The reaction of 1,3-dimethylindole (**5**) and DMAD In carbon tetrachloride with 0.5 ml of boron trifluoride etherate at 0-4° under nitrogen during 16 hours gave a three




component mixture (tlc). Flash chromatography gave a mixture of maleate and fumarate **6** (40%) and a red oil (30%). This red oil was identified as the 6,7-bis(methoxycarbonyl)-2,5-dimethyl-3,4-benzo-2-azabicyclo[3.2.0]hepta-3,6-diene (**7**) with pmr data identical to the cyclobutene isolated by Neckers [5] in 0.6% yield. The benzazepine **8** isolated from the column in 8% yield, was not present in the crude reaction product as revealed by pmr analysis, but was formed by the isomerization of the cyclobutene during the process of isolation. On heating, the cyclobutene **7** was ring-expanded to benzazepine **8** with an identical melting point as the compound isolated by Taylor [4]. This reaction is much slower in acetonitrile. After 7 days it gave 41% yield of a mixture of maleate and fumarate **6**, 13% yield of a [2 + 2] adduct **7** and 26% yield of benzazepine **8**.




In conclusion, to obtain the cyclobutenes in good yields, it is necessary to carry out the reaction in non polar solvents, and to control the temperature carefully. In contrast, to obtain the dienone **4**, it is necessary to work in polar solvents and a large excesss of catalyst.

## EXPERIMENTAL

All melting points were obtained on a Mettler FP 52 melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Jasco A-202 spectrophotometer. The pmr spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained on a Finningan 1015 S/L quadrupole spectrometer.

Isolation of 6,7-Bis(methoxycarbonyl)-1,2,5-trimethyl-3,4-benzo-2-azabicyclo[3.2.0]hepta-3,6-diene (**2**).

To 1,2,3-trimethylindole (**1**) (0.318 g, 0.002 mole) and dimethyl acetylenedicarboxylate (0.284 g, 0.002 mole) under nitrogen at 0-4° was added 3 drops of boron trifluoride etherate. After 20 hours at 20° the dark red residue was purified by flash column chromatography (silica gel Merck 9385) using hexane-ether (9:1) as eluent and yielded a red oil (0.48 g, 82%); uv (ethanol 95%): λ max nm log ε 429 (2.99), 349 (3.97); pmr (carbon tetrachloride): δ 1.24 (s, 3H, C-$CH_3$), 1.27 (s, 3H, C-$CH_3$), 2.72 (s, 3H, N-$CH_3$), 3.49 (s, 6H, O-$CH_3$), 6.01-6.97 (m, 4H, aromatic H); ms: m/e 301 ($M^+$, 12), 159 (33), 158 (16), 130 (47), 56 (100); ir (film 1720 $cm^{-1}$.

*Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.79; H, 6.36; N, 4.65.

Ring Opening of 6,7-Bis(methoxycarbonyl)-1,2,5-trimethyl-3,4-benzo-2-azabicyclo[3.2.0]hepta-3,6-diene (**2**).

A benzene solution of **2** (0.602 g, 0.007 mole) was refluxed for 10 hours. The solvent was removed and the residue recrystallized from ether-hexane to give 3,4-bis(methoxycarbonyl)-1,2,5-trimethyl-6,7-1*H*-benzazepine (**3**) 0.5 g, (83%) as yellow crystals mp 144-145° [7]; pmr (deuteriochloroform): δ 2.37 (s, 3H, C-$CH_3$), 2.49 (s, 3H, C-$CH_3$), 3.12 (s, 3H, N-$CH_3$), 3.59 (s, 3H, O-$CH_3$), 3.74 (s, 3H, O-$CH_3$), 6.83-7.50 (m, 4H, aromatic H); ir (potassium bromide): 1717 and 1706 $cm^{-1}$; ms: m/e 301 ($M^+$, 10), 159 (10), 56 (100).

*Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.78; H, 6.35; N, 4.66.

Reaction of 1,2,3-Trimethylindole (**1**) With DMAD and an Excess of Catalyst.

To a mixture of 1,2,3-trimethylindole (0.318 g, 0.002 mole) and DMAD (0.284 g, 0.002 mole) under nitrogen at 0-4° was added boron trifluoride etherate (0.3 ml). After 24 hours at 20° the residue was chromatographed on silica gel by flash chromatography.

a. 6,7-Bis(methoxylcarbonyl)-1,2,5-trimethyl-3,4-benzo-2-azabicyclo-[3.2.0]hepta-3,6-diene (**2**).

Elution with hexane-ether (9:1) gave **2** as a viscous red oil (0.3 g, 50%).

b. 4-Methoxycarbonyl-2,4a-dihydro-4a,9-dimethyl-2-oxacarbazole (**4**).

Elution with ether gave **4** (0.24 g, 40%) as orange crystals mp 112° dec [7]; pmr (deuteriochloroform): δ 1.86 (s, 3H, C-$CH_3$), 3.27 (s, 3H, N-$CH_3$), 3.93 (s, 3H, O-$CH_3$), 5.68 (d, 1H, $J^5$ 1.5 Hz), 6.89 (d, 1H, $J^5$ 1.5 Hz), 6.73-8.07 (m, 4H, aromatic H); ir (potassium bromide): 1713 $cm^{-1}$; ms: m/e 270 (16), 269 ($M^+$, 83), 255 (20), 254 (100), 226 (40), 182 (11), 167 (14).

*Anal.* Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.62; N, 5.20. Found: C, 71.38; H, 5.63; N, 5.20.

Reaction of 1,3-Dimethylindole (**5**) and DMAD.

To a solution of 1,3-dimethylindole (**5**) (0.58 g, 0.004 mole) and DMAD (0.568 g, 0.004 mole) in carbon tetrachloride (20 ml) at 0-4° under nitrogen was added boron trifluoride etherate (0.6 ml). After 16 hours the solvent was removed and the residue chromatographed on silica gel. Elution with dichloromethane-hexane (1:2) gave a 1:1 mixture of the maleate and fumarate derivatives (0.46 g, 40%). This mixture was separated by fractional crystallization (ether-hexane).

a. 2-(1,3-Dimethylindol-2-yl)fumarate (**6a**).

This compound was obtained as red crystals mp 103-104° (lit 103-105° [5]).

*Anal.* Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.87. Found: C, 66.89; H, 5.97; N, 4.89.

b. 2-(1,3-Dimethylindol-2-yl)maleate (**6b**).

This compound was obtained as yellow crystals mp 189-191° (lit 189-191° [5]).

*Anal.* Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.87. Found: C, 66.88; H, 5.98; N, 4.89.

c. 6.7-Bis(methoxycarbonyl)-1,5-dimethyl-3,4-benzo-2-azabicyclo[3.2.0]-hepta-3,6-diene (**7**).

Elution with dichloromethane gave **7** (0.35 g, 30%); pmr (deuteriochloroform): δ 1.66 (s, 3H, C-$CH_3$), 3.06 (s, 3H, N-$CH_3$), 3.84 (s, 6H, O-$CH_3$), 4.33 (s, 1H), 6.40-7.40 (m, 1H, aromatic H).

*Anal.* Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.87. Found: C, 66.90; H, 5.99; N, 4.90.

d. 3,4-Bis(methoxycarbonyl)-1,5-dimethyl-6,7-1*H*-1-benzazepine (**8**).

Elution with dichloromethane-ether (9:1) gave **8** (0.095 g, 8%) mp 86-88° (lit 87-89° [4]).

Acknowledgement.

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