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An Unexpected Reaction Between 6,7-Dimethoxy-2*H*-1,3-benzothiazine and Dimethyl Acetylenedicarboxylate[#]

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Summary. 6,7-Dimethoxy-2*H*-1,3-benzothiazine reacted with dimethyl acetylenedicarboxylate in aqueous methanol to give heterocycles with unexpected structures. A mechanism is proposed for the reaction.

Keywords. S,N-Heterocycles; Dimethyl acetylenedicarboxylate cycloadditions; 5,13-Dithiaxylopinine; Benzothiopyrane; Reaction mechanism.

Introduction

Earlier work has demonstrated that 6,7-dimethoxy-2*H*-1,3-benzothiazine (**1**) reacts with dimethyl acetylenedicarboxylate (*DMAD*) in anhydrous diethyl ether to yield the 1:2 adduct **3** by 1,4-dipolar cycloaddition [1]. However, it now turned out that the reaction of **1** with *DMAD* in refluxing aqueous methanol did not yield the expected product, but instead (±)-2,3,10,11-tetramethoxy-6*H*,8*H*,13a*H*-[1,3]benzothiazino[4,3-*b*][1,3]benzothiazine (5,13-dithiaxylopinine, **4**) and the benzothiopyran derivative **5**.

Results and Discussions

The mechanism of this reaction has not yet been completely clarified. At present, we have only a tentative explanation for the formation of **4** and **5**. In the presence

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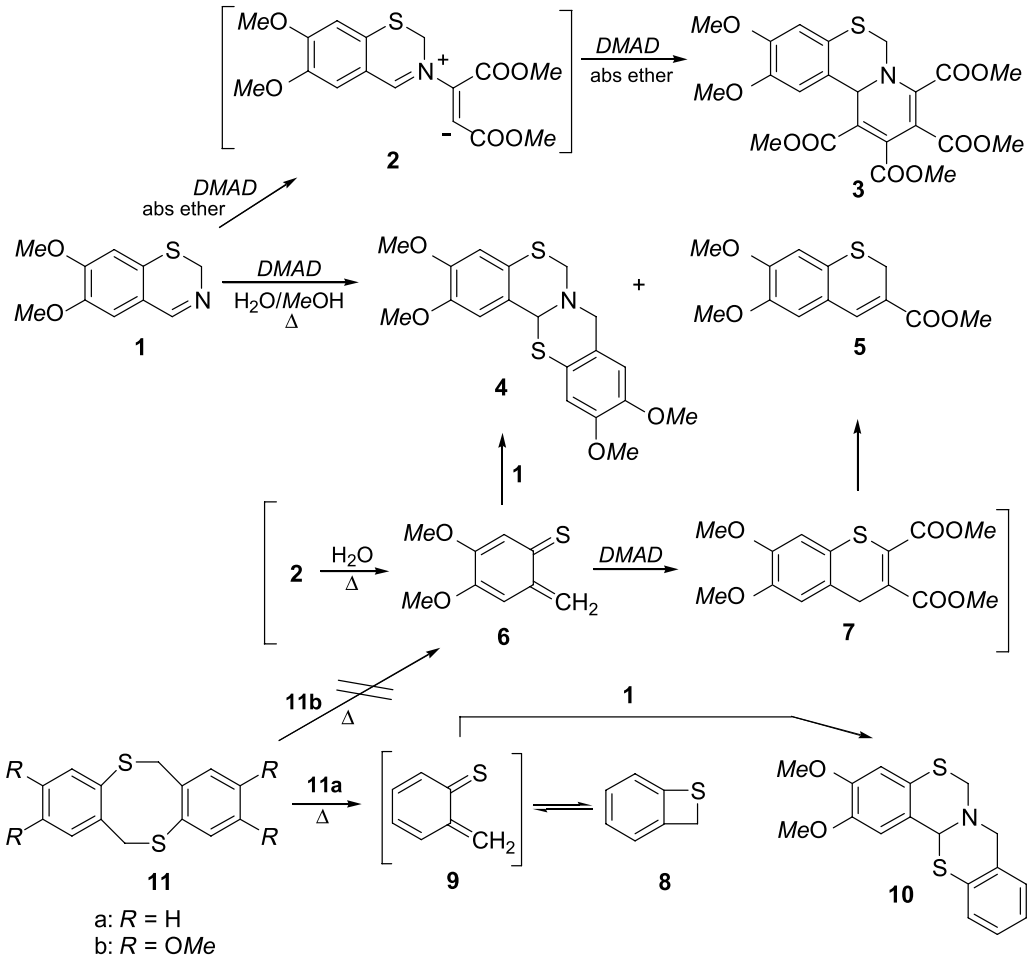
[#] Dedicated to Professor Dr. *András Lipták* on the occasion of his 70th birthday



Scheme 1

of water, intermediate **2** may be transformed to the *ortho*-quinoidal form **6**, which may react with **1** to furnish **4**. Compound **5** may be formed from **6** by *DMAD* addition and subsequent decarboxylation and rearrangement of the adduct **7** (Scheme 1).

Several procedures are known for the generation of **9**, *e.g.* from 6*H*,12*H*-dibenzo[*b*,*f*][1,5]dithiocine (**11a**) by flash pyrolysis, or from benzothiete (**8**) by heating above 90°C or by irradiation [2, 3]. Compound **8** can be used for various cycloaddition reactions. Facile thermal opening of the 4-membered ring confers on **8** the character of a heterodiene. We treated **8** with 6,7-dimethoxy-2*H*-1,3-benzothiazine (**1**) as dienophile and obtained (±)-2,3-dimethoxy-6*H*,8*H*,13a*H*[1,3]benzothiazino[4,3-*b*][1,3]benzothiazine (**10**) in a yield of 50%. The regioselectivity of the cycloaddition corresponds to those of the processes observed for other imines [4, 5].

The flash pyrolysis of 2,3,8,9-tetramethoxy-6*H*,12*H*-dibenzo[*b*,*f*][1,5]dithiocine (**11b**) has been investigated [6] under modified conditions. It emerged that the activation barrier for the reaction of the two *ortho* methoxy groups is lower than

that for the cleavage of the 8-membered ring [7]. Further experiments are currently in progress.

Experimental

Melting points were determined on a *Kofler* apparatus and are uncorrected. Elemental analyses (C, H, N, S) were performed with a Perkin-Elmer 2400 CHNS elemental analyser, their results were found to be in good agreement (±0.2%) with the calculated values. Merck Kieselgel $60F_{254}$ plates were used for TLC and Merck Silica gel 60 (0.040–0.063 mm) for column chromatography. 6,7-Dimethoxy-2*H*-1,3-benzothiazine (**1**) was prepared according to Ref. [8].

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at rt, on a Bruker DRX 500 spectrometer at 500 (^1H) and 125 MHz (^{13}C), using *TMS* as internal reference with the deuterium signal of the solvent as the lock. The MS spectra were run on a Finnigan TSQ 7000 mass spectrometer (Finnigan MAT Ltd, San Jose, USA).

(±)-2,3,10,11-Tetramethoxy-6H,8H,13aH-[1,3]benzothiazino[4,3-b][1,3]benzothiazine (5,13-dithiaxylopinine, **4**, $C_{19}H_{21}NO_4S_2$) and *6,7-Dimethoxy-3-methoxycarbonyl-2H-benzo[b]thiopyrane* (**5**, $C_{13}H_{14}O_4S$)

Compound **1** (2.09 g, 10 mmol) was dissolved in aqueous methanol (40 cm^3 methanol + 5 cm^3 H_2O) and 1.42 g *DMAD* (10 mmol) were added. The solution was stirred under reflux. After 4 h, the reaction mixture was allowed to stand at rt overnight and the colourless radial needles that separated out were filtered off and washed with methanol (**4**, 0.96 g, 25%, mp 183–184°C, acetone). This product was identical in every respect with an authentic sample [9].

The mother liquor was evaporated to dryness, the residue was dissolved in the minimum amount of $CHCl_3$, and the solution was developed on a silica column. The elution was carried out with a 1% solution of methanol in $CHCl_3$. The eluted product **5** was recrystallized from methanol to yield 0.67 g (26%). Mp 115–116°C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.67$ (d, 2H, 2-H), 3.78 (s, CO_2CH_3), 3.82 (s, OCH_3), 3.85 (s, OCH_3), 6.73 (s, 5-H), 6.74 (s, 8-H), 7.47 (s, 4-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 24.2$ (C-2), 52.0 (OCH_3, ester), 56.0 (OCH_3), 56.0 (OCH_3), 109.8 (C-8), 113.3 (C-5), 120.1/124.2/126.3 (C-3, C-4a, C-8a), 137.2 (C-4), 147.2/150.6 (C-6, C-7), 166.5 (CO) ppm; EI MS (70 eV): m/z (%) =266 [M^+] (87), 251 (100), 207 (53), 163 (21).

(±)-2,3-Dimethoxy-6H,8H,13aH[1,3]benzothiazino[4,3-b][1,3]benzothiazine (**10**, $C_{17}H_{17}NO_2S_2$)

A mixture of 245 mg benzothiete (**8**) (2.0 mmol) and 628 mg **1** (3.0 mmol) was refluxed in 100 cm^3 dry toluene for 5 h. The solvent was removed and the residue was purified by column chromatography (4×80 cm SiO_2, toluene:ethyl acetate 10:1). A pale-yellow product (335 mg, 50%) was obtained. Mp 157°C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.71/4.76$ (AB, $^2J = 11.3$ Hz, *2H*, 6-H), 3.82 (s, OCH_3), 3.83 (s, OCH_3), 4.04/4.62 (AB, $^2J = 17.0$ Hz, *2H*, 8-H), 6.09 (s, 13a-H), 6.59 (s, 4-H), 6.63 (s, 1-H), 6.59–7.12 (m, *4H*, arom H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 47.0$ (C-6), 55.8 (OCH_3), 55.9 (OCH_3), 57.8 (C-8), 65.9 (C-13a), 109.4 (C-4), 111.1 (C-1), 121.2/122.3/126.0/132.9 (C-4a, C-8a, C-12a, C-13b), 124.5/126.6/127.3/127.7 (C-9, C-10, C-11, C-12), 146.5/149.0 (C-2, C-3) ppm; EI MS (70 eV): m/z (%) =331 [M^+] (30) [$M–C_7H_6SH]^+$ (100).

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