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Diels-Alder Reactions with 2-Methylpyridazin-3(2*H*)-ones Bearing Electron-Withdrawing Substituents at the 4- or 5-Position

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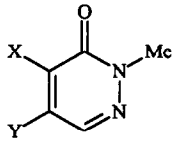
Abstract: Diels-Alder reactions of 2-methylpyridazin-3(2*H*)-ones, substituted with ethylsulphonyl, cyano and methoxycarbonyl groups at the 4- or 5-positions, with 1,3-dienes have been investigated. Pyridazinones behave as poor dienophiles and their reactivity depends on the nature and position of the substituents. 5-Substituted pyridazinones are more reactive than the 4-substituted isomers and high conversions to the expected adducts can be obtained after prolonged reaction times. Cycloadditions of (*E*)-1-methoxybuta-1,3-diene proved to be regiospecific. The experimental results are largely in accordance with FMO calculations.

The Diels-Alder reaction with olefinic and acetylenic dienophiles has been extensively studied and is one of the most useful methods for the construction of carbocyclic systems. In contrast, there are only few examples of Diels-Alder reactions involving heterocyclic dienophiles, which include those performed with 3-pyrazolones,[2a] pyridazindiones,[2b] pyrimidones,[2c] pyridones,[2d,e] pyrrolinones,[2f,g] and isoxazoles.[2h,i] Similarly, 1,3-dipolar cycloadditions with heteroaromatic dipolarophiles have not received much attention. Examples of this type of reaction are the addition of diazopropane to 2-methyl-6-phenylpyridazin-3(2*H*)-one,[3] the addition of diazomethane to pyridones[4] and to heterocyclic systems with two fused rings.[5] A few years ago, we reported the 1,3-dipolar cycloadditions of diazomethane to pyridazinone **1** and to a variety of 4- and 5-substituted derivatives[6] and we demonstrated that the more reactive derivatives are those substituted with ethylsulphonyl, cyano and methoxycarbonyl groups[6b] (**2a-c**, **3a-c**).



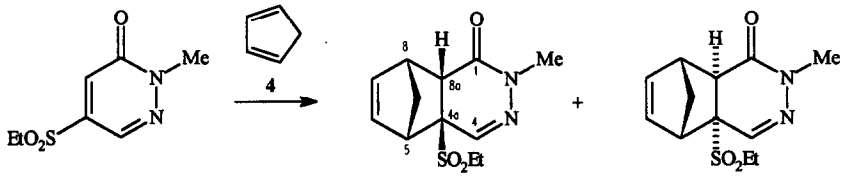
	1	2a	2b	2c	3a	3b	3c
X	H	$EtSO_2$	CN	CO_2Me	H	H	H
Y	H	H	H	H	$EtSO_2$	CN	CO_2Me

As the behaviour of pyridazinones in Diels-Alder reactions had not been described,[7] it was of interest to extend our study to test the suitability of the above mentioned pyridazinones as dienophiles in order to widen the scope and synthetic utility of these cycloaddition reactions. A preliminary account of our results was published[8] and we report now the full details of this work.

RESULTS AND DISCUSSION

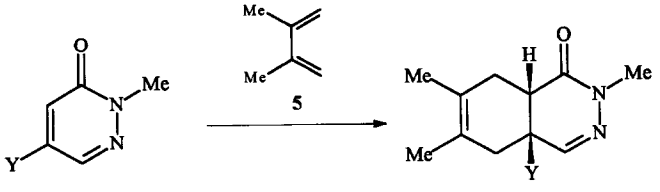
Reaction with Symmetric Dienes

Cyclopentadiene (**4**) and 2,3-dimethylbuta-1,3-diene (**5**) were chosen first to examine the dienophilic properties of pyridazinone **1** and its 4- and 5-substituted derivatives, **2a-c** and **3a-c**, as the use of these symmetric dienes precludes the formation of regioisomers.



3a **6a** **6'a**

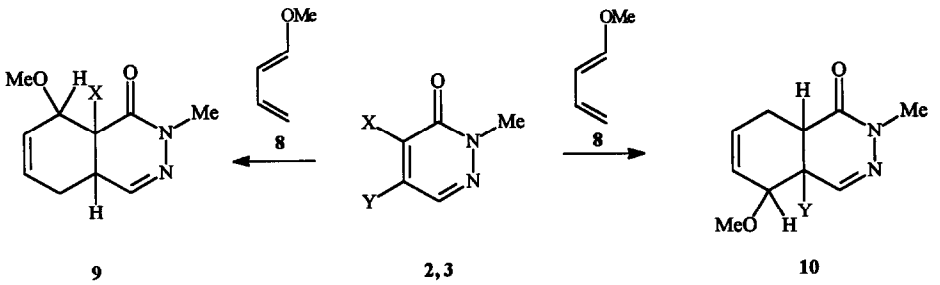
5-Ethylsulphonyl-2-methylpyridazin-3(2*H*)-one (**3a**) reacts with an excess of cyclopentadiene, in chloroform at room temperature for 10 days, to furnish a 9:1 mixture of the isomeric *endo*- and *exo*-adducts, **6a** and **6'a**[9], in 70% yield. After purification of the crude mixture by chromatography on silica gel, only the major *endo*-adduct (**6a**) was isolated, and its structure was assigned on the basis of its ^{1}H-NMR spectrum. The magnitude of the coupling between H-8 and H-8a (J=3.7 Hz) established the *exo* orientation of H-8a and, as a consequence, the pyridazinone ring must occupy the *endo* positions[10]. In contrast to the reactivity of **3a**, attempts to react pyridazinones **1**, **2a-c** and **3b,c** failed to afford the expected adducts with cyclopentadiene, even after periods of one month. When a 5:1 excess of 2,3-dimethylbuta-1,3-diene (**5**) was allowed to react with pyridazinones **1**, **2a-c** and **3a-c** in refluxing benzene for prolonged periods of time, cycloaddition was only successful with the 5-substituted pyridazinones **3a** and **3c**, which afforded the corresponding Diels-Alder adducts **7a** and **7c** in 90% and 70% yield, respectively.



3a, c **7a, c**

Reaction with Unsymmetric Dienes

In view of the above results, it was of interest to study the behaviour of pyridazinones **1**, **2a-c** and **3a-c** towards an electron-rich diene, such as (*E*)-1-methoxybuta-1,3-diene (**8**), with an increased Diels-Alder reactivity. Moreover, the use of an unsymmetrically substituted diene would allow the study of the regiochemistry of these cycloadditions. The reactions were carried out in refluxing benzene with excess of diene **8** (3:1) and purification of the adducts was performed by flash column chromatography; the results of the reactions are summarized in Table I.



9 **2,3** **10**

In spite of the high reactivity of (*E*)-1-methoxybuta-1,3-diene (**8**), 2-methylpyridazin-3(2*H*)-one (**1**) did not react as a dienophile under the conventional conditions employed. The 4-substituted pyridazinones **2b,c** reacted with diene **8** in a regiospecific manner to give adducts of type **9** in good yields. These reactions require, however, long reaction times (40-50 days) to go to completion. In contrast, pyridazinone **2a** did not react with diene **8**, the cycloaddition presumably being inhibited by the steric interaction between the methoxy substituent of the diene and the ethylsulphonyl group of the pyridazinone.

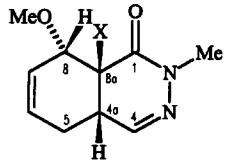
Table I. Diels-Alder reactions of 2-methylpyridazin-3(2*H*)-ones with (*E*)-1-methoxybuta-1,3-diene

Pyridazinone	X	Y	Time	Adduct (yield %)
1	H	H	20 d	-[a]
2a	$EtSO_2$	H	15 d	-[a]
2b	CN	H	50 d	**9b**(66)+**9'b**(27)
2c	CO_2Me	H	40 d	**9c**(40)+**9'c**(40)
3a	H	$EtSO_2$	4 d	**10a**(90%)
3b	H	CN	2 d	**10b**(55)+**10'b**(40)
3c	H	CO_2Me	4 d	**10c**(70)+**10'c**(25)

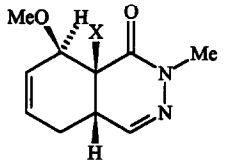
[a] Cycloadducts were not detected.

Regioorientations of type **9** were assigned to the adducts on the basis of their ^{1}H-NMR spectra. In each case, we observed that H-4a showed a coupling to proton H-4 of the pyridazinone ring and to each of the two 5-methylene protons, whereas coupling was not observed between H-4 and H-8, the proton bonded to the carbon supporting the methoxy group. These assignments were corroborated by decoupling experiments.

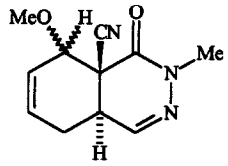
The cycloaddition of the cyanopyridazinone **2b** to diene **8** gave two isomeric adducts **9b** and **9'b** in a 2:1 ratio, probably resulting from the *endo* and *exo* addition, respectively. These tentative assignments have been made on the assumption that the major adduct has been formed from an *endo* approach of the pyridazinone. Similarly, the reaction between 4-methoxycarbonyl-2-methylpyridazin-3(2*H*)-one (**2c**) and diene **8** gave two stereoisomeric adducts **9c** and **9'c** in a 1:1 ratio. The structures **9c** and **9'c** were tentatively assigned by analogy with those of **9b** and **9'b**, respectively. In fact, a comparison of the ^{1}H-NMR coupling constants of the adducts (Table II) reveals that the geometry of each pair of adducts is similar.



9b: X = CN
9c: X = CO_2Me



9'b: X = CN
9'c: X = CO_2Me



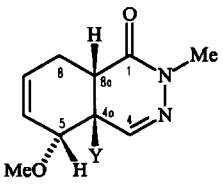
9"b

Table II. Comparison of ^{1}H-NMR coupling constants of type **9** adducts.

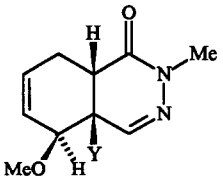
Adduct			Coupling Constants (Hz)		
N°	X	Y	$J_{4,4a}$	$J_{4a,5}$	$J_{4a,5'}$
9b	CN	H	1.8	6.7	1.9
9'b	CN	H	3.1	6.2	6.2
9"b	CN	H	1.7	6.9	7.0
9c	CO_2Me	H	1.8	6.4	1.9
9'c	CO_2Me	H	4.6	6.5	6.9

Attempts to purify the reaction mixture containing the stereoisomeric adducts **9b** and **9'b** by column chromatography resulted in formation of two additional products: a third isomer **9''b** along with small amounts of 2-methylphthalazin-1(2*H*)-one (**11**), the latter formed by aromatization of the adducts. The presence of the new isomer **9''b** was not detected in the crude reaction mixture and, therefore, its formation

occurred in the subsequent purification step, probably mediated by silica gel, via isomerization of the initial adducts **9b** and/or **9'b**. Treatment of adduct **9b** with a strong base, such as sodium methoxide, gave only 2-methylphthalazin-1(2*H*)-one (**11**). Moreover, isomer **9''b** was obtained upon treatment of **9b**[11] with a Lewis acid catalyst (boron trifluoride etherate in chloroform), presumably by isomerization of the initial adduct, possessing a *cis* ring fusion to a product with a *trans* stereochemistry at the ring juncture.[12] Some evidence for this is our observation that adduct **9b**, on heating for 30 hours in refluxing xylene, underwent a retro-Diels-Alder reaction to afford the starting pyridazinone **2b**, while isomer **9''b** failed to give the cycloreversion under the same reaction conditions.



10a: Y = $EtSO_2$
10b: Y = CN
10c: Y = CO_2Me



10'b: Y = CN
10'c: Y = CO_2Me

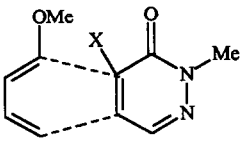
The 5-substituted pyridazinones (**3a-c**) are more reactive than the corresponding 4-substituted isomers (**2b-c**) and reacted with diene **8** in a regiospecific manner to give adducts of type **10**. Thus, cycloaddition of 5-ethylsulphonyl-2-methylpyridazin-3(2*H*)-one (**3a**) with the diene **8** gave a single adduct **10a**, which on the subsequent purification by column chromatography afforded a small amount of 2-methylphthalazin-1(2*H*)-one (**11**). By contrast, the reaction of diene **8** with the 5-cyano- and 5-methoxycarbonylpyridazinones (**3b** and **3c**) afforded in both cases two stereoisomeric adducts, assigned to **10b** and **10'b** (1.4:1) and to **10c** and **10'c** (3:1), respectively. Structures **10b** and **10c** were tentatively assigned to the major isomers on the assumption that they are formed through an *endo* transition state. The ^{1}H-NMR spectra of adducts **10** were consistent with the proposed regiochemistry. In particular, the spectra showed coupling between H-8a and the 8-methylene protons, whereas such coupling was not observed between H-8a and H-5. These assignments were confirmed by decoupling experiments.

The above experimental results, which show the influence of electron-attracting substituents on the reactivity of the pyridazinones and on the regiochemistry of the addition of (*E*)-1-methoxybuta-1,3-diene to 4- or 5-substituted 3(2*H*)-pyridazinones (**2a-c** and **3a-c**), can be rationalized in terms of FMO theory.[13]

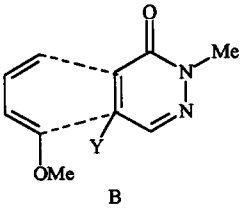
The stabilization energies were calculated considering only the electronic interaction term of the Klopman and Salem equations.[14] It is possible to make an additional simplification to this equation, because cycloadditions of (*E*)-1-methoxybuta-1,3-diene to pyridazinones belong to type I in the Sustmann

classification;[15] therefore we employed only the term corresponding to the main interaction: $HOMO_{diene}$-$LUMO_{pyridazinone}$. The values calculated for the stabilization energies of approximations A and B in these cycloadditions to give adducts of type **9** and **10**, respectively, are summarized in Table III. The values shown in Table III agree largely with the experimental results. It is possible to establish a rough qualitative relationship between the stabilization energies (ΔE) and the observed reactivities. These data justify the lack of reactivity of the unsubstituted pyridazinone **1** and the experimental fact that the 5-substituted pyridazinones **3a-c** are more reactive than the corresponding 4-substituted derivatives **2b,c**. There is also a direct

Table III. Stabilization energies (kcal/mol) in cycloadditions of (*E*)-1-methoxybuta-1,3-diene to 2-methylpyridazin-3(2*H*)-ones



A



B

	Pyridazinone					Orientation	
N°	X	Y	ΔE_A[a]	ΔE_B[a]	$\Delta\Delta E$[b]	Predicted	Observed
1	H	H	12.11	12.08	0.03	A	-
2a	$EtSO_2$	H	13.31	13.08	0.23	A	-
2b	CN	H	12.96	12.75	0.21	A	A
2c	CO_2Me	H	12.44	12.19	0.25	A	A
3a	H	$EtSO_2$	13.06	13.22	-0.16	B	B
3b	H	CN	13.03	13.10	-0.07	B	B
3c	H	CO_2Me	12.45	12.58	-0.13	B	B

[a]Approximations A and B lead to adducts of type **9** and **10**, respectively.
[b]$\Delta\Delta E = \Delta E_A - \Delta E_B$

relationship between the differences in the stabilization energies (ΔΔE) for the two possible approximations and the experimental results. Thus, the 4-substituted pyridazinones **2b,c**, where $\Delta E_A > \Delta E_B$, lead regiospecifically to adducts of type **9**, while the 5-substituted pyridazinones **3**, in which $\Delta E_A < \Delta E_B$, afford only cycloadducts of type **10**. As an exception, the lack of reactivity of **2a**, theoretically the most reactive, may be ascribed to the presence of steric effects of relatively bulky groups not considered in the present approach.

In summary, the results reported herein demonstrate that pyridazin-3(2*H*)-ones bearing electron-attracting substituents at the 4- or 5-positions undergo successful cycloadditions to several dienes stopping at the initial Diels-Alder adduct stage without aromatization, to provide partially saturated phthalazin-1(2*H*)-ones in good yields. This method, in principle, could be extended to the construction of other difficultly accessible fused pyridazine systems.

EXPERIMENTAL

Melting points are uncorrected and were determined with a Kofler hot-stage apparatus. Microanalyses were performed with a Perkin-Elmer analyzer model 240 C and with a Heraeus analyzer model CHN-O-Rapid. IR spectra were recorded on Perkin-Elmer models 681 and Infracord 137 E grating spectrophotometers, ν values in cm^{-1}. ^{1}H-NMR spectra were determined on a Varian EM-390 or on a Varian XL-300 spectrometer, in $CDCl_3$ solutions (unless otherwise stated). Chemical shifts are reported in ppm (δ) downfield from TMS. Mass spectra were determined on either a Hitachi-Perkin-Elmer spectrometer model RMU-6MG or a VG-12-250. Silica gel Merck 60 (70-230 mesh), 60 (230-400 mesh) and DC-Alufolien 60 F_{254} were used for conventional, flash column chromatography, and analytical t.l.c., respectively. The eigenvalues and eigenvectors (energies and coefficients) of FMO of pyridazinones have been obtained from CNDO/2 program running on an IBM 360/65 computer, starting from standard bond lengths and dihedral angles. The HOMO and LUMO eigenvalues and eigenvectors for dienes **4**, **5** and **8** and resonance overlap integral (ß) values have been taken from Houk[13] and Alston and Ottenbrite[16]. The starting pyridazinones **1**, **2a-c** and **3a-c** were prepared according to the literature[17].

Cycloaddition of Cyclopentadiene to 2-Methylpyridazin-3(2*H*)-ones. General Procedure.
To a solution of the 2-methylpyridazin-3(2*H*)-ones **1-3** (1 mmol) in chloroform (10 ml) was added freshly distilled cyclopentadiene (330 mg, 5 mmol). The reaction was kept at 0 °C or at room temperature during the period indicated in each case. The solvent was removed under reduced pressure and the residue was analyzed by ^{1}H-NMR.

Attempted Cycloaddition to 1, 2a-c, 3b-c. Starting pyridazinones were recovered unchanged and cycloaddition products were not detected after 15-20 days of reaction.

Cycloaddition to 3a. Reaction time 10 days. The crude product was a 9:1 mixture of **6a** and **6'a** (determined by integration of H-4 signals at δ 7.01 and 7.20 respectively). Yield 70%. The residue was chromatographed (hexane-acetone 4:1) to give adduct **6a** and the starting pyridazinone **3a**.
4a-*exo*-Ethylsulphonyl-2-methyl-*endo*-4a,5,8,8a-tetrahydro-5,8-methanophthalazin-1(2*H*)-one(6a).M.p. 109-110 °C (cyclohexane). Anal. Calcd. for $C_{12}H_{16}N_2O_3S$: C, 53.73; H, 5.97; N, 10.45; S, 11.94. Found: C, 54.00; H, 6.00; N, 10.62; S, 11.60. IR (nujol): 1660, 1585, 1470, 1370, 1140. ^{1}H-NMR: 7.01 (s, 1H, H-4); 6.39 (m, 1H, H-7, $J_{6,7}$=5.6 Hz); 6.27 (m, 1H, H-6); 3.93 (m, 1H, H-5, $J_{5,9}$=1.8 Hz, $J_{5,9'}$=1.8 Hz);

3.66 (m, 1H, H-8, $J_{8,8a}$=3.7 Hz, $J_{8,9}$=1.8 Hz, $J_{8,9'}$=1.8 Hz); 3.42 (d, 1H, H-8a); 3.32 (s, 3H, NCH_3); 2.94 (m, 2H, $SO_2C\underline{H}_2CH_3$); 2.20 (m, 1H, H-9, $J_{9,9'}$=9.4 Hz); 1.47 (m, 1H, H-9'); 1.38 (t, 3H, $SO_2CH_2C\underline{H}_3$, J=8.5 Hz). MS, m/z: 203 (M^+-65), 175, 147, 66 (100).

Cycloaddition of 2,3-dimethylbuta-1,3-diene to 2-methylpyridazin-3(2*H*)-ones. General procedure. To a solution of the pyridazinone **1-3** (1 mmol) in benzene (10 ml) was added 2,3-dimethylbuta-1,3-diene (**5**) (410 mg, 5 mmol). The reaction mixture was refluxed during the period indicated in Table I. The solvent was removed under reduced pressure and the residue was analyzed by ^{1}H-NMR.

Attempted Cycloaddition to 1, 2a-c and 3b. Starting pyridazinones were recovered unchanged and cycloaddition products were not detected after 15 days of reaction.

Cycloaddition to 3a. Reaction time 10 days. Yield 90%. The crude product was chromatographed (benzene-acetone 4:1) to give adduct **7a**.

4a-Ethylsulphonyl-2,6,7-trimethyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one (7a). M.p. 115-116 °C (cyclohexane). Anal. Calcd. for $C_{13}H_{20}N_2O_3S$: C, 54.93; H, 7.04; N, 9.85; S, 11.26. Found: C, 55.12; H, 7.26; N, 9.75; S, 11.40. IR (nujol): 1680, 1620, 1460, 1360, 1140. ^{1}H-NMR: 6.90 (d, 1H, H-4, $J_{4,8a}$=1.6 Hz); 3.38 (s, 3H, NCH_3); 3.14 (m, 1H, H-8a, $J_{5',8a}$=1.6 Hz, $J_{8,8a}$=5.3 Hz, $J_{8',8a}$=5.5 Hz); 2.93 (q, 2H, $SO_2C\underline{H}_2CH_3$, J=8.2 Hz); 2.76 (m, 1H, H-5, $J_{5,5'}$=17.5 Hz); 2.40 (m, 2H, H-5 and H-8, $J_{8,8'}$=17.5 Hz); 2.10 (m, 1H, H-8); 1.70 and 1.66 (2s, 6H, C-6, C-7 CH_3); 1.43 (t, 3H, $SO_2CH_2C\underline{H}_3$). MS, m/z: 284 (M^+), 203, 192, 191 (100), 91, 67.

Cycloaddition to 3c. Reaction time 10 days. Yield 70%. The crude product was chromatographed (benzene-acetone 4:1) to give adduct **7c**.

4a-Methoxycarbonyl-2,6,7-trimethyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one (7c). IR (neat): 1745, 1685, 1620. ^{1}H-NMR: 6.97 (s, 1H, H-4); 3.76 (s, 3H, CO_2CH_3); 3.34 (s, 3H, NCH_3); 3.05 (t, 1H, H-8a, $J_{8,8a}$=6.4 Hz, $J_{8',8a}$=6.5 Hz); 2.47 to 2.15 (m, 4H, H-5 and H-8); 1.62 (2s, 6H, C-6, C-7 CH_3). MS, m/z: 250 (M^+), 191, 169, 91, 82 (100), 67.

Cycloaddition of (*E*)-1-Methoxybuta-1,3-diene to 2-Methylpyridazin-3(2*H*)-ones. General Procedure. To a solution of the pyridazinone **1-3** (1 mmol) in benzene (10 ml) was added (*E*)-1-methoxybuta-1,3-diene (**8**) (252 mg, 3 mmol). The reaction mixture was refluxed during the period indicated in each case in Table II. The solvent and the unreacted diene were removed under reduced pressure and the residue was analyzed by ^{1}H-NMR. Adducts were isolated by chromatography (hexane-ethyl acetate 3:2).

Attempted Cycloaddition to 1 and 2a. Starting pyridazinones were recovered unchanged and cycloaddition products were not detected.

Cycloaddition to 2b. Reaction time 50 days. Total yield 93%. The crude residue was a 2:1 mixture of adducts **9b** and **9'b**. This mixture was chromatographed affording three isomers **9b**, **9'b** and **9''b**, 2-methylphthalazin-1(2*H*)-one (**11**) and the starting pyridazinone **2b**. Isomer **9'b** could not be isolated in pure state and was only obtained as inseparable mixtures with **9b** or **2b**.

8a-Cyano-8-methoxy-2-methyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one.

Isomer **9b**. M.p. 140 °C (benzene-cyclohexane 2:1). Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.27; H, 5.94; N, 19.17. Found: C, 60.02; H, 6.04; N, 19.18. IR (nujol): 2225, 1670, 1630. ^{1}H-NMR: 6.94 (d, 1H, H-4, $J_{4,4a}$=1.8 Hz); 6.04 (m, 2H, H-6 and H-7, $J_{7,8}$=3.3 Hz); 4.06 (m, 1H, H-8, $J_{5,8}$=1.9 Hz); 3.43 (s, 3H, OCH_3); 3.37 (s, 3H, NCH_3); 3.26 (dt, 1H, H-4a, $J_{4a,5}$=6.7 Hz; $J_{4a,5'}$=1.9 Hz); 2.65 (m, 1H, H-5, $J_{5,5'}$=19.0 Hz); 2.51 (m, 1H, H-5'). MS, m/z: 219 (M^+), 204, 161, 135, 120, 107, 84 (100).

Isomer **9'b**. ^{1}H-NMR: 7.23 (d, 1H, H-4, $J_{4,4a}$=3.1 Hz); 5.88 (m, 2H, H-6 and H-7); 4.18 (m, 1H, H-8); 3.51 (s, 3H, OCH_3); 3.44 (s, 3H, NCH_3); 3.27 (m, 1H, H-4a, $J_{4a,5}$=6.2 Hz; $J_{4a,5'}$=6.2 Hz); 2.62 (m, 1H, H-5, $J_{5,5'}$=19.7 Hz); 2.18 (m, 1H, H-5').

Isomer **9''b**. M.p. 106-107 °C (cyclohexane). Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.27; H, 5.94; N, 19.17. Found: C, 60.00; H, 5.90; N, 19.03. IR (nujol): 2215, 1680, 1635. ^{1}H-NMR: 7.10 (d, 1H, H-4, $J_{4,4a}$=1.7 Hz); 6.06 (m, 2H, H-6 and H-7, $J_{7,8}$=4.8 Hz); 4.38 (d, 1H, H-8); 3.50 (s, 3H, OCH_3); 3.45 (s, 3H, NCH_3); 3.26 (m, 1H, H-4a, $J_{4a,5}$=6.9 Hz, $J_{4a,5'}$=7.0 Hz); 2.58 (m, 2H, H-5 and H-5'). MS, m/z: 219 (M^+), 204 (100), 189, 185, 103, 84.

2-Methylphthalazin-1(2*H*)-one (11). M.p. 111-112 °C (cyclohexane). Lit. 111-112 °C[18a]; 105-108 °C[18b]. IR (nujol): 1640, 1610. ^{1}H-NMR: 8.45 (m, 1H arom.); 8.15 (s, 1H, H-4); 7.75 (m, 3H arom.); 3.8 (s, 3H, NCH_3). MS, m/z: 160 (M^+), 132 (100), 104, 89.

Assays of Isomerization of Adduct 9b.

(a) To a solution of adduct **9b** (50 mg) in methanol (1 ml) was added a catalytical amount of sodium methoxide and the mixture was kept at room temperature for 4 days. The solvent was removed, the residue was taken in chloroform and was washed with water. After drying ($MgSO_4$), the crude product, analyzed by ^{1}H-NMR, contained 2-methylphthalazin-1(2*H*)-one (**11**) as the only identifiable compound.

(b) To a solution of adduct **9b** (50 mg) in chloroform (1 ml) were added 3 drops of a 20% solution of boron trifluoride etherate in chloroform and the mixture was kept at room temperature for 3 days. The reaction mixture was washed with water and, after drying ($MgSO_4$), the solvent was removed. The residue was analyzed by ^{1}H-NMR and the isomer **9''b** was detected as the sole product.

Assays of Cycloreversion of 9b and 9''b.

(a) A solution of adduct **9b** (50 mg) in xylene (4 ml) was refluxed for 30 hours. The solvent was removed and the residue was analyzed by ^{1}H-NMR. Pyridazinone **2b** was found as the only product.

(b) A solution of isomer **9''b** (25 mg) in xylene (4 ml) was heated under reflux for 30 hours. The solvent was removed and the residue was analyzed by ^{1}H-NMR. Only the starting compound **9''b** was recovered.

Cycloaddition to 2c. Reaction time 40 days. Total yield 80%. The crude residue was a 1:1 mixture of adducts **9c** and **9'c**.

8-Methoxy-8a-methoxycarbonyl-2-methyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one.

Isomer **9c**. M.p. 110-111 °C (cyclohexane). Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.14; H, 6.34; N, 11.11. Found: C, 57.43; H, 6.30; N, 10.76. IR (nujol): 1740, 1660, 1630. ^{1}H-NMR: 6.95 (d, 1H, H-4, $J_{4,4a}$=1.8 Hz); 6.07 (m, 1H, H-7, $J_{5,7}$=1.5 Hz, $J_{5',7}$=1.3 Hz, $J_{6,7}$=10.4 Hz, $J_{7,8}$=4.2 Hz); 5.85 (m, 1H, H-6, $J_{5,6}$=4.2 Hz, $J_{5',6}$=1.9 Hz); 4.38 (d,1H, H-8); 3.79 (s, 3H, CO_2CH_3); 3.53 (m, 1H, H-4a, $J_{4a,5}$=1.9 Hz, $J_{4a,5'}$=6.4 Hz); 3.39 (s, 3H, OCH_3); 3.35 (s, 3H, NCH_3); 2.36 (m, 1H, H-5, $J_{5,5'}$=18.8 Hz); 2.19 (m, 1H, H-5'). MS, m/z: 252 (M^+), 237, 193, 161, 84 (100).

Isomer **9'c**. M.p. 105-106 °C (cyclohexane). Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.14; H, 6.34; N, 11.11. Found: C, 57.52; H, 6.39; N, 10.79. IR (nujol): 1740, 1680, 1630. ^{1}H-NMR: 7.49 (d, 1H, H-4, $J_{4,4a}$=4.6 Hz); 6.09 (m, 1H, H-7, $J_{6,7}$=10.0 Hz, $J_{7,8}$=4.8 Hz); 5.85 (m, 1H, H-6, $J_{5,6}$=4.7 Hz); 4.59 (d,1H, H-8); 3.76 (s, 3H, CO_2CH_3); 3.38 (s, 3H, OCH_3); 3.32 (s, 3H, NCH_3); 3.24 (m, 1H, H-4a, $J_{4a,5}$=6.5 Hz, $J_{4a,5'}$=6.9 Hz); 2.44 (m, 1H, H-5, $J_{5,5'}$=17.5 Hz); 1.92 (m, 1H, H-5'). MS, m/z: 252 (M^+), 237, 193 (100), 169, 161, 137, 84.

Cycloaddition to 3a. Reaction time 4 days. Yield 90%. The crude product was chromatographed to give a 9:1 mixture of adduct **10a** and 2-methylphthalazin-1(2*H*)-one (**11**).

4a-Ethylsulphonyl-5-methoxy-2-methyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one (10a). M.p. 131 - 132 °C (cyclohexane); Anal. Calcd. for $C_{12}H_{18}N_2O_4S$: C, 50.34; H, 6.29; N, 9.79; S, 11.19. Found: C, 50.59; H, 6.61; N, 9.70; S, 11.44. IR (nujol): 1690, 1600, 1460, 1350, 1130. ^{1}H-NMR: 7.11 (d, 1H, H-4, $J_{4,8a}$=1.8 Hz); 5.84 (m, 2H, H-6 and H-7, $J_{5,6}$=2.2 Hz, $J_{7,8}$=1.5 Hz); 4.43 (m, 1H, H-5, $J_{5,8}$=1.4 Hz, $J_{5,8'}$=1.5 Hz); 3.50 (s, 3H, OCH_3); 3.35 (s, 3H, NCH_3); 3.25 (m, 1H, H-8a, $J_{8,8a}$=8.0 Hz; $J_{8',8a}$=9.3 Hz); 3.25 (q, 2H, $SO_2C\underline{H}_2CH_3$, J=8.2 Hz); 2.66 (m, 1H, H-8, $J_{8,8'}$=19 Hz); 2.09 (m, 1H, H-8); 1.43 (t, 3H, $SO_2CH_2C\underline{H}_3$). MS, m/z: 286 (M^+), 202, 194, 193 (100), 161, 133, 84.

Cycloaddition to 3b. Reaction time 2 days. The crude residue was a 1.4:1 mixture of adducts **10b** and **10'b**. Total yield 95%.

4a-Cyano-5-methoxy-2-methyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one.

Isomer **10b**. IR (neat): 2220, 1680, 1625. ^{1}H-NMR: 7.35 (s, 1H, H-4); 5.90 (m, 1H, H-7, $J_{6,7}$=10.5 Hz, $J_{7,8}$=3.5 Hz, $J_{7,8'}$=3.5 Hz); 5.79 (m, 1H, H-6, $J_{6,8}$=2.1 Hz, $J_{6,8'}$=2.1 Hz); 3.95 (m, 1H, H-5); 3.48 (s, 3H, OCH_3); 3.40 (s, 3H, NCH_3); 3.05 (m, 1H, H-8a, $J_{8,8a}$=1.9 Hz; $J_{8',8a}$=6.7 Hz); 2.98 (m, 1H, H-8, $J_{8,8'}$=18.9 Hz); 2.46 (m, 1H, H-8'). MS, m/z: 219 (M^+), 187, 135, 84 (100).

Isomer **10'b**. M.p. 99-100 °C (cyclohexane). Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.27; H, 5.94; N, 19.17. Found: C, 59.97; H, 6.00; N, 19.10. IR (nujol): 2225, 1670, 1630. ^{1}H-NMR: 7.19 (s, 1H, H-4); 5.93 (m, 1H, H-7, $J_{5,7}$=1.3 Hz, $J_{6,7}$=10.5 Hz, $J_{7,8}$=3.5 Hz, $J_{7,8'}$=3.5 Hz); 5.85 (m, 1H, H-6, $J_{5,6}$=2.6 Hz, $J_{6,8}$=2.1 Hz, $J_{6,8'}$=2.1 Hz); 4.09 (m, 1H, H-5, $J_{5,8}$=1.8 Hz, $J_{5,8'}$=1.8 Hz); 3.53 (s, 3H, OCH_3); 3.38 (s, 3H, NCH_3); 3.04 (t, 1H, H-8a, $J_{8,8a}$=7.3 Hz, $J_{8',8a}$=7.3 Hz); 2.40 (m, 2H, H-8 and H-8'). MS, m/z: 161 (M^+-58), 160, 136, 104, 84 (100).

Cycloaddition to 3c. Reaction time 4 days. The crude residue was a 3:1 mixture of adducts **10c** and **10'c**. Total yield 95%.

5-Methoxy-4a-methoxycarbonyl-2-methyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one.

Isomer **10c**. M.p. 103-104 °C (cyclohexane). Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.14; H, 6.34; N, 11.11. Found: C, 56.99; H, 6.57; N, 11.02. IR (nujol): 1745, 1685, 1625. ^{1}H-NMR: 6.80 (d, 1H, H-4, $J_{4,8a}$=1.5 Hz); 6.05 (m, 2H, H-6 and H-7, $J_{5,6}$=3.6 Hz, $J_{7,8}$=3.5 Hz, $J_{7,8'}$=1.5 Hz); 4.04 (dd, 1H, H-5, $J_{5,8'}$=1.5 Hz); 3.77 (s, 3H, CO_2CH_3); 3.36 (s, 3H, OCH_3); 3.30 (s, 3H, NCH_3); 3.19 (m, 1H, H-8a, $J_{8,8a}$=7.6 Hz, $J_{8',8a}$=9.9 Hz); 2.52 (m, 1H, H-8, $J_{8,8'}$=19 Hz); 1.94 (m, 1H, H-8'). MS, m/z: 221 (M^+-31), 193, 168, 161, 140, 109, 84 (100).

Isomer **10'c**. IR (neat): 1740, 1680, 1610. ^{1}H-NMR: 7.13 (s, 1H, H-4); 5.78 (m, 2H, H-6 and H-7, $J_{6,8}$=1.8 Hz, $J_{6,8'}$=1.8 Hz, $J_{7,8}$=1.8 Hz, $J_{7,8'}$=1.8 Hz); 4.10 (t, 1H, H-5, $J_{5,8}$=2.0 Hz, $J_{5,8'}$=2.0 Hz); 3.70 (s, 3H, CO_2CH_3); 3.32 (s, 3H, OCH_3); 3.25 (s, 3H, NCH_3); 3.07 (t, 1H, H-8a, $J_{8,8a}$=7.5 Hz, $J_{8',8a}$=7.5 Hz); 2.28 (m, 2H, H-8 and H-8', $J_{8,8'}$=18 Hz). MS, m/z: 252 (M^+), 193, 168, 161, 133, 104, 91, 84 (100).

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10. Consistent with this assignment, in the ^{1}H-NMR spectrum of the crude reaction mixture, the *N*-methyl protons for the major *endo*-isomer (δ 3.32) are shielded relative to those of the minor *exo*-isomer (δ 3.42); the same order is observed for the H-4 protons, major δ 7.01, minor δ 7.20.
11. A similar isomerization of **9'b** was not attempted because of the difficulty of obtaining pure samples of this isomer.
12. The isomerization of the initial *cis* adducts to the presumably more stable *trans* fused isomers is precedented[2c,d] in related adducts of other heterocyclic dienophiles. In agreement with this structural assignment are the values of the coupling constants of H-4a in **9"c**, noticeably different from those of **9b** and **9'b** (see Table II), which suggest a different stereochemistry.
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