Diels-Alder Adducts of a Spirocyclopentenotriazoloazodienophile. Assignment of their ^1H and ^{13}C NMR Spectra

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Dedicated to the memory of Professor Nicholas Alexandrou

1-Phenyl-cyclopenteno[1,2-*d*]-1,2,3-triazolo-5-spiro-4'-[perhydropyrazolino-3',5'-dione] (**5**) afforded *in situ*, by oxidation with lead tetraacetate, the corresponding cyclopentenotriazolo-spiropyrazolodione **6**, which was trapped with dienes giving the hetero-Diels-Alder adducts **10-12** in good yields. The Diels-Alder reactions were examined on the basis of AM1 MO calculations. Total assignment of the ^1H- and ^{13}C-nmr chemical shifts as well as the relative configuration of these adducts was accomplished with the help of 2D (^1H-^1H COSY, ^1H-^1H NOESY, ^1H-^{13}C XHCORR, ^1H-^{13}C COLOC) and NOE difference spectroscopy. The structures of compounds **11a** and **11b** were also examined by molecular modeling.

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Electron poor *cis*-azo compounds are known to be extremely reactive dienophiles in the Diels-Alder reaction and lead to the formation of pyridazine ring systems when allowed to react with dienes [1]. Recently, a 1,2,3-triazolopyridazinedione was synthesized and its dienophilic properties were examined [2]. The present investigation was undertaken as a further study on the 1,2,3-triazole chemistry and also as an examination of the dienophilic properties of the first, to our knowledge, spiro-dienophile.

The parent compound 1-phenyl-cyclopenteno[1,2-*d*]-1,2,3-triazolo-5-spiro-4'-[perhydropyrazolino-3',5'-dione] (**5**) was prepared in good yield with a sequence of reactions shown in Scheme 1. By heating a solution of diethyl malonate and 4,5-bisbromomethyl-1-phenyl-1,2,3-triazole (**1**) in dimethylformamide [3,4] in the presence of potassium carbonate, 4',4'-biscarboethoxy-1-phenyl-cyclopenteno-

Scheme 1

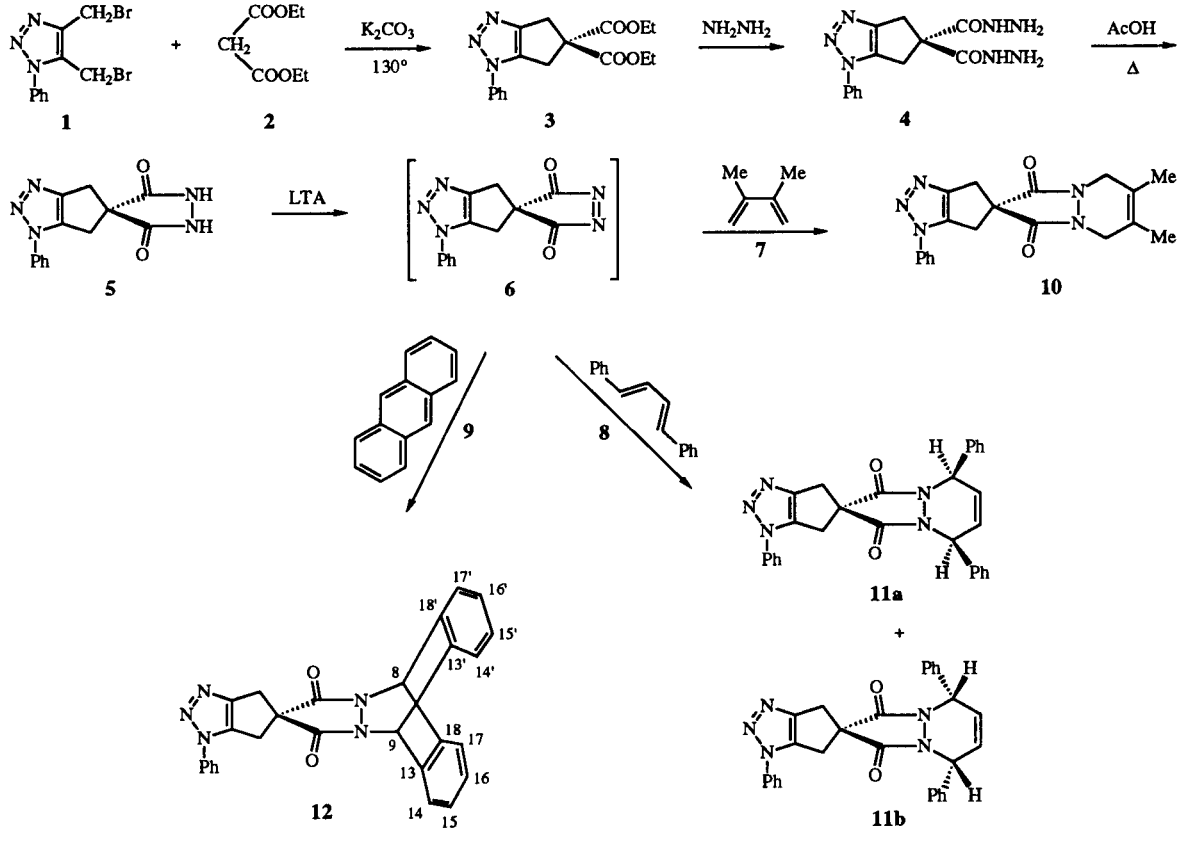

Table 1

Physical, Spectral and Analytical Data of Compounds **10**, **11** and **12**

Compound	Yield %	Mp °C	IR ν, cm^{-1} (C=O)	^{1}H-NMR $CDCl_3$ (δ ppm)	MS m/z (% Rel. Int.)	Formula MW	Elemental Analysis % Calcd./Found C	H	N
10	29	124-127	1735 w 1680 s	1.77 (6H, s), 3.31 (2H, s), 3.41 (2H, s), 4.04 (4H, s), 7.37-7.44 (1H, m), 7.47-7.54 (2H, m), 7.62-7.68 (2H, m)	349 ($M^{+\cdot}$, 94), 321 (26), 210 (16), 143 (75), 129 (100)	$C_{19}H_{19}N_5O_2$ 349.397	65.32 65.28	5.48 5.58	20.04 19.98
11a	26	202-204	1740 w 1685 s	2.89 (2H, s), 3.37 (2H, s), 5.61 (2H, d, J = 1.64 Hz), 6.00 (2H, d, J = 1.64 Hz), 7.36-7.51 (13H, m), 7.61-7.64 (2H, m)	473 ($M^{+\cdot}$, 100), 445 (27), 206 (77), 143 (80)	$C_{29}H_{23}N_5O_2$ 473.541	73.56 73.42	4.90 5.02	14.79 14.63
11b	10	256-258	1740 w 1685 s	3.04 (2H, s), 3.30 (2H, s), 5.65 (2H, d, J = 1.61 Hz), 6.02 (2H, d, J = 1.61 Hz), 7.34-7.52 (15H, m)	473 ($M^{+\cdot}$, 16), 206 (31), 143 (100)	$C_{29}H_{23}N_5O_2$ 473.541	73.56 73.68	4.90 4.83	14.79 14.63
12	9	>310	1740 w 1685 s	3.19 (4H, s), 6.39 (2H, s), 7.27-7.39 (5H, m), 7.41-7.50 (6H, m), 7.56-7.60 (2H, m),	445 ($M^{+\cdot}$, 25), 416 (8), 177 (100), 143 (51)	$C_{27}H_{19}N_5O_2$ 445.486	72.80 72.69	4.30 4.38	15.72 15.57

[1,2-*d*]-1,2,3-triazole (**3**) was isolated in 30% yield, after column chromatography. By refluxing the diester **3** with hydrazine hydrate the bishydrazide **4** was obtained in 90% yield, which was transformed in 91% yield to the spirohydrazide **5** by refluxing in acetic acid. The oxidation of **5** to the corresponding pyrazoledione **6** was carried out with lead tetraacetate in dichloromethane in the presence of dienes **7, 8** and **9**. All these reactions afforded the expected [5] hetero-Diels-Alder adducts **10**, **11a,b** and **12** in moderate yields, which provide evidence for the generation of **6** (Scheme 1). In the case of the reaction of **6** with (*E,E*)-1,4-diphenylbutadiene (**8**) two stereoisomers **11a** and **11b** were formed, which were separated by column chromatography and characterized. The presence of a phenyl group in the triazole ring of **6** renders the compound asymmetrical and therefore upon reaction with **8** two stereoisomeric cycloadducts can be formed, **11a** with the two pyridazine *cis*-phenyl groups and the triazole phenyl group on the opposite site of the plane of pyridazinopyrazole ring and **11b** with the two pyridazine phenyls on the same site with respect to the triazole phenyl group.

All cycloadducts **10-12** exhibit in the ir spectra two carbonyl absorptions: a weak one at 1735-1740 cm^{-1} and a strong one at 1680-1685 cm^{-1}. In the ^{1}H nmr they give resonance signals of expected δ values (Table 1) and in the mass spectra show ion peaks corresponding to retro-Diels-Alder ion fragmentations.

Theoretical AM1 calculations [6] performed on the addition of the spiroazodienophile **6** to 2,3-dimethyl-1,3-butadiene (**7**) and (*E,E*)-1,4-diphenyl-1,3-butadiene (**8**) showed that the reaction is $HOMO_{diene}$ controlled, since this process leads to a smaller E_{LUMO}-E_{HOMO} energy difference ΔE (Figure 1). This energy difference $\Delta E = E_{LUMO\ (dienophile)} - E_{HOMO\ (diene)}$ for 2,3-dimethyl- and (*E,E*)-1,4-diphenyl-1,3-butadiene is 7.32 and 6.69 eV, respectively. Comparing these ΔE values it is concluded that the diphenyl derivative **8** should be slightly more reactive than the dimethyl one **7** in accordance with experimental results, where **11a,b** were isolated in 36% total yield whereas **10** was isolated in 29% yield. In addition, the dienophilic character of compounds **6** and **13** was compared and it was found, to be in agreement with the experimental results [2], that the dienophilic character of **6** is smaller than that of **13**, because E_{LUMO} (**13**) < E_{LUMO} (**6**).

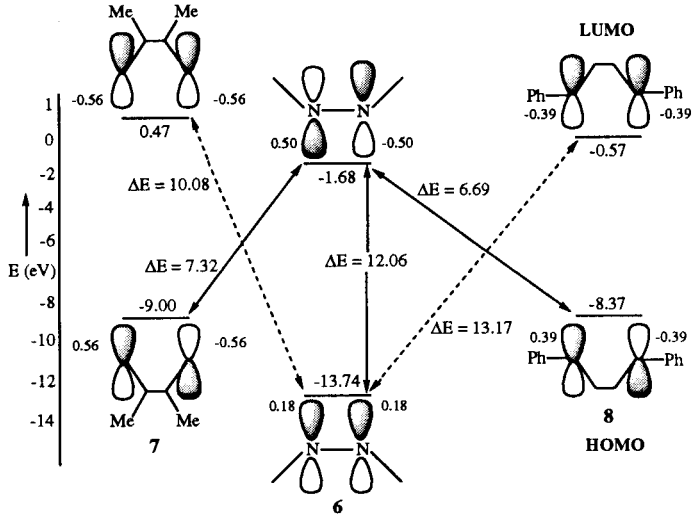

Figure 1. HOMO-LUMO interactions between the dienophile **6** and the dienes 2,3-dimethyl-1,3-butadiene (**7**) and (*E,E,*)-1,4-diphenyl-1,3-butadiene (**8**) calculated by AM1 method.

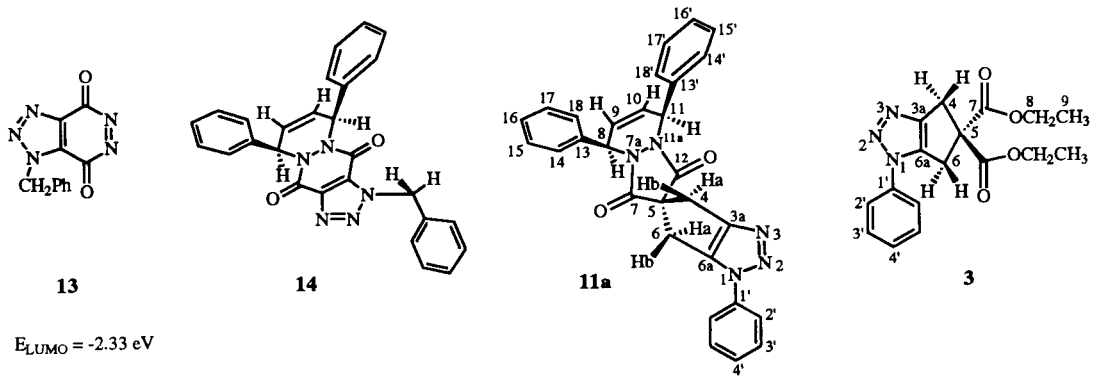

Figure 2. Structures of compounds **13** (with E_{LUMO}), **14**, **11a**, **3** and the numbering used

The structures of **11a** and **11b** were modeled in order to visualize the low energy conformations of these isomers and assist the assignment of their proton and carbon nmr spectra. To test the reliability of the molecular modeling package [7] the conformation of an analogous product **14** with the known crystal structure [2] was also investigated. For simplicity reasons and due to the resemblance of the tetrahydropyridazine segment in compounds **11a**, **11b** and **14** the same numbering was used. The absolute numbering of atoms C_8-C_{11} and C_4-C_6 in isomer **11b** must be reversed. The calculated conformation of **14** (Figure 2) is in very good agreement with the experimental results. Consequently, we proceeded to the study of the isomers **11a** and **11b** and the results are given in Table 2.

Table 2

Calculated Data for the Conformation of Compounds **14** and **11a,b**

	14	**11a**	**11b**
Dihedral angles (Deg)			
11a-7a-8-13 [a]	-120°	-114°	-134°
7a-11a-11-13'	122°	112°	132°
7a-8-13-14	-118°	-99°	-127°
11a-11-13'-14'	152°	154°	127°
7a-8-9-10	-3°	-10°	10°
13-8-11-13'	-0.6°	-0.8°	0.4°
H_8-C_8-C_9-H_9		51°	72°
Interatomic distances (Ang)			
H_{4a}-$H_{14'}$		6.5	6.0
H_{4a}-$H_{18'}$		3.2	3.6
H_{4a}-H_{18}		5.6	4.2
H_{4b}-H_{14}		5.4	6.3
H_{4b}-H_{18}		6.7	4.1
H_{4b}-$H_{18'}$		5.6	4.6
H_{6a}-$H_{14'}$		7.0	5.8
H_{6a}-$H_{18'}$		5.4	5.9
H_{6a}-H_{18}		7.0	6.3
H_{6b}-H_{14}		5.4	6.0
H_{6b}-H_{18}		6.7	6.0
H_{6b}-$H_{18'}$		5.6	6.4
H_{18} - $H_{18'}$	2.3	2.5	2.6

[a] For the numbering see compound **11a** in Figure 2 (see also in text for absolute numbering of compound **11b**).

In adducts **10-12** the presence of the two amide nitrogen atoms with increased sp^2 character renders the pyrazolinedione ring planar (plane 1). For the compound **11a** a dihedral angle of about -10° is formed between plane 1 and plane $C_8C_9C_{10}$, that is the atoms C_9 and C_{10} are below the plane 1, whereas for compound **11b** the corresponding dihedral angle is about 13°. The molecular modeling study reveals that in structure **11b** the Van der Waals interactions between N_1 phenyl and C_8-C_{11} phenyls cause the last two phenyls to adopt a pseudoequatorial conformation. As a result the C_8 and C_{11} phenyl groups are calculated to be almost parallel to each other and almost perpendicular to the plane 1. The protons of C_6 methylene group in compound **11b** are closer to these phenyl groups than the protons at C_4 methylene group and the reverse is held for compound **11a**. In addition, compound **11a** has a similar conformation with compound **14**, with the two phenyl groups in the right distance and direction to cause a bigger upfield shielding in the C_4 methylene protons compared to that for the corresponding protons in **11b**.

In the ^1H nmr spectrum of the slower moving tlc isomer a multiplet was observed at 7.34-7.52 ppm for the 15 aromatic protons of the three phenyl groups, whereas in the faster moving isomer in addition to the multiplet at 7.36-7.51 (13H) a second two protons multiplet at 7.61-7.64 was observed. This multiplet was assigned to the two *o*-protons of the N_1 phenyl. By means of NOE difference experiment the methylene protons at 3.37 ppm were unambiguously assigned to the C_6 methylene group, because a positive NOE (+4%) was measured for the signal at 7.61-7.64 ppm, when the singlet peak at 3.37 ppm was irradiated. The NOESY experiment also showed a weak cross peak between these two proton groups. The singlet peak at 2.89 ppm was therefore assigned to the C_4 methylene protons. In compounds **10** and **11a,b** a bigger upfield shift was observed (Table 3) for the C_4 than the C_6 methylene protons. The biggest shift difference ($\Delta\delta$ = 0.42 ppm) was observed for the faster moving isomer. Consequently, the structure **11a** could be assigned to this isomer, where the C_8

Table 3

^{13}C and ^{1}H NMR Chemical Shifts of Compounds **3**, **10**, **11a,b** and **12** [a]

Atom	Compound **3**	**10**	**11a**	**11b**	**12**
C_{3a}	152.6 [b]	153.1	151.6	153.7	152.7
C_4	32.0 (3.54)	32.1 (3.31)	32.4 (2.89)	31.9 (3.04)	31.7 (3.19)
C_5	66.2	57.5	57.7	57.3	57.4
C_6	31.4 (3.66)	31.3 (3.41)	29.0 (3.37)	30.1 (3.30)	30.0 (3.19)
C_{6a}	136.9(7) [b,c]	137.5	137.8	136.2	137.3
C_7	170.3	172.0	172.3	172.1	170.6
C_8	62.5 (4.25)	46.2 (4.04)	57.4 (5.61)	57.3 (5.65)	62.5 (6.39)
C_9	14.0 (1.26)	119.9(9) [d]	124.3 (6.00)	124.2 (6.02)	
$C_{1'}$	136.9(8) [c,e]	136.9	136.7	136.6	136.8
$C_{2'}$	119.9	120.0(2) [d] (7.65) [f]	119.5 (7.62) [f]	119.9 (7.50) [f]	120.0 (7.58) [f]
$C_{3'}$	129.8	129.7 (7.50) [f]	129.5	129.5	129.7 (7.46) [f]
$C_{4'}$	128.3	128.4 (7.40) [f]	128.2	128.2	128.3 (7.33) [f]
CH_3	16.1 (1.77)				
C_{13}			137.2	137.4	137.5(8), 137.6(3) [g]
C_{14}			127.2	127.4	124.0, 124.2 (7.46)
C_{15}			128.9	128.8	128.4, 128.5 (7.33)
C_{16}			128.6	128.5	

[a] Chemical shift values are given in ppm downfield from internal TMS in deuteriochloroform solutions. The values in parentheses are the ^{1}H data. [b] Reference 8. [c] May be interchanged. [d] May be interchanged. [e] Reference 9 [f]. Approximately in the middle of the multiplet. [g] Reference 10.

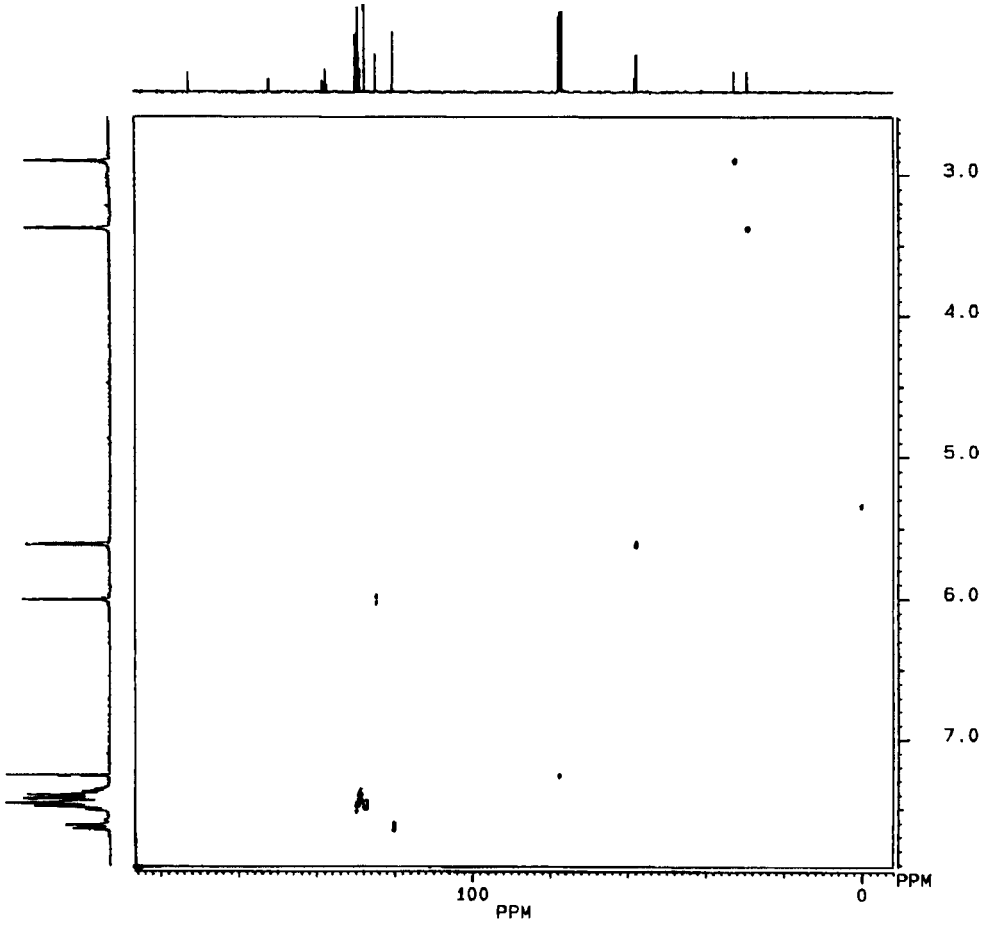

Figure 3. The Heteronuclear COSY of adduct **11a** (297°K) in $CDCl_3$.

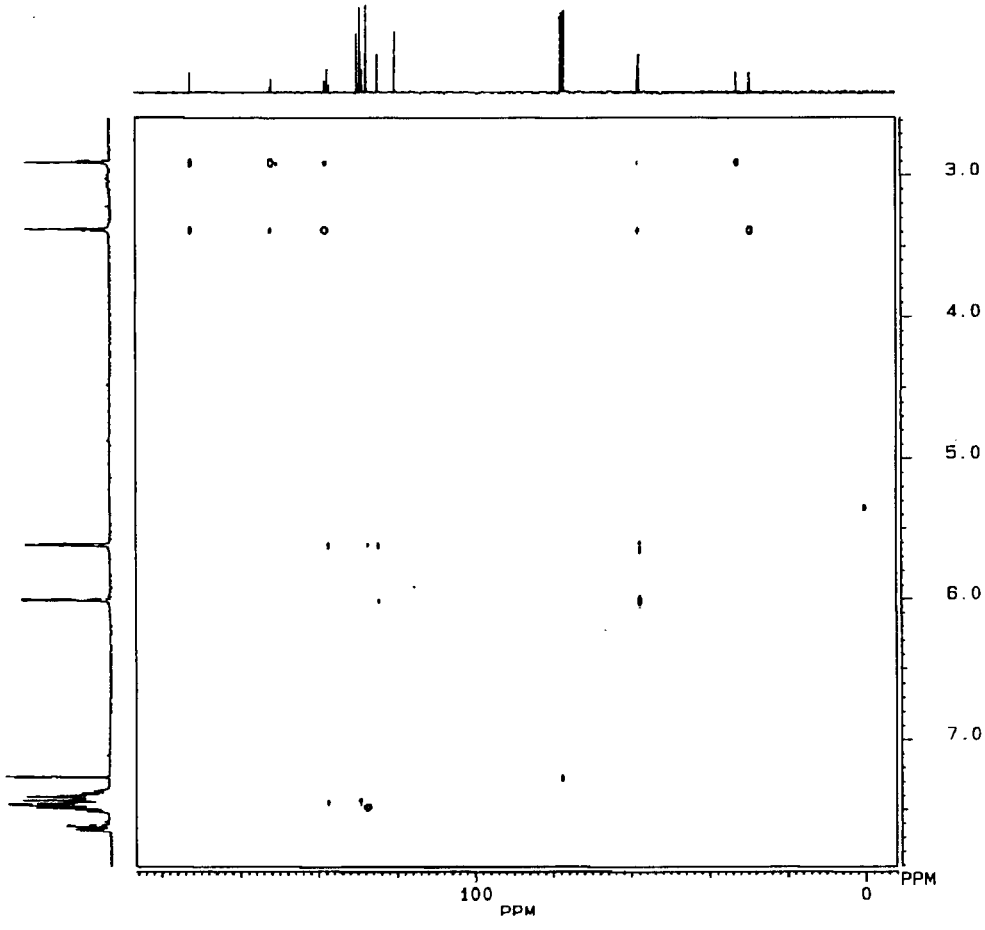

Figure 4. The C-H COSY by long range coupling (COLOC) of adduct **11a** (297°K) in $CDCl_3$.

and C_{11} phenyls are closer to C_4 and hence structure **11b** could be assigned to the slower moving isomer. By analogy the two singlets at 3.04 and 3.30 ppm observed for **11b** were attributed to the C_4 and C_6 methylene protons, respectively. In compound **12** the C_4 and C_6 methylene protons have the same chemical shifts of 3.19 ppm, probably due to the fast oscillations of the two fused phenyls. The carbon resonances of these phenyls are six (three pairs) and the assignment is uncertain. Most probably, for symmetry reasons, each pair of values belongs to the pairs C_{13}-$C_{13'}$ and C_{18}-$C_{18'}$, C_{14}-$C_{14'}$ and C_{17}-$C_{17'}$, C_{15}-$C_{15'}$ and C_{16}-$C_{16'}$.

The complete assignment of all resonances in ^1H and ^{13}C nmr spectra was achieved using the data of the simpler compound **3** and the data from ^1H-^1H COSY, ^1H-^1H NOESY, ^1H-^{13}C COSY and COLOC 2D spectra. The results are presented in Table 3.

The assignment for compound **3** was made according to the literature [8,9]. The data obtained for compound **11a** from the heteronuclear COSY (Figure 3) showed a cross peak between the multiplet at 7.61-7.64 ppm (^1H) and the peak at 119.9 ppm (^{13}C) in agreement with the assignment for **3**. The correlation of the carbon resonating at 124.3 ppm with the proton peak at 6.00 ppm led to the assignment of C_9-H moiety. Therefore the cross peak between resonances at 5.61 ppm (^1H) and 57.4 (^{13}C) was due to the C_8-H unit, whereas for C_4 and C_6 methylene groups the pairs at 2.89 ppm-32.4 ppm and at 3.37 ppm-29.0 ppm were assigned. The rest of protonated aromatic carbons were assigned according to their chemical shifts as well as their relative intensities. The long range correlations observed in the COLOC spectrum provided additional evidence for the chain connection especially for quaternary carbons (Figure 4). The C_4 and C_6 methylene protons are connected to carbonyl carbon at 172.3 ppm, to C_{3a} at 151.6 ppm, to C_{6a} at 137.8 ppm and to C_5 at 57.7 ppm. The C_9 proton is connected to C_8 at 57.4 ppm and the C_8 proton is connected to C_9 at 124.3 ppm, to the peak at 137.2 ppm assigned to C_{13} and to the peak at 127.2 ppm assigned to C_{14}. The rest of the aromatic carbons are easily assigned according to their intensity and chemical shifts (Table 3). From the H-C COSY of **11b** we could deduce that the carbon signal at 119.9 ppm ($C_{2'}$) is connected to a proton multiplet at 7.47-7.52 ppm assigned to $H_{2'}$. Accordingly, the signals for the spectra of the other compounds are assigned.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The nmr spectra, reported in δ units, were recorded at 297°K on a Bruker AM-300 spectrometer operating at 300 MHz for protons using tetramethylsilane as internal standard. The ir spectra were measured with a Perkin-Elmer 297 spectrometer and the mass spectra were measured with a VG TS-250 double focusing spectrometer in the EI mode (70 eV). Elemental microanalyses were performed with a Perkin-Elmer model 240B CHN analyser.

The theoretical calculations were carried out using version 6 of the MOPAC package [11] on a DEC 2000 workstation. The molecular geometries were fully optimised using the AM1 method (with PRECISE option) by minimizing the energy with respect to all internal coordinates.

4,4'-Biscarboethoxy-1-phenyl-cyclopenteno[1,2-*d*]-1,2,3-triazole (**3**).

To a solution of 4,5-bisbromomethyl-1-phenyl-1,2,3-triazole (**1**) [12] (165 mg, 0.5 mmole) and diethyl malonate (80 mg, 0.5 mmole) in dry dimethylformamide (4 ml) anhydrous potassium carbonate (276 mg, 2 mmoles) was added and the mixture was heated at 130° for 15 minutes. Addition of water to the reaction mixture was followed by extraction with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated and the residue was chromatographed (silica gel, petroleum ether 3:1) to give the triazole derivative **3** (50 mg, 30%), mp 89-92° (dichloromethane-ether); ir (nujol): 1730 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.26 (t, 6H, J = 7 Hz), 3.54 (s, 2H), 3.66 (s, 2H), 4.25 (q, 4H, J = 7 Hz), 7.33-7.85 (m, 5H); ms: m/z 329 (22, $M^{+\cdot}$), 256 (11), 228 (58), 154 (49), 129 (100).

Anal. Calcd. for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.82; N, 12.76. Found: C, 62.10; H, 5.98; N, 12.95.

Bishydrazide of 4',4'-Biscarboxy-1-phenylcyclopenteno[1,2-*d*]-1,2,3-triazole (**4**).

A mixture of the bisester **3** (658 mg, 2.0 mmoles) and hydrazine hydrate (1.0 g, 20 mmoles) was refluxed for 20 hours. Upon cooling, white crystals of the bishydrazide **4** (542 mg, 90%) were precipitated, filtered and washed with ether, mp 206-208°; ir (nujol): 3310 (NH), 1640 (C=O) cm^{-1} ; ms: m/z 301 (-, $M^{+\cdot}$), 269 (6), 143 (7), 129 (100).

Anal. Calcd. for $C_{13}H_{15}N_7O_2$: C, 51.82; H, 5.02; N, 32.54. Found: C, 51.88; H, 5.09; N, 32.63.

1-Phenylcyclopenteno[1,2-*d*]-1,2,3-triazolo-5-spiro-4'-[perhydropyrazolino-3',5'-dione] (**5**).

The bishydrazide **4** (150 mg, 0.5 mmole) was dissolved in glacial acetic acid (2 ml) and was refluxed for 5 minutes. Upon addition of petroleum ether the spirodione **5** was precipitated, filtered and washed with ether (122 mg, 91%), mp >300°; ir (nujol): 3190 (NH), 1665 (C=O) cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 57.88; H, 4.08; N, 25.88.

Oxidation of **6** with Lead Tetraacetate in the Presence of Dienes. General Procedure.

To a suspension of **6** (269 mg, 1 mmole) and excess of the corresponding diene (1.5 mmoles) in dichloromethane (10 ml) a solution of lead tetraacetate (664 mg, 1.5 mmoles) in the same solvent (5 ml) was added gradually by cooling. The mixture was stirred for 24 hours, filtered from the precipitated lead oxides and washed with 10% aqueous sodium thiosulfate, with 5% sodium bicarbonate and finally with water. It was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The cycloadducts **10-12** were separated from the mixture by column chromatography using silica gel and light petroleum-ethyl acetate (1:1) as eluant. Recrystallization from dichloromethane-ether afforded pure samples of the compounds. Melting points and other spectral data are given in Table 1.

REFERENCES AND NOTES

+ This is the last publication of the late Nicholas Alexandrou published posthumously, the balance of the research being completed by his colleagues.

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