Cycloaddition Reactions of 2,3-Dihydro-1*H*-1,4-diazepines with Nitrile Oxides and Imines. Synthesis of bis[1,2,4]Oxadiazolo- and bis[1,2,4]Triazolo[1,4]diazepine Derivatives [1]

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New heterotricyclic systems, 6,10a,11,11a-tetrahydro-5*H*-bis[1,2,4]oxadiazolo[4,5-*d*:5',4'-*g*][1,4]diazepines **6,7,9-11** and 5,6,10,10a,11,11a-hexahydro-1*H*-bis[1,2,4]triazolo[4,3-*d*:3',4'-*g*][1,4]diazepines **8,12** have been obtained by double site- and regio-specific 1,3-dipolar cycloaddition of mesitylnitrile oxide (**1**) or diphenylnitrile imine (**2**) to 5,7-disubstituted 2,3-dihydro-1*H*-1,4-diazepines **3-5**. The structure of the synthesized bis-adducts **6-12** shows that the hetero double bonds are much more reactive than the olefinic ones in the dipolarophiles under study. No evidence for the formation of mono-adducts was obtained.

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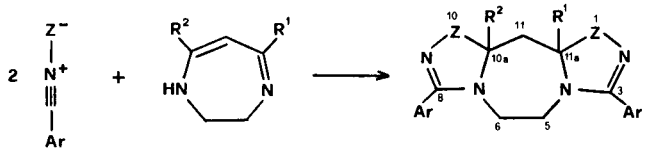
2,3-Dihydro-1*H*-1,4-diazepines, which are easily obtained in preparative amounts by the condensation of ethylenediamine with 1,3-diketones [2], are useful synthons for the construction of polycyclic systems, since their double bonds can undergo various cycloaddition reactions. Two of us have shown that some 3*H*-1,5-benzodiazepines, structurally related to **3-5**, readily react with diphenylnitrile imine to produce 3a,4,4a,5-tetrahydro-3*H*-bis[1,2,4]triazolo-[4,3-*a*:3',4'-*d*][1,5]benzodiazepines [3]. It therefore seemed appropriate to investigate the reactivity of some 5,7-disubstituted 2,3-dihydro-1*H*-1,4-diazepines **3-5** toward nitrile imines and oxides, which undergo 1,3-dipolar cycloaddition reactions with alkenes as well with Schiff bases [4,5].

Initially we chose mesitylnitrile oxide (**1**) [6] as the dipole since it does not dimerize to the corresponding furoxane at room temperature. Reaction with the 1,4-diazepines **3-5** gave satisfactory yields of the 2:1 adducts **6,7,9-11** the structures of which were determined mainly through ^1H and ^{13}C nmr spectroscopy (Tables I and II). These bis-adducts formally arise from a double regiospecific 1,3-dipolar cycloaddition of the oxide onto the C,N double bonds of the diimine tautomeric form of **3-5**. This chemical behaviour is consistent with the high site-selectivity generally observed in 1,3-dipolar cycloadditions involving 1-azabutadienes [4]. Moreover, in the reaction of both **3** and **4** with **1**, in each case both possible 2:1 cycloadduct diastereomers were obtained, arising from the double cycloaddition of **1** on the opposite sides, or on the same sides of the seven-membered ring in **3** or **4**: the obtained isomeric bis-adducts are denoted in the scheme as *trans* or *cis* with respect to the relative stereochemistry of their 10a- and 11a-substituents. From the reaction of **5** with nitrile oxide **1**, only the adduct **11** was obtained in substantial yield. It is characterized by the *anti* relationship of the two five-membered rings fused to the heptatomic one, presumably due to the steric requirements of the two angular phenyl groups. No evidence for the formation of mono-adducts was obtained in the reactions under study, even though equimolecular amounts of dipole and dipolarophile were used, taking care to add dipole to diazepine in small sequential amounts. This confirms that the hetero-double bonds are much more reactive than the olefinic ones in the investigated dipolarophiles.



1-2 3-5 6-12

	Ar	Z	R^1	R^2		
1	Mes	O	--	--		
2	Ph	NPh	--	--		
3	---	---	Me	Me		
4	---	---	Me	Ph		
5	---	---	Ph	Ph		
6	Mes	O	Me	Me	R^1/R^2	*cis*
7	Mes	O	Me	Me		*trans*
8	Ph	NPh	Me	Me		*trans*
9	Mes	O	Me	Ph		*cis*
10	Mes	O	Me	Ph		*trans*
11	Mes	O	Ph	Ph		*trans*
12	Ph	NPh	Ph	Ph		*trans*

Mes = $C_6H_2Me_3$-2,4,6

Table I

^{1}H NMR Chemical Shifts (δ_H/ppm) and Coupling Constants (J/Hz) for Compounds **6-10** in Deuteriochloroform

Protons	**6** 200 MHz	**7** 200 MHz	**8** 250 MHz	**9** 60 MHz	**10** 200 MHz	**11** 200 MHz	**12** 60 MHz
10a-Me 11a-Me	1.76, s	1.67, s	1.70, s	1.88, s	2.10, s		
Ar-Me	2.20, s 2.23, s 2.25, s	2.17, s 2.22, s 2.33, s		2.1-2.4, m	2.2-2.4, m	2.06, br s 2.24, s 2.40, br s	
H_2-11	2.53, d 2.99, d J_{gem} = -14.0	2.72, s	3.07, s	2.91, d 3.14, d J_{gem} = -14.0	3.17, d 3.24, d J_{gem} = -14.0	3.53, s	4.27, s
H_2-5 H_2-6	2.95, m [a]	2.82, m [a]	3.32, m [a]	2.87, m [a]	3.07, m [a]	3.33, m [a]	3.09, m [a]
ArH	6.83, m [b]	6.82, m [b]	6.8-7.5, m	6.6-7.6, m	6.8-7.6, m	6.7-7.2, m	6.8-8.2, m

[a] Centre of the AA'BB' system.
[b] Centre of the multiplet.

Table II

^{13}C NMR Chemical Shifts (δ_C/ppm) for Compounds **6-8, 10-12** in Deuteriochloroform [a]

Carbon	**6** 50 MHz	**7** 50 MHz	**8** 63 MHz	**10** 50 MHz	**11** 50 MHz	**12** 20 MHz
3; 8	155.04	154.09	149.61	154.56 155.03	155.09	149.65
5; 6	40.88 (2.95) [b]	43.66 (2.82) [b]	44.20	40.99 45.23	44.67 (3.33) [b]	44.23
10a;11a	96.41	97.48	85.58	96.31 99.40	98.57	88.67
11	50.19 (2.53) (2.99)	49.01(2.72)	44.60	47.79	46.94 (3.53)	47.93
Ar-Me	19.39 (2.20) 19.83 (2.25) 21.07 (2.23)	19.34 (2.17) 19.81 (2.33) 21.04 (2.22)		19.26 19.94 21.12	19.82 (2.06) 20.49 (2.40) 21.07 (2.24)	
10a-Me 11a-Me	24.13 (1.76)	23.34 (1.67)	23.90	24.64		
Ar-C	120.84 128.40 (6.82) 128.58 (6.84) 137.65 138.11 140.03	120.70 128.60 (6.81) 128.76 (6.83) 137.77 140.10	116.30- 143.61	120.63- 141.08	120.77- 140.59	114.03- 142.70

[a] Figures in parentheses refer to the related proton absorptions verified by C,H-correlation experiments. [b] The reported proton chemical shift is the centre of the AA'BB' pattern.

The nmr data of the bis-adducts **6,7,9-11** show the resonances of three methylene groups, unequivocally indicating double cycloaddition to the hetero-double bonds. Also the expected orientation of addition is confirmed by ^{1}H and ^{13}C nmr spectroscopy. For example, C-10a and C-11a resonate in the range 96-99 ppm, definitely excluding the alternative regioisomers for which chemical shifts of about 50 ppm would be expected [7].

The stereoisomers **6** and **7** show very similar electron impact mass fragmentation patterns, ir spectra, and ^{13}C

nmr data, but their ^{1}H nmr absorptions give conclusive evidence of their different structures: the *trans*-isomer **7** has a C_2 symmetry axis, so that both its H_2-11 protons resonate as an only singlet, whilst the corresponding 11-methylene protons in the *cis*-isomer **6** appear as a typical AB system ($J_{gem} = -14.0$ Hz). COSY experiments [8] show that the singlet at δ 2.72 (H_2-11) is coupled to the angular methyl groups in the *trans*-isomer **7**, but the same interaction is shown only by the low field proton of the H_2-11 AB system in the *cis*-compound **6**; moreover long-range coupling ($J < 1$ Hz) between some aromatic protons and the hydrogens of the aryl methyl groups is observed for both products **6** and **7**.

The stereochemical configuration of the pair of isomers **9** and **10** was determined by nuclear Overhauser enhancement (nOe) experiments. In the compound **10**, irradiation of the methylene proton at 3.17 ppm (H_B-11) gave an enhancement of several signals in the aromatic region (7.3-7.6 ppm), but had no effect upon the methyl signal at 2.10 ppm. However, irradiation of the geminal proton at 3.24 ppm (H_A-11) gave a large nOe (5%) in the methyl signal at 2.10 ppm but no enhancement in the aromatic region of the spectrum. As expected, therefore, irradiation of the 11a-methyl group (2.10 ppm) only affected the resonance at 3.24 ppm (H_A-11). These results are only consistent with a relative *trans*-orientation of the 10a- and 11a-substituents in the adduct **10**, since a *cis*-stereochemistry (the one attributed to the adduct **9** by exclusion) would require that *only one* (rather than the two observed) of the geminal methylene protons could possibly produce nOe effects on the adjacent methyl and phenyl substituents and, indeed, that it should produce them in both.

The 3,8-dimesityl-6,10a,11,11a-tetrahydro-5*H*-bis[1,2,4]-oxadiazolo[4,5-*d*:5′,4′-*g*][1,4]diazepines represent a new heterocyclic system which can be obtained in satisfactory yields from the appropriate readily available monocyclic diazepines.

We next turned our attention to diphenylnitrile imine prepared *in situ* from *N*-phenylbenzenecarbohydrazonic chloride [9]. Here too, 2:1 adducts **8**,**12** were obtained, both showing a *trans*-stereochemistry of 10a- and 11a-substituents. Evidently, owing to the presence of 1- and 10-phenyl substituents, severe non-bonding interactions preclude the formation of the corresponding *cis*-isomers. As observed for mesitylnitrile oxide (**1**), the reaction of diazepines **3** and **5** with equimolecular amounts of **2** did not lead to the formation of monoadducts, but instead afforded the corresponding 5,6,10,10a,11,11a-hexahydro-1,3,8,-10-tetraphenyl-1*H*-bis[1,2,4]triazolo[4,3-*d*:3′,4′-*g*][1,4]-diazepines **8** and **12**, albeit in low yields.

EXPERIMENTAL

Melting points were obtained with a Kofler apparatus and are uncorrected. The ir spectra were obtained from Nujol mulls using a Perkin-Elmer 682 spectrophotometer. The nmr spectra were recorded on Varian EM-360A and FT-80A, Bruker AM-200 and 250 spectrometers, in deuteriochloroform solutions using TMS as the internal standard. Mass spectra were obtained using a Varian MAT CH7 spectrometer. Microanalyses were performed on a Carlo Erba Model 1106 instrument. Silica gel (Merck type 60, 70-230 mesh, 0.063-0.200 mm) was used for column chromatography. Note: the free 2,3-dihydro-1*H*-1,4-diazepines **3-5** were prepared from their perchlorate salts by treatment with base [2] just before their use in the cycloaddition reactions.

Cycloaddition Reactions of 2,3-Dihydro-1*H*-1,4-diazepines **3-5** with Mesitylnitrile Oxide (**1**).

General Procedure.

The 2,3-dihydro-1*H*-1,4-diazepine [2] (2 mmoles) and mesitylnitrile oxide (**1**) [6] (6 mmoles) were dissolved in anhydrous diethyl ether (20 ml) and stirred for 4 days at room temperature. The solution was then evaporated under reduced pressure and the residue was subjected to column chromatography [diethyl ether/petroleum ether (bp 30-50°) as eluant, initially in a 1:4 ratio in order to recover unreacted nitrile oxide **1**, and subsequently in a 1:1 ratio] to afford the reaction products - 3,8-dimesityl-6,10a,-11,11a-tetrahydro-5*H*-bis[1,2,4]oxadiazolo[4,5-*d*:5′,4′-*g*][1,4]-diazepines - as pale yellow crystals of sharp melting point.

3,8-Dimesityl-*r*-10a,*c*-11a-dimethyl-6,10a,11,11a-tetrahydro-5*H*-bis[1,2,4]oxadiazolo[4,5-*d*:5′,4′-*g*][1,4]diazepine (**6**).

This compound had mp 169-171° (35% yield); ir: 1620, 1595, 1210, 875 cm^{-1}; ms: (70 eV) m/z (% relative intensity) 446 (25, M$^+$), 389 (20), 347 (18), 228 (20), 227 (100), 187 (28), 146 (20), 144 (27).

Anal. Calcd. for $C_{27}H_{34}N_4O_2$: C, 72.62; H, 7.67; N, 12.55. Found: C, 72.87; H, 7.60; N, 12.47.

3,8-Dimesityl-*r*-10a,*t*-11a-dimethyl-6,10a,11,11a-tetrahydro-5*H*-bis[1,2,4]oxadiazolo[4,5-*d*:5′,4′-*g*][1,4]diazepine (**7**).

This compound had mp 221-223° (35% yield); ir: 1620, 1610, 1590, 1220, 868 cm^{-1}; ms: (70 eV) m/z (% relative intensity) 446 (34, M$^+$), 389 (24), 347 (20), 228 (20), 227 (100), 187 (27), 146 (19), 144 (27).

Anal. Calcd. for $C_{27}H_{34}N_4O_2$: C, 72.62; H, 7.67; N, 12.55. Found: C, 72.83; H, 7.62; N, 12.35.

3,8-Dimesityl-*r*-11a-methyl-*c*-10a-phenyl-6,10a,11,11a-tetrahydro-5*H*-bis[1,2,4]oxadiazolo[4,5-*d*:5′,4′-*g*][1,4]diazepine (**9**).

This compound was a low melting product (18% yield); ms: (70 eV) m/z (% relative intensity) 508 (26, M$^+$), 451 (16), 290 (29), 289 (100), 227 (48), 187 (32), 186 (19), 160 (19), 159 (19), 146 (43), 145 (45), 144 (73), 130 (27), 117 (21), 105 (100).

Anal. Calcd. for $C_{32}H_{36}N_4O_2$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.62; H, 7.47; N, 10.71.

3,8-Dimesityl-*r*-11a-methyl-*t*-10a-phenyl-6,10a,11,11a-tetrahydro-5*H*-bis[1,2,4]oxadiazolo[4,5-*d*:5′,4′-*g*][1,4]diazepine (**10**).

This compound had mp 121-123° (42% yield); ir: 1620, 1600, 1234, 1060 cm^{-1}; ms: (70 eV) m/z (% relative intensity) 508 (21, M$^+$), 451 (15), 290 (15), 289 (61), 227 (100), 187 (30), 186 (21), 160 (21), 159 (24), 146 (48), 145 (45), 144 (85), 130 (27), 117 (21), 105

(67).

Anal. Calcd. for $C_{32}H_{36}N_4O_2$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.36; H, 7.03; N, 10.66.

3,8-Dimesityl-*r*-10a,*t*-11a-diphenyl-6,10a,11,11a-tetrahydro-5*H*-bis[1,2,4]oxadiazolo[4,5-*d*:5',4'-*g*][1,4]diazepine (**11**).

This compound had mp 113-115° (40% yield); ir: 1620, 1600, 1260, 1180 cm^{-1}; ms: (70 eV) m/z (% relative intensity) 570 (6, M^+), 451 (3), 306 (3), 304 (4), 291 (10), 290 (9), 289 (50), 222 (4), 187 (8), 186 (4), 161 (8), 160 (4), 159 (5), 146 (17), 145 (19), 144 (33), 130 (13), 117 (9), 105 (100), 91 (13).

Anal. Calcd. for $C_{37}H_{38}N_4O_2$: C, 77.87; H, 6.71; N, 9.82. Found: C, 78.29; H, 6.79; N, 9.59.

Cycloaddition Reactions of 2,3-Dihydro-1*H*-1,4-diazepines **3-5** with Diphenylnitrile Imine (**2**).

General Procedure.

To a stirred solution of the 2,3-dihydro-1*H*-1,4-diazepine [2] (2 mmoles) and *N*-phenylbenzenecarbohydrazonic chloride (nitrile imine precursor) [9] (4 mmoles) in anhydrous benzene (20 ml), was added dropwise a solution of triethylamine (4 mmoles) in anhydrous benzene (5 ml) over a few minutes. The mixture was then refluxed for 10 hours. After cooling to room temperature, the precipitated hydrochloride was filtered off, the solvent evaporated at reduced pressure, and the residue subjected to column chromatography [diethyl ether/petroleum ether (bp 30-50°) 3:7 as eluant] to afford the reaction products, 5,6,10,10a,11,11a-hexahydro-1,3,8,10-tetraphenyl-1*H*-bis[1,2,4]triazolo[4,3-*d*:3',4'-*g*][1,4]diazepines, as pale green crystals of sharp melting point.

r-10a,*t*-11a-Dimethyl-5,6,10,10a,11,11a-hexahydro-1,3,8,10-tetraphenyl-1*H*-bis[1,2,4]triazolo[4,3-*d*:3',4'-*g*][1,4]diazepine (**8**).

This compound had mp 202-204° (60% yield); ms: (70 eV) m/z (% relative intensity) 512 (17, M^+), 277 (65), 262 (100), 248 (25), 236 (29), 235 (66), 194 (16), 185 (64), 130 (29), 118 (47), 117 (25), 105 (37), 104 (82), 103 (43), 98 (21), 97 (33), 95 (29), 93 (24), 92 (56), 91 (74).

Anal. Calcd. for $C_{33}H_{32}N_6$: C, 77.32; H, 6.29; N, 16.39. Found: C, 77.41; H, 6.47; N, 16.19.

5,6,10,10a,11,11a-Hexahydro-1,3,8,10,*r*-10a,*t*-11a-hexaphenyl-1*H*-bis[1,2,4]triazolo[4,3-*d*:3',4'-*g*][1,4]diazepine (**12**).

This compound had mp 283-285° (30% yield); ms: (40 eV) m/z (% relative intensity) 636 (1, M^+), 326 (30), 297 (100), 284 (30), 194 (100).

Anal. Calcd. for $C_{43}H_{36}N_6$: C, 81.10; H, 5.70; N, 13.20. Found: C, 80.91; H, 5.72; N, 13.35.

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