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SITE SELECTIVITY IN THE REACTIONS OF 1,3-DIPOLES AND DIENES WITH TETRACYCLO [5.3.2.$0^{2,10}$. $0^{3,6}$]DODECA-4,8,11-TRIENE.

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Abstract - 1,3-Dipoles and dienes reacted smoothly with excess tetracyclo [5.3.2.$0^{2,10}$. $0^{3,6}$]dodeca-4,8,11-triene (1) to give good yields of monoadducts in a highly selective reaction. The attack by 1,3-dipoles and dienes to 1 occurred only at the cyclobutene moiety anti to the homotropilidene residue. Temperature dependent ^{1}H NMR spectra clearly showed that the homotropilidene moiety of all 1,3-dipolar adducts isomerised anisodynamically. In the case of benzonitrile oxide-1 adduct the ratio between the two equilibrating valence tautomers was evaluated. Site selectivity and face selectivity of the cycloadditions as well as anisodynamicity of the valence isomerization processes are briefly discussed. In particular conformational and angle strain effects are advanced as explanation for the anisodynamicity of 1,3-dipolar adducts.

INTRODUCTION

Cyclobutenes are known to be fairly good dipolarophiles and to react smoothly with several 1,3-dipoles with the exception of azides.[1,2] Some years ago we showed that the double bonds of a homotropilidene system (i.e., bullvalene) can enter 1,3-dipolar cycloadditions.[3] Tetracyclo [5.3.2.0.^{2,10} .$0^{3,6}$]dodeca-4,8,11-triene (1) contains both a cyclobutene residue and a homotropilidene moiety so that it lends itself as an appropriate substrate to study the competition between these two systems in the reaction with 1,3-dipoles. Moreover, the attack by 1,3-dipoles at either one of the two cyclobutene faces affords two constitutionally different valence tautomers which, in principle, must have different energies. Consequently we felt interesting to find out whether or not, actually, the effect of the heterocyclic nucleus "filtered" through the cyclobutane ring induces a detectable anisodynamicity (i.e., different concentrations of valence tautomers)[4] in the valence isomerization processes of the 1,3-dipolar adducts.
We also report here on the selectivity in Diels-Alder reactions of 1 with heterocyclic dienes.

RESULTS AND DISCUSSION

Benzonitrile oxide (generated in situ), mesitonitrile oxide and 2,6-dichlorobenzonitrile oxide, respectively, reacted smoothly with excess 1 to give good yields of adducts 2 - 4 (Scheme). The mass spectrum of 2 [m/z, 275 (1.0%, $M^{+\cdot}$)] displays the characteristic peaks of bullvalene [m/z, 130 (71%, $C_{10}H_{10}^{+\cdot}$), 129 (base peak, $C_{10}H_9^+$), and 115 (48%, $C_9H_7^+$)] and a peak [m/z, 146 (38%)] which can be ascribed to a protonated 3-phenyl isoxazole fragment ion. This fragmentation pattern

is fully consistent with an attack by the 1,3-dipole at the cyclobutene residue. A definitive confirmation of the assigned structure was obtained from its ^{1}H NMR spectrum. It is temperature dependent thus unambigously disclosing the presence of an equilibrating homotropilidene moiety (**2a** ⇌ **2b**). Moreover, a systematic series of decoupling experiments on the 200 MHz spectrum in the fast exchange limit (depicted in the Figure) allowed us to assign all signals to individual protons and to determine coupling relationships between them. The resulting assignements were as follows: δ (25°C, $CDCl_3$) 1.98 (ddd, H-2, $J_{2,3}$ = 6.2 Hz and $J_{1,2}$ = $J_{2,13}$ = 9.0 Hz), 2.35 (ddd, H-10, $J_{9,10}$ = 4.5 Hz and $J_{10,11}$ = $J_{10,15}$ = 8.5 Hz), 2.72 (m, H-1 and H-13), 2.81 (dddd, H-9, $J_{3,9}$ = 10.5 Hz, $J_{8,9}$ = 3.8 Hz and $J_{4,9}$ = 0.5 Hz), 3.30 (dddd, H-3, $J_{3,4}$ = 4.3 Hz and $J_{3,8}$ = 1.7 Hz), 3.85 (ddd, H-8, $J_{4,8}$ = 8.2 Hz), 4.80 (m, H-11, $J_{11,12}$ = 10.5 Hz), 5.08 (m, H-15, $J_{14,15}$ = 10.5 Hz), 5.15 (ddd, H-4), 5.72 (dd, H-12, $J_{12,13}$ = 8.0 Hz) and 6.05 (dd, H-14, $J_{1,14}$ = 8.1 Hz).[5] Some residual line broadening is still apparent in the signals of H-1, H-13 and H-11, H-15 either as a consequence of incomplete averaging of protons which experience the most different chemical shifts in the two equilibrating tautomers or because of unresolved coupling $J_{1,13}$ and $J_{11,15}$.

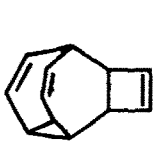
The chemical shifts of H-1 and H-13 (δ 2.72) compared to those of H-11 and H-15 (δ 4.80 and 5.08) indicate that the two former protons chiefly reside in a cyclopropyl environment whilst the two latter protons in an olefinic one. Of the two bridgehead protons, H-2 (δ 1.98) is the one that exhibits a higher cyclopropyl character whereas H-10 (δ 2.35) can be classified as allylic. These data confirm that the homotropilidene residue of **2** isomerises anisodynamically, that is, valence tautomers **a** and **b** are present in different concentrations.

In the low temperature spectra (-80°C, CD_2Cl_2) the protons of **2a** and **2b** give rise to broad signals overlapping each other, thus precluding determination of which isomer is prevalent. However the dominance of isomer **a** can clearly be inferred from ^{1}HNMR data reported above. In fact coupling constant values reveal that the "lowest field" of the cyclobutyl protons (which must reside next to the oxygen atom, i.e., H-4) bears a vicinal trans relationship to that one of the other cyclobutyl protons [H-3, since $J_{3,4}$ = 4.3 Hz (^{3}J trans), $J_{4,9}$ = 0.5 Hz (^{4}J trans) and $J_{4,8}$ = 8.2 Hz (^{3}J cis)] which in its turn is vicinal to the "highest field" proton (highest cyclopropyl character, H-2, $J_{2,3}$ = 6.9 Hz) of the homotropilidene residue. Further inspection of the ^{1}H NMR data of **2** shows how the same conclusion can be arrived at starting from H-8 via H-9 ($J_{8,9}$ = 3.8 Hz while $J_{3,8}$ = 1.7 Hz) to reach the "lower field" (H-10, $J_{9,10}$ = 4.5 Hz) of the two bridgehead protons. Consequently the cyclopropyl moiety and the oxygen atom must be located in the same half of the structure of the dominant isomer, i.e., the bottom half of **2a**.

At this point the need arose to quantify the prevalence of **2a**. Some reasonable assumptions enabled us to roughly estimate the **2a/2b** ratio on the basis of the well known equation (1)

$$\% \text{ (2a)} = \frac{\delta_m - \delta_c}{\delta_o - \delta_c} \cdot 100 = 77\% \qquad (1)$$

As "true" olefinic shift, δ_o, for H-11 and H-15 we have chosen the median value (δ 5.88) of H-12 and H-14 at 32°C (these protons occupy an olefinic position both in **2a** and **2b**). Moreover the two broad signals of vinyl protons at -80°C are centered at this value. As "true" cyclopropyl shift, δ_c, we have chosen the chemical shift of cyclopropyl protons of **2a** and **2b** at -80°C (broad signal with center at δ 1.80).[6,7] The calculated ratio (**2a/2b** = 77/23) shows that **2a** is favoured by $\simeq$ 0.7 kcal mol^{-1}.



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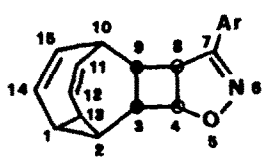
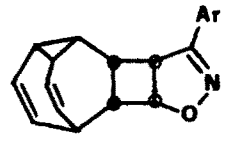
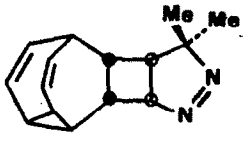


a



b

2 : Ar = Ph ; 3 : Ar = 2,4,6-$Me_3C_6H_2$; 4 : Ar = 3,5-$Cl_2C_6H_3$



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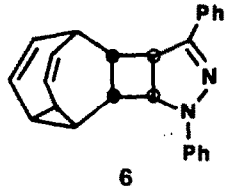

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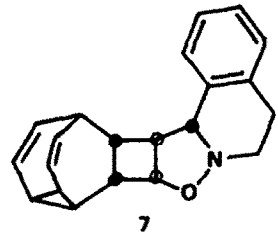

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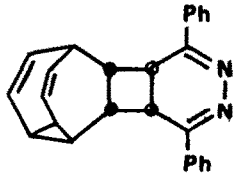

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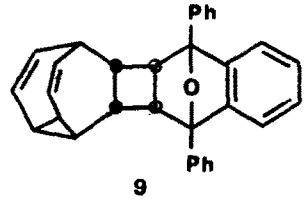

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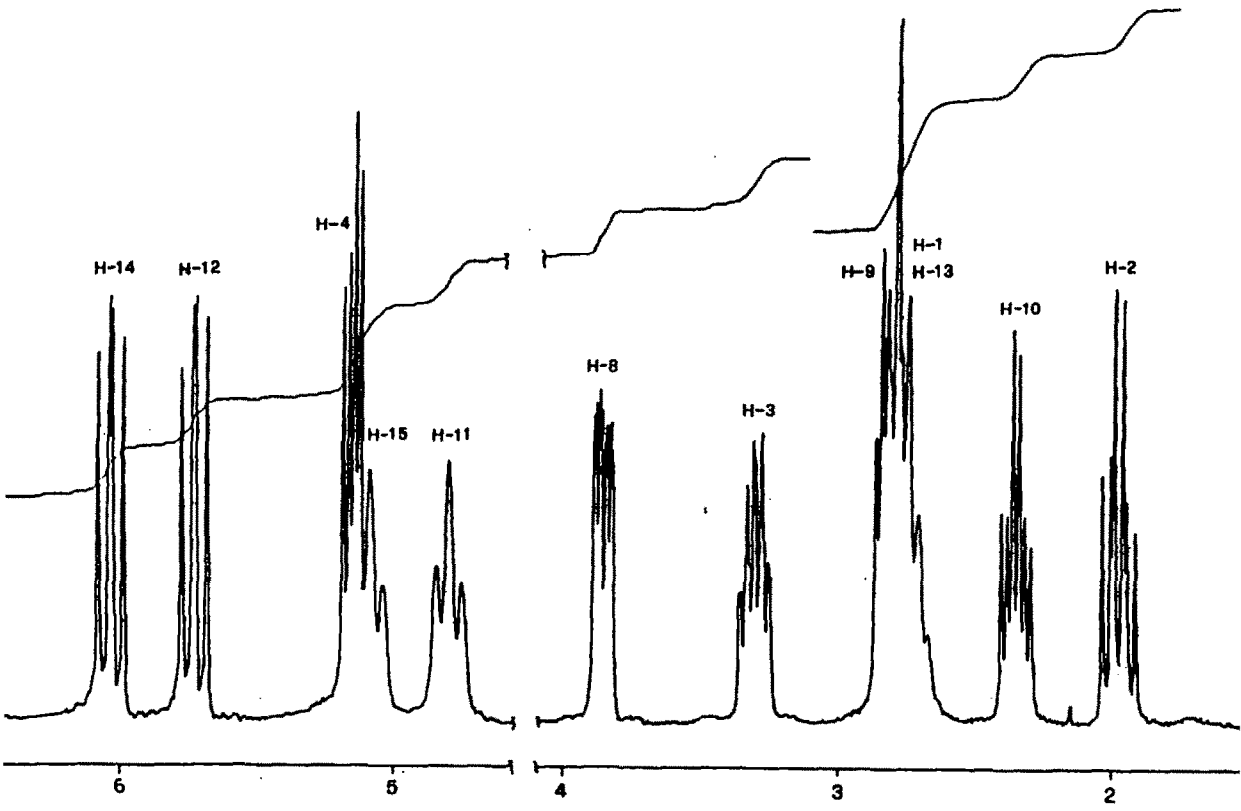

Figure. ^{1}HNMR spectrum (200 MHz, $CDCl_3$, 25°C) of compound 2.

As for the face selectivity of benzonitrile oxide attack to **1**, the trans relationship between H-3, H-4 and H-8, H-9, respectively, is supported by their low coupling constants ($\leq$ 4.0 Hz) whilst a cis relationship in this type of condensed cyclobutane system would require a J $\geq$6.0 Hz.[8,9]

The ^{1}HNMR spectra of **3** and **4** are very similar in all relevant aspects to that of **2**. The 77/23 ratio is thus confirmed as the result of an isoxazoline nucleus induced anisodynamicity.

Then we extended our study to other 1,3-dipoles with the aim of investigating both the site selectivity of the cycloaddition and the effect of different heterocyclic nuclei on the homotropilidene isomerization process. The reaction of 2-diazopropane, diphenylnitrilimine and 3,4-dihydroisoquinoline-N-oxide, respectively, with **1** once again proved to be highly selective affording only one type of adduct, i.e., **5**, **6** and **7**. The temperature dependent ^{1}HNMR spectra of these adducts were not resolved enough (even in their fast exchange limit) to make possible a complete analysis as for **2** and to establish which was the dominant isomer. However the average chemical shift values of H-11 and H-15 [δ 4.50 for **5** and 4.45 for **6** (**a**/**b** or **b**/**a** ratios $\simeq$ 66/34) and 4.25 for **7** (**7a**/**7b** $\simeq$ 60/40)] suggest that the homotropilidene moiety of all these adducts keeps on equilibrating anisodynamically although the energy difference between the two isomers slightly decreases along the series.

In the case of **6** the structure was further confirmed by mass spectral data and by its thermal framentation at 300°C to give 1,3-diphenyl pyrazole and bullvalene.

Finally two heterocyclic dienes were reacted with **1** but the reaction outcome did not change: 3,6-diphenyltetrazine and 1,3-diphenylisobenzofuran gave rise to anti adducts **8** and **9**, respectively.

The site specificity found in the reactions described above suggests that condensed cyclobutenes are, in general, more active than homotropilidene systems as dipolarophiles and dienophiles. Accordingly, angle strain is more effective at enhancing the reactivity of a double bond in Diels-Alder and 1,3-dipolar cycloadditions than conjugation with a cyclopropane ring. Certainly steric hindrance also plays some role, disfavouring the attack at conjugated double bonds of **1**, which are sterically more shielded than the anti-face of the cyclobutene double bond.

In fact steric hindrance to attack on the syn (with respect to the homotropilidene moiety) cyclobutene face as well as the easier syn bending than the anti one of the hydrogens of the cyclobutene double bond[9] cooperate in dictating the anti specificity found.

The degree of anisodynamicity found by us for adducts **2** - **7** is similar to that previously evaluated by Hoesch and coworkers for the cyclooctatetraene tetramer (67/33) where the asymmetry felt by the homotropilidene residue through a cyclobutane ring is due to an anti carbocyclic cyclohexene system instead of our heterocyclic rings. The anti relationship between heterocyclic or carbocyclic ring and the equilibrating moiety obviously eliminates any direct steric and electronic interaction as a possible explanation for the anisodynamicity found. Likewise the parallel behaviour exhibited by carbocyclic and heterocyclic rings rules out a specific role for the heteroatoms of the latter systems. We suggest that the heterocyclic (or carbocyclic) nucleus imposes a definite non planar (envelope) conformation to the cyclobutane ring so that of the two homotropilidene orientations the one preferred is that which can accomodate this conformation with less angle strain. To verify this hypothesis a X-Ray study on **2** is under way. For the time being we can add that if the cyclobutane ring in **2**-**7** were planar the geometrical relationship between H-2 and H-3 should be very similar to that between H-9 and H-10 in contrast to the remarkable difference of the related coupling constants ($J_{2,3}$ = 6.2 Hz, $J_{9,10}$ = 4.5 Hz).

A related conformational effect can be advanced as an important factor in determining the anisodynamicity previously found for adducts of chlorosulphonylisocyanate,[7] dichloroketene[10] and 1,3-dipoles to bullvalene[3] in which the heterocyclic or carbocyclic nucleus is directly condensed to a dihydrobullvalene skeleton. In these cases orbital interactions and steric effects can also be at work.

We have started investigating the reaction of 1 with azides and chlorosulphonyl isocyanate. The low reactivity of azides with cyclobutenes and the highly polar transition states, with development of partial charges, in the reactions of the latter compound might give rise to a competition between the cyclobutene double bond and the homotropilidene system. In fact we have recently shown that polar attacks on 1 occur at this latter site.[11]

EXPERIMENTAL

Melting points are uncorrected, Elemental analyses were made on a Carlo Erba CHN analyzer mod. 1106. IR Spectra were measured as Nujol suspensions on a Perkin Elmer 157 spectrophotometer. ^{1}HNMR spectra of compound 2 - 9 were recorded on a Bruker WP 80 SY spectrometer (operating at 80 MHz) and that of 2a also on a Varian Spectrometer (operating at 200 MHz) with TMS as internal standard. Mass spectra were measured on a Dupont 21-492B using electron impact ionization mode. Thin layer chromatography was carried out on plates precoated with Silicagel GF_{254} Merck. Spots were revealed either by spraying with 3% chromic oxide in sulphuric acid (50%) followed by heating at 120°C or under UV light (254 nm). Column chromatography were performed with Silicagel 60 (70-230 mesh) Merck eluting with cyclohexane-ethyl acetate mixtures.

Reactions of nitrile oxides with 1. A mixture of the appropriate nitrile oxide and of 4.0 fold excess of 1 in ether was left at room temperature until complete disappearance of the dipole (TLC analysis). Benzonitrile oxide was generated in situ from benzohydroximic acid chloride and Et_3N whilst 2,6-dichloro and 2,4,6-trimethylbenzonitrile oxide were reacted as such. Excess 1 was separated from adducts 2 (80%), 3 (75%) and 4 (73%), respectively, by column chromatography. Monoadducts were found homogeneus by ^{1}HNMR and TLC techniques. Adduct 2: colourless prisms from EtOH, m.p. 144-5°C. (Found: C, 82.5; H, 6.0; N, 5.4. Calculated for $C_{19}H_{17}NO$: C, 82.9; H, 6.2; N, 5.1). Adduct 3: colourless prisms from petrol ether, m.p. 139-142°C. (Found: C, 66.0; H, 4.5; N, 4.2. Calculated for $C_{19}H_{15}Cl_2NO$: C, 66.3; H, 4.4; N, 4.1). ^{1}HNMR ($CDCl_3$): δ 1.98 (m, H-2), 2.15 (m, H-10), 2.67 (m, H-1 and H-13), 2.95 (m, H-9), 3.55 (m, H-3), 3.90 (ddd, H-8, J3,8 = 1.8 Hz, J4,8 = 8.0 Hz and J8,9 = 3.5 Hz), 4.88 (m, H-11), 5.13 (m, H-15), 5.30 (dd, H-4, J3,4 = 4.3 Hz), 5.75 (m, H-12), 6.03 (m, H-14).Adduct 4: colourless prisms from MeOH, m.p. 150-1°C. (Found: C, 83.2; H, 7.3; N, 4.4. Calculated for $C_{22}H_{23}NO$: C, 82.9; H, 7.4; N, 4.6). ^{1}HNMR ($CDCl_3$): δ 1.98 (m, H-2), 2.06 (m, H-10), 2.30 (s, 9H, Me), 2.67 (m, H-1, H-13 and H-9), 3.45 (m, H-3), 3.71 (ddd, H-8, J3,8 = 1.5 Hz, J4,8 = 3.5 Hz, J8,9 = 8.0 Hz), 4.83 (m, H-11), 5.11 (m, H-15), 5.21 (dd, H-4, J3,4 = 4.5 Hz), 5.73 (m, H-12), 6.01 (m, H-14). Small amounts (5%) of 3,4-diphenyl furazane-N-oxide were isolated in the reaction of benzonitrile oxide. Trace amounts of by products could be detected by TLC in all the reaction mixtures but we were not able to characterize them.

Reaction of 1 with 2-diazopropane. A solution of 1 (0.842 g, 5.4 mmoles) and 2-diazopropane (10 mmoles) in ether (50 ml) was left at room temperature for six hours. The solvent was evaporated off and the residue chromatographed to give unreacted 1 (500 mg) and 5 (290 mg, 24%) as the only reaction product. [Colourless prisms from petrol ether, m.p. 64-67°C. (Found: C, 79.2; H, 7.95; N, 12.6. Calculated for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0; N, 12.4). ^{1}HNMR ($CDCl_3$): δ 1.08 and 1.52 (two s, Me), 1.78 (m, H-8), 2.15-2.78 (m, 4H, H-2, H-10, H-3 and H-9), 3.23 (m, H-1 and H-13), 4.50 (m, H-11 and H-15), 4.93 (dd, H-4, J4,8 = 6.0 Hz, J3,4 = 2.0 Hz), 5.75 (t, H-12, J11,12 = J12,13 = 9.0 Hz), 5.99 (t, H-14, J1,14 = J14,15 = 9.0 Hz)].

Reaction of 1 with diphenylnitrilimine. A solution of N-(α-chlorobenzylidene)-N-phenylhydrazine (200 mg, 0.87 mmoles), excess 1 (500 mg, 3.2 mmoles) and Et_3N (0.5 ml) in anhydrous benzene was kept at room temperature for 24 hours. The triethylamine hydrochloride was filtered off, the solvent removed under reduced pressure and the residue chromatographed to give, besides unreacted 1 (300 mg), pure 6 [239 mg, 79%; yellow needles from benzene, m.p. 156-159°C. (Found: C, 85.2; H, 6.5; N, 8.0. Calculated for $C_{25}H_{22}N_2$: C, 85.7; H, 6.3; N, 8.0). ^{1}HNMR ($CDCl_3$): δ 2.08 (ddd, H-2, J1,2 = J2,13 = 9.0 Hz, J2,3 = 5.4 Hz), 2.25 (ddd, H-10, J10,11 = J10,15 = 9.0 Hz, J9,10 = 4.5 Hz), 2.75 - 3.75 (m, H-1, H-3, H-9 and H-13), 3.95 (dd, H-8, J4,8 = 8.0 Hz, J8,9 = 4.0 Hz), 4.30 (m, H-11), 4.60 (m, H-15), 4.73 (dd, H-4, J3,4 = 4.0 Hz and J4,8 = 9.5 Hz), 5.75 (dd, H-12, J = 9.5 and 10.0 Hz), 6.12 (dd, H-14, J = 9.5 and 10.0 Hz); Mass spectrum (70 e V): m/z, 350 ($M^{+\cdot}$, 11%), 221 (54%), 220 ($C_{15}H_{12}N_2^{+\cdot}$, 100%), 130 ($C_{10}H_{10}^{+\cdot}$, 18%), 129 ($C_{10}H_9^+$, 39%), 115 ($C_9H_7^+$, 21%)].

Compound **6** (50 mg) was melted in a sealed ampoule and heated at 300°C for fifteen minutes. Column chromatography of the dark-brown crude product afforded bullvalene (5 mg) and 1,3-diphenylpyrazole (10 mg).

Reaction of **1** with 3,4-Dihydroisoquinoline-N-oxide. A solution of 3,4-Dihydroisoquinoline-N-oxide (375 mg, 2.5 mmoles) and **1** (703 mg, 4.5 mmoles) in benzene was refluxed overnight. Usual work up furnished pure **7** [640 mg, 83%; colourless needles from methanol, m.p. 139-141°C. (Found: C, 83.4; N, 7.1; N, 4.5. Calculated for $C_{21}H_{21}NO$: C, 83.1; H, 7.0; N, 4.6). ^{1}HNMR ($CDCl_3$): δ 2.05 (m, H-2), 2.20 (m, H-10), 2.40-3.75 (series of overlapping multiplets, 9H), 4.25 (m, H-11 and H-15), 4.35 (bs, H-7), 4.50 (dd, H-4, J3,4 = 3.2 Hz and J4,8 = 7.0 Hz), 5.80 (dd, H-12, J11,12 J12,13 = 9.5 Hz), 5.93 (dd, H-14, J1,14 J14,15 = 9.5 Hz)].

Reaction of **1** with 3,6-diphenyltetrazine. A solution of diphenyltetrazine (100 mg, 0.43 mmoles) and **1** (110 mg, 0.7 mmoles) in toluene (10 ml) was heated under reflux for 20 hrs. The solvent was evaporated off and the yellow residue washed with little cold petrol ether to remove unreacted **1**. There was left 140 mg (84%) of **8** which crystallized from methanol as yellow needles with one molecule of methanol as crystallization solvent, m.p. 165-169°C dec. (Found: C, 82.0; H, 6.7; N, 7.1. Calculated for $C_{26}H_{22}N_2 \cdot$ MeOH: C, 82.2; H, 6.6; N, 7.1). ^{1}HNMR ($CDCl_3$): δ 2.13 (m, 2H, bridgehead homotropilidene protons), 3.16 and 3.80 (two m, cyclobutyl protons, $\Delta\nu_{1/2}$ = 10.0 and 6.0 Hz, respectively) 3.80 and 4.12 (ddd, interchanging cyclopropyl and vinyl protons, J = 9.5, 8.5 and 4.5 Hz), 5.73 and 6.25 (two t, vinyl protons, J = 9.5 Hz). The crude reaction product was homogeneous by ^{1}HNMR and it was partly converted into the corresponding isomeric 1,4-dihydropyridazine during crystallization.

Reaction of **1** with diphenylisobenzofuran. A solution of **1** (90 mg, 0.58 mmoles) and diphenylisobenzofuran (90 mg, 0.33 mmoles) in benzene were heated in a sealed ampoule at 120°C for 40 hrs. After that time the yellow colour of isobenzofuran had disappeared. Evaporation of the solvent followed by column chromatography furnished pure **9** [100 mg, 70%; colourless needles from cyclohexane, m.p. 175-180°C. (Found: C, 89.95; H, 6.1. Calculated for $C_{32}H_{26}O$: C, 90.1; H,6.1). ^{1}HNMR ($CDCl_3$): δ 1.82 (m, 2H, bridgehead homotropilidene protons), 2.35 and 2.82 (two m, 4H, cyclobutyl protons, $\Delta\nu_{1/2}$ = 8.0 and 4.0 Hz respectively), 3.63 and 3.83 (two ddd, 4H, interchanging cyclopropyl and vinyl protons, J = 9.0, 9.5 and 4.5 Hz), 5.65 and 5.88 (two t, J = 9.0 Hz, vinyl protons)].

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