Tetrahedron Vol. 48, No. 25, pp. 5283-5300, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Rearrangement of Isoxazoline-5-spiro Derivatives. Part 7.[1] Thermal Rearrangement of 4,5-Dihydro and Tetrahydroisoxazole-5-spirocyclobutanes to Azepin-4-one Derivatives

Andrea Goti,* Alberto Brandi, Francesco De Sarlo, and Antonio Guarna

Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, C. N. R., Dipartimento di Chimica Organica "U. Schiff", Università di Firenze, via G. Capponi 9, I-50121 Firenze, Italy

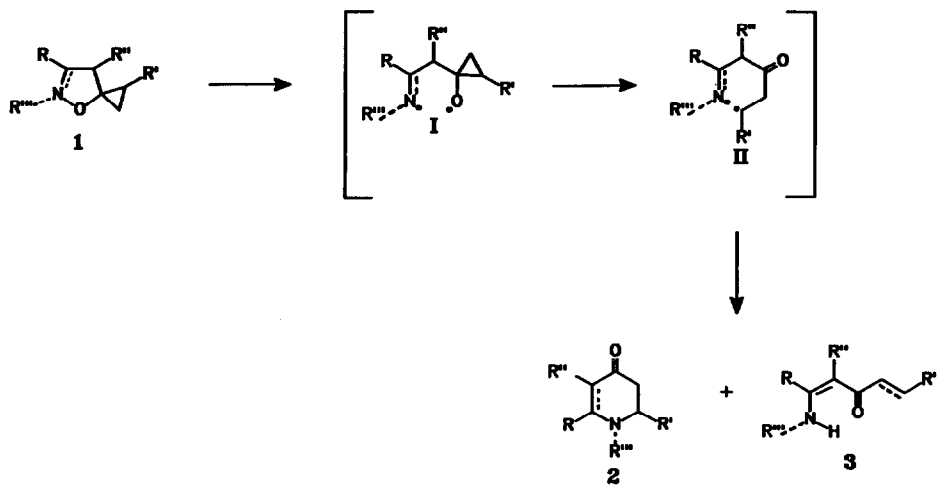
(*Received in UK 24 April* 1992)

Abstract: Some representative 4,5-dihydro and tetrahydroisoxazole-5-spirocyclobutanes have been synthesized by 1,3-dipolar cycloaddition of alkylidenecyclobutanes to nitrile oxides and nitrones, respectively. When subjected to flash vacuum thermolysis conditions, the spiranic cycloadducts rearranged to afford mainly the desired azepin-4-one derivatives. In addition, the isoxazoline cycloadducts gave unexpected by-products, which were identified as 1-alkenyl-2-pyrrolidinones. Analogies and differences with respect to the lower homologue cyclopropanes are evidenced in both cycloaddition and rearrangement reactions.

In the last years we have been involved in the study of the rearrangement of 5-spirocyclopropaneisoxazolines and isoxazolidines **1** (readily accessible by 1,3-dipolar cycloaddition of alkylidenecyclopropanes to nitrile oxides and nitrones, respectively) and all the possible combinations of substituents in the system have been tested (Scheme 1).[2]

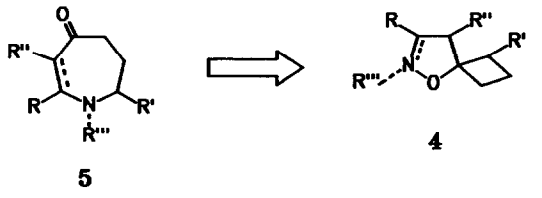
In most cases the predominant products were the pyridones **2**. The enaminones **3** were obtained as side-products in variable amounts, depending on the type and location of the substituents and on the reaction conditions, being less favored in rarefied or more diluted reaction conditions.[2] Since the piperidine nucleus is present in the backbone of many natural alkaloids, the method has been applied to the formal total synthesis of a number of alkaloids containing the quinolizine, indolizine, isoquinoline, or indole ring systems.[2d,e] The rearrangement sequence is based on the principle of combining a source of strain (the cyclopropane ring) with an adjacent reactive site (the N-O bond).[3] This combination made possible the homolytic fission of the N-O bond to occur smoothly to give an unstable diradical **I** in which the cyclopropyloxy moiety readily rearranges to a more stable oxopropyl radical species **II** in order to release the ring strain; this latter in turn evolves to the pyridone **2** by radical coupling or to the enaminone **3** *via* 1,5-hydrogen shift (Scheme 1).[2c] The remarkable features of the process are: *i)* the milder conditions required to open the heterocyclic ring compared with other simple isoxazole derivatives;[4] *ii)* the absence of decomposition products deriving from ring fragmentation; *iii)* the complete regioselectivity of the cyclopropane ring-opening step, leading exclusively to the products **2** (with R' α to nitrogen) and **3** (with R' in the terminal position) represented in Scheme 1.

Scheme 1



As an extension of the process we then considered the homologous spirocyclobutane derivatives **4**, which could lead by an analogous rearrangement to valuable azepin-4-ones **5** (Scheme 2).[5]

Scheme 2

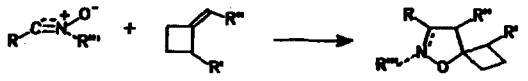


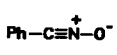
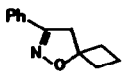
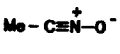
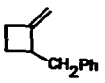
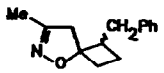
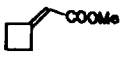
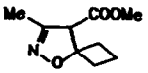
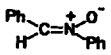
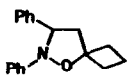
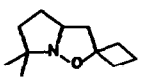
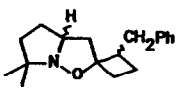
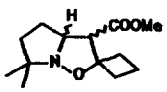
Results and Discussion

Cycloaddition Reactions of Nitrile Oxides and Nitrones to Alkylidenecyclobutanes. The starting 5-spirocyclobutaneisoxazole derivatives **4** were expected to be accessible by [3+2] cycloaddition of nitrile oxides or nitrones to alkylidenecyclobutanes. Indeed, two previous reports in the literature dealt respectively with the cycloaddition of benzonitrile oxide (**6**) to methylenecyclobutane (**10**), which led selectively to the 5-spirocyclobutaneisoxazoline **13**,[6] and with the cycloadditions of some *N*-phenyl-*C*-acyl or carbamoyl nitrones to methylenecyclobutane, which were also reported to give exclusively the 5-spirocyclobutaneisoxazolidines.[7]

The reaction between **6** and **10** to give the adduct **13** has been repeated and, in addition, compounds **14-16** have been synthesized by analogous cycloadditions of acetonitrile oxide (**7**) with the alkylidenecyclobutane derivatives **10-12**[8] (Table 1, entries 1-4). In the same way, products **17-20** have been obtained by 1,3-dipolar cycloaddition of *C*,*N*-diphenylnitrone (**8**) to **10** and of 2,2-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (DMPO, **9**) to the same dipolarophiles **10-12**[8] (Table 1, entries 5-8).

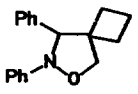
Table 1. Cycloadditions of Dipoles 6-9 to Alkylidenecyclobutanes 10-12.



entry	dipole	alkylidene cyclobutane	cycloadduct	diastereomeric ratio	yield[a]
1[b]	 **6**	 **10**	 **13**		91
2	 **7**	**10**	 **14**		72
3	**7**	 **11**	 **15 a,b**	55:45	70
4	**7**	 **12**	 **16**		49
5[c]	 **8**	**10**	 **17**		70[d]
6	 **9**	**10**	 **18**		90
7	**9**	**11**	 **19 a–d**	40:40:13:7	80
8	**9**	**12**	 **20 a,b**	66:34	81

[a]Yield of isolated products. [b]See ref. 6. [c]See ref. 11. [d]See ref. 12.

The products **13-20** were unequivocally assigned the structure of 5-spirocyclobutanes on the basis of the lack of coupling of the deshielded C5 isoxazole carbon atom (80-90 ppm) in the proton coupled ^{13}C NMR spectrum. This result contrasts significantly with the already observed lower regioselectivity of methylenecyclopropanes,[2,13] but is consistent with the regiospecificity observed in the cycloadditions to 1,1-disubstituted acyclic alkenes,[14] as well as to larger methylenecycloalkanes.[15] Among the reactions of Table 1, only in the case of entry 5 traces of compound **22** (<5%) with the opposite regiochemistry were detected in the crude reaction mixture.[16]



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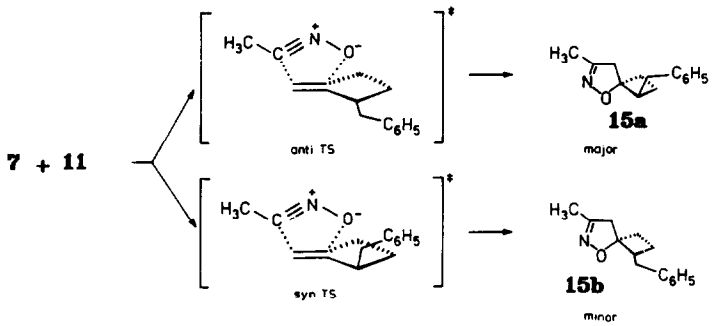
While the regioselectivity of the cycloadditions of nitrile oxides and nitrones is more pronounced with alkylidenecyclobutanes than with alkylidenecyclopropanes, the diastereoselectivity of the cycloadditions to their 2-substituted derivatives is much poorer. In fact, 2-benzylmethylenecyclobutane (**11**) gave with acetonitrile oxide (**7**) a 1.2:1 diastereomeric mixture of **15a** and **15b** (Table 1, entry 3) and with DMPO (**9**) four diastereoisomers **19a-d** in a 6:6:2:1 ratio (Table 1, entry 7). The two isomers **15a,b** derive from either *anti* and *syn* transition states (Scheme 3), in contrast to the complete *anti* selectivity observed in cycloadditions to substituted methylenecyclopropanes.[2c-e]

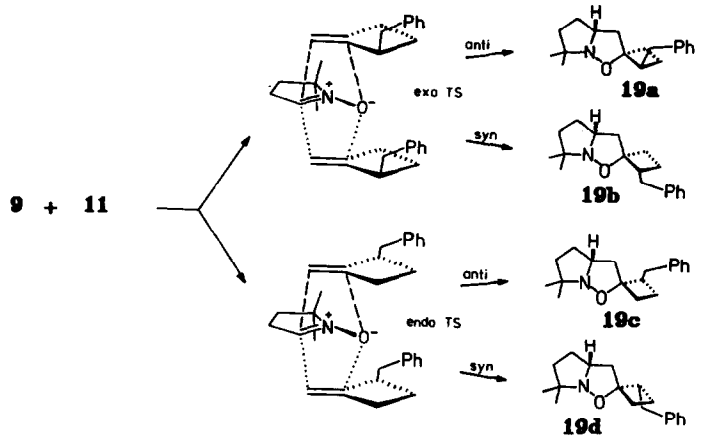
The major isomer was assigned the *trans* oxygen-benzyl stereochemistry (which derived from the *anti* TS) and the other way around for the minor one on the basis of their ^1H NMR spectra. The proton on the tertiary carbon atom of the cyclobutane ring is indeed more deshielded in the adduct **15a** than in **15b** (δ 2.95 ppm vs. 2.61 ppm), due to the deshielding effect of the *cis* oxygen atom. This assignment is confirmed by the deshielding of one hydrogen on the C4 isoxazoline ring in **15a** due to the presence of a *cis* benzyl group and by the deshielding of one of the two benzylic hydrogens in **15b** for the presence of the *cis* oxygen atom (see Experimental Section; the assignments were made by means of 2D-COSY spectra).

Scheme 3



The same trend is present in the ^1H NMR spectra of **19a** and **19c** with respect to **19b** and **19d**; this suggests that the former have the benzyl group *trans* to the oxygen atom and derive from *anti* TS (dashed approach in Scheme 4) and the latter have the benzyl *cis* to the oxygen and come from *syn* TS (dotted approach). The major products **19a** and **19b** must derive from *exo* TS, the other from *endo* TS.[17] The *anti/syn* ratios are therefore 1:1 for the *exo* isomers (**19a:19b**) and 2:1 for the *endo* isomers (**19c:19d**), while the *exo/endo* ratios are 3:1 for the *anti* (**19a:19c**) and 6:1 for the *syn* approaches (**19b:19d**). In the case of methylenecyclopropanes we observed exclusively the products derived from *anti* TS, but with much lower *exo/endo* selectivity.[2e]

Scheme 4



This great difference in the selectivities of 1,3-dipolar cycloadditions to substituted methylenecyclopropanes or methylenecyclobutanes deserves some comments. The divergent behavior can be ascribed to geometrical parameters and especially to conformational differences between the two ring-systems.

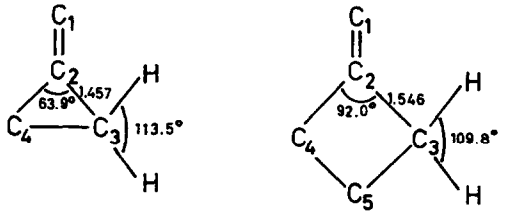


Figure 1. Comparison of selected geometrical parameters of methylenecyclopropane and methylenecyclobutane.

The minor $C_3\widehat{C_2}C_4$ angle, the shorter C_2-C_3 bond distance, and the greater $H\widehat{C_3}H$ angle estimated for methylenecyclopropane with respect to methylenecyclobutane[18] (Figure 1), cause a substituent at C3 in the former ring to crowd much more the attacking dipole in the transition state. More importantly, methylenecyclopropanes are rigid systems, so that the substituents on the ring cannot be removed from their encumbering position. On the contrary, the conformationally non rigid methylenecyclobutanes can reduce the dihedral angle φ formed by the substituent and the double bond plane, in such a way to place the substituent R in a less encumbering position like in the gauche conformation **B** (represented in Newman projection in Figure 2), preferred over the eclipsed **A**.

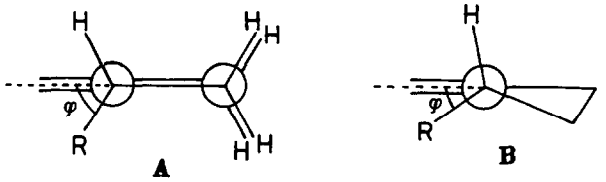


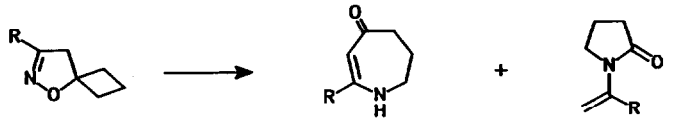
Figure 2. Newman projections of the planar (A) and non-planar (B) conformations of methylenecyclobutane.

As a result of all these effects, the facial selectivity in the cycloaddition to substituted methylenecyclobutanes (at least with small substituents) is very scarce and becomes appreciable only in the *endo* cycloaddition mode, for which the steric effects play a more significant role. The same effects are also able to explain the difference in the *exo/endo* ratios between substituted methylenecyclopropanes and methylenecyclobutanes.

The cycloaddition of DMPO (**9**) to methyl cyclobutylideneacetate (**12**) led to both the possible diastereoisomers **20a** and **20b** in 2:1 ratio (Table 1, entry 8). The major one was assigned the structure of *exo*-carbomethoxy **20a** and the minor of *endo*-carbomethoxy **20b** on the basis of their ^{1}H NMR spectra, and particularly of the frequencies and the coupling constants of the hydrogens on the C4 of the isoxazolidine nuclei. These are doublets which resonate at 2.88 δ (J 5.2 Hz) in **20a** and at 3.59 δ (J 6.4 Hz) in **20b**. The deshielding of this proton in the minor isomer is ascribed to its *cis* relationship with the nitrogen lone pair. The values of the coupling constants confirm this assignment; the larger one is observed in fact in the minor isomer, as expected for a 1,2-*cis* stereochemistry in a fused [3.3.0] bicyclic system. As it could be expected, the *exo* selectivity for the cycloaddition of **9** to **12** does not differ from that of the same nitrone to the lower homologue methyl cyclopropylideneacetate.[2g]

Rearrangement Reactions of Spirocyclobutane Isoxazole Derivatives 13-20. The reaction conditions required to perform the rearrangement of 5-spirocyclobutane isoxazole derivatives were much more severe than for their 5-spirocyclopropane counterparts.[5,19] Indeed, by treatment of **13** and **14** in flash vacuum thermolysis (FVT)[21] conditions at 700 °C, we obtained the expected azepin-4-ones **23** and **25** (Scheme 5), together with unexpected side-products, which were erroneously assigned the structure of α-methylene-*N*-acylpyrrolidines in the preliminary report.[5] A more careful investigation showed these side-products to be in fact the 1-alkenylpyrrolidin-2-ones **24** and **26**,[22] as shown in Scheme 5.

Scheme 5

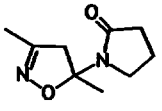


R = Ph: **13** **23** 37% **24** 28%

R = Me: **14** **25** 28% **26** 17%

These structures have been assigned on the basis of the spectral data of the rearranged products. The azepinones display IR and ^{1}H and ^{13}C NMR spectra very similar to those of the homologous piperidones; both the NMR spectra show a more shielded signal due to the additional methylene group. The side-products possess a terminal vinyl group of an enamine, as indicated by the signals at δ 141-144 ppm (s) and 98-110 ppm (t) in the ^{13}C NMR spectrum and those at δ 4.4-5.5 ppm in the ^{1}H NMR spectrum, and a carbonyl amide function (δ 174-175 ppm in the ^{13}C NMR spectrum and $\nu_{CO} = 1695$ cm^{-1} in the IR spectrum, at values typical for a γ-lactam), according with the proposed structures. This assignment was confirmed by the obtainment of small amounts of product **27** in a FVT experiment in which the adduct **14** was heated for longer times and at a higher temperature to be vaporized. Apparently, **14** gave a

partial retro-cycloaddition to the starting nitrile oxide **7**, which cycloadded to **26**. Only another example of a thermal 1,3-dipolar cycloreversion of a 2-isoxazoline to nitrile oxide (also accomplished by FVT at high temperatures) has been reported in the literature so far.[23]



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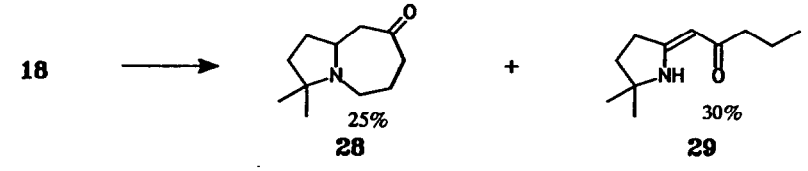
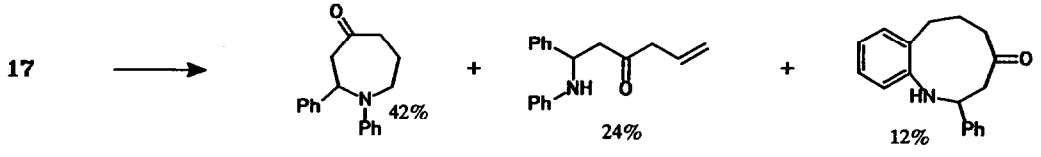
The rearrangement of the nitrone adduct **18** gave the expected products **28** and **29**, in analogy with the rearrangement of the lower spirocyclopropane homologues (Scheme 6).[5]

Scheme 6



The adduct **17** rearranged in a similar way, leading to **30** and **31**; in that case another product, **32**, derived from an annulation on the *N*-phenyl ring, was also observed (Scheme 7).[11]

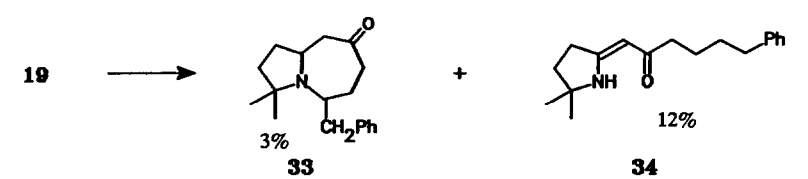
Scheme 7



The results of the thermal rearrangements of the substituted adducts (either at the cyclobutane or at the isoxazoline nucleus) could give us more information about the synthetic relevance of the process and/or its mechanistic details. Indeed, a different or a competitive mechanism should be operative at least in the case of the nitrile oxide adducts, to account for the formation of the *N*-alkenylpyrrolidinones.

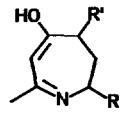
Isoxazolidines **19** and **20** gave, by thermolysis, mainly decomposition products. However, from the FVT of **19** at 600 °C[24] small amounts of the pyrroloazepinone **33** and of the enaminone **34** were recovered (Scheme 8), thus suggesting that also spirocyclobutaneisoxazolidines possibly undergo a regioselective cleavage.[2d,e]

Scheme 8



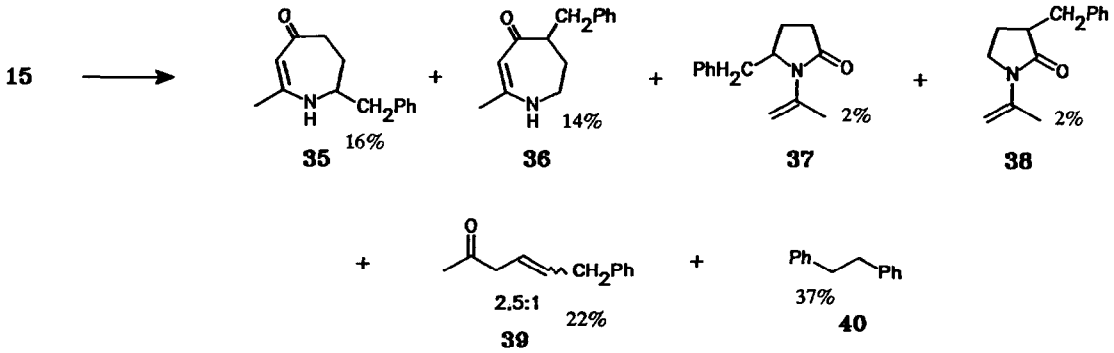
On the contrary, the isoxazolines **15** and **16** gave results contrasting with those of the corresponding cyclopropane derivatives. The benzyl derivative **15** gave almost the same results, when subjected to FVT either as a mixture or as a single diastereoisomer. It gave rise to a multitude of compounds (Scheme 9), in part deriving from isomerization (**35-38**), mainly from

decomposition (**39** and **40**) of the starting material. All the isomerization products were identified on the basis of their NMR spectra recorded on pure or enriched fractions, in analogy with the unsubstituted parent compounds. The substituent positions (α to nitrogen or to the oxo function) were established on the basis of the multiplicity and the integral of the more deshielded signal (within the region of saturated C-H signals), *i.e.* of the signal ascribed to the proton(s) α to nitrogen. The reported amounts of all compounds (except **40**, isolated) were calculated by the integrals of the signals in the proton NMR spectrum of the crude reaction mixture in the range 4-6 ppm, in which all the compounds **35-39** display some distinct resonances (see Experimental Section). The complexity of the reaction mixture (and of its ^{1}H NMR spectrum) is further increased by the tautomerization of the azepinones **35** and **36** in $CDCl_3$ solution to the more stable azadienols **35'** and **36'**, in analogy with the already observed protomerization of **25** to **25'**.[5,25]



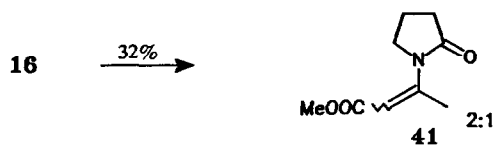
R=R'=H: **25'**
R=CH_2Ph,R'=H: **35'**
R=H,R'=CH_2Ph: **36'**

Scheme 9



The adduct **16** behaved in a consistently different manner, the *N*-carbomethoxypropenyl-pyrrolidinones **41** being the sole identified and isolated products (Scheme 10), as a 2:1 mixture of diastereoisomers.

Scheme 10



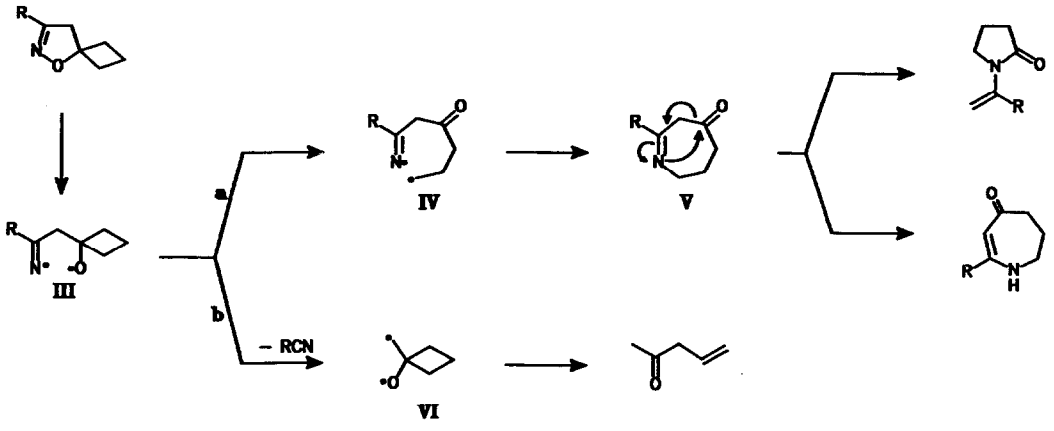
In conclusion, the rearrangement of spirocyclobutane isoxazole derivatives produces valuable azepin-4-ones, which are accessible by a relative limited number of general synthetic methods.[26] *N*-Bridgehead pyrroloazepines, obtained by starting from a pentacyclic nitrone, are particularly attractive since their ring system occurs in a number of natural alkaloids, such as cephalotaxine,[26] whose esters exhibit antitumor activity, and some other alkaloids, having insecticide properties, extracted very recently from Chinese plants of the *Stemonaceae* family.[27]

Moreover, the obtainment of the side-products is also of some relevance, in consideration of the substantial lack of methods for the synthesis of α-substituted 1-alkenyl-2-pyrrolidinones.[28]

It is also noteworthy that the rearrangement of spirocyclobutaneisoxazolines features some interesting differences with respect to the analogous reaction of the spirocyclopropane derivatives: *i)* the absence of enaminones; *ii)* the formation of the 1-alkenylpyrrolidin-2-ones; *iii)* the formation of two substituted azepinones and two *N*-alkenylpyrrolidinones, with almost no selectivity, when there is a substituent in the cyclobutane ring on the carbon adjacent to the spiro carbon atom; *iv)* the formation of decomposition products.

Although the mechanistic peculiarities able to bring about these differences are far from being fully understood, some speculations, directly deriving from the experimental observations, can be drawn, according to Scheme 11.

Scheme 11



The enhanced stability of the initially formed diradical **III** with respect to the analogous cyclopropyloxy **I** could be responsible for alternative cleavages (route b), leading to the observed decomposition products. The usual ring-opening to the diradical **IV** (route a) gives the Δ^1-azepinones **V** which, in turn, give the expected conjugated azepinones by 1,3-hydrogen shift or, in the reaction conditions, might undergo a ring contraction to the alkenylpyrrolidinone by-products. Since 1-vinylpyrrolidin-2-one and other substituted *N*-alkenylpyrrolidinones have been reported to undergo a ring-enlargment to tetrahydro-4*H*-azepin-4-ones under photolysis,[29] it could be expected that the same reaction occurred in our case. This possibility has been excluded by subjecting the pyrrolidinone **24** to the same thermolytic conditions (FVT at 700 °C): the product was recovered quantitatively; the same result was obtained in a control FVT of 1-vinylpyrrolidin-2-one. Similarly, we also ensured that azepinone **23** is not converted to the pyrrolidinone **24** in FVT conditions. However, the production of the *N*-alkenylpyrrolidinones by an alternative mechanism cannot be ruled out.

The results of the rearrangement reaction are scarcely reproducible, in terms of product distribution, on changing the FVT conditions. The overall yield seems, however, not to be affected. For example, the azepinone/pyrrolidinone ratio was substantially enhanced to 9:1 when the pyrolysis time was decreased by applying a higher vacuum (ca. 10^{-3} mmHg) in the FVT of isoxazoline **13**. This allowed a practical obtainment of pure azepinone **23** in good yield (51%) by a two step cycloaddition-rearrangement process starting from readily available compounds, thus establishing an easy access to these heterocycles.

Experimental

The pyrolysis oven used in the flash vacuum thermolysis (FVT) experiments was a MV W.C. Heraeus oven with a 10 cm combustion path; the temperature at the centre of the oven is reported. The substance was vaporized by heating with a Büchi GKR-50 distillator oven (its temperature is reported) and was passed under vacuum through a quartz tube (i.d. 10 mm) ending in a liquid nitrogen cooled flask. The distillations were performed with the same kugelrohr Büchi apparatus. Chromatographic separations were performed under pressure, using the flash column technique (silica gel); *Rf* values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}) obtained using the same eluent as in the column chromatographies. Melting points were observed with a microscope RCH Kofler apparatus. NMR spectra ($CDCl_3$ as solvent) were recorded on Perkin-Elmer R 32 or Varian M390 (^1H, 90 MHz), Varian XL 300 (^1H, 300 MHz), and Varian FT-80A (^{13}C, 20 MHz) spectrometers; chemical shift values are reported in ppm from tetramethylsilane; coupling constants J are given in Hz: notations s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer. Mass spectra were recorded at 70 eV by GC inlet on a 5790-5970A Hewlett-Packard instrument: m/e values and relative abundances are reported. Exact mass measurements by high resolution mass spectra were performed with a VG 70-70 EQ mass spectrometer, at an ionization potential of 70 eV. Combustion analyses were carried out with a Perkin-Elmer 240 C elemental analyzer.

Materials. Nitrile Oxides **6** and **7** were prepared *in situ*. *C,N*-Diphenylnitrone (**8**) and 3,4-dihydro-2,2-dimethyl-2*H*-pyrrole 1-oxide (DMPO, **9**) are commercially available. Methylenecyclobutane (**10**) was purchased from Fluka. 2-Benzyl-1-methylenecyclobutane (**11**) was prepared as reported.[9]

Methyl cyclobutylideneacetate (**12**) was obtained similarly to the homologous ethyl ester,[10,30] from carbomethoxymethylenetriphenylphosphorane (6.635 g, 20 mmol) and cyclobutanone (1 ml, 13.4 mmol) in refluxing anhydrous benzene (10 ml) during 2 days. After cooling, light petroleum ether was added (10 ml), the mixture stored in refrigerator, and the precipitate removed. On distillation, the ester was collected (1.19 g, 9.45 mmol, 73%), bp 95-110 °C/12 mmHg.

Anal. Found: C, 67.00; H, 8.19, using a sealed aluminium sample holder. Calc. for $C_7H_{10}O_2$: C, 66.66; H, 7.94%. ^1H NMR (300 MHz): δ 5.54 (quintet, J 2.1, 1 H), 3.63 (s, 3 H), 3.08 (br t, J 7.9, 2 H), 2.79 (br t, J 7.9, 2 H), 2.04 (quintet, J 7.9, 2 H); ^{13}C NMR: δ 167.66 s, 166.73 s, 111.76 d, 50.56 q, 33.51 t, 32.12 t, 17.43 t; MS: 126 (M^+, 49%), 125 (67), 111 (78), 96 (31), 95 (86), 67 (100), 66 (42), 59 (56), 41 (70); IR (CCl_4): 3000, 2960, 1710, 1680, 1345, 1200 cm^{-1}.

Cycloadducts.

4',5'-Dihydro-3'-phenylspiro[cyclobutane-1,5'-isoxazole](13). According to the reported procedure,[6] **13** was obtained from methylenecyclobutane (680 mg, 10 mmol), benzohydroxymoyl chloride (777 mg, 5 mmol) and triethylamine (0.69 ml, 5 mmol) in anhydrous diethyl ether (5 ml) at 0 °C for 2 h, then at room temperature overnight. The precipitate was filtered off and the solution concentrated to give the adduct **13** (853 mg, 4.56 mmol, 91%). White crystals, mp 96-98 °C, from MeOH (reported[6] mp 94-95 °C).

Anal. Found: C, 76.78; H, 7.03; N, 7.39. Calc. for $C_{12}H_{13}NO$: C, 76.98; 7.00; N, 7.48%. ^1H NMR (300 MHz): δ 7.75-7.60 (m, 2 H), 7.45-7.35 (m, 3 H), 3.42 (s, 2 H), 2.59 (m, 2 H), 2.24 (m, 2 H), 1.86 (m, 1 H), 1.68 (m, 1 H); ^{13}C NMR: δ 156.53 s, 129.79 s, 129.69 d, 128.44 d (2 C), 126.30 d (2 C), 85.85 s, 45.48 t, 36.47 t (2 C), 12.33 t; MS: 187 (M^+, 8%), 186 (2), 159 (11), 158 (5), 144 (13), 117 (100), 77 (33); IR (KBr): 1360, 915, 755 cm^{-1}.

4',5'-Dihydro-3'-methylspiro[cyclobutane-1,5'-isoxazole] (14). A solution of nitroethane (1.44 ml, 20 mmol) and dry triethylamine (280 μl, 2 mmol) in anhydrous diethyl ether (10 ml) was added at room temperature to a solution of methylenecyclobutane (2.04 g, 30 mmol) and phenylisocyanate (4.765 g, 40 mmol) in the same solvent (20 ml), under stirring during 1 h. The mixture was set aside for 1 day at room temperature and the precipitate (diphenylurea) was removed. Concentration and Kugelrohr distillation afforded the adduct **14** (1.795 g, 14.36 mmol, 72%), bp 50 °C/0.1 mmHg.

Anal. Found: C, 67.13; H, 8.90; N, 11.63. Calc. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19%. ^1H NMR (90 MHz): δ 3.03 (s, 2 H), 2.75-2.05 (m, 4 H), 2.01 (s, 3 H), 1.95-1.30 (m, 2 H); ^{13}C NMR: δ 155.30 s, 84.59 s, 49.19 t, 36.32 t (2 C), 13.15 q, 12.11 t; MS: 125 (M^+, 5%), 97 (29), 55 (100), 54 (16), 42 (43); IR (CCl_4): 2995, 2940, 1615, 1330 cm^{-1}.

2-Benzyl-4',5'-dihydro-3'-methylspiro[cyclobutane-1,5'-isoxazole] (15). A solution of nitroethane (1.8 ml, 25 mmol) and triethylamine (0.25 ml, 1.5 mmol) in anhydrous benzene (35 ml) was added at room temperature to a solution of 2-benzyl-1-methylenecyclobutane (**11**, 872 mg, 5.52 mmol) and 4-chlorophenylisocyanate (7.65 g, 50 mmol) in the same solvent (15 ml), under stirring during 5 h. The mixture was reacted at room temperature for 3 days; then it was filtered on celite and the solution washed with 1% aqueous HCl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue distilled to give 827 mg (70%) of a mixture of the adducts **15a** and **15b** in 1.2:1 molar ratio, bp 100-130 °C/0.05 mmHg.

Anal. Found: C, 77.72; H, 8.33; N, 6.99. Calc. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51%.

A chromatographic separation (eluent petroleum ether + ethyl acetate 70:30) gave pure **15b** (Rf 0.47) and **15a** (Rf 0.37).

15a (1*S**,2*S**): ^1H NMR (300 MHz): δ 7.30-7.15 (m, 5 H), 3.17 (d, J 17.3, 1 H), 2.94 (dq, J 6.1, 9.8, 1 H), 2.82 (dd, J 13.9, 5.9, 1 H), 2.73 (d, J 17.3, 1 H), 2.62 (dd, J 14.0, 9.7, 1 H), 2.28 (q, J 10.5, 1 H), 2.05-1.75 (m, 2 H), 1.93 (s, 3 H), 1.23 (quintet, J 9.8, 1 H); ^{13}C NMR: δ 155.39 s, 139.39 s, 128.43 d (4 C), 126.04 d, 87.44 s, 49.59 d, 43.33 t, 37.08 t, 34.63 t, 19.73 t, 13.49 q; MS: 215 (M^+, 2%), 200 (2), 187 (5), 174 (5), 131 (10), 118 (23), 117 (58), 115 (28), 104 (27), 97 (56), 91 (62), 55 (100); IR ($CDCl_3$): 3090, 3070, 3035, 2985, 2940, 2875, 2860, 1605, 1495, 1455, 1440, 1430, 1390, 1335 cm^{-1}. HRMS: found M^+, 215.1298, direct inlet. $C_{14}H_{17}NO$ requires M, 215.1309.

15b (1*S**,2*R**): ^1H NMR (300 MHz): δ 7.30-7.15 (m, 5 H), 2.98 (dd, J 13.8, 6.9, 1 H), 2.88 (d, J 17.5, 1 H), 2.75 (dd, J 13.8, 8.8, 1 H), 2.68 (d, J 17.5, 1 H), 2.61 (br quintet, J 8.5, 1 H), 2.42 (ddd, J 12.3, 9.3, 6.1, 1 H), 2.13 (ddt, J 11.5, 1.7, 9.3, 1 H), 1.90-1.75 (m, 2 H), 1.87 (s, 3 H); ^{13}C NMR: δ 155.10 s, 140.37 s, 128.66 d (2 C), 127.93 d (2 C), 125.51 d, 87.26 s, 49.34 t, 45.96 d, 35.27 t, 32.68 t, 20.89 t, 13.04 q; MS: 215 (M^+, 3%), 200 (1), 187 (5), 174 (6), 131 (12), 118 (27), 117 (75), 115 (29), 104 (27), 97 (68), 91 (63), 55 (100).

4'-Carbomethoxy-4',5'-dihydro-3'-methylspiro[cyclobutane-1,5'-isoxazole] (16). The same procedure reported above for the preparation of the adducts **15**, carried out on methylcyclobutylideneacetate (**12**, 483 mg, 3.83 mmol), gave 340 mg (49%) of the adduct **16**, bp 70 °C/0.05 mmHg.

^{1}H NMR (300 MHz): δ 3.82 (s, 1 H), 3.76 (s, 3 H), 2.54-2.36 (m, 2 H), 2.27-2.12 (m, 2 H), 1.99 (s, 3 H), 1.93-1.78 (m, 1 H), 1.63 (dquintet, J 11.2, 8.7, 1 H); ^{13}C NMR: δ 168.23 s, 152.98 s, 88.09 s, 63.95 d, 52.28 q, 37.51 t, 31.46 t, 12.84 q, 12.78 t; MS: 183 (M^+, 21%), 168 (8), 155 (27), 114 (22), 111 (22), 96 (50), 82 (74), 69 (68), 68 (100), 59 (81), 56 (66), 55 (54), 42 (88), 41 (53); IR (CCl_4): 3000, 2960, 1750, 1725, 1435, 1255, 1220, 1160 cm^{-1}. HRMS: found, M^+ 183.0887, direct inlet. $C_9H_{13}NO_3$ requires M, 183.0895.

Tetrahydro-2',3'-diphenylspiro[cyclobutane-1,5'-isoxazole] (17). See ref. 11.

Tetrahydro-6',6'-dimethylspiro[cyclobutane-1,2'(3'*H*)-pyrrolo[1,2-*b*]isoxazole] (18). The nitrone **9** (1 g, 8.85 mmol) and excess methylenecyclobutane (**10**, 0.9 g, 13.2 mmol) were reacted in a sealed tube at 100 °C for 4 days; then the adduct **18** was distilled (1.45 g, 90%), bp 50 °C/0.1 mmHg.

Anal. Found: C, 73.01; H, 10.45; N, 7.86. Calc. for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73%. ^{1}H NMR (300 MHz): δ 3.83 (dddd, J 11.8, 7.5, 4.5, 2.9, 1 H), 2.59 (dd, J 12.2, 7.5, 1 H), 2.42-1.75 (m, 6 H), 2.18 (dd, J 12.2, 2.9, 1 H), 1.72-1.38 (m, 4 H), 1.30 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR: δ 80.72 s, 67.58 s, 63.98 d, 47.42 t, 36.99 t, 35.28 t, 35.02 t, 30.62 t, 26.27 q, 23.80 q, 11.65 t; MS: 181 (M^+, 13%), 166 (25), 153 (3), 138 (8), 114 (27), 110 (25), 96 (100), 95 (24), 81 (24), 56 (39), 42 (68), 41 (70); IR (neat): 2970, 2940, 2880, 1465, 1380, 1365, 1305, 1290, 1250, 1140, 1110 cm^{-1}.

2-Benzyltetrahydro-6',6'-dimethylspiro[cyclobutane-1,2'(3'*H*)pyrrolo[1,2-*b*]isoxazole] (19). A mixture of the nitrone **9** (305 mg, 2.7 mmol) and 2-benzyl-1-methylenecyclobutane (**11**, 430 mg, 2.7 mmol) was reacted in toluene (1.5 ml) in a sealed tube at 100 °C for 7 days. The crude mixture was purified by a passage through a short pad of silica gel to give 589 mg (80%) of the adducts **19a-d**.

Anal. Found: C, 79.21; H, 9.37; N, 5.56, using a sealed aluminium sample holder. Calc. for $C_{18}H_{25}NO$: C, 79.70; H, 9.22; N, 5.17%.

The isomeric molar ratio in the mixture is 6:6:2:1. This was derived by three gas-chromatographic peaks in 12:1:2 ratio; the two major isomers have the same RT, but are distinguishable by ^{1}H NMR of the mixture (two methyl groups have identical chemical shifts, two have not and are of the same intensity). Flash column chromatography of the mixture (eluent methylene chloride + ethyl acetate 2:1) gave the adducts **19b-d** (*Rf* 0.40) and **19a** (*Rf* 0.22). Repeated chromatographies allowed the obtainment of fractions enriched in the diastereoisomers **19b**, **19c**, and **19d**.

19a (1*S**,2*S**,3a'*R**): ^{1}H NMR (300 MHz): δ 7.35-7.15 (m, 5 H), 3.86 (tt, J 8.4, 4.2, 1 H), 2.88 (dq, J 6.3, 9.3, 1 H), 2.76 (dd, J 14.0, 6.3, 1 H), 2.65 (dd, J 14.0, 9.3, 1 H), 2.41 (dd, J 12.0, 8.4, 1 H), 2.12-1.96 (m, 3 H), 2.08 (dd, 12.0, 4.2, 1 H), 1.87-1.68 (m, 2 H), 1.49-1.40 (m, 1 H), 1.47 (dd, J 11.2, 2.8, 1 H), 1.35-1.15 (m, 1 H), 1.25 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR: δ 139.98 s, 128.34 d (2 C), 128.07 d (2 C), 125.63 d, 83.60 s, 67.09 s, 63.51 d, 43.29 d, 42.16 t, 37.48 t, 35.54 t, 35.39 t, 31.55 t, 26.66 q, 23.77 q, 19.67 t; MS: 271 (M^+, 3%), 256 (5), 183 (5), 153 (20), 129 (11), 117

(27), 114 (100), 98 (31), 96 (72), 91 (58), 83 (33), 81 (35), 55 (35), 42 (38), 41 (52); IR ($CDCl_3$): 3090, 3070, 3040, 2980, 2950, 2870, 1645, 1610, 1500, 1465, 1455, 1370, 1140 cm^{-1}.

19b (1*S**,2*R**,3a'*R**): ^1H NMR (300 MHz): δ 7.35-7.15 (m, 5 H), 3.94 (dddd, J 9.4, 6.9, 4.0, 1.9, 1 H), 2.95 (dd, J 13.1, 3.5, 1 H), 2.83-2.65 (m, 1 H), 2.71 (dd, J 12.2, 7.1, 1 H), 2.44 (dd, J 13.1, 12.0, 1 H), 2.15-2.00 (m, 4 H), 1.90-1.10 (m, 5 H), 1.39 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR: δ 140.35 s, 128.42 d (2 C), 128.09 d (2 C), 125.55 d, 83.66 s, 68.41 s, 64.53 d, 47.63 d, 40.98 t, 36.89 t, 35.84 t, 34.00 t, 30.78 t, 26.54 q, 24.28 q, 19.01 t; MS: 271 (M^+, 9%), 256 (7), 243 (8), 187 (10), 138 (20), 124 (25), 114 (84), 111 (38), 110 (25), 96 (74), 91 (100), 81 (26), 55 (36), 41 (44).

19c (1*R**,2*R**,3a'*R**): ^1H NMR (300 MHz): δ 3.82 (m, 1 H), 2.91-2.80 (m, 1 H) 2.63 (dd, J 13.5, 7.7, 1 H), 1.24 (s, 3 H), 1.04 (s, 3 H); MS: 271 (M^+, 2%), 256 (40), 154 (17), 153 (31), 138 (19), 117 (41), 114 (39), 98 (79), 96 (100), 91 (63), 83 (63), 82 (49), 81 (45), 56 (36), 55 (37), 42 (37), 41 (46).

19d (1*R**,2*S**,3a'*R**): ^1H NMR (300 MHz): δ 4.00-3.90 (m, 1 H), 3.19 (dd, J 13.6, 5.5, 1 H), 2.29 (dd, J 13.5, 2.7, 1 H), 1.40 (s, 3 H), 1.16 (s, 3 H); MS: 271 (M^+, 15%), 256 (15), 243 (15), 174 (22), 138 (23), 124 (26), 114 (88), 111 (40), 96 (75), 91 (100), 55 (36), 41 (41).

3'-Carbomethoxy-hexahydro-6',6'-dimethylspiro[cyclobutane-1,2'(3'*H*)-pyrrolo[1,2-*b*] isoxazole] (20). A solution of the nitrone **9** (160 mg, 1.41 mmol) and methyl cyclobutylideneacetate (**12**, 126 mg, 1 mmol) in toluene (1 ml) was reacted in a sealed tube at 100 °C for 7 days. The solvent was removed *in vacuo* and the residue chromatographed on a short column (eluent ethyl acetate) to give 194 mg (81%) of a mixture of the *exo*-adduct **20a** and the *endo*-adduct **20b** in 2:1 molar ratio (^1H NMR).

Anal. Found: C, 65.03; H, 8.99; N, 6.04. Calc. for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85%.

Partial separation of **20a** (*Rf* 0.50) and **20b** (*Rf* 0.36) was accomplished by flash column chromatography (eluent petroleum ether + ethyl acetate 70:30).

20a (3'*R**,3a'*R**): ^1H NMR (300 MHz): δ 4.11 (ddd, J 8.9, 5.1, 3.6, 1 H), 3.75 (s, 3 H), 2.88 (d, J 5.2, 1 H), 2.38-2.32 (m, 2 H), 2.20-2.04 (m, 3 H), 1.92-1.69 (m, 2 H), 1.59-1.45 (m, 3 H), 1.29 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR: δ 171.41 s, 83.27 s, 67.02 s, 66.61 d, 64.06 d, 51.67 q, 35.16 t, 32.50 t, 31.76 t, 31.52 t, 26.07 q, 23.60 q, 12.99 t; MS: 239 (M^+, 50%), 224 (100), 196 (20), 154 (39), 122 (43), 114 (86), 110 (67), 96 (89), 42 (72), 41 (80); IR ($CDCl_3$): 2970, 2880, 1740, 1440, 1370, 1275, 1200, 1160 cm^{-1}.

20b (3'*S**,3a'*R**): ^1H NMR (300 MHz): δ 3.96 (dt, J 8.8, 6.0, 1 H), 3.74 (s, 3 H), 3.59 (d, J 6.4, 1 H), 2.53-1.48 (m, 10 H), 1.33 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR: δ 170.31 s, 82.06 s, 67.86 s, 66.46 d, 58.50 d, 51.32 q, 36.62 t, 35.71 t, 32.86 t, 26.54 q, 26.49 t, 23.89 q, 12.53 t; MS: 239 (M^+, 40%), 224 (73), 196 (23), 154 (29), 122 (50), 114 (60), 110 (61), 96 (100), 42 (70), 41 (78).

Rearrangements.

Rearrangement of 13: 1,5,6,7-Tetrahydro-2-phenyl-4*H*-azepin-4-one (23) and 1-(1-Phenylvinyl)pyrrolidin-2-one[28] (24). The adduct **13** (187 mg, 1 mmol) was vaporized at 110-120 °C and 0.1 mmHg and the products from FVT (700 °C) were collected in dichloromethane, then concentrated and column-chromatographed (eluent methylene chloride + methanol 10:1) to give the pyrrolidinone **24**, *Rf* 0.52 (52 mg, 28%) and the azepinone **23**, *Rf* 0.32 (69 mg, 37%).

Another FVT experiment run at the same temperature and 10^{-3} mmHg on a 2 mmol scale gave, after chromatographic separation, 208 mg of **23** (56%) and 18 mg of **24** (5%).

23: mp 144-146 °C, from acetone. Anal. Found: C, 77.08; H, 6.97; N, 7.77. Calc. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48%. ^{1}H NMR (300 MHz): δ 7.55-7.30 (m, 5 H), 5.63 (br s, 1 H), 5.21 (d, J 2.0, 1 H), 3.57 (q, J 5.5, 2 H), 2.70 (t, J 6.5, 2 H), 2.06 (m, 2 H); ^{13}C NMR : δ 199.51 s, 157.77 s, 139.37 s, 129.90 d, 128.46 d (2 C), 126.72 d (2 C), 101.34 d, 47.13 t, 42.46 t, 24.22 t; MS: 187 (M^+, 31%), 159 (29), 108 (27), 158 (100), 144 (31), 130 (10), 104 (14), 103 (12), 102 (45), 77 (12); IR ($CDCl_3$): 3450, 3300 (br), 3060, 2950, 2850, 1580, 1565, 1530, 1490, 1445, 1365, 1350, 1340, 1290, 1215 cm^{-1}.

24:[28] ^{1}H NMR (300 MHz): δ 7.40 (s, 5 H), 5.40 (s, 1 H), 5.29 (s, 1 H), 3.54 (t, J 6.5, 2 H), 2.55 (t, J 7.8, 2 H), 2.11 (quintet, J 7.3, 2 H); ^{13}C NMR: δ 174.44 s, 143.41 s, 136.06 s, 128.55 d, 128.26 d (2 C), 126.19 d (2 C), 109.14 t, 49.37 t, 31.73 t, 18.36 t; MS: 187 (M^+, 100%), 159 (32), 158 (54), 144 (44), 132 (29), 131 (39), 130 (35), 104 (36), 103 (97), 102 (20), 91 (27), 77 (57), 51 (33); IR ($CDCl_3$): 3060, 3030, 2950, 2880, 1695, 1630, 1495, 1410, 1325, 1265 cm^{-1}.

Rearrangement of 14: 1,5,6,7-Tetrahydro-2-methyl-4*H*-azepin-4-one (25), 1-(1-Methylvinyl) pyrrolidin-2-one (26), and 4,5-Dihydro-3,5-dimethyl-5(2-oxopyrrolidin-1-yl)isoxazole (27). The adduct **14** (1.25 g, 10 mmol) was vaporized at 90 °C and 0.5 mmHg and the products from FVT (700 °C) condensed in the pyrolysis tube were washed with methylene chloride: a solid residue was collected (**25**, 166 mg) and the oil obtained from the solution was column-chromatographed (eluent methylene chloride + methanol 10:1) to give **26** + **27**, *Rf* 0.64, 178 mg, **27**, *Rf* 0.56, 41 mg (5%), and **25**, *Rf* 0.23, 220 mg. 386 mg of pure **25** were collected together (overall yield 31%). Compound **25**, set aside for 6 days in a $CDCl_3$ solution (NMR tube) at room temperature or for one year as a pure solid at 4 °C, completely isomerized to the azadienol **25'**.

Another FVT experiment (700 °C) run on a 1 mmol scale by heating isoxazoline **14** at 50 °C/0.1 mmHg, gave after chromatographic separation pure **25** (28%) and **26** (17%) exclusively.

25: pale yellow solid, mp 87-88 °C, from toluene. Anal. Found: C, 67.40; H, 8.58; N, 11.20. Calc. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19%. ^{1}H NMR (90 MHz): δ 6.53 (br s, 1 H), 4.95 (s, 1 H), 3.46 (q, J 4.5, 2 H), 2.66 (t, J 6.0, 2 H), 2.16-1.80 (m, 2 H), 2.00 (s, 3 H); ^{13}C NMR : δ 198.67 s, 156.14 s, 100.35 d, 46.54 t, 42.48 t, 24.50 q, 22.71 t; MS: 125 (M^+, 81%), 110 (39), 97 (77), 96 (32), 82 (48), 69 (69), 68 (39), 54 (88), 42 (100), 41 (69), 39 (78); IR ($CDCl_3$): 3460, 3300 (br), 3130, 2950, 2860, 1585, 1540, 1445, 1365, 1340, 1295, 1240 cm^{-1}.

25': ^{1}H NMR (90 MHz): δ 9.80 (br s, 1 H), 5.27 (s, 1 H), 3.70 (t, J 7.5, 2 H), 2.68 (t, J 7.5, 2 H), 2.27-1.83 (m, 2 H), 2.10 (s, 3 H); ^{13}C NMR: δ 194.79 s, 167.36 s, 89.64 d, 47.29 t, 32.10 t, 28.39 q, 21.13 t; MS: 125 (M^+, 31%), 110 (100), 82 (8), 55 (11), 54 (21), 43 (25); IR ($CDCl_3$): 3280 (br), 3070, 2960, 2930, 2860, 1620, 1545, 1500, 1360, 1315, 1295, 1245 cm^{-1}.

26: yellow oil. ^{1}H NMR (90 MHz): δ 4.53 (s, 1 H), 4.43 (br s, 1 H), 3.62 (t, J 7.0, 2 H), 2.65-2.35 (m, 2 H), 2.24 (s, 3 H), 2.22-1.90 (m, 2 H); ^{13}C NMR: δ 178.76 s, 141.92 s, 98.83 t, 48.58 t, 32.69 t, 29.72 q, 17.56 t; MS: 125 (M^+, 71%), 97 (16), 96 (33), 82 (39), 70 (85), 68 (16), 42 (100), 41 (74), 39 (69); IR ($CDCl_3$): 2980, 2930, 2880, 1695, 1625, 1390, 1325, 1310, 1265 cm^{-1}.

27: brown oil. ^{1}H NMR (90 MHz): δ 3.91 (d, J 18.0, 1 H), 3.58 (t, J 7.5, 2 H), 2.98 (d, J 18.0, 1 H), 2.58-1.87 (m, 4 H), 2.03 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR: δ 174.84 s, 158.55 s, 94.95 s, 48.79 t, 45.16 t, 32.74 t, 22.02 q, 17.54 t, 13.05 q; MS: 167 ($M-CH_3^+$, 3%), 165 (3), 141 (19), 123 (24), 110 (12), 98 (100), 97 (37), 86 (75), 82 (66), 70 (36), 56 (76), 43 (78), 42 (63), 41 (63).

Rearrangement of 15: 7-Benzyl-1,5,6,7-tetrahydro-2-methyl-4*H*-azepin-4-one (35), 5-Benzyl-1,5,6,7-tetrahydro-2-methyl-4*H*-azepin-4-one (36), 5-Benzyl-(1-methylvinyl)pyrrolidin-2-one (37), 3-Benzyl-1-(1-methylvinyl)pyrrolidin-2-one (38), *Z*- and *E*-6-Phenyl-4-hexen-2-one[31] (39), and 1,2-Diphenylethane (40). The cycloadduct **15** (223 mg, 1.03 mmol) was subjected to FVT at 650 °C/0.01 mmHg by vaporization at 120 °C. In the collecting flask at the end of the pyrolysis tube were collected 60 mg of a mixture (molar ratio 1.25:1) containing the β,γ-unsaturated ketone **39** (as a 2.5:1 *E/Z* diastereomeric mixture) and dibenzyl (**40**). From the washing (acetone) of the pyrolysis tube were recovered 90 mg of a complex product mixture. By integration of the ^{1}H NMR spectrum of the crude mixture the following yields have been calculated: **35**, 16% (including also tautomer **35'**); **36**, 14% (including also tautomer **36'**); **37**, 2%; **38**, 2%; **39**, 4% (total 22%); **40**, 8% (total 37%). Attempted chromatographic separation of this mixture (eluent methylene chloride + methanol 15:1) allowed partial resolution affording some enriched fractions, from which distinctive analytical data have been derived for all the compounds. The azepinones **35** and **36**, set aside for 1 month in $CDCl_3$ solutions (NMR tube) at room temperature, completely isomerized to the corresponding azadienol tautomers **35'** and **36'**.

35: ^{1}H NMR (300 MHz): δ 4.91 (d, J 1.7, 1 H), 4.69 (br, 1 H), 3.66 (m, 1 H), 2.93 (dd, J 13.6, 5.6, 1 H), 2.82 (dd, J 13.6, 9.0, 1 H), 2.70-2.54 (m, 2 H), 2.10-1.95 (m, 1 H), 1.84 (s, 3 H), 1.80-1.65 (m, 1 H); ^{13}C NMR: δ 198.54 s, 153.58 s, 137.01 s, 128.90 d (4 C), 127.04 d, 101.42 d, 57.88 d, 41.50 t, 40.40 t, 28.07 t, 25.18 q; MS: 215 (M^+, 81%), 124 (100), 96 (91), 91 (33); IR ($CDCl_3$): 3420, 1590, 1535 cm^{-1}.

35': ^{1}H NMR (300 MHz): δ 9.87 (br, 1 H), 5.05 (s, 1 H), 4.05 (quintet, J 6.7, 1 H), 2.81 (d, J 6.8, 2 H), 2.55 (t, J 7.9, 2 H), 2.10-1.90 (m, 1 H), 2.02 (s, 3 H), 1.80-1.60 (m, 1 H); MS: 215 (M^+, 9%), 200 (3), 124 (100), 106 (20), 91 (7).

36: ^{1}H NMR (300 MHz): δ 7.40-7.15 (m, 5 H), 5.19 (br, 1 H), 4.95 (d, J 2.0, 1 H), 3.46-3.34 (m, 1 H), 3.37 (dd, J 13.9, 4.3, 1 H), 3.28-3.16 (m, 1 H), 2.85-2.75 (m, 1 H), 2.65-2.53 (m, 1 H), 1.92 (s, 3 H), 2.00-1.85 (m, 1 H), 1.75-1.63 (m, 1 H); ^{13}C NMR: δ 197.47 s, 153.74 s, 137.00 s, 128.88 d (2 C), 128.12 d (2 C), 125.78 d, 101.06 d, 52.49 t, 44.74 d, 38.64 t, 29.12 t, 24.23 q; MS: 215 (M^+, 78%), 200 (23), 187 (21), 186 (23), 172 (24), 110 (44), 97 (100), 91 (34).

36': ^{1}H NMR (300 MHz): δ 9.85 (br, 1 H), 7.35-7.15 (m, 5 H), 5.15 (s, 1 H), 3.42 (t, J 7.5, 2 H), 3.05 (m, 2 H), 2.61 (dd, J 14.9, 10.9, 1 H), 2.07 (s, 3 H), 1.96 (ddt, J 12.5, 7.8, 6.8, 1 H), 1.69 (dq, J 12.5, 7.0, 1 H); ^{13}C NMR: δ 194.25 s, 164.49 s, 139.00 s, 128.89 d (2 C), 128.50 d (2 C), 126.48 d, 89.38 d, 46.03 t, 45.76 d, 38.92 t, 29.04 q, 27.72 t; MS: 215 (M^+, 100%), 214 (19), 200 (78), 172 (28), 158 (42), 138 (25), 108 (34), 91 (64); IR ($CDCl_3$): 3290 (br), 1620, 1540 cm^{-1}.

37: ^{1}H NMR (300 MHz): δ 4.95 (s, 1 H), 4.90 (q, J 1.3, 1 H), 4.13 (ddt, J 8.9, 7.7, 3.9, 1 H), 3.08 (dd, J 13.5, 3.9, 1 H), 2.63 (dd, J 13.5, 8.9, 1 H), 2.11 (d, J 1.3, 3 H); MS: 215 (M^+, 8%), 124 (100), 91 (10), 84 (20).

38: ^{1}H NMR (300 MHz): δ 4.47 (s, 1 H), 4.38 (q, J 1.3, 1 H), 3.46-3.34 (m, 2 H), 3.24 (dd, J 13.5, 3.9, 1 H), 2.21 (d, J 1.3, 3 H); ^{13}C NMR: δ 98.61 t, 46.47 t, 38.90 t, 36.84 d, 29.29 q, 23.80 t; MS: 215 (M^+, 100%), 172 (23), 124 (11), 96 (15), 91 (30), 70 (83).

39a (*E* isomer):[31] ^{1}H NMR (300 MHz): δ 7.35-7.15 (m, 5 H), 5.80-5.50 (m, 2 H), 3.40 (d, J 6.8, 2 H), 3.16 (d, J 6.1, 2 H), 2.16 (s, 3 H); ^{13}C NMR: δ 208.35 s, 125.98 d, 125.77 d, 47.30 t, 38.89 t, 29.27 q; MS: 174 (M^+, 15%), 131 (24), 91 (31), 43 (100); IR ($CDCl_3$): 1720 cm^{-1}.

39b (*Z* isomer): ^{1}H NMR (300 MHz): δ 7.35-7.15 (m, 5 H), 5.80-5.50 (m, 2 H), 3.41 (d, J 6.0, 2 H), 3.30 (d, J 6.9, 2 H), 2.20 (s, 3 H).

Rearrangement of 16: *Z*- and *E*-1-(2-Carbomethoxy-1-methylvinyl)pyrrolidin-2-one (41). The adduct **16** (109 mg, 0.6 mmol) was subjected to FVT at 650 °C/0.005 mmHg by vaporization at 70 °C. The products collected from the pyrolysis tube contained the diastereoisomers **41a,b** in an approximate 2:1 ratio. By column chromatography separation (eluent petroleum ether + ethyl acetate 2:1), 35 mg (32% total yield) of **41a**, *Rf* 0.35 and **41b**, *Rf* 0.23 were obtained.

41a: ^{1}H NMR (300 MHz): δ 5.56 (br s, 1 H), 3.68 (s, 3 H), 3.65 (t, J 7.1, 2 H), 2.68 (d, J 0.8, 3 H), 2.54 (t, J 8.1, 2 H), 2.06 (quintet, J 7.6, 2 H); MS: 183 (M^+, 13%), 152 (18), 151 (19), 124 (100), 123 (31), 96 (40); IR ($CDCl_3$): 2980, 2930, 2885, 2845, 1750, 1695 cm^{-1}.

41b: ^{1}H NMR (300 MHz): δ 5.73 (q, J 1.3, 1 H), 3.68 (s, 3 H), 3.65 (t, J 6.9, 2 H), 2.47 (t, J 8.0, 2 H), 2.13 (quintet, J 7.5, 2 H), 2.04 (d, J 1.3, 3 H); MS: 183 (M^+, 36%), 152 (36), 151 (39), 124 (100), 123 (96), 96 (49), 41 (68).

Rearrangement of 17. See ref. 11.

Rearrangement of 18: Hexahydro-3,3-dimethyl-1*H*-pyrrolo[1,2-*a*]azepin-8(5*H*)-one (28) and 5,5-Dimethyl-2-(2-oxopentylidene)pyrrolidine (29). The adduct **18** (905 mg, 5 mmol) was vaporized at 50 °C/0.1 mm Hg and the products from FVT (600 °C) were collected and column-chromatographed (eluent methylene chloride + methanol 10:1) to give **29**, *Rf* 0.55, 272 mg (30%), **28**, *Rf* 0.25, 224 mg (25%), and nitrone **9**, *Rf* 0.13, 74 mg (13%).

28: yellow oil, bp 80 °C/0.04 mmHg. Anal. Found C, 72.75, H, 10.72, N, 7.67. Calc. for $C_{11}H_{19}NO$ C, 72.88, H, 10.56, N, 7.73 %. ^{1}H NMR (300 MHz): δ 3.02 (m, 1 H), 2.96 (quintet, J 4.4, 1 H), 2.55-2.44 (m, 4 H), 2.28 (ddd, J 12.3, 10.6, 2.6, 1 H), 2.16-1.18 (m, 6 H), 1.09 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR: δ 213.02 s, 62.85 s, 58.58 d, 52.41 t, 48.50 t, 43.02 t, 37.85 t, 29.30 t, 27.31 q, 25.71 t, 19.27 q; MS: 181 (M^+, 8%), 166 (100), 124 (24), 96 (10), 86 (10), 85 (15), 82 (34), 55 (38), 41 (54); IR ($CDCl_3$): 2960, 2880, 2810, 1700, 1620, 1460, 1440, 1385, 1180 cm^{-1}.

29: yellow oil. Anal. Found C, 72.79, H, 10.29, N, 7.88. Calc. for $C_{11}H_{19}NO$ C, 72.88, H, 10.56, N, 7.73 %. ^{1}H NMR (300 MHz): δ 9.72 (br s, 1 H), 4.97 (s, 1 H), 2.64 (t, J 7.7, 2 H), 2.20 (t, J 7.5, 2 H), 1.77 (t, J 7.7, 2 H), 1.57 (quintet, J 7.4, 2 H), 1.28 (s, 6 H), 0.90 (t, J 7.4, 3 H); ^{13}C NMR: δ 197.95 s, 165.30 s, 88.53 d, 62.18 s, 43.75 t, 35.54 t, 31.77 t, 28.45 q (2 C), 19.28 t, 13.97 q; MS: 181 (M^+, 16), 138 (100), 111 (11), 110 (20), 96 (37), 41 (23); IR ($CDCl_3$): 3280 (br), 2980, 2940, 2880, 1620, 1550, 1530, 1460, 1300, 1205, 1155 cm^{-1}.

Rearrangement of 19: 5-Benzyl-hexahydro-3,3-dimethyl-1*H*-pyrrolo[1,2-*a*]azepin-8(5*H*)-one (33) and 5,5-Dimethyl-2-(2-oxo-6-phenylhexylidene)pyrrolidine (34). By heating of the adduct **19** (271 mg, 1 mmol) at 120 °C/0.01 mmHg some products from FVT (600 °C) were collected. A column-chromatography separation (eluent petroleum ether + ethyl acetate 4:1) gave the enaminone **34**, *Rf* 0.21 (ca. 12%) and the azepinone **33**, *Rf* 0.10 (ca. 3%), besides major amounts of unidentified decomposition products.

33: ^{1}H NMR (300 MHz): δ 7.30-7.10 (m, 5 H), 4.09 (m, 1 H), 2.91 (m, 1 H), 2.80-1.15 (m, 12 H), 1.23 (s, 3 H), 1.05 (s, 3 H); MS: 271 (M^+, 5%), 256 (100), 131 (14), 91 (19).

34: ^{1}H NMR (300 MHz): δ 9.77 (br, 1 H), 7.35-7.15 (m, 5 H), 4.98 (d, J 0.3, 1 H), 2.66 (t, J 7.5, 2 H), 2.62 (m, 2 H), 2.27 (m, 2 H), 1.79 (t, J 7.5, 2 H), 1.65 (m, 4 H), 1.30 (s, 6 H); ^{13}C NMR: δ 197.74 s, 165.53 s, 88.56 d; MS: 271 (M^+, 20%), 166 (23), 153 (51), 138 (100), 111 (37), 96 (31), 91 (18).

Acknowledgments

The authors thank Consiglio Nazionale delle Ricerche (CNR) and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for financial support, Mrs. B. Innocenti and Mr. S. Papaleo for technical assistance, and Prof. G. Moneti for exact mass measurements.

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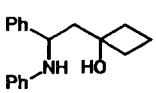

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