4,5-Dihydroisoxazoles, VII[1,2]

Rearrangement Reactions of Cycloadducts from 5-Amino-4,5-dihydro-4-methyleneisoxazoles and Cyclopentadienones: Synthesis of 2-Azatetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane Derivatives

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Reaction of 4,5-dihydro-3-(4-methoxyphenyl)-4-methylene-5-morpholinoisoxazole (**1**) with cyclopentadienones **2** afforded thermally labile Diels-Alder cycloaddition products **3**. On heating these products underwent a stereocontrolled *retro*-Michael process affording a mixture of the corresponding (5-aminoisoxazolylmethyl)-3- and -2-cyclopenten-1-ones **6** and **7**, respectively. At higher temperatures the isoxazole ring of compounds **7** was isomerized to form two epimeric azirines. Only pure **8** was isolated since the other isomer underwent a facile intramolecular [4 + 2] π-cycloaddition yielding the corresponding 2-azatetracyclo-[4.3.0.0^{2,4}.0^{3,7}]nonane derivatives **9**.

4,5-Dihydroisoxazole, VII[1,2]. – Umlagerung von Cycloaddukten aus 5-Amino-4,5-dihydro-4-methylenisoxazolen und Cyclopentadienonen: Synthese von 2-Azatetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonan-Derivaten

Die Reaktion von 4,5-Dihydro-3-(4-methoxyphenyl)-4-methylen-5-morpholinoisoxazol (**1**) mit den Cyclopentadienonen **2** lieferte thermisch labile Diels-Alder-Addukte **3**. Erhitzen dieser Addukte führt über eine stereokontrollierte Retro-Michael-Reaktion zu einer Mischung der (5-Aminoisoxazolylmethyl)-3- und -2-cyclopenten-1-one **6** und **7**. Starkes Erhitzen bewirkt eine Isomerisierung des Isoxazol-Rings von **7** unter Bildung von zwei epimeren Aziridinen. Isoliert werden konnte nur reines **8**, das andere Isomere ergab in einer leicht erfolgenden intramolekularen [4 + 2]-Cycloaddition die entsprechenden 2-Azatetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonan-Derivate **9**.

5-Amino-3-aryl-4,5-dihydro-4-methyleneisoxazoles are readily accessible[3] heterocyclic systems which show an interesting and multiple reactivity of the exocyclic double bond. Several papers dealing with the reactions of these substrates with nucleophiles[4,5] and 1,3-dipolar reagents[5,6] have been published by our research group. As a further contribution to this subject we now report on Diels-Alder reactions of 5-amino-4-methyleneisoxazolines with cyclopentadienones and on the thermal behavior of the cycloaddition products.

Reactions of **1** with 2,3-dimethyl-1,3-butadiene or 1,3-cyclopentadiene, under a variety of experimental conditions, were completely unsuccessfull, evidencing the relatively low reactivity of the double bond in **1**. On the other hand, reaction of **1** with the dimeric form of 2,5-dimethyl-3,4-diphenyl-2,4-cyclopentadienone (**2a**) in methylene chloride at reflux temperature for 25 h partially resulted in the formation of the [4 + 2]-cycloaddition product **3**. The spiro cycloadduct was separated with relative ease from the starting materials by column chromatography.

Compound **3** was identified on the basis of its analytical and spectroscopic data. The strained carbonyl group in the norbornen-7-one structure gave as expected an IR absorption at 1770 cm^{-1} and a ^{13}C-NMR signal at δ = 203.8 Besides, compound **3** exhibited in the ^{1}H-NMR spectrum a diastereotopic methylene group (3-CH$_2$: δ = 2.17, 2.64) and a singlet at δ = 5.22 for 5′-H. The FD mass spectrum of **3** is in agreement with the structure proposed showing the molecular ion at *m/z* = 534 and low intensity fragments at *m/z* = 274 and 260, which corresponds to the products of the *retro*-Diels-Alder cleavage. This behavior is better observed in the EI mass spectrum which shows the ions at *m/z* = 260 (**2a**) and 274 (**1**) with some fragments deriving from these two precursors. This fragmentation pattern is quite similar to that previously described for similar heterocycles[7].

The spectroscopical data do not allow to assign the configuration at the chiral centers C-5′ and C-4′, but some evidence that the structure at the spiro carbon is as shown in the formula can be given by the following alternative route of formation of product **3**. A 1,3-dipolar cycloaddition of 4-methoxybenzonitrile oxide was performed under standard conditions on substrate **5**, easily prepared by reaction of **4** with morpholine. The cycloaddition was complicated by secondary reactions, and also by the acylation at the nitrogen atom, eventually leading, after hydrolysis, to the starting aldehyde and 4-methoxybenzohydroxamic acid morpholide.

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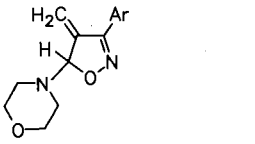
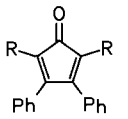
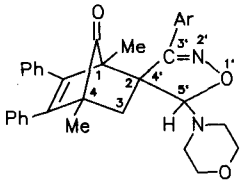
Although the yield of **3** was low, this alternative synthetic route supports the proposed stereochemistry at the spiro carbon of **3**, since it is known that dipoles react with methylenenorbornene substrates with a great preference for the *exo* side[8-10]. When **2b** was treated under similar conditions with **1**, no adduct of type **3** could be isolated. However, their transient formation has been demonstrated by the isolation of their transformation products **6b**, **7b**, showing that in this case their rearrangement occurs at a rate comparable with that of the cycloaddition of the starting materials. The greater reactivity of cyclopentadienones with respect to unfunctionalized dienes is rationalized by considering the double bond of **1** as an alkene bearing an electron-withdrawing substituent with no conjugative effect. This is in agreement with ^{13}C-NMR data[11] and with the observed behavior with the same 1,3-dipoles[6]. This allows to estimate values of about 0 and -10 eV for the LUMO and HOMO, respectively. Taking into account the HOMO and the LUMO values reported by Harano et al.[12] for cyclic dienes and dienones, it is seen that the energy gap in the case of dienones is appreciably smaller.



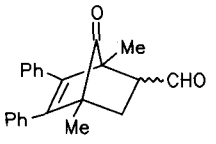
1: Ar = C_6H_4–OCH_3-(4)



2a: R = CH_3
2b: R = C_6H_5



3: Ar = C_6H_4–OCH_3-(4)



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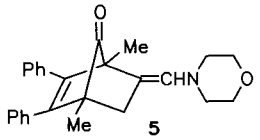

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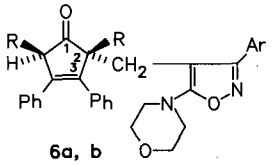
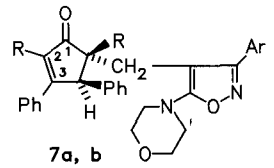
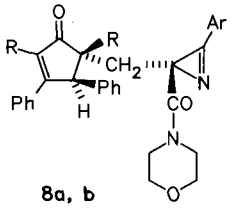


6a, b

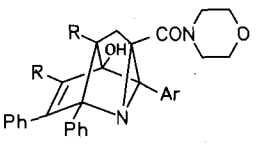
6-9	R	Ar
a	CH_3	C_6H_4–OCH_3-(4)
b	C_6H_5	C_6H_4–OCH_3-(4)



7a, b



8a, b



9a, b

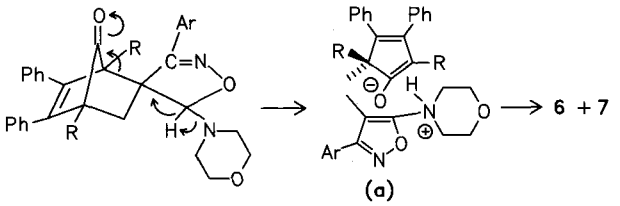
On heating at higher temperature (boiling toluene for 90 min, compound **3** gave rise to a complex mixture containing mainly the two isomeric cyclopentenones **6a** and **7a**, together with minor amounts of the cycloreversion products **1** and **2a**.

The 3-cyclopentenone and 2-cyclopentenone structures for **6a** and **7a**, respectively, were easily deduced from IR bands at 1730 and 1690 cm^{-1} typical of such carbonyl groups. EI mass spectra for **6a** and **7a** show very low-intensity molecular ions, confirmed by FD. The fragmentation pattern is characterized by the cleavage of the molecule which originates ions at m/z = 260 (**2a**) and 273–274 (isoxazole moiety) accompanied by their fragments. A similar behavior is shown by compounds **6b** and **7b**. In the ^{1}H-NMR spectrum of compound **7a**, the signal of the 2-methyl shows an allylic coupling (1.8 Hz) with 4-H, while the 5-methyl group is remarkably shielded (δ = 0.52) by the neighboring phenyl group which is restrained in a position nearly perpendicular to the 2-cyclopentenone ring, as confirmed by molecular models. Another feature which characterizes the ^{1}H-NMR spectra of compounds **7** is a broad multiplet in the range δ = 6.0–6.5 which corresponds to two hydrogens of the phenyl group at C-4. This shielding effect is not present in the spectra of the isomers **6**, in which the steric hindrance about C-4 is reduced by the sp^2 character of this center. In fact one can argue that the shielding difference of the corresponding methyl protons (5-CH_3 in **7a**: δ = 0.52; 2-CH_3 in **6a**: δ = 1.02) is due to the increased freedom of rotation of the nearby phenyl group in compound **6a** with respect to **7a**. For this reason the phenyl group itself does not present chemical shift anomalies in compounds **6**.

The structure of **7a** was determined by X-ray single-crystal analysis[20]. The structure of the analog **7b** was assigned by similarity of spectral data. The structural assignments on the 3-cyclopentenones **6** presented the problem of determining whether the substitution at C-2 and C-5 was *cis* or *trans*. ^{13}C-chemical shifts of the methylene bridge carbon worked as a good indication of the relative stereochemistry of substitution in a similar series of compounds in which the heteroaromatic substituent was different[9]. In the *cis* analogs, the methylene bridge carbon exhibited chemical shifts of about δ = 30, while in the *trans* analogs the shift was about δ = 37. The corresponding data for **6** (δ = 28.5–29.4) seem to be in accord with the *cis* disubstitution case.

Both cyclopentenones **6** and **7** are remarkably stable to heat, and remained unchanged when refluxed in benzene solution for 2–3 h. However, the conjugated ketones **7** are characterized by a thermal stability greater than **6**. Indeed, on heating **6a** for 8 h in refluxing anisol partial conversion into **7a** was observed. On the other hand heating of **7a** under the same conditions afforded only unchanged starting material. From the foregoing it is assumed that the reaction mixture produced from the cycloadduct **3** contains both, a kinetic (**6a**) and a thermodynamic product (**7a**). The question arises whether **7a** derives from **6a** or is formed directly from **3**. When **3** was heated in refluxing toluene for 1.5 h, both **6a** (minor product) and **7a** (major product) were produced. Since, as shown, **6a** is substantially stable under these conditions, it is concluded that **7a** must derive directly from **3**. Accordingly, the rearrangement mechanism of the spiro heterocycle **3** must account both for the formation of two products and also for the observed stereochemistry. A log-

ical hypothesis is the following: the decomposition of **3** occurs through an elimination mechanism in which the morpholino group acts as the base, which can be described as a *retro*-Michael type process leading to the zwitterionic intermediate (**a**). The enolate moiety is intramolecularly protonated by the morpholinium group at the α (kinetic) and at the γ (thermodynamic) positions[13,14]. Owing to the conformation of (**a**), the protonation occurs on the same face bearing the isoxazolylmethyl group, thus producing the observed stereochemistry.



(a)

Further heating of **7a** (refluxing anisol for 14 h) resulted in its transformation into mixture of the azirine derivative **8a** and a derivative of the new heterocycle 2-azatetracyclo-[4.3.0.0^{2,4}.0^{3,7}]nonane (or 1-aza-1,2,3,3a,4,6a-hexahydro-1,2,4-methenopentalene or azadeltacyclane) **9a**. Similarly, but at a greater rate (refluxing anisol for 4 h), **7b** was transformed into **8b** (main product) and **9b**.

The structures of compounds **8** follow from IR absorptions at 1710–1720 cm^{-1} (C=N)[15], 1690 and 1610–1620 cm^{-1} (C=O, ketone and amide, respectively). Mass spectra of **8a** and **8b** are very similar to those of their precursors. This fact can be probably ascribed to the relative ease of interconversion of structures **7** and **8** which, after ionization, isomerize to give a common molecular ion which subsequently fragments in the same way for both derivatives. In the ^{1}H-NMR spectrum of **8a** the signals pertaining to the 2-cyclopentenone structure did not differ from the corresponding signals observed in **7a**, except for 4-H (δ = 4.96) which in **8a** is almost 1 ppm more deshielded than in **7a**. On the other end, the corresponding ^{13}C signal was found at δ = 55.5 (in **7a**: δ = 56.2) pointing to an anisotropic deshielding effect experienced by 4-H in **8a** and due to the azirine substituent. Similar data exist for **8b**.

The confirmation of the configuration in **8a** as the *R*S** diastereoisomer was given by X-ray analysis[20]. The structures of **9a,b** follow from IR (3200 and 1590 cm^{-1}, OH and C=O) and ^{1}H-NMR data (δ = 1.75; 2.53 for **9a** and δ = 2.40; 3.09 for **9b**, CH_2). A complementary confirmation of the structures of **9a,b** was given also by EI mass spectra which easily show recognizable molecular ions at *m/z* = 534 and 658, owing to the greater stability of these products with respect to their precursors. The fragmentation pattern differs from that of the isomers **6**, **7**, and **8** only for the intensity of the same ions, showing large M − 86 peaks (loss of a morpholine residue). There are also fragments corresponding to a cyclopentadienone and to an isoxazole or azirine moiety. An interesting difference can be observed between the mass spectra of **9a** and of **9b**: in the spectrum of **9a** the formation of the isoxazole or azirine moiety is accompanied by an hydrogen rearrangement to give an ion at *m/z* = 275; in **9b** another hydrogen rearrangement in the opposite direction is taking place originating an ion at *m/z* = 273.

The structure of **9a** was given by X-ray single-crystal analysis[20].

The formation of both **8** and **9** from **7** is explained as follows. Through the thermal rearrangement of the isoxazole ring an azirine compound is formed. This reaction is per se known[16,17], and a diradical intermediate is involved. Accordingly, a diastereospecific reaction is hardly to be expected. However, of the two possible azirines only **8** was found. It is suggested that the other diastereoisomer (epimer at the azirine carbon) could not be formed since it is rapidly transformed into compound **9**. This rearrangement is rationalized by an intramolecular [4+2] π-cycloaddition involving as the diene the enol form of the cyclopentenone moiety and as the dienophile the azirine double bond. Other examples of Diels-Alder reactions with azirine compounds have been reported[18], but to our knowledge no cases of intramolecular reactions were hitherto known. By the same rearrangement, **8** would afford the 1-hydroxy-7-phenyl isomer of **9**. However, **8a,b** were found to be very stable to heat. They were converted into **9a,b** on very long heating at high temperature. This is explained by considering that the Diels-Alder product from **8** would be rather unstable having a hemiaminal structure, which would allow the rearrangement to the starting compound by an elimination pathway. Instead, **9** is slowly formed, clearly after epimerization at the azirine carbon, probably through the same diradical intermediate involved in its formation from **7**[17]. From the preparative point of view, compounds **9a,b** could be easily prepared in a one-pot reaction in about 50% yield by direct melting of **1** and **2a,b** at about 200°C for 3–5 h, making the synthesis of this new heterocyclic ring a relatively easy task.

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Experimental

IR spectra: Perkin-Elmer 197 Infrared spectrophotometer. – ^{1}H-NMR spectra (tetramethylsilane as internal standard, $CDCl_3$): Varian EM-390, 90 MHz, and Varian XL-200 instruments. – ^{13}C-NMR spectra: Varian XL-200 instrument. – Mass spectra: Varian MAT-311-A spectrometer (FD: ion source temp. 150°C; volt. diff. emitter–cathode 9 kV, emitter heating current 13–18 mA; EI: direct inlet technique, probe temp. 130–160°C, ion source temp. 250°C, electron energy 70 eV). – TLC: Ready-to-use silica gel plates with benzene/ethyl acetate (1:9 – 9:1) as eluent. Column chromatography: silica gel with the eluent indicated. – M. p.'s are not corrected.

4,5-Dihydro-3-(4-methoxyphenyl)-4-methylene-5-morpholino-isoxazole (**1**): Compound **1** was obtained by a method analogous to that described previously[5]. Yield 61%, colorless crystals (isopropyl ether); m.p. 98–100°C. – ^{1}H NMR: δ = 2.70–3.10, 3.70–4.05 (2m, 8H, morpholine); 3.90 (s, 3H, OCH_3); 5.60–5.90 (m, 3H, CH_2 and CH); 6.85–7.70 (m, 4 aromat. H).

exo- and endo-1,4-Dimethyl-7-oxo-5,6-diphenylbicyclo[2.2.1]hept-5-en-2-carboxaldehyde (**4**): The dimeric derivative of **2a** (4.0 g, 15.3 mmol) was dissolved in benzene (50 ml). Acrolein (0.86 g, 15.3 mmol) was added to the solution, and the mixture was refluxed for 1.5 h. The benzene was evaporated, the residue was taken up with diisopropyl ether, and the solid product was filtered with suction yielding pure **4**, m.p. 122°C, yield 4.0 g (83%). – IR (nujol): 1770 cm^{-1} (C=O); 1715 (HC=O). – ^{1}H NMR: δ = 1.36, 1.60 (2s, 6H,

CH_3); 1.97, 2.48, 3.05 (ABX system, J = 13, 9, 7 Hz, 3H, CH_2CH); 6.8–7.35 (m, 10 aromat. H); 9.81 (d, J = 2 Hz, 1H CHO).

$C_{22}H_{20}O_2$ (316.4) Calcd. C 83.51 H 6.37
Found C 83.71 H 6.45

1,4-Dimethyl-5-morpholinomethylene-2,3-diphenylbicyclo[2.2.1]-hept-2-en-7-one (**5**): The aldehyde **4** (4.0 g, 12.6 mmol) and morpholine (1.2 g, 13.7 mmol) were dissolved in anhydrous benzene (100 ml). A trace amount of *p*-toluenesulfonic acid was added, and the mixture was refluxed with continuous azeotropic elimination of the reaction water. After disappearing of the 1715 cm^{-1} band in the IR spectrum of the reaction solution, sodium sulfate (2 g) was added and the solvent evaporated after filtration. The residue was taken up with *n*-pentane, the solvent was separated, and the residue crystallized with CH_2Cl_2/diisopropyl ether, yielding **5**, m.p. 117°C, yield 3.0 g (62%). – IR (nujol): 1770 cm^{-1} (C=O); 1670 (C=C–N). – ^{1}H NMR: δ = 1.25, 1.35 (s, 6H, $2CH_3$); 2.7 (d, J = 2 Hz, 2H, CH_2); 3.00, 3.75 (m, 8H, morpholine); 5.55 (t, J = 2 Hz, 1H, CH); 6.90–7.30 (m, 10 aromat. H).

3'-(4-Methoxyphenyl)-1,4-dimethyl-5'-morpholino-5,6-diphenyl-spiro[bicyclo[2.2.1]hept-5-en-2,4'(5'H)-isoxazol]-7-one (**3**): a) **1** (0.18 g, 0.65 mmol) and the dimeric form of 2,5-dimethyl-3,4-diphenyl-2,4-cyclopentadienone[17] (**2a**) (0.18 g, 0.69 mmol) were dissolved in CH_2Cl_2 (5 ml) and refluxed for 25 h. The reaction was evaporated at reduced pressure, and the residue was chromatographed on a column with ethyl acetate/benzene, 1:4, as eluent. Fraction 1 containing **2a** was discarded. Fraction 2, containing **3** and **2a**, was evaporated and the residue crystallized from CH_2Cl_2/isopropyl ether affording pure **3**, m.p. 167°C, yield 250 mg (69%).

b) Enamine **5** (3.2 g, 8.2 mmol) was dissolved in CH_2Cl_2. Triethylamine (0.48 g, 8.2 mmol) was added and the solution brought to boiling. To this solution 4-methoxybenzohydroxamoyl chloride (1.53 g, 8.2 mmol), dissolved in CH_2Cl_2 (70 ml), was dropped during 6 h. After 4 h of refluxing, the solution was evaporated and the residue chromatographed (benzene/ethyl acetate, 4:1) affording three main fractions: I) (3.0 g) containing a mixture of **3** and by-products; II) (0.5 g) which after recrystallization from CH_2Cl_2/isopropyl ether gave pure **3** (0.33 g, 11%); III) (0.2 g, 4.5%) pure **7a**, m.p. 190–192°C.

3: IR (nujol): 1770 cm^{-1} (C=O). – ^{1}H NMR: δ = 1.26 (s, 3H, 1-CH_3); 1.36 (s, 3H, 4-CH_3); 2.17, 2.64 (dd, J = 12.8 Hz, 2H, CH_2); 2.54, 3.66 (2m, 8H, morpholine); 3.83 (s, 3H, OCH_3); 5.22 (s, 1H, 5'-H); 6.90–7.40 (m, 9 aromat. H). – ^{13}C NMR: δ = 9.3 (1-CH_3); 11.8 (4-CH_3); 35.1 (C-6); 48.6, 66.7 (morpholine); 55.3 (OCH_3); 102.6 (C-5); 203.6 (C=O). – FD-MS: m/z (%) = 534 (100, $M^{+\cdot}$), 274 (16), 260 (8); EI-MS: m/z (%) = 534 (1), 448 (1), 420 (0.5), 274 (80), 273 (100), 260 (90), 232 (46), 188 (60), 178 (13), 160 (26), 116 (84), 115 (81), 86 (55).

$C_{34}H_{34}N_2O_4$ (534.6) Calcd. C 76.40 H 6.41 N 5.24
Found C 76.00 H 6.52 N 4.94

7a: IR (nujol): 1690 cm^{-1} (C=O). – ^{1}H NMR: δ = 0.52 (s, 3H, 5-CH_3); 1.96 (d, J = 1.8 Hz, 3H, 2-CH_3); 2.83 (s, 2H, CH_2); 3.45, 3.79 (m, 8H, morpholine); 3.86 (s, 3H, OCH_3); 4.00 (d, J = 1.8 Hz, 1H, 4-H); 6.44 (m, 2 aromat. H); 6.90–7.50 (m, 12 aromat. H). – ^{13}C NMR: δ = 10.2 (5-CH_3); 21.0 (2-CH_3); 32.7 (CH_2); 48.0, 66.2 (morpholine); 52.7 (C-5); 55.3 (OCH_3); 56.2 (C-4); 212.1 (C=O). – FD-MS: m/z (%) = 534 (100, $M^{+\cdot}$); EI-MS: m/z (%) = 534 (1), 448 (1), 420 (0.5), 274 (20), 273 (100), 260 (3), 232 (2), 188 (40), 178 (2), 160 (31), 134 (16), 115 (10).

$C_{34}H_{34}N_2O_4$ (534.6) Calcd. C 76.40 H 6.41 N 5.24
Found C 76.76 H 6.41 N 5.29

(2R,5R*)-2-[3-(4-Methoxyphenyl)-5-morpholino-4-isoxazolylmethyl]-2,5-dimethyl-3,4-diphenyl-3-cyclopenten-1-one* (**6a**), *(4S*,5R*)-5-[3-(4-Methoxyphenyl)-5-morpholino-4-isoxazolylmethyl]-2,5-dimethyl-3,4-diphenyl-2-cyclopenten-1-one* (**7a**), *and (2R*)-2-[(1R*,5S*)-1,3-Dimethyl-2-oxo-4,5-diphenyl-3-cyclopenten-1-ylmethyl]-3-(4-methoxyphenyl)-2H-azirine-2-carboxylic Acid Morpholide* (**8a**): a) Compounds **2a** (1.0 g, 3.84 mmol) and **1** (1.0 g, 3.60 mmol) were mixed and melted within 50 min up to 140°C. After cooling, the glassy residue was taken up with CH_2Cl_2, and after addition of isopropyl ether a crystalline precipitate of **7a** was formed (730 mg, 36%). The mother liquor was chromatographed on a silica gel column (ethyl acetate/benzene, 1:4). Three main fractions were obtained.

1) (150 mg) which after recrystallization from $CHCl_3$/isopropyl ether yielded pure **6a** (100 mg, 4.9%), m.p. 192–193°C. – IR (nujol): 1730 cm^{-1} (C=O). – ^{1}H NMR δ = 1.02 (d, J = 7.7 Hz, 3H, 5-CH_3); 1.26 (s, 3H, 2-CH_3); 2.58, 2.80 (dd, J = 15.4 Hz, 2H, CH_2); 3.12, 3.75 (m, 8H, morpholine); 3.16 (q, J = 7.6 Hz, 1H, 5-H); 3.83 (s, 3H, OCH_3); 6.90–7.20 (m, 14 aromat. H). – ^{13}C NMR: δ = 14.9 (2-CH_3); 24.2 (5-CH_3); 24.9 (CH_2); 47.9 (C-5); 48.9, 66.4 (morpholine); 55.3 (OCH_3); 57.7 (C-2); 219.1 (C=O). – FD-MS: m/z (%) = 534 (100, $M^{+\cdot}$), 273 (8), 261 (5); EI-MS: m/z (%) = 534 (1), 448 (4), 420 (3), 274 (20), 273 (100), 260 (7), 232 (4), 188 (53), 178 (2), 160 (31), 134 (17), 115 (10).

$C_{34}H_{34}N_2O_4$ (534.6) Calcd. C 76.40 H 6.41 N 5.24
Found C 76.20 H 6.35 N 5.20

2) (300 mg) which was a mixture of **6a** and **7a**.

3) (710 mg) which was recrystallized from $CHCl_3$/isopropyl ether yielding pure **8a** (400 mg, 19%); m.p. 143–144°C. – IR (nujol): 1720 cm^{-1} (C=N); 1690 (C=O); 1620 (N–C=O). – ^{1}H NMR: δ = 0.55 (s, 3H, 1-CH_3); 1.78 (d, J = 22 Hz, 3H, 3-CH_3); 2.17, 2.56 (dd, J = 15.1 Hz, 2H, CH_2); 3.69 (m, 8H, morpholine); 3.78 (s, 3H, OCH_3); 4.96 (d, J = 2.2 Hz, 1H, 5-H); 6.86–7.85 (2m, 4 aromat. H), 7.00–7.20 (m, 10 aromat. H). – ^{13}C NMR: δ = 10.0 (1-CH_3); 23.1 (3-CH_3); 39.1 (C-2, azirine); 41.7 (CH_2); 44.3, 66.9 (morpholine); 50.2 (C-1); 54.5 (OCH_3) 55.5 (C-5); 165.7 (N–C=O); 211.2 (C=O). – FD-MS: m/z (%) = 534 (100, $M^{+\cdot}$), 273 (4), 261 (11); EI-MS: m/z (%) = 534 (1), 448 (2), 420 (1), 274 (20), 273 (100), 260 (6), 232 (3), 188 (35), 178 (2), 160 (53), 115 (12).

$C_{34}H_{34}N_2O_4$ (534.6) Calcd. C 76.40 H 6.41 N 5.24
Found C 76.10 H 6.43 N 5.26

Thermal Rearrangement of **3**: Compound **3** (190 mg, 0.35 mmol) was refluxed in toluene (5 ml) for 1.5 h until the starting material disappeared. By TLC (benzene/ethyl acetate, 4:1), IR, and ^{1}H-NMR analysis the formation of **6a** and **7a** in a 1:2 ratio next the unreacted starting material was evidenced.

Thermal Rearrangement of **6a**: By heating of **6a** (100 mg, 0.15 mmol) in refluxing anisol (5 ml) for 8 h a partial conversion of **6a** into **7a** was observed (TLC, benzene/ethyl acetate, 4:1, and IR).

7-Hydroxy-3-(4-methoxyphenyl)-6,8-dimethyl-1,9-diphenyl-2-azatetracyclo[4.3.0.0^{2,4}.0^{3,7}]non-8-en-4-carboxylic Acid Morpholide (**9a**): a) Compound **7a** (350 mg, 0.65 mmol) was dissolved in anisol (5 ml) and refluxed for 14 h. The reaction mixture was evaporated and the residue taken up with CH_2Cl_2/isopropyl ether yielding a precipitate of **8a** (150 mg, 43%). The mother liquor was chromatographed on a silica gel column with benzene/ethyl acetate, 3:2, yielding a first fraction containing **8a** and **9a** (50 mg) and a second fraction of pure **9a** (10 mg, 2.9%), m.p. 280°C (dec).

b) Compound **2a** (1.0 g, 3.8 mmol) and **1** (1.0 g, 3.6 mmol) were mixed and heated to 200°C with an oil bath for 3 h. The crude mixture was taken up with ethanol (20 ml), and a solid was formed, filtered, and washed with ethanol (10 ml). Pure compound **9a** was obtained (0.96 g, 50%), m.p. 280°C (dec). – IR (nujol): 3400 cm^{-1} (OH); 1590 (N–C=O). – ^{1}H NMR: δ = 0.92 (s, 3H, 6-CH_3); 1.71

(s, 3H, 8-CH_3); 1.75, 2.53 (dd, J = 12.9 Hz, 2H, CH_2); 3.00–4.25 (m, 8H, morpholine); 3.29 (s, 1H, OH, H/D exchange with D_2O); 3.74 (s, 3H, OCH_3); 6.78, 7.46 (2m, 4 aromat. H); 7.10–7.20 (m, 10 aromat. H). – ^{13}C NMR: δ = 8.8 (6-CH_3); 12.0 (8-CH_3); 37.0 (CH_2); 45.9, 46.0, 66.7 (morpholine); 55.2 (OCH_3); 166.2 (N–C=O). – EI-MS: m/z (%) = 534 (29, $M^{+\cdot}$), 448 (100), 421 (32), 275 (78), 260 (94), 232 (50), 188 (57), 178 (12), 160 (46), 116 (36).

$C_{34}H_{34}N_2O_4$ (534.6) Calcd. C 76.40 H 6.41 N 5.24
Found C 76.40 H 6.48 N 5.43

Thermal Rearrangement of **8a**: Compound **8a** (50 mg, 0.093 mmol) was refluxed in ethylene glycol (5 ml) for 35 h. TLC showed a conversion of **8a** into **9a** of not more than about 20%.

(2S,5R*)-2-[3-(4-Methoxyphenyl)-5-morpholino-4-isoxazolylmethyl]-2,3,4,5-tetraphenyl-3-cyclopenten-1-one* (**6b**), *(4S*,5R*)-5-[3-(4-Methoxyphenyl)-5-morpholino-4-isoxazolylmethyl]-2,3,4,5-tetraphenyl-2-cyclopenten-1-one* (**7b**), *(2R*)-3-(4-Methoxyphenyl)-2-[(1R*,5S*)-2-oxo-1,3,4,5-tetraphenyl-3-cyclopenten-1-ylmethyl]-2H-azirine-2-carboxylic Acid Morpholide* (**8b**), *and 7-Hydroxy-3-(4-methoxyphenyl)-1,6,8,9-tetraphenyl-2-azatetracyclo[4.3.0.0^{2,4}.0^{3,7}]non-8-en-4-carboxylic Acid Morpholide* (**9b**): Compounds **1** (1.5 g, 5.5 mmol) and **2b** (2.1 g, 5.5 mmol) were dissolved in toluene (30 ml) and refluxed for 20 h. After evaporation of the solvent the crude mixture was chromatographed (ethyl acetate/benzene, 1:9). The first fraction contained **7b** (1.3 g) which was recrystallized with CH_2Cl_2/isopropyl ether yielding the pure product (1.1 g, 30.6%), m.p. 225°C. – IR (nujol): 1690 cm^{-1}. – ^1H NMR: δ = 2.80–4.00 (m, 10H, morpholine and CH_2); 3.90 (s, 3H, OCH_3); 4.40 (s, 1H, 4-H); 6.12 (m, 2 aromat. H); 6.60–7.80 (m, 22 aromat. H). – FD-MS: m/z (%) = 658 (100, $M^{+\cdot}$), 385 (2), 273 (5); EI-MS: m/z (%) = 658 (0.5), 572 (1), 384 (4), 356 (2), 274 (12), 273 (100), 188 (39), 178 (15), 160 (22).

$C_{44}H_{38}N_2O_4$ (658.8) Calcd. C 80.21 H 5.81 N 4.25
Found C 80.51 H 5.80 N 4.34

The second fraction (0.4 g) contained a mixture of **7b** and **6b**.

The third fraction (0.3 g) was recrystallized yielding pure **6b**, m.p. 206°C, (200 mg, 5.6%). – IR (nujol): 1740 cm^{-1}. – ^1H NMR: δ = 3.15, 3.85 (m, 8-H, morpholine); 3.20, 3.90 (dd, J = 15 Hz, 2H, CH_2); 3.90 (s, 3H, OCH_3); 4.40 (s, 1H, 5-H); 6.60–7.80 (m, 24 aromat. H). – FD-MS: m/z (%) = 658 (100, $M^{+\cdot}$), 385 (8), 273 (8); EI-MS: m/z (%) = 658 (2), 572 (3), 544 (3), 384 (33), 356 (22), 274 (11), 273 (68), 188 (27), 178 (100), 160 (19).

$C_{44}H_{38}N_2O_4$ (658.8) Calcd. C 80.21 H 5.81 N 4.25
Found C 79.85 H 5.82 N 4.39

The fourth fraction (0.9 g) contained **8b** which after crystallization (CH_2Cl_2/isopropyl ether) yielded the pure product; m.p. 169°C; (800 mg, 22%). – IR (nujol): 1710 cm^{-1} (C=N); 1690 (C=O); 1630 (N–C=O). – ^1H NMR: δ = 2.90, 3.40 (dd, J = 15 Hz, 2H, CH_2); 3.35–3.80 (m, 8H, morpholine); 3.85 (s, 3H, OCH_3); 4.90 (s, 1H, 5-H); 6.40–7.35 (m, 22 aromat. H); 7.90 (d, J = 9 Hz, 2 aromat. H). – FD-MS: m/z (%) = 658 (100, $M^{+\cdot}$), 385 (2), 273 (4); EI-MS: m/z (%) = 658 (1), 572 (1), 544 (1), 384 (11), 356 (7), 274 (14), 273 (100), 188 (36), 178 (37), 160 (48).

$C_{44}H_{38}N_2O_4$ (658.8) Calcd. C 80.21 H 5.81 N 4.25
Found C 79.94 H 6.14 N 4.49

The last fraction (80 mg) after evaporation and crystallization from CH_2Cl_2/isopropyl ether yielded pure **9b**, m.p. 225°C, (40 mg, 1.1%). – IR (nujol): 3300 cm^{-1} (OH); 1590 (C=O). – ^1H NMR ([D_6]DMSO): δ = 2.40, 3.02 (dd, J = 12.0 Hz, 2H, CH_2); 3.40 (m, 8H, morpholine); 3.72 (s, 3H, OCH_3); 6.40–7.50 (m, 24 aromat. H). – EI-MS: m/z (%) = 658 (14, $M^{+\cdot}$), 572 (25), 544 (8), 384 (93), 356 (42), 273 (51), 188 (32), 178 (100), 160 (37).

$C_{44}H_{38}N_2O_4$ (658.8) Calcd. C 80.21 H 5.81 N 4.25
Found C 79.99 H 6.09 N 4.28

Thermal Rearrangement of **7b**: Compound **7b** (300 mg, 0.45 mmol) was refluxed in anisol (10 ml) for 4 h. After solvent evaporation the residue was taken up with CH_2Cl_2/isopropyl ether and pure **9b** (73 mg, 25%) was precipitated. The mother liquor was chromatographed (ethyl acetate/benzene, 1:4) and a main fraction (150 mg) was obtained which after crystallization from CH_2Cl_2/isopropyl ether gave pure **8b** (50 mg, 17%). The second fraction afforded pure **9b** (30 mg, 10%).

Thermal Rearrangement of **8b**: Compound **8b** (110 mg, 17 mmol) in anisol (20 ml) was refluxed for 28 h. TLC and IR showed that the reaction mixture contained **8b** and **9b** in a ratio of about 5:1.

Preparation of **9b**: The mixture of **1** (1.0 g, 3.6 mmol) and **2b** (1.5 g, 3.9 mmol) was melted by heating with an oil bath for 5 h at 190–200°C. After cooling the crude reaction mixture was taken up with CH_2Cl_2/ethyl acetate giving a solid which after filtration was recrystallized from CH_2Cl_2/ethanol yielding pure **9b** (1.0 g, 42%). The mother liquor was chromatographed (ethyl acetate/benzene, 1:4), yielding a fraction containing **8b** which after crystallization from CH_2Cl_2/isopropyl ether yielded the pure compound (150 mg, 6.3%).

CAS Registry Numbers

1: 110027-92-4 / **2a**: 26307-17-5 / **2b**: 479-33-4 / **3**: 110027-95-7 / **4** (isomer 1): 110027-93-5 / **4** (isomer 2): 110028-02-9 / **5**: 110027-94-6 / **6a**: 110045-32-4 / **6b**: 110027-99-1 / **7a**: 110045-31-3 / **7b**: 110027-98-0 / **8a**: 110027-96-8 / **8b**: 110028-00-7 / **9a**: 110027-97-9 / **9b**: 110028-01-8 / acrolein: 107-02-8 / 4-methoxybenzohydroxamoyl chloride: 38435-51-7

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[1] This work has been presented in part at the IV Convegno Nazionale sulle Reazioni Pericicliche, Pavia Italy, 1986.
[2] Part VI: E. Arlandini, M. Ballabio, L. Da Prada, L. M. Rossi, P. Trimarco, *J. Chem. Res. S* **1983**, 1970.
[3] D. Pocar, L. M. Rossi, P. Trimarco, L. Vago, *J. Heterocycl. Chem.* **17** (1980) 881.
[4] D. Pocar, L. M. Rossi, F. Scorca, P. Trimarco *J. Heterocycl. Chem.* **17** (1980) 887.
[5] A. Lazzarini, L. M. Rossi, P. Trimarco, *Gazz. Chim. Ital.* **111** (1981) 309.
[6] M. Ballabio, P. Dalla Croce, V. Massari, D. Pocar, A. Riva, P. Trimarco, *J. Chem. Res. S* **1983**, 140.
[7] N. Almirante, M. Ballabio, M. L. Gelmi, B. Gioia, D. Pocar, M. Valsecchi, *Tetrahedron* **42** (1986) 51.
[8] H. Taniguchi, T. Ikeda, E. Imoto, *Bull. Chem. Soc. Jpn.* **51** (1978) 1859, and references.
[9] M. L. Gelmi, D. Pocar, P. Trimarco, M. Valsecchi, R. Destro, M. Ballabio, *Tetrahedron* **40** (1984) 4025.
[10] N. Almirante, M. L. Gelmi, P. Marelli, D. Pocar, E. Arlandini, M. Ballabio, *Tetrahedron* **42** (1986) 57.
[11] P. Dalla Croce, C. La Rosa, private communication.
[12] K. Harano, M. Yasuda, T. Ban, K. Kanematsu, *J. Org. Chem.* **45** (1980) 4455.
[13] S. K. Malhotra, H. J. Ringold, *J. Am. Chem. Soc.* **85** (1963) 1538.
[14] D. L. Whalen, J. F. Weimaster, A. M. Ross, R. Radhe, *J. Am. Chem. Soc.* **98** (1976) 7319.
[15] A. Padwa, A. D. Woolhouse, in *Comprehensive Heterocyclic Chemistry* (A. R. Katritzky, Ed.), vol. 7, p. 50, Pergamon Press, Oxford 1984.
[16] S. A. Lang, Y.-i Lin. in ref.[15], vol. 6, p. 12–16.
[17] T. Nishiwaki, A. Nakano, H. Matsuoka, *J. Chem. Soc. C* **1970**, 1825.
[18] Ref.[16], p. 59.
[19] F. R. Japp, C. I. Burton, *J. Chem. Soc.* **51** (1887) 431.
[20] The complete crystallographic discussion of this structure is to be published elsewhere.